Note to the reader

The information in this volume has been carefully reviewed for accuracy of dosage and indications. Before prescribing any drug, however, the clinician should consult the manufacturer's current package labeling for accepted indications, absolute dosage recommendations, and other information pertinent to the safe and effective use of the product described. This is especially important when drugs are given in combination or as an adjunct to other forms of therapy. Furthermore, some of the medications described herein, as well as some of the indications mentioned, had not been approved by the US Food and Drug Administration at the time of publication. This possibility should be borne in mind before prescribing or recommending any drug or regimen.

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Preface

The concept for *Cancer Management: A Multidisciplinary Approach* arose nearly 10 years ago. This seventh annual edition reflects the ongoing commitment of the authors, editors, and publishers to rapidly disseminate to oncologists the most current information on the clinical management of cancer patients.

Each chapter in this seventh edition has been updated to keep pace with the most current diagnostic and treatment recommendations. In addition, and in accordance with the recommendations of users of previous editions of this treatment handbook, the common chemotherapy regimens have again been included within the treatment sections of each chapter, rather than as a separate Appendix as in the fifth and previous editions. Information on biological therapies, too, is now included in the treatment sections of appropriate chapters, rather than as a separate chapter. Again, readers tell us this reorganization makes the treatment guide easier to use.

The current volume also provides information on newly approved drugs, such as gefitinib (Iressa), lonafarnib (Sarasar), pemetrexed (Alimta), flavorpiridol (cyclin-dependent kinase inhibitor), epirubicin (Ellence), citalopram hydrobromide (Celexa), oxandrolone (Oxandrin), infliximab (Remicade), troxacitabine (Troxatyl), temozolomide (Temodar), tariquidar, antithymocyte globulin (Atgam), voriconazole (Vfend), micafungin, as well as new indications for alemtuzumab (Campath), capecitabine (Xeloda), darbepoetin alfa (Aranesp), zoledronic acid (Zometa), Actiq (oral transmucosal fentanyl citrate), and rituximab (Rituxan). Reports on newer clinical trials with imatinib mesylate (Gleevec), oxaliplatin (Eloxatin), erlotinib (Tarceva), thalidomide (Thalomid), raloxifene (Evista), anastrozole (Arimidex), letrozole (Femara), and others also are included.

The 49 chapters, one Addendum, and 2 Appendices in the latest edition represent the efforts of 120 contributors (9 of whom are new) from 60 institutions in the United States and Canada.

Three consistent goals continue to guide our editorial policies:

- To provide practical information for physicians who manage cancer patients
- To present this information concisely, uniformly, and logically, emphasizing the natural history of the malignancy, screening and diagnosis, staging and prognosis, and treatment
- To emphasize a collaborative multidisciplinary approach to patient management that involves surgical, radiation, and medical oncologists, as well as other health care professionals, working as a cohesive team

As with the first six annual editions, each chapter (as appropriate) in the current volume has been authored jointly by practicing medical, surgical, and radiation oncologists. In some cases, other specialists have been asked to contribute their expertise to a particular chapter.

All of our contributors personally manage patients using a multidisciplinary approach in their respective institutions. Thus, these chapters reflect the recommendations of practitioners cognizant that therapies must be based on evidence-based research directed at practical patient care in a cost-effective manner.

To write, edit, and publish a 1,000-page text in less than 6 months requires the dedication of all of the authors, as well as a professional publication staff to coordinate the technical aspects of editing and publishing. We, the authors and editors, are indebted to the following individuals: especially Gail van Koot, senior project manager for the book; Susan Reckling, managing editor of the volume; Jim McCarthy, Senior Vice-President/Editorial; Cara Glynn, Editorial Director; and Melissa Warner, President of The Oncology Group. We also thank Andrea Bovee Caldwell, Angela Cibuls, Jeannine Coronna, Christina Fennessey, Ed Geffner, Terri Gelfand, Lisa Katz, Andrew Nash, and Stacey Cuozzo for their efforts. We extend our special thanks to Robert A. Smith, PhD, and Kim Andrews Sawyer of the American Cancer Society for their guidance in helping us to update screening guidelines.

We were able to produce this edition in such a short time frame by drawing on the oncology expertise of the editors of *ONCOLOGY* and *Oncology News International*. These periodic publications, the seventh annual edition of this book, and continuously updated, clinically relevant oncology information can be accessed, at no charge, at The Oncology Group website, CancerNetwork.com.

The background of this text's cover should look familiar to readers. It is identical to that of *ONCOLOGY,* the flagship publication of The Oncology Group, which has provided continuing medical information to oncology professionals for the past 16 years and is consistently ranked as the most widely read oncology journal by an independent readership audit. This cover symbolizes the ongoing commitment to oncology education of The Oncology Group and the editors and authors of this text.

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CHAPTER 1

Principles of surgical oncology

Lawrence D. Wagman, MD

Surgical oncology, as its name suggests, is the specific application of surgical principles to the oncologic setting. These principles have been derived by adapting standard surgical approaches to the unique situations that arise when treating cancer patients.

The surgeon is often the first specialist to see the patient with a solid malignancy, and, in the course of therapy, he or she may be called upon to provide diagnostic, therapeutic, palliative, and supportive care. In each of these areas, guiding paradigms that are unique to surgical oncology are employed.

In addition, the surgical oncologist must be knowledgeable about all of the available surgical and adjuvant therapies, both standard and experimental, for a particular cancer. This enables the surgeon not only to explain the various treatment options to the patient but also to perform the initial steps in diagnosis and treatment in such a way as to avoid interfering with future therapeutic options.

Invasive diagnostic modalities

As the surgeon approaches the patient with a solid malignancy or abnormal nodal disease or the rare individual with a tissue-based manifestation of a leukemia, selection of a diagnostic approach that will have a high likelihood of a specific, accurate diagnosis is paramount. The advent of high-quality invasive diagnostic approaches guided by radiologic imaging modalities has limited the open surgical approach to those situations where the disease is inaccessible, a significant amount of tissue is required for diagnosis, or a percutaneous approach is too dangerous (due, for example, to a bleeding diathesis, critical intervening structures, or the potential for unacceptable complications, such as pneumothorax).

Lymph node biopsy

The usual indication for biopsy of the lymph node is to establish the diagnosis of lymphoma or metastatic carcinoma. Each situation should be approached in a different manner.

Lymphoma The goal of biopsy in the patient with an abnormal lymph node and suspected lymphoma is to make the general diagnosis and to establish the lymphoma type and subtype. Additional analyses of the cells in the node, its internal architecture, and the subpopulations of cells are critical for subsequent treatment. Although advances in immunocytochemical and histochemical analyses have been made, adequate tissue is the key element in accurate diagnosis.

Consequently, the initial diagnosis of lymphoma should be made on a completely excised node that has been minimally manipulated to ensure that there is little crush damage. When primary lymphoma is suspected, the use of needle aspiration does not consistently allow for the complete analyses described above and can lead to incomplete or inaccurate diagnosis and treatment delays.

When recurrent lymphoma is the primary diagnosis, the analysis of specific cell type is very important for assessing changes in the type of lymphoma and whether a transformation has occurred. In the rare situation in which recurrent Hodgkin's disease is suspected, a core biopsy may be adequate if the classic Reed-Sternberg cells are identified. However, in the initial and recurrent settings, biopsy of an intact node is often required.

Carcinoma The diagnosis of metastatic carcinoma often requires less tissue than is needed for lymphoma. Fine-needle aspiration (FNA), core biopsy, or subtotal removal of a single node will be adequate in this situation. For metastatic disease, the surgeon will use a combination of factors, such as location of the node, physical examination, and symptoms, to predict the site of primary disease. When this information is communicated to the pathologist, the pathologic evaluation can be focused on the most likely sites so as to obtain the highest diagnostic yield. The use of immunocytochemical analyses can be successful in defining the primary site, even on small amounts of tissue.

Head and neck adenopathy The head and neck region is a common site of palpable adenopathy that poses a significant diagnostic dilemma. Nodal zones in this area serve as the harbinger of lymphoma (particularly Hodgkin's disease) and as sites of metastasis from the mucosal surfaces of the upper aerodigestive tract, nasopharynx, thyroid, lungs, and, occasionally, from intra-abdominal sites, such as the stomach, liver, and pancreas.

Since treatment of these nodal metastases varies widely, and since subsequent treatments may be jeopardized by inconveniently placed biopsy incisions, the surgical oncologist must consider the most likely source of the disease prior to performing the biopsy. FNA or core biopsy becomes a very valuable tool in this situation, as the tissue sample is usually adequate for basic analysis (cytologic or histologic), and special studies (eg, immunocytochemical analyses) can be performed as needed.

Biopsy of a tissue-based mass

Several principles must be considered when approaching the seemingly simple task of biopsying a tissue-based mass. As each of the biopsy methods has unique risks, yields, and costs, the initial choice can be a critical factor in the

timeliness and expense of the diagnostic process. It is crucial that the physician charged with making the invasive diagnosis be mindful of these factors.

Mass in the aerodigestive tract In the aerodigestive tract, biopsy of a lesion should include a representative amount of tissue taken preferably from the periphery of the lesion, where the maximum amount of viable malignant cells will be present. Since the treatment of in situ and invasive disease varies greatly, the biopsy must be of adequate depth to determine penetration of the tumors. This is particularly true for carcinomas of the oral cavity, pharynx, and larynx.

Breast mass Although previously a common procedure, an open surgical biopsy of the breast is rarely indicated today. Palpable breast masses that are highly suspicious (as indicated by physical findings and mammography) can be diagnosed as malignant with close to 100% accuracy with FNA. However, because the distinction between invasive and noninvasive disease is often required prior to the initiation of treatment, a core biopsy, performed either under image guidance (ultrasound or mammography) or directly for palpable lesions, is the method of choice.

The spectrum of therapeutic options guides the method of tissue diagnosis. For example, the woman who chooses preoperative chemotherapy for a breast lesion is best served with a core biopsy. This biopsy method establishes the histologic diagnosis, provides adequate tissue for analyses of hormone-receptor levels and other risk factors, causes little or no cosmetic damage, does not perturb sentinal analyses, and does not require extended healing prior to the initiation of therapy. In addition, a small radio-opaque clip can be placed in the tumor to guide the surgical extirpation. This is important because excellent treatment responses can make it difficult for the surgeon to localize the original tumor site.

Mass in the trunk or extremities For soft-tissue or bony masses of the trunk or extremities, the biopsy technique should be selected on the basis of the planned subsequent tumor resection. The incision should be made along anatomic lines in the trunk or along the long axis of the extremity. When a sarcoma is suspected, FNA can establish the diagnosis of malignancy, but a core biopsy will likely be required to determine histologic type and plan neoadjuvant therapy.

Preoperative evaluation

As with any surgical patient, the preoperative evaluation of the cancer patient hinges primarily on the individual's underlying medical condition(s). Because most new cancers occur in older patients, careful attention must be paid to evaluation of cardiovascular risks. Adequate information usually can be obtained from a standard history, physical examination, and electrocardiogram (ECG), but any concerns identified should be subjected to a full diagnostic work-up.

The evaluation should also include a detailed history of previous therapies. Previous use of doxorubicin (Adriamycin and others) may be associated with cardiac dysfunction and the use of bleomycin (Blenoxane) with severe lung sensitivity to oxygen concentrations > 30%. Prior radiation therapy is associated with fibrosis and delayed healing. An appreciation of potential postoperative problems secondary to these factors is important in planning the surgical extirpation and reconstruction.

For example, in a patient who requires mastectomy after failed breast-conserving surgery, the zone of tissue damage from the original radiation therapy can be assessed by reviewing the port and boost site films or by examining the irradiated site for tattoo marks used to align the radiation field. Plans for resection of heavily irradiated tissues should be made preoperatively in concert with the reconstructive surgeon, and the relative increased risk of postoperative problems should be discussed with the patient. This evaluation should include the type of tissue to be transferred, analysis of potential donor and recipient sites and vessels, and assurance that the appropriate microvascular equipment is available, in the event that it is needed during surgery.

Pathologic confirmation of the diagnosis

The treatment of cancer is based almost exclusively on the organ of origin and, to a lesser degree, on the histologic subtype. Unless the operative procedure is being performed to make a definitive diagnosis, review of the pathologic material is needed to confirm the diagnosis preoperatively.

There are few exceptions to this doctrine, and it behooves the surgeon to have a confirmed diagnosis, including the in situ or invasive nature of the cancer, prior to performing an operation. This tenet assumes paramount importance when one is performing procedures for which there is no recourse once the specimen is removed, eg, laryngectomy, mastectomy, removal of the anal sphincter, and extremity amputation.

Ironically, in some situations, a preoperative or intraoperative diagnosis cannot be confirmed, despite the fact that the preoperative and intraoperative physical findings, laboratory data, and radiologic studies (pre- and intraoperative) overwhelmingly suggested the cancer diagnosis. The classic example of this dilemma is the jaundiced patient with a firm mass in the pancreatic head. The Whipple procedure (pancreaticoduodenectomy) causes significant morbidity but is required to make the diagnosis and treat the cancer. In any of these situations, the preoperative discussion with the patient must include the possibility that the final diagnosis may be a benign lesion.

Resection

The principles of resection for malignant disease are based on the surgical goal (complete resection vs debulking), degree of functional significance of the involved organ or structure, and the ability to reconstruct the involved and surrounding structures. Also important are the technical abilities of the surgeon

or availability of a surgical team, adequacy of adjuvant and neoadjuvant therapies, and the biological behavior (local and systemic) of the disease. The definition of "resectable" varies, and this term can be defined only in the context of the aforementioned modifying parameters.

Wide excision

A wide excision includes the removal of the tumor itself and a margin of normal tissue, usually exceeding 1 cm in all directions from the tumor. The margin is quite variable in a large, complex (multiple tissue compartments) specimen, and the limiting point of the resection is defined by the closest approximation of cancerous tissue to the normal tissue excised.

Wide margins are recommended for tumors with a high likelihood of local recurrence (eg, dermatofibrosarcoma protuberans) and for tumors without any reliable adjuvant therapeutic options.

Breast The use of adjuvant radiation therapy has permitted the use of breast-conserving surgery, which limits the excision of wide margins of normal breast tissue.

Colon and rectum For carcinoma of the colon and rectum, the width of excision is defined by the longitudinal portion of the bowel and the inclusion of adjacent nodal tissue. The principles of wide resection of normal bowel include at least 5 cm of uninvolved tissue, the associated mesenteric leaf, and adjacent rectal soft tissue (mesorectum).

This general principle has been modified in the distal rectum, where longitudinal bowel margins of 2 cm are accepted. This modification reflects the emphasis on functional results (ie, maintenance of anal continence) and the availability of adequate adjuvant radiation therapy to improve local control.

No touch technique

This principle is based on the concept that direct contact with the tumor during resection can lead to an increase in local implantation and embolization of tumor cells. Theoretically, the metastatic potential of the primary lesion would be enhanced by the mechanical extrusion of tumor cells into local lymphatic and vascular spaces. There may be some validity to this theory with respect to tumors that extend directly into the venous system (eg, renal cell tumors with extension to the vena cava) or that extensively involve local venous drainage (eg, large hepatocellular carcinomas).

Extensive palpation and manipulation of a colorectal primary have been shown to result in direct shedding of tumor cells into the lumen of the large bowel. The traditional strategy to lessen this risk was to ligate the proximal and distal lumen of the segment containing the tumor early in the resection. These areas were then included in the resection, limiting the contact of shed tumor cells with the planned anastomotic areas.

Neither of the above theoretical situations (ie, manipulation of the tumor and direct contact of the tumor with the anastomotic area) has been definitively

tested in controlled, prospective, randomized trials. However, the risk-benefit ratio clearly favors adherence to the general principles of minimal tumor manipulation, protection of the anastomotic areas, and exclusion of the resection bed from potential implantation with tumor cells.

Lymphadenectomy

Early surgical oncologic theory proposed that breast cancer progressed from the primary site to the axillary lymph nodes to the supraclavicular nodes and nodes of the neck. This theory led to the radical surgical approach that included resection of all of the breast tissue and some or all of the above-noted draining nodal basins (ie, modified radical or radical mastectomy).

Absent in this approach was an appreciation of the nodes not only as a deposit of regional metastatic disease but also as a predictor of systemic disease. Modern treatment approaches view nodal dissection as having a triple purpose: the surgical removal of regional metastases, the prediction of prognosis, and the planning of adjuvant therapy.

The surgical technique for lymphadenectomy is based on nodal basins that are defined by consistent anatomic structures. For example, dissection of the neck is defined by the mandible, anterior strap muscles of the neck, clavicle, trapezius muscle, carotid artery, vagus nerve, brachial plexus, and fascia overlying the deep muscles of the neck.

Modifications of classic techniques Each of the classic anatomic lymphadenectomies has been modified along lines that consider the predicted positivity and functional impact of the dissection. To use the example of radical neck dissection, the modifications include supraomohyoid dissection for tumors of the floor of the mouth (a high-risk zone) and sparing of the spinal accessory nerve (functional prevention of shoulder drop and loss of full abduction of the shoulder).

As alluded to in the previous paragraphs, lymph node dissection has therapeutic value only in patients with positive nodes. In individuals with pathologically negative nodes, the benefit is limited to prediction of prognosis and documentation of pathologic negativity. Therefore, in the pathologically negative nodal basin, there is minimal benefit to outweigh the risks and untoward sequelae of the dissection.

Sentinel node biopsy

Technique The technique of sentinel node identification is being developed to address clinically negative nodal basins. With this technique, node or nodes that preferentially drain a particular primary tumor are identified by mapping and then surgically excised. The mapping agents include radiolabeled materials and vital dyes that are specifically taken up by, and transported in, the lymphatic drainage systems. These mapping and localizing agents, used alone or in combination, are critical in defining the unique flow patterns to specific lymph node(s) and in defining ambiguous drainage patterns (eg, a truncal melanoma that may drain to the axilla, supraclavicular, or inguinal spaces).

Unresolved issues As this field of directed diagnostic node biopsy and dissection develops, many technical issues related to the timing and location of the injections are being evaluated. In addition, the type of pathologic evaluation (ie, the number of sections examined per node, and the use of immunohistochemical analysis) is undergoing intense scrutiny.

A study of 200 consecutive patients who had sentinel lymph node biopsies performed for breast cancer examined the concepts of injecting dye and radioactive tracer into either the breast or the overlying dermis. The authors believed that the technical aspects of intradermal injection were simpler and more easily reproduced than those of injections into the breast. Injections were performed in group 1 intraparenchymally, and in group 2 intradermally. The combination of blue dye and isotope localization produced a 92% success rate in group 1 and a 100% success rate in group 2. The authors concluded that dermal and parenchymal lymphatics of the breast drain to the same lymph node and that the more simple approach of dermal injection may simplify and optimize sentinel lymph node localization.

For melanoma, for which these techniques were originally developed, researchers are studying the feasibility and clinical relevance of evaluating nodal material with polymerase chain reaction (PCR) techniques. These techniques also are being studied in breast cancer, where the clinical relevance of the presence of micrometastases or PCR-only metastases is highly controversial and, therefore, questions the need for this intense level of pathologic scrutiny.

Elective lymph node dissection has limited value in intermediate-thickness melanoma. In clinically node-negative patients, the use of the sentinel node technique can avoid postoperative complications, increase confidence about the better prognosis, and avoid the significant side effects of adjuvant immunologic therapy. However, the identification of histologically positive nodes via sentinel node biopsy technique is expected to have significant benefit, as it will result in a complete therapeutic dissection and adjuvant therapy with interferon-α (Intron A, Roferon-A).

Palliation

In the continuum of care for the cancer patient, aspects of palliation, or the reduction of suffering, are delegated to the surgeon. This text includes many examples of palliative surgical procedures: venous access, surgical relief of ascites with shunt procedures, neurosurgical intervention for chronic pain, fixation of pathologic fractures, and placement of feeding tubes to deliver food and medications. The surgeon must be versed in the techniques of and indications for such interventions and discuss their risks and benefits with the patient, caregivers, and referring physician. The barriers to the initiation and practice of palliative surgery include the reluctance of patients, family and referring physicians, health care system administrative obstacles, and cultural factors.

Resuscitation issues An ethical issue of resuscitation must be addressed when considering palliative surgical intervention. Some may take the position that if

a patient is to have surgery, he or she must be willing to undergo full resuscitation if required. That tenet may be set aside in the palliative setting, in which the operative intervention is planned only to relieve suffering. In such a situation, a frank discussion with the patient and appropriate family members can avoid the distressing situation of the patient being placed on unwanted, fruitless life support. Again, the surgeon is called upon not only to provide a technical service but also to achieve a comprehensive understanding of the disease process and how it affects each individual cancer patient.

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CHAPTER 2

Principles of radiation therapy

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This chapter provides a brief overview of the principles of radiation therapy. The topics to be discussed include the physical aspects of how radiation works (ionization, radiation interactions) and how it is delivered (treatment machines, treatment planning, and brachytherapy). Recent relevant techniques of radiation oncology, such as conformal and stereotactic radiation, also will be presented. These topics are not covered in great technical detail, and no attempt is made to discuss the radiobiological effects of radiation therapy. It is hoped that a basic understanding of radiation treatment will benefit those practicing in other disciplines of cancer management.

How radiation works

IONIZING RADIATION

Ionizing radiation is energy sufficiently strong to remove an orbital electron from an atom. This radiation can have an electromagnetic form, such as a high-energy photon, or a particulate form, such as an electron, proton, neutron, or alpha particle.

High-energy photons By far, the most common form of radiation used in practice today is the high-energy photon. Photons that are released from the nucleus of a radioactive atom are known as gamma rays. When photons are created electronically, such as in a clinical linear accelerator, they are known as x-rays. Thus, the only difference between the two terms is the origin of the photon.

Inverse square law The intensity of an x-ray beam is governed by the inverse square law. This law states that the radiation intensity from a point source is inversely proportional to the square of the distance away from the radiation source. In other words, the dose at 2 cm will be one-fourth of the dose at 1 cm.

Electron volt Photon absorption in human tissue is determined by the energy of the radiation, as well as the atomic structure of the tissue in question. The basic unit of energy used in radiation oncology is the electron volt (eV); 10^3 eV = 1 keV, 10^6 eV = 1 MeV.

PHOTON-TISSUE INTERACTIONS

Three interactions describe photon absorption in tissue: the photoelectric effect, Compton effect, and pair production.

Photoelectric effect In this process, an incoming photon undergoes a collision with a tightly bound electron. The photon transfers practically all of its energy to the electron and ceases to exist. The electron departs with most of the energy from the photon and begins to ionize surrounding molecules. This interaction depends on the energy of the incoming photon, as well as the atomic number of the tissue; the lower the energy and the higher the atomic number, the more likely that a photoelectric effect will take place.

An example of this interaction in practice can be seen on a diagnostic x-ray film. Since the atomic number of bone is 60% higher than that of soft tissue, bone is seen with much more contrast and detail than is soft tissue. The energy range in which the photoelectric effect predominates in tissue is about 10-25 keV.

Compton effect The Compton effect is the most important photon-tissue interaction for the treatment of cancer. In this case, a photon collides with a "free electron," ie, one that is not tightly bound to the atom. Unlike the photoelectric effect, in the Compton interaction both the photon and electron are scattered. The photon can then continue to undergo additional interactions, albeit with a lower energy. The electron begins to ionize with the energy given to it by the photon.

The probability of a Compton interaction is inversely proportional to the energy of the incoming photon and is independent of the atomic number of the material. When one takes an image of tissue using photons in the energy range in which the Compton effect dominates (~25 keV-25 MeV), bone and soft-tissue interfaces are barely distinguishable. This is a result of the atomic number independence.

The Compton effect is the most common interaction occurring clinically, as most radiation treatments are performed at energy levels of about 6-20 MeV. Port films are films taken with such high-energy photons on the treatment machine and are used to check the precision and accuracy of the beam; because they do not distinguish tissue densities well, however, they are not equal to diagnostic films in terms of resolution.

Pair production In this process, a photon interacts with the nucleus of an atom, not an orbital electron. The photon gives up its energy to the nucleus and, in the process, creates a pair of positively and negatively charged electrons. The positive electron (positron) ionizes until it combines with a free electron. This generates two photons that scatter in opposite directions.

The probability of pair production is proportional to the logarithm of the energy of the incoming photon and is dependent on the atomic number of the material. The energy range in which pair production dominates is ≥ 25 MeV. This interaction does occur to some extent in routine radiation treatment with high-energy photon beams.

ELECTRON BEAMS

With the advent of high-energy linear accelerators, electrons have become a viable option in treating superficial tumors up to a depth of about 5 cm. Electron depth dose characteristics are unique in that they produce a high skin dose but exhibit a falloff after only a few centimeters.

Electron absorption in human tissue is greatly influenced by the presence of air cavities and bone. The dose is increased when the electron beam passes through an air space and is reduced when the beam passes through bone.

Common uses The most common clinical uses of electron beams include the treatment of skin lesions, such as basal cell carcinomas, and boosting of (giving further radiation to) areas that have previously received photon irradiation, such as the postoperative lumpectomy or mastectomy scar in breast cancer patients, as well as select nodal areas in the head and neck.

MEASURING RADIATION ABSORPTION

The dose of radiation absorbed correlates directly with the energy of the beam. An accurate measurement of absorbed dose is critical in radiation treatment. The deposition of energy in tissues results in damage to DNA and diminishes or eradicates the cell's ability to replicate indefinitely.

Gray The basic unit of radiation absorbed dose is the amount of energy (joules) absorbed per unit mass (kg). This unit, known as the gray (Gy), has replaced the unit of rad used in the past (100 rads = 1 Gy; 1 rad = 1 cGy).

Exposure In order to measure dose in a patient, one must first measure the ionization produced in air by a beam of radiation. This quantity is known as exposure. One can then correct for the presence of soft tissue in the air and calculate the absorbed dose in Gy.

Percentage depth dose The dose absorbed by tissues due to these interactions can be measured and plotted to form a percentage depth dose curve. As energy increases, the penetrative ability of the beam increases and the skin dose decreases.

How radiation is delivered

TREATMENT MACHINES

Linear accelerators

High-energy radiation is delivered to tumors by means of a linear accelerator. A beam of electrons is generated and accelerated through a waveguide that increases their energy to the keV to MeV range. These electrons strike a tungsten target and produce x-rays.

X-rays generated in the 10–30-keV range are known as grenz rays, whereas the energy range for superficial units is about 30–125 keV. Orthovoltage units generate x-rays from 125–500 keV.

Orthovoltage units continue to be used today to treat superficial lesions; in fact, they were practically the only machines treating skin lesions before the recent emergence of electron therapy. The maximum dose from any of these low-energy units is found on the surface of patients; thus, skin becomes the dose-limiting structure when treating patients at these energies. The depth at which the dose is 50% of the maximum is about 7 cm. Table 1 lists the physical characteristics of several relevant x-ray energies.

Megavoltage units The megavoltage linear accelerator has been the standard radiotherapy equipment for the past 20-30 years. Its production of x-rays is identical to that of lower-energy machines. However, the energy range of megavoltage units is quite broad–from 4 to 20 MeV. The depth of the maximum dose in this energy range is 1.5-3.5 cm. The dose to the skin is about 30%-40% of the maximum dose.

Most megavoltage units today also have electron-beam capabilities, usually in the energy range of about 5-20 MeV. In order to produce an electron beam, the tungsten target is moved away from the path of the beam. The original electron beam that was aimed at the tungsten target is now the electron beam used for treatment. Unlike that of photons, the electron skin dose is quite high, about 80%-95% of the maximum dose. A rule of thumb regarding the depth of penetration of electrons is that 80% of the dose is delivered at a depth (in cm) corresponding to one-third of the electron energy (in MeV). Thus, a 12-MeV beam will deliver 80% of the dose at a depth of 4 cm.

Altering beam intensity and field size When measurements are made at the point just past the target, the beam is more intense in the center than at the edges. Optimal treatment planning is obtained with a relatively constant intensity across the width of the beam. This process is accomplished by placing a flattening filter below the target.

In order for the radiation beam to conform to a certain size, high atomic number collimators are installed in the machine. They can vary the field size from 4×4 cm to 40×40 cm at a distance of 100 cm from the target, which is the distance at which most treatments are performed.

TABLE 1: Depth dose characteristics for clinical radiotherapy beams

Nominal energy	Depth of maximum dose (cm)	Skin dose (%)
240 kV(p)	Surface	100
Cobalt-60	0.500	50
6 MeV	1.500	35
10 MeV	2.500	25
18 MeV	3.000	15

kV(p) = kilovolt (peak)

If it is decided that a beam should be more intense on one side than the other, high atomic number filters, known as wedges, are placed in the beam. These filters can shift the dose distribution surrounding the tumor by 15°-60°. Wedges can also be used to optimize the dose distribution if the treatment surface is curved or irregular.

Shielding normal tissue Once the collimators have been opened to the desired field size that encompasses the tumor, the physician may decide to block out some normal tissue that remains in the treatment field. This is accomplished by placing blocks (or alloy), constructed of a combination of bismuth, tin, cadmium, and lead, in the path of the beam. In this way, normal tissues are shielded, and the dose can be delivered to the tumor at a higher level than if the normal structures were in the field. These individually constructed blocks are used in both x-ray and electron treatments. A more modern technique involves multileaf collimators mounted inside the gantry. They provide computerized, customized blocking instead of having to construct a new block for each field. (See "Intensity-modulated radiation therapy.")

PRETREATMENT PROCEDURES

Certain imaging procedures must be done before radiation therapy is begun:
Pretreatment CT Before any treatment planning can begin, a pretreatment CT scan is often performed. This scan allows the radiation oncologist to identify both tumor and surrounding normal structures.

Simulation The patient is then sent for a simulation. The patient is placed on a diagnostic x-ray unit that geometrically simulates an actual treatment machine. With use of the CT information, the patient's treatment position is simulated by means of fluoroscopy. A series of orthogonal films are taken, and block templates that will shield any normal structures are drawn on the films. These films are sent to the mold room, where technicians construct the blocks to be used for treatment. CT simulation is a modern alternative to "conventional" simulation and is described later in this chapter.

Guides for treatment field placement Small skin marks, or tattoos, are placed on the patient following proper positioning in simulation. These tattoos will guide the placement of treatment fields and give the physician a permanent record of past fields should the patient need additional treatment in the future.

It is imperative that the patient be treated in a reproducible manner each day. In order to facilitate this, Styrofoam casts that conform to the patient's contour and place the patient in the same position for each treatment are constructed. Lasers also help line up the patient during treatment.

TREATMENT PLANNING AND DELIVERY

Determining optimal dose distribution The medical physicist or dosimetrist uses the information from CT and simulation to plan the treatment on a computer. A complete collection of machine data, including depth dose and beam profile information, is stored in the computer. The physics staff aids the radia-

tion oncologist in deciding the number of beams (usually two to four) and angles of entry. The goal is to maximize the dose to the tumor while minimizing the dose to surrounding normal structures.

Several treatment plans are generated, and the radiation oncologist chooses the optimal dose distribution. The beam-modifying devices discussed earlier, such as blocks and wedges, may be used to optimize the dose distribution around the tumor.

Establishing the treatment plan The planning computer will calculate the amount of time each beam should be on during treatment. All pertinent data, such as beam-on time, beam angles, blocks, and wedges, are recorded in the patient's treatment chart and sent to the treatment machine. The radiation therapist will use this information, as well as any casts, tattoos, and lasers, to set up and treat the patient consistently and accurately each day.

Port films As part of departmental quality assurance, weekly port films are taken for each beam. They ensure that the beams and blocks are consistently and correctly placed for each treatment. Port films are images generated by the linear accelerator at energies of 6-20 MeV. Because of the predominance of the Compton effect in this energy range, these images are not as detailed as those at diagnostic film energies (as mentioned earlier), but they still add important information on treatment accuracy and ensure the quality of setup and treatment.

BRACHYTHERAPY

Brachytherapy is the term used to describe radiation treatment in which the radiation source is in contact with the tumor. This therapy contrasts with external-beam radiotherapy, in which the radiation source is 80-100 cm away from the patient.

In brachytherapy, dose distribution is almost totally dependent on the inverse square law because the source is usually within the tumor volume. Because of this inverse square dependence, proper placement of radiation sources is crucial.

TABLE 2: Physical characteristics of commonly used radioisotopes

Isotope	Energy (MeV)	Half-life
Radium-226	0.830	1,600 yr
Cesium-137	0.662	30 yr
Cobalt-60	1.250	5.26 yr
Iridium-192	0.380	74.2 d
Iodine-125	0.028	60.2 d
Gold-198	0.412	2.7 d

Isotopes Table 2 lists commonly used isotopes and their properties. In the past, radium was the primary isotope used in brachytherapy. Recently, because of its long half-life and high energy output, radium has been replaced with cesium (Cs), gold (Au), and iridium (Ir). These isotopes have shorter half-lives than radium and can be shielded more easily because of their lower energies.

Types of implants Brachytherapy procedures can be performed with either temporary or permanent implants. Temporary implants usually have long half-lives and higher energies than permanent implants. These sources can be manufactured in several forms, such as needles, seeds, and ribbons.

All temporary sources are inserted into catheters that are placed in the tumor during surgery. A few days after surgery, the patient is brought to the radiation clinic and undergoes pretreatment simulation. Wires with nonradioactive metal seeds are threaded into these catheters. Several films are taken, and the images of the seed placement can be digitized into a brachytherapy treatment planning computer.

Once the treatment plan is complete and the physician has chosen the optimal dose rate (usually 50-60 cGy/h), the sources can be implanted. The actual implantation takes place in the patient's private room. The duration of treatment is usually 1-3 days. The majority of temporary implants are loaded interstitially.

Common uses Interstitial low-dose-rate (LDR) brachytherapy is commonly used for cancer of the oral cavity and oropharynx and sarcoma. Prostate cancer is probably the most common site for which LDR brachytherapy "seeds" are used today. Intracavitary LDR brachytherapy is frequently used in gynecologic applications. High-dose-rate (HDR) brachytherapy is used with remote afterloading techniques, as described below.

Remote afterloading brachytherapy

Because brachytherapy requires numerous safety precautions and entails unnecessary exposure of personnel and family members to radiation, remote afterloading of temporary implants has become popular in recent years. The two types of remote afterloading that can be used for treatment are LDR and HDR sources. The most popular LDR source used today is Cs-137, which has a dose rate of about 1 cGy/min. The most widely used HDR source is Ir-192. This isotope has a dose rate of about 100 cGy/min.

General procedures The pretreatment brachytherapy procedures outlined above are also implemented in remote afterloading brachytherapy. Once the treatment plan has been approved by the physician, the patient is brought into the treatment room. The LDR cesium source or HDR iridium source is connected to the end of a cable inside its respective afterloading unit. This unit is programmed with the data from the planning computer. The cable is sent out from the unit into one of the patient's catheters. Several catheters can be connected to the unit. Each catheter is irradiated, one at a time, until the prescribed dose has been delivered.

The motor that drives the source out of the treatment unit is connected electronically to the door of the treatment room. If the treatment must be stopped for any reason, simply opening the door triggers an interlock that draws the source back into the unit. Because of this device, oncology personnel will not be exposed to any radiation should they need to see the patient during treatment. This interlock is the main safety advantage of remote afterloading over manual afterloading.

LDR treatment Uterine cancer is the most popular site for intracavitary treatment with LDR remote afterloading brachytherapy. These procedures are performed in the patient's room. The interlock is connected to the patient's door so that nurses can take vital signs and give medication and family members can visit the patient without risk of radiation exposure.

HDR treatment The most common applications of HDR brachytherapy are for tumors of the vaginal apex, esophagus, lungs, and, most recently, breast and prostate. Most HDR treatments are performed on an outpatient basis. Allowing the patient to return home the same day after therapy is one advantage of HDR afterloading brachytherapy. Patients with prostate cancer are the exception. They may remain in the hospital for 2-3 days during the treatment.

Recent advances in planning and treatment

CT SIMULATION

Until recently, CT and simulation were separate pretreatment procedures. Within the past decade, many cancer centers have combined CT and simulation into a single diagnostic-treatment planning unit, known as a CT-simulator. The major advantage of this combination is that both procedures can be performed by one unit and, thus, the patient does not have to make two separate visits to the clinic. Also, CT simulation is bringing the radiation clinic into the digital age, with hospitals reporting an increase in speed, efficiency, and accuracy of treatment planning and delivery.

Procedure In brief, in the first step of this new procedure, the patient is placed on the CT-simulator table and undergoes a normal CT study. The physician has the capability of outlining the tumor and any normal structures on each CT slice. A computer performs a three-dimensional (3D) transformation of the CT slices and creates a digitally reconstructed radiograph (DRR).

The DRR resembles a normal diagnostic film, except that it is digital and can be manipulated to achieve better contrast and detail than regular film. The outlines of the tumor and organs are displayed on the DRRs for any viewing angle. The physician can then draw blocks on the DRRs with a more accurate idea of where the tumor and normal tissues actually lie.

The DRRs are digitized into the treatment planning computer, and any CT slices and their contours drawn by the physician are transferred as well. These DRRs are either sent to the mold room for block construction or are trans-

ferred to the treatment planning software for multileaf collimator optimization. Treatment plans are generated as discussed earlier.

At the time of the patient's first treatment, DRRs and port films are digitized and saved on a local area network (LAN). Physicians can then call up these images on their desktop computers for weekly patient quality assurance.

CONFORMAL RADIATION THERAPY

Conformal radiation therapy is a geometric shaping of the radiation beam that conforms with the beam's eye view of the tumor. Conformal therapy utilizes the outlining capabilities of the CT-simulator. The physician outlines the tumor volume, generates DRRs, and draws an appropriate margin from 1-2 cm around the tumor. These fields conform closely to the shape of the tumor and, thus, shield more critical structures than do normal blocks. The margin allows for setup errors of a few millimeters each day. Appropriate immobilization of the target volume must be achieved in each patient through the use of devices that constrain movement ("casts") so that the target is accurately localized.

These films are sent to the mold room for block construction. Since the fields are "tighter" around the tumor, the prescribed dose can be increased. Clinicians believe that by increasing the dose to the tumor, local control will be improved.

Intensity-modulated radiation therapy (IMRT), an extension of conformal therapy, allows for shaping of the intensity of the radiation beam. This is an important improvement, especially when the target is not well separated from normal tissues.

A uniform dose distribution can be created around the tumor by either modulating the intensity of the beam during its journey through the linear accelerator or by the use of multileaf collimators. Multileaf collimators consist of 80 or more individual collimators, or "leaves," located at the head of the linear accelerator, which can be adjusted to the shape of the tumor. (For a technical description, the reader is referred to the text by Khan; see "Suggested Reading.")

Both of these methods alter the fluence of radiation exiting the accelerator. The final result is a uniform dose distribution around the tumor and minimal dose to the surrounding normal tissues, often below tolerance levels. This improves the risk-benefit ratio.

The clinical use of IMRT has grown as computer power increases and costs decline. Preliminary clinical data have shown that prostate doses can be increased significantly without increasing the complication rate. IMRT must be administered within a closely monitored program with rigorous quality assurance since it can potentially cause significant injury if not appropriately applied.

Several types of IMRT delivery are now becoming standard in radiation oncology clinics. Dynamic conformal therapy with multileaf collimators is being used routinely in hospitals around the country. With this approach, collimators conform to the tumor volume with the beam on while the treatment unit is

rotating around the patient. This is an example of totally computer-controlled radiation delivery.

Another method of IMRT delivery–*serial* tomotherapy–is an enhancement of the method described above. An accelerator is equipped with mini-multileaf collimators that form a "slit" of radiation (normally 2 × 20 cm). The gantry is rotated through an entire arc around the patient while the mini-multileaf collimators are driven in and out of the field, thus modulating the intensity of the beam. The treatment couch is advanced by a few millimeters and the next arc is treated. An entire treatment is given once all the adjoining arcs have been delivered.

Instead of treating the patient on a normal linear accelerator, with helical tomotherapy the patient travels continuously through a modified CT ring. This CT ring has the capability of administering 6-mV x-rays, as in a standard linear accelerator, while at the same time performing a conventional diagnostic CT scan. Any anatomic or position changes that might require replanning can be performed before that day's treatment. Following treatment, a daily, real-time image of the dose distribution can be obtained.

PROTON THERAPY

Protons, a form of particulate radiation, have been investigated recently as a means to improve tumor control. A proton has a charge of +1, is a stable particle, and, together with the neutron, makes up the atomic nucleus.

Protons are delivered to the tumor in the same manner as are photons and electrons. The dose deposited by protons remains relatively constant as they travel through the normal tissues proximal to the target.

The kinetic energy of the protons is transferred to the tumors by electrons knocked out of atoms. These electrons ionize DNA, and their biological effectiveness resembles that of megavoltage photons.

Bragg peak At the end of the path, biological effectiveness increases sharply as the protons slow down and eventually stop. This increase in dose is called the Bragg peak. The size of the Bragg peak is usually smaller than the tumor, however. This problem can be resolved by scanning the Bragg peak through the tumor volume by sequentially irradiating the target with lower energies. The dose falloff of the Bragg peak is sharp enough that the normal tissues distal to the tumor receive a negligible radiation dose.

Current clinical applications Uveal melanomas and skull-base sarcomas adjacent to CNS tissues are two areas that have been under clinical study with promising results. Clinical studies have also begun recently in treating non–small-cell lung, hepatocellular, and paranasal sinus carcinomas.

STEREOTACTIC RADIOSURGERY

Stereotactic radiosurgery is a 3D technique that delivers the radiation dose in one fraction. Specially designed collimators are attached to a linear accelerator, which delivers a high dose of radiation to a small volume, usually about

3 cm in diameter. Several stationary beams or multiple arc rotations concentrate the radiation dose to the lesion while sparing surrounding normal tissue.

Use in treating arteriovenous malformations Stereotactic radiosurgery is used to treat certain patients with arteriovenous malformations. These intracranial lesions arise from the abnormal development of arteries and venous sinuses. Surgical excision is the standard treatment of choice for operable lesions, but stereotactic radiosurgery has become a viable option for inoperable malformations.

Use in treating brain tumors As with conformal radiotherapy, clinical trials involving stereotactic radiosurgery for brain tumors are being conducted at major cancer centers. However, based on positive early results, many community centers have begun instituting a stereotactic radiosurgery program, either with a dedicated cobalt unit (gamma knife) or a linear accelerator–based system. Small ($<$ 4 cm) tumors of the brain, whether primary, metastatic, or recurrent, may benefit from this treatment technique.

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CHAPTER 3

Principles of chemotherapy

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The effective use of cancer chemotherapy requires an understanding of the principles of tumor biology, cellular kinetics, pharmacology, and drug resistance. Thanks to the development of new, effective chemotherapeutic agents, coupled with our expanding knowledge about the administration and combination of these agents, we now are able to cure almost 20% of all new cases of cancer through chemotherapy alone.

This chapter focuses on the principles responsible for the development of modern combination chemotherapy regimens. This discussion is followed by descriptions of the major classes of chemotherapeutic drugs and their mechanisms of action.

Cellular kinetics

Cytokinetic studies have shown how the kinetics of cellular growth defines the characteristics of tumor growth and, in part, explains the biological behavior and heterogeneity of tumors.

Normal cell cycle

Inherent to cytokinetic principles is the concept of the cell cycle. Daughter cells formed as a result of mitosis consist of three subpopulations: (1) cells that are nondividing and terminally differentiated, (2) cells that are continually proliferating, and (3) cells that are resting but may be recruited into the cell cycle (ie, stem cells). All three populations exist simultaneously in tumors.

The cell cycle is composed of four phases during which the cell prepares for and effects mitosis. Cells that are committed to divide again enter the G_1 phase. Preliminary synthetic cellular processes occur that prepare the cell to enter the DNA synthetic (S) phase. Specific protein signals regulate the cell cycle and allow replication of the genome where the DNA content becomes tetraploid (4N). After completion of the S phase, the cell enters a second resting phase, G_2, prior to undergoing mitosis. The cell progresses to the mitotic (M) phase, in which the chromosomes condense and separate and the cell divides, producing two daughter cells.

Chemotherapeutic agents can be classified according to the phase of the cell cycle in which they are active (Table 1). Agents that are cell-cycle-phase–

TABLE 1: Cell-cycle-phase–specific drugs

S phase–dependent	M phase–dependent
Antimetabolites	Vinca alkaloids[a]
Capecitabine	Vinblastine
Cytarabine	Vincristine
Doxorubicin	Vinorelbine
Fludarabine	Podophyllotoxins
Floxuridine	Etoposide
Fluorouracil	Teniposide
Gemcitabine	Taxanes
Hydroxyurea	Docetaxel
Mercaptopurine	Paclitaxel
Methotrexate	**G_2 phase–dependent**
Prednisone	Bleomycin
Procarbazine	Irinotecan
Thioguanine	Mitoxantrone
	Topotecan
	G_1 phase–dependent
	Asparaginase
	Corticosteroids

[a] Have greatest effects in S phase and possibly late G_2 phase; cell blockade or death, however, occurs in early mitosis.

Adapted, with permission, from Dorr RT, Von Hoff DD (eds): The Cancer Chemotherapy Handbook, 2nd ed, p 5. East Norwalk, Connecticut, Appleton & Lange, 1993.

nonspecific (eg, alkylating agents) have a linear dose-response curve; that is, the greater the dose of drug, the greater is the fraction of cell kill. However, cell-cycle-phase–specific drugs have a plateau with respect to cell killing ability, and cell kill will not increase with further increases in drug dosage.

Tumor kinetics

The rate of growth of a tumor is a reflection of the proportion of actively dividing cells (the growth fraction), the length of the cell cycle (doubling time), and the rate of cell loss. Variations in these three factors are responsible for the variable rates of tumor growth observed among tumors of differing histologies, as well as among metastatic and primary tumors of the same histology.

Tumors characteristically exhibit a sigmoid-shaped Gompertzian growth curve, in which tumor doubling time varies with tumor size. Tumors grow most rapidly at small tumor volumes. As tumors become larger, growth slows based on a complex process dependent on cell loss and tumor blood and oxygen supply.

In order to have the best chance for cure, chemotherapy must achieve a fractional cell kill in a logarithmic fashion (ie, 1-log-kill is 90% of cells, 2-log-kill is 99% of cells). From these concepts, chemotherapy models have been developed utilizing alternating non–cross-resistant therapies, induction-intensification approaches, and adjuvant chemotherapy regimens.

Principles of combination chemotherapy

Using kinetic principles, a set of guidelines for designing modern combination chemotherapy regimens have been derived. Combination chemotherapy accomplishes three important objectives not possible with single-agent therapy: (1) It provides maximum cell kill within the range of toxicity tolerated by the host for each drug; (2) it offers a broader range of coverage of resistant cell lines in a heterogeneous tumor population; and (3) it prevents or slows the development of new drug-resistant cell lines.

Selection of drugs for combination regimens

The following principles have been established to guide drug selection in combination regimens:

- Drugs known to be active as single agents should be selected for combinations. Preferentially, drugs that induce complete remissions should be included.
- Drugs with different mechanisms of action should be combined in order to allow for additive or synergistic effects on the tumor.
- Drugs with differing dose-limiting toxicities should be combined to allow each drug to be given at full or nearly full therapeutic doses.
- Drugs should be used in their optimal dose and schedule.
- Drugs should be given at consistent intervals. The treatment-free interval between cycles should be the shortest possible time for recovery of the most sensitive normal tissue.
- Drugs with different patterns of resistance should be combined to minimize cross-resistance.

Terminology used in describing chemotherapy

Chemotherapy is administered with a variety of treatment schedules designed according to the intent and responsiveness of therapy. Definitions of chemotherapy are generally based on the purpose of achieving certain therapeutic goals as described in Table 2.

Definitions of response

Tumors can be classified according to their general sensitivity to chemotherapy. Response to chemotherapy is defined precisely as complete response, partial response, minimal response (stable disease), and progression. Complete response is defined as the disappearance of all evidence of disease and no ap-

TABLE 2: Terminology used in describing chemotherapy

Induction: High-dose, usually combination, chemotherapy given with the intent of inducing complete remission when initiating a curative regimen. The term is usuallly applied to hematologic malignancies but is equally applicable to solid tumors.

Consolidation: Repetition of the induction regimen in a patient who has achieved a complete remission after induction, with the intent of increasing cure rate or prolonging remission.

Intensification: Chemotherapy after complete remission with higher doses of the same agents used for induction or with different agents at high doses with the intent of increasing cure rate or remission duration.

Maintenance: Long-term, low-dose, single or combination chemotherapy in a patient who has achieved a complete remission, with the intent of delaying the regrowth of residual tumor cells.

Adjuvant: A short course of high-dose, usually combination chemotherapy in a patient with no evidence of residual cancer after surgery or radiotherapy, given with the intent of destroying a low number of residual tumor cells.

Neoadjuvant: Adjuvant chemotherapy given in the preoperative or perioperative period.

Palliative: Chemotherapy given to control symptoms or prolong life in a patient in whom cure is unlikely.

Salvage: A potentially curative, high-dose, usually combination, regimen given in a patient who has failed or recurred following a different curative regimen.

From: Yarbro J: The scientific basis of cancer chemotherapy, in Perry MC (ed): The Chemotherapy Sourcebook, p 12. Baltimore, MD, Lippincott, Williams and Wilkins, 1996.

pearance of new disease for a specified interval (usually 4 weeks). Partial response is defined as a reduction by at least 50% in the sum of the products of the two longest diameters of all lesions, maintained for at least one course of therapy, with no appearance of new disease. Minimal response is any response less than a partial response and is usually not reported in clinical trials. Progression is defined as growth of existing disease or appearance of new disease during chemotherapy.

The NCI (National Cancer Institute) has adopted standardized response criteria and is requiring their use by all cooperative groups. These criteria, called RECIST (Response Evaluation Criteria in Solid Tumors), were developed and recently revised by the World Health Organization (WHO). The goals are consistency of evaluation and comparison of regimens within a single trial and regimens of different trials. A comparison of RECIST and WHO guidelines is listed in Table 3.

Dose intensity

Kinetic principles predict that, for drug-sensitive cancers, the factor limiting the capacity to cure is proper dosing. Reduction in dose is associated with a decrease in cure rate before a significant reduction in the complete remission rate occurs. A dose reduction of approximately 20% can lead to a loss of up to

Tariquidar (XR9576) is an investigational intravenous drug that is a potent *p*-glycoprotein inhibitor that reverses MDR associated with common chemotherapy drugs. It can be safely and conveniently administered with full doses of paclitaxel, doxorubicin, and vinorelbine with no compromise of pharmacokinetics. Phase III studies in lung cancer are ongoing to evaluate the efficacy and response of tariquidar in combination therapy *(Boniface G, Ferry D, Atsmon J, et al: Proc Am Soc Clin Oncol [abstract] 21:90b, 2002).*

50% of the cure rate. Conversely, a twofold increase in dose can be associated with a 10-fold (1-log) increase in tumor cell kill in animal models.

Overcoming chemotherapy resistance

There are multiple reasons for chemotherapy failure in cancer patients, involving a variety of anatomic, pharmacologic, and biochemical mechanisms. Tumor sanctuary sites (brain, testes) and blood flow to the tumor represent anatomic barriers; pharmacologic and biochemical explanations include altered drug activation/inactivation in normal tissues, decreased drug accumulation, increased repair of drug-induced damage to the cell, altered drug targets, and altered gene expression.

Overexpression of the MDR_1 (multidrug resistance) gene is the most notable mediator of drug resistance and encodes a 170-kd transmembrane *p*-glycoprotein. *p*-Glycoprotein is an energy-dependent pump that serves to remove toxins or endogenous metabolites from the cell. A high level of MDR_1 expression is reliably correlated with resistance to cytotoxic agents. Tumors that intrinsically express the MDR_1 gene prior to chemotherapy characteristically display poor durable responses.

TABLE 3: Comparison of RECIST and WHO guidelines

Characteristic	RECIST	WHO
Objective response (LD is the longest diameter)	**Target lesions** (change in sum of LDs, maximum 5 per organ up to 10 total [more than one organ])	**Measurable disease** (change in the sum of the products of LDs and greatest perpendicular diameters, no maximum number of lesions specified)
Complete response (CR)	Disappearance of all target lesions, confirmed at ≥ 4 weeks	Disappearance of all known disease, confirmed at ≥ 4 weeks
Partial response (PR)	≥ 30% decrease from baseline, confirmed at ≥ 4 weeks	≥ 50% decrease from baseline, confirmed at ≥ 4 weeks
Progressive disease (PD)	≥ 20% increase over smallest sum observed or appearance of new lesions	≥ 25% increase in one or more lesions or appearance of new lesions
Stable disease (SD)	Neither PR nor PD criteria met	Neither PR nor PD criteria met (no change)

RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization

TABLE 4: Advantages of liposomal drug delivery

- Provides selective passive targeting to tumor sites
- Increases efficacy and therapeutic index
- Improves delivery of hydrophobic molecules
- Reduces the toxicities of the encapsulated agent
- Avoids accumulation in vital organs and tissues
- Improves pharmacokinetics (reduced elimination, increased drug exposure time)
- Increases stability via encapsulation
- Enhances intracellular drug delivery to overcome drug resistance

Chemotherapy agents subject to MDR_1- mediated resistance include the anthracyclines, vinca alkaloids, taxanes, and topoisomerase inhibitors. Targeted therapies that inhibit *p*-glycoprotein are under evaluation in combination with cytotoxic drugs subject to MDR (see sidebar on previous page).

Liposomal formulations of chemotherapeutic drugs are a promising new approach to overcoming these resistance mechanisms. Liposomes are well-defined lipid and lipoprotein vesicles that offer immense potential for targeting drugs to tumors. The advantages of these drug carriers over the conventional administration of chemotherapy agents are described in Table 4.

FDA-approved liposomal preparations of doxorubicin (Doxil), daunorubicin (DaunoXome), cytarabine (DepoCyt), and amphotericin B (Abelcet) have proven to be attractive, less toxic alternatives to the conventional drug formulations. Liposomal daunorubicin and amphotericin B have clearly shown less cardiac and renal damage, respectively. Daunorubicin liposomal is efficacious in induction regimens for acute leukemia; cytarabine liposomal appears to be superior to intrathecal cytarabine for treatment of CNS leukemia and lymphoma.

An additional advantage of the liposomal delivery system is the ability to encapsulate and stabilize very hydrophobic molecules such as paclitaxel (Taxol). Nanoparticle, albumin-stabilized paclitaxel has allowed much higher doses of drug to be given with far fewer side effects than paclitaxel which contains the toxic carrier material cremophor. Currently, a phase III randomized study comparing the efficacy of nanoparticle paclitaxel with conventional paclitaxel in metastatic breast cancer is under way.

Several liposomal formulations of conventional anticancer drugs are currently in phase I/II evaluation, including liposomal vincristine, platinum, mitoxantrone, all-*trans* retinoic acid (ATRA), and lurtotecan. There is a strong probability that these drug carriers will allow better administration of poorly soluble cancer drugs, enhance drug delivery and uptake in the tumor, and boost dose intensity, subsequently improving antitumor response, overcoming drug resistance, and decreasing chemotherapy toxicities.

Text continues on page 35

TABLE 5: Alkylating agents and their uses, dosages, and toxicities

Drug and its uses[a]	Dosages	Toxicities[b]
Nitrogen mustards		
Chlorambucil *CLL, HD, NHL,* ovarian cancer, choriocarcinoma, lymphosarcoma	0.1-0.2 mg/kg PO daily for 3-6 wk as required (usually 4-10 mg/d) or intermittent 0.4 mg/kg every 3-4 wk; increase by 0.1 mg/kg until control of disease or toxicity	*Bone marrow depression,* gonadal dysfunction, leukemia, hyperuricemia, pulmonary fibrosis
Cyclophosphamide *AML, ALL, CLL, HD, and NHL, multiple myeloma, mycosis fungoides, neuroblastoma, ovarian and breast cancers, retinoblastoma,* lung, testicular, and bladder cancers, sarcoma	40-50 mg/kg IV in divided doses over 2-5 d to start, followed by 10-15 mg/kg IV every 7-10 d; or 3-5 mg/kg IV twice weekly; or 1-5 mg/kg/d PO	*Bone marrow depression,* hemorrhagic cystitis, immunosuppression, alopecia, stomatitis, SIADH
Estramustine *Prostate, renal cell carcinoma*	14 mg/kg/d PO in 3-4 equally divided doses; 300 mg/d IV for 3-4 wk, followed by 300-450 mg/wk IV over 3-8 wk	*Bone marrow depression,* ischemic heart disease, thromboembolism, thrombophlebitis gynecomastia, nausea and vomiting, hepatotoxicity
Ifosfamide *Germ-cell testicular cancer,* sarcoma, NHL, lung cancer	1.2 g/m^2/d via slow IV infusion for 5 consecutive days; repeat every 3 wk; give with mesna	*Bone marrow depression, hemorrhagic cystitis,* confusion, somnolence
Mechlorethamine *HD, NHL, CML, CLL, mycosis fungoides, bronchogenic carcinoma,* lymphosarcoma, polycythemia vera, malignant effusions (intracavitary)	0.4 mg/kg ideal body weight given as single dose or in divided doses of 0.1-0.2 mg/kg/d	*Bone marrow depression, nausea and vomiting,* local phlebitis, severe skin necrosis if extravasated, gonadal dysfunction
Melphalan *Multiple myeloma, breast and ovarian cancers, sarcoma,* testicular and lung cancers	Continuous therapy: 6 mg PO daily for 2-3 wk, no therapy for 2-4 wk, then maintenance with 2-4 mg PO daily Pulse: 10 mg/m^2 PO daily for 4 d every 4-6 wk	*Bone marrow depression,* anorexia, nausea and vomiting, gonadal testicular dysfunction, leukemia

[a] FDA-approved uses in italics; neoplasms are carcinomas unless otherwise indicated

[b] Dose-limiting effects in italics

continued on following page

TABLE 5: Alkylating agents and their uses, dosages, and toxicities *(continued)*

Drug and its uses[a]	Dosages	Toxicities[b]
Aziridine		
Thiotepa *Ovarian, breast, and superficial bladder cancers,* HD, CML, CLL, bronchogenic carcinoma, malignant effusions (intracavitary), BMT for refractory leukemia, lymphomas	IV: 0.3-0.4 mg/kg by rapid IV infusion Intravesical: 60 mg/60 mL sterile water instilled and retained in bladder for 2 h; repeat weekly for 4 wk Intracavitary: 0.6-0.8 mg/kg	*Bone marrow depression,* nausea and vomiting, mucositis, skin rashes
Alkyl sulfonate		
Busulfan *CML,* BMT for refractory leukemia, lymphomas	2-8 mg PO daily for remission induction; adjust dosage to WBC count; 1-3 mg PO daily for maintenance; withhold induction if WBC count < 15,000/μL; resume therapy when WBC count > 50,000/μL	*Bone marrow depression, pulmonary fibrosis,* aplastic anemia, amenorrhea, gynecomastia, skin hyperpigmentation
Nitrosoureas		
Carmustine *Brain tumor, multiple myeloma, HD, NHL,* melanoma, BMT for refractory solid tumors and lymphomas	150-200 mg/m^2 IV every 6-8 wk	*Delayed bone marrow depression,* nausea and vomiting, reversible hepatotoxicity, local phlebitis, pulmonary and renal damage (high dose)
Gliadel wafers *Glioblastoma multiforme*	Up to 8 wafers placed in the brain cavity created by tumor removal	Fever, pain, and abnormal healing
Lomustine *Brain tumors, HD,* GI carcinomas, NSCLC	130 mg/m^2 PO every 6 wk; adjust dose in combination chemotherapy	*Delayed bone marrow depression,* nausea and vomiting, reversible hepatotoxicity, pulmonary and renal damage, neurologic reactions, leukemia
Streptozocin *Pancreatic islet-cell,* carcinoid, colon, hepatoma, NSCLC, HD	Daily: 500 mg/m^2 IV for 5 d every 6 wk until maximum benefit or toxicity Weekly: 1,000 mg/m^2 IV weekly for first 2 wk, then escalate dose to response or toxicity, not to exceed a single dose of 1,500 mg/m^2	*Renal damage,* nausea and vomiting, diarrhea, altered glucose metabolism, liver dysfunction

Drug and its uses[a]	Dosages	Toxicities[b]
Platinum complexes		
Carboplatin *Ovarian cancer,* endometrial, head and neck, lung, testicular, and breast cancers, relapsed acute leukemia, NHL	Single agent: 360 mg/m^2 IV every 4 wk Combination: 300 mg/m^2 IV every 4 wk Calvert formula: Total dose (mg) = Target AUC × (GFR + 25)	*Bone marrow depression,* nausea and vomiting, peripheral neuropathy, ototoxicity
Cisplatin *Testicular, ovarian, bladder,* uterine, cervical, and lung cancers, squamous cell cancer of the head and neck, sarcoma, NHL	50 mg/m^2 IV or more every 3 wk; or 20 mg/m^2 IV daily for 4-5 d every 3-4 wk; give vigorous hydration before and after chemotherapy	*Renal damage,* nausea and vomiting, electrolyte disturbance, peripheral neuropathy, bone marrow depression, ototoxicity, radiosensitizer
Oxaliplatin Colorectal (second-line)	85 mg/m^2 IV over 120 min on d 1 followed by infusional 5-FU and leucovorin on d 1-2, every 2 wk	*Bone marrow depression, diarrhea,* nausea and vomiting, neuropathies exacerbated by cold exposure, pharyngolaryngeal dysesthesia
Nonclassic alkylators		
Altretamine *Ovarian,* lung, breast, and cervical cancers, NHL	4-12 mg/kg/d or 260 mg/m^2, PO divided in 3-4 doses for 14-21 d of a 28-d regimen	*Nausea and vomiting,* bone marrow depression, paresthesias, CNS toxicity
Dacarbazine *Malignant melanoma, HD,* soft-tissue sarcomas, neuroblastoma	Melanoma: 2.0-4.5 mg/kg/d IV for 10 d every 4 wk; or 250 mg/m^2/d IV for 5 d every 3 wk HD: 375 mg/m^2 IV on d 1, repeated every 15 d (single agent); 150 mg/m^2/d IV for 5 d every 4 wk (combination therapy)	*Bone marrow depression,* nausea and vomiting, flulike syndrome, transient hepatotoxicity, local irritation, facial flushing, alopecia
Procarbazine *HD,* NHL, brain tumors, lung cancer	Single agent: 4-6 mg/kg/d PO until maximum response HD (MOPP): 100 mg/m^2/d PO for 14 d	*Bone marrow depression,* nausea and vomiting, lethargy, depression, paresthesias, headache, flulike symptoms
Temozolomide *Anaplastic astrocytoma (relapsed),* renal cell cancer, melanoma	150 mg/m^2/d PO for 5 d every 28 d	*Bone marrow depression,* nausea and vomiting

ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; AUC = area under the curve; BMT = bone marrow transplantation; CLL = chronic lymphocytic leukemia; CML = chronic myelogenous leukemia; CMML = chronic myelomacrocytic leukemia; 5-FU = fluorouracil; GFR = glomerular filtration rate; HD = Hodgkin's disease; MDS = myelodysplastic syndromes; MOPP = mechlorethamine, Oncovin, procarbazine, and prednisone; NHL = non-Hodgkin's lymphoma; NSCLC = non–small-cell lung cancer; SIADH = syndrome of inappropriate antidiuretic hormone secretion; WBC = white blood cell

TABLE 6: Antimetabolites and their uses, dosages, and toxicities

Drug and its uses[a]	Dosages	Toxicities[b]
Folate analog		
Methotrexate *Breast, head and neck, GI, and lung cancers, ALL, CNS leukemia (intrathecal), gestational trophoblastic tumors, NHL (advanced stage),* Burkitt's lymphoma, osteosarcoma, mycosis fungoides	Numerous dosing schedules with combination therapy: Low dose: 2.5-5.0 mg PO daily; or 5-25 mg/m^2 PO, IM, IV twice weekly; or 50 mg/m^2 IV every 2-3 wk High dose: 1-12 g/m^2 IV with leucovorin rescue every 1-3 wk Intrathecal: 5-10 mg/m^2 (up to 15 mg) every 3-7 d	*Mucositis, GI ulceration (may produce hemorrhage or perforation), bone marrow depression, pulmonary fibrosis (previously irradiated area),* nerve root irritation and convulsion (intrathecal), liver cirrhosis and osteoporosis (chronic therapy), renal damage (high dose), diarrhea, skin erythema
Purine analogs		
Fludarabine *CLL,* AML, NHL (low-grade)	25 mg/m^2/d IV over 30 min for 5 d; repeat every 28 d	*Bone marrow depression,* nausea and vomiting, fever, malaise, pulmonary infiltrates, tumor lysis syndrome, CNS effects (high dose)
Mercaptopurine *ALL, CML, AML*	1.5-2.5 mg/kg/d PO (100-200 mg in average adult) until response or toxic effects are seen; may increase dose to 5 mg/kg/d; adjust for maintenance dose; reduce dose by 50%-75% if given with allopurinol or if renal or hepatic insufficiency ensues	*Bone marrow depression,* nausea and vomiting, anorexia, diarrhea, cholestasis
Thioguanine *AML,* ALL, CML, advanced colorectal cancer, multiple myeloma	2 mg/kg/d PO until response or toxic effects are seen; may cautiously increase to 3 mg/kg/d	*Bone marrow depression,* liver damage, stomatitis
Adenosine analogs		
Cladribine *Hairy-cell leukemia,* NHL, mycosis fungoides, AML, CML, CLL	0.09 mg/kg/d (4 mg/m^2/d) by continuous IV infusion for 7 consecutive days	*Bone marrow depression,* febrile episodes, rash, infections, septicemia
Pentostatin *Hairy-cell leukemia,* ALL, CLL, lymphoblastic lymphoma, mycosis fungoides	4 mg/m^2 IV over 30 min every other week or for 3 consecutive weeks; give vigorous hydration before and after chemotherapy	*Nephrotoxicity, CNS depression,* bone marrow depression, nausea and vomiting, conjunctivitis

[a] FDA-approved uses in italics; neoplasms are carcinomas unless otherwise indicated

[b] Dose-limiting effects in italics

Drug and its uses[a]	Dosages	Toxicities[b]
Pyrimidine analogs		
Capecitabine *Breast cancer (relapsed), colorectal cancer, and other GI malignancies*	1,250 mg/m^2 bid PO with food (2 weeks on drug, 1 week of rest)	*Diarrhea*, stomatitis, nausea and vomiting, fatigue, hand-foot syndrome, bone marrow depression (minimal)
Cytarabine *AML,* ALL, CML, NHL, CNS leukemia (intrathecal)	AML induction: 100 mg/m^2/d by continuous IV infusion on days 1-7; or 100 mg/m^2 IV every 12 h on days 1-7 Relapsed ALL: 3 g/m^2 IV over 1-3 h every 12 h for 4 doses	*Bone marrow depression,* nausea and vomiting, diarrhea, arachnoiditis (intrathecal), stomatitis, hepatic dysfunction, fever, conjunctivitis, confusion, somnolence, cerebellar toxicity
DepoCyt (liposomal cytarabine) *CNS leukemia/lymphoma*	Intrathecal: DepoCyt, 50 mg over 1-5 min every 14 d, with dexamethasone, 4 mg PO bid × 5 d	
Floxuridine *GI adenocarcinomas metastatic to liver,* including oral, pancreatic, biliary, colon, and hepatic cancers, and metastatic breast cancer	0.1-0.6 mg/kg/d over several days via continuous arterial infusion supplying well-defined tumor; treatments given over 1-6 wk	*Stomatitis and GI ulcers, bone marrow depression,* abdominal pain, nausea and vomiting, diarrhea, liver dysfunction (transient)
Fluorouracil *Colon, rectal, stomach, pancreas, breast,* head and neck, renal cell, prostate, and ovarian cancers, squamous cell carcinoma of esophagus, basal and squamous cell carcinoma of skin (topical), hepatic cancer (intra-arterial)	Numerous dosing schedules with combination therapy: Loading dose: 300-500 mg/m^2; or 12 mg/kg IV daily for 3-5 d, followed by weekly maintenance Maintenance: 10-15 mg/kg IV weekly, as toxicity permits Infusion: 20-25 mg/kg by continuous IV infusion over 24 h daily for 4-5 d, every 4 wk	*Stomatitis and GI ulcers (infusion) bone marrow depression (bolus), diarrhea,* nausea and vomiting, esophagitis, angina, cerebellar ataxia, radiosensitizer
Gemcitabine *Pancreatic cancer, lung,* ovarian, breast, and bladder cancers	1,000 mg/m^2 IV over 30 min, once weekly for up to 7 weeks (or until toxicity necessitates reducing or withholding a dose), followed by 1 week of rest Subsequent cycles: Infusions once weekly for 3 consecutive weeks out of every 4 weeks	*Bone marrow depression,* transient fever, flulike syndrome, skin rash, mild nausea and vomiting
Substituted urea		
Hydroxyurea *CML, acute leukemia (emergent treatment), head and neck cancer, ovarian cancer, melanoma,* essential thrombocytosis, polycythemia vera	Intermittent: 80 mg/kg PO every third day Continuous: 20-30 mg/kg PO daily	*Bone marrow depression,* mild nausea and vomiting, skin rashes, radiosensitizer

(See Table 5 for abbreviations)

TABLE 7: Natural products and their uses, dosages, and toxicities

Drug and its uses[a]	Dosages	Toxicities[b]
Antitumor antibiotics		
Bleomycin *Testicular cancer, HD, reticulum cell sarcoma, lymphosarcoma, squamous cell cancer of the head and neck, skin, cervix, vulva, and penis*	10-20 U/m^2 given IV, IM, or SC weekly or twice weekly; maximum total dose, 400 U; a 2-U test dose should be given because of a possible anaphylactoid reaction	*Pneumonitis and pulmonary fibrosis,* fever and allergic reactions, anaphylaxis, hyperpigmentation, Raynaud's phenomenon, alopecia
Dactinomycin *Testicular cancer, gestational trophoblastic tumors, Wilms' tumor, rhabdomyosarcoma, Ewing's sarcoma*	0.010-0.015 mg/kg IV daily for 5 d every 3 wk (usual adult dose, 0.5 mg), or 2 mg/m^2 IV as a single dose every 3-4 wk	*Stomatitis, bone marrow depression,* anorexia, nausea and vomiting, diarrhea, alopecia, skin changes, anaphylactoid reaction
Daunorubicin *AML, ALL*	Remission induction: 30-45 mg/m^2/d IV for 3 d in combination therapy; total cumulative dose, 550 mg/m^2	*Bone marrow depression,* cardiotoxicity, alopecia, nausea and vomiting, diarrhea, stomatitis, fever, dermatitis at previously irradiated sites, red urine, anaphylactoid reaction
DaunoXome (liposomal daunorubicin) *Kaposi's sarcoma*	Liposomal preparation: 40 mg/m^2 IV every 2 wk	
Doxorubicin *ALL, AML, breast, ovarian,* bladder cancers, HD, NHL, SCLC, gastric cancer, sarcoma, Wilms' tumor, neuroblastoma, thyroid cancer	60-90 mg/m^2 single IV injection every 21 d, 20-30 mg/m^2/d IV for 3 d every 3-4 wk, or 20 mg/m^2 IV weekly; total cumulative dose of 550 mg/m^2; reduce dose for liver dysfunction	*Bone marrow depression, cardiotoxicity, stomatitis (continuous infusion),* alopecia, nausea and vomiting, diarrhea, fever, dermatitis at previously irradiated sites, red urine, anaphylactoid reaction
Doxil (liposomal doxorubicin) *Ovarian cancer (refractory to paclitaxel- and platinum-based regimens),* *Kaposi's sarcoma*	50 mg/m^2 IV every 4 wk 20 mg/m^2 IV every 3 wk	*Bone marrow depression,* hand-foot syndrome *Bone marrow depression,* hand-foot syndrome
Epirubicin *Breast cancer*	100 mg/m^2 IV on day 1, or 60 mg/m^2 IV on days 1 and 8 in combination therapy	*Bone marow depression, cardiotoxicity, stomatitis,* alopecia
Idarubicin *AML,* CML (blast phase), ALL	12 mg/m^2/d IV for 3 d every 3 wk in combination therapy	*Bone marrow depression,* nausea and vomiting, stomatitis, alopecia, cardiotoxicity

[a] FDA-approved uses in italics; neoplasms are carcinomas unless otherwise indicated

[b] Dose-limiting effects in italics

Drug and its uses[a]	Dosages	Toxicities[b]
Mitoxantrone *AML, prostate,* ALL, CML, breast and ovarian cancers	Remission induction: 12 mg/m^2/d IV for 3 days, in combination with Ara-C	*Bone marrow depression*, cardiotoxicity, alopecia, stomatitis, nausea and vomiting, blue urine and sclera
Mitomycin *Gastric, colorectal, pancreatic adenocarcinomas,* NSCLC, breast, uterine, cervical, and head and neck cancers	20 mg/m^2 IV every 6-8 wk as a single agent, or 5-10 mg/m^2 IV every 6 wk in combination therapy	*Bone marrow depression (cumulative),* nausea and vomiting, anorexia, alopecia, stomatitis, fever, pulmonary fibrosis
Valrubicin *Bladder*	800 mg IV once a week for 6 wk	*Local bladder symptoms*
Epipodophyllotoxins		
Etoposide *Testicular cancer (refractory), SCLC,* HD, NHL, AML, gestational trophoblastic tumors	Testicular: 50-100 mg/m^2/d IV for 5 d, or 100 mg/m^2/d IV on days 1, 3, and 5 Lung: 35-50 mg/m^2/d IV for 5 d, or 100 mg/m^2/d PO for 5 d For both indications, given with combination therapy and repeated every 3-4 wk	*Bone marrow depression,* nausea and vomiting, diarrhea, fever, hypotension with rapid infusion, alopecia, rash
Teniposide *Relapsed ALL in children,* SCLC	ALL: 100 mg/m^2 once or twice weekly, or 20-60 mg/m^2/d for 5 days in combination with Ara-C Lung: 80-90 mg/m^2/d for 5 days as a single agent	*Bone marrow depression,* nausea and vomiting, alopecia, hypotension with rapid infusion, increased liver enzymes
Microtubule agents		
Docetaxel *Breast cancer (relapsed), lung,* ovarian, pancreatic cancer, head and neck, esophagus, stomach, cervical, Kaposi's sarcoma, uterine, prostate, and bladder	60-100 mg/m^2 IV over 1 hour every 21 days; or up to 42 mg/m^2 IV every week	*Bone marrow depression,* fluid retention, hypersensitivity reaction, paresthesias, rash, alopecia, myalgias
Paclitaxel *Ovarian cancer (relapsed), NSCLC (in combination with cisplatin), Kaposi's sarcoma, breast cancer (relapsed),* head and neck, gastric, colon, esophagus, uterine, prostate, bladder cancers and melanomas	135-175 mg/m^2 by IV infusion (ranging from 3-96 h) every 3 wk; or 80 mg/m^2 IV every week	*Bone marrow depression* peripheral neuropathy, alopecia, mucositis, anaphylaxis, dyspnea, myalgias

continued on following page

TABLE 7: Natural products and their uses, dosages, and toxicities *(continued)*

Drug and its uses[a]	Dosages	Toxicities[b]
Vinblastine *HD, NHL, gestational trophoblastic tumors, testicular and breast cancers, mycosis fungoides, Kaposi's sarcoma, histiocytosis X,* bladder and renal cancers, NSCLC, CML (blast crisis)	4-12 mg/m^2 IV as a single agent every 1-2 wk; titrate dose to myelosuppression; adjust for hepatic insufficiency	*Bone marrow depression,* nausea and vomiting, ileus, alopecia, stomatitis, myalgias, vesication
Vincristine *ALL, HD, NHL, rhabdomyosarcoma, neuroblastoma, Wilms' tumor,* multiple myeloma, sarcomas, breast cancer	0.4-1.4 mg/m^2 IV weekly; maximum total dose, 2 mg/wk; reduce dose for hepatic insufficiency	*Peripheral neuropathy,* ileus, abdominal pain, SIADH, bone marrow depression (mild)
Vinorelbine *NSCLC,* breast, ovarian, head and neck cancers, HD	30 mg/m^2 IV over 10 min; repeat weekly	*Peripheral neuropathy, bone marrow depression,* nausea and vomiting, hepatic dysfunction
Camptothecin analogs		
Irinotecan *Colorectal cancer,* lung, ovarian, and cervical cancers	125 mg/m^2 IV over 90 min once weekly for 4 wk; then 2 weeks rest; or 350 mg/m^2 every 21 days	*Bone marrow depression, diarrhea,* nausea and vomiting anorexia, weight loss
Topotecan *Ovarian cancer (relapsed), SCLC (relapsed),* MDS, CMML	1.5 mg/m^2 IV over 30 min for 5 consecutive days at 21-d intervals	*Bone marrow depression,* fever, flulike symptoms, nausea and vomiting
Enzyme		
Asparaginase *ALL,* CML, AML	6,000 IU/m^2 IM 3 times weekly for 9 doses, or 100 IU/kg/d IV for 10 continuous days, starting on day 22 of treatment; usually given with vincristine and prednisone	*Allergic reactions (fever, chills skin rash, anaphylaxis),* nausea and vomiting, anorexia, liver dysfunction, CNS depression, coagulopathy, hyperglycemia

(See Table 5 for abbreviations)

Chemotherapeutic agents classified by mechanism of action

Alkylating agents

The alkylating agents impair cell function by forming covalent bonds with the amino, carboxyl, sulfhydryl, and phosphate groups in biologically important molecules. The most important sites of alkylation are DNA, RNA, and proteins. The electron-rich nitrogen at the 7 position of guanine in DNA is particularly susceptible to alkylation.

Alkylating agents depend on cell proliferation for activity but are not cell-cycle-phase–specific. A fixed percentage of cells are killed at a given dose. Tumor resistance probably occurs through efficient glutathione conjugation or by enhanced DNA repair mechanisms. Alkylating agents are classified according to their chemical structures and mechanisms of covalent bonding; this drug class includes the nitrogen mustards, nitrosoureas, and platinum complexes, among other agents (see Table 5).

Nitrogen mustards The nitrogen mustards, which include such drugs as mechlorethamine (Mustargen), cyclophosphamide, ifosfamide (Ifex), and chlorambucil (Leukeran), are powerful local vesicants; as such, they can cause problems ranging from local tissue necrosis, to pulmonary fibrosis, to hemorrhagic cystitis. The metabolites of these compounds are highly reactive in aqueous solution, in which an active alkylating moiety, the ethylene imonium ion, binds to DNA. The hematopoietic system is especially susceptible to these compounds.

Nitrosoureas The nitrosoureas are distinguished by their high lipid solubility and chemical instability. These agents rapidly and spontaneously decompose into two highly reactive intermediates: chloroethyl diazohydroxide and isocyanate. The lipophilic nature of the nitrosoureas enables free passage across membranes; therefore, they rapidly penetrate the blood-brain barrier, achieving effective CNS concentrations. As a consequence, these agents are used for a variety of brain tumors.

Platinum agents Cisplatin (Platinol) is an inorganic heavy metal complex that has activity typical of a cell-cycle-phase–nonspecific alkylating agent. The compound produces intrastrand and interstrand DNA cross-links and forms DNA adducts, thereby inhibiting the synthesis of DNA, RNA, and proteins. Carboplatin (Paraplatin) has the same active diamine platinum moiety as cisplatin, but it is bonded to an organic carboxylate group that allows increased water solubility and slower hydrolysis to the alkylating aqueous platinum complex, thus altering toxicity profiles. Oxaliplatin (Eloxatin) is distinguished from the other platinum compounds by a di-amino-cyclohexane ring bound to the platinum molecule, which interferes with resistance mechanisms to the drug.

Antimetabolites

Antimetabolites are structural analogs of the naturally occurring metabolites involved in DNA and RNA synthesis. As the constituents of these metabolic pathways have been elucidated, a large number of structurally similar drugs that alter the critical pathways of nucleotide synthesis have been developed.

Antimetabolites exert their cytotoxic activity either by competing with normal metabolites for the catalytic or regulatory site of a key enzyme or by substituting for a metabolite that is normally incorporated into DNA and RNA. Because of this mechanism of action, antimetabolites are most active when cells are in the S phase and have little effect on cells in the G_0 phase. Consequently, these drugs are most effective against tumors that have a high growth fraction.

Antimetabolites have a nonlinear dose-response curve, such that after a certain dose, no more cells are killed despite increasing doses (fluorouracil [5-FU] is an exception). The antimetabolites can be divided into folate analogs, purine analogs, adenosine analogs, pyrimidine analogs, and substituted ureas (see Table 6).

Natural products

A wide variety of compounds possessing antitumor activity have been isolated from natural substances, such as plants, fungi, and bacteria. Likewise, selected compounds have semisynthetic and synthetic designs based on the active chemical structure of the parent compounds, and they, too, have cytotoxic effects (see Table 7).

Antitumor antibiotics Bleomycin (Blenoxane) preferentially intercalates DNA at guanine-cytosine and guanine-thymine sequences, resulting in spontaneous oxidation and formation of free oxygen radicals that cause strand breakage.

Anthracyclines The anthracycline antibiotics are products of the fungus *Streptomyces percetus* var *caesius.* They are chemically similar, with a basic anthracycline structure containing a glycoside bound to an amino sugar, daunosamine. The anthracyclines have several modes of action. Most notable are intercalation between DNA base pairs and inhibition of DNA topoisomerases I and II. Oxygen free radical formation from reduced doxorubicin intermediates is thought to be a mechanism associated with cardiotoxicity.

Epipodophyllotoxins Etoposide is a semisynthetic epipodophyllotoxin extracted from the root of *Podophyllum peltatum* (mandrake). It inhibits topoisomerase II activity by stabilizing the DNA-topoisomerase II complex; this process ultimately results in the inability to synthesize DNA, and the cell cycle is stopped in the G_1 phase.

Vinca alkaloids The vinca alkaloids are derived from the periwinkle plant *Vinca rosea.* Upon entering the cell, vinca alkaloids bind rapidly to the tubulin. The binding occurs in the S phase at a site different from that associated with paclitaxel and colchicine. Thus, polymerization of microtubules is blocked, resulting in impaired mitotic spindle formation in the M phase.

Taxanes Paclitaxel and docetaxel (Taxotere) are semisynthetic derivatives of extracted precursors from the needles of yew plants. These drugs have a novel

14-member ring, the taxane. Unlike the vinca alkaloids, which cause microtubular disassembly, the taxanes promote microtubular assembly and stability, therefore blocking the cell cycle in mitosis. Docetaxel is more potent than paclitaxel in enhancing microtubular assembly and also induces apoptosis.

Camptothecin analogs include irinotecan (CPT-11 [Camptosar]) and topotecan (Hycamtin). These semisynthetic analogs of the alkaloid camptothecin, derived from the Chinese ornamental tree *Camptotheca acuminata*, inhibit topoisomerase I and interrupt the elongation phase of DNA replication.

SUGGESTED READING

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CHAPTER 4

Head and neck tumors

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In 2003, it is estimated that head and neck cancers will comprise 2%-3% of all cancers in the United States and account for 1%-2% of all cancer deaths. This total includes 19,400 cases of oral cavity cancers, 9,500 cases of laryngeal cancer, and 8,300 cases of pharyngeal cancer. Most patients with head and neck cancer have metastatic disease at the time of diagnosis (regional nodal involvement in 43% and distant metastasis in 10%).

Head and neck cancers encompass a diverse group of uncommon tumors that frequently are aggressive in their biological behavior. Moreover, patients with a head and neck cancer often develop a second primary tumor. These tumors occur at an annual rate of 3%-7%, and 50%-75% of such new cancers occur in the upper aerodigestive tract or lungs.

The anatomy of the head and neck is complex and is divided into sites and subsites (Figure 1). Tumors of each site have a unique epidemiology, anatomy, natural history, and therapeutic approach. This chapter will review these lesions as a group and then individually by anatomic site.

Epidemiology

Gender Head and neck cancer is more common in men; 66%-95% of cases occur in men. The incidence by gender varies with anatomic location and has been changing as the number of female smokers has increased. The male-female ratio is currently 3:1 for oral cavity and pharynx cancers. In patients with Plummer-Vinson syndrome, the ratio is reversed, with 80% of head and neck cancers occurring in women.

Age The incidence of head and neck cancer increases with age, especially after 50 years of age. Although most patients are between 50 and 70 years old, head and neck cancer does occur in younger patients. There are more women and fewer smokers in the younger patient group.

It is controversial whether head and neck cancer is more aggressive in younger patients than in older individuals. This "aggressiveness" probably reflects the common delay in diagnosis in the younger population, since, in most studies, younger patients do not have a worse prognosis than their older counterparts.

Race Overall, there is no racial predominance of head and neck cancer in the United States. However, in recent years, the incidence appears to have declined among white and black males.

Among blacks, head and neck cancer is associated with lower survival for similar tumor stages. The overall 5-year survival rate is 56% in whites and 34% in blacks.

Geography There are wide variations in the incidence of head and neck cancer among different geographic regions. The risk of laryngeal cancer, for example, is two to six times higher in Bombay, India, than in Scandinavia. The higher incidence of the disease in Asia is thought to reflect the prevalence of risk factors, such as betel nut chewing and use of smokeless tobacco. In the United States, the high incidence among urban males is thought to reflect exposure to tobacco and alcohol. Among rural women, there is an increased risk of oral cancer related to the use of smokeless tobacco (snuff).

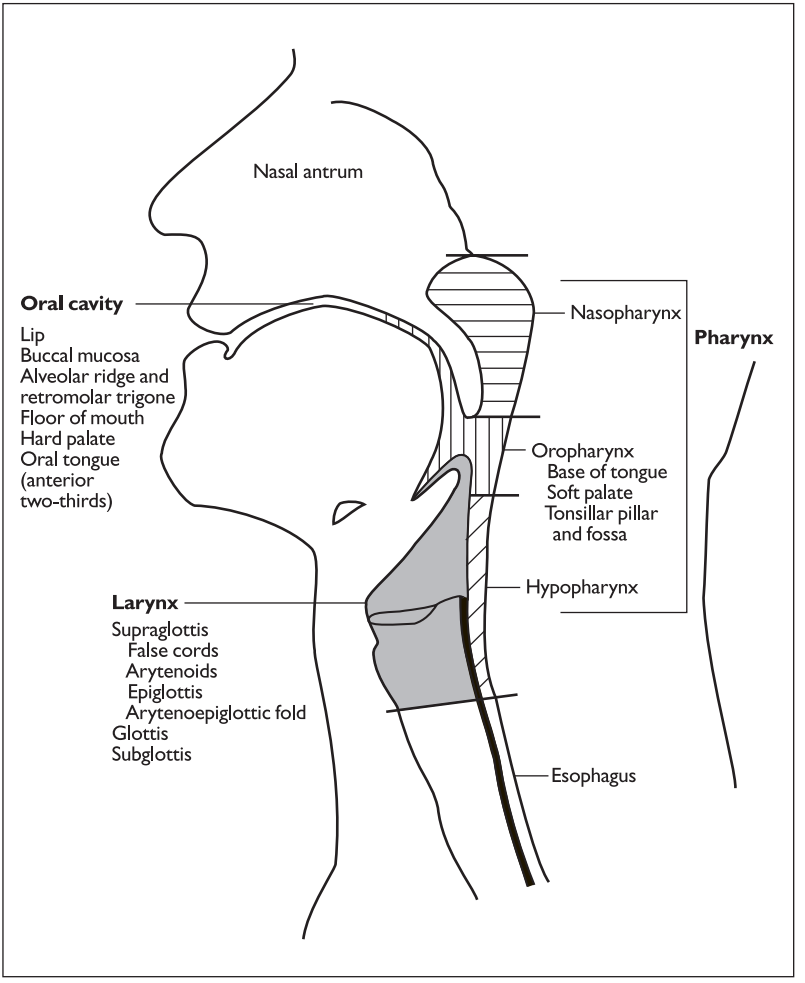

FIGURE 1: Anatomic sites and subsites of the head and neck.

Nasopharyngeal carcinoma is another head and neck tumor with a distinct ethnic predilection. Endemic areas include southern China, northern Africa, and regions of the far Northern Hemisphere—areas in which the diet of inhabitants includes large quantities of salted meat and fish. When people from these regions migrate to areas with a lower disease incidence, their risk falls but remains elevated. Cancer of the nasopharynx in these geographic areas also has been associated with Epstein-Barr virus (EBV) infection (see "Etiology and risk factors" section).

Disease site The approximate distribution of head and neck cancer follows: oral cavity, 44%; larynx, 31%; and pharynx, 25%.

Etiology and risk factors

Risk factors for head and neck cancer include tobacco and alcohol use, ultraviolet (UV) light exposure, viral infection, and environmental exposures.

Tobacco The incidence of head and neck tumors correlates most closely with the use of tobacco.

Cigarettes Head and neck tumors occur six times more often among cigarette smokers than nonsmokers. The age-standardized risk of mortality from laryngeal cancer appears to rise linearly with increasing cigarette consumption. For the heaviest smokers, death from laryngeal cancer is 20 times more likely than for nonsmokers. Furthermore, active smoking by head and neck cancer patients is associated with significant increases in the annual rate of second primary tumor development (compared with former smokers or those who have never smoked). Use of unfiltered cigarettes or dark, air-cured tobacco is associated with further increases in risk.

Cigars Total cigar consumption increased by nearly 50% in the United States in the 1990s. Often misperceived as posing a lower health risk than cigarette smoking, cigar smoking results in a change in the site distribution for aerodigestive tract cancer, according to epidemiologic data. Although the incidence of cancer at some sites traditionally associated with cigarette smoking (eg, larynx, lungs) is decreased in cigar smokers, the incidence of cancer is actually higher at other sites where pooling of saliva and associated carcinogens tends to occur (oropharynx, esophagus).

Smokeless tobacco Use of smokeless tobacco also is associated with an increased incidence of head and neck cancer, especially in the oral cavity. Smokeless tobacco users frequently develop premalignant lesions, such as oral leukoplakia, at the site where the tobacco quid rests against the mucosa. Over time, these lesions may progress to invasive carcinomas. The use of snuff has been associated with an increase in cancers of the gum and oral mucosa.

Alcohol Alcohol consumption, by itself, is a risk factor for the development of pharyngeal and laryngeal tumors, although it is a less potent carcinogen than tobacco. For individuals who use both tobacco and alcohol, these risk factors appear to be synergistic and result in a multiplicative increase in risk.

Head & Neck ch 4

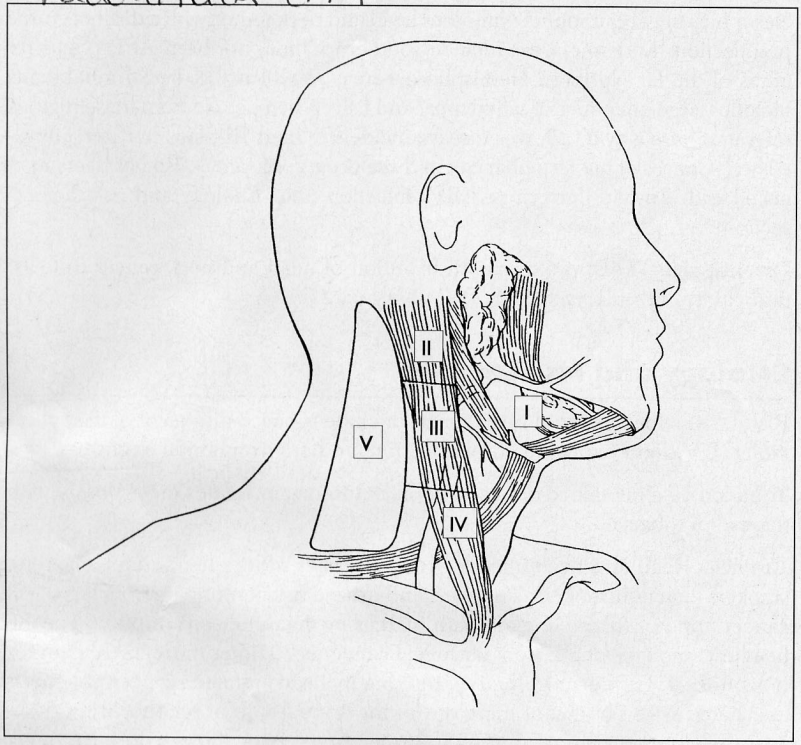

FIGURE 2: Levels of the neck as determined by lymphatic drainage patterns.

UV light exposure is a risk factor for the development of cancer of the lips. At least 33% of lip cancer patients have outdoor occupations.

Occupational exposures A small group of head and neck cancers may be attributable to occupational exposures. Nasal cancer has been associated with wood dust exposure, and squamous cell cancer of the maxillary sinus, with nickel exposure. Petroleum exposure may be associated with pharyngeal cancer, but the relationship has not been proven.

Radiation exposure Exposure to radiation is clearly an important risk factor for thyroid cancer and has been associated with cancer of the salivary glands.

Viruses There is a strong link between EBV exposure and the development of nasopharyngeal cancer. The relationship between other viruses, such as herpes simplex virus and human papillomavirus, and head and neck cancer is uncertain.

Diet Epidemiologic studies suggest that dietary intake of vitamin A, β-carotene, and α-tocopherol may reduce the risk of developing head and neck cancer.

Marijuana Smoking marijuana is associated with the development of head and neck cancer, but the degree of risk is unknown.

Anatomy

As mentioned above, the anatomy of the head and neck region is complex. The anatomic sites are illustrated in Figure 1. More detailed descriptions are included below in the discussions of specific sites and subsites.

Levels of the neck

The anatomy of the neck is relevant to the treatment of all head and neck cancers. The neck may be divided into levels (Figure 2). The lymphatic drainage of the unmanipulated neck is systematic and predictable; knowledge of these drainage patterns assists the clinician in locating the primary tumor that has given rise to a neck metastasis (Table 1).

Signs and symptoms

Head and neck cancer typically produces symptoms referable to the upper aerodigestive tract, including alterations in deglutition, phonation, hearing, and respiration. In particular, patients should be questioned about dysphagia, odynophagia, globus sensation, hoarseness, a change in the ability to form words, epistaxis, epiphora, otalgia, hemoptysis, stuffiness of the ears, and trismus. (Signs and symptoms of cancer at specific anatomic sites and subsites can be found in the respective discussions of these tumors.)

It is important to ascertain the duration and course (progression or improvement) of symptoms. Progression of disease is often noted during the evaluation and worsens prognosis.

Level I includes the submental and submandibular triangles.

Level II includes the superior jugular chain nodes extending from the mandible down to the carotid bifurcation and posteriorly to the posterior border of the sternocleidomastoid muscle.

Level III consists of the jugular nodes from the carotid bulb inferiorly to the omohyoid muscle.

Level IV continues from the omohyoid muscle inferiorly to the clavicle.

Level V represents the posterior triangle bounded by the sternocleidomastoid anteriorly, the trapezius posteriorly, and the omohyoid inferiorly. Few lesions metastasize to level V without involvement of more central nodes.

TABLE 1: Lymphatic drainage of the head and neck and associated sites of primary tumors

Lymphatic drainage	Likely primary sites
Level I	
Submental	Lower lip, chin, anterior oral cavity (including anterior one-third of the tongue and floor of the mouth)
Submandibular	Upper and lower lips, oral tongue, floor of the mouth, facial skin
Level II	Oral cavity and pharynx (including soft palate, base of the tongue, and piriform sinus)
Level III	Larynx, hypopharynx, and thyroid
Level IV	Larynx, hypopharynx, thyroid, cervical esophagus, and trachea
Level V	Nasopharynx, thyroid, paranasal sinuses, and posterior scalp
Supraclavicular	Infraclavicular sites (including lungs, esophagus, breasts, pancreas, GI tract, GU and gynecologic sources)

Screening and diagnosis

SCREENING

Because the cure rates for early-stage head and neck cancers are high, the concept of screening for the disease has intuitive appeal. Evaluation of asymptomatic individuals has not been shown to decrease mortality from head and neck cancer, however. The US Preventive Health Service Task Force does not recommend screening for oral cancer due to the lack of evidence supporting screening as a means of decreasing mortality. In countries with a high incidence of oral cavity cancer, such as India, screening may be helpful and is currently under evaluation.

DIAGNOSIS

The need for expeditious diagnosis of head and neck cancer and referral to a skilled head and neck specialist cannot be overemphasized, as early diagnosis can lead to a reduction in mortality. One study suggested that in the 24 months prior to the diagnosis of head and neck cancer, patients had a median of 10.5 health-care visits. These visits provide an opportunity to evaluate patients' symptoms and underscore the important role of dentists and primary care physicians in the early diagnosis of head and neck cancer.

History

Risk factors as outlined above, including a history of tobacco and alcohol use and environmental exposures, should be reviewed. Any adult patient with symptoms referable to the upper aerodigestive tract that have lasted longer than 2 weeks or with an asymptomatic neck mass should undergo a thorough examination with a high index of suspicion for carcinoma.

Physical examination

The physical examination is the best means for detecting lesions of the upper aerodigestive tract. Frequently, the initial assessment also will indicate the severity and chronicity of the disease. Due to the frequent occurrence of multiple primary tumors in patients with a head and neck tumor, careful evaluation of the entire upper aerodigestive tract is necessary at the time of diagnosis. The examination should always follow a systematic approach.

Skin/scalp A search should be made for ulcers, nodules, and pigmented or other suspicious lesions. This part of the evaluation is frequently overlooked.

Cranial nerves A cranial nerve evaluation is essential for any patient with a head and neck tumor or neck mass (which may be a manifestation of occult cancer). This evaluation should include assessing eye motion (cranial nerve [CN] III, IV, and VI); testing sensation of the face (CN V); examining the muscles of facial expression by having the patient grin, grimace, raise eyebrows, close eyes tightly, show teeth, and puff out the cheeks (CN VII); testing of hearing (CN VIII); assessing gag reflex (CN IX); evaluating vocal cord mobility (CN X); and having the patient fully abduct the shoulder (CN XI) and protrude the tongue (CN XII). Even the slightest abnormality may be helpful in identifying a primary tumor.

Eyes/ears/nose The eyes, ears, and nose should be evaluated for any sign of mass effect, abnormal drainage/discharge, bleeding, or effusion.

Oral cavity Halitosis may be the first indication of a lesion in the upper aerodigestive tract. The teeth, gingivae, and entire mucosal surface should be inspected. (Dentures should be removed.) The lymphoid tissue of the tonsillar pillars should be inspected and any asymmetry noted. Tongue mobility also should be evaluated.

The floor of the mouth, tongue, and cheeks should be palpated using a bimanual technique (one gloved finger inside the mouth and the second hand under the mandible). Palpation should be the last step of the examination due to stimulation of the gag reflex. Worrisome lesions should be biopsied.

Neck A systematic examination of the neck consistently documents the location of any mass. Palpation is the cornerstone of the examination. It is performed by grasping the tissue and feeling the nodes between the thumb and index and long fingers. The relationship of a mass to major structures, such as the salivary gland, thyroid, and carotid sheath, should be considered.

Important qualities of a mass include location, character, tenderness, size, mobility, and associated thrill or bruit. The thyroid should be palpated.

Indirect laryngoscopy The nasopharynx, hypopharynx, and larynx should all be examined with care. The vocal cords should be visualized and their mobility evaluated. Mirror examination provides an overall impression of mobility and asymmetry, which may point to a hidden tumor.

Direct laryngoscopy Nasopharyngoscopes permit a thorough inspection of the upper aerodigestive tract in the office setting. Attention should be focused individually on the piriform sinuses, tongue base, pharyngeal walls, epiglottis, arytenoids, and true and false vocal cords. Also, any pooling of secretions should be noted.

Endoscopy Approximately 5% of patients with head and neck cancer have a synchronous primary squamous cell cancer of the head and neck, esophagus, or lungs. "Triple" endoscopy includes direct laryngoscopy, esophagoscopy, and bronchoscopy with directed biopsy and should be performed in all patients with an occult primary squamous cell cancer and in many patients with a *known* head and neck primary. Triple endoscopy also can provide information regarding the extent of the tumor.

The most common sites of silent primary tumors are the tonsils, base of the tongue, and piriform sinuses. Tumors of the nasopharynx have become easier to identify with the increased use of flexible nasopharyngoscopy. Biopsies should be performed in common areas of silent primaries in addition to the primary anatomic sites associated with lymphatic drainage of any neck mass.

Laboratory evaluation

There are no specific screening laboratory tests other than preoperative studies performed in the diagnostic evaluation of most head and neck carcinomas. EBV, anticapsid antibodies, and serum IgG are tumor markers for nasopharyngeal carcinomas.

Diagnostic imaging

Plain x-rays PA and lateral chest x-rays should be obtained in all adult patients to eliminate the possibility of occult lung metastasis or a second primary. A Panorex film may be helpful in delineating bony involvement in some cases of oral cavity lesions.

Ultrasonography is of limited use in evaluating squamous cell cancer of the head and neck.

CT The CT scan is probably the single most informative test in the assessment of a head and neck tumor. It may delineate the extent of disease and the presence and extent of lymphatic involvement and will distinguish cystic from solid lesions. CT scans of the chest, abdomen, and pelvis sometimes may identify the site of an occult primary tumor presenting with a node low in the neck. CT

offers high spatial resolution and discriminates among fat, muscle, bone, and other soft tissues and surpasses MRI in the detection of bony erosion.

Dynamic contrast CT provides an increased ability to distinguish blood vessels from enlarged lymph nodes or masses and maintains image quality with the use of less contrast agent.

Spiral CT is a faster approach than dynamic contrast CT and has the capability for multiplanar reconstruction while maintaining the quality of the scan.

MRI may provide accurate information regarding the size, location, and extent of tumor. The advantages of MRI over CT include discrimination of tumor from normal tissue, multiplanar imaging without patient repositioning, and the ability to depict blood vessels clearly without iodinated contrast. The main disadvantage of MRI is movement artifact, which is a particular problem in the larynx and hypopharynx. Gadolinium-enhanced MRI is probably superior to CT for imaging tumors of the nasopharynx and oropharynx.

Angiography There are two indications for arteriography: a pulsatile neck mass and clinical evidence of a paraganglioma. High-resolution angiography is preferred over digital subtraction angiography because the former provides more information and permits embolization to be performed. Angiography is not used routinely in evaluating other primary tumors of the head and neck. In particular, angiography is not used routinely to assess arterial invasion or determine resectability of primary laryngeal tumors.

Nuclear scans are helpful in evaluating hyperthyroid patients but otherwise are of limited use.

PET has been evaluated in both primary and recurrent squamous cell carcinoma of the head and neck. Initial results are encouraging, but this tool should still be considered investigational.

Biopsy

Biopsies of the primary tumor often can be performed in an outpatient setting.

Punch or cup forceps biopsy is important in the diagnosis of mucosal lesions. The biopsy should be obtained at the border of the lesion away from areas of obvious necrosis.

Fine-needle aspiration (FNA) is a useful diagnostic modality. Multiple passes are made through the lesion with a fine-gauge (22-gauge) needle while suction is applied. Suction should be released before withdrawing the needle through surrounding soft tissue of the neck. FNA has an associated false-negative rate as low as 7%. The diagnostic accuracy depends on the physician's skill and the cytopathologist's experience.

Cytology is particularly useful in distinguishing a metastatic squamous cell carcinoma from other malignant histologies. However, a negative result should not be interpreted as "absence of malignancy."

Core biopsy should not be performed on a neck mass, with the rare exception of a proven lymphoma.

Open biopsy should be performed only when a diagnosis has not been made after extensive clinical evaluation and FNA is nondiagnostic. The operation should be performed only by a surgeon prepared to conduct immediate definitive surgical treatment at that time (which may entail radical neck dissection).

Pathology

Squamous cell carcinoma

More than 90% of all head and neck cancers are squamous cell carcinomas.

Histologic grade There are three histologic grades based on the amount of keratinization: A well-differentiated tumor is characterized by $> 75\%$ keratinization, a moderately differentiated tumor by 25%-50%, and a poorly differentiated tumor by $< 25\%$.

In general, the more poorly differentiated a lesion, the higher is the incidence of regional metastases and the poorer the prognosis. Histologic grade has not been a consistent predictor of clinical behavior, however. Features that predict aggressive behavior include perineural spread, lymphatic invasion, and tumor spread beyond the lymph node capsule.

Morphologic growth patterns Four morphologically distinct growth patterns have been recognized. The ulcerative type is the most common form and begins as a round or oval ulcer that is friable. Ulcerative lesions progress toward infiltration. Infiltrative lesions extend deeply into underlying tissues. The exophytic type tends to grow more superficially and metastasize later than the other types. It begins as an area of thickened epithelium.

Verrucous cancer is an uncommon variant that, in the United States, typically occurs in elderly patients with poor oral hygiene or ill-fitting dentures. It is characterized by a warty, bulky, elevated, fungating appearance. Verrucous cancers seldom metastasize.

Other tumor types

Other less common head and neck cancers include mucoepidermoid carcinoma, adenoid cystic carcinoma, and adenocarcinoma, all of which may arise in the salivary glands. Head and neck cancers with neuroendocrine features include small-cell undifferentiated cancer and esthesioneuroblastoma (olfactory neuroblastoma). Both Hodgkin's disease and non-Hodgkin's lymphoma may also be diagnosed as head and neck tumors, often involving the lymph nodes of the neck or Waldeyer's ring.

Sequence of disease progression

There is a sequence of disease progression from atypia/dysplasia through carcinoma in situ to frankly invasive cancer. Leukoplakia and erythroplakia are terms applied to clinically identifiable lesions that may harbor invasive cancer or undergo malignant transformation.

Leukoplakia results from chronic irritation of mucous membranes by carcinogens; this irritation stimulates the proliferation of white epithelial and connective tissue. Histopathologic examination reveals hyperkeratosis variably associated with underlying epithelial hyperplasia. In the absence of underlying dysplasia, leukoplakia rarely ($< 5\%$) is associated with progression of disease to malignancy.

Erythroplakia is characterized by superficial, friable, red patches adjacent to normal mucosa. It is commonly associated with underlying epithelial dysplasia and has a much greater potential for malignancy than leukoplakia. Carcinoma is found in nearly 40% of erythroplakia.

Dysplasia is characterized by cellular atypia, loss of normal maturation, and loss of normal epithelial stratification. It is graded as mild, moderate, or severe, based on the degree of nuclear abnormality present. In the transition from mild to severe dysplasia, nuclear abnormalities become more marked, mitoses become more apparent, and these changes involve increasing depth of epithelium. The likelihood of developing a carcinoma relates to the degree of dysplasia. In the case of *severe dysplasia*, as many as 24% of patients may develop invasive squamous cell cancer.

Carcinoma in situ is characterized by the presence of atypical changes throughout the epithelium with complete loss of stratification. It is estimated that approximately 75% of invasive squamous cell carcinomas have an associated in situ component. Specific DNA mutations have also been identified in the sequence of disease progression from mild dysplasia to atypia to carcinoma in situ to invasive carcinoma.

Regional and distant metastases

The incidence of lymph node metastases is related to the size and thickness of the primary tumor. If the primary site is near the midline, contralateral or bilateral metastases should be anticipated. In the presence of lymph node metastases, extracapsular spread of tumor is an important prognostic factor.

Staging and prognosis

Staging system The TNM staging system of the American Joint Committee on Cancer (AJCC) maintains uniformity in the staging of head and neck tumors. The staging of primary mucosal tumors of the head and neck varies with the anatomic location and will be covered later by site. However, the staging system for metastases and stage groupings are nearly uniform for all mucosal sites.

Prognosis correlates strongly with stage at diagnosis. For many head and neck cancer sites, survival for patients with stage I disease exceeds 80%. For patients with locally advanced disease at the time of diagnosis, stages III and IV disease, survival drops below 40%. Development of nodal metastases reduces survival of a patient with a small primary tumor by ~50%. Involvement of even a single lymph node is associated with a marked decline in survival. Most patients with head and neck cancer have stage III or IV disease at diagnosis.

Pattern of relapse Despite aggressive primary treatment, the majority of relapses that occur following a head and neck cancer are within the head and neck. Locoregional relapse accounts for ~80% of primary treatment failures. Distant metastases increase as the disease progresses and most often involve the lungs, bones, and liver. By the time of death, 10%-30% of patients will have clinically detected distant metastases.

Field cancerization is an important concept related to the natural history of head and neck cancer. This term describes the diffuse epithelial injury throughout the head and neck, lungs, and esophagus that results from chronic exposure to carcinogens.

Clinically, field cancerization is manifested by the frequent occurrence of (1) mucosal abnormalities, such as leukoplakia and dysplasia, beyond the margins of a head and neck cancer and (2) second primary tumors within this exposed field. The lifetime risk of a head and neck cancer patient developing a new cancer is 20%-40%. Over time, as the risk of relapse of the initial cancer declines, the development of a new cancer represents the greatest risk for these patients.

Treatment approaches

Head and neck tumors may be treated with curative intent using surgery, radiation therapy, or a combination of the two modalities. Chemotherapy may be combined with irradiation (chemoradiation) in the management of advanced (stage III/IV) lesions of the oropharynx, hypopharynx, and larynx and for nasopharyngeal cancers more advanced than stage T2b.

Stages I and II disease at most sites may be treated with either resection or radiation therapy. The best therapeutic approach for the primary tumor depends on the anatomic site. The approach to treatment of the neck also varies with the site and treatment of the primary tumor. A neck dissection in a clinically negative neck might be considered optional for primary tumors of the oral cavity but would typically be performed in association with pharynx operations since resection would require incision/dissection in the neck. Neck dissections should remain standardized (ie, complete anatomic dissections, as opposed to "berry picking" or random biopsy) in these settings so as to avoid incomplete surgery.

Preoperative assessment Before surgical resection, preoperative assessment of the extent of disease is essential. Complete physical examination and appropriate radiologic evaluation are necessary. Triple endoscopy (laryngoscopy, bronchoscopy, and esophagoscopy) or "quad scopes" (adding nasopharyngoscopy) with an examination with the patient under anesthesia may be helpful to assess the full extent of disease and to search for concomitant primaries. Biopsy for histologic confirmation may also be performed in this setting.

Surgical principles Classic principles of surgical oncology apply to head and neck cancer. Complete resection is necessary. Securing sufficient margins may be challenging due to the many structures in this area. Reconstruction is complex after resection of head and neck tumors, as the surgery may have an impact on appearance, speech, and swallowing. Decisions regarding the extent of resection should be made by experienced surgeons.

Surgery plus radiation therapy

The combination of radical surgery and radiation therapy has been used for several decades to reduce the rate of locoregional recurrence in patients with advanced head and neck cancers.

Postoperative vs preoperative radiation therapy Postoperative radiation therapy (60-70 Gy in 6-7 weeks) reduces the rate of locoregional recurrence from ~50% to 15% for tumors with pathologic features predictive of locoregional recurrence (positive margins, extracapsular nodal disease, and multiple involved lymph nodes) that are resected using radical extirpative surgery.

Preoperative radiotherapy (45-50 Gy in 4-5 weeks) has been used for patients with advanced primary tumors, but rates of locoregional recurrence appear to be lower and complications fewer with postoperative radiation therapy. Preoperative radiotherapy is indicated for marginally resectable tumors, such as those with fixed cervical lymph nodes. In this setting, preoperative irradiation often permits resection of an otherwise unresectable tumor.

Postoperative chemotherapy/radiation therapy The indications for postoperative radiation therapy are well established and include a large primary tumor (T3/T4), close or positive margins, an involved lymph node >3 cm or multiple involved lymph nodes, extracapsular extension, tumor fixation, and connective tissue invasion. The addition of postoperative radiation therapy reduces the risk of locoregional failure but does not decrease the risk of developing distant metastases or change the overall survival rate.

The RTOG sponsored a phase III randomized prospective trial to determine whether the addition of postoperative chemotherapy would enhance locoregional control. The initial results and failure patterns of RTOG 95-01 were presented in 2002. This study randomized 459 patients who underwent primary surgery but who had high-risk disease (two or more involved lymph nodes, extracapsular extension, or positive margins) to receive 6,000-

6,600 cGy of postoperative irradiation with or without cisplatin (Platinol) (given days 1, 22, and 43). The median follow-up was 26.6 months and the locoregional control was 74% vs 79% for the radiotherapy and radiotherapy and chemotherapy arms respectively ($P = .16$). Two-year overall survival was 57% and 63% ($P = .51$) and disease-free survival was 43% and 54% ($P = .049$), respectively. The incidence of grade 3 and higher acute toxicity was 33% for the radiotherapy alone arm and 75% for the radiotherapy and cisplatin arm ($P < .0001$). The authors concluded that the addition of postoperative chemotherapy increased acute toxicity but did not significantly improve clinical end points compared with radiotherapy alone.

Curative radiation therapy

Radiation therapy with curative intent usually involves daily treatment for 6-7 weeks (total dose, 60-70 Gy). Although there is no tissue loss with radiation therapy, complications include dry mouth, tissue fibrosis, trismus, bone necrosis, and hypothyroidism. Some problems are common and sufficiently debilitating to warrant significant concern in treatment planning for head and neck cancer. Surgery often produces less morbidity.

Radiation fractionation

The RTOG 90-03 trial was conducted to determine the efficacy of various fractionation schemes in the treament of locally advanced head and neck cancer. Four schedules were tested: (1) standard fractionation at 2 Gy/fraction/day, 5 days/week, to 70 Gy/35 fractions/7 weeks; (2) hyperfractionation at 1.2 Gy/fraction, twice daily, 5 days/week to 81.6 Gy/68 fractions/7 weeks; (3) accelerated fractionation with split at 1.6 Gy/fraction, twice daily, 5 days/week, to 67.2 Gy/42 fractions/6 weeks, including a 2-week rest after 38.4 Gy; or (4) accelerated fractionation with concomitant boost at 1.8 Gy/fraction/day, 5 days/week, and 1.5 Gy/fraction/day to a boost field as a second daily treatment for the last 12 treatment days to 72 Gy/42 fractions/6 weeks. A total of 1,113 patients were entered in the study, with a median follow-up of 23 months. Patients treated with both hyperfractionation and accelerated fractionation with a concomitant boost had significantly increased locoregional control rates compared with patients on the other two arms. All three groups treated with the altered fractionation schemes had more acute, but not late, side effects. The study concluded that hyperfractionation and accelerated fractionation with a concomitant boost are the optimal treatment schemes.

Intensity-modulated radiation therapy

Intensity-modulated radiation therapy (IMRT) is a new approach to obtaining highly conformal radiation dose distributions needed to irradiate complex targets positioned near sensitive normal structures. In the case of head and neck cancer, these sensitive normal structures include the parotid glands, spinal cord, and eyes. Treatment planning for IMRT (also known as inverse planning) is different from that of conventional or three-dimensional cranial

radiation therapy. The starting point with IMRT is a description of the desired dose distribution rather than the application of traditional fields and beam modifiers to generate an acceptable plan. Conventional radiation treatment utilizes relatively uniform beams of radiation (typically between 2-4 beams), whereas IMRT, instead of using 4 beams of 50 cGy each, could use 50 beams of 4 cGy each. Each beam direction is divided into multiple segments to modulate the radiation dose. The use of IMRT in the treatment of head and neck cancer has focused primarily on sparing the parotid glands and preserving salivary function.

Various groups have examined dosimetric and quality-of-life differences between IMRT and conventional radiation techniques. The group at Memorial Sloan-Kettering Cancer Center compared its IMRT planned treatment for nasopharyngeal cancer with conventional treatment with a conformal boost. Locoregional control was 97% vs 78% at 2 years. The University of Michigan and Washington University have reported reductions in xerostomia.

A recent meta-analysis evaluating the role of chemotherapy in squamous cell carcinoma of the head and neck was reported. This study compared treatment of 10,741 patients in 63 trials with or without chemotherapy. The pooled data showed an absolute survival benefit of 4% at 2 and 5 years in favor of chemotherapy. This report also evaluated 861 patients in 6 trials comparing induction chemotherapy followed by irradiation with concomitant or alternating chemoradiotherapy. These data revealed a 3% absolute (but not statistically significant) survival benefit at 2 and 5 years favoring concomitant chemotherapy (*Pignon JP, Bourhis J, Domenge C, et al: Lancet 355[9208]:949-955, 2000).*

Chemotherapy

Induction (neoadjuvant) chemotherapy

The high response rates achieved with induction chemotherapy (clinical response rates of 70% with cisplatin-based regimens, including complete histologic responses) (Table 2) have not resulted in improved locoregional control or survival when compared with radiotherapy alone. However, several studies have documented a decreased rate of distant metastasis with induction chemotherapy.

Although response to chemotherapy is a strong predictor of response to radiation therapy, chemotherapy does not confer an additional survival benefit. Whether or not chemotherapy may allow a reduction in the type of surgery or radiation therapy that must be given to cure these patients is disputed and remains open to study.

Concomitant chemotherapy and radiation therapy The major goal of administering chemotherapy concurrently with irradiation is to "radiosensitize" the tissue in the radiation field and increase the likelihood of locoregional control. This approach has been associated with improvements in locoregional control and survival in several randomized trials, and its benefits have been confirmed in recent meta-analyses. The optimal way in which to combine these two modalities is the focus of much ongoing research in head and neck oncology.

Preliminary results from a Head and Neck Intergroup study confirm the superiority of concurrent chemoradiation therapy compared with irradiation alone for patients with unresectable squamous cell cancer. A total of 295 patients with stage III and IV head and neck were randomized to participate in one of three arms: (A) radiotherapy alone to 70 Gy in 35 fractions; (B) 70 Gy in 35 fractions plus concurrent cisplatin on days 1, 22, and 43; and (C) split-course radiotherapy and three cycles or concurrent cisplatin/5-FU chemotherapy with 30 Gy given with cycle 1 and 30-40 Gy given with cycle 3. Grade 3 or worse toxicity occurred in 53% of arm A patients; 86% in arm B patients, and 77% of arm C patients. The 2- and 3-year Kaplan-Meier projected survivals for arm A are 30% and 20%, compared with 43% and 37% for arm B ($P = .016$), and 40% and 27% for arm C ($P = .13$). Median survival is 12.6 months for arm A, 19.1 months for arm B, and 14.0 months for arm C. The addition of concurrent high-dose single-agent cisplatin to conventional radiotherapy significantly improves survival with acceptable toxicity. Additionally, concurrent multiagent chemotherapy did not offset the loss of efficacy resulting from split-course irradiation.

Induction chemotherapy followed by radiation therapy has been shown in a Veterans Affairs (VA) trial to produce survival comparable to that attained with primary surgery in patients with laryngeal cancer. The advantage of this approach is preservation of the larynx. Combinations of chemother-

TABLE 2: Chemotherapy regimens for head and neck tumors

Drug/combination	Dose and schedule
Cisplatin + fluorouracil	
Cisplatin	100 mg/m^2 IV on day 1
Fluorouracil	1 mg/m^2 IV infused continuously over 4 days
Repeat cycle every 3-4 weeks	
Jacobs C, Lyman G, Velez-Garcia E, et al: J Clin Oncol 10:257–263, 1992.	
Carboplatin + paclitaxel	
Carboplatin	Dose calculated by the Calvert formula to an area under the curve between 6 and 7.5 mg/mL/min infused over 1-2 hours on day 1 after paclitaxel
Paclitaxel	175 mg/m^2 IV infused continuously over 3 hours
Repeat cycle every 21 days	
PREMEDICATIONS: Dexamethasone, 20 mg PO 12 and 6 hours prior to paclitaxel; as well as diphenhydramine, 50 mg IV, and ranitidine, 50 mg IV, both 30 to 60 minutes prior to paclitaxel	
Dang TP, Murphy BA, Cmelak A, et al: Proc Am Soc Clin Oncol 17:393a, 1998.	

Table prepared by Ishmael Jaiyesimi, DO

ECOG (Eastern Cooperative Oncology Group) 1393 randomized patients with recurrent squamous cell cancer of the head and neck to receive cisplatin (100 mg/m^2 day 1) and 5-FU (1 g/m^2 days 1-4; arm 1) or cisplatin (75 mg/m^2 day 1) and paclitaxel (75 mg/m^2 day 1; arm 2). Patients could have had no prior treatment for recurrent disease and were required to have ECOG performance status of 0 or 1. A total of 194 patients were studied, with 96 and 92 patients eligible on arms 1 and 2, respectively. Overall response and median survival rates were equivalent (arm 1: 22% and 8 months; arm 2: 28% and 9 months). The toxicity analysis favored arm 2, which was associated with fewer cases of stomatitis, diarrhea, myelosuppression, and infection. Quality of life did not favor either arm *(Murphy B, Li Y, Cella D, et al: Proc Am Soc Clin Oncol [abstract] 20:224a, 2001).*

apy and radiation therapy are being actively studied, and other approaches, such as concomitant treatment, appear to be effective.

Adjuvant chemotherapy following surgery or irradiation Adjuvant chemotherapy has been given following initial surgery or radiation therapy in an attempt to eliminate microscopic residual disease and distant metastases. Although this approach has resulted in a reduced rate of distant metastasis, it has not been associated with improved locoregional control or survival. As concomitant approaches evolve and locoregional control for advanced disease becomes the rule rather than the exception, the value of additional chemotherapy (as induction or adjuvant therapy) will need to be reexplored to address the problem of distant metastasis.

Locally advanced head and neck cancer Data from prospective trials continue to support the use of concurrent chemotherapy and irradiation as an alternative to surgery or irradiation alone for locally advanced cancers of the head and neck. RTOG 90-03 randomized 1,113 patients with stage III and IV squamous cell carcinoma of the oral cavity, oropharynx, or supraglottic larynx and stage II-IV squamous cell carcinoma of the base of the tongue or hypopharynx to receive one of four different schedules of irradiation alone. They included 7,200 cGy in 42 fractions (180 cGy/fraction initially, followed by 150 cGy/fraction to a boost field for the last 12 fractions bid). Locoregional control, disease-free survival, and overall survival rates were 54.5%, 39.3%, and 50.9%, respectively, which were superior to those obtained with single daily fractions of 2.0 Gy over 7 weeks.

RTOG 99-14 was a phase II study designed to integrate this altered fractionated irradiation regimen with chemotherapy. Cisplatin was given during weeks 1 and 3. When results on 77 evaluable patients were reported, 82% of patients were alive at the time of analysis. One-year overall survival was 81.3%; grade 3 and 4 chronic toxicity were 23% and 8%, respectively. The next RTOG phase III trial for advanced head and neck cancer will incorporate this regimen as the "experimental" arm.

Chemotherapy for recurrent or metastatic disease The combination of cisplatin/fluorouracil (5-FU) produces overall response rates of approximately 30% and survival rates of 6 months. In randomized trials comparing this combination with single-agent cisplatin, 5-FU, or methotrexate,

response rates with the single agents are lower but survival is equivalent. However, because many practitioners believe response is a surrogate for palliation, cisplatin/5-FU has been used widely in this setting.

The taxanes are the most active cytotoxins yet identified in head and neck cancer, with overall response rates of approximately 35% in patients with recurrent or incurable disease. In a recent randomized trial, the combination of paclitaxel (Taxol)/cisplatin has been compared with cisplatin/5-FU in patients with recurrent disease (see box on previous page). Although primary efficacy outcomes were equivalent for the two arms, paclitaxel/cisplatin was less toxic overall and can now be considered a safer, more convenient alternative to cisplatin and infusional 5-FU in recurrent disease. The evaluations of taxane-based neoadjuvant therapy and concurrent therapy with irradiation are ongoing.

Other drugs receiving recent attention are those targeting growth factors and their receptors. The epidermal growth factor receptor (EGFR) is particularly notable, since nearly 100% of head and neck tumors overexpress this receptor. A number of EGFR inhibitors are currently being evaluated alone and in combination with other drugs.

Photodynamic therapy

Photodynamic therapy may have some promise in the treatment of mucosal dysplasia and small head and neck tumors.

Small studies of photodynamic therapy, performed at several institutions, suggest that widespread areas of carcinoma in situ or severe dysplasia, as well as cancer, are often extirpated after photodynamic therapy. Although some patients have experienced durable remissions, the long-term efficacy of this modality remains uncertain.

Chemoprevention

The area of chemoprevention has received a great deal of attention in recent years, and the concept of "field cancerization" is important in this context. As mentioned previously, this concept refers to the diffuse epithelial injury incurred by upper aerodigestive tract mucosa due to chronic exposure to carcinogens (most commonly alcohol and tobacco). These mucosal changes increase the risk of developing premalignant lesions (leukoplakia and erythroplakia), as well as multiple primary lesions.

The retinoids (vitamin A analogs) have shown the greatest promise in achieving effective chemoprevention. The mechanism of action involves changes in gene expression mediated by nuclear retinoic acid receptors, which appear to function as transcription factors. In the mouse skin tumor and hamster buccal pouch models, retinoids have been shown to significantly prevent tumor growth and development. They have also been shown to significantly decrease the prevalence of premalignant lesions in humans in both randomized and nonrandomized clinical trials. Prospective trials have demonstrated

that serum levels of retinoids are lower in patients who subsequently develop upper aerodigestive tract tumors.

Ongoing clinical trials are investigating the possible role of retinoids in the prevention of second primary tumors in both the upper aerodigestive tract and lungs. However, a recent phase III ECOG (Eastern Cooperative Oncology Group) trial showed no benefit in prevention of recurrence with low-dose *cis*-retinoic acid (10 mg/d) in stage I/II patients. The ECOG trial used very low doses (7.5-10 mg/d). A study by Hong et al using high doses (1-2 mg/kg/d) produced positive results, but morbidity and compliance were problems. Results are pending from a trial employing intermediate dosing (30 mg/d).

Rehabilitation

Rehabilitation also is very important in the perioperative care of head and neck cancer patients. It includes physical and occupational therapy, speech and swallowing rehabilitation, and nutritional support. For example, resection of the spinal accessory nerve, which innervates the trapezius muscle, leads to scapular winging, inability to abduct the arm fully, and, eventually, to severe pain around the shoulder. These symptoms may be ameliorated with appropriate physical therapy.

Adapting to the loss of the larynx also requires intensive rehabilitation and patient motivation. Voice rehabilitation options include esophageal speech, artificial larynges (portable, battery-operated devices), and tracheoesophageal shunts.

Nutritional support is facilitated by temporary nasoduodenal tubes or gastrostomy tubes (which impose added morbidity but are more socially acceptable and ease the patient's transition to normal activities).

Management of symptoms and treatment side effects

Eating problems At the time of diagnosis, many head and neck cancer patients will have lost a significant amount of weight. Maintaining adequate nutrition is a major problem for these patients, as both the tumor and treatment side effects, such as mucositis from chemotherapy and radiation therapy, may be contributory. For patients who are unable to eat or who are being treated with aggressive concomitant chemotherapy and radiation therapy protocols, placement of a gastrostomy tube is often desirable in order to maintain caloric intake and adequate hydration.

Pain Clinicians must also be aware of the significant pain associated with these lesions and use narcotic analgesics appropriately to relieve discomfort.

Mucositis The use of chemotherapy concomitantly with radiation therapy increases the occurrence of mucositis.

Nephrotoxicity and ototoxicity For patients treated with cisplatin-containing regimens, renal insufficiency and ototoxicity are potential serious side effects.

Xerostomia Following radiation therapy of a head and neck cancer, xerostomia may be a significant long-term side effect. In some patients, pilocarpine hydrochloride (Salagen) has been useful in stimulating the production of saliva.

The use of organic thiophosphates, such as amifostine (Ethyol), in patients undergoing radiotherapy for head and neck cancer may reduce the severity of acute and late xerostomia without compromising the antitumor activity of the irradiation.

Gastroesophageal reflux Often asymptomatic or "silent" gastroesophageal reflux disease (GERD) is a common finding in patients treated for pharyngolaryngeal squamous cell carcinoma. In addition, cisplatin-containing chemotherapy may aggravate GERD.

Treatment of the neck

Either irradiation alone or radical neck dissection will control metastatic squamous cell cancer to a single small neck node more than 90% of the time if there is no extracapsular tumor spread. Hence, radiation treatment may easily provide prophylactic treatment of the neck if control of the primary tumor is un-

TABLE 3: Types of neck dissection and structures removed in the treatment of head and neck cancer

Type of neck dissection	Structures removed
Comprehensive neck dissection	
"Classic" radical neck dissection	All lymph-bearing tissue (levels I-V), spinal accessory nerve (cranial nerve [CN] XI), sternocleidomastoid muscle, and internal jugular vein
Modified radical neck dissection	Neck dissection with sparing of one or more of the above structures
Type I	CN XI spared
Type II	CN XI and internal jugular vein spared
Type III (functional neck dissection)	All three structures spared (CN XI, internal jugular vein, and sternocleidomastoid muscle)
Selective neck dissection	Removal of lymph-bearing tissue from:
Lateral	Levels II-IV
Posterolateral	Levels II-V
Supraomohyoid	Levels I-III

From Medina JE, Rebual NM: Neck dissection, in Cummings CW, Fredrickson J, Harker LE, et al (eds): Otolaryngology: Head and Neck Surgery, pp 1649–1672. St. Louis, Mosby Yearbook, 1993.

dertaken with irradiation. Traditionally, if the tumor in the neck was N2 or greater, or if there was tumor beyond the confines of a node, radical neck dissection and irradiation were combined for optimal control of the neck tumor. More recently, evidence suggests that N2-N3 disease that has a complete clinical and radiologic response to induction chemoradiotherapy may not require a complete neck dissection. This concept continues to evolve.

Types of dissection

There are several approaches to the surgical treatment of the neck nodes in patients with head and neck cancer (Table 3). This discussion will be limited to two types of neck dissection: comprehensive and selective dissection.

Comprehensive neck dissection entails complete removal of all lymphatic tissue from the neck (levels I-V). A radical neck dissection includes comprehensive node dissection with removal of the sternocleidomastoid muscle, jugular vein, and spinal accessory nerve. Modified radical neck dissection was developed to diminish the morbidity of the classic operation. The most important structure to preserve is the spinal accessory nerve.

Selective neck dissection consists of the removal of lymph node groups at highest risk of containing metastases from a primary cancer. In such procedures, the lymph nodes removed correspond to the most significant drainage basins of specific head and neck tumor sites. These are staging operations usually performed in patients with a clinically N0 neck cancer. If metastases are identified, further treatment to the neck will be required. A selective neck dissection should not be employed as the sole treatment of clinically palpable disease.

Sentinel lymph node biopsy for oral cavity lesions has been evaluated. Forty patients with clinically N0 necks underwent sentinel lymph node biopsy followed by complete neck dissection. A sentinal node was identified in 90% of necks, with a 97% accuracy rate in predicting the nodal status of the remainder of the neck. This finding corresponded to a sensitivity of 94% and a specificity of 100%. Although these results are encouraging, they need to be validated in a larger trial. An ongoing American College of Surgeons Oncology Group study (Z0360) is examining this technique in patients with T1 or T2, N0 oral cavity cancer. Sentinel lymph node biopsy may prove useful in small lesions without deep penetration, but it remains investigational.

Follow-up of long-term survivors

As mentioned, head and neck cancers are aggressive tumors. The majority (80%) of recurrences will develop within 2 years. Since many recurrences are treatable with curative intent, patients should be followed closely during the months following their treatment. This period coincides with the time of greatest need from the standpoint of rehabilitation.

TABLE 4: TNM staging system for cancers of the lips and oral cavity

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4	(lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, ie, chin or nose[a]
T4a	(oral cavity) Tumor invades adjacent structures (eg, through cortical bone, into deep [extrinsic] muscle of the tongue, maxillary sinus, or skin of face)
T4b	Tumor involves masticator space, pterygoid plates, or skull base and/or encases internal carotid artery
Regional lymph nodes (N)	
Nx	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension

After 2 years, second primary tumors of the head and neck and lungs become important causes of death and morbidity. Late complications of treatment such as radionecrosis, radiation-induced fibrosis, and hypothyroidism, as well as sequelae of spinal accessory nerve sacrifice or injury, may develop even after years. Complications and second primary cancers are more common in patients who continue to smoke.

Timing of follow-up evaluations Follow-up evaluations at regular intervals should be complete and should include a focused history and examination, as outlined above. Physicians who are able to perform a head and neck examination (including laryngoscopy) should direct follow-up. After surgical treatment, this evaluation will usually require visits with the head and neck surgeon. Patients treated with irradiation should be followed by both their radiation oncologist and a head and neck surgeon or otolaryngologist.

Distant metastases (M)			
Mx	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastases		
Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

[a] Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4.

Evaluations should be scheduled every 1-2 months during the first year after treatment, every 2-4 months during the second year, every 3-6 months during the third year, and every 6 months thereafter for several more years.

Imaging and laboratory studies Any mucosal abnormality should be biopsied. There are no tumor markers or other useful laboratory studies to follow. Chest x-rays should be obtained yearly. There is little justification for performing CT scans or MRI in the follow-up of asymptomatic patients. Thyroid-stimulating hormone (TSH) should be measured yearly in patients who have received irradiation to the larynx or nasopharynx.

HEAD AND NECK TUMOR REGIONS

As mentioned above, tumors occurring at different anatomic sites and subsites of the head and neck vary considerably with regard to epidemiology, risk factors, anatomy, natural history, staging of the primary tumor, and therapy. The following sections highlight these differences.

ORAL CAVITY

Sites of the oral cavity include the lips, hard palate, floor of the mouth, buccal mucosa, and tongue. Cancers at these sites comprise < 5% of all malignancies in the United States.

Etiology and risk factors

Tobacco and alcohol As with other head and neck tumors, there is a correlation between the use of tobacco and development of oral cavity cancers. There is a clear dose-response relationship between tobacco exposure and tumor development. A full 90% of patients with oral cancers use tobacco, and many drink alcohol.

Vitamin A Patients with vitamin-A deficiency seem to be at higher risk, whereas diets high in fruits and vegetables seem to be protective.

Chronic irritants, including mouthwash and poor oral hygiene, are associated with tumor development.

Viruses Herpes simplex virus type 1 and human papillomavirus have been implicated in the development of oral cancer.

Anatomy

The oral cavity extends from the cutaneous vermilion junction of the lips to the junction of the hard and soft palate above and to the line of the circumvallate papillae below. It includes the lips, buccal mucosa, upper and lower alveolar ridges, retromolar trigone, floor of the mouth, hard palate, and anterior two-thirds of the tongue (the "oral" tongue). The primary lymphatic drainage is to the submental triangle, submandibular nodes, and upper deep jugular nodes.

Natural history

The most common presenting complaint is a sore in the mouth or on the lips. One-third of patients present with a neck mass.

The differential diagnosis includes other malignancies and benign diseases or lesions. Other malignancies to be considered include salivary gland tumors,

sarcoma, lymphoma, and melanoma. Benign diseases include pyogenic granuloma, tuberculous disease, aphthous ulcers, and chancres.

Benign mucosal lesions include papillomas and keratoacanthomas, which may be exophytic or infiltrative. The exophytic lesions are less aggressive. The infiltrative papillomas and keratoacanthomas are more often associated with destruction of surrounding tissues and structures. These lesions may progress to malignancy. The TNM staging system for cancers of the lips and oral cavity is outlined in Table 4. T4 lesions have been divided into T4a (resectable) and T4b (unresectable) in the sixth edition of the *AJCC Cancer Staging Manual*.

Treatment

Radiation therapy has been widely used in patients with cancers of the oral tongue and floor of the mouth. Interstitial radiation therapy alone may be used for early (T1-T2) tumors, with local control rates of 80%-95%. A combination of external-beam radiation therapy (60 Gy in 6 weeks) plus interstitial radiotherapy provides excellent local control for early tumors.

Cancers arising at other sites within the oral cavity, such as the gingiva or buccal mucosa, usually are best treated with a primary surgical approach, but postoperative radiation therapy is added when poor pathologic features are present.

Surgical approaches to the primary cancer include peroral, transcervical, or combined operations. A comprehensive neck dissection should be performed in all patients with palpable cervical metastases. When an N0 lesion approaches the midline, bilateral supraomohyoid dissection should be considered. If the lymph nodes from the contralateral side of the neck contain cancer, contralateral neck treatment is needed. If there are bilateral, palpable nodes, both sides of the neck should be dissected.

Combined-modality treatment, including surgical resection and radiation therapy (60-70 Gy in 6-7 weeks), is advised for the treatment of advanced (stage III-IV) disease.

ORAL CAVITY SITE: LIPS

The lips are the most common site of oral cavity cancer. There are approximately 3,600 new cases per year in the United States. The lower lip is affected most often. The vast majority (90%) of patients with lip cancer are men, and 33% have outdoor occupations.

Natural history

The most frequent presentation is a slow-growing tumor of the lower lip that may bleed and hurt. Physical examination must include assessment of hypo-

esthesia in the distribution of the mental nerve (cutaneous sensation of chin area). Currently, fewer than 10% of American patients with squamous cell carcinoma of the lower lip have cervical metastases.

Treatment

Treatment of the primary tumor The primary tumor may be treated with radiation therapy (60-70 Gy in 6-7 weeks) or surgical resection. Currently, operations are more common than irradiation in the United States.

Resection involves excision with at least 0.5 cm of normal tissue circumferentially beyond the recognized border of the tumor. After the resection of larger lesions, reconstruction may pose a major challenge. Small tumors are excised with a V incision.

Patients with advanced disease (stage III or IV) are usually managed with a combination of surgery and postoperative radiation therapy (60-70 Gy in 6-7 weeks).

Treatment of the neck Elective treatment of the neck is seldom recommended for patients with squamous cell carcinoma of the lower lip and a clinically negative neck because few of these patients have cervical metastases. Neck dissection is recommended only in patients with palpable cervical metastases. In these individuals, the recommended approach often includes neck dissection and radiation therapy.

Results The cure rate for T1-T3 tumors is 90% with surgical excision alone. Smaller lesions (T1-T2) may be treated equally well with radiation therapy. Survival rates for patients with T1 and T2 lesions are 90% and 80%, respectively. Overall, younger patients have a poorer prognosis, as do those with involvement of the mandible and extension of the tumor within the oral cavity.

ORAL CAVITY SITE: TONGUE

The oral tongue (anterior two-thirds) is the site of 75% of all tongue cancers. There are approximately 7,100 new cases of oral tongue cancer each year in the United States.

Epidemiology and risk factors

Gender and age The male-female ratio is 3:1. Although the median age of onset is 60 years, tongue cancer may occur in patients younger than 30 years of age. Young patients may have no recognized risk factors.

Risk factors Tongue cancers are associated with poor oral hygiene and with alcohol and tobacco use.

Natural history

The most common presenting symptom in patients with cancer of the tongue is pain. Other symptoms include difficulty with deglutition and speech. There may be a history of leukoplakia, especially in younger women.

Rate of growth Cancer of the tongue seems to grow more rapidly than other oral cavity cancers. Tongue cancers may grow in an infiltrative or exophytic fashion. The infiltrative tumors may be quite large at presentation.

Lesion thickness Thicker lesions have a worse prognosis than thin cancers, and lesion thickness is a more important prognostic factor than is simple tumor stage.

Cervical metastases occur more frequently from tongue cancer than from any other tumor of the oral cavity. At initial evaluation, 40% of patients have node metastases. Bilateral and contralateral metastases from lateral tongue cancers are uncommon.

Treatment

Early-stage disease Treatment usually entails partial glossectomy. Margins should be assessed at the time of resection, as the disease spreads along muscle bundles, leading to more extensive tumor than is appreciated grossly.

Radiation therapy (60-70 Gy in 6-7 weeks) is a suitable option for small or minimally infiltrating tumors. Large, infiltrative lesions should be treated with combined-modality therapy (radiation therapy and surgical resection).

Advanced disease More advanced tumors with mandibular involvement require composite resection, including a partial glossectomy, mouth floor resection, and partial mandibulectomy.

Treatment of the neck A selective neck dissection is often recommended for the clinically N0 disease neck. Comprehensive neck dissection is required in the presence of palpable cervical metastases.

Results Control of disease closely correlates with the extent of the primary tumor and presence of metastases. Rates of local control using radiation therapy or surgery are similar for T1 (~85%) and T2 (~80%) tumors. T3 tumors should be treated using surgery and radiation therapy. Only 10%-15% of local recurrences are amenable to repeat resection.

Overall survival is approximately 50%. Rates of survival at 5 years by stage are stage I, 80%; stage II, 60%; and stage III-IV, 15%-35%. For equivalent primary cancers, the presence of lymph node metastases decreases the survival rate by 50%.

ORAL CAVITY SITE: FLOOR OF THE MOUTH

There are approximately 1,500 cases of floor of the mouth cancer in the United States annually. Mouth floor cancer accounts for 10%-15% of all oral cavity cancers.

Epidemiology and risk factors

Gender and age The male-female ratio is 3:1, but the incidence among women is increasing. The median age at presentation is 60 years.

Tobacco and alcohol Approximately two-thirds of patients with cancer of the mouth floor are heavy smokers and 50% are alcoholics. Alcohol acts synergistically with tobacco. Alcohol may act as a promoter, a direct irritant, or a solvent to increase the solubility of carcinogens from tobacco.

Smokeless tobacco There is a strong association between the use of smokeless tobacco and oral carcinogenesis. Data from the southern United States reveal a 50-fold increased risk of oral cavity cancer in women who use smokeless tobacco.

Pathology

Most lesions are moderately differentiated to well-differentiated squamous cell cancers and are exophytic in character.

Natural history

Patients usually present with a painful mass located near the oral tongue. Since these lesions do not cause pain until they are deep, they are frequently advanced at presentation.

Extension of disease into the soft tissues of the submandibular triangle is not uncommon. Fixation of the tumor to bone suggests possible mandibular involvement. A Panorex film of the mandible may reveal invasion of the mandible via direct extension (through a tooth socket) or via perineural invasion spreading along the mental nerve through the mental foramen. Changes in the mental foramen can be distinct or demonstrate slight asymmetry when compared with the contralateral anatomy. Restricted tongue mobility reflects invasion into the root of the tongue. Palpation demonstrates the depth of infiltration much better than does inspection alone.

Tumors near the midline may obstruct the duct of the submandibular gland, leading to swelling and induration, which may be difficult to distinguish from lymph node metastases. Level I nodes are the first-echelon metastatic sites.

Multifocality Multifocal cancers are more common in the floor of the mouth than in other oral cavity sites. Approximately 20% of patients with mouth

floor tumors have a second primary tumor, half of which are in the head and neck.

Treatment

Early invasive lesions (T1-T2) involving the mucosa alone may be treated with either surgery or irradiation (60-70 Gy in 6-7 weeks) alone, with comparable results. Primary tumors with mandibular involvement should be surgically resected.

Cancer invades the mandible through tooth sockets. Hence, if the tumor merely abuts the mandible, a marginal mandibulectomy (which removes the bone margin but preserves continuity) may be performed. Otherwise, a segmental resection is needed.

Selective neck dissection for treatment planning is advisable for thick stage I or II cancers.

Advanced disease The treatment of choice for advanced disease is combined-modality therapy with surgery and radiation therapy. Complete surgical resection may require a composite resection of the mandible, including a partial glossectomy and neck dissection for advanced primary cancers.

Lesions near the midline with a clinically positive lymph node require ipsilateral comprehensive neck dissection with a contralateral selective (supraomohyoid) neck dissection. Otherwise, both sides of the neck should be treated with irradiation. If there is clinical evidence of bilateral involvement, bilateral comprehensive neck dissection should be performed.

Results Overall, ~40% of patients are cured of their disease; 80% of recurrences appear within the first 2 years. Survival rates at 5 years by stage are as follows: stage I, 85%; stage II, 75%; stage III, 66%; and stage IV, 30%. Signs of poor prognosis include involvement of both the tongue and mandible and extension of the tumor beyond the oral cavity.

NASOPHARYNX

Nasopharyngeal carcinoma is uncommon in most of the world. Endemic areas include southern China, northern Africa, and regions of the far Northern Hemisphere. The incidence (per 1,000 population) ranges from 25.6 in men and 10.2 in women in Hong Kong to 0.6 in men and 0.1 in women in Connecticut.

Epidemiology and risk factors

Gender and age The incidence of nasopharyngeal cancer peaks in the fourth to fifth decades of life, and the male-female ratio is 2.2:1. Both patient age at disease onset and male-female ratio are lower for nasopharyngeal cancer than for other head and neck malignancies.

TABLE 5: TNM staging system for cancers of the pharynx (including base of tongue, soft palate, and uvula)

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Nasopharynx	
T1	Tumor confined to the nasopharynx
T2	Tumor extends to soft tissue of oropharynx and/or nasal fossa
T2a	Without parapharyngeal extension[a]
T2b	With parapharyngeal extension[a]
T3	Tumor invades bony structures and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit
Oropharynx	
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible (resectable)
T4b	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery (unresectable)
Hypopharynx	
T1	Tumor limited to one subsite of hypopharynx and 2 cm or less in greatest dimension
T2	Tumor involves more than one subsite of hypopharynx or an adjacent site or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx
T3	Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx
T4a	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue[b] (resectable)
T4b	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures (unresectable)

Risk factors Nasopharyngeal carcinoma appears to have different determinants than other head and neck cancers. They include diet, viral agents, and genetic susceptibility. Populations of endemic areas have a diet characterized by high consumption of salt-cured fish and meat. Studies reveal an association between EBV and nasopharyngeal carcinoma. Anti-EBV antibodies have been found in the sera and saliva of patients with this type of carcinoma. Major histocompatibility (MHC) profiles associated with increased relative risk include H2, BW46, and B17 locus antigens.

Regional lymph nodes (N): Nasopharynx	
Nx	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa[c]
N2	Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa[c]
N3	Metastasis in a lymph node(s) > 6 cm and/or to supraclavicular fossa
N3a	Greater than 6 cm in dimension
N3b	Extension to the supraclavicular fossa[c]

Regional lymph nodes (N): Oropharynx and hypopharynx	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension

Distant metastases (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastases

[a] Parapharyngeal extension denotes posterolateral infiltration of tumor beyond the pharyngobasilar fascia
[b] Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat
[c] Midline nodes are considered ipsilateral nodes

continued on following page

Anatomy and pathology

The nasopharynx communicates anteriorly with the nasal cavity and inferiorly with the oropharynx. The superior border is the base of the skull. The lateral and posterior pharyngeal walls are composed of muscular constrictors. Posteriorly, the nasopharynx overlies the first and second cervical vertebrae. The eustachian tubes open into the lateral walls. The soft palate divides the nasopharynx from the oropharynx.

TABLE 5: TNM staging system for cancers of the pharynx (including base of tongue, soft palate, and uvula) ***(continued)***

Stage grouping: Nasopharynx			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T2a	N1	M0
	T2b	N0	M0
	T2b	N1	M0
Stage III	T1	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1
Stage grouping: Oropharynx and hypopharynx			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

Cancers arising in the nasopharynx are classified using World Health Organization (WHO) criteria: type 1 denotes differentiated squamous cell carcinoma; type 2, nonkeratinizing carcinoma; and type 3, undifferentiated carcinoma. The TNM staging system for cancers of the pharynx is outlined in Table 5.

Natural history

A mass in the neck is the presenting complaint in 90% of patients. Other presenting symptoms include a change in hearing, sensation of ear stuffiness, tinnitus, nasal obstruction, and pain.

Cranial nerve involvement Invasion of disease into the base of the skull is seen in ~25% of cases and may lead to cranial nerve involvement. CN VI is the first cranial nerve to be affected, followed by CN III and CN IV. Deficits are manifested by changes in ocular motion. Involvement of CN V may also occur; this is manifested by pain or paresthesia high in the neck or face.

Level V metastases Unlike malignancies of the oral cavity and oropharynx, nasopharyngeal cancers often metastasize to level V lymph nodes. Bilateral metastases are common.

Treatment

Treatment of nasopharyngeal cancer usually involves radiation therapy (65-70 Gy) for the primary tumor and draining lymph nodes. Overall survival is 50% at 5 years. Surgical resection has very high morbidity and is seldom entertained, even after recurrence of a small cancer.

Nasopharyngeal cancer is distinguished from other sites of head and neck cancer by its radiosensitivity and chemosensitivity. Although advanced nodal disease can be controlled by irradiation alone in ~50% of patients, eventual distant metastasis remains a problem.

The final report of the intergroup trial 0099 confirmed that for patients with locally advanced nasopharyngeal cancer, concurrent cisplatin chemotherapy with radiation therapy (followed by systemic chemotherapy) provided a clear survival benefit compared with treatment with irradiation alone. At 5 years, patients who received combined-modality therapy had overall survival rates of 67%, compared with 37% if they received radiation thrapy alone ($P = .001$). Disease-free survival at 5 years was 74% for the chemoradiation therapy arm vs 46% for the radiation therapy-alone arm.

OROPHARYNX

Carcinoma of the oropharynx affects 4,000 patients in the United States annually.

Epidemiology and risk factors

Gender and age Oropharyngeal cancer usually occurs in the fifth to seventh decades of life. The male-female ratio is 3-5:1.

Tobacco and alcohol The most significant risk factors are tobacco and alcohol use.

Anatomy and pathology

The opening to the oropharynx is a ring bounded by the anterior tonsillar pillars (faucial arch), extending upward to blend with the uvula and inferiorly across the base of the tongue (behind the circumvallate papillae). The walls of the oropharynx are formed by the pharyngeal constrictor muscles, which overlie the cervical spine posteriorly. The superior boundary is the soft palate, which separates the oropharynx from the nasopharynx.

Inferiorly, the oropharynx is divided conceptually from the hypopharynx (laryngopharynx) at the level of the epiglottis. Subsites include the base of the tongue, soft palate, tonsillar area, and posterior pharyngeal wall. The extent of a primary tumor may be difficult to assess due to its location.

The jugulodigastric nodes (levels II and III) constitute the first echelon of lymphatic drainage. Metastases may also appear in the parapharyngeal and retropharyngeal nodes and may be detected only through imaging studies.

Premalignant lesions occur in the oropharynx but are less common than in the oral cavity.

Treatment

Radiation therapy External-beam radiation therapy (65-70 Gy over 7 weeks) and interstitial irradiation have been used in the curative treatment of oropharyngeal carcinomas for over 70 years. Radiation therapy represents a reasonable alternative to surgery and may also be required following radical resection of tumors with poor pathologic features to reduce the likelihood of local recurrence.

Altered fractionation schedules (accelerated and/or hyperfractionated) have gained interest in the past several years based on both theoretical grounds and the results of mainly retrospective data. One prospective, randomized trial in patients with oropharyngeal cancer (excluding base of the stongue cancer) documented a 20% increase in locoregional control and a 14% survival benefit at 5 years in patients who receive 8,050 cGy in a hyperfractionated schedule, as opposed to 7,000 cGy in a conventionally fractionated schedule. This improvement in outcome was not offset by any significant increase in acute or late tissue toxicity. Adoption of this strategy as a standard of care awaits confirmation of its superiority in a large, four-arm cooperative group trial that has completed accrual and is under analysis.

Local control rates with radiation therapy for all primary sites (including the tonsil, soft palate, base of the tongue, and posterior oropharyngeal wall) are as follows: T1, 90%; T2, 80%; T3, 65%; and T4, 55%. Cancers of the tonsillar

fossa are better controlled with irradiation than cancers arising in other subsites of the oropharynx.

Chemoradiation Recent additions to the literature support the use of concurrent chemotherapy with irradiation as an alternative to surgery or radiation alone for locally advanced cancers of the oropharynx. Brizel et al reported the results from a phase III randomized prospective study from Duke University. Patients were randomized to receive either hyperfractionated irradiation alone to a total dose of 7,500 cGy or hyperfractionated irradiation to a dose of 7,000 cGy with concurrent cisplatin and 5-FU chemotherapy during irradiation and two cycles of the drugs after radiation therapy. At 3 years, the rate of overall survival was 55% vs 34% in favor of the combined-modality arm; locoregional control was also superior in the combined-therapy arm, 70% vs 44%. Complications were similar between the two treatment arms.

A second study by the RTOG compared three different chemo/radiation therapy regimens for patients with stage III/IV squamous cell carcinoma of the head and neck. RTOG 97-03 randomized patients to receive 70 Gy in 7 weeks with either cisplatin and 5-FU during the last 10 days of treatment, hydroxyurea (Hydrea) and 5-FU with radiation therapy delivered on alternating weeks, or weekly cisplatin and paclitaxel. Two-year survival rates for all three arms ranged from 60%-67%.

Surgery Excision through the open mouth of all but small palatal and tonsillar lesions is generally inadequate. Substantial dissection is needed to provide exposure, and reconstruction is often required. A mandibulotomy, composite resection of the mandible, and/or total laryngectomy are occasionally required.

OROPHARYNGEAL SITE: BASE OF THE TONGUE

Cancer of the base of the tongue is far less common than that of the oral tongue.

Anatomy

The base of the tongue is bordered anteriorly by the circumvallate papillae and posteriorly by the epiglottis. There is a rich lymphatic network, with metastases frequently seen in levels II-V.

Natural history

The base of the tongue is notorious for lesions that infiltrate deeply into muscle and are advanced at diagnosis. This finding is probably due to the relatively asymptomatic anatomic location. Thus, bimanual oral examination with digital palpation is a critical part of the physical examination.

Most patients present with pain and dysphagia. Other symptoms include a neck mass, weight loss, otalgia, and trismus.

All oropharyngeal cancers have a strong propensity to spread to the lymph nodes, and base of the tongue tumors are no exception. Approximately 70% of patients with T1 primary base of the tongue tumors have clinically palpable disease in the neck and 20%-30% have palpable, bilateral lymph node metastases. The risk of nodal metastases increases with increasing T stage and approaches 85% for T4 lesions.

Treatment

Early-stage disease Stage I or II cancers may be treated equally effectively with either surgical resection or radiation therapy (65-70 Gy in 6-7 weeks) alone. Radiation therapy often results in a lesser functional deficit.

With surgery, lymphadenectomy is recommended due to the high frequency of metastatic spread. If irradiation of the primary is employed, both sides of the neck should be treated, even if the nodes do not seem to be involved.

Advanced disease More advanced disease may require total resection of the tongue base with supraglottic or total laryngectomy to ensure complete removal of disease. Limited laryngeal resection may result in recurrent aspiration, which is not tolerated by many patients. Total laryngectomy may be the only way to isolate the airway from oral secretions and eliminate the risk of aspiration. Chemoradiation via external-beam irradiation or irradiation alone combined with an implant can be curative for patients with advanced tumors of the tongue base and is often the treatment of choice.

Results In general, the prognosis of cancers of the tongue base is poor due to their advanced stage at presentation. The extent of nodal disease predicts survival. For T1 and T2 cancers, local control rates approach 85%. The major determinant of treatment failure is the tumor's growth pattern, with a high local control rate for exophytic lesions and a far worse rate for infiltrative tumors.

OROPHARYNGEAL SITE: TONSIL AND TONSILLAR PILLAR

The tonsil and the tonsillar pillar are the most common locations for tumors in the oropharynx.

Natural history

Tonsillar fossa tumors tend to be more advanced and more frequently metastasize to the neck than do tonsillar pillar cancers. At presentation, 55% of patients with fossa tumors have N2 or N3 disease, and contralateral metastases are common. Symptoms include pain, dysphagia, weight loss, a mass in the neck, and trismus.

Treatment

Single-modality therapy (irradiation or surgery alone) is acceptable for T1 and T2 tumors. Irradiation alone (60-70 Gy in 6-7 weeks) may be curative for more advanced tumors, although many of these lesions will require surgery combined with irradiation. The neck should always be included in treatment planning. More advanced disease usually requires surgery combined with irradiation (60-70 Gy in 6-7 weeks).

HYPOPHARYNX

Hypopharyngeal cancers are approximately one-third as common as laryngeal cancers.

Epidemiology and risk factors

Approximately 80% of cases occur in men. Plummer-Vinson syndrome is a known risk factor, and, in endemic areas, the male-female ratio is 1:4, reversing the otherwise 4:1 male-female ratio.

Anatomy

The hypopharynx (or laryngopharynx) is the entrance to the esophagus. The superior aspect (above the plane of the hyoid bone) communicates with the oropharynx, and the inferior border is situated in the plane of the lowest part of the cricoid cartilage (the esophageal inlet). The anterior surface (postcricoid area) is contiguous with the posterior surface of the larynx. The pharyngeal musculature forms the lateral and posterior walls. The piriform sinuses are within the hypopharynx on each side of the larynx.

The hypopharynx contains three subsites: the paired piriform sinuses (lateral, pear-shaped funnels); the posterior pharyngeal wall, from the level of the vallecula to the level of the cricoarytenoid joints; and the postcricoid area (pharyngoesophageal junction), which begins just below the arytenoids and extends to the inferior border of the cricoid cartilage. Seventy percent of hypopharyngeal cancers occur in the piriform sinuses.

Natural history

Hypopharyngeal tumors produce few symptoms until they are advanced (~70% are stage III at presentation). They may cause a sore throat, otalgia, a change in voice, odynophagia, or an isolated neck mass. Subtle changes on physical examination, including pooling of secretions, should be regarded with concern.

Nodal metastases Diffuse local spread is common and is due to tumor extension within the submucosa. Abundant lymphatic drainage results in a higher incidence of lymph node metastases than with other head and neck tumors. At

TABLE 6: TNM staging system for cancers of the larynx

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Supraglottis	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of piriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic tissues
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck [resectable], including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures (unresectable)
Glottis	
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, or with impaired vocal cord mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck, including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus) (resectable)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures (unresectable)
Subglottis	
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck, including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus) (resectable)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures (unresectable)

presentation, 70%-80% of patients with hypopharyngeal tumors have palpable cervical lymph node metastases; in half of these patients, palpable cervical nodes are the presenting complaint. Levels II and III are most commonly involved. Bilateral metastases are seen in only 10% of patients with piriform sinus cancers but in 60% of those with postcricoid tumors.

Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node(s), more than 6 cm in greatest dimension
Distant metastases (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastases

Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

Synchronous lesions are common. Overall, 20%-25% of patients with hypopharyngeal cancer develop a second primary within 5 years, usually in the head and neck.

Chemotherapy and external-beam radiotherapy Similar in design to the VA Cooperative Laryngeal Cancer Study, a randomized trial of the European Organization for Research on the Treatment of Cancer (EORTC) has shown that initial therapy with cisplatin and 5-FU, followed by definitive irradiation in patients with complete remissions (or, alternatively, surgical salvage) results in at least equivalent survival relative to immediate pharyngolaryngectomy. Of patients treated with initial chemotherapy, 28% retained a functional larynx at 3 years.

Results In general, even when treatment includes both surgery and radiation therapy, hypopharyngeal cancer is difficult to control. The overall 5-year survival rate is 25%; this rate decreases by 50% in the presence of lymph node metastases.

LARYNX

Laryngeal cancers constitute approximately 1.2% of all new cancer diagnoses in the United States. Approximately 9,500 new cases are expected in the year 2003.

To evaluate nonsurgical management of patients with stage III/IV laryngeal cancer, a phase III study tested three arms: (A) induction cisplatin/5-FU followed by radiation therapy; (B) concurrent cisplatin and radiation therapy; (C) radiation therapy alone. Total radiation dose was 70 Gy in 7 weeks with 2 Gy/fractions in all arms. A total of 507 patients were entered in the study, with 65% of them having stage III disease. Two-year laryngectomy-free survival was 58% for arm A, 66% for arm B, and 55% for arm C. The study concluded that concurrent chemoradiotherapy significantly increased the time to laryngectomy *(Forastiere AA, Berkey B, Maor M, et al: Proc Am Soc Clin Oncol [abstract] 20:2a, 2001).*

Epidemiology and risk factors

Laryngeal cancer most commonly affects middle-aged to older men who smoke tobacco and drink alcohol. There is no racial predominance,s but, in the past, blacks have presented at a younger age with a poorer prognosis. Most laryngeal squamous cell carcinomas result from exposure to carcinogens that cause diffuse mucosal changes (field effect).

Anatomy and pathology

Laryngeal anatomy is complex and includes cartilages, membranes, and muscles. The three subsites of the larynx are the glottis, or true vocal cords; the supraglottis, which includes the false cords, epiglottis, and aryepiglottic folds; and the subglottis, which is the region below the glottis and within the cricoid cartilage. The TNM staging system for cancers of the larynx is outlined in Table 6.

Treatment

Laryngectomy All or part of the larynx may need to be removed to achieve surgical control of laryngeal cancer. Decision-making for partial laryngectomy is complex and depends on the patient's wishes, the extent of local disease, and

the skills of the surgeon and radiation oncologist. Pharyngocutaneous fistula occurs in < 15% of patients but remains the most common complication following total laryngectomy. Spontaneous closure with conservative treatment and local wound care occurs in the majority of patients.

External-beam radiation therapy and chemoradiation With improvements in techniques and fractionation schedules, external-beam radiation therapy, which allows for laryngeal preservation, is an option for all but the most advanced tumors. A combination of induction chemotherapy (cisplatin plus 5-FU) and subsequent radiation therapy (6,600-7,600 cGy) may be used to preserve the larynx in the majority of patients with T3 laryngeal cancer without compromising survival. This approach is complex and requires careful attention during all phases of treatment.

Results In patients with T1 and T2 tumors of the glottic or supraglottic larynx, radiation therapy is associated with local control rates of 75%-95%. Patients with T3 tumors can expect local control rates of 50%-65% with radiation therapy alone.

The VA Cooperative Laryngeal Cancer Study randomized patients with resectable squamous cell carcinoma of the larynx to receive either standard surgery followed by radiation therapy or neoadjuvant therapy with cisplatin and 5-FU followed by radiation therapy for those achieving a good response to chemotherapy. Approximately two-thirds of patients survived 2 years following the combination of either chemotherapy plus irradiation or resection plus irradiation. Of those patients initially treated with chemotherapy and irradiation, one-third required a total laryngectomy because of a lack of response to treatment; the larynx was successfully preserved in two-thirds of these patients.

As in all head and neck cancer patients, the development of second cancers continues to result in mortality for several years following successful therapy.

LARYNGEAL SITE: SUPRAGLOTTIS

Supraglottic tumors occur less frequently than tumors of the true vocal cords. The epiglottis is the most common location for supraglottic cancers.

Natural history

Tumors close to the glottis produce symptoms sooner than tumors at other subsites. However, nearly 60% of patients with supraglottic tumors have T3 or T4 primary tumors at presentation.

The supraglottis has a rich lymphatic network. There is an associated high incidence of lymph node metastases in early-stage tumors (40% for T1 tumors). The incidence of metastases in a clinically N0 neck is about 15%. The incidence of bilateral cervical lymph node involvement is about 10%, and this rate increases to 60% for anterior tumors. The neck is a frequent site of recurrence in patients with supraglottic malignancies.

Treatment

Treatment of the primary tumor Appropriate cancers may be treated with partial laryngectomy. A supraglottic laryngectomy removes the upper portion of the thyroid cartilage and its contents, including the false vocal cords, as well as the epiglottis and aryepiglottic folds. This approach preserves speech and swallowing, but more extensive resections increase the demands on lung function, limiting their utility. Supraglottic laryngectomy is not well tolerated by patients with impaired lung function because of aspiration.

In patients with T1-T2 tumors, local control rates with radiation therapy (65-70 Gy in 6-7 weeks) exceed 80%. Also, as noted above, T3 tumors may be treated with radiation therapy (same regimen). Supraglottic laryngectomy is seldom appropriate as salvage therapy following irradiation due to complications, including swelling, difficulty swallowing, and poor wound healing. The usual salvage operation for persistent supraglottic cancer following radiation therapy is total laryngectomy.

More advanced disease requires combined-modality treatment and often requires total laryngectomy. Radiation therapy may be employed with curative intent, as may induction chemotherapy followed by irradiation, as described earlier.

Treatment of the neck The high incidence of cervical metastases makes treatment of the neck a necessity. About one-third of clinically negative necks contain involved nodes, and the incidence of recurrence in the untreated neck is high. In the surgical treatment of T1-T2 primary tumors, bilateral selective neck dissection is recommended.

Larynx preservation Data from RTOG 91-11 continue to mature, and an update to this trial was reported at the 2002 American Society of Therapeutic Radiology and Oncology (ASTRO) meeting, including rates of locoregional control, laryngectomy-free survival, and overall survival. This three-arm study randomized 517 evaluable patients to receive one of the following regimens: induction chemotherapy (with cisplatin and 5-FU) and conventional irradiation of 7,000 cGy, concurrent chemotherapy (cisplatin given days 1, 22, and 43), or irradiation therapy alone to 7,000 cGy. Locoregional control for the three arms was 61%, 78%, and 56%, respectively ($P < .01$). The number of laryngectomies was 43, 21, and 49, respectively, for the three arms. Overall survival was about 75% for each arm. The authors concluded that concurrent chemoradiation therapy was superior to the other regimens, with the highest locoregional control rates and laryngectomy-free survival.

Results The cure rate for early cancers of the larynx approaches 80% or more. Half of patients with T3 cancer are cured, whereas more than two-thirds of patients with T4 cancer will die of cancer.

LARYNGEAL SITE: GLOTTIS

The glottis is the most common location of laryngeal cancer in the United States, comprising more than half of all cases.

Natural history

The cure rate for tumors of the true vocal cords is high. These cancers produce symptoms early, and, thus, most are small when detected. Approximately 60% are T1 and 20% are T2. Normal cord mobility implies invasion of disease limited to the submucosa. Deeper invasion results in impaired vocal cord motion; this finding is most common in the anterior two-thirds of the vocal cord.

The true vocal cords have very little lymphatic drainage. Cervical metastases are infrequent with T1 and T2 tumors.

Treatment

Treatment of the primary tumor Carcinoma in situ is highly curable and may be treated equally well with microexcision, laser vaporization, or radiation therapy. Treatment decisions should be based on the extent of local disease. Multiple recurrences should heighten suspicion for an invasive component, and a more aggressive approach, such as partial or total laryngectomy, should be employed. T1 and T2 tumors may be treated by partial laryngectomy or radiation therapy (65-70 Gy in 6.5-7 weeks). In selected patients, partial laryngectomy can be performed after irradiation failure for T1-T2 glottic cancer, with excellent tumor control, satisfactory laryngeal function, and no increase in morbidity.

Advanced T4 disease is best treated with total laryngectomy. The standard treatment for T3 glottic cancer has been laryngectomy. However, many T3 lesions are now being treated with concomitant chemoradiotherapy, with salvage laryngectomy required in ~25% of patients for residual/recurrent disease or laryngeal dysfunction. Induction chemotherapy followed by irradiation can also be used, as described earlier.

Treatment of the neck Due to the sparse lymphatic network and low incidence of cervical metastases, elective neck dissection is indicated only for transglottic lesions. Palpable disease obviously requires neck treatment.

Results Cure rates by tumor size alone are as follows: T1, 90%; T2, 80%; T3, 50%; and T4, 40%. Neck involvement worsens the prognosis dramatically.

LARYNGEAL SITE: SUBGLOTTIS

Subglottic cancer is unusual, accounting for fewer than 10% of all laryngeal cancers.

Natural history

These cancers tend to be poorly differentiated, and, as the region is clinically "silent," most present as advanced lesions (~70% are T3-T4). The subglottis also has rich lymphatic drainage, and the incidence of cervical metastases is 20%-30%.

Treatment

Partial laryngectomy is not practical for the treatment of tumors in the subglottis, and, thus, therapy usually includes total laryngectomy plus neck dissection. Combination therapy (surgery plus radiation therapy [60-65 Gy in 6-7 weeks]) is recommended for more advanced disease.

Results The cure rate for the uncommon T1 and T2 tumors is ~70%. Most failures occur in the neck. The cure rate for more advanced lesions is ~40%.

UNKNOWN HEAD AND NECK PRIMARY SITE

The cervical lymph nodes are the most common metastatic site at which squamous cell carcinoma is found.

Natural history

Most patients who present with squamous carcinoma involving cervical lymph nodes, especially in the upper or middle portion of the cervical chain, will have a primary site within the head and neck. When the lower cervical or supraclavicular lymph nodes are involved, a primary lung cancer should be suspected.

In the overwhelming majority of these cases, the primary lesion will be discovered based on history, physical examination, proper radiographic evaluation (CT and/or MRI), and examination with the patient under anesthesia with endoscopy (direct laryngoscopy, nasopharyngoscopy, esophagoscopy, and bronchoscopy). "Silent" primary tumors are most often discovered in the base of the tongue or tonsillar fossa.

Treatment

A substantial percentage of patients achieve long-term disease-free survival after treatment of the involved side of the neck. Locoregional control and survival are diminished by multiple lymph nodes and the presence of extracapsular extension of disease in the involved neck.

Irradiation alone Patients with early-stage neck disease (N1 disease or small, mobile N2a disease) can often be treated with radiotherapy alone. Radiation therapy dosages and techniques should be similar to those used in patients

with advanced primary head and neck cancer. The nasopharynx, oropharynx, and hypopharynx should be included in the irradiated field.

Surgery alone When neck dissection is used at the initial treatment, a primary tumor in the head and neck subsequently becomes obvious in about 20% of patients.

Irradiation alone or combined with surgery Combination therapy (surgery plus radiation therapy [60-65 Gy in 6-7 weeks]) is recommended for patients who are found at surgery to have multiple involved nodes or extracapsular extension or who have suspected residual microscopic disease in the neck without a clinically detectable tumor. Open nodal biopsy does not appear to compromise outcome as long as adequate radiotherapy is delivered subsequently.

In most modern series utilizing predominantly combination therapy, 5-year survival rates exceed 50%. The volume of tumor in the involved neck influences outcome, with N1 and N2 disease having a significantly higher cure rate than N3 disease or massive neck involvement. Regional relapse is usually predicted by extranodal disease.

Chemotherapy The role of chemotherapy for metastatic squamous carcinoma in cervical lymph nodes remains undefined.

RECURRENT HEAD AND NECK CANCER

As mentioned previously, surveillance after treatment of head and neck cancer is mandatory, as early detection of second primary cancers or locoregional recurrence affords the best chance for disease control. Nearly two-thirds of patients whose head and neck cancer recurs develop tumor at (or near) the primary site or in the neck nodes. Eighty percent of head and neck cancer recurrences eventuate within 2 years. Development of recurrent tumor in the neck is the single most common type of treatment failure in patients with squamous cell carcinoma of the upper aerodigestive tract.

Differentiating recurrence from late complications of irradiation Differentiating between recurrent carcinoma and significant sequelae of radiotherapy is a difficult clinical problem at all sites within the head and neck. Any suspicious mucosal changes, enlarged nodes in the neck, or discrete subcutaneous nodules warrant prompt biopsy.

Candidates for surgery Different choices of first treatment (ie, surgery or radiation therapy) and the intensity of follow-up influence success in treating recurrence. Aggressive surgical intervention should be offered to two groups of patients with recurrent local or regional disease: those whose therapy is chosen with curative intent and those who have the prospect for significant palliation.

The types of recurrence that may be approached surgically with the greatest likelihood of success include (1) metastases in the neck after initial treatment limited to the primary tumor alone and (2) reappearance or persistence of cancer at a site previously treated with radiotherapy alone. Salvage resection may also be considered in other situations, however. They include the appearance of cancer in the neck after prior irradiation or neck dissection, at the margins after previous resection, and even at the base of the skull.

Although surgery is the standard of care for the treatment of recurrent disease, there is a growing body of evidence suggesting that reirradiation with concurrent chemotherapy can save selected patients when resection is not possible. Several institutions have reported experiences retreating patients, and these results led to the development of the first multi-institution reirradiation study.

A single-arm, phase II study (RTOG 96-10) evaluated toxicity and therapeutic results for patients with recurrent squamous cell carcinoma of the head and neck. Eighty-six patients received four weekly courses of 1.5 Gy fractions twice daily with concurrent 5-FU and hydroxyurea. Each cycle was separated by 1 week of rest. The median survival was 8.1 months and the 1- and 2-year survival rates were 41.7% and 16.2%, respectively. Compared with patients who experienced early recurrences, patients whose disease recurred 3 years after the original irradiation fared better, with 1- and 2-year survival rates of 48.1% and 32.1%, respectively.

Unless a patient cannot tolerate an operation, resection of discrete local or regional recurrent tumors should be entertained as the first course of treatment. Management of recurrences involves complex decision-making and requires familiarity with multidisciplinary care.

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CHAPTER 5

Thyroid and parathyroid cancers

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Endocrine malignancies, although relatively uncommon, are often difficult to diagnose and treat effectively. According to American Cancer Society estimates, 23,800 new cases of endocrine neoplasms will be diagnosed in the United States in the year 2003, and 2,300 deaths will result from these cancers. This chapter will focus on thyroid and parathyroid cancers. (A discussion of carcinoid tumors, insulinomas, gastrinomas, and other gastrointestinal neuroendocrine tumors, as well as adrenocortical cancer, can be found in chapter 14.)

THYROID CANCER

Thyroid cancer is the most common endocrine cancer. The number of deaths from thyroid cancer projected for the year 2003 is 1,400, or 7% of all new thyroid cancer cases. Between 1973 and 1997, the incidence of thyroid cancer increased by 24%, whereas mortality from this cancer decreased by 24%.

The prevalence rate for occult thyroid cancers found at autopsy is 5%-10%, except in Japan and Hawaii, where the rate can be as high as 28%. Autopsy rates do not correlate with clinical incidence.

The incidence of thyroid nodules in the general population is 4%-6%, with nodules being more common in females than males. The prevalence of thyroid cancer in a solitary nodule or in multinodular thyroid glands is 10%-20%; this increases with irradiation of the neck in children and older men (see "Etiology and risk factors" section).

Tumor types

Thyroid cancer is classified into four main types according to their morphology and biological behavior: papillary, follicular, medullary, and anaplastic. Differentiated (papillary and follicular) thyroid cancers account for > 90% of thyroid malignancies and constitute approximately 0.8% of all human malignancies. Medullary thyroid cancers represent 5%-10% of all thyroid neoplasms. About 80% of patients with medullary cancer have a sporadic form of the

disease, whereas the remaining 20% have inherited disease. Anaplastic carcinoma represents ≤ 5% of all thyroid carcinomas.

Papillary thyroid carcinoma is the most common subtype and has an excellent prognosis. Most papillary carcinomas contain varying amounts of follicular tissue. When the predominant histology is papillary, the tumor is considered to be a papillary carcinoma. Because the mixed papillary-follicular variant tends to behave like a pure papillary cancer, it is treated in the same manner and has a similar prognosis.

Papillary tumors arise from thyroid follicular cells, are unilateral in most cases, and are often multifocal within a single thyroid lobe. They vary in size from microscopic to large cancers that may invade the thyroid capsule and infiltrate into contiguous structures. Papillary tumors tend to invade the lymphatics, but vascular invasion (and hematogenous spread) is uncommon.

Up to 40% of adults with papillary thyroid cancer may present with regional lymph node metastases, usually ipsilateral. Distant metastases occur, in decreasing order of frequency, in the lungs, bones, and other soft tissues. Older patients have a higher risk for locally invasive tumors and for distant metastases. Children may present with a solitary thyroid nodule, but cervical node involvement is more common in this age group; up to 10% of children and adolescents may have lung involvement at the time of diagnosis.

Follicular thyroid carcinoma is less common than papillary thyroid cancer, occurs in older age groups, and has a slightly worse prognosis. Follicular thyroid cancer can metastasize to the lungs and bones, often retaining the ability to accumulate radioactive iodine (which can be used for therapy). Metastases may be appreciated many years after the initial diagnosis.

Follicular tumors, although frequently encapsulated, commonly exhibit microscopic vascular and capsular invasion. Microscopically, the nuclei tend to be large and have atypical mitotic figures. There is usually no lymph node involvement.

Follicular carcinoma can be difficult to distinguish from its benign counterpart, follicular adenoma. This distinction is based on the presence or absence of capsular or vascular invasion, which can be evaluated after surgical excision but not by fine-needle aspiration (FNA).

Thyroglobulin, normally synthesized in the follicular epithelium of the thyroid, is present in well-differentiated papillary and follicular carcinomas and infrequently in anaplastic carcinomas but not in medullary carcinomas. Therefore, thyroglobulin immunoreactivity is considered to be indicative of follicular epithelial origin.

Hürthle cell carcinoma Hürthle cell, or oxyphil cell, carcinoma is a variant of follicular carcinoma. Hürthle cell carcinoma is composed of sheets of Hürthle cells and has the same criteria for malignancy as does follicular carcinoma. Hürthle cell carcinoma is thought to have a worse outcome than follicular carcinoma and is less apt to concentrate radioactive iodine.

Medullary thyroid carcinoma originates from the C cells (parafollicular cells) of the thyroid and secretes calcitonin. On gross examination, most tumors are firm, grayish, and gritty.

Sporadic medullary thyroid carcinoma usually presents as a solitary thyroid mass; metastases to cervical and mediastinal lymph nodes are found in half of patients and may be present at the time of initial presentation. Distant metastases to the lungs, liver, bones, and adrenal glands most commonly occur late in the course of the disease. Secretory diarrhea, related to calcitonin secretion, can be a clinical feature of advanced medullary thyroid carcinoma.

Familial medullary thyroid carcinoma presents as a bilateral, multifocal process. Histologically, familial medullary carcinoma of the thyroid does not differ from the sporadic form. However, the familial form is frequently multifocal, and it is common to find areas of C-cell hyperplasia in areas distant from the primary carcinoma. Another characteristic feature of familial medullary carcinoma is the presence of amyloid deposits.

Anaplastic carcinoma Anaplastic tumors are high-grade neoplasms characterized histologically by a high mitotic rate and lymphovascular invasion. Aggressive invasion of local structures is common, as are lymph node metastases. Distant metastases tend to occur in patients who do not succumb early to regional disease. Occasional cases of anaplastic carcinoma have been shown to arise from preexisting differentiated thyroid carcinoma or in a preexisting goiter.

Other tumor types Lymphomas of the thyroid account for $< 5\%$ of primary thyroid carcinomas. Other tumor types, such as teratomas, squamous cell carcinomas, and sarcomas, may also rarely cause primary thyroid cancers.

Epidemiology

Age and gender Most patients are between the ages of 25 and 65 years at the time of diagnosis of thyroid carcinoma. Women are affected more often than men (2:1 ratio for the development of both naturally occurring and radiation-induced thyroid cancer).

Etiology and risk factors

Differentiated thyroid cancer

Therapeutic irradiation External low-dose radiation therapy to the head and neck during infancy and childhood, frequently used between the 1940s and 1960s for the treatment of a variety of benign diseases, has been shown to predispose an individual to thyroid cancer. The younger a patient is at the time of radiation exposure, the higher is the subsequent risk of developing thyroid carcinoma. Also, as mentioned above, women are at increased risk

of radiation-induced thyroid cancer. There is approximately a 25- to 30-year mean latency period from the time of low-dose irradiation to the development of thyroid cancer.

As little as 11 cGy and as much as 2,000 cGy of external radiation to the head and neck have been associated with a number of benign and malignant diseases. It was once thought that high-dose irradiation (> 2,000 cGy) to the head and neck did not increase the risk of neoplasia. However, recently it has been shown that patients treated with mantle-field irradiation for Hodgkin's disease are at increased risk of developing thyroid carcinoma, compared with the general population, although they are more likely to develop hypothyroidism than thyroid cancer.

Radiation-associated thyroid cancer has an identical natural history and prognosis as sporadic thyroid cancer.

Other factors Besides radiation-induced thyroid cancer, there are only sparse data on the etiology of differentiated thyroid cancer.

Medullary thyroid cancer

Genetic factors In addition to sporadic medullary thyroid cancer, which represents the majority of cases, there are three hereditary forms: familial medullary thyroid carcinoma; multiple endocrine neoplasia type 2A (MEN-2A), characterized by medullary thyroid cancer, pheochromocytomas, and hyperparathyroidism; and multiple endocrine neoplasia type 2B (MEN-2B), characterized by medullary thyroid cancer, marfanoid habitus, pheochromocytomas, and neuromas. These syndromes are associated with germ-line mutations of the *RET* proto-oncogene, which codes for a receptor tyrosine kinase (RTK). Familial medullary thyroid carcinoma is inherited as an autosomal-dominant trait with high penetrance and variable expression. (For a discussion of genetic testing to screen for *RET* mutations in MEN-2A kindreds, see "Screening and prognosis" section.)

Signs and symptoms

Most thyroid cancers present as asymptomatic thyroid nodules. Patients may feel pressure symptoms from nodules as they begin to increase in size. A change in the voice can be caused by a thyroid cancer or benign goiter. The voice change usually occurs when there is compression of the larynx or invasion of the recurrent laryngeal nerve.

On physical examination, a thyroid nodule that is hard or firm and fixed may represent a cancer. The presence of palpable enlarged nodes in the lateral neck, even in the absence of a palpable nodule in the thyroid gland, could represent metastases to the lymph nodes.

Diagnostic work-up

As mentioned above, thyroid nodules are present in 4%-6% of the general population and in a higher percentage of individuals who have had irradiation to the head and neck region. Most thyroid nodules are benign (colloid nodules or adenomas); therefore, it is important for the work-up to lead to surgical resection for malignant nodules and avoid unnecessary surgery for benign lesions. Although most solid nodules are benign, thyroid carcinomas usually present as solid nodules. A cystic nodule or a "mixed" (cystic-solid) lesion is less likely to represent a carcinoma and more likely to be a degenerated colloid nodule.

History The history is very important in the evaluation of thyroid nodules. If there is a history of irradiation to the head and neck, the risk of there being a cancer in the nodule is higher (as great as 50%, compared with a 10%-20% risk in nonirradiated patients).

Age also is important in the evaluation of thyroid nodules. Nodules that occur in either the very young or the very old are more likely to be cancerous, particularly in men.

A new nodule or a nodule that suddenly begins to grow is worrisome as well.

FNA should be the initial diagnostic test for the evaluation of thyroid nodules. First, FNA can determine whether the lesion is cystic or solid. For solid lesions, cytology can yield one of three results: benign, malignant, or suspicious, or indeterminate. The accuracy of cytologic diagnosis from FNA is 70%-80%, depending on the experience of the person performing the aspiration and the pathologist interpreting the cytologic specimen.

Imaging modalities Ultrasonographic and radionuclide (radioiodine and technetium) scans are also used in the evaluation of thyroid nodules.

Ultrasonography can be used to determine whether a nodule is cystic or solid. It cannot differentiate a benign solid nodule from a malignant one but can be used to assess the number of nodules present and their size. A nodule in a gland with multiple other nodules of similar size is unlikely to be malignant. A dominant nodule in a multinodular gland carries a risk of malignancy similar to that of a true solitary nodule. Ultrasonographically guided FNA can be performed, increasing the diagnostic efficacy.

Thyroid isotope scans cannot differentiate absolutely a benign from a malignant nodule but can, based on the functional status of the nodule, assign a probability of malignancy. "Hot" thyroid nodules (ie, those that concentrate radioiodine) represent functioning nodules, whereas "cold" nodules are nonfunctioning lesions that do not concentrate the isotope. Most thyroid carcinomas occur in cold nodules, but only 10% of cold nodules are carcinomas. It is not necessary to operate on all cold thyroid nodules. CT or MRI scan of the neck may be appropriate in some cases.

Calcitonin level Medullary thyroid carcinomas usually secrete calcitonin, which is a specific product of the thyroid C cells (parafollicular cells). In patients who have clinically palpable medullary carcinoma, the basal calcitonin level is almost always elevated. In patients with smaller tumors or C-cell hyperplasia, the basal calcitonin level may be normal, but administration of synthetic gastrin (pentagastrin) or calcium results in marked elevation of calcitonin levels. The use of calcitonin levels as a tumor marker and stimulation screening in familial forms of medullary cancers has been largely replaced by genetic testing (see below).

Carcinoembryonic antigen (CEA) Serum CEA levels are also elevated in patients with medullary thyroid cancer.

Ruling out pheochromocytoma Medullary thyroid carcinoma can be associated with MEN-2A, MEN-2B, or familial non-MEN. Both the MEN-2A and MEN-2B syndromes are characterized by medullary thyroid cancer and pheochromocytoma. Thus, in any patient with familial medullary thyroid carcinoma, it is imperative that the preoperative work-up include a determination of 24-hour urinary catecholamine levels (metanephrine and vanillylmandelic acid) to rule out the presence of a pheochromocytoma.

Genetic testing Germ-line mutations in the *RET* proto-oncogene are responsible for familial non-MEN medullary thyroid carcinoma in addition to MEN-2A and MEN-2B. DNA analysis performed on a peripheral blood sample is a highly reliable method for identifying the presence of a *RET* mutation. The natural history of the disease appears to vary according to the specific mutation.

Because all persons who inherit the mutation develop medullary thyroid carcinoma, total thyroidectomy is recommended for all such affected individuals. This procedure should be performed by age 5 or 6 years for carriers of the mutations for familial non-MEN medullary thyroid carcinoma and MEN-2A. Those with the mutation for MEN-2B should undergo total thyroidectomy during infancy because of the very early onset of aggressive medullary thyroid carcinoma in that syndrome.

Periodic determinations of stimulated calcitonin levels may help make the early diagnosis of medullary thyroid carcinoma in those who do not undergo surgery but will not always prevent the development of metastatic medullary thyroid carcinoma.

Screening

At this time, no organization recommends periodic screening for thyroid cancer using neck palpation or ultrasonography in average-risk, asymptomatic adults. However, the American Cancer Society recommends examination of the thyroid during a routine checkup, since this surveillance can result in case findings.

TABLE 1: UICC staging of thyroid cancer

Primary tumor (T)

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 1 cm in greatest dimension, limited to the thyroid
T2	Tumor > 1 cm but not > 4 cm in greatest dimension, limited to the thyroid
T3	Tumor > 4 cm in greatest dimension, limited to the thyroid
T4	Tumor of any size extending beyond the thyroid capsule

Note: All categories may be subdivided: (a) solitary tumor, (b) multifocal tumor (the largest determines the classification).

Regional lymph nodes (N)

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis in ipsilateral cervical lymph node(s)
N1b	Metastasis in bilateral, midline, or contralateral cervical or mediastinal lymph node(s)

Distant metastasis (M)

Mx	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping: Papillary or follicular							Stage grouping: Medullary			
	< 45 years old			≥ 45 years old						
Stage I	Any T	Any N	M0	T1	N0	M0	Stage I	T1	N0	M0
Stage II	Any T	Any N	M1	T2	N0	M0	Stage II	T2	N0	M0
				T3	N0	M0		T3	N0	M0
Stage III				T4	N0	M0		T4	N0	M0
				Any T	N1	M0	Stage III	Any T	N1	M0
Stage IV				Any T	Any N	M1	Stage IV	Any T	Any N	M1

Stage grouping: Undifferentiated[a]

Stage IV	Any T	Any N	Any M

UICC = International Union Against Cancer

[a] For undifferentiated cancers (eg, anaplastic carcinoma), all cases are classified as stage IV.

Staging and prognosis

Unlike most other cancers, in which staging is based on the anatomic extent of disease, the International Union Against Cancer (UICC) staging of thyroid cancer also takes into consideration patient age at the time of diagnosis and tumor histology (Table 1).

Differentiated thyroid cancers Recurrence and death following initial treatment of differentiated thyroid cancer can be predicted using a number of risk

classification schemes. The most commonly used systems are the AMES (age, metastases, extent, and size) and AGES (age, grade, extent, and size) classifications.

Low-risk patients are generally those < 45 years of age with low-grade nonmetastatic tumors that are confined to the thyroid gland and are < 1-5 cm in size. Low-risk patients enjoy a 20-year survival rate of 97%-100% after surgery alone.

High-risk patients are those ≥ 45 years old with a high-grade, metastatic, locally invasive tumor in the neck or with a large tumor. Large size is defined by some authors as > 1 cm and by other authors as > 2 or > 5 cm. The 20-year survival rate in the high-risk group drops to between 54% and 57%.

Intermediate-risk patients include young patients with a high-risk tumor (metastatic, large, locally invasive, or high grade) or older patients with a low-risk tumor. The 20-year survival rate in this group of patients is ~85%.

Medullary thyroid carcinoma is associated with an overall 10-year survival rate of 40%-60%. When medullary carcinoma is discovered prior to becoming palpable, the prognosis is much better: Patients with stage I medullary tumors (ie, tumors < 1 cm or nonpalpable lesions detected by screening and provocative testing) have a 10-year survival rate of 95%.

Stage II medullary cancers (tumors > 1 cm but < 4 cm) are associated with a survival rate of 50%-90% at 10 years. Patients who have lymph node involvement (stage III disease) have a 10-year survival rate of 15%-50%.

When there are distant metastases (stage IV), the long-term survival rate is < 15%. In patients with metastatic medullary thyroid cancer, the disease often progresses at a very slow rate, and patients may remain alive with disease for many years.

Anaplastic thyroid cancer does not have a generally accepted staging system, and all patients are classified as having stage IV disease. Anaplastic carcinoma is highly malignant and has a poor 5-year survival rate (0%-25%). Most patients die of uncontrolled local disease within several months of diagnosis.

Treatment

As most thyroid nodules are not malignant, it is important to differentiate malignant from benign lesions to determine which patients should undergo surgery. If the cytologic result from FNA indicates that the nodule is benign, which is the case most of the time, the nodule can be safely followed. The patient may be placed on thyroxine therapy to suppress thyroid-stimulating hormone (TSH) and reevaluated in 6 months. Adequate suppression is considered to be a TSH level of 0.2-0.4 μU/mL for 6 months.

SURGERY

Malignant or indeterminate cytologic features are the main indications for surgery.

Malignant nodule

Differentiated thyroid cancer If the cytologic result shows a malignant lesion, thyroidectomy should be performed. There is significant debate in the literature regarding the extent of thyroid surgery for primary tumors confined to one lobe. The surgical options include total lobectomy, total lobectomy with contralateral subtotal lobectomy (subtotal thyroidectomy), or total thyroidectomy. The decision about which procedure to perform should be based on the risk of local recurrence and the anticipated use of radioactive iodine (see "Radioactive I-131" section).

Most authorities agree that a good-risk patient (age < 45 years) with a 1-cm or smaller papillary thyroid cancer should undergo ipsilateral total lobectomy alone. Most experts also agree that total thyroidectomy (or at least subtotal thyroidectomy) is appropriate for high-risk patients with high-risk tumors. Intermediate-risk patients are treated with total lobectomy alone or total (or subtotal) thyroidectomy plus postoperative radioactive iodine.

The necks of all patients should be palpated intraoperatively. If positive nodes are found, a regional lymph node dissection should be performed.

Medullary carcinoma Patients with medullary thyroid cancer should be treated with total thyroidectomy and a sampling of the regional nodes. If there is involvement of the nodes, a modified neck dissection should be performed (see "Lymph node dissection" section). If the cancer is confined to the thyroid gland, the patient is usually cured. Postoperative adjuvant external irradiation may be used in certain circumstances (see "External radiation therapy" section).

Anaplastic carcinoma A tracheostomy often is required in patients with anaplastic thyroid cancer because of compression of the trachea. If the tumor is confined to the local area, total thyroidectomy may be indicated to reduce local symptoms produced by the tumor mass. Radiation therapy is used to improve locoregional control, often together with radiosensitizing chemotherapy.

Indeterminate or suspicious nodule

The nodule that yields indeterminate or suspicious cytologic results and is cold on thyroid scanning should be removed for histologic evaluation. The initial operation performed in most patients should be total lobectomy, which entails removal of the suspicious nodule, hemithyroid, and isthmus. The specimen can be sent for frozen-section analysis during surgery. If the diagnosis is a colloid nodule, no further resection of the thyroid is required.

Follicular lesion If frozen-section biopsy results indicate a follicular lesion in a patient who is a candidate for total thyroidectomy, and a decision cannot be made as to whether the lesion is benign or malignant, two options are available: (1) stop and wait for final confirmation of the diagnosis, which may require a future operation; or (2) proceed with subtotal or total thyroidectomy, which obviates the need for a later operation.

Hürthle cell carcinoma If the nodule is diagnosed as a Hürthle cell carcinoma, total thyroidectomy is generally recommended for all large (>4 cm) invasive lesions. Small lesions can be managed with total lobectomy. However, controversy remains over the optimal treatment approach for this cancer.

Lymph node dissection

Therapeutic dissection Therapeutic central neck node dissection should be performed for medullary carcinomas and other thyroid neoplasms with nodal involvement. The dissection should include all of the lymphatic tissue in the pretracheal area and along the recurrent laryngeal nerve and anterior mediastinum. If there are clinically palpable nodes in the lateral neck, a modified neck dissection is performed.

Prophylactic dissection There is no evidence that performing prophylactic neck dissection improves survival. Therefore, aside from medullary thyroid cancer patients, who have a high incidence of involved nodes, only therapeutic neck dissection is indicated.

Removal of individual abnormal nodes ("berry picking") is not advised when lateral neck nodes are palpable, because of the likelihood of missing involved nodes and disrupting involved lymphatic channels.

Metastatic or recurrent disease

Survival rates from the time of the discovery of metastases (lung and bone) from differentiated thyroid cancer are less favorable than those associated with local recurrence (5-year survival rates of 38% and 50%, respectively). Survival also depends on whether the metastatic lesions take up I-131. Fortunately, most lesions take up radioactivity and can be treated with I-131.

Surgery, with or without I-131 ablation (discussed below), can be useful for controlling localized sites of recurrence. Approximately half of patients who undergo surgery for recurrent disease can be rendered free of disease with a second operation.

Iodine-123 (I-123) may also be used in the postoperative setting. In a series of 14 patients, I-123 showed an improved quality of imaging compared with I-131 *(Mandel SJ, Shankar LK, Bernard F, et al: Clin Nucl Med 26:6-9, 2001).*

RADIOACTIVE I-131

Uses in papillary or follicular carcinoma

There are two basic uses for I-131 in patients diagnosed with papillary or follicular thyroid

carcinoma: ablation of normal residual thyroid tissue after thyroid surgery and treatment of thyroid cancer, either residual disease in the neck or metastasis to other sites in the body. It should be emphasized that patients with medullary, anaplastic, and most Hürthle cell cancers do not benefit from I-131 therapy.

Postoperative ablation of residual thyroid tissue should be considered in high-risk patients and patients with high-risk tumors. Ablation of residual normal thyroid tissue allows for the use of I-131 scans to monitor for future recurrence, possibly destroys microscopic foci of metastatic cancer within the remnant, and improves the accuracy of thyroglobulin monitoring.

Ablation must also be accomplished in patients with regional or metastatic disease prior to the use of I-131 for treatment, as the normal thyroid tissue will preferentially take up iodine compared to the cancer.

Following surgery, the patient should not be given thyroid hormone replacement. The TSH level should be determined approximately 4-6 weeks after surgery; in patients who underwent total or subtotal thyroidectomy, TSH levels will generally be > 50 μU/mL. A postoperative iodine scan can then be performed. If this scan documents residual thyroid tissue, an ablative dose of I-131 should be given. The patient should be advised not to undergo any radiographic studies with iodine during ablation therapy and to avoid seafood and vitamins or cough syrups containing iodine. Patients are prepared wtih a specific diet prior to the I-131 therapy.

Iodine-131 dose In general, a dose of 75-100 mCi will ablate residual thyroid tissue within 6 months following ingestion. In some patients, it may take up to 1 year for complete ablation to occur. Patients should be monitored following ablation, and when they become hypothyroid, hormone replacement therapy should be given until they are clinically euthyroid and TSH is suppressed. TSH levels should be < 0.1 μU/mL.

Berg et al have reported on the use of recombinant TSH for treatment with I-131 in patients who could not be withdrawn from thyroid replacement *(Berg G, Lindstedt G, Suurkula M, et al: J Endocrinol Invest 25:44-52, 2002).*

Follow-up I-131 scan Approximately 6-12 months after ablation of the thyroid remnant, a follow-up I-131 scan should be performed. Recombinant human thyrotropin (Thyrogen) is now available. Patients may continue on thyroid replacement and receive two doses of thyrotropin prior to I-131 scanning; this approach can prevent the symptoms of hypothyroidism.

As an alternative, the patient may be withdrawn from levothyroxine (T_4) for a minimum of 4 weeks prior to the scan. The patient may be switched to liothyronine (T_3[Cytomel, Triostat]) for their first 2 weeks to decrease the period of hypothyroidism but must remain off T_3 for a minimum of 2

Recombinant TSH-stimulated serum thyroglobulin in patients with undetectable basal levels of thyroglobulin may replace whole-body scanning for follow-up *(Pacini F, Molinaro E, Lipi F, et al: J Endocrinol Metab 86:5686-5690, 2001).*

PET may also be useful in diagnosing and following differentiated thyroid carcinoma *(Larson SM, Robbins R: Semin Roentgenol 37:169-174, 2002).*

weeks prior to I-131 scanning. The TSH level at this time should be > 50 μU/mL to confirm adequate thyroid ablation.

In general, a dose of 2-5 mCi of I-131 is given and the patient is scanned 24-48 hours later. If there is any abnormal uptake of I-131, the patient is presumed to have residual thyroid cancer and should be treated.

Recombinant human TSH is now available and can replace thyroxine withdrawal in selected patients.

Treatment of residual cancer For disease in the tumor bed or lymph nodes, an I-131 dose of 150 mCi is given. For disease in the lungs or bone, the I-131 dose is 200 mCi. Following this therapy, the patient is again put on thyroid hormone replacement and adequate suppression is maintained by monitoring TSH levels.

Follow-up Some clinicians advocate obtaining a repeat scan in 1 year, along with a chest x-ray, and repeating this procedure until a negative scan is obtained. However, the frequency of repeat scans and the dose of I-131 are rather controversial and should be guided by the individual's risk profile.

Following thyroid remnant ablation, serum thyroglobulin measurements are useful in monitoring for recurrence. Since thyroglobulin measurements in a patient receiving thyroid hormone replacement may be suppressed, a negative test may be incorrect ~10% of the time. In general, the presence of disease is accurately predicted by a thyroglobulin value > 5 ng/mL while the patient is in the suppressed state and by a value > 10 ng/mL, in the hypothyroid state. However, measurable disease may not be identified in many patients. Whether they should be treated on the basis of thyroglobulin if I-131 scan is negative is a subject of current debate.

Chest x-rays should continue to be performed at yearly intervals for at least 10 years. Neck ultrasonography is also useful to evaluate locoregional recurrence. Continued monitoring is necessary, as late recurrence can occur. It should be pointed out that certain aggressive tumors may neither be radioactive iodine-avid nor synthesize thyroglobulin. PET scanning may contribute to localization of disease in some cases and may even carry prognostic value.

Side effects and complications of I-131

Acute effects The acute side effects of I-131 therapy include painful swelling of the salivary glands and nausea. Ibuprofen or other pain relievers are usually used to decrease salivary gland discomfort. Nausea may be treated with standard antiemetics.

Rarely, in patients with significant residual thyroid tissue, radioactive iodine may cause acute thyroiditis due to a rapid release of thyroid hormone. This problem can be treated with steroids and β-blockers.

Patients must also be cautioned not to wear contact lenses for at least 3 weeks following ingestion of I-131, as the tears are radioactive and will contaminate the lenses and possibly lead to corneal ulceration.

Bone marrow suppression and leukemia are potential long-term complications of I-131 therapy but are poorly documented and appear to be extremely rare. Patients should have a CBC count performed prior to ingestion of an I-131 dose to ensure adequate bone marrow reserve. They should also have yearly blood counts. Leukemia occurs rarely with doses of I-131 < 1,000 mCi.

Pulmonary fibrosis may be seen in patients with pulmonary metastases from papillary or follicular thyroid cancer who are treated with I-131. Those with a miliary or micronodular pattern are at greater risk, as a portion of normal lung around each lesion may receive radiation, leading to diffuse fibrosis.

Effects on fertility Recent data have documented an increase in follicle-stimulating hormone (FSH) levels in one-third of male patients treated with I-131. Changes in FSH after one or two doses of I-131 are generally transitory, but repeated doses may lead to lasting damage to the germinal epithelium.

The effects of I-131 on female fertility have been investigated. A recently published article showed no significant difference in the fertility rate in women receiving radioactive iodine. However, it is generally recommended to avoid pregnancy for 1 year after therapeutic I-131 administration.

No ill effects have been noted in the offspring of treated patients.

EXTERNAL RADIATION THERAPY

Papillary or follicular thyroid cancer

There are a number of indications for external irradiation of papillary or follicular thyroid carcinoma. Surgery followed by radioactive iodine may be used for disease that extends beyond the capsule. However, if all gross disease cannot be resected, or if residual disease is not radioactive iodine-avid, external irradiation is used as part of the initial approach for locally advanced disease in older patients.

Unresectable disease External irradiation is useful for unresectable disease extending into the connective tissue, trachea, esophagus, great vessels, and anterior mediastinum. For unresected disease, doses of 6,000-6,500 cGy are recommended. The patient should then undergo I-131 scanning, and, if uptake is detected, a dose of I-131 should be administered.

Recurrence after resection External irradiation may also be used after resection of recurrent papillary or follicular carcinoma that no longer shows uptake of I-131. In this situation, doses of 5,000-6,000 cGy are delivered to the tumor bed to prevent local recurrence. Multiple-field techniques and extensive treatment planning are necessary in order to deliver high doses to the target volume without the risk of significant complications.

Palliation of bone metastases External radiation therapy is useful in relieving pain from bone metastasis. If the metastasis shows evidence of I-131 uptake, the patient should be given a therapeutic dose of I-131 followed by local external radiation therapy to the lesion of up to 4,000-5,000 cGy. Ten thyroid cancer patients with bone metastasis were treated with monthly pamidronate (Aredia). The patients experienced a significant decrease in bone pain and improved quality of life.

Anaplastic thyroid carcinoma

Anaplastic carcinoma of the thyroid is an exceptionally aggressive disease. It often presents as a rapidly expanding mass in the neck and may not be completely resected. External irradiation to full dose (6,000-6,500 cGy) may slow the progress of this disease but rarely controls it.

Chemoradiation therapy There are reports of the use of accelerated fractionation regimens of external irradiation (160 cGy twice daily to 5,700 cGy) with weekly doxorubicin in patients with anaplastic thyroid cancer, as well as reports of the combination of doxorubicin and cisplatin (Platinol) with external irradiation. These regimens have improved local control but at the expense of increased toxicity. Unfortunately, the majority of patients die of progressive disease.

Medullary thyroid carcinoma

External irradiation has been used for medullary thyroid cancer in the postoperative setting. Indications include positive surgical margins, gross residual disease, or extensive lymph node metastasis. The recommended dose is 5,000 cGy in 5 weeks.

ROLE OF MEDICAL THERAPY

Differentiated thyroid cancer

Thyroid hormone replacement As mentioned above, thyroid hormone replacement is used to suppress TSH in most patients with differentiated thyroid cancer after surgery and prior to I-131 scanning and (as appropriate) treatment.

Systemic chemotherapy is used for widespread disease, although regimens have not been very effective to date.

Medullary thyroid carcinoma

In patients with medullary thyroid carcinoma, the usual treatment is surgery. In patients with familial medullary carcinoma who have a coexisting pheochromocytoma, appropriate control of catecholamine hypersecretion should precede thyroid surgery.

Anaplastic thyroid carcinoma

As mentioned above, the usual treatment for patients with anaplastic thyroid cancer is surgery. Like radiotherapy, chemotherapy is an important alternative approach, but further evaluation is needed to optimize its effectiveness.

PARATHYROID CARCINOMA

Parathyroid carcinoma is a rare cause of hypercalcemia, accounting for < 2% of cases with primary hyperparathyroidism.

Epidemiology and etiology

The disease presents in midlife and occurs with similar frequency in both genders. The etiology of parathyroid carcinoma is obscure; an association with prior neck irradiation is not apparent. Treatment of parathyroid carcinoma is primarily surgical.

Signs and symptoms

Most patients with parathyroid cancer have symptomatic moderate to severe hypercalcemia (mean serum calcium level, 15 mg/dL) and very high parathyroid hormone levels. They often present with a palpable neck mass. Unlike benign hyperparathyroidism, renal and bone abnormalities are relatively common in patients with parathyroid cancer.

Rarely, nonfunctioning tumors may present as neck masses; their clinical course is similar to that of functioning tumors. Clinical concern about parathyroid cancer should be raised in the presence of a palpable neck mass and severe hypercalcemia, recurrent hyperparathyroidism, or associated vocal cord paralysis.

Pathology

The principal features of parathyroid cancer include a trabecular pattern, mitotic figures, thick fibrous bands, and capsular or vascular invasion of disease. Other important features include lymphatic or hematogenous metastases and histologic evidence of tumor infiltration into the surrounding tissues (including macroscopic adherence or vocal cord paralysis).

Although cytologic evidence of mitoses is necessary to establish the diagnosis of carcinoma, mitotic activity alone is an unreliable indicator of malignancy. The only reliable microscopic finding of malignancy is invasion of surrounding structures or metastasis to lymph nodes or other organs.

Treatment

Surgical treatment of primary hyperparathyroidism

The diagnosis of parathyroid carcinoma is sometimes made during surgical exploration for primary hyperparathyroidism. Most surgeons advocate identification of all four parathyroid glands. In most cases, the upper glands can be found on the posterior aspect of the upper third of the thyroid lobe, just cephalad to the inferior thyroid artery and adjacent to the recurrent laryngeal nerve as it enters the larynx.

The inferior parathyroid glands are more variable in location. Most are found on the posterior or lateral aspect of the lower pole of the thyroid gland, but the inferior parathyroid glands may be ectopically placed in the superior or true mediastinum, often within the thymus.

The inferior and, less commonly, superior glands can be located in an ectopic location in the upper or lateral neck, adjacent to the esophagus, or within the carotid sheath.

Surgical exploration for primary hyperparathyroidism Most cases of primary hyperparathyroidism are caused by a single hyperfunctioning parathyroid adenoma. If the surgeon finds one (or occasionally two) enlarged abnormal gland(s) and the remaining glands are normal, the enlarged gland should be removed.

If four enlarged glands are found, indicating the rare case of primary parathyroid hyperplasia, subtotal parathyroidectomy including 3.5 glands should be performed. Consideration should be given to transplanting the remaining gland remnant to an ectopic location that would be easily accessible to the surgeon if hyperparathyroidism recurs. Scintigraphic intraoperative tumor localization and intraoperative rapid parathyroid hormone determinations are available to improve the precision of surgery and shorten its duration.

If only normal glands are found at exploration, a missed adenoma in an ectopic location should be suspected. Thorough intraoperative neck and superior mediastinal exploration should be performed, and if the missing gland cannot be found, thymectomy and hemithyroidectomy should be performed to exclude an intrathymic or intrathyroidal adenoma. Localization studies, including CT/MRI or radionuclide imaging, should precede reexploration for a missed adenoma.

If parathyroid carcinoma is suspected based on the severity of hyperparathyroidism or invasion of surrounding tissues by a firm parathyroid, aggressive wide excision is indicated. This procedure should include ipsilateral thyroidectomy and en bloc excision of surrounding tissues as necessary.

Intraoperative parathyroid level measurement is under evaluation in some centers and, if established, may alter surgical practice.

Patterns of recurrence of cancer The average time from initial surgery to the first recurrence of cancer is approximately 3 years but may be as long as 10 years. The thyroid gland is the usual site of involvement, followed by the recurrent nerve, strap muscles, esophagus, and trachea.

Distant metastases can be present at the time of initial surgery, or local spread to contiguous structures in the neck may be followed subsequently by distant metastases to the lungs, bone, and liver.

Only 50% of patients with parathyroid carcinoma are still alive 5 years after diagnosis; death usually results from complications of the hypercalcemia rather than from the tumor burden.

Treatment of isolated metastases Isolated metastases should be aggressively resected to enhance survival and control hypercalcemia.

Medical therapy

Morbidity and mortality are generally caused by the effects of unremitting hypercalcemia rather than tumor growth. Medical treatment provides temporary palliation of hypercalcemia. Drugs used include calcitonin (Calcimar, Miacalcin), 4-8 IU/kg q6-12h; mithramycin (plicamycin [Mithracin]), 25 μg/kg q4-6d; gallium nitrate (Ganite), 100-200 mg/m^2/d IV for 5 days; and bisphosphonates, such as pamidronate (60-80 mg q4-6d) or zoledronic acid (Zometa).

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CHAPTER 6

Small-cell lung cancer

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Lung cancer has been the leading cause of cancer death in American men for years, and since 1988, it also has become the number-one cause of cancer death in American women. It is estimated that, in the year 2003, 171,900 new cases of lung cancer will be diagnosed, and 157,200 deaths due to this cancer will occur.

Lung cancer appears to develop from a stem cell that can differentiate along multiple lines. Although it is not uncommon to find multiple cell types within a single lung tumor, one type usually predominates. Based on therapeutic approach, there are two major subdivisions of lung cancer: small-cell carcinoma (SCLC), for which chemotherapy is the primary treatment, and non–small-cell carcinoma (NSCLC), which, in its early stages (I and II) is treated primarily with surgery. Approximately 20% of all lung cancers are SCLC.

This chapter will focus on the epidemiology, etiology, screening and prevention, and diagnosis of lung cancer in general. In addition, chapter 6 provides information on the staging and prognosis, pathology and pathophysiology, and treatment of SCLC. Chapter 7 covers NSCLC, including carcinoid tumors of the lungs and mesothelioma, and discusses staging evaluation, as well as the pulmonary assessment of lung cancer patients and the follow-up of long-term survivors.

Epidemiology

Gender From 1995 to 1999, there were 86 cases of lung cancer per 100,000 men. Although the incidence of lung cancer had been rising in women, the rate of increase has begun to slow recently. From 1995 to 1999, there were 57 cases of lung cancer per 100,000 women.

Age Although the age at which lung cancer patients are diagnosed varies widely, the median age at diagnosis is approximately 70 years.

Race In the United States, the highest incidence of lung cancer is found in Hawaiians and African-Americans.

Geography There are geographic variations in the incidence of lung cancer, with the highest rates worldwide observed in Scotland and Wales and the highest rates in the United States found in northern urban areas and along the southern coast from Texas to Florida.

Survival The overall 5-year survival rate for lung cancer is 15%.

Etiology and risk factors

Cigarette smoking Approximately 87% of all cases of lung cancer are related to cigarette smoking. There is a relatively strong dose-response relationship between cigarette smoking and the development of this cancer. An individual who smokes one pack of cigarettes daily has a 20-fold increased risk of lung cancer compared to a nonsmoker. The greater the number of cigarettes smoked on a daily basis and the greater the number of years of smoking, the greater is the risk of lung cancer.

Overall, there has been a decrease in the incidence of cigarette smoking from 1974 through 1992. Smoking cessation decreases the risk of lung cancer, but a significant decrease in risk does not occur until approximately 5 years after stopping. In addition, the risk of lung cancer in former smokers remains higher than the risk in nonsmokers for at least 25 years. The benefit of smoking cessation is greater if it occurs at a younger age.

Recently, Videtic et al assessed the impact of smoking status during concurrent chemoradiation for limited-stage SCLC. In a retrospective analysis, they found a significantly decreased survival among those who continued to smoke (5-year survival,4%) vs those who were nonsmokers (5-year survival, 9%; $P = .002$), despite the fact that smokers had no more toxicity breaks than nonsmokers. This study further underscored the importance of smoking cessation *(Videtic G, Stitt L: Proc Am Soc Clin Oncol [abstract] 21:295a, 2002).*

Smoking cessation is difficult. Recent data have suggested that certain individuals have an increased risk of addiction to nicotine based on a variety of hereditary factors. Nevertheless, millions of former smokers have quit successfully. Smoking cessation programs that address both physical withdrawal from nicotine and psychological dependence appear to be more effective than either of these approaches alone. In addition, continued efforts are needed to prevent adolescents and preadolescents from beginning to smoke or to encourage them to quit after a brief period of experimentation.

Several cancer centers have recently reported that more than half of their patients with newly diagnosed lung cancer are former smokers, having quit more than a year before diagnosis. Healthy ex-smokers represent a large group of individuals who may benefit from effective tools for early detection and/or chemoprevention of lung cancer.

Secondhand smoke Not only is smoking risky for those who smoke, but it also poses a hazard to nonsmokers who either live or work with smokers. It is estimated that approximately 3,000 lung cancer deaths per year in the United States are due to secondhand smoke. Individuals who live in a household with a smoker have a 30% increase in the incidence of lung cancer compared to nonsmokers who do not live in such an environment.

Asbestos exposure is another risk factor for lung cancer. Cigarette smokers who are exposed to asbestos develop lung cancer at an extremely high rate. Exposure to asbestos is also a major risk factor for the development of mesothelioma (see discussion of this cancer later in this chapter).

Radioactive dust and radon exposure Uranium miners who have been exposed to radioactive dust and radon gas also have an increased incidence of lung cancer. Although there has been some controversy about the risk posed by exposure to residential radon gas, a recent study conducted in Sweden showed an increased incidence of lung cancer in individuals who were exposed to a high level of radon in their homes.

Screening and prevention

Screening

Currently, screening for lung cancer among asymptomatic individuals at elevated risk due to smoking history or occupational exposures is not recommended by any organization. However, the potential to screen for lung cancer has recently received renewed interest due to the superior performance of low-dose helical CT compared with chest radiography in detecting small lesions. Although there is insufficient evidence to establish policy related to routine screening for lung cancer with spiral CT, there is a growing trend toward promoting screening with this new technology to individuals at increased risk for lung cancer.

Three randomized screening trials conducted in the United States in the 1970s failed to show a reduction in lung cancer mortality among the smokers who were screened by sputum cytology and chest x-ray for lung cancer. Despite the fact that these American trials were not designed to evalute chest x-ray as a screening tool, the results led most experts to conclude that screening for lung cancer was not worthwhile. In addition, most investigators recommended that research efforts and resources be allocated to the *prevention* of lung cancer. A more recent, randomized, prospective trial from Czechoslovakia showed that screening with a chest x-ray increased the diagnosis of early-stage lung cancer but failed to reduce the mortality from lung cancer.

Numerous studies are currently under way to evaluate chest CT scan for lung cancer screening. Several recent reports from Japan, Germany, and the United States have documented the ability of low-dose spiral CT scans to detect lung cancer at an early stage. Kaneko screened male smokers > 50 years of age. Of the 15 cancers detected by CT scan, only 4 were seen on chest x-ray; 14 of the 15 cancers were stage I, with an average diameter of 1.6 cm. Ohmatsu found 35 lung cancers (0.37% detection rate) with 9,452 CT scans. Of these cancers, 27 were stage IA. These patients had a 3-year survival rate of 83%.

Henschke et al recently reported similar encouraging results of screening with spiral CT scan for the Early Lung Cancer Action Project (ELCAP). Included in the initial report were 1,000 symptom-free volunteers, aged 60 years or older, with at least 10 pack-years of cigarette smoking and no previous cancer who were medically fit to undergo thoracic surgery. Noncalcified pulmonary nodules were detected in 233 participants (23% [95% CI: 21-26]) by low-dose CT at baseline, compared with 68 (7% [95% CI: 5-9]) by chest radiography. Lung

cancer was detected in 27 patients (2.7% [95% CI: 1.8-3.8]) by CT and 7 patients (0.7% [95% CI: 0.3-1.3]) by chest radiography, respectively.

Of the 27 CT-detected cancers, 26 were resectable. Stage I cancers were diagnosed in 23 of 27 patients (85%) by CT and 4 of 7 patients (57%) by chest radiography. In addition, low-dose CT detected four more nonparenchymal cases of lung cancer: two with endobronchial lesions and two in the mediastinum. These cases show an added benefit of low-dose CT over chest radiography, although the data were not included in the analysis (the study primarily focused on malignant disease in noncalcified pulmonary nodules detected by low-dose CT or radiography).

It remains to be seen, however, whether lung cancer screening with low-dose spiral CT will reduce the lung cancer mortality of the study population or only improve the 5-year survival rate of the patients diagnosed with lung cancer.

Two prospective randomized controlled trials currently are under way to evaluate the efficacy of lung cancer screening. The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) has randomized men and women to receive annual chest x-ray vs usual care. In this study, eligibility was not based on risk of lung cancer because given the large size of the study (> 100,000 participants), it was expected that there would be appreciable numbers of current and former smokers among the participants

More recently, and based on growing evidence that spiral CT may truly provide for a successful early detection strategy, the National Cancer Institute (NCI) launched the National Lung Screening Trial (NLST) in September 2002. The trial enrolled 50,000 current and former smokers (aged 55-74) who will be randomized to join an experimental group who will receive annual spiral CT, or a control group (receiving annual chest x-rays).

The lack of demonstrated benefit for the older screening approaches should not be misinterpreted as nihilism about the early detection of patients with lung cancer. Individuals at risk (current and former smokers) who present with symptoms consistent with lung cancer deserve appropriate evaluation. The lack of resolution of radiographic abnormalities on a chest x-ray obtained after the completion of empiric antibiotic therapy for pneumonia should prompt further evaluation for possible lung cancer. Failure to do so constitutes inappropriate therapeutic nihilism.

Chemoprevention

Second primary lung tumors develop at a rate of 1%-3% annually for the first 5 years following resection of stage I lung cancer. The retinoid 13-*cis*-retinoic acid (isotretinoin) has reduced the incidence of second primary cancer in head and neck cancer patients.

The intergroup randomized trial that assessed the ability of 13-*cis*-retinoic acid to prevent the occurrence of a second primary cancer in patients with completely resected stage I lung cancer has completed accrual (1,486 patients have been enrolled). The early findings have demonstrated a higher-than-expected

recurrence rate in patients with early-stage lung cancer who received 13 *cis*-retinoic acid and continued to smoke. Also, there was no reduction in second primary tumors in the 13-*cis*-retinoic acid-treated group.

Educational programs Although the information from the intergroup randomized chemoprevention study is being collected, it is important to continue educational efforts to prevent adolescents from starting to smoke cigarettes and to advocate smoking cessation in active smokers. Some experts believe that educational programs must begin during childhood, probably between the ages of 6 and 10 years.

Signs and symptoms

The clinical manifestations of lung cancer depend on the location and extent of the tumor. In patients who have localized disease, the most common symptoms are related to obstruction of major airways, infiltration of lung parenchyma, and invasion of surrounding structures, including the chest wall, major blood vessels, and viscera.

Cough is a major manifestation of lung cancer. However, it is important to remember that the majority of lung cancer patients are current or former smokers and may have a cough related to chronic irritation of the upper and/or lower airways from cigarette smoke. Therefore, smokers should be asked whether there has been a change in their cough, such as an increase in frequency or severity.

Dyspnea and hemoptysis Increasing dyspnea and hemoptysis may be signs of lung cancer.

Pneumonia Postobstructive pneumonia secondary to partial or complete bronchial obstruction occurs relatively frequently in association with lung cancer. It is important to obtain repeat chest x-rays in adults who have been treated for pneumonia to be certain that the radiographic abnormalities have cleared completely.

Pleural effusion Lung cancer may spread to the pleural surface, resulting in pleural effusion and increased dyspnea.

Chest pain Approximately 5% of lung tumors invade the chest wall. The resultant pain is a better predictor of chest wall invasion than are chest CT findings. An individual who complains of persistent chest pain should have a chest x-ray to exclude the presence of peripheral lung cancer that has invaded the chest wall.

Shoulder and arm pain Apical tumors that infiltrate surrounding structures (also called Pancoast's tumors) produce shoulder and/or arm pain as a result of brachial plexus compression. Tumors in the apical lung segments may be difficult to detect on a routine chest x-ray; therefore, a person who complains of persistent shoulder pain, particularly with signs of neurologic involvement, should have a CT scan of the chest to look for an apical tumor. It is also important to examine the lung apex in bone films obtained to evaluate shoulder pain.

Horner's syndrome Invasion of the sympathetic ganglion by an apical lung tumor causes Horner's syndrome (ptosis, myosis, and ipsilateral anhyidrosis).

Hoarseness secondary to vocal cord paresis or paralysis occurs when tumors and lymph node metastases compress the recurrent laryngeal nerve. This situation is more common on the left side, where the recurrent laryngeal nerve passes under the aortic arch, but it may also occur with high lesions on the right side of the mediastinum.

Other symptoms of tumor compression Lung tumors may also cause dysphagia by compression or invasion of the esophagus or superior vena cava syndrome by compression or invasion of this vascular structure.

Some tumors may result in wheezing or stridor secondary to compression or invasion of the trachea and may also cause signs of cardiac tamponade secondary to involvement of the pericardial surface and subsequent accumulation of pericardial fluid.

Signs and symptoms of metastatic disease Lung cancer can metastasize to multiple sites, the most common of which are bone, liver, brain, lungs (contralateral or ipsilateral), and adrenal glands.

Lung cancer patients who have brain metastases may complain of headaches or specific neurologic symptoms, or family members may notice a decrease in the patient's mental acuity. Also, metastatic lung cancer may cause spinal cord compression, resulting in a characteristic sequence of symptoms: pain, followed by motor dysfunction, followed by sensory symptoms. The patient may have any or all of these symptoms.

It is important to note that patients who complain of bandlike pain encircling one or both sides of the trunk may have spinal cord compression. In addition, coughing and sneezing may cause significant exacerbation of pain from spinal cord compression.

Bone x-rays and/or a bone scan are warranted in lung cancer patients who complain of persistent pain in the trunk or extremities. MRI of the spine is the most effective way to evaluate suspected spinal cord compression.

Lung cancer frequently metastasizes to the adrenal glands, and occasionally, this may cause flank pain. However, in general, adrenal metastases are asymptomatic. It is relatively uncommon for adrenal metastases to result in adrenal insufficiency.

Systemic paraneoplastic symptoms Lung cancer is commonly associated with systemic manifestations, including weight loss (with or without anorexia). In addition, patients frequently complain of fatigue and generalized weakness. SCLC is associated with hormone production, which causes endocrine syndromes in a subset of patients, such as SIADH (syndrome of inappropriate antidiuretic hormone secretion) and via secretion of ACTH (adrenocorticotropic hormone) hypercortisolism.

Specific neurologic syndromes, such as Lambert-Eaton syndrome (see chapter 47), cortical cerebellar degeneration, and peripheral neuropathy, may occur in lung cancer patients, but they are relatively rare.

Clubbing Although clubbing may occur in a variety of conditions, it is important for the clinician to evaluate a patient's hands, because if clubbing is noted, obtaining a chest x-ray may result in the early diagnosis of lung cancer.

Hypertrophic osteoarthropathy A relatively small percentage of patients with lung cancer may present with symptomatic hypertrophic osteoarthropathy. In this syndrome, periosteal inflammation results in pain in affected areas, most commonly the ankles and knees.

Carcinoid syndrome is extremely uncommon in patients who have a bronchial carcinoid tumor. Most of these patients are asymptomatic (tumors are found by x-ray), and a few have cough from an endobronchial lesion.

Staging and prognosis

Unlike NSCLC, in which the TNM staging system is used for all patients, the TNM staging classification is generally not utilized in SCLC, as it does not predict well for survival. Rather, SCLC is usually described as either limited (M0) or extensive (M1), although these general terms are inadequate when evaluating the role of surgery. For surgical staging, the TNM system is usually used (see chapter 7, Table 1). Patients with SCLC who have stages I-III disease, excluding those with a malignant pleural effusion, are classified as having limited disease. These patients constitute approximately one-third of all SCLC patients. The remaining SCLC patients fall into the extensive-disease category, which includes any patient with a malignant pleural effusion or any site of distant disease—brain, liver, adrenal gland, bone, bone marrow, and others.

The staging of lung cancer must be conducted in a methodical and detailed manner in order to permit appropriate therapeutic recommendations and to allow comparison of treatment results from different institutions.

Stage is commonly reported as either clinical or pathologic. The former is based on noninvasive (or minimally invasive) tests, whereas the latter is based on tissue obtained during surgery (see chapter 7).

The most important prognostic factor in lung cancer is the stage of disease. Within a given disease stage, the next most important prognostic factors are performance status and recent weight loss. The two scales used to define performance status are the Eastern Cooperative Oncology Group (ECOG) performance status system and the Karnofsky system (see Appendix 1). In short, patients who are ambulatory have a significantly longer survival than those who are nonambulatory. Also, patients who have lost ≥ 5% of body weight during the preceding 3-6 months have a worse prognosis.

Pathology and pathophysiology

SCLC tumors tend to be large central masses with extensive mediastinal lymph node metastases and also have a high likelihood of spreading to distant sites; two-thirds of patients have detectable distant metastases at the time of diagnosis. SCLC has characteristic electron microscopic features that include the presence of neurosecretory granules and neurofilaments.

These tumors contain enzymes that can decarboxylate amino acids, resulting in biologically active amines, and also promote the synthesis of polypeptide hormones, such as antidiuretic hormone and ACTH. Overproduction of polypeptide hormones may result in SIADH, which occurs in approximately 10% of SCLC patients (see chapter 47 for a more extensive discussion of this syndrome), or clinically apparent signs of hypercortisolism, which is relatively rare, occurring in approximately 1% of patients.

Treatment

TREATMENT OF DISEASE LIMITED TO LUNG PARENCHYMA

Surgery

The majority of patients with SCLC present with advanced-stage disease. In the 5%-10% of patients whose tumor is limited to the lung parenchyma, very often the diagnosis is established only after the lung mass has been removed. If, however, the histology has been determined by bronchoscopic biopsy or fine-needle aspiration and there is no evidence of metastatic disease following extensive scanning, examination of the bone marrow, and biopsy of the mediastinal lymph nodes, resection should be performed. Adjuvant chemotherapy is recommended because of the high likelihood of the development of distant metastases following surgery.

The surgical approach in SCLC is similar to that used in NSCLC: A lobectomy or pneumonectomy should be followed by a thorough mediastinal lymph node dissection. Tumor resection in SCLC should be limited to patients who have no evidence of mediastinal or supraclavicular lymph node metastases. Recent data suggest that patients with SCLC, presenting as a solitary pulmonary nodule and proven pathologically to be stage I, have a 5-year survival rate of ~70% when resected and given adjuvant chemotherapy.

TREATMENT OF DISEASE LIMITED TO THE THORAX

As mentioned above, approximately one-third of SCLC patients present with disease that is limited to the thorax and can be encompassed within a tolerable radiation portal. In early studies in which either radiation therapy or surgery alone was used to treat such patients, median survival was only 3-4 months, and the 5-year survival rate was in the range of 1%-2%. The reason for the failure of these therapies was rapid appearance of distant metastases.

Chemotherapy

During the 1970s, it became apparent that SCLC was relatively sensitive to chemotherapy. Various combination chemotherapy regimens were used to treat limited SCLC. Although none of the regimens was clearly superior, median survival was approximately 12 months, and the 2-year survival rate was approximately 10%-15%.

It appears that maintenance chemotherapy adds little to survival in patients with limited SCLC.

Outcomes for patients with limited-stage SCLC have improved significantly over the past 20 years. In an analysis of phase III trials during this time period, median survival was 12 months in the control arm in 26 phase III studies initiated between 1972 and 1981 compared with 17 months in studies between1982 and 1992 ($P < .001$). Five studies demonstrated a statistically significant improvement in survival in the experimental arm compared with the control arm. Interestingly, all 5 studies involved some aspect of thoracic RT (3 trials compared chemotherapy alone vs chemoradiation; 1 compared early with late radiation therapy; and 1 compared daily vs twice-daily thoracic RT). Similarly, data from the Surveillance, Epidemiology, and End Results (SEER) database demonstrate that the 5-year survival rate has more than doubled from 1973 to 1996 (5.2% vs 12.2%, $P = .0001$) *(Janne PA, Freidlin B, Saxman S, et al: Proc Am Soc Clin Oncol [abstract] 20:317a, 2001).*

Chemotherapy plus thoracic irradiation

One of the major advances in treating SCLC in the past 15 years is the recognition of the value of early and concurrent thoracic chemoradiation therapy. This advance was clearly facilitated by the increase in therapeutic index when etoposide/cisplatin chemotherapy is given with thoracic irradiation, as opposed to older anthracycline or alkylator-based regimens. Although the major impact from this approach is improved locoregional control, there are also hints from randomized trials that early control of disease in the chest can also reduce the risk of distant metastasis.

An intergroup trial directly compared once-daily with twice-daily fractionation (45 Gy/25 fractions/5 weeks vs 45 Gy/30 fractions/3 weeks) given at the beginning of concurrent chemoradiation therapy with cisplatin (Platinol) and etoposide (PE). Initial analysis showed excellent overall results, with median survival for all patients of 20 months and a 40% survival rate to 2 years. With a minimum follow-up of 5 years, survival was significantly better in the twice-daily than in the once-daily irradiation group (26% vs 16%). The only difference in toxicity was a temporary increase in grade 3 esophagitis in patients receiving twice-daily radiation therapy.

A randomized trial of concurrent vs sequential thoracic radiotherapy in combination with PE in over 200 patients with limited-stage SCLC demonstrated a benefit to concurrent therapy, with median survival of 27.0 months (30%; concurrent arm) vs 19.7 months (20%; sequential arm, $P = .097$). Thoracic radiation therapy consisted of 45 Gy over 3 weeks, starting either with the first cycle of PE in the concurrent arm or after the fourth cycle in the sequential arm *(Takada M, Fukuoka M, Kawahara M, et al: J Clin Oncol 20:3054-3060, 2002).*

Current recommendations Although important questions remain as to the optimal radiation doses, volumes, and timing with regard to chemotherapy, a reasonable present standard is to deliver thoracic irradiation concurrently with PE chemotherapy (cisplatin

[60 mg/m^2 IV day 1] and etoposide [120 mg/m^2 IV days 1-3]). An attempt is made to integrate thoracic irradiation during cycle one or two. Hyperfractionated accelerated fractionation should be considered, given the results of the intergroup 0096 trial. The data extant do not indicate that chemotherapy beyond four cycles has a favorable impact on long-term outcome.

Irradiation can be incorporated sequentially to chemotherapy; however, this approach appears to be inferior to early concurrent therapy and should be reserved for use in those for whom concurrent approaches are predicted to be excessively toxic.

Results of an intergroup trial indicate that radiation therapy strategies that increase biological dose can improve local control and survival. Further exploration of accelerated fractionation or of conventional doses $>$ 45 Gy is warranted and is currently being investigated in prospective trials.

Recently, Movsas et al reported the results of the first Patterns of Care Study (PCS) for lung cancer in the United States. This study was conducted to determine the national patterns of radiotherapy practice in patients treated for nonmetastatic lung cancer in 1998-1999. As supported by clinical trials, patients with limited-stage SCLC received chemotherapy plus radiotherapy greater than radiotherapy T alone (92% vs 5%; $P < .0001$). However, the median radiotherapy dose was 50 Gy, 80% at 1.8-2.0 Gy per fraction. Only 6% of patients received hyperfractionated (twice-daily) radiotherapy. A total of 22% received prophylactic cranial irradiation (PCI), with a median dose of 30 Gy in 15 fractions. As key studies supporting twice-daily radiotherapy in PCI and NSCLC were published in 1999, the penetration of these trials will be assessed in the next PCS lung survey.

Interestingly, Choi et al recently reported long-term survival data from their phase I trial assessing chemotherapy with either standard daily radiotherapy vs accelerated twice-daily radiotherapy from the Cancer and Leukemia Group B (CALGB) trial CALGB 8837. They previously reported that the maximum tolerated dose was 45 Gy in 30 fractions for twice-daily radiotherapy and $>$ 70 Gy in 35 fractions for once-daily radiotherapy. The 5-year survival estimated (from this phase I trial) for the twice-daily arm was 20%, vs 36% for the once-daily radiotherapy arm. They suggest a phase III randomized trial to compare standard daily radiotherapy (to 70 Gy) vs twice-daily radiotherapy (to 45 Gy).

Although surgical resection is not part of the standard therapy for SCLC, the Japan Clinical Oncology Lung Cancer Study Group reported the results of a phase II trial of postoperative adjuvant cisplatin/etoposide in patients with completely resected stage I-IIIA SCLC. The 5-year survival rates (in a cohort of 62 patients) for pathologic stages I, II, and IIIA SCLC were 69%, 38%, and 40%, respectively.

Prophylactic cranial irradiation

Recognition that patients with SCLC were at high risk for the development of brain metastases led to the suggestion that they be given PCI to prevent the clinical manifestation of previously present but occult CNS disease. The role of PCI has been controversial. Most trials have shown a reduction in CNS relapse rates but little effect on survival. There also has been concern about the contribution of prophylactic irradiation to the late neurologic deterioration seen in some patients with SCLC, although recent studies show neurologic impairment in many patients with SCLC prior to any treatment.

A recent meta-analysis of all randomized trials of PCI in patients with SCLC who achieved a complete or near-complete response to induction chemotherapy (alone or combined with thoracic irradiation) showed a statistically significant improvement in survival in patients treated with PCI (20.7% at 3 years vs 15.3% in those not given PCI). The survival improvement with PCI was seen in all patient subgroups, regardless of age, stage, type of induction treatment, or performance status.

Model calculations from data on patterns of failure in patients achieving a systemic complete response suggest that the greatest gain in survival to be expected with PCI is in the range of 5%. To demonstrate this convincingly would require randomized trials of about 700 patients—substantially larger than trials conducted to date. However, the recent meta-analysis of randomized trials of PCI in SCLC patients achieving complete or near-complete response of systemic disease showed a survival improvement of this magnitude with PCI.

Current recommendations When PCI is to be used, patients should be treated only if they have achieved a complete or near-complete remission of disease outside the CNS. Use of chemotherapeutic agents with known CNS toxicity (eg, methotrexate, procarbazine [Matulane], nitrosoureas) should be avoided, and chemotherapy should not be given during or after irradiation.

Radiation doses for PCI should probably be in the range of 25-30 Gy, with a daily fraction size of 2-2.5 Gy, although recent data suggest that such doses delay and reduce rates of CNS relapse but may not eliminate it; thus, higher doses may warrant exploration. Larger fraction sizes would be expected to produce greater toxicity. Smaller fractions given twice daily may reduce toxicity, and trials of this approach are underway.

TREATMENT OF EXTENSIVE DISEASE

As mentioned above, two-thirds of SCLC patients have extensive disease at diagnosis. Without treatment, median survival in this group of patients is 6-8 weeks. Treatment with combination chemotherapy increases the median survival duration to approximately 8-10 months.

Combination chemotherapy

The combination of cisplatin or carboplatin (Paraplatin)/etoposide (see Table 1 for common dose ranges) is considered the standard of care in the United States at this time. This is primarily based on therapeutic index, as randomized trials have not demonstrated a survival benefit for this combination relative to the older regimen of cyclophosphamide (Cytoxan, Neosar), doxorubicin, and vincristine. The regimen is repeated at 3-week intervals for 4-6 courses. Randomized trials of maintenance chemotherapy, either with other drugs or reduced doses of the induction regimen, show improvement in duration of remission but no impact on overall survival.

Based on promising preliminary survival data, patients with extensive SCLC (aged 70 years or younger) were randomly assigned to receive irinotecan/cisplatin vs etoposide/cisplatin in a phase III trial completed in Japan. Results of this trial indicate a 3.4-month median survival benefit (P = .002). Although the complete response rate was lower, the partial response rate was higher with irinotecan/cisplatin (overall response rates 84% vs 67%, P = .013). The etoposide arm was associated with a high rate of grade 3-4 neutropenia (92% vs 65%), whereas irinotecan therapy induced a 16% incidence of grade 3-4 diarrhea. There was 1 treatment-related death on the etoposide arm (radiation pneumonitis) and 3 on the irinotecan arm (2 with neutropenic sepsis, 1 with hemorrhage from a metastatic tumor). The improvement in median survival seen is provocative, and the study results are being confirmed in an ongoing trial in the United States. If these results are reproduced, irinotecan/cisplatin may become a new standard in the treatment of SCLC. Further study will determine whether this regimen is reasonably tolerated in patients older than age 70 *(Noda K, Nishiwake Y, Kawahara M, et al: N Engl J Med 346:85-91, 2002).*

New agents

A variety of novel agents have been investigated in SCLC. Of these agents, the taxanes and topoisomerase I inhibitors, particularly topotecan (Hycamtin), have demonstrated the greatest efficacy.

Taxanes Because of their novel mechanism of action and clinical activity in other solid tumors, including NSCLC, the taxanes—paclitaxel and docetaxel (Taxotere)—are particularly attractive agents for evaluation in the treatment of SCLC.

Paclitaxel Ettinger et al reported that single-agent paclitaxel produces an overall response rate of 34% in untreated patients with SCLC. This taxane is currently being evaluated in combination with a variety of different agents, including etoposide and cisplatin (or carboplatin), in SCLC patients.

Docetaxel Compared with paclitaxel, docetaxel appears to have a slightly lower response rate of 26% (12 out of 46 patients), even when administered at a dose of 100 mg/m^2, as reported by the Southwest Oncology Group (SWOG). This lower response rate with docetaxel was offset somewhat by the fact that median survival was promising at 9 months, similar to that obtained with combination chemotherapy. Disturbingly, however, median time to disease progression was only 3 months.

Topoisomerase I inhibitors The topoisomerase I inhibitors—topotecan and irinotecan (CPT-11 [Camptosar])—are clearly active in SCLC, with single-agent

TABLE 1: Common chemotherapy regimens for SCLC

Drug/combination	Dose and schedule
Etoposide + cisplatin or carboplatin	
Etoposide	100-120 mg/m^2 IV on days 1-3
Cisplatin	60-75 mg/m^2 IV on day 1
	or
Etoposide	100 mg/m^2 IV on days 1-3
Carboplatin	Area under the curve of 5 IV on day 1
Repeat cycle every 3 weeks	
Irinotecan + cisplatin	
Irinotecan	60 mg/m^2 on days 1, 8, and 15
Cisplatin	60 mg/m^2 IV on day 1
Repeat cycle every 4 weeks for 4 cycles	

Noda K, Nishiwaki Y, Kawahara M, et al: N Engl J Med 346:85–91, 2002.

Table prepared by Ishmael Jaiyesimi, DO

response rates of 40%-60%. Due to their novel mechanism of action, the topoisomerase I inhibitors are currently being tested in patients with recurrent or refractory disease, as many of these patients have been previously exposed to topoisomerase II inhibitors (epipodophyllotoxins/anthracyclines) during the induction phase of therapy. Furthermore, preclinical data suggest that topoisomerase I levels are up-regulated in cells resistant to topoisomerase II inhibitors, via down-regulation of topoisomerase II levels.

Topotecan A randomized, phase III trial compared topotecan vs CAV (cyclophosphamide, doxorubicin [Adriamycin], vincristine) in patients who had a response to initial therapy and a minimum drug-free interval of 60 days. Overall response rates were 24% for topotecan alone vs 18% for CAV ($P > .05$). Time to disease progression and median survival also were similar in the two arms. However, topotecan offered superior palliation for many disease-related symptoms, including dyspnea, fatigue, and hoarseness, and also improved patients' ability to carry out daily taskss. Moreover, topotecan had toxicities similar to those of CAV, with the exception of a slight increase in grade 4 thrombocytopenia.

Irinotecan also has been investigated in recurrent or refractory SCLC in a limited number of patients. Like topotecan and other new agents, irinotecan produced a disappointingly low response rate among patients with SCLC resistant to primary chemotherapy, with only 1 of 27 patients exhibiting a response. In contrast, the response rate to irinotecan among patients with initially sensitive disease that later recurred was 29%.

Data from Japan (see box on page 115) suggest a 4-month overall survival benefit for irinotecan and cisplatin combined as induction therapy for patients

with extensive disease. The data await confirmation; a randomized American trial is ongoing.

Other agents, such as gemcitabine (Gemzar) and vinorelbine (Navelbine), have shown activity in SCLC, but it has been less impressive than that reported for the taxanes and topoisomerase I inhibitors.

Phase II trials of new combinations, such as cisplatin/etoposide/paclitaxel (PET) and topotecan/paclitaxel, have yielded promising median and 2-year survival estimates in patients with extensive disease. Two phase III trials testing PET vs PE have, however, shown only excessive toxicity in the experimental arms without improvement in efficacy. Final data from similar trials with topotecan/paclitaxel are awaited.

Experimental approaches

A variety of experimental approaches have been tested in SCLC. They include high doses of chemotherapy and autologous bone marrow transplantation (BMT), alternating regimens of chemotherapy, and weekly administration of chemotherapy.

High-dose chemotherapy plus BMT Most phase II trials using high doses of chemotherapy plus BMT appear to show no advantage of the high-dose approach over standard doses of chemotherapy.

Alternating chemotherapy regimens have been used in an attempt to overcome drug resistance. In randomized trials, alternating chemotherapy regimens have shown a slight improvement in terms of median survival (4-6 weeks) when compared with a single chemotherapeutic regimen but no improvement in long-term survival.

PALLIATION OF LOCAL AND DISTANT SYMPTOMS

Radiation therapy

Many patients with lung cancer have distressing local symptoms at some point in their disease course. They may arise from airway obstruction by the primary tumor, compression of mediastinal structures by nodal metastases, or metastatic involvement of distant organs. Radiation therapy is quite effective in palliating most local symptoms, as well as symptoms at common metastatic sites, such as bone and brain.

Doses In the United States, most radiation oncologists use doses in the range of 30 Gy in 10 fractions for palliative treatment. Data from the United Kingdom suggest that similar efficacy without greater toxicity may be achieved with more abbreviated schedules, such as 17 Gy in 2 fractions 1 week apart or single fractions of 11 Gy (see Table 4, chapter 7). Such schedules may facilitate the coordination of irradiation and chemotherapy and also reduce patient travel and hospitalization.

Endobronchial irradiation with cobalt-60 or iridium-192 has been used to palliate symptoms arising from partial airway obstruction, including cough, dyspnea, and hemoptysis. The dosimetric advantage of being able to deliver a high radiation dose to the obstructing endobronchial tumor while sparing adjacent normal structures, such as the lungs, spinal cord, and esophagus, has clear appeal, particularly in the patient whose disease has recurred following prior external-beam irradiation. Although good rates of palliation have been reported with endobronchial irradiation, significant complications, including fatal hemoptysis, are seen in 5%-10% of patients. Whether this represents a true treatment complication vs the underlying disease remains unclear.

Other local approaches

Endobronchial irradiation should be considered as only one of several approaches (including laser excision, cryotherapy, and stent placement) that can be used in the management of patients with symptomatic airway obstruction, and management should be individualized. All of these approaches are more suitable for partial rather than complete airway obstruction.

Chemotherapy

Several recent trials have explored the use of chemotherapy to palliate specific symptoms in patients with lung cancer. In general, these trials have found that rates of symptomatic improvement were considerably higher than objective response rates and were not dissimilar to symptomatic response rates with local radiation therapy. Chemotherapy in the newly diagnosed patient is highly palliative for relief of symptoms related to superior vena cava syndrome, obstructive lung disease, and painful bony metastases. In the patient with recurrent disease, irradiation is more commonly associated with symptomatic relief from these localized problems. Radiation therapy remains the standard of care for even chemotherapy-naïve patients with spinal cord compression or symptomatic brain metastasis.

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CHAPTER 7

Non–small-cell lung cancer, mesothelioma, and thymoma

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In the United States, lung cancer has been the leading cause of cancer death in men for years, and since 1988, it has become the number-one cause of cancer death in women. It is estimated that 171,900 new cases of lung cancer will be diagnosed in 2003, and 157,200 deaths due to this disease will occur. This exceeds the combined number of deaths from the second, third, and fourth leading causes of cancer (breast, prostate, and colon cancer, respectively).

Lung cancer appears to develop from a stem cell that can differentiate along multiple lines. Although multiple cell types are often found within a single lung tumor, one type usually predominates. Based on therapeutic approach, there are two major subdivisions of lung cancer: small-cell lung cancer (SCLC), for which chemotherapy is the primary treatment, and non–small-cell lung cancer (NSCLC), which in its early stages (I and II) is treated primarily with surgery.

This chapter will focus on the diagnosis, staging, pathology, and treatment of NSCLC, including carcinoid tumors of the lungs, as well as the pulmonary evaluation of lung cancer patients and the follow-up of long-term survivors. This chapter will conclude with a brief discussion of mesothelioma.

Chapter 6 will provide information on the staging, pathology and pathophysiology, and treatment of the far less common SCLC. In addition, this chapter will also provide basic information on the epidemiology, etiology, screening and prevention, and signs and symptoms of lung cancer in general.

NON–SMALL-CELL LUNG CANCER

Non–small-cell tumors account for approximately 80% of all lung cancers. The three major tumor types included under this category are adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma.

Staging and prognosis

Staging

The staging of lung cancer must be conducted in a methodical and detailed manner in order to permit appropriate therapeutic recommendations to be made and to allow treatment results from different institutions to be compared. The TNM staging system, recently updated by Mountain (Table 1), applies equally well to all histologies. However, TNM staging is generally not utilized in SCLC, as it does not predict well for survival. Rather, SCLC is generally staged as limited (M0) or extensive (M1) disease.

Stage is commonly reported as either clinical or pathologic. The former is based on noninvasive (or minimally invasive) tests, whereas the latter is based on tissue obtained during surgery (see section on "Diagnosis and staging evaluation").

Prognostic factors

Stage The most important prognostic factor in lung cancer is the stage of disease.

Performance status and weight loss Within a given disease stage, the next most important prognostic factors are performance status and recent weight loss. The two scales used to define performance status are the Eastern Cooperative Oncology Group (ECOG) performance status system and the Karnofsky system (see Appendix 1). In short, patients who are ambulatory have a significantly longer survival than those who are nonambulatory. Similarly, patients who have lost > 5% of body weight during the preceding 3-6 months have a worse prognosis than patients who have not lost a significant amount of weight.

Molecular prognostic factors Several studies published over the past decade have indicated that mutations of *ras* proto-oncogenes, particularly K-*ras*, portend a poor prognosis in individuals with stage IV NSCLC. Accordingly, research has focused on developing molecularly targeted therapeutic approaches to the *ras* proto-oncogenes, in particular, the farnesyl transferase inhibitors (see section on "Promising novel agents").

Of equal relevance was the completion of large studies by Pastorino et al and Kwiatowski et al evaluating the prognostic importance of immunocytochemical and molecular pathologic markers in stage I NSCLC. The findings of these two studies suggest that pathologic invasion and extent of surgical resection may yield the most critical prognostic information, but mutation of the K-*ras* oncogene and absence of expression of the H-*ras* p21 proto-oncogene may augment the pathologic information obtained.

TABLE 1: TNM staging of lung cancer

Primary tumor (T)

Tx	Tumor proven by the presence of malignant cells in bronchopulmonary secretions but not visualized roentgenographically or bronchoscopically or any tumor that cannot be assessed, as in pretreatment staging
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3.0 cm in greatest dimension, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy
T2	Tumor > 3.0 cm in greatest dimension, or tumor of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region (but involving less than the entire lung). At bronchoscopy, the proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina
T3	Tumor of any size with direct extension into the chest wall (including superior sulcus tumors), diaphragm, or mediastinal pleura or pericardium without involving the heart, great vessels, trachea, esophagus, or vertebral body; or tumor in the main bronchus within 2 cm of, but not involving, the carina
T4	Tumor of any size with invasion of the mediastinum or involving the heart, great vessels, trachea, esophagus, vertebral body, or carina; or presence of malignant pleural effusion

Regional lymph nodes (N)

Nx	Regional lymph nodes cannot be assessed
N0	No demonstrable metastasis to regional lymph nodes
N1	Metastasis to lymph nodes in the peribronchial and/or ipsilateral hilar region, including direct extension
N2	Metastasis to ipsilateral mediastinal and subcarinal lymph nodes
N3	Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes

Distant metastasis (M)

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T3	N1	M0
	T1-3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

From Mountain CF: Revisions in the international system for staging lung cancer. Chest 111:171–1717, 1997.

Diagnosis and staging evaluation

History and physical examination

The diagnosis and preoperative staging of lung cancer begin with a good history and physical examination. When obtaining the history, the clinician should keep in mind the tendency for lung cancer to involve major airways and other central structures. Similarly, the patterns of metastatic dissemination and systemic manifestations must be considered when conducting the physical examination.

Patients should be questioned specifically about the presence of palpable masses, dysphagia, bone pain, headache, or changes in vision. Careful auscultation and percussion may suggest the presence of atelectasis or pleural effusion. Also, auscultation of the chest may show evidence of large airway obstruction and pulmonary consolidation. An enlarged liver may indicate hepatic metastases.

Examination of supraclavicular fossa Clinicians should be careful to examine the supraclavicular fossa, as detection of an enlarged lymph node in this area may provide the means for establishing a tissue diagnosis.

In addition, identification of supraclavicular lymph node metastases has important therapeutic and prognostic implications. In particular, supraclavicular nodal metastases immediately eliminate the patient from consideration for surgery.

Imaging studies

Chest x-rays should always be done in a high-risk patient with new respiratory symptoms. Not only are PA and lateral chest x-rays of fundamental importance in assessing the local extent of the primary tumor, they also may provide valuable information regarding metastatic disease.

The chest x-ray should be inspected for the presence of a pleural effusion or synchronous pulmonary nodules, and the bones should be examined for evidence of osseous metastases. A widened mediastinum usually indicates metastatic disease within the mediastinal lymph nodes. Comparison with previous x-rays is frequently helpful and well worth the effort expended in their retrieval.

Chest CT A CT scan of the chest, including the liver and adrenal glands, is performed routinely to further define the primary tumor and to identify lymphatic or parenchymal metastases. Metastatic tumor is found in approximately 8% of mediastinal lymph nodes < 1 cm in greatest diameter, 30% of nodes 1-2 cm in greatest diameter, and 60% of those > 2 cm. Benign enlargement of mediastinal nodes is more common in patients with postobstructive infection. Histologic documentation of the presence or absence of tumor within the mediastinal lymph nodes is necessary whenever this information will change treatment recommendations.

It is important to remember that patients with persistent symptoms, such as cough and dyspnea, who have a normal chest x-ray may be harboring a central lesion that is not obvious on chest x-ray but can be easily detected by chest CT. Also, as mentioned above, apical tumors (Pancoast's tumors) may be

difficult to detect on a chest radiograph but are usually readily apparent on a CT scan.

PET Current data suggest that PET may be very helpful for the evaluation of lung masses, lymph nodes, and distant metastases. When a lung mass "lights up" on a PET scan, there is a 90%-95% chance that it is cancerous. The positive predictive value of a PET scan is lower in areas with a high prevalence of granulomatous disease. If the mass is at least 1 cm and cannot be imaged by PET scanning, there is only a 5% chance that it is malignant. Both the sensitivity and specificity of PET for detecting nodal metastases are approximately 90%.

PET scanning may prove a valuable tool for evaluation of NSCLC patients treated with chemoradiotherapy or radiation therapy. In a recent study, the PET response was a powerful predictor of survival ($P = .0001$) *(MacManus RJ, Hicks RJ, Matthews JP, et al: Proc Am Soc Clin Oncol [abstract] 21:338a, 2002).*

Several trials have evaluated the prognostic significance of fluorodeoxyglucose (FDG) uptake on PET scan in NSCLC. Most of these studies used a standardized uptake value (SUV), a semiquantitative measurement of FDG uptake. Utilizing multivariate Cox analysis, these studies noted that SUV, particularly when > 7, was a highly important prognostic factor. Other studies indicated that the use of PET combined with chest CT was almost as sensitive as surgery alone in the evaluation of pathologically positive mediastinal lymph nodes.

Adrenal gland biopsy The adrenal gland may be the sole site of metastatic disease in as many as 10% of patients with NSCLC. Patients should not be assumed to have metastatic disease and denied a potentially curative operation on the basis of a scan. An enlarged or deformed adrenal gland should be biopsied.

Obtaining a tissue diagnosis

The next step is to try to obtain a histologic or cytologic diagnosis of the radiologic lesion, although preoperative histologic diagnosis need not be obtained in a high-risk patient with a new, peripheral lung mass and no evidence of distant or locoregional metastases (see below).

Central lesions Although collecting sputum cytologies for 3 consecutive days frequently provides a cytologic diagnosis for central lesions, most clinicians proceed directly to bronchoscopy. In centrally located lesions, this procedure establishes a cytologic and/or histologic diagnosis in 80%-85% of cases. In addition, bronchoscopy may provide important staging information, such as whether the tumor involves the distal trachea or carina, and may help plan the appropriate operation (lobectomy or sleeve resection vs pneumonectomy).

Peripheral lesions Bronchoscopy is less likely to yield a diagnosis in patients with peripherally located lesions. The false-negative rate in such cases may range from 20% to 50%.

A CT-guided needle biopsy may diagnose up to 90% of peripheral lung cancers. However, needle biopsy is usually reserved for patients who are not candi-

TABLE 2: Selective indications for mediastinoscopy

Enlarged N1 or N2 lymph nodes on chest CT scan
Centrally located tumors
Poorly differentiated tumors
T3 tumors
Patients who are marginal candidates for resection

dates for an operation due to distant metastatic disease or poor performance status. If the patient is a candidate for surgery, resection is generally recommended for any suspicious mass whether the needle biopsy is positive or nondiagnostic. Therefore, for patients with a suspicious peripheral lesion that is not associated with pleural effusion or mediastinal adenopathy, it is reasonable to proceed directly to surgery.

Mediastinoscopy provides not only a histologic diagnosis but also yields important staging information (Table 2). Median radiologic techniques of CT and PET scanning have largely replaced mediastinoscopy. If multiple lymph node levels contain tumor, most thoracic surgeons would not proceed directly to operation, but would offer these patients neoadjuvant therapy as part of a clinical trial. Alternatively, such patients could receive nonoperative primary therapy. However, if only one ipsilateral nodal level is positive for metastatic tumor, many surgeons will perform a pulmonary resection and lymph node dissection and advise participation in an adjuvant therapy trial. Surprisingly, the survival for patients with ipsilateral mediastinal nodal disease (IIIA) was the same as the survival for patients with contralateral mediastinal nodal disease (IIIB) in the neoadjuvant study by SWOG.

Thoracentesis and thoracoscopy Individuals who have pleural effusions should undergo thoracentesis. Video-assisted thoracoscopic surgery (VATS) is being used increasingly in patients with such effusions if thoracentesis does not show malignant cells. VATS permits direct visualization of the pleural surface, enables one to directly biopsy pleural nodules, and also may facilitate biopsy of ipsilateral mediastinal lymph nodes.

Measurement of serum tumor-associated antigens has no current role in the staging of NSCLC.

Evaluation for distant metastases

Once a tissue diagnosis has been established, the possibility of distant metastases should be assessed. Again, this process starts with a careful history and physical examination.

Clinical stage I/II patients Patients with clinical stage I or II lung cancers based on chest x-ray and CT scan, no evidence of skeletal or neurologic metastases, and normal blood chemistries and blood counts do not require brain or bone scans.

Symptomatic, clinical stage I/II patients, including those who have lost > 5% of their usual body weight and those who cannot work on a regular basis due to decreased performance status (ECOG performance status ≤ 2), should have bone and brain scans. Although these patients do not require an abdominal CT scan per se, CT scans of the chest should routinely include the adrenal glands and virtually all of the liver.

Clinical stage III patients Patients who have physical findings, laboratory findings (such as an elevated alkaline phosphatase), or symptoms suggestive of distant metastases should undergo appropriate scans to evaluate these areas. In addition, most clinical trials of combined-modality therapy for stage III disease require radiologic imaging of the brain and bone. Thus, it seems reasonable to perform these imaging studies in clinical stage III patients who are receiving potentially curative therapy (high-dose radiation therapy or combined-modality therapy). If brain and bone are to be investigated, brain MRI with gadolinium and a technetium radionuclide bone scan should be performed.

Diagnosis and evaluation of suspected carcinoid tumor

A carcinoid tumor of the lung may be suspected in a patient with a slowly enlarging pulmonary mass and a prolonged history of respiratory symptoms. Patients in whom a primary carcinoid tumor of the lung is suspected or documented should be evaluated in a manner identical to that used in patients with NSCLC. The diagnosis is usually made during bronchoscopy.

Pulmonary carcinoid tumors rarely produce 5-hydroxyindoleacetic acid (5-HIAA). Therefore, it is only necessary to measure urinary 5-HIAA excretion prior to surgery in symptomatic patients.

Intraoperative staging

Intraoperative staging represents an integral part of any operation for lung cancer. In addition to a thorough visual and tactile inspection of the lung, diaphragm, and pleura, the ipsilateral mediastinal lymph nodes must be either completely removed or, at a minimum, sampled.

The American Thoracic Society has assigned numbered levels to locations in which lymph nodes are regularly found, defined by their relation to constant anatomic structures. For instance, right level IV lymph nodes are those that are found between the cephalic border of the azygous vein and the caudal border of the innominate artery where it crosses the trachea. A complete mediastinal lymph node dissection is associated with little morbidity and lengthens the operation only slightly.

Pulmonary evaluation

In order to determine the volume of lung that can be removed without rendering the patient a pulmonary cripple and to identify those individuals at risk for postoperative complications, each patient must undergo pulmonary function testing.

Forced expiratory volume in 1 second Postoperative respiratory failure occurs rarely if the postresection forced expiratory volume in 1 second (FEV_1) is > 800 mL. Regardless of the extent of the scheduled resection, if the preoperative FEV_1 is < 2 L, a split-function perfusion scan should be obtained to determine the contribution of each lung to overall pulmonary function. This information may be critical when an unplanned pneumonectomy is required to achieve complete tumor resection.

Other pulmonary function tests A diffusing capacity of the lung for carbon monoxide (D_LCO) < 60% of the predicted value or a maximum voluntary ventilation (MVV) < 35% is associated with increased postoperative morbidity. Similarly, an arterial pO_2 < 60 mm Hg or a pCO_2 > 45 mm Hg has been linked to increased operative morbidity and mortality.

Measurement of oxygen consumption during exercise has also proved useful in determining which patients can tolerate a pulmonary resection. Oxygen consumption values > 15 mg • kg^{-1} • min^{-1} have been associated with minimal morbidity.

Pathology

Three major types of tumors are included under the NSCLC category: adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma.

Adenocarcinoma is currently the most common type of NSCLC, accounting for approximately 40% of cases. Of all the types of lung cancer, adenocarcinoma is most likely to occur in nonsmokers or former smokers. In addition, it is the most common tumor in women.

Typically, adenocarcinoma presents as a small peripheral lesion that has a high propensity to metastasize to both regional lymph nodes and distant sites. Because of the tendency of the primary tumor to occur in peripheral locations, it frequently produces no symptoms.

Bronchoalveolar adenocarcinoma During the last decade, it has become apparent that the incidence of the bronchoalveolar type of adenocarcinoma is increasing. This tumor appears to rise from type 2 pneumocytes, and it may present as a pneumonic infiltrate, as multiple nodules scattered throughout the lung, and occasionally, as a single nodule.

Squamous cell tumors comprise approximately 30% of all cases of lung cancer. This tumor tends to occur in a central location and tends to spread to regional lymph nodes; it is the most likely of all the lung cancers to remain localized and to cavitate. In fact, autopsy studies have shown that about 15%-30% of patients with squamous cell carcinoma may expire from local disease without evidence of distant metastases.

Large-cell carcinoma accounts for approximately 10%-15% of all lung cancers. It tends to be a relatively large peripheral lesion and, like adenocarcinoma, it has a high propensity to metastasize to regional lymph nodes and distant sites.

Carcinoids These neoplasms, which contain neurosecretory granules and neural filaments, are relatively rare. The classic carcinoid tumor presents as an endobronchial lesion, tends to be quite indolent, and rarely metastasizes. Some carcinoid tumors spread to regional lymph nodes and distant sites. These tumors are classified as atypical carcinoids or anaplastic carcinoids. More recently, some investigators have suggested that the more aggressive carcinoids be called well-differentiated neuroendocrine carcinoids.

Treatment

All investigators agree that patients with clinically staged IA, IB, IIA, and IIB NSCLC should undergo resection of their tumors. There is a similar consensus that, except for the rare individual with a solitary brain metastasis, patients with stage IV disease should be treated nonoperatively. While multimodality therapy is routinely recommended for stage IIIA and IIIB disease, its exact nature and sequence remain controversial.

SURGICAL APPROACH

The appropriate treatment of NSCLC is resection of the lobe containing the tumor. Occasionally, a bilobectomy or pneumonectomy is required. Mortality following lobectomy and pneumonectomy approximates 3% and 7%, respectively. A wedge or segmental resection has a 3-5 times higher incidence of local recurrence and a lower 5-year survival than a lobectomy. Therefore, if the patient can tolerate the procedure, the standard operation should be a lobectomy, rather than a wedge resection or segmentectomy.

Video-assissted thoracoscopic surgery (VATS) Traditionally, lung cancers have been resected through a posterolateral thoracotomy incision. Many surgeons have switched to a muscle-sparing incision, because studies have shown that this approach reduces pain. Currently, the trend is toward an even less invasive approach: lobectomy and lymph node dissection with VATS. It appears that this approach offers the same cancer operation and survival with perhaps lower morbidity and mortality.

Patients with pathologic stage IA disease have an 80% 5-year survival rate after resection, whereas 5-year survival rates are 60% in those with stage IB disease and 40%-50% in those with stage IIA/IIB disease. Patients found to have N2 (stage IIIA) disease located at a single nodal level have a 25%-30% 5-year survival rate.

Mediastinal lymph node involvement The standard lung cancer operation should include sampling or dissection of mediastinal lymph nodes. The presence of metastases in any of the mediastinal lymph nodes (N2 disease) is indicative of advanced disease and is thought by some to represent a contraindication to surgery. However, resection of N2 disease has prognostic significance, implications for postoperative care, and, probably, therapeutic value. Some series of patients with N2 disease have shown a 5-year survival rate of 20%-30%, but patients in these series are highly selected.

The American College of Surgeons is currently conducting a randomized, prospective study comparing survival following mediastinal lymph node sampling vs dissection. Also, clinical trials are currently testing preoperative chemotherapy or chemoradiation in patients with mediastinal node involvement.

Preoperative histologic assessment of the mediastinal lymph nodes is essential if multilevel metastases are suspected, as there have been few long-term survivors among patients with metastatic disease at more than one level. Such patients should be treated nonsurgically or offered participation in a trial designed to assess the benefits of neoadjuvant therapy. Although patients with stage IIIB tumors are usually treated with radiation and chemotherapy (see later discussions), the occasional patient with isolated involvement of the vena cava or atrium can undergo resection.

Carcinoid tumors Although the majority of carcinoid tumors remain localized, regional lymph node metastases are identified in a significant percentage of patients. The surgical approach, therefore, should be similar to that used in NSCLC; namely, resection. If a small tumor in a proximal airway is identified and there is no histologic evidence of lymph node disease, a bronchoplastic procedure with preservation of lung tissue can sometimes be performed. Rates of survival at 10 years are $>$ 90% for patients with stage I disease and 60% for patients with stage II disease.

ADJUVANT THERAPY

Radiation therapy

A trial conducted by the Lung Cancer Study Group (LCSG) clearly showed that, in patients with squamous cell carcinoma of the lung and resected N1/N2 disease, administration of postoperative radiation reduced the risk of recurrence in the chest from 20% to 1%. While there was no improvement in overall survival, postoperative radiation was associated with a significant improvement in disease-free survival for patients with N2 disease. A trial by the British Medical Research Council reached similar conclusions.

These results created a lack of consensus about treatment recommendations, with some experts advocating the use of postoperative radiation therapy to reduce local recurrence, and others avoiding it because of the absence of an effect on survival. This complicated subject has recently been extensively reviewed using an evidence-based approach.

A recently published meta-analysis of nine randomized trials assessing postoperative radiation therapy in lung cancer reported a 21% increase in mortality in patients receiving this therapy. However, many of the patients in these trials had N0 disease, for whom few would advocate radiation therapy. Also, most of the patients were treated with cobalt-60 beams and technically limited treatment planning, not with modern radiation therapy techniques.

At present, therefore, the appropriate role of postoperative radiation therapy remains controversial. However, it should be seriously considered in patients at high risk for locoregional relapse (ie, those with N2 disease, squamous his-

tology, multiple positive lymph nodes, extracapsular extension, or close or microscopically positive margins).

Chemotherapy

Classic postsurgical adjuvant chemotherapy also has been tested in three randomized trials conducted by the LCSG.

A randomized intergroup trial of adjuvant therapy for patients with resected T2 N0, T1 N1, or T2 N1 NSCLC is now accruing patients under the direction of the National Cancer Institute of Canada. Following operation, patients are being randomized to receive cisplatin (Platinol) and vinorelbine (Navelbine) or no further treatment.

Stage I disease In one trial, adjuvant therapy with 6 courses of cyclophosphamide (Cytoxan, Neosar), Adriamycin, and Platinol (CAP) failed to produce a significant survival advantage in patients with stage I lung cancer. Therefore, at present, adjuvant chemotherapy is not recommended for stage I disease.

Stage II/III disease In two earlier trials, postoperative adjuvant chemotherapy with 6 courses of CAP, given alone in one study and following postoperative radiation therapy in the other, resulted in a modest improvement in median survival but had no impact on long-term survival. Adjuvant chemotherapy is not recommended for these patients.

A recent randomized trial of observation vs postoperative adjuvant chemotherapy (3 cycles of cisplatin 80 mg/m^2 on day 1 and vindesine 3 mg/m^2 on days 1 and 8 every 4 weeks) in patients with completely resected pathologic stage IIIA (N2) NCSLC showed no improvement with adjuvant chemotherapy *(Ichinose Y, Tada H, Koike T, et al: Proc Am Soc Clin Oncol [abstract] 20:331a, 2001).*

An intergroup, randomized, prospective trial of adjuvant therapy for patients with resected stage II or IIIA NSCLC recently reported results. Patients with histologically proven metastases to N1 or N2 lymph nodes were randomized to receive either postoperative mediastinal radiation therapy alone (50 Gy) or 4 cycles of concomitant cisplatin and etoposide plus radiation therapy. The study demonstrated no benefit from the addition of chemotherapy to mediastinal radiation in the adjuvant setting.

Similarly, a recent randomized trial comparing adjuvant radiotherapy (50 Gy/5 wk) vs adjuvant chemotherapy (cisplatin, 75 mg/m^2 on day 1, plus ifosfamide (Ifex), 1.5 g/m^2 on days 1-4, for 3 cycles every 4 weeks) followed by the same radiation in patients with resected N2 disease showed no improvement in outcome with the addition of chemotherapy to radiotherapy (Wolf M, Muller, H, Seifart U, at al: Proc Am Soc Clin Oncol 20:311a [abstract], 2001).

NEOADJUVANT CHEMOTHERAPY OR CHEMORADIATION

During the past decade, numerous phase II trials showed that, in general, it is feasible to perform pulmonary resection following chemotherapy or chemoradiation. Although surgery can be more difficult after preoperative treatment, morbidity and mortality were generally acceptable.

Stage IIIA/IIIB disease The greater effectiveness of current chemotherapeutic regimens in settings of reduced disease bulk suggested that their use prior to

surgery, either alone or in combination with radiation therapy, might increase both resectability and survival in patients with stage IIIA or IIIB NSCLC. Multiple phase II trials have shown such an approach to be feasible; however, it is not clear that, among patients who initially have more than minimal N2 disease, such a strategy improves median or long-term survival over best non-surgical chemoradiotherapy.

Recently, an intergroup trial demonstrated an impressive 50% *pathologic* complete response rate and a 50% 3-year survival rate with preoperative chemotherapy (cisplatin/etoposide) administered concurrently with irradiation (45 Gy) to patients with T3-T4 N0 M0 Pancoast tumors.

Surgeons have a wide variety of opinions regarding the use of preoperative irradiation. A few surgeons believe that irradiation should never be given preoperatively, but most of them believe that the preoperative dose should be limited to 45-50 Gy. The current trend is toward the use of > 60 Gy preoperatively.

Based on these initial observations, three groups conducted small randomized trials testing preoperative therapy. Two of these studies showed significantly improved survival among patients who received three courses of cisplatin-containing chemotherapy prior to surgery. In the third trial (reported in abstract form only), Brazilian investigators observed significantly higher rates of resection and significantly longer survival in patients who received preoperative chemoradiation than in those given preoperative chemotherapy alone.

In a recent analysis of 686 patients who underwent surgical resection of N2 NSCLC, preoperative chemotherapy was associated with better survival outcome in a subgroup of patients with clinically evident N2 disease ($P < .0001$). Five-year survival rate was 18% for patients treated with preoperative chemotherapy compared with 5% for those not treated.

Current recommendations In selected patients, preoperative treatment may have a favorable effect on outcome in surgically resectable stage III NSCLC. Although aggressive neoadjuvant approaches may have treatment-associated mortality in the range of 5%-12%, in experienced institutions potential benefits seem to outweigh the risks. However, the results of a randomized trial (recently closed) comparing preoperative chemoradiation to definitive chemoradiation (in pathologic N2 disease) are not yet availabe.

Stage I-IIIA disease Neoadjuvant chemotherapy may even play a role in early-stage disease. A multicenter trial from France randomized 373 stage I-IIIA NSCLC patients to either surgery alone or chemotherapy (mitomycin [Mutamycin; 6 mg/m^2 on day 1], ifosfamide [1.5 g/m^2 on days 1-3], and cisplatin [30 mg/m^2 on days 1-3]) at 3-week intervals for 3 cycles followed by surgery. Disease-free survival was significantly longer in the patients randomized to receive neoadjuvant chemotherapy than in those treated with surgery alone ($P = .02$). The most striking benefit of chemotherapy was seen in patients who had minimal lymphadenopathy (either N0 or N1; $P = .008$). No excessive complications were seen in the chemotherapy-treated patients.

A phase III trial comparing neoadjuvant chemotherapy with paclitaxel/carboplatin (Paraplatin) vs surgery alone in early-stage NSCLC (the Bimodality Lung Oncology Team [BLOT] vs NOT study) is now ongoing in the United States, based on promising phase II results (3-year survival rates of 64%) with this strategy (Pisters K, Ginsberg R, Giroux D, et al: Proc Am Soc Clin Oncol 20:323a [abstract], 2001)

TREATMENT OF MEDICALLY INOPERABLE PATIENTS WITH STAGE I/II DISEASE

Some patients with resectable stage I or II NSCLC are high-risk operative candidates because of poor cardiopulmonary function, other medical problems, or advanced age. Other patients refuse to undergo surgery despite the recommendation of their treating physicians. In such patients, an attempt should be made to optimize pulmonary function by encouraging smoking cessation and initiating vigorous treatment with bronchodilators, corticosteroids, and antibiotics.

Radiation therapy

Several institutions have reported their experience with definitive radiation therapy for such patients. Although the results are not as good as those reported in patients selected for surgery (possibly due to differences in patient selection and between clinical vs pathologic staging), medically inoperable patients with early-stage NSCLC clearly should be offered radiation therapy, with reasonable expectation of cure. Recently, Timmerman et al reported the results of a phase I study of extracranial stereotactic radioablation (ESR) in patients with medically inoperable stage I NSCLC. ESR was delivered in 3 fractions over 2 weeks, with a starting dose of 800 cGy per fraction. The dose was escalated to 2,000 cGy per fraction for 3 fractions (6,000 cGy total). Of 36 patients, 1 developed grade 3 hypoxemia and another symptomatic radiation pneumonitis. The maximum tolerated dose was not reached.

Radio-frequency ablation

Patients who are not operative candidates can also be treated with radio-frequency ablation (RFA). There is considerable experience with RFA for cancer in other organs, and its use for lung cancer is growing. It can be performed either intraoperatively or percutaneously with CT guidance. The preliminary findings show these radiological results: complete response (0%), partial response (50%), stable disease (30%), and disease progression (20%).

TREATMENT OF PATIENTS WITH STAGE IIIA/IIIB DISEASE

Radiation therapy

In the past, radiation therapy was considered the standard therapy for patients with stage IIIA or IIIB disease. Long-term survival was poor, in the range of 5%-10%, with poor local control and early development of distant metastatic disease.

Altered fractionation schedules A randomized trial compared standard daily radiation therapy (66 Gy) with an accelerated regimen that delivered 54 Gy over 2½ weeks (CHART). The altered fractionation schedule resulted in improved 2-year survival.

Various efforts are currently under way to look at combining altered fractionation schema with chemotherapy. Although the preliminary results of RTOG 9410 do not favor altered fractionation (see "Concurrent vs sequential chemoradiation"), the long-term results of another study support this strategy. Jeremic et al compared hyperfractionated radiation therapy (bid to 69.6 Gy) and concurrent low-dose daily carboplatin/etoposide with or without weekend carboplatin/etoposide in a randomized trial of approximately 200 patients. Although they found no benefit to the addition of weekend carboplatin/etoposide, both arms demonstrated promising median survival times of 20 and 22 months and excellent 5-year survival ratios of 20% and 23% (Proc Am Soc Clin Oncol 19:504a [abstract], 2000).

Conformal radiation therapy

Hayman et al reported updated results of the Michigan phase I dose-escalation trial of 3D conformal radiation therapy for NSCLC. In this study, the radiation dose was escalated based on the effective volume of irradiated lung (up to 102.9 Gy). Such doses produced acceptable toxicity and no cases of isolated failures in purposely unirradiated, clinically uninvolved nodal regions. This strategy is beginning to be integrated with chemotherapy.

Socinski et al reported a dose-escalation radiotherapy (from 60-74 Gy) trial, using 3D computer-assisted planning techniques, in patients receiving induction carboplatin and paclitaxel and concurrent weekly carboplatin/paclitaxel. Ninety-seven percent (31/32) of the patients completed therapy to 74 Gy, as planned. The grade 3/4 esophagitis rate overall was relatively low at only11%. Moreover, the results found a promising median survival of 26 months and 3-year survival of 47% (Proc Am Soc Clin Oncol 19:496a [abstract], 2000).

Interestingly, investigators at M. D. Anderson Cancer Center found that the maximum tolerated dose (MTD) of gemcitabine (Gemzar) administered weekly concurrent with conventional (2D) thoracic radiation was only 125 mg/m^2/wk × 7 weeks vs 190 mg/m^2/wk × 7 weeks utilizing 3D conformal radiotherapy (Proc Am Soc Clin Oncol 20:312a [abstract], 2001). Further escalation of the radiation therapy dose in the context of chemotherapy will need to be evaluated.

Chemoradiation therapy

Chemoradiation vs radiation therapy alone At least 11 randomized trials have compared thoracic irradiation alone to chemoradiation in patients with stage III NSCLC. Several meta-analyses have demonstrated a small, but statistically significant, improvement in survival with the combined-modality regimens. Indeed, six randomized trials have demonstrated a statistically significant survival advantage favoring chemoradiation: three of these trials employed sequential chemoradiation and three, concurrent chemoradiation.

In the three trials using sequential chemoradiation, the combination of cisplatin with a vinca alkaloid (either vinblastine or vindesine) significantly improved survival rates over radiation therapy alone.

The first of the concurrent chemoradiation trials, the European Organization for Research and Treatment of Cancer (EORTC) trial 08844, compared radiotherapy alone to radiotherapy and concomitant (daily or weekly) low-dose cisplatin therapy. This study demonstrated a significant survival advantage for daily cisplatin and radiotherapy compared to radiotherapy alone (3-year survival rates, 16% vs 2%); the weekly cisplatin/radiation arm produced intermediate results (3-year survival rate, 13%).

A three-arm, randomized study comparing hyperfractionated radiotherapy (1.2 Gy twice daily to a total dose of 64.8 Gy) alone to a combination of hyperfractionated radiotherapy and carboplatin plus etoposide (administered weekly or every other week) demonstrated 3-year survival rates of 6.6%, 23%, and 16%, respectively ($P = .003$).

In the third phase III concurrent chemoradiation trial, the combination of hyperfractionated radiation and low-dose daily chemotherapy (carboplatin plus etoposide) was superior to hyperfractionated radiation alone (to 69.6 Gy), with 4-year survival rates of 22% vs 9% ($P = .02$).

Analyses of these positive randomized trials favoring chemoradiation over radiation alone suggest a difference in the patterns of failure that relates to the method of combining chemotherapy with thoracic radiotherapy. In the three trials employing sequential chemoradiation, the improvement in survival rates over radiation alone appeared to be linked to a decrease in the development of distant metastases. In contrast, in the three positive trials employing concurrent chemoradiation, the survival advantage appeared to be associated with an improvement in locoregional control.

It may be that the use of high-dose induction chemotherapy combats systemic disease, whereas the simultaneous delivery of low-dose chemotherapy (cisplatin or carboplatin) with radiation may be necessary to improve local tumor control. Such a construct fits well with prior observations that platinum-based chemotherapy can act as a radiosensitizer.

Few studies in lung cancer report 5-year survival results. The median survival generally reported for stage IV disease is about 8 months even with novel therapeutic approaches, which is similar to the median survival reported for stage IIIB NSCLC with malignant pleural effusion. As the preceding and other trials in the literature show, 5-year survival rates are rarely reported for stage IIIA/IIIB lung cancers. Most studies report a median survival and 3-year survival rates. The Furuse trial of chemoradiation is one of the few lung cancer trials reporting 5-year survival results. Furuse et al evaluated mitomycin, vindesine, and Platinol (MVP), administered either concurrently with or prior to thoracic irradiation (56 Gy), in patients with unresectable stage III NSCLC. With over 300 patients randomized, survival favored concurrent over sequential therapy (median survival, 16.5 vs 13.3 months, and 5-year survival rates, 15.8% vs 8.9%; $P = .04$).

Concurrent vs sequential chemoradiation A phase III trial has previously reported an advantage for concurrent over sequential chemoradiation. Furuse et al recently reported the patterns of failure, which demonstrated a benefit of concurrent chemoradiotherapy in improving the local relapse-free survival ($P = .04$) but not the distant relapse-free survival ($P = .6$) (Proc Am Soc Clin Oncol 19:484a [abstract]), 2000).

Curran et al presented the preliminary results of a larger randomized trial (>600 patients) comparing sequential vs concurrent chemoradiotherapy (RTOG [Radiation Therapy Oncology Group] 9410). The median survival with concurrent cisplatin/vinblastine and once-daily radiation was 17.0 months vs 14.6 months with sequential treatment ($P = .03$). The third treatment arm (concurrent cisplatin/oral etoposide and hyperfractionated radiation) was intermediate with a median survival of 15.6 months. Even elderly (≥ 70 years) patients on RTOG 94-10 benefited from concurrent chemotherapy and once-daily radiation therapy.

Movsas et al reported the results of a quality-adjusted time without symptoms of toxicity (QTWiST) analysis of RTOG 94-10. Despite the increase in reversible nonhematologic toxicities in the concurrent arms, the overall mean toxicity was highest in the sequential arm, which involved the longest treatment time. The concurrent once-daily arm had the optimal QTWiST, further supporting concurrent chemoradiation as a new treatment paradigm.

Recently, two randomized phase II trials also appear to support the use of concurrent chemoradiation for locally advanced NSCLC. Choy et al performed a randomized phase II study in 276 patients of three chemoradiation regimens with paclitaxel, carboplatin, and thoracic irradiation in their locally advanced multimodality protocol (LAMP). They found that concurrent chemoradiation followed by adjuvant chemotherapy appeared to have the best therapeutic outcome, with a median survival of 16.1 months, compared with either induction chemotherapy followed by concurrent chemoradiation (median survival, 11 months) or sequential chemotherapy followed by irradiation (median survival, 12 months).

Similarly, in another randomized phase II study, Zatloukal et al studied 102 patients treated with concurrent chemoradiation and sequential chemotherapy followed by irradiation. The chemotherapy consisted of four cycles of cisplatin and vinorelbine. They reported a median survival in the concurrent arm of ~20 months, vs ~13 months in the other arm ($P = .02$).

As supported by clinical trials, the PCS-Lung Study demonstrated that patients with clinical stage (CS) III NSCLC received chemotherapy plus radiation therapy (RT) more than RT alone ($P < .0001$). In clinical stage I NSCLC, though, RT alone was the primary treatment ($P < .0001$). Factors correlating with increased use of chemotherapy included lower age ($P < .0001$), histology (SCLC > NSCLC, $P < .0001$), increasing CS ($P < .0001$), increasing KPS ($P < .0001$), and lack of comorbidities ($P = .0002$) but not academic vs nonacademic facilities ($P = .81$). Of all patients receiving chemotherapy, approximately three-quarters received it concurrently with RT. Only 3% of all patients were treated on IRB-approved trials, demonstrating the need for improved accrual to clinical trials *(Movsas V, Moughan J, Komaki R, et al: Int J Radiat Oncol Biol Phys 54:101, 2002).*

TABLE 3: Active new agents for NSCLC chemotherapy

Agent	Number of studies	Number of patients	Response rate (%) (range)
Irinotecan	3	150	34 (32-37)
Docetaxel	7	257	33 (21-54)
Paclitaxel	4	151	22 (10-24)
Gemcitabine	7	566	21 (20-26)
Vinorelbine	4	501	21 (12-32)

Movsas et al reported the results of the first Patterns of Care Study (PCS) for lung cancer, which was conducted to determine the national patterns of radiation therapy practice in patients treated for nonmetastatic lung cancer in 1998-1999 (see box on previous page).

New chemotherapeutic agents plus radiation Several recent phase I/II trials evaluated carboplatin and paclitaxel given concurrently with thoracic radiation. These studies showed acceptable toxicity and relatively high response rates, and in one of the studies the 3-year survival rate was quite high (39%).

A strategy under investigation to reduce the toxicity of intensive combined-modality strategies is the use of the radioprotector amifostine (Ethyol). A small randomized trial (n = 62) suggests that twice-weekly amifostine (500 mg/m^2 IV) administered before chemotherapy and twice-daily radiation therapy for locally advanced NSCLC can reduce the incidence of acute esophagitis and pneumonitis, with no suggestion of tumor protection (*Komaki R, Lee JS, Milas L, et al: Proc ASTRO [abstract] 54:105, 2002*). This radioprotective agent has been further tested as a strategy to reduce chemo-radiation-induced esophagitis in a larger phase III study (RTOG 98-01), which has also prospectively collected critical quality-of-life data.

In addition to paclitaxel and carboplatin, many other chemotherapeutic agents with activity in NSCLC have emerged in the 1990s, including docetaxel (Taxotere), vinorelbine, gemcitabine, UFT (uracil and tegafur), and irinotecan (CPT-11 [Camptosar]). A trial from Japan tested induction chemotherapy with irinotecan and cisplatin followed by radiation therapy with weekly irinotecan (30 mg/m^2 during radiation therapy). The study reported a response rate of 65% and median survival rate of 16.5 months, with a grade 3/4 esophagitis rate of only 4%.

Typically, it can be difficult to deliver systemic doses of chemotherapy following concurrent chemoradiotherapy. However, the Southwest Oncology Group (SWOG) recently reported a phase II study of concurrent chemoradiation (cisplatin/etoposide) followed by consolidation docetaxel (75-100 mg/m^2 q21d × 3). In this group of pathologically documented stage IIIB NSCLC patients (pleural effusion excluded), a promising median survival of 27 months was found. Toxicity during consolidation consisted primarily of neutropenia (56% grade 4).

TABLE 4: Results of selected randomized trials of chemotherapy comparing cisplatin alone vs cisplatin plus a newer agent in advanced NSCLC

Investigator	Chemotherapy regimen	Pts (n)	Response rate (%)	Median survival (mo)	1-yr survival (%)
Klastersky (1989)	Cisplatin	81	19	6.0	NA
	Cisplatin + etoposide	81	26[a]	5.	NA
Wozniak (1998)	Cisplatin	209	12	6	20
	Cisplatin + vinorelbine	206	26	8[a]	36[a]
Gatzemier (1998)	Cisplatin	206	17	8.6	NA
	Cisplatin + paclitaxel	202	26[a]	8.1	NA
Sandler (1998)	Cisplatin	262	10	7.6	28
	Cisplatin + gemcitabine	260	26[a]	9.0[a]	39[a]
Von Pawel (1998)	Cisplatin	219	13.7	6.3	21
	Cisplatin + tirapazamine	218	27.5[a]	8.5[a]	33[a]

[a] The difference between the groups was statistically significant ($P < .05$).

NA = data not available

Current treatment recommendations

At present, it is reasonable to consider concurrent chemoradiation as a new treatment paradigm in stage III (inoperable) lung cancer patients with an ECOG performance status of 0/1 who have not lost more than 5% of their usual body weight.

TREATMENT OF PATIENTS WITH STAGE IV DISEASE

Until recently, there was considerable controversy over the value of treating stage IV NSCLC patients with chemotherapy. Treatment with older cisplatin-containing regimens, such as cisplatin/etoposide, showed only a modest effect on survival, improving median survival by approximately 6 weeks, according to a meta-analysis, and yielding a 1-year survival rate of approximately 20% (as compared with a rate of approximately 10% for supportive care).

However, several new chemotherapeutic agents have produced response rates in excess of 20% in NSCLC (Table 3). The potentially useful new agents include the taxanes (paclitaxel and docetaxel), vinorelbine, gemcitabine, and irinotecan. Several of these new drugs have unique mechanisms of action compared to the mechanisms of agents that have previously shown some effectiveness against NSCLC. For instance, paclitaxel and docetaxel cause increased polymerization of tubulin, gemcitabine is an antimetabolite, and irinotecan is a topoisomerase I inhibitor.

Furthermore, randomized trials demonstrated that a new agent plus cisplatin combination significantly improves the response rate over cisplatin monotherapy (historically considered the most active agent for NSCLC). This increase in response rates translates into significant, although modest, improvement in survival outcome for patients receiving vinorelbine, gemcitabine and also tirapazamine, which is a hypoxic cell cytotoxin. Although tirapazamine is not a chemotherapy agent in a classical sense, it will be a very useful addition to the chemotherapy armamentarium because it does not cause myelosuppression (Table 4).

These studies suggest that combination chemotherapy with newer agents will significantly improve the outcome of NSCLC patients, as discussed below. It seems clear that conducting randomized trials comparing newer chemotherapy regimens with best supportive care is no longer acceptable.

Optimal chemotherapy for advanced NSCLC

Until the early 1990s, regimens of cisplatin plus a vinca alkaloid or etoposide were most common. More recently, regimens that employ newer agents are more widely used. However, choosing one regimen from many options is a very difficult task because there is no survival advantage documented for one regimen over another or standard regimen vs regimens containing newer agents.

Table 5 summarizes the results of selected randomized trials in which combination regimens containing a newer agent are compared with old "standard" regimens or regimens containing another newer agent. Subtle differences in the eligibility criteria (eg, inclusion of patients with stage III tumors or those with poor performance status) make it difficult to directly compare the results between the trials. Nevertheless, there is a trend indicating that regimens containing newer agents show higher response rates and also better survival outcome in some series when compared with older regimens.

Vinorelbine plus cisplatin combination

Vinorelbine was the first agent that demonstrated improved activity against NSCLC in combination with cisplatin. The European multicenter trial reported by Le Chevalier showed the results favoring cisplatin plus vinorelbine combination (vinorelbine, 30 mg/m^2 weekly; cisplatin, 120 mg/m^2 on days 1 and 29, then every 6 weeks) over a vindesine plus cisplatin combination (vindesine, 3 mg/m^2 weekly; cisplatin, 120 mg/m^2 on days 1 and 29, then every 6 weeks) and vinorelbine alone (30 mg/m^2 weekly). The median survival duration of 40 weeks in the vinorelbine/cisplatin treatment arm was significantly longer than the 32 weeks in the vindesine/cisplatin arm ($P = .04$) and 31 weeks in the vinorelbine monotherapy arm ($P < .001$). This trial, however, did not confirm the role of vinorelbine in NSCLC therapy, even though it confirmed the role of cisplatin.

To address this issue, the SWOG conducted a study comparing cisplatin alone (100 mg/m^2 every 4 weeks) with vinorelbine/cisplatin combination (cisplatin, 100 mg/m^2 every 4 weeks, vinorelbine, 25 mg/m^2 weekly × 3 every 4 weeks)

Survival outcome was analyzed for 415 patients, 92% with stage IV tumors. The vinorelbine/cisplatin treatment significantly improved the progression-free survival (median, 2 vs 4 months; $P = .0001$) and overall survival (median, 6 vs 8 months; 1-year survival 20% vs 36%; $P = .0018$).

Recently, Comella et al reported interim analysis results of a phase III trial of the Southern Italy Cooperative Oncology Group. A three-drug regimen (cisplatin, gemcitabine, and vinorelbine) was associated with a substantial survival gain over the cisplatin and vinorelbine regimen (median survival time, 51 and 35 weeks, respectively).

TABLE 5: Results of selected randomized trials evaluating chemotherapy regimens of newer agents in advanced NSCLC

Investigator	Chemotherapy regimen	No. of patients	Response rate (%)	Median survival	1-yr survival rate (%)
LeChavalier (1994)	Vinorelbine + cisplatin	206	30	40 wk	35
	Vindesine + cisplatin	200	19	32 wk	27
	Vinorelbine	206	14	31 wk	30
Bonomi (1996)	Etoposide + cisplatin	560	12.0	7.69 mo	31.6
	Paclitaxel + cisplatin	(total)	26.5	9.56 mo	36.9
	Paclitaxel + cisplatin + G-CSF		32.1	9.99 mo	39.1
Giaccone (1997)	Teniposide + cisplatin	157	28	9.9 mo	41
	Paclitaxel + cisplatin	152	41	9.7 mo	43
Belani (1998)	Etoposide + cisplatin	179	14.0	9.9 mo	37
	Paclitaxel + carboplatin	190	21.6	9.5 mo	32
Crino (1998)	Mitomycin + ifosfamide + cisplatin	152	28	38 wk	NA
	Gemcitabine + cisplatin	154	40	35 wk	NA
Georgoulias (1999)	Docetaxel + cisplatin	152	32	10 mo	42
	Docetaxel + gemcitabine	144	34	9 mo	34
Masuda (1999)	Irinotecan + cisplatin	378	43	50.3 wk	47.5
	Vindesine + cisplatin	(total)	31	47.4 wk	37.9
	Irinotecan		21	46.1 wk	40.7
Kelly (1999)	Paclitaxel + carboplatin	184	27	8 mo	36
	Vinorelbine + cisplatin	181	27	8 mo	33
Schiller (2000)	Paclitaxel + cisplatin	1,163	21.3	7.8 mo	31
	Gemcitabine + cisplatin	(total)	21.0	8.1 mo	36
	Docetaxel + cisplatin		17.3	7.4 mo	31
	Paclitaxel + carboplatin		15.3	8.2 mo	35
Frasci (2000)	Gemcitabine + vinorelbine	60	22	29 wk	30
	Vinorelbine	60	15	18 wk	13
Lilenbaum (2002)	Paclitaxel + carboplatin	292	29	10 mo	NA
	Paclitaxel	290	17	8.6 mo	NA

Paclitaxel plus platinum compound

A number of studies demonstrate promising results with paclitaxel in combination with cisplatin or carboplatin, and other agents. Two large randomized trials compared paclitaxel plus cisplatin with standard regimens. In a three-arm, randomized ECOG trial (ECOG 5592) reported by Bonomi et al, 550 eligible patients with chemotherapy-naive stage IIIB to IV NSCLC were randomly assigned to a combination of cisplatin (75 mg/m^2) plus etoposide (100 mg/m^2 daily on days 1 to 3) vs either low-dose (135 mg/m^2 over 24 hours) or high-dose paclitaxel (250 mg/m^2 over 24 hours with growth factor) plus cisplatin (75 mg/m^2). The response rates for the low-dose and high-dose paclitaxel arms were 26.5% and 32.1%, respectively, significantly better than the cisplatin/etoposide arm (12.0%). Superior survival was observed with the combined paclitaxel regimens (median survival time, 9.9 months; 1-year survival rate, 38.9%) compared with etoposide plus cisplatin (median survival time, 7.6 months; 1-year survival rate, 31.8%; $P = .048$). Comparing survival rates for the two dose levels of paclitaxel revealed no significant differences.

In a European trial of similar design reported by Giaconne et al, cisplatin/paclitaxel improved the response rate and the quality of life parameters. There was no improvement in overall survival, however, compared with a standard regimen of cisplatin/teniposide (Vumon).

Paclitaxel/carboplatin has been the most widely favored regimen for first-line chemotherapy in all NSCLC stages among US medical oncologists, mainly due to promising phase II trial results and the ease of administration as an out-patient with manageable toxicity profiles compared with cisplatin-containing regimens. One of the early phase II trials, for example, reported a response rate of 62%, a median survival duration of 53 weeks, and a 1-year survival rate of 54%. However, a randomized trial sponsored by the manufacturer of paclitaxel failed to demonstrate a survival advantage over the standard cisplatin plus etoposide regimen. Nevertheless, paclitaxel plus carboplatin may remain a community standard because a recently completed SWOG trial reported results equivalent to the time-tested vinorelbine/cisplatin regimen (see Table 5).

Second-line chemotherapy

A randomized phase III study conducted by the Cancer and Leukemia Group B (CALGB) further supported the superiority of combination chemotherapy over single-agent therapy. Previous trials had indicated that a platinum plus a novel agent was superior to a platinum alone. Lilenbaum et al demonstrated that for patients with stage IIIb-IV NSCLC, carboplatin and paclitaxel are superior to paclitaxel alone, even for performance status 2 patients. This randomized CALGB trial showed a median survival advantage for the combination of ~6 weeks in 582 patients.

Gemcitabine plus cisplatin

Gemcitabine is also FDA-approved for use against NSCLC based on a series of successful phase II trials of cisplatin/gemcitabine and three major phase III trials. The Hoosier Oncology Group study, reported by Sandler et al, compared gemcitabine/cisplatin with cisplatin alone and showed a modest improvement in median and 1-year survival comparable to that seen in the vinorelbine trials (Table 4). The Spanish and Italian trials, reported by Cardenal et al and Crino et al, compared gemcitabine plus cisplatin with standard-regimen cisplatin plus etoposide and mitomycin plus ifosfamide plus cisplatin, respectively. Although there was a significant improvement in overall response, these two studies failed to demonstrate a survival benefit.

Since gemcitabine is relatively well tolerated without dose-limiting myelosuppression, it is being evaluated for use as a single agent or in combination with other agents in older or medically compromised patients. Italian investigators report that the gemcitabine combined with vinorelbine regimen is associated with significantly better survival than single-agent vinorelbine in elderly NSCLC patients.

Other combination regimens that contain cisplatin plus newer agents, such as docetaxel or irinotecan, also showed similar results when compared with other two-drug regimens of either two newer or two older agents (Table 5).

Major randomized trials comparing new regimens

To identify a better chemotherapy regimen for NSCLC, the US cooperative study groups conducted large phase III trials. The SWOG investigators compared paclitaxel/carboplatin with vinorelbine/cisplatin (the time-tested regimen in previous European and SWOG trials). A total of 404 evaluable patients were randomized to receive either paclitaxel (225 mg/m^2 over 3 hours) plus carboplatin (at an area under the curve [AUC] of 6 mg/mL on day 1) every 21 days, or vinorelbine (25 mg/m^2 weekly) plus cisplatin (100 mg/m^2 on day 1) every 28 days. Overall response rates were 27% for both groups. The median survival times were also identical (8 months) with virtually identical 1-year survival rates (35% and 33%, respectively). While both regimens provided effective palliation in advanced NSCLC, the investigators identified paclitaxel/carboplatin for future studies because of a favorable toxicity profile and better tolerability and compliance.

The ECOG 1594 trial compared three platinum-based regimens containing new agents in the treatment of NSCLC with a control arm of cisplatin and paclitaxel. The regimens were gemcitabine (1,000 mg/m^2 on days 1, 8, 15) plus cisplatin (100 mg/m^2 on day 1) every 4 weeks, docetaxel (75 mg/m^2) plus cisplatin (75 mg/m^2 on day 1) every 3 weeks, and paclitaxel (225 mg/m^2 over 3 hours) plus carboplatin (at AUC of 6 mg/mL on day 1) every 21 days; the reference regimen was paclitaxel (175 mg/m^2 over 24 hours) plus cisplatin (75 mg/m^2 on day 1) every 21 days.

Analysis of 1,163 eligible patients showed no statistically significant differences in overall response rates, median survival, and 1-year survival rates when com-

pared with the control arm, paclitaxel and cisplatin. Gemcitabine plus cisplatin was associated with statistically significant prolongation of time to disease progression when compared with the control arm (4.5 vs 3.5 months, $P = .002$), but was also associated with a higher percentage of grade 4 thrombocytopenia, anemia, and renal toxicity.

Since all the regimens showed similar efficacy, quality of life becomes a critical issue in choosing a particular regimen. The decision to use one regimen over another will depend not only on ease of administration and side effects, but also on the personal preference and experience of the treating oncologist.

Second-line chemotherapy for NSCLC

Before the new generation of more effective agents became available, few, if any, significant benefits were expected from second-line chemotherapy. As a result, reports in the literature seldom address this issue specifically or systematically. The most experience with second-line chemotherapy in NSCLC is with docetaxel, which recently received FDA approval for this indication based on two randomized phase III trials confirming the promising phase II results of docetaxel monotherapy in advanced NSCLC patients previously treated with platinum-based chemotherapy.

In a multicenter US trial reported by Fossella et al, 373 patients were randomized to receive either docetaxel, 100 mg/m^2 (D100) or 75 mg/m^2 (D75) vs a control regimen of vinorelbine (30 mg/m^2/wk) or ifosfamide (2 g/m^2 × 3 days) every 3 weeks. Overall response rates were 10.8% with D100 and 6.7% with D75, each significantly higher than the 0.8% response of the control arm ($P = .001$ and $P = .036$, respectively). Although overall survival was not significantly different between the three groups, the 1-year survival was significantly greater with D75 than with the control treatment (32% vs 19%; $P = .025$).

The second trial reported by Shepherd et al compared single-agent docetaxel with best supportive care. The initial docetaxel dose was 100 mg/m^2, which was changed to 75 mg/m^2 midway into the trial because of toxicity. A total of 204 patients were enrolled; 49 received D100, 55 received D75, and 100 received best supportive care. Treatment with docetaxel was associated with significant prolongation of survival (7.0 vs 4.6 months; log-rank test, $P = .047$) and time to disease progression (10.6 vs 6.7 weeks, $P < .001$).

Duration of chemotherapy

The American Society of Clinical Oncology (ASCO) has recommended that no more than 8 cycles of chemotherapy should be administered to patients with stage IV NSCLC (Clinical Practice Guidelines. J Clin Oncol: 2996-3018, 1997). However, therapy should be individualized depending on the quality of tumor response and the patient's tolerance.

Promising novel agents

Several novel agents are being developed for the treatment of solid tumors, including lung cancer. For example, farnesyl transferase inhibitors target

prenylation of the *ras* family of proto-oncogenes. Farnesylation causes the *ras* oncogene to be constitutively active.

Other novel agents include signal transduction inhibitors, such as tyrosine kinase inhibitors (eg, ZD1839 [Iressa]), antiangiogenic agents, and monoclonal antibodies (C225 [anti-EGF receptor antibody], trastuzumab [Herceptin]). Many of these novel agents are being tested in combination with chemotherapeutic agents, as their mechanisms of action suggest that these agents may be far more effective as chronic inhibitors of cancer progression than as classic cytotoxics.

To date, most phase I studies of these various compounds have suffered from a difficulty in developing pharmacologically or molecularly driven end points that will serve as reasonable intermediate biomarkers of efficacy or even surrogates for toxicity. Further research has focused on the novel small molecule tyrosine kinase inhibitors erlotinib (Tarceva) and gefitinib (Iressa). Two phase II trials of gefitinib in the second- and third-line settings were conducted in Europe and Japan. Patients were randomized to receive either 250 mg/d vs 500 mg/d. The drug was found to be active, with an 11%-18% response rate, and there was no superiority for the higher dose. Similar data were seen for erlotinib.

Unfortunately, randomized combination trials of gefitinib at 250 and 500 mg/d with cytotoxic chemotherapy, either paclitaxel and carboplatin in one trial or gemcitabine and cisplatin in the other study vs placebo in front-line therapy failed to demonstrate any survival advantage. These results have cast a pall over the development of tyrosine kinase inhibitors in combination with chemotherapy. Regardless, the question of whether or not to approve these new agents for third-line therapy of lung cancer in cisplatin/docetaxel-refractory patients remains open for debate.

In general, there apears to be little to favor triplet cytotoxic drug combinations vs doublet combinations in NSCLC (Kelly K, Mikhaeel-Kamel N, Pan Z, et al: Clin Cancer Res 6:3474-3479, 2000). However, an area of great excitement has been the addition of novel biologically or molecularly targeted agents to cytotoxic chemotherapy combinations. Several recent trials have demonstrated the potential advantages of adding a small molecule targeted to either the epidermal growth factor receptor (EGFR) or *ras* (namely the farnesyl transferase inhibitors).The interest in these agents in advanced NSCLC appears to have superseded the new cytotoxic agents with activity in other diseases, such as oxaliplatin, tirapazamine, and UFT.

The mechanisms of action of these new small molecules is widely divergent, and their combinations with the cytotoxics may not necessarily lead to an enhanced response rate. Khuri and colleagues demonstrated, however, that the combination of cisplatin, vinorelbine, and bexarotene (a retinoid-X-receptor [RXR]-specific novel retinoid), resulted in substantial median and 2-year survival rates in stage IIIB NSCLC patients with malignant pleural effusion or stage IV NSCLC patients. Median survival on this multicenter study was 14 months in the phase II portion; 2-year survival was 32%; and 3-year survival was 18%. The combination yielded modest response rates (25%), not markedly superior to what was expected with cisplatin and vinorelbine alone.

This has led to an uncoupling of the requirement for higher response rates when adding cytotoxic agents to one another in the belief that adding these novel biologic agents may lead to enhanced survivals. There now appears to be a great deal of promise associated with several small molecules, either alone or combined with chemotherapy. Novel agents such as ZD1839 or the farnesyl transferase inhibitor SCH66336 have shown promising efficacy in small trials that have included NSCLC patients; ZD1839 alone resulted in an 18% response rate in second- or third-line therapy of NSCLC in a study population recruited across several continents.

However, there have been some provocative phase I and II data with both the rexinoid bexarotene and the farnesyl transferase inhibitor lonafarnib (Sarasar) in combination with chemotherapy leading to the recent launch of phase III trials of both agents in combination with cytotoxic chemotherapy. These trials are ongoing and are expected to accrue between 600 and 800 patients over the next 2 years. They will test the principle of whether the preclinical and clinical synergy seen with these compounds and either platinums or taxanes is vindicated in phase III front-line trials of NSCLC.

Current treatment recommendations

It is important to note that patients who have lost significant amounts of weight or who have poor performance status are at greater risk for toxicity, including a higher likelihood of lethal toxicity, when they are treated with modest doses of chemotherapy. Based on currently available data, a reasonable approach for stage IV NSCLC patients who have good performance status (ECOG performance status, 0/1) and have not lost a significant amount of weight ($< 5\%$ of usual weight) would be to encourage them to participate in a clinical trial.

However, it would also be appropriate to treat this group of patients with etoposide plus cisplatin or with one of the newer combination regimens, such as gemcitabine/cisplatin, vinorelbine/cisplatin, paclitaxel/cisplatin, paclitaxel/carboplatin, or docetaxel/cisplatin (Tables 6, 7).

ROLE OF PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT), which combines Photofrin (a hematoporphyrin derivative in which the less active porphyrin monomers have been removed) with an argon-pumped dye laser, has been explored in a variety of different tumors, with varying results. Several investigators have reported excellent results with PDT in early-stage head and neck cancers, as well as intrathoracic tumors. However, initial studies have involved a limited number of patients.

Although this novel technique seems to be extremely promising, it appears to be applicable to only a small minority of NSCLC patients. Nevertheless, PDT appears to be particularly useful for the treatment of early-stage lung cancer for a variety of reasons. First, it appears to effectively preserve lung function and can be repeated as additional tumors appear—an important consideration since such patients appear to be at high risk for developing other new tumors. Furthermore, this technique does not preclude ultimate surgical intervention when deemed necessary.

TABLE 6: Single-agent chemotherapy regimens for NSCLC

Drug	Dose and schedule
Vinorelbine	30 mg/m^2 IV weekly
Le Chevalier T, Brisgand D, Douillard J-Y, et al: J Clin Oncol 12:360–367, 1994.	
Vinorelbine	For patients 70 years old or older: 30 mg/m^2 IV on days 1and 8, every 21 days
Gridelli C, Perrone F, Cigolari S, et al: Proc Am Soc Clin Oncol 20:308a [abstract], 2001.	
Docetaxel	75 mg/m^2 IV on day 1 every 3 weeks
Shephaerd FA, Dancey J, RamlauR, et al: J Clin Oncol 18:2095–2103, 2000.	
Gemcitabine	1,000 mg/m^2 IV on days 1, 8, and 15 every 4 weeks
Vansteenkiste J, Vandebroek J, Nackaerts K, et al: Proc Am Soc Clin Oncol 19:1910a [abstract], 2000.	

Table prepared by Ishmael Jaiyesimi, DO

Results in early-stage NSCLC Perhaps most striking are the results reported by Furuse et al, who treated 54 patients with 64 early-stage lung cancers using Photofrin (2.0 mg/kg) and 630-nm illumination of 100-200 J/cm^2. Of 59 accessible tumors, 50 responded completely and 6 showed partial responses. Five of the complete responders developed recurrences 6-18 months after treatment.

The major predictor of response in this study was tumor length. The likelihood of achieving a complete response was 97.8% if the tumor was $<$ 1 cm, as opposed to only a 42.9% if the lesion was $>$ 1 cm. The overall survival rate in these patients was 50% at 3 years.

A similar study by Kato et al also indicated a 96.8% complete response rate for tumors $<$ 0.5 cm but only a 37.5% rate for tumors $>$ 2 cm. The overall 5-year survival rate for the 75 patients treated in this study was 68.4%, which is quite acceptable by current standards.

Further work by Lam et al supported these promising results of PDT in early-stage NSCLC.

Results in advanced-stage NSCLC Two prospective, randomized trials (European; US/Canadian) compared PDT with the neodymium–yttrium-aluminum-garnet (Nd:YAG) laser for partially obstructive, advanced NSCLC. Investigators analyzed results from the two trials both individually and collectively. Collective analysis included data from 15 centers in Europe and 20 centers in the United States and Canada, and involved a total of 211 patients. In the European trial, 40% of the patients had received prior therapy, whereas in the US/Canadian trial, all of the patients had received previous treatment.

Tumor response was similar for both therapies at 1 week. However, at 1 month, 61% and 42% of the patients treated with PDT in the European and US/Canadian trials, respectively, were still responding, compared with 36% and 19% of patients who underwent laser therapy in the two trials.

TABLE 7: Chemotherapy regimens recommended for NSCLC

Regimen	Agents	Dose and schedule	Treatment interval
PE	Cisplatin Etoposide	60 mg/m^2 IV on day 1 120 mg/m^2 IV on days 1-3	3 weeks
MIC	Mitomycin Ifosfamide Cisplatin	6 mg/m^2 IV on day 1 3 g/m^2 IV on day 1 100 mg/m^2 IV on day 2	4 weeks
PT	Cisplatin Paclitaxel	75 mg/m^2 IV on day 2 135 mg/m^2 IV on day 1 (24-h infusion)	3 weeks
CP	Carboplatin Paclitaxel	AUC of 6 IV on day 1 225 mg/m^2 IV on day 1 (3-h infusion)	3 weeks
PG	Cisplatin Gemcitabine	100 mg/m^2 IV on day 1 1,000 mg/m^2 IV on days 1, 8, and 15	4 weeks
PD	Cisplatin Docetaxel	75 mg/m^2 IV on day 1 75 mg/m^2 IV on day 1	3 weeks
PV	Cisplatin Vinorelbine	100 mg/m^2 IV on day 1 25 mg/m^2 IV on days 1, 8, 15, and 22	4 weeks
GV	Gemcitabine Vinorelbine	1,200 mg/m^2 IV on days 1 and 8 30 mg/m^2 IV on days 1 and 8	3 weeks

PDT also produced more dramatic improvements in dyspnea and cough than did Nd:YAG therapy in the European trial, but the two treatments had similar effects on these symptoms in the US/Canadian trial. Both sets of investigators concluded that PDT appears to be superior to laser therapy for the relief of dyspnea, cough, and hemoptysis. Also, the overall incidence of adverse reactions was similar with the two therapies (73% for PDT vs 64% for Nd:YAG therapy).

PALLIATION OF LOCAL AND DISTANT SYMPTOMS

Radiation therapy

Many patients with lung cancer experience distressing local symptoms at some time. These may arise from airway obstruction by the primary tumor, compression of mediastinal structures by nodal metastases, or metastatic involvement of distant organs. Radiation therapy is quite effective in palliating most local symptoms, as well as symptoms at common metastatic sites, such as bone and brain. For selected patients with a solitary brain metastasis and controlled disease in other sites, resection followed by radiation appears to be superior to radiation therapy alone in improving both survival and quality of life.

Recent studies have demonstrated varying degrees of benefit for strategies beyond palliative whole-brain irradiation in the management of brain metastases.

TABLE 8: Percentage of patients with NSCLC symptoms palliated by external-beam irradiation

Symptom	Standard RT (24-30 Gy in 6-10 fractions)	17 Gy in 2 fractions (first trial/second trial)	1 fraction of 10 Gy
Cough	56	65/48	56
Hemoptysis	86	81/75	72
Chest pain	80	75/59	72
Anorexia	64	68/45	55
Depression	57	72/NA	NA
Anxiety	66	71/NA	NA
Breathlessness	57	66/41	43

NA = data not available, RT = radiation therapy

Data from Bleehen NM, Girling DJ, Fayers PM, et al: Br J Cancer 63:265-270, 1991; Bleehen NM, Bolger JJ, Hasleton PS, et al: Br J Cancer 65:934–941, 1992.

Sperduto et al reported the results of RTOG 95-08, a randomized trial comparing whole brain irradiation (3,750 cGy in 250 cGy fractions) vs WBRT + stereotactic radiosurgery boost in 333 patients with 1-3 brain metastases. They found a statistically significant survival advantage with WBRT + SRS for the stratified group of patients with solitary brain metastases (mean survival, 6.5 vs 4.9 months, $P = .04$). Other subsets that appeared to benefit included those with NSCLC, among others. All subsets of patients in the WBRT + SRS group were more likely to have stable or improved performance status than those in the WBRT alone group.

In another randomized trial, 401 patients with unresected brain metastases (KPS ≥ 70) were randomized to receive WBRT (30 Gy) ± the redox mediator motexafin gadolinium (MGd). Overall, there was no improvement in survival, but time to neurologic progression (as determined by investigators) was significantly prolonged with MGd ($P = .02$). Interestingly, the benefit of MGd was primarily seen in lung cancer (which made up 63% of the cases). In a final randomized trial, Antonadou et al compared WBRT± temozolomide (TMZ, Temodar), 75 mg/m^2 daily during WBRT and 1 month afterward (at 200 mg/m^2) on days 1-5 q 28 days × 6 cycles. A total of 134 eligible patients were randomized to undergo treatment, 82% with lung primaries. Median survival was 8.3 months in the TMZ + WBRT arm and 6.3 months in the WBRT arm ($P = .18$). Of note, a significantly higher response rate was observed in the combined-modality arm (53%) than in the WBRT arm (33%, $P = .04$). The optimal management of patients with brain metastases should be tailored to the individual situation.

Doses In the United States, most radiation oncologists use doses of ~30 Gy in 10 fractions for palliative treatment. Data from the United Kingdom suggest that similar efficacy without greater toxicity may be achieved with more ab-

breviated schedules, such as 17 Gy in 2 fractions 1 week apart or single fractions of 10 Gy (see Table 8). Such schedules may facilitate the coordination of radiation and chemotherapy and also reduce patient travel and hospitalization.

Recently, just over 400 patients with inoperable NSCLC (stage III /IV) were randomized to receive three different fractionation regimens (8.5 Gy × 2, 2.8 Gy × 15, or 2.0 Gy × 25). Using the EORTC QLQ C-30 questionnaire with the lung cancer-specific module (LC-13), Sundstrom et al found the effect of hypofractionated irradiation (17 Gy in 2 fractions) was comparable to that with longer fractionation schemes with regard to symptom relief and survival.

Endobronchial irradiation with cobalt-60 or iridium-192 has been used to palliate symptoms arising from partial airway obstruction, including cough, dyspnea, and hemoptysis. The dosimetric advantage of being able to deliver a high radiation dose to the obstructing endobronchial tumor while sparing adjacent normal structures, such as lung, spinal cord, and esophagus, has clear appeal, particularly in the patient whose disease has recurred following prior external-beam irradiation. Although good rates of palliation have been reported with endobronchial irradiation, significant complications, including fatal hemoptysis, are seen in 5%-10% of patients. It remains unclear, however, how often this complication is actually due to the radiation vs the underlying disease itself.

Endobronchial irradiation should be considered as only one of several approaches (including laser excision, cryotherapy, and stent placement) that can be used in the management of patients with symptomatic airway obstruction, and management should be individualized. All of these approaches are more suitable for partial rather than complete airway obstruction.

Chemotherapy

Several recent trials have explored the use of chemotherapy to palliate specific symptoms in patients with lung cancer. In general, these trials have found that rates of symptomatic improvement were considerably higher than objective response rates and were not dissimilar to symptomatic response rates with local radiation therapy.

A randomized phase II study suggests that rhuMAb VEGF (15 mg/kg) in combination with carboplatin/paclitaxel chemotherapy may increase response rates and prolong time to disease progression in patients with previously untreated NSCLC when compared with carboplatin/paclitaxel (CP) chemotherapy alone. CP alone patients with progressive disease were allowed to cross over to receive rhuMAb VEGF. The median survival time was 7.7 months with high-dose rhuMAb VEGF (15 mg/kg q3wk) and 4.9 months with CP alone. Although sudden and life-threatening hemoptysis occurred in 6 rhuMAb VEGF-treated subjects and was fatal in 4, survival data are encouraging, and a phase III trial is in progress without crossover to rhuMAb VEGF.

Thus, while radiation therapy remains the most appropriate modality for the treatment of such problems as superior vena cava obstruction, spinal cord compression, brain metastases, or localized bone pain, patients who have

TABLE 9: Staging of mesothelioma according to Butchart

Stage	Description
Stage I	Tumor confined within the "capsule" of the parietal pleura, ie, involving only ipsilateral pleura, lungs, pericardium, and diaphragm
Stage II	Tumor invading chest wall or involving mediastinal structures, eg, esophagus, heart, opposite pleura; lymph node involvement within the chest
Stage III	Tumor penetrating diaphragm to involve peritoneum; involvement of opposite pleura; lymph node involvement outside the chest
Stage IV	Distant blood-borne metastases

more extensive disease without these local emergencies may be considered for palliative chemotherapy, which may both relieve local symptoms and prolong survival.

Follow-up of long-term survivors

At present, no standard follow-up protocol exists for patients with cured NSCLC or SCLC. However, at a minimum, long-term follow-up should include serial physical examinations once the patient has reached the 5-year mark. Controversy currently exists about the value of utilizing CT scanning or even chest x-rays for the long-term follow-up of these patients.

In this vein, retrospective reviews of the literature have revealed that SCLC patients appear to have the highest rate of second primary tumor development–as high as 30% over the course of their lifetime, with some studies reporting annual second primary tumor rates of 5%-10%. Therefore, the concept of chemoprevention appears to have particular merit in these patients.

A recently completed, randomized chemoprevention study of patients with stage I NSCLC showed a surprisingly high annual recurrence rate of 6.5% in patients with T1 tumors, as opposed to 11.2% in patients with T2 tumors. Whether retinoids are effective chemopreventive agents remains to be seen. Nevertheless, there is clearly a need for effective chemoprevention for both of these tumor subsets, as well as the establishment of consistent guidelines for routine long-term follow-up. Given the current controversy over lung cancer screening, however, it is unlikely that this issue will be resolved without the performance of another prospective screening trial.

MESOTHELIOMA

Mesotheliomas are uncommon neoplasms derived from the cells lining the pleura and peritoneum. Currently, 2,000-3,000 new cases are diagnosed in the United States each year.

Epidemiology

Gender Males are affected five times more commonly than females.

Age The median age at diagnosis is 60 years.

Etiology and risk factors

Asbestos exposure The relationship between asbestos exposure and diffuse pleural mesothelioma was first reported by Wagner, who documented 33 pathologically confirmed cases from an asbestos mining region in South Africa. Selikoff and colleagues documented a 300-fold increase in mortality from mesothelioma among asbestos insulation workers in the New York metropolitan region when compared to the general population. The interval between asbestos exposure and tumor formation is commonly 3-4 decades.

Asbestos fibers are generally divided into two broad groups: serpentine and amphibole. The latter includes crocidolite, the most carcinogenic form of asbestos. The inability of phagocytic cells to digest the fiber appears to initiate a cascade of cellular events that results in free-radical generation and carcinogenesis.

Diagnosis

Patients with mesothelioma usually seek medical attention while the disease is limited to a single hemithorax and commonly complain of dyspnea and pain. Dyspnea results from diffuse growth of the tumor on both the parietal and visceral pleura, which encases the lung in a thick rind. Pain is caused by direct tumor infiltration of intercostal nerves.

Chest x-ray and CT Chest x-ray demonstrates pleural thickening, pleural-based masses, or a pleural effusion. Chest CT scan more accurately portrays the extent of disease and frequently reveals chest wall invasion, as well as pericardial and diaphragmatic extension.

Thoracentesis and thoracoscopy Thoracentesis and pleural biopsy usually are sufficient to establish the diagnosis of malignancy, but a thoracoscopic or open biopsy is often required to provide enough tissue to make an accurate histologic diagnosis of mesothelioma.

Distinguishing mesothelioma from other neoplasms Light microscopy is often insufficient for differentiating among mesothelioma, metastatic adenocarcinoma, and sarcoma. Immunohistochemistry and electron microscopy are frequently necessary to establish the diagnosis.

Although adenocarcinomas stain positive for carcinoembryonic antigen (CEA), Leu-M1, and secretory component, mesotheliomas are negative for these markers. Mesotheliomas stain positive for cytokeratin, whereas sarcomas do not. Mesotheliomas have characteristic long microvilli that are well demonstrated by the electron microscope; adenocarcinomas have short microvilli.

Pathology

Mesotheliomas may contain both epithelial and sarcomatoid elements and are classified by the relative abundance of each component. Epithelial mesotheliomas are most common (50%), followed by mixed (34%) and sarcomatoid (16%) tumors. Survival for the epithelial type is 22 months, compared to only 6 months for the other types.

Staging and prognosis

The most commonly utilized staging system for mesothelioma, that of Butchart, is based on inexact descriptions of the extent of local tumor growth or distant metastases (Table 9). Other, more detailed staging systems based on TNM criteria have been proposed.

Median survival following diagnosis ranges from 9-21 months. Although autopsy series have demonstrated distant metastases in as many as 50% of patients with mesothelioma, death usually results from local tumor growth.

Treatment

Treatment rarely results in cure and should be considered palliative.

Surgical options include chest tube insertion and pleurodesis to control the pleural effusion. Currently, there is renewed interest in aggressive treatment that includes extrapleural pneumonectomy with concomitant resection of the diaphragm and pericardium, followed by chemotherapy and radiotherapy. Subtotal pleurectomy is a less extensive surgical procedure that debulks the majority of tumor, permits reexpansion of the lung, and prevents recurrence of the pleural effusion.

Chemotherapy and radiotherapy appear to offer no survival benefit. Radiation therapy is useful in relieving symptoms due to local tumor invasion, however.

Although the median survival of patients treated with aggressive multimodality regimens that include surgery appears to be superior to survival of patients treated with chemotherapy and radiotherapy alone, the apparent improvement may be the result of selection bias.

Innovative treatments There are many new agents being tested for malignant mesothelioma, including ranpirnase (Onconase [p30 protein]), gemcitabine, paclitaxel, docetaxel, pemetrexed (Alimta), liposomal N-DDP, and gene therapy. In particular, pemetrexed, a novel multitargeted antifolate inhibited thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyl transferase (GARFT), showed a promising activity in malignant pleural mesothelioma in the recently conducted phase II trial. The overall response rate was 16% in the vitamin-supplemented group. The responders also had marked improvement in quality of life. In parallel, the largest phase III randomized trial was recently reported at the 2002 meeting of the American Society of Clinical Oncology (ASCO).

In this phase III single-blind study for malignant pleural mesothelioma, pemetrexed plus cisplatin was compared with cisplatin alone in chemotherapy-naive patients with malignant pleural mesothelioma. The largest phase III trial to date enrolled 456 patients, of whom 280 patients also received folic acid and vitamin B supplementation to reduce toxicity. The group of patients who were treated with pemetrexed plus cisplatin showed a better survival benefit than those who were treated with cisplatin alone. Therefore, pemetrexed plus cisplatin with folic acid/vitamin B supplementation should be considered standard front-line therapy for patients with malignant pleural mesothelioma.

THYMOMA

Thymoma is a rare mediastinal tumor that occurs mainly in the anterosuperior mediastinum.

Epidemiology

Gender The tumor affects both sexes equally.

Age Thymoma is most often seen in people in the fourth and fifth decades of life.

Etiology and associated syndromes

The etiology of thymomas is unknown, and the risk factors have not been identified. Thymoma is a tumor originating within the epithelial cells of the thymus. One-third to one-half of patients present with an asymptomatic anterior mediastinal mass, one-third present with local symptoms (eg, cough, chest pain, superior vena cava syndrome, and/or dysphagia), and one-third of cases are detected during the evaluation of myasthenia gravis. Distant metastases are distinctly uncommon at initial presentation of this tumor.

In addition to myasthenia gravis, which occurs in approximately 30% of patients with thymoma, a host of paraneoplastic syndromes have been seen in association with thymoma. These other syndromes, which occur in less than 5% of patients, include pure red cell aplasia, hypogammaglobulinemia, and a variety of other autoimmune disorders.

Diagnosis

The most commonly described symptoms are pleuritic chest pain or discomfort, dry cough, and dyspnea. Physical examination may reveal adenopathy, wheezing, fever, superior vena cava syndrome, vocal cord paralysis, and other paraneoplastic syndromes.

Chest x-ray and CT scan A chest x-ray provides an initial basis for diagnosis. The location, size, density, and presence of calcification within the mass can all be determined. Comparison of the film to previously obtained films is usually

TABLE 10: Clinicopathologic correlates of thymoma

Authors	Number of patients	Subgroups (percentage)
Verley and Hollman (Cancer 55:1074, 1985)	200	Type I: Spindle and oval cells (30) Type II: Lymphocyte rich (30) Type III: Differentiated epithelial rich (33) Type IV: Undifferentiated epithelial rich (equivalent to thymic carcinoma) (7)
Bernatz, et al (Surg Clin North Am 53:885, 1973)	283	Predominantly lymphocytic (25) Mixed lymphoepithelial (43) Predominantly epithelial (25) Spindle cell (6)
Muller-Hermelink, et al (Curr Top Pathol 75:207, 1986)	58	Cortical (43) Mixed: Predominantly cortical (8) Mixed: Common (36) Medullary (5) Mixed: Predominantly medullary (8)

helpful. Following identification of a mediastinal mass on conventional radiography, contrast-enhanced CT scanning should be performed. CT scanning can differentiate the cystic form from solid lesions as well as the presence of fat, calcium, or fluid within the lesion. MRI is increasingly available for use in the evaluation of mediastinal pathology, but it is less frequently utilized than CT. MRI is superior to CT scanning in defining the relationship between mediastinal masses and vasular structures and is useful in the assessment of vascular invasion by the tumor.

TABLE 11: Thymoma staging systems of Masaoka et al

Stage	Description
Stage I	Macroscopically completely encapsulated Microscopically no capsular invasion
Stage II	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura Microscopic invasion into capsule
Stage III	Macroscopic invasion into neighboring organs (pericardium, great vessels, lungs)
Stage IVA	Pleural or pericardial dissemination
Stage IVB	Lymphogenous or hematogenous metastasis

Masaoka A, Monden Y, Nakahara K, et al: Follow-up study of thymomas with special reference to their clinical stages. Cancer 48:2485, 1981.

TABLE 12: Common chemotherapy regimens for thymoma

Drug	Dose and schedule
Cyclophosphamide, doxorubicin, cisplatin, and prednisone	
Cyclophosphamide	500 mg/m^2 IV on day 1
Doxorubicin	20 mg/m^2/d infused continuously on days 1-3
Cisplatin	30 mg/m^2/d IV on days 1-3
Prednisone	100 mg/d PO on days 1-5
Repeat cycle every 3-4 weeks	

Adapted from Shin DM, Walsh GL, Komaki R, et al: Ann Intern Med 129:100–104, 1998.

Table prepared by Ishmael Jaiyesimi, DO

Invasive diagnostic tests CT-guided percutaneous needle biopsy specimens are obtained using fine-needle aspiration techniques and cytologic evaluation or with larger-core needle biopsy and histologic evaluation. Fine-needle specimens are usually adequate to distinguish carcinomatosis lesions, but core biopsies may be necessary to distinguish most mediastinal neoplasms. Immunohistochemical techniques and electron microscopy have greatly improved the ability to differentiate the cell of origin in mediastinal neoplsms. Most series reported diagnostic yields for percutaneous needle biopsy of 70%-100%.

Mediastinoscopy is a relatively simple surgical procedure accomplished under general anesthesia. It is an adequate approach to the superior, middle, and upper posterior mediastinum, and most series report a diagnostic accuracy of 80%-90%. Anterior mediastinotomy (Chamberlain approach) provides for direct biopsy of tissue and has a diagnostic yield of 95%-100%. Thoracotomy is occasionally necessary to diagnose mediastinal neoplasms, but its indications have been largely supplanted by video-assisted thoracoscopic techniques, which yield 100% accuracy.

The most common tumors one must include in the differential diagnosis of an anterior mediastinal tumor are lymphomas and germ-cell tumors. Immunohistochemical markers are helpful to differentiate thymoma from tumors originating from other cell types.

Pathology

Three of the most common classification schemes for thymoma are listed in Table 10. Verley and Hollman propose a classification system based on tumor architecture, cellular differentiation, and predominant cell type. Bernatz et al describe a simpler classification by presenting thymoma based on the percentage of epithelial cells and lymphocytes. In both of these systems, thymoma with a predominance of epithelial cells was associated with a greater increased incidence of invasion and a subsequently worse prognosis.

Staging and prognosis

The staging system prognosed by Masaoka et al has been widely adopted (Table 11). Stage is an independent predictor of recurrence and long-term survival, as the 5-year survival rate for stage I thymoma was 96%; stage II, 86%; stage III, 69%; and stage IV, 50%.

Treatment

SURGICAL TREATMENT

All patients whose tumors are potentially resectable should undergo surgery. If the patients have evidence of myasthenia gravis, a preoperative consultation with a clinical neurologist should be considered. The incision of choice is almost always a median sternotomy, which is quick and easy to make, and provides excellent exposure to the anterior mediastinum and neck. Although the surgeon is considered the best judge of the tumor's invasiveness, it is often difficult to grossly separate invasion from adherence to surrounding tissue.

Complete resection of thymoma has been found to be the most significant predictor of long-term survival. Several studies have examined the extent of surgical resection on survival and disease-free survival rates. In 241 operative cases, Maggi and colleagues found an 82% overall survival rate in those whose tumors underwent complete resection, and a 26% survival rate at 7 years in those undergoing biopsy alone. Other investigators reported similar results in surgical patients. Therefore, regardless of stage, tumor resectability is one of the important predictors of treatment outcome.

RADIATION TREATMENT

Thymomas are generally radiosensitive tumors, and the use of radiation therapy in their treatments is well established. It has been used to treat all stages of thymoma, either before or after surgical resection. General agreements exist regarding the postoperative treatment of invasive thymoma (stage II and III), while the role of radiation in the treatment of encapsulated (stage I) thymomas is less clear. The value of adjuvant radiation therapy for invasive thymomas is well documented and should be included in the treatment regimen regardless of the completeness of tumor resection.

CHEMOTHERAPY

Chemotherapy has been used in the treatment of invasive thymomas with increasing frequency during the past decade (Table 12). The most active agents appear to be cisplatin, doxorubicin, ifosfamide, and corticosteroids. Combination chemotherapy has generally shown higher response rates and has been used in both neoadjuvant and adjuvant settings and in the treatment of metastatic or recurrent thymomas. CAP (cyclophosphamide, doxorubicin [Adriamycin], and Platinol) or CAPPr (cyclophosphamide, Adriamycin, Platinol, and prednisone) regimens have been used in neoadjuvant and/or adjuvant settings. These regimens have also been used in recurrent thymoma.

Unresectable thymoma

Advanced-stage (III/IVA) thymomas are usually difficult to remove completely. Multidisciplinary approaches, including induction chemotherapy followed by surgical resection, postoperative radiation therapy, and consolidation chemotherapy have recently been reported.

Induction chemotherapy consists of cyclophosphamide (500 mg/m^2 IV on day 1), doxorubicin (20 mg/m^2/d, continuous infusion, days 1-3), cisplatin (30 mg/m^2/d IV on days 1-3), and prednisone (100 mg PO on days 1-5), repeated every 3-4 weeks for 3 courses. Twenty-two evaluable patients were consecutively treated from 1990 to 2000 in a prospective phase II study at M. D. Anderson Cancer Center. After induction chemotherapy, 17 of 22 patients (77%) had major responses, including three complete responses.

Twenty-one patients underwent surgical resection. All patients received postoperative radiation therapy and consolidation chemotherapy. With median follow-up time of 50.3 months, overall survival rates at 5 years and 7 years were 95% and 79%, respectively. Progression-free survival rates were 77% at 5 years and 7 years. The multidisciplinary approaches to unresectable thymoma appear to be promising.

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ON MESOTHELIOMA

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ON THYMOMA

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CHAPTER 8

Breast cancer overview

Risk factors, screening, genetic testing, and prevention

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Breast cancer is the most common malignancy in women, accounting for 32% of all female cancers. Breast cancer also is responsible for 15% of cancer deaths in women, making it the number-two cause of cancer death. An estimated 212,600 new breast cancer cases will be diagnosed in the United States in the year 2003, and 39,800 women will die of this cancer.

This chapter provides an overview of breast cancer, with discussions of epidemiology, etiology and risk factors, genetic cancer risk assessment, signs and symptoms, screening and diagnosis, prevention (including lifestyle changes and chemoprevention), staging, and prognosis. The three chapters to follow focus on the management of stages 0 and I, stage II, and stages III and IV breast cancer, respectively.

Epidemiology

Gender Breast cancer is relatively uncommon in men; the female-to-male ratio is approximately 100:1.

Age The risk of developing breast cancer increases with age. The disease is uncommon in women younger than the age of 40 years; only about 0.8% of breast cancers occur in women < 30 years old and approximately 6.5% develop in women between 30 and 40 years old.

Race White women have a higher overall rate of breast cancer than African-American women; however, this difference is not apparent until age 50 and is marked only after menopause. The incidence of breast cancer in American Asian and Hispanic women is approximately half that in American Caucasian women. Breast cancer risk is extremely low in Native American women.

Geography There is at least a fivefold variation in the incidence of breast cancer among different countries, although this difference appears to be narrowing. The incidence of breast cancer is significantly lower in Japan, Thailand, Nigeria, and India than in Denmark, the Netherlands, New Zealand, Switzerland, the United Kingdom, and the United States. It has been suggested that these trends in breast cancer incidence may be related, in some way, to

dietary influences, particularly dietary fat consumption (see "Etiology and risk factors" section).

Socioeconomic status The incidence of breast cancer is greater in women of higher socioeconomic background. This relationship is most likely related to lifestyle differences, such as age at first birth.

Disease site The left breast is involved more frequently than the right, and the most common locations of the disease are the upper outer quadrant and retroareolar region.

Survival Survival rates for patients with nonmetastatic breast cancer (all stages) have improved in recent years (Table 1). These improvements may be secondary to advances in adjuvant chemotherapy and radiation therapy. In addition, early detection of recurrent disease after breast-conservation therapy allows for salvage surgery.

Etiology and risk factors

Numerous risk factors have been associated with the development of breast cancer, including genetic, environmental, hormonal, and nutritional influences. Despite all of the available data on breast cancer risk factors, 75% of women with this cancer have no risk factors.

Genetic factors Hereditary forms of breast cancer constitute only 5%-7% of breast cancer cases overall. However, the magnitude of the probability that a woman will develop cancer if she inherits a highly penetrant cancer gene mutation justifies the intense interest in predictive testing. Commercial testing is available for several genes (*BRCA1, BRCA2,* and *p53)* that are associated with a high risk for breast cancer development (see "Genetic cancer risk assessment" section).

Elevated risk for breast cancer is also associated with mutations in the *PTEN* gene in Cowden's syndrome (described below), and modest increased risk (relative risk of 3.9-6.4) may be seen in women who are heterozygous for a mutation in the *ATM* gene, which is associated with the recessive disease ataxia-telangiectasia in the homozygous state. A moderately increased risk for breast cancer (2-fold for women and 10-fold for men) was recently associated with a variant (1100 delC) in the cell-cycle checkpoint kinase gene, CHEK2, among families without *BRCA* gene mutations.

TABLE 1: Survival of women with breast cancer, according to stage

Stage	Survival rate at 8 years (%)
Stage I	90
Stage II	70
Stage III	40
Stage IV	10

BRCA1 gene The *BRCA1* gene is located on chromosome 17. This gene is extremely large and complex, and more than 1,000 different mutations have been discovered, distributed along the entire gene. *BRCA1* mutations are inherited in an autosomal-dominant fashion and are associated with an increased risk for breast, ovarian, and, to a lesser degree, prostate cancers. A *BRCA1* mutation carrier has a lifetime risk of developing breast cancer on the order of 56%-85% and a 15%-45% lifetime risk of developing ovarian cancer.

BRCA2 gene The *BRCA2* gene has been localized to chromosome 13. *BRCA2* is approximately twice as large as *BRCA1* and similarly complex.

Alterations in *BRCA2* have been associated with an increased incidence of breast cancer in both women (similar to *BRCA1)* and men (6% lifetime risk). Increased risk for ovarian cancer, pancreatic cancer, and melanoma has also been reported. Together, *BRCA1* and *BRCA2* account for most hereditary breast and ovarian cancer families and approximately half of hereditary breast cancer families.

The incidence of *BRCA* gene mutations in the general breast cancer population is unknown since most of the data have come from studies of high-risk populations. In one population-based study of women with breast cancer, only 9.4% of women < 35 years of age at the time of diagnosis and 12.0% of women < 45 years old who also had a first-degree relative with breast cancer had germline *BRCA1* or *BRCA2* mutations. However, a 40-year-old woman of Ashkenazi Jewish ancestry who has breast cancer has a 20%-30% probability of bearing one of three founder *BRCA* gene mutations, based on data from high-risk clinics, testing vendors, and Israeli series.

Li-Fraumeni syndrome This rare syndrome is characterized by premenopausal breast cancer in combination with childhood sarcoma, brain tumors, leukemia and lymphoma, and adrenocortical carcinoma. Tumors frequently occur in childhood and early adulthood and often present as multiple primaries in the same individual. Germline mutations in the *p53* gene on chromosome 17p have been documented in persons with this syndrome. Inheritance is autosomal dominant with a penetrance of at least 50% by age 50.

Cowden's syndrome is inherited as an autosomal-dominant trait and is notable for a distinctive skin lesion (trichilemmoma) and mucocutaneous lesions. Patients with this uncommon syndrome have a high incidence of GI polyps and thyroid disorders; lifetime estimates for breast cancer among women with this syndrome range from 25%-50%. Germline mutations in the *PTEN* gene, located on chromosome 10q23, are responsible for this syndrome.

Family history The overall relative risk of breast cancer in a woman with a positive family history in a first-degree relative (mother, daughter, or sister) is 1.7. Premenopausal onset of the disease in a first-degree relative is associated with a threefold increase in breast cancer risk, whereas postmenopausal diagnosis increases the relative risk by only 1.5. When the first-degree relative has bilateral disease, there is a fivefold increase in risk. The relative risk for a woman whose first-degree relative developed bilateral breast cancer prior to menopause is nearly 9.

Proliferative breast disease The diagnosis of certain conditions after breast biopsy is also associated with an increased risk for the subsequent development of invasive breast cancer. They include moderate or florid ductal hyperplasia and sclerosing adenosis, which pose only a slightly increased risk of breast cancer (1.5-2.0 times); atypical ductal or lobular hyperplasia, which moderately increases risk (4-5 times); and lobular carcinoma in situ (LCIS), which markedly increases risk (8-11 times; see more detailed discussion of LCIS in chapter 9). Patients who have a family history of breast cancer along with a personal history of atypical epithelial hyperplasia have an 8-fold increase in breast cancer risk when compared with patients with a positive family history alone and an 11-fold increase in breast cancer risk when compared with patients who do not have atypical hyperplasia and have a negative family history.

Personal cancer history A personal history of breast cancer is a significant risk factor for the subsequent development of a second, new breast cancer. This risk has been estimated to be as high as 1% per year from the time of diagnosis of an initial sporadic breast cancer. The risk for development of a second primary breast cancer is significantly higher for women with hereditary breast cancer, approximately 5% per year (50%-60% lifetime risk). Women with a history of endometrial, ovarian, or colon cancer also have a higher likelihood of developing breast cancer than those with no history of these malignancies.

Menstrual and reproductive factors Early onset of menarche ($<$ 12 years old) has been associated with a modest increase in breast cancer risk (twofold or less). Women who undergo menopause before age 30 have a twofold reduction in breast cancer risk when compared to women who undergo menopause after age 55. A first full-term pregnancy before age 30 appears to have a protective effect against breast cancer, whereas a late first full-term pregnancy or nulliparity may be associated with a higher risk. There is also a suggestion that lactation protects against breast cancer development.

Radiation exposure An increased rate of breast cancer has been observed in survivors of the atomic bomb explosions in Japan, with a peak latency period of 15-20 years. More recently, it has been noted that patients with Hodgkin's disease who are treated with mantle irradiation, particularly women who are younger than age 20 at the time of radiation therapy, have an increased incidence of breast cancer.

Exogenous hormone use Epidemiologic data provide strong evidence for an association between plasma estrogens and breast cancer risk.

The 1996, large meta-analysis of the relationship between oral contraceptive use and breast cancer risk showed that a history of recent oral contraceptive use, rather than duration of use, was a better predictor of breast cancer risk. (Meta-analysis was of 54 earlier studies including 53,297 women with breast cancer and 100,239 women without breast cancer.) The increase in risk for current users was modest (24% for ever users vs never users). These data were based primarily on older high-dose and moderate-dose oral contraceptive pills and not the recently introduced low-dose pills. It is, therefore, likely that the

TABLE 2: Risk management options for *BRCA* mutation carriers[a]

Recommended for breast cancer detection
Monthly self-examination of the breast beginning in late teen years
Beginning at age 25-35 (or at least 10 years before the earliest onset cancer in the kindred):
Clinician breast examination every 6 months
Annual mammography
Discussed as options:
Bilateral risk reduction mastectomy (total or skin-sparing)
Participation in clinical trials for chemoprevention (ie, STAR)
Recommended for ovarian cancer detection or prevention
Pelvic examination and PAP smear annually
Serum CA-125 q 6-12 months
Transvaginal ultrasonography q 6-12 months
Discussed as options:
Risk reduction salpingo-oophorectomy upon completion of childbearing
Oral contraceptive use
Reproductive counseling (? earlier childbearing)

[a] Also offered to women at increased risk because of a positive family history of hereditary breast and ovarian cancer but for whom genotypic information is not available.

small increase in breast cancer risk associated with the early formulations of oral contraceptives will diminish with the new low-dose pills.

In regard to hormone replacement therapy (HRT), all meta-analyses have concluded that ever users of postmenopausal estrogens have little or no increase in the risk of breast cancer compared with women who have never used this therapy. Duration of use, however, strongly predicts breast cancer risk, with risk measurably increasing after 5 years of use compared with never used. The increase in risk for unopposed estrogens is between 30% and 45%. Thus, although a majority of women are likely short-term users and experience little in the way of significant excess risk, current users and especially long-term users do appear to have an increased risk.

More recent research has looked at estrogen alone vs combination therapy. The addition of progestin to estrogen significantly increased the risk relative to estrogen alone, and sequential therapy carried a higher risk than combination therapy.

The only clear benefits of exogenous HRT for menopausal women are short-term use to decrease menopausal symptoms. Possible benefits may include reductions in the risk of cardiovascular disease and prevention of osteoporosis. Patients considering HRT should carefully weigh the risks and benefits.

Alcohol Moderate alcohol intake (two or more drinks per day) appears to modestly increase breast cancer risk.

High-fat diet Diets that are high in fat have been associated with an increased risk for breast cancer. As mentioned previously, it has been suggested that differences in dietary fat content may account for the variations in breast cancer incidence observed among different countries.

Obesity Alterations in endogenous estrogen levels secondary to obesity may enhance breast cancer risk.

Genetic cancer risk assessment

Dramatic advances in our understanding of the genetic basis for cancer have led to the development of new technologies and tools for genetic cancer risk assessment. Tests for *BRCA1* and *BRCA2* mutations, responsible for the majority of hereditary breast and ovarian cancer (HBOC) families, are now available commercially.

Genetic testing clearly has the potential to benefit carefully selected and counseled families. Education and adequately trained health care professionals are key elements in the successful integration of genetic cancer risk assessment into clinical practice.

The genetic risk assessment process begins with an assessment of perceived risk and the impact of cancer on the patient and her family. This information forms the framework for counseling.

Comprehensive personal and family histories Detailed information regarding personal, reproductive, and hormonal risk factors is noted. Family history, including age at disease onset, types of cancer, and current age or age at death, is obtained for all family members going back at least three generations.

Documentation of cancer cases is crucial to accurate risk estimation. Pathology reports, medical record notes, and death certificates may all be used in determining the exact diagnosis.

Pedigree construction and evaluation The family pedigree is then constructed and analyzed to determine whether a pattern of cancer in the family is consistent with genetic disease. Sometimes, small family structure or lack of information about the family limits assessment of a hereditary trait; other times, clues, such as ancestry or early age at diagnosis, influence risk assessment and the usefulness of genetic testing.

Individual risk assessment Empiric cancer risk estimates are derived from the information gathered, as well as an estimate of the likelihood that a detectable *BRCA1* or *BRCA2* mutation is responsible for the disease in the family. The BRCAPRO computer program is a cancer risk assessment tool that uses a family history of breast or ovarian cancer in first- and second-degree relatives and includes a Bayesian calculation to account for age-specific penetrance differences, to calculate the probabilities that either a *BRCA1* or *BRCA2* mutation is responsible for the disease.

TABLE 3: Features indicating an increased likelihood of a *BRCA* mutation

Multiple cases of early-onset breast cancer
Ovarian cancer (with a family history of breast or ovarian cancer)
Breast and ovarian cancer in the same woman
Bilateral breast cancer
Ashkenazi Jewish heritage
Male breast cancer

Education about the principles of genetics and hereditary cancer patterns is provided. Information on the application of genetic testing (appropriateness, limitations, advantages, and disadvantages) is also given.

Genetic counseling and testing Informed consent is obtained before genetic testing is performed. For individuals who decide to undergo testing, a post-test counseling session is scheduled to disclose and explain the results in person.

Customized screening and prevention recommendations Regardless of whether or not the woman undergoes genetic testing, a customized management plan is delineated, with the goal of prevention or early detection of malignancy, within the context of her personal preferences and degree of risk (Table 2).

Follow-up care and support The genetic cancer risk assessment service also provides follow-up care and support. This may include cancer surveillance measures, as well as assistance with family dynamics and advising patients about sharing information with at-risk relatives.

Models for predicting the likelihood of a BRCA *mutation*

Several studies have assessed the frequency of *BRCA1* or *BRCA2* mutations in women with breast or ovarian cancer from clinical referral centers. These data are likely to be subject to some selection biases. Personal and family characteristics that are associated with an increased likelihood of a *BRCA1* or *BRCA2* mutation are summarized in Table 3.

Laboratory methods

Several techniques/strategies for detecting mutations in cancer genes have been adopted by different researchers and commercial vendors. Current technology misses 8%-10% of pathologic alterations in *BRCA1* and *BRCA2* (generally large rearrangements).

Directed assays are available for specific founder or ancestral mutations that are common in a given population. Among Ashkenazi Jews, 1 in 40 individuals bear one of three founder mutations (185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2)*, and these mutations account for 25% of early-onset

breast cancer in this population. Moreover, 95% of Ashkenazi Jews with a *BRCA* gene mutation will have one of the three founder mutations.

Limitations All of the approaches to detecting mutations have limitations. In general, discovery of an inactivating or "deleterious" mutation of either *BRCA1* or *BRCA2* indicates a high probability that the person will develop breast and/or ovarian cancer.

One of the greatest challenges is the interpretation of missense mutations. These mutations are more likely to be significant if located in an evolutionarily conserved or functionally critical region of the protein. In the absence of a clear disease association, it is often difficult to exclude the possibility that a given missense alteration simply represents a rare polymorphism. A testing service may designate such changes as "genetic variants of uncertain significance."

Testing strategies

In general, testing should be initiated with the youngest affected individual in a given family. Even if one is convinced that a family has HBOC based on clinical criteria, there is only a 50% chance that an offspring or sibling of an affected patient will have inherited the deleterious allele. Therefore, only a positive test (detection of a known or likely deleterious mutation) is truly informative.

Until the "familial mutation" is known, a negative test result could mean either that the unaffected person being tested did not inherit the cancer susceptibility mutation or that the person inherited the disease-associated gene but the mutation was not detectable by the methods used.

In many cases, no affected family members are available for testing. In that case, one may proceed with genetic testing of an unaffected person, but only after she has been thoroughly counseled regarding its risks, benefits, and limitations.

Unless there is a suggestive family history, cancer susceptibility testing is not considered appropriate for screening unaffected individuals in the general population. However, it may be reasonable to test unaffected persons who are members of an ethnic group in which specific ancestral mutations are prevalent and whose family structure is limited (ie, the family is small, with few female relatives or no information due to premature death from noncancerous causes).

Impact of genetic cancer risk status on management

Data from the Breast Cancer Linkage Consortium (BCLC) suggest that the cumulative risk of developing a second primary breast cancer is approximately 5% per year (up to 65% by age 70) among *BRCA* gene mutation carriers who have already had breast cancer. Thus, knowledge of the genetic status of a woman affected with breast cancer might influence the initial surgical approach (eg, bilateral mastectomy might be recommended for a mutation carrier instead of a more conservative procedure). Moreover, since ovarian cancer risk may be markedly increased in women with *BRCA1* mutations (and to a lesser degree with *BRCA2* mutations), additional measures, such as surveillance for presymptomatic detection of early-stage tumors or consideration of oophorectomy, may be warranted. According to data from *BRCA* carriers

The results of a prospective study of the impact of risk reduction salpingo-oophorectomy among women with *BRCA* gene mutations indicated a 75% reduction in breast and ovarian cancer risk *(Kauf ND, Satagopan JM, Robson ME, et al: N Engl J Med 346:1609-1615, 2002)*. A larger retrospective study (n = 551) estimated the protective effect of RRSO as a hazard ratio of 0.04 [0.01-0.16] for ovarian cancer and 0.47 [0.29-0.77] for breast cancer *(Rebbeck TR, Lynch HT, Neuhausen SL, et al: N Engl J Med 346:1616-1622, 2002)*.

who underwent risk reduction salpingo-oophorectomy (RRSO), breast cancer risk may also be decreased by the reduction in ovarian hormone exposure.

Recent retrospective data suggest that risk reduction bilateral mastectomy significantly decreases (by approximately 90%), but does not eliminate, the risk of developing breast cancer in women with a family history of the disease. Skin-sparing techniques should involve the removal of all mammary tissue, including the nipple and areola. Contralateral prophylactic mastectomy in women with a previous history of breast cancer appears to be efficacious in the prevention of new primary tumors.

Potential benefits and risks of genetic testing

The ability to identify individuals at highest risk for cancer holds the promise of improved prevention and early detection of cancers. Patients who are *not* at high risk can be spared anxiety and the need for increased surveillance. Recent studies suggest a better emotional state among at-risk relatives who undergo testing than among those who choose not to know their status. The patient's perception of risk is often much higher than risk estimated by current models.

Potential risks Potential medical, psychological, and socioeconomic risks must be addressed in the context of obtaining informed consent for genetic testing.

Concerns about insurance Fear about adverse effects of testing on insurability remains the premier concern among patients. Close behind that is concern about the costs of analyzing large complex genes ($2,680 for *BRCA1* and *BRCA2)* in an uncertain insurance coverage and reimbursement environment.

Legal and privacy issues The legal and privacy issues surrounding genetic testing are as complex as the testing technologies. Although several state laws regarding the privacy of medical information, genetic testing, and insurance and employment discrimination have been passed, they vary widely.

The 1996 Health Insurance Portability and Accountability Act (US public law 104-191) stipulates that genetic information may not be treated as a preexisting condition in the absence of a diagnosis of the condition related to such information. It further prohibits group medical plans from basing rules for eligibility or costs for coverage on genetic information. However, the law does not address genetic privacy issues and does not cover individual policies. Many states have laws addressing genetic discrimination, but gaps remain.

ASCO recommendations for genetic testing

The American Society of Clinical Oncology (ASCO) recommends that cancer predisposition testing be offered only when: (1) the person has a strong family history of cancer or very early onset of disease; (2) the test can be adequately

FIGURE 1: Malignant calcifications (comedocarcinoma) in a classic linear dot and dash configuration (BI-RAD 5 lesion). BI-RAD = Breast Imaging Reporting Data System.

FIGURE 2: Left panel: A dense mass with partially unsharp margins (BI-RAD 4 lesion), which proved to be a fibroadenoma. Right panel: A small, spiculated mass (BI-RAD 5 lesion), which has engulfed a coarse, benign calcification. This lesion proved to be an invasive ductal carcinoma, not otherwise specified (NOS). BI-RAD = Breast Imaging Reporting Data System.

FIGURE 3: Left panel: This focal mass with truly nonsharp margins (BI-RAD 4 lesion) was diagnosed as a tubular carcinoma on stereotactic core biopsy. Right panel: A well-circumscribed lesion containing fat (BI-RAD 2 lesion), which is pathognomonic for a breast hamartoma (fibroadenolipoma). BI-RAD = Breast Imaging Reporting Data System.

FIGURE 4: Focal architectural distortion may be difficult to see, but, if confirmed, it has the highest positive predictive value for breast carcinoma. This BI-RAD 4 lesion proved to be an invasive lobular carcinoma, which often has a subtle mammographic appearance. BI-RAD = Breast Imaging Reporting Data System.

FIGURE 5: This breast ultrasonographic image demonstrates a hypoechoic, solid mass, which exhibits posterior shadowing and is taller than wide. This BI-RAD 4 lesion proved to be an invasive ductal carcinoma, not otherwise specified (NOS). BI-RAD = Breast Imaging Reporting Data System.

interpreted; and (3) the results will influence the medical management of the patient or family member. The National Comprehensive Cancer Network (NCCN) recently published practice guidelines for genetics/familial high-risk cancer screening.

Signs and symptoms

Mammographic findings Increasing numbers of breast malignancies are being discovered in asymptomatic patients through the use of screening mammography. Mammographic features suggestive of malignancy include asymmetry, microcalcifications, a mass, or an architectural distortion (see Figures 1-5).

When these features are identified on a screening mammogram, they should, in most cases, be further evaluated with a diagnostic mammogram (and, in some cases, with a breast ultrasonographic image), prior to determining the need for a tissue diagnosis. Often, pseudolesions, such as those caused by summation artifact, dust on the mammographic cassettes, and dermal calcifications, are correctly identified in this manner. All mammographic lesions (and the examinations themselves) must be unambiguously categorized according

TABLE 4: BI-RAD classification of mammographic lesions

BI-RAD class	Description	Probability of malignancy (%)	Follow-up
0	Needs additional evaluation	1	Diagnostic mammogram, ultrasonographic image
1	Normal mammogram	0	Yearly screening
2	Benign lesion	0	Yearly screening
3	Probably benign lesion	< 2	Short interval follow-up
4	Suspicious for malignancy	20	Biopsy
5	Highly suspicious for malignancy	90	Biopsy

BI-RAD = Breast Imaging Reporting Data System

to one of the six Breast Imaging Reporting Data System (BI-RAD) classifications developed by the American College of Radiology (Table 4).

Breast lump When signs or symptoms are present, the most common presenting complaint is a lump within the breast. The incidence of this complaint can range from 65%-76%, depending on the study.

Paget's disease has been associated with intraductal carcinoma involving the terminal ducts of the breast and may have an associated invasive component. It presents as an eczematoid change in the nipple, a breast mass, or bloody nipple discharge. Cytology may be helpful in establishing the diagnosis; however, negative cytologic results should not preclude a biopsy.

Other local symptoms Breast pain is the presenting symptom in ~5% of patients, breast enlargement in 1%, skin or nipple retraction in ~5%, nipple discharge in ~2%, and nipple crusting or erosion in 1%.

Screening and diagnosis

Screening

Breast self-examination The American Cancer Society recommends that women begin monthly breast self-examination at the age of 20. A recent meta-analysis of 12 studies involving a total of 8,118 patients with breast cancer correlated the performance of breast self-examination with tumor size and regional lymph node status. Women who performed breast self-examination were more likely to have smaller tumors and less likely to have axillary node metastases than those who did not.

A major problem with breast self-examination as a screening technique is that it is rarely performed well. Only 2%-3% of women do an ideal examination a year after instruction has been provided.

Clinical breast examination The American Cancer Society recommends that women begin clinical breast examination at the age of 20 and have an examination every 3 years between ages 20 and 39, and annually beginning at age 40. Beginning at age 40, the clinical breast examination should be timed to occur near to/prior to screening mammography. If the clinician detects an abnormality, the patient should then undergo diagnostic imaging rather than screening. Clinical breast examination should be performed and a complete breast history obtained when a woman presents for routine health care. The clinical examination should include inspection and palpation of the breast and regional lymph nodes. Between 14% and 21% of breast cancers are detected by clinical breast examination.

Mammography Despite conflicting coverage in the lay press, the benefit of screening mammography is well established by the findings of an evidence-based clinical trial (see Jackson reference). The American Cancer Society, the American College of Radiology, and the American Medical Association each have updated their guidelines since 1997 and recommend annual mammography beginning at age 40. The National Cancer Institute (NCI) also updated its guidelines in 1997, recommending that women undergo screening mammography every 1-2 years beginning in their 40s. The United States Preventive Services Task Force updated its guidelines in 2002 and now recommends mammography every 1-2 years, alone or with clinical breast examination, for women aged 40 and older.

Screening mammography is performed in the asymptomatic patient to detect an occult breast cancer. This contrasts with diagnostic mammography, which is performed in a patient with a breast abnormality (palpable mass, bloody nipple discharge, or some other clinical finding) to further identify the etiology of the problem.

Physical examination and mammography are complementary. Mammography has a sensitivity of 85%-90% and, thus, would miss 10%-15% of clinically evident tumors while detecting the majority of cases an average of 2 years prior to any perceptible clinical signs or symptoms.

Screening recommendations for average-risk patients No upper age limit has been suggested, and the previous recommendation for a "baseline" mammographys between the ages of 35 and 40 has been withdrawn.

Screening recommendations for high-risk patients Based on epidemiologic evidence that premenopausal familial breast cancer often presents at similar ages among affected family members, many breast imaging centers recommend that yearly screening for such high-risk individuals begin 5-10 years prior to the youngest age at which their first-degree relative was diagnosed with breast cancer. For example, according to this algorithm, a woman whose mother developed breast cancer at age 45 could begin yearly screening at age 35, in addition to biannual clinical breast examinations. Screening for women at genetic risk may begin at age 25.

Digital mammography was approved by the FDA in 2000 and is rapidly being adopted by leading breast centers worldwide. Initial trials indicate a com-

parable sensitivity to film-based mammography, with the benefit of a reduced risk of women called back from screening for additional work-up. The FDA also approved computer-aided diagnosis systems for mammography beginning in 2001. For a small additional fee, mammograms are scanned by a computer and possible lesions are marked for further review by the radiologist. A number of studies have shown a reduced risk of "missed cancers" when computer-aided diagnosis is thus employed.

Screening ultrasonography Sensitivity of mammography is diminished when the breast tissue is dense. There have been recent reports in the literature concerning the role of screening breast ultrasonography in women with dense breasts on mammography and normal mammography and clinical breast examination. In a study by Kolb, approximately 4,900 women with dense breast tissue on mammography who had a normal mammogram and an unremarkable clinical breast examination underwent screening breast ultrasonography. The studies were performed by a single radiologist. The time required to perform the screening study ranged from 2 minutes 11 seconds to 11 minutes 30 seconds. The length of time required to perform the screening ultrasonography was related to the breast size and pathologic findings. There were 320 biopsies performed and 33 cancers were detected. Further studies are necessary to validate these results.

Evaluation of a cystic mass

Fine-needle aspiration (FNA) When a dominant breast mass is present and the history and physical examination suggest that it is a cyst, the mass can simply be aspirated with a fine needle. Aspiration of a simple benign breast cyst should yield nonbloody fluid and result in complete resolution of the lesion.

Ultrasonography can also be used to determine whether a lesion is solid or cystic and whether a cyst is simple or complex. A complex cyst does not meet the strict criteria of a simple cyst. For example, a complex cyst may demonstrate low level echoes within the cyst fluid or a thickened cyst wall. These features may also be caused by cyst aspiration (presumably due to postaspiration bleeding).

Biopsy A biopsy is indicated if the cyst fluid is bloody, the lesion does not resolve completely after aspiration, or the cyst recurs after repeated aspirations. Cytologic examination of the fluid is not routinely indicated, as the yield for positive cytology is so low. Cystic carcinoma accounts for $< 1\%$ of all breast cancers. However, an intraluminal solid mass is a worrisome sign suggesting (intra) cystic carcinoma and should be biopsied.

Evaluation of a solid mass

A solid mass can be evaluated in a variety of ways. The decision to observe a patient with a breast mass that appears to be benign should be made only after careful clinical, radiologic, and cytologic examinations.

Mammography is used to assess the radiologic characteristics of the mass and is important for the evaluation of the remainder of the ipsilateral breast as well as the contralateral breast.

FNA is a simple, easy-to-perform method for obtaining material for cytologic examination. The overall incidence of false-positive results ranges from 0%-2.5% (0.7% when performed by experienced technicians) and the incidence of false-negative results varies from 3%-27% (3%-9% in experienced hands). Reasons for false-negative readings include less-than-optimal techniques in preparing the cytologic material, missing the lesion on aspiration, tumor necrosis, and incorrect cytologic interpretation.

Biopsy A core biopsy (typically 14 gauge) can be advantageous since architectural as well as cellular characteristics can be evaluated. An excisional biopsy, in which the entire breast mass is removed, definitively establishes the diagnosis. When the mass is extremely large, an incisional biopsy (which entails removal of only a portion of the mass) may be more appropriate.

Evaluation of nonpalpable mammographic abnormalities

Excisional biopsy Prior to 1991, almost all nonpalpable mammographic lesions were diagnosed by surgical excision, and this remains a major diagnostic tool today. Prior to surgery, a breast imager places a hook-wire at the lesion in order to guide the surgeon to it accurately. After the target lesion has been excised, a specimen film is then obtained to ensure that it was successfully removed and, in some cases, to assess the gross adequacy of the margins around the lesion.

Stereotactic- and ultrasonography-guided core biopsies have revolutionized the management of nonpalpable mammographic lesions, and currently the majority of these lesions can be diagnosed with these percutaneous techniques. At various facilities around the United States, the percentage of benign (false-positive) breast biopsies with these techniques ranges from 60%-93%.

Stereotactic-guided core biopsy Several different biopsy devices are available, from a 14-gauge core biopsy needle, to an 11-gauge vacuum-assisted biopsy gun (Mammotome and MIB), to a 20-mm wide percutaneous excisional cannula (ABBI). With each device, the lesion is accurately localized in three dimensions by the use of a stereotactic table, which takes a pair of mammographic images at a fixed angle to each other for lesion triangulation.

Numerous studies comparing the sensitivity and specificity of stereotactic biopsy vs biopsy have consistently found the two procedures to be statistically equivalent. A recent large series demonstrated a false-negative rate of 1.4% for stereotactic core biopsy after long-term follow-up, which equals best published results with surgical biopsy.

Up to 80% of nonpalpable mammographic lesions are candidates for stereotactic core biopsy. Lesions near the chest wall or immediately behind the nipple often cannot be reached on the stereotactic table. Diffuse lesions, such as scattered calcifications or a large asymmetric density, are subject to undersampling with the percutaneous approaches. Some patients are unable to lie prone on the stereotactic table for the duration of the examination. Finally, stereotactic units and trained personnel are not universally available.

TABLE 5: Examples of eligible risk profiles used in the Breast Cancer Prevention Trial

Age (yr)	Risk profile
35	Two affected first-degree relatives plus personal history of biopsy
40	Two affected first-degree relatives plus no live births
45	Two affected first-degree relatives *or*
	One affected first-degree relative plus personal history of biopsy

Ultrasonography-guided core biopsies are another accurate percutaneous technique, useful for lesions best imaged by ultrasonography. Since the biopsy gun is handheld and guided in real time by the ultrasound imager, there is more variability in performance, depending on the experience and skill of the practitioner. The overall reported accuracy rate of ultrasonography-guided biopsy is comparable to rates achieved with stereotactic and surgical biopsies.

Ultrasonography- or stereotactic-guided FNA is another biopsy option. Although somewhat less invasive than core biopsy, FNA provides only cytologic (not histologic) pathology results. This technique can result in both false-positive and false-negative results, whereas a false-positive result has not been reported to date for core breast biopsies. FNA is most successful in centers that have an experienced cytopathologist, who, ideally, is available on site to review smears for adequacy during FNA procedures.

Breast MRI is a sensitive tool for detecting occult breast cancer foci. Due to its limited specificity and high cost, however, MRI is not likely to become a screening tool for average-risk women. However, a recent study indicated that breast MRI was superior to mammography and/or ultrasonography for detecting breast cancers in high-risk women (ie, *BRCA* gene mutation carriers).

MRI is currently used primarily to search for a subtle primary breast carcinoma in a patient with metastatic disease, to evaluate the extent of disease in a biopsy-proven breast carcinoma (useful if breast conservation is being considered), or to screen very high-risk women with dense breast on mammograms

TABLE 6: Number of breast cancer events among Breast Cancer Prevention Trial participants[a]

Type of event	Placebo	Tamoxifen	Total
Invasive breast cancer	154 (5)	85 (3)	239 (8)
Noninvasive breast cancer	59	31	90
Total	**213 (5)**	**116 (3)**	**329 (8)**

[a] Numbers in parentheses indicate the number of deaths due to breast cancer.

TABLE 7: Number of fracture events among Breast Cancer Prevention Trial participants

Type of fracture	Placebo	Tamoxifen	Total
Hip	20	9	29
Colles'	12	7	19
Spine	39	31	70
Total	**71**	**47**	**118**

and nondiagnostic ultrasonography. There is increasing availability of imaging centers capable of MRI localization of breast lesions.

Ultrasonography Stavros et al have described ultrasonographic features of solid masses that suggest benign or malignant disease, such as sharp margins (benign) and taller-than-wide lesions (malignant). Although these features are useful for clinical decision-making, their utility in increasing the specificity of the breast lesion work-up has not been verified.

Sestamibi nuclear medicine scanning can help differentiate benign from malignant mammographic asymmetries and may play a role in evaluating palpable masses. Due to its limited spatial resolution and scatter, this technique is not reliable for lesions 1 cm or smaller.

Prevention

LIFESTYLE CHANGES ASSOCIATED WITH BREAST CANCER RISK REDUCTION

There is increasing evidence that lifestyle changes may alter an individual's breast cancer risk.

Physical activity has been associated with a reduction in breast cancer risk. The benefit was greatest in premenopausal women, as compared with postmenopausal women, and was larger in younger as opposed to older women. The activity can be related to leisure or work time activities.

TABLE 8: Number of invasive cancer events among Breast Cancer Prevention Trial participants

Type of cancer	Placebo	Tamoxifen	Total
Breast	154	85	239
Endometrial	14	33	47
All other	88	85	173
Total	**256**	**203**	**459**

TABLE 9: Number of vascular events among Breast Cancer Prevention Trial participants

Vascular event	Placebo	Tamoxifen	Total
Fatal stroke	3	4	7
Nonfatal stroke	21	30	51
Transient ischemic attack	21	18	39
Fatal pulmonary embolism	0	2	2
Nonfatal pulmonary embolism	6	15	21
Deep vein thrombosis requiring hospitalization	3	3	6
Deep vein thrombosis not requiring hospitalization	16	27	43
Total	**70**	**99**	**169**

It has been suggested that women who exercise 3.5-4.0 times per week have a reduced incidence of breast cancer, compared with women who do not exercise. Exercise's protective effect may be associated with a reduction in the frequency of ovulatory cycles and circulating estrogen and progesterone levels.

Alcohol consumption Numerous studies that have evaluated the effects of alcohol consumption on breast cancer risk and the results of a cohort study addressing this issue were recently published. When compared with nondrinkers, women who consumed 2.3-4.5 bottles of beer per day, 2.5-5.6 glasses of wine per day, or 2-4 shots of liquor per day had a 41% higher risk of developing invasive breast cancer. Therefore, a reduction in alcohol consumption is likely to reduce breast cancer risk.

The biological basis for the association between alcohol consumption and an increased risk of breast cancer is unclear. It has been proposed that there is a positive correlation between alcohol and estrogen levels.

Alterations in diet and tobacco use A reduced incidence of breast cancer has been observed in countries where the diet is typically low in fat. However, no reduction in breast cancer risk has been observed in the United States when women followed low-fat diets. An association between red meat consumption or tobacco use and breast cancer risk has not been demonstrated.

Lactation Although it has been suggested that lactation may protect against breast cancer, it is unclear whether lactation reduces breast cancer risk. A recent study failed to demonstrate any breast cancer risk reduction in women who breast-fed and showed no dose-response effect in women who breast-fed for longer time periods.

TABLE 10: TNM staging system for breast cancer

Primary tumor (T)

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	(DCIS) Carcinoma in situ
Tis	(LCIS) Carcinoma in situ
Tis	Paget's disease of the nipple with no tumor
T1	Tumor ≤ 2 cm in greatest dimension
T1mic	Microinvasion ≤ 0.1 cm in greatest dimension
T1a	Tumor > 0.1 but not > 0.5 cm in greatest dimension
T1b	Tumor > 0.5 cm but not >1 cm in greatest dimension
T1c	Tumor > 1 cm but not > 2 cm in greatest dimension
T2	Tumor > 2 cm but not > 5 cm in greatest dimension
T3	Tumor > 5 cm in greatest dimension
T4	Tumor of any size, with direct extension to (a) chest wall or (b) skin only, as described below
T4a	Extension to chest wall, not including pectoralis muscle
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

Regional lymph nodes (N)

Nx	Regional lymph nodes cannot be assessed (eg, previously removed)
N0	No regional lymph node metastasis
N1	Metastasis in movable ipsilateral axillary lymph node(s)
N2	Metastasis in ipsilateral axillary lymph node(s) fixed or matted, or in clinically apparent[a] ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis
N2a	Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastasis only in clinically apparent[a] ipsilateral internal mammary nodes and in the *absence* of clinically evident axillary lymph node metastasis

CHEMOPREVENTION

Breast Cancer Prevention Trial

The National Institutes of Health (NIH) and NCI have publicized the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT). Women who had a risk of developing breast cancer equivalent to that of women 60 years of age qualified as participants in this double-blind, randomized trial. (For representative eligibility profiles, see Table 5.) A total of 13,388 women were randomized to receive tamoxifen (Nolvadex) or placebo.

Regional lymph nodes (N) ***(continued)***

N3	Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent[a] ipsilateral internal mammary lymph node(s) and in the *presence* of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastasis in ipsilateral infraclavicular lymph node(s) and axillary lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)

Distant metastasis (M)

Mx	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1[b]	N0	M0
Stage IIA	T0	N1	M0
	T1[b]	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1[b]	N2	M0
	T2	N2	M0
	T3	N1-2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ

[a] Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

[b] T1 includes T1mic

From: Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

Benefits of therapy The summary results indicate that tamoxifen prevented about half of both invasive and noninvasive breast cancers in all age groups (Table 6). In addition to this reduction in invasive and noninvasive breast cancer, a secondary benefit of tamoxifen appeared to be a reduction in the incidence of hip fracture (Table 7).

At present, no survival advantage has been shown for participants in this trial. A recent study of *BRCA* genotypes among BCPT participants suggested that tamoxifen may not be an effective chemopreventive for *BRCA1* carriers, though the magnitude of benefit for *BRCA2* carriers was similar to that for the rest of the cohort.

Side effects Tamoxifen-treated women younger than age 50 had no apparent increase in side effects. However, women older than age 50 experienced serious side effects, including vascular events and endometrial cancer. Particularly worrisome was the increased incidence of endometrial cancer in the tamoxifen-treated patients (Table 8). In addition, a significant increase in pulmonary embolism and deep vein thrombosis was noted, especially in women older than age 50 (Table 9).

Ultrasonography-guided core biopsies

Technology is now available to perform ultrasonography-guided core biopsies with vacuum assistance using an 8- or 11-gauge needle.

Ductal lavage

Ductal lavage is currently being developed and analyzed as a minimally invasive tool to identify cellular atypia within breast ducts in women who are already at high risk for developing breast cancer. Nipple aspiration is performed and those ducts that produce fluid undergo lavage. The ductal orifice is cannulated and infused with 2-6 mL of saline. The ductal effluent is collected and evaluated by cytology. A careful record is maintained of each duct that has been lavaged by means of a nipple grid and photography.

The results of the cytologic evaluation may then be used to guide women in their decision-making process with respect to interventions to reduce their risk for breast cancer. Those high-risk women who undergo ductal lavage and the cytology is benign could undergo repeat lavage in 1-3 years. The optimal time for repeat lavage is not currently known. When mild atypia is identified by ductal lavage, the location of the duct should be carefully recorded using a nipple grid and photography to ensure the accurate localization of the duct. A repeat lavage can then be performed in 6-12 months. Women who have benign cytology and mild atypia on ductal lavage should also consider tamoxifen or participation in a chemoprevention trial.

Severe atypia is seen in approximately 6% of women who undergo ductal lavage. Patients with severe atypia on ductal lavage should undergo a thorough evaluation, including a repeat lavage, to confirm this diagnosis and exclude malignancy. The evaluation could also include repeat mammography with ductography, breast MRI, and/or ductoscopy. If no suspicious lesions are found, patients should be carefully followed. Fewer than 1% of patients have had malignant cells identified on ductal lavage.

The lavage of the duct producing the malignant cells should be repeated to confirm the diagnosis. If the diagnosis is confirmed, patients should then undergo the same evaluation as patients with marked atypia. Any suspicious le-

sion should be biopsied. Patients without suspicious lesions can be offered duct excision after the ductal system has been injected with dye or close follow-up. These patients should also consider tamoxifen.

Current recommendations

Based on results of the BCPT, the FDA has approved tamoxifen for use in women at high risk of breast cancer.

The NCI and NSABP are in the process of developing risk profiles based on age, number of affected first-degree relatives with breast cancer, number of prior breast biopsies, presence or absence of atypical hyperplasia or LCIS, age at menarche, and age at first live birth. These risk profiles may help guide women in making the decision as to whether or not to take tamoxifen.

An ASCO working group published an assessment of tamoxifen use in the setting of breast cancer risk reduction. All women older than 35 years with a Gail model risk of > 1.66% (or the risk equivalent to that of women 60 years of age) should be considered candidates for this treatment strategy. Comorbid conditions, such as a history of deep vein thrombosis, must be a part of the consent process and treatment decision.

Staging and prognosis

Staging system The most widely used system to stage breast cancer is the American Joint Committee on Cancer (AJCC) classification, which is based on tumor size, the status of regional lymph nodes, and the presence of distant metastasis (Table 10).

Clinical staging is performed initially and is determined after the physical examination and appropriate radiologic studies have been performed.

Pathologic staging Pathologic stage is determined following surgery for operable breast cancer. Pathologic tumor size may differ from clinical tumor size. In addition, axillary nodal metastases that were not clinically evident may be detected after pathologic examination.

Prognostic factors Numerous prognostic factors for breast cancer have been identified.

Lymph node status Axillary nodal metastases are the most important prognostic factor. Axillary nodal involvement and survival were evaluated in patients with breast cancer. Survival was examined relative to the number of nodes involved and the location of nodes that contained metastatic deposits. For any given number of positive nodes, survival was independent of the *level* of involvement but was directly related to the *number* of involved nodes.

Overall, patients who are node-negative have a 10-year survival rate of 70% and a 5-year recurrence rate of 19%. As the number of positive nodes increases, so does the likelihood of relapse. Patients with > 10 positive lymph nodes have a recurrence rate of 72%-82%. The majority of patients who develop recur-

rence after initial curative treatment for early-stage breast cancer will have distant metastases.

Tumor size and hormone-receptor status also correlate with outcome.

Other factors that have been utilized to predict outcome are histologic grade, lymphovascular permeation, S-phase fraction, and ploidy.

More recently, molecular prognostic factors have been evaluated to determine their utility in predicting outcome. They include the growth factor receptors (epidermal growth factor receptor and c-*erb*B-2/*neu*), tumor-suppressor genes *(p53)*, proteolytic enzymes that may be associated with invasion of disease and metastasis (cathepsin D), and metastasis-suppressor genes *(nm23)*.

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CHAPTER 9

Stages 0 and I breast cancer

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This chapter focuses on the diagnosis and management of "minimal" breast cancer, ie, stages 0 and I disease. This is an important area since more noninvasive and small breast cancers are being diagnosed due to the increasing use of screening mammography. Treatment of these malignancies continues to evolve and will continue to change as the results of clinical trials lead to further refinements in therapy.

STAGE 0 BREAST CANCER

Stage 0 breast cancer includes noninvasive breast cancer—lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS)—as well as Paget's disease of the nipple when there is no associated invasive disease.

LOBULAR CARCINOMA IN SITU

LCIS is nonpalpable, produces no consistent mammographic changes, and is often an incidental finding after breast biopsy performed for another reason.

In the past, it was thought that LCIS was a marker for an increased risk for breast cancer. However, recent investigations suggest that LCIS is heterogeneous, and there is biological variability. Therefore, there may be certain subtypes of LCIS that are more likely to progress to invasion.

Epidemiology and etiology

The incidence of LCIS has doubled over the past 25 years and is now 2.8 per 100,000 women. In the past, the peak incidence of LCIS was in women in their 40's. Over the past 3 decades, the peak incidence has increased to the 50's. The incidence of LCIS decreases in women who are in their 60's-80's. It has been suggested that the increase in the age of peak incidence of LCIS is related to the use of hormone replacement therapy (HRT). It is also possible that the use of HRT prevents the usual regression of LCIS normally seen at the time of menopause.

Signs and symptoms

LCIS is nonpalpable and has no consistent features on breast imaging. Most often, LCIS is found in association with a completely separate mammographic abnormality or palpable mass.

Risk of invasive cancer

Similarities have been noted between the behavior of LCIS and low-grade DCIS in that some low-grade DCIS will progress to invasion over a span of many years, whereas others will not. At this point, there are no reliable molecular markers to determine which patients with LCIS will progress to invasive cancer.

Just as the incidence of LCIS has increased, there has also been an associated increase in the incidence of cases of infiltrating lobular carcinoma in postmenopausal women. The increase in invasive lobular carcinoma peaks in women in their 70's.

Pathology

LCIS appears to arise from the terminal duct-lobular apparatus, and the disease tends to be multifocal, multicentric, and bilateral. Subsequently, other types of LCIS have also been described and include pleomorphic LCIS. This entity tends to be associated with infiltrating lobular carcinoma, and the cytologic features are similar to those of intermediate- or high-grade DCIS. Pleomorphic LCIS may be more aggressive, with a higher likelihood of progressing to invasion than classic LCIS.

Treatment options

The management of LCIS is continuing to evolve since the disease appears to be heterogeneous. Presently, treatment options include close follow-up, participation in a chemoprevention trial, tamoxifen, or bilateral total mastectomy with or without reconstruction. At present, the decision for a given treatment will depend upon the patient's individual risk profile after careful counseling. In the future, treatment decisions may be based upon an analysis of a series of molecular markers, which can separate those patients with a low risk for invasion from those who are at high risk for disease progression.

DUCTAL CARCINOMA IN SITU

DCIS is being encountered more frequently with the expanded use of screening mammography. In some institutions, DCIS accounts for 25%-50% of all breast cancers.

Epidemiology

DCIS, like invasive ductal carcinoma, occurs more frequently in women, although it accounts for approximately 5% of all male breast cancers. The average age at diagnosis of DCIS is 54-56 years, which is approximately a decade later than the age at presentation for LCIS.

Signs and symptoms

The clinical signs of DCIS include a mass, breast pain, or bloody nipple discharge. On mammography, the disease most often appears as microcalcifications.

Risk of invasive cancer

The risk of developing an invasive carcinoma following a biopsy-proven diagnosis of DCIS is between 25%-50%. Virtually all invasive cancers that follow DCIS are ductal and ipsilateral and generally present in the same quadrant within 10 years of the diagnosis of DCIS. For these reasons, DCIS is considered a more ominous lesion than LCIS and appears to be a more direct precursor of invasive cancer.

Pathology

A variety of histologic patterns are seen with DCIS, including solid, cribriform, papillary, and comedo. Some researchers have divided DCIS into two subgroups: comedo and noncomedo types. As compared with the noncomedo subtypes, the comedo variant has a higher proliferative rate, overexpression of HER-2/*neu*, and a higher incidence of local recurrence and microinvasion. DCIS is less likely to be bilateral and has approximately a 30% incidence of multicentricity.

Treatment of noninvasive breast carcinoma

LOBULAR CARCINOMA IN SITU

Treatment options

Since the risk of invasive breast cancer in patients with LCIS is equal for either breast, the treatment options for LCIS are bilateral mastectomy, biopsy followed by close follow-up, or participation in a breast cancer chemoprevention trial. Ablative surgery may be indicated in patients with LCIS who have other risk factors. In these cases, bilateral total mastectomy is indicated. Patients undergoing this procedure can be offered immediate reconstruction.

DUCTAL CARCINOMA IN SITU

Breast-conserving surgery

Breast-conservation surgery, followed by radiation therapy to the intact breast, is now considered the standard treatment for patients with DCIS. Since the incidence of positive lymph nodes after axillary lymph node dissection for DCIS is ~1%-2%, axillary dissection is not indicated in most instances.

Sentinel node biopsy for DCIS

The sentinel lymph node is the first node in the draining lymphatic basin that receives primary lymph flow. The technique of sampling the first draining lymph node was initially described in the management of patients with melanoma to determine who would benefit from regional lymph node dissection and was performed using a blue vital dye. This same technique has been used in patients with breast cancer, and sentinel node biopsy represents a minimally invasive way to determine whether the axilla is involved with disease. If the sentinel node is negative, the patient may be spared lymph node dissection. The precise method for identifying the sentinel node (filtered vs unfiltered Tc-99m sulfur colloid and/or blue dye) along with the method for studying the node (hematoxylin and eosin staining vs immunohistochemistry vs polymerase chain reaction) are being studied. The location of the injection is also being evaluated to determine whether there is an advantage to the injection being administered either subdermally or intraparenchymally at the site of the primary tumor or in the periareolar location.

Axillary lymph node dissection is not routinely recommended for patients with DCIS. Recently, however, investigators have used this less invasive tool to determine whether individuals with DCIS may harbor occult nodal metastases. Current studies have identified metastatic disease to the axillary nodes in up to 12% of patients who have undergone sentinel node biopsy. Despite this relatively high percentage of positive sentinel nodes, recurrence in the nodal basins is very rare (about 2%).

Factors associated with an increased risk of axillary metastasis with a diagnosis of DCIS: (1) extensive DCIS requiring mastectomy, (2) suspicion of microinvasion, (3) DCIS associated with a palpable mass, and (4) evidence of lymphovascular permeation or invasion seen on review of the slides. These factors likely are associated with unknown (nondiagnosed) invasive disease.

Technique used in breast cancer In breast cancer, lymphatic mapping has been performed using a vital blue dye and/or lymphoscintigraphy. The primary tumor site is injected with the blue dye or a radioactive tracer, usually technetium-labeled sulfur colloid. When a vital dye is used, the axillary dissection is carefully carried out to identify the blue-stained afferent lymphatic vessels that lead to the sentinel node. When the radioactive tracer is injected peritumorally, a handheld gamma counter is used to locate the sentinel node.

Adjuvant radiation therapy

Retrospective series of patients with DCIS, as well as subsets of patients with early invasive cancer, have been treated with conservative surgery alone, omitting radiation therapy to the intact breast. In addition, several prospective, randomized trials have attempted to address this issue of omission of breast irradiation for both invasive cancer and DCIS. It is clear from all of these series that omission of breast irradiation results in a significantly higher ipsilateral breast tumor recurrence rate but has not, as yet, had an impact on overall survival.

Two large prospective randomized trials have demonstrated a significant reduction in local relapse with the use of postlumpectomy irradiation in treatment of DCIS. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17, local recurrence rates at 8 years were reduced from 27% to 12% with postlumpectomy irradiation.

Similar results were recently reported by a European cooperative group study of 1,010 women with DCIS randomly assigned to receive either 50 Gy of radiotherapy to the whole breast over 5 weeks or no further treatment. With a median follow-up of 4.25 years, the 4-year local relapse-free rate was 91% in the radiotherapy arm vs 84% in the observation arm. Hazard ratios with postexcision radiotherapy were 0.62 for all local relapses, 0.65 for DCIS recurrences, and 0.60 for noninvasive recurrences.

Both trials showed that radiotherapy reduces the risk of both noninvasive and invasive recurrences. Identification of a subgroup of patients who did not benefit from postlumpectomy irradiation has not as yet been clearly defined.

Although there may be some patients in whom wide excision alone is appropriate therapy, the available literature has not consistently identified a specific subgroup of patients in whom radiation therapy should routinely be omitted. Clearly, the omission of radiation therapy in subsets of patients remains a controversial issue worthy of further investigation. Hopefully, ongoing randomized studies will help resolve some of the controversy generated by selective, retrospective studies.

One study demonstrated acceptable local control in patients with DCIS treated by excision alone, provided that wide negative margins were obtained. In this retrospective series of 469 patients, radiation therapy did not lower the local recurrence rate in patients with wide (≥10 mm) negative margins but did produce a significant benefit in patients with close (≤ 1 mm) margins. The authors concluded that radiation therapy is unlikely to benefit patients with wide negative margins. These findings need to be confirmed in prospective, randomized trials.

Adjuvant tamoxifen therapy

Adjuvant therapy is not routinely employed in patients with DCIS. However, the use of tamoxifen (Nolvadex) for the prevention of secondary breast cancers in women at high risk for breast cancer, which includes women previously diagnosed with DCIS, has led some clinicians to consider the use of tamoxifen in women diagnosed with DCIS. In a National Surgical Adjuvant Breast and Bowel Project trial (NSABP-24), 1,804 women with DCIS treated with lumpectomy and irradiation were randomly assigned to receive placebo or tamoxifen. At a median follow-up of 74 months, women in the tamoxifen group had fewer breast cancer events than those in the placebo group (8.2% vs 13.4%; $P = .0009$). Tamoxifen decreased the incidence of both ipsilateral and contralateral events. The risk of ipsilateral invasive can-

cers was reduced by tamoxifen, regardless of the presence or absence of comedonecrosis or margin involvement.

Clearly, based on these results, tamoxifen may be considered as an adjuvant therapy in women with DCIS. The role of tamoxifen or other estrogen receptor modulators is likely to evolve rapidly over the next decade.

STAGE I BREAST CANCER

Stage I breast cancer includes small primary malignancies (≤ 2 cm in greatest dimension that have not spread to the lymph nodes), as well as microinvasive tumors ≤ 0.1 cm in greatest dimension.

Pathology of invasive breast cancer

Ductal carcinoma Most cases of invasive carcinomas of the breast are ductal in origin. Of the different histologic subtypes of ductal carcinoma that have been described, tubular, medullary, mucinous (colloid), and papillary subtypes have been associated with a favorable outcome.

Lobular carcinoma Approximately 5%-10% of invasive breast cancers are lobular in origin. This histology has been associated with synchronous and metachronous contralateral primary tumors in as many as 30% of cases.

Treatment of stage I breast cancer

SURGICAL AND RADIATION TREATMENT

Multiple studies have demonstrated that patients with stage I breast cancer who are treated with either breast-conservation therapy (lumpectomy and radiation therapy) or modified radical mastectomy have similar disease-free and overall survival rates.

TABLE 1: Contraindications to breast conservation

Absolute contraindications	Relative contraindications
Multicentric disease[a]	Tumor size vs breast size
Diffuse malignant microcalcification	Tumor location
Pregnancy	Collagen vascular disease (excluding rheumatoid arthritis)
Persistently positive surgical margins	
Previous breast or mantle irradiation	

[a] If a satisfactory cosmetic outcome is anticipated, multicentric disease is considered to be a relative contraindication.

Breast-conservation therapy

Extent of local surgery The optimal extent of local surgery has yet to be determined and, in the literature, has ranged from excisional biopsy to quadrantectomy. A consensus statement on breast-conserving therapy issued by the National Cancer Institute (NCI) recommended that the breast cancer be completely excised with negative surgical margins and that a level I-II axillary lymph node dissection be performed. The patient should subsequently be treated with adjuvant breast irradiation.

Patient selection Specific guidelines must be followed when selecting patients for breast conservation. Patients may be considered unacceptable candidates for conservative surgery and radiation therapy either because the risk of breast recurrence following the conservative approach is significant enough to warrant mastectomy or the likelihood of an unacceptable cosmetic result is high. Some patients who are candidates for breast conservation can undergo breast MRI to identify sites of additional disease within the breast that may preclude breast-conserving treatment, although this is not a standard for evaluation. Contraindications to breast-conserving surgery are listed in Table 1.

Risk factors for ipsilateral recurrence For patients undergoing conservative surgery followed by radiation therapy to the intact breast, the risk of ipsilateral breast tumor recurrence has been reported to range from 0.5% to 2.0% per year, with long-term failure rates varying from 7% to 20%. Risk factors for ipsilateral breast tumor recurrence include, but are not limited to, young age ($<$ 35-40 years), an extensive intraductal component, major lymphocytic stromal reaction, peritumoral invasion, presence of tumor necrosis, and positive resection margins. After a wide excision has been performed, the specimen should be oriented for the pathologist who will then ink each margin a different color. If a positive surgical margin is present, the color-coded system will guide the reexcision to obtain negative surgical margins with the removal of the least amount of breast tissue possible. The amount of breast tissue excised correlates with cosmetic outcome.

Patients whose tumors have an extensive intraductal component who undergo adequate surgical therapy with negative surgical margins do not have a higher local failure rate than those with lesions that do not have an extensive intraductal component. Although it is desirable to achieve negative surgical margins, the available data do not preclude the use of conservative treatment, provided that adequate radiation doses ($>$ 6,000 cGy) to the tumor bed are employed. The role of the remaining risk factors cited above in predicting recurrence is unclear, and patients should not be denied breast conservation because of their presence.

Cosmetic considerations include primary tumor size and location, overall breast size, total body weight, and a history of preexisting collagen vascular disease.

The primary tumor is excised with a margin of normal breast tissue (no absolute margin has been defined). Therefore, tumor size and breast size are im-

In a recent study from Yale University, 127 women with early-onset breast cancer diagnosed at age 42 or younger who were conservatively treated with lumpectomy and irradiation underwent genetic testing. A total of 105 women had normal wild-type *BRCA1* or *BRCA2* and 22 women had deleterious mutations. With a median follow-up of over 12 years from the original diagnosis, the deleterious mutation group had a high rate (approximately 40%) of ipsilateral and contralateral new primary tumors. None of the women had undergone prophylactic oophorectomy or were on tamoxifen. The rate of second primary tumors in the contralateral and ipsilateral breasts followed a similar course over the 12 years of follow-up. The authors suggest that women with deleterious mutations in *BRCA1* or *BRCA2* who elect for breast-conserving therapy consider some additional prophylactic measure to reduce the incidence of second primary breast tumors *(Haffty BG, Harrold E, Khan AJ, et al: Lancet 359:1471-1477, 2002).*

portant in determining whether the patient will have an acceptable cosmetic outcome after surgical resection. Patients with large tumors with respect to breast size may consider neoadjuvant chemotherapy to downstage the size of the primary tumor and allow breast preservation. (See Chapter 11 for discussion of neoadjuvant chemotherapy.)

Obese women with large, pendulous breasts may experience marked fibrosis and retraction of the treated breast, making a good to excellent cosmetic outcome less likely. Women in this situation can undergo bilateral reduction mammoplasty after the wide excision of the primary tumor site has been completed. The partial mastectomy specimen should be evaluated by the pathologist to ensure adequate resection margins. Radio-opaque clips can be left to mark and identify the primary tumor site for the radiation oncologist.

Patients with collagen vascular disease may develop marked fibrosis and bone necrosis following adjuvant radiation therapy. Most patients with active collagen vascular disease are not candidates for conservative therapy; however, patients with minimal manifestations of the disease or those with rheumatoid arthritis may be considered for breast-preserving treatment.

In some instances, it is necessary to excise skin in order to obtain a negative surgical margin. This does not necessarily preclude the patient from having breast-conserving therapy and does not mean the patient should have a poor cosmetic outcome. When skin must be removed to obtain a negative surgical margin, complex skin closures, such as V-Y advancement flaps or Z-plasties, can be utilized to enhance cosmesis.

Patients with centrally located tumors Traditionally, patients who have centrally located tumors requiring excision of the nipple-areolar complex have not been offered the option of breast conservation. However, the cosmetic result achieved after local tumor excision that includes the nipple-areolar complex may not differ significantly from that obtained following mastectomy and reconstruction.

Furthermore, conservatively treated patients with subareolar lesions do not necessarily need to have the nipple-areolar complex sacrificed as long as negative surgical margins can be achieved. However, if the complex is not

TABLE 2: Adjuvant chemotherapy regimens in node-negative breast cancer

Regimen	Dose and frequency
MF	
Methotrexate	100 mg/m^2 IV on days 1 and 8
5-FU	600 mg/m^2 IV on days 1 and 8 (1 h after methotrexate)
Folinic acid	10 mg/m^2 PO q6h × 6 doses (24 h after methotrexate)
Repeat every 4 weeks for 12 cycles	
CMF (Bonadonna regimen)	
Cyclophosphamide	600 mg/m^2 IV on day 1
Methotrexate	40 mg/m^2 IV on day 1
5-FU	600 mg/m^2 IV on day 1
Repeat every 3 weeks for 9 cycles	
CMFP	
Cyclophosphamide	100 mg/m^2 PO on days 1-14
Methotrexate	40 mg/m^2 IV on days 1 and 8
5-FU	600 mg/m^2 IV on days 1 and 8
Prednisone	40 mg/m^2 PO on days 1 and 14
Repeat every 4 weeks for 6 cycles	
AC	
Adriamycin	60 mg/m^2 IV on day 1
Cyclophosphamide	600 mg/m^2 IV on day 1
Repeat every 21-28 days depending on hematologic recovery	

removed, the remaining breast tissue and overlying skin remain sensitive. Recent studies also indicate that the incidence of local recurrence is not increased when primary tumors in this location are treated conservatively.

Genetically predisposed breast cancer patients For women harboring germline mutations in *BRCA1* or *BRCA2*, there are limited data regarding long-term outcome. Studies, to date, have shown acceptable local control rates in the short term and increased but acceptable rates of acute, subacute, and chronic normal tissue reactions with lumpectomy followed by radiation therapy. Women with germline *BRCA1* and *BRCA2* mutations, however, are at high risk for second primary tumors in the contralateral breast.

A recent study from Yale University, also demonstrated high rates of second primary tumors in the ipsilateral breast (see sidebar on previous page). This study suggests that if one chooses breast-conserving therapy, some prophylactic measure such as selective estrogen receptor modulators or oophorectomy might be considered to reduce the risk of second primary tumors in the ipsilateral or contralateral breast. Other studies also indicate a trend toward

A recently published clinical trial of over 5,000 conservatively managed breast cancer patients randomized to receive or not receive an additional 16 Gy boost to the tumor bed following 50 Gy of external-beam irradiation to the intact breast demonstrated a statistically significant reduction in local relapse with the use of a radiation boost. With a median follow-up of 5.1 years, local relapses were observed in 182 of the patients with no boost, compared with 109 relapses in the boost group. The 5-year rates of local relapse were 7.3% vs 4.3% ($P < .0001$). The reduction in local relapse with the additional boost was particularly evident in patients < 50 years of age *(Bartelink H, Horiot JC, Poortmans P, et al: N Engl J Med 345:1378-1387, 2001).*

higher rates of late local relapses in *BRCA* carriers. Further studies are clearly warranted to assess the long-term risks and benefits of breast-conserving strategies in women harboring mutations in *BRCA1* and *BRCA2*.

Role of axillary node dissection The role of axillary lymph node dissection in the management of breast cancer has been questioned, particularly when a patient with a clinically negative axilla is undergoing breast-conservation therapy. In most instances, the breast surgery is performed under local anesthesia and sedation and the patient does not require hospital admission. When axillary lymph node dissection is added, the surgery is performed with the patient under general anesthesia.

It has also been suggested that if the status of the nodes will not change therapy, the dissection is unnecessary and the axilla can be treated with irradiation. On the other hand, if an axillary lymph node dissection is not performed, the patient will not be accurately staged and important prognostic information will be unavailable.

Patients who may not be candidates for sentinel node biopsy are women who are pregnant or breast-feeding and women who have had prior irradiation. A prior excisional biopsy does not preclude the use of lymphatic mapping and sentinel node biopsy. It has recently been suggested that sentinel node biopsy accurately evaluates the axilla even in patients with tumors > 5 cm.

Once the sentinal node(s) have been identified, they can be sent to pathology for frozen section or touch prep analysis.

Sensitivity and specificity In breast cancer, lymphatic mapping has been performed using a vital blue dye and/or lymphoscintigraphy. Studies have suggested that the success rate for identifying the sentinel node can be increased when these techniques are used in combination. The ability to identify the sentinel node can reach as high as 97% when blue dye and Tc-99m sulfur colloid are used together. When blue dye is used alone, the success rate is 83% and when Tc-99m sulfur colloid is used alone, the success rate is 94%.

Recent results in a multi-institution practice demonstrate that sentinel lymph node biopsy using dual-agent injection provides optimal sensitivity. In the study, 806 patients were enrolled by 99 surgeons for sentinel lymph node biopsy by single-agent (blue dye alone or radioactive colloid alone) or dual-agent injection at the discretion of the surgeons. All patients underwent complete level I/II dissection following the sentinel procedure. There were no

significant differences in the identification rate among patients who underwent single- compared with dual-agent injection. The false-negative rates were 11.8% for single-agent vs 5.8% for dual-agent injections ($P = .05$).

The sensitivity and specificity of sentinel lymph node biopsy is high and the likelihood of a false-negative result is extremely low. False-negative rates vary between series and between 0% and 11%. In one series, 18% of the cases where the frozen-section evaluation of the node was negative, the final pathologic evaluation revealed metastatic disease, and the patient ultimately required a lymph node dissection. This potential result can be distressing to patients; however, they should be informed of this possibility at the time of the sentinel lymph node biopsy.

The decision to eliminate axillary lymph node dissection when the sentinel node is negative is being evaluated in a clinical trial. There are, however, many surgeons who are well experienced with the technique and thus have a low false-negative rate. Many of these surgeons are comfortable eliminating a complete axillary dissection in the face of a negative sentinel node biopsy. The decision to eliminate axillary lymph node dissection in the face of a positive sentinel node is being examined by a large clinical trial.

Radiation therapy after breast-conserving surgery

Based on the results of a number of retrospective single-institution experiences, as well as several prospective randomized clinical trials, breast-conserving surgery followed by radiation therapy to the intact breast is now considered a standard treatment for the majority of patients with stage I or II invasive breast cancer.

Radiation dose and protocol Radiation therapy after breast-conservation surgery should employ careful treatment planning techniques that minimize treatment of the underlying heart and lungs. In order to achieve the optimal cosmetic result, efforts should be made to obtain a homogeneous dose distribution throughout the breast. Doses of 180-200 cGy/d to the intact breast, to a total dose of 4,500-5,000 cGy, are considered standard.

Additional irradiation to the tumor bed is often administered. Although the necessity of a boost to the tumor bed has been questioned, at least two randomized clinical trials have demonstrated a small, but statistically significant reduction in ipsilateral breast tumor relapses with the use of a radiation boost to the tumor bed following whole-breast irradiation of 50 Gy. The boost is directed at the original tumor bed with either electron-beam irradiation or interstitial implant to bring the total dose to 50-66 Gy.

Regional nodal irradiation For patients who undergo axillary dissection and are found to have negative nodes, regional nodal irradiation is no longer routinely employed. For patients with positive nodes, radiation therapy to the supraclavicular fossa and/or internal mammary chain may be considered on an individualized basis (see chapter 10).

MEDICAL TREATMENT

Medical management of local disease depends on clinical and pathologic staging. Systemic therapy is indicated only for invasive (infiltrating) breast cancers.

In the past, systemic therapy was not offered to patients with stage I disease (tumors up to 2.0 cm in size). However, adjuvant chemotherapy and hormonal therapy have been shown to improve disease-free and overall survival in selected node-negative patients.

The sequence of systemic therapy and definitive radiation therapy in women treated with breast-conserving surgery is a subject of continued clinical research. The use of concomitant chemotherapy and irradiation is not recommended due to radiomimetic effects of chemotherapy and the potential for increased locoregional toxicity. Delaying chemotherapy up to 8-10 weeks after surgery does not appear to have a negative impact on the development of metastasis or survival.

Treatment regimens

Multiagent therapy with cyclophosphamide (Cytoxan, Neosar), methotrexate, and fluorouracil (5-FU; CMF regimen); cyclophosphamide, methotrexate, 5-FU, and prednisone (CMFP); sequential methotrexate and 5-FU (MF); and doxorubicin and cyclophosphamide (AC) have been used in node-negative patients (Table 2). Hormonal therapy with tamoxifen (20 mg PO qd for 5 years) has been shown to be of value in women ≥ 50 years of age with estrogen- and/or progesterone-receptor–positive tumors. (See Chapter 10 for further discussion about tamoxifen and the ATAC trial [Arimidex and Tamoxifen Alone or in Combination].)

The role of the taxanes, ie, paclitaxel and docetaxel (Taxotere), in adjuvant therapy is being investigated in clinical trials.

Node-negative tumors < 1.0 cm The reduction in the odds of recurrence and death with adjuvant therapy is similar in node-negative and node-positive patients. Therefore, patients who have the lowest risk of recurrence are least likely to benefit from systemic treatment when the attendant risks of treatment are considered. None of the reported trials in node-negative breast cancer included women with tumors < 1.0 cm, and because of the low risk of recurrence (≤ 10%) in this group, systemic adjuvant therapy should not be used routinely. However, recent results from the NSABP in this group of patients are provocative in suggesting a potential benefit from systemic therapy.

Node-negative tumors ≥ 1.0 cm The selection of a specific treatment program and the characteristics that predict risk of recurrence and death in women with node-negative breast cancer require further delineation and clarification in clinical trials. At present, women with tumors ≥ 1.0 cm that have poor histologic or nuclear differentiation, negative estrogen receptors, high S-phase percentage, or high Ki-67 can be considered appropriate candidates for adjuvant systemic therapy.

An update of the NSABP B-20 trial indicated a significant advantage in the estrogen-receptor–positive, node-negative population when chemotherapy with CMF or sequential MF is added to tamoxifen in the adjuvant setting. Patients receiving CMF plus tamoxifen appeared to derive the greatest benefit. Benefits with respect to both disease-free and overall survival have been reported for patients given chemotherapy and tamoxifen.

Other tumors in the breast

Lymphomas Primary breast lymphomas are very rare, accounting for 0.04%-0.5% of all breast malignancies and < 3% of extranodal non-Hodgkin's lymphoma.

Soft-tissue sarcomas of the breast also are uncommon; they account for < 1% of all breast malignancies.

Follow-up of long-term survivors

There is no consensus among oncologists as to the optimal follow-up routine for long-term breast cancer survivors. For patients with stage I disease, follow-up physical examinations typically are performed at 6- to 12-month intervals, and mammograms are obtained every 12 months. All other follow-up evaluations are dictated by the development of symptoms.

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CHAPTER 10

Stage II breast cancer

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This chapter focuses on the treatment of stage II breast cancer, which encompasses primary tumors > 2 cm in greatest dimension that involve ipsilateral axillary lymph nodes, as well as tumors up to 5 cm without nodal involvement.

Stage II breast cancer is further subdivided into stages IIA and IIB. Patients classified as having stage IIA breast cancer include those with T0-1, N1, and T2, N0 disease. Stage IIB breast cancer includes patients with T2, N1 and T3, N0 disease. Therefore, this patient population is more heterogeneous than the populations with stage 0 and stage I disease. The pretreatment evaluation and type of treatment offered to patients with stage II breast cancer are based on tumor size, nodal status, and estrogen receptor status.

Treatment

SURGICAL AND RADIATION TREATMENT

Multiple studies have demonstrated that patients with stage II breast cancer who are treated with either breast-conservation therapy (lumpectomy and radiation therapy) or modified radical mastectomy have similar disease-free and overall survival rates.

Breast-conservation therapy

The optimal extent of local surgery has yet to be determined and, in the literature, has ranged from excisional biopsy to quadrantectomy. A consensus statement issued by the National Cancer Institute (NCI) recommended that the breast cancer be completely excised with negative surgical margins and that a level I-II axillary lymph node dissection be performed. Patients should subsequently be treated with adjuvant breast irradiation.

Patients with tumors > 4-5 cm may not be candidates for breast conservation due to the risk of significant residual tumor burden and the potential for a poor cosmetic result following lumpectomy (or partial mastectomy). A more detailed discussion of patient selection criteria, axillary dissection, and the role of sentinel node biopsy can be found in chapter 9.

Radiation therapy after breast-conserving surgery

For patients with stage I and II breast cancer, radiation therapy following lumpectomy remains an acceptable standard of care. Randomized trials as well as single-institution experiences have consistently demonstrated a significant

reduction in local relapse rates for radiotherapy following breast-conserving surgery. Furthermore, small but significant differences in distant metastasis and disease-free survival have been observed in randomized trials comparing lumpectomy alone to lumpectomy with radiation therapy for patients with invasive breast cancer.

Based on the results of a number of retrospective single-institution experiences, as well as several prospective randomized clinical trials, breast-conserving surgery followed by radiation therapy to the intact breast is now considered standard treatment for the majority of patients with stage II invasive breast cancer.

Radiation dose and protocol Radiation dose to the intact breast follows the same guidelines as are used in patients with stage 0-I disease, described in chapter 9.

Regional nodal irradiation For patients who undergo axillary lymph node dissection and are found to have negative lymph nodes, regional nodal irradiation is no longer employed routinely. For patients with positive lymph nodes, radiation therapy to the supraclavicular fossa and/or internal mammary chain may be considered on an individualized basis.

Regional nodal irradiation should be administered using careful treatment planning techniques to minimize the dose delivered to the underlying heart and lungs. Prophylactic nodal irradiation to doses of 4,500-5,000 cGy results in a high rate of regional nodal control and may improve disease-free survival in subsets of patients.

Given the widespread use of systemic therapy for both node-negative and node-positive patients, the role of axillary dissection has recently come into question. In patients with clinically negative axillae who do not undergo axillary dissection, radiation therapy to the supraclavicular and axillary regions at the time of breast irradiation results in a high rate ($>95\%$) of regional nodal control with minimal morbidity.

Radiation therapy after mastectomy

Available data suggest that in patients with positive postmastectomy margins, primary tumors >5 cm, or involvement of 4 or more lymph nodes at the time of mastectomy, the risk of locoregional failure remains significantly high enough to consider postmastectomy radiation therapy. Even with the use of high-dose chemotherapy, locoregional failure is a significant problem in these patients without the use of postmastectomy irradiation. Most ongoing trials evaluating dose-intensive chemotherapy, with or without bone marrow or stem-cell transplantation, routinely include postmastectomy radiation therapy to the chest wall and/or regional lymph nodes to minimize locoregional recurrence.

Several prospective randomized trials have evaluated the role of postmastectomy radiotherapy in addition to chemotherapy. Most of these trials have been limited to patients with pathologic stage II disease or patients with T3 or T4 primary lesions. All of these trials have shown an improvement in locoregional control with the addition of adjuvant radiation, and several recent

trials have demonstrated a disease-free survival and overall survival advantage in selected patients. Clinical practice guidelines recently developed by the American Society of Clinical Oncology (ASCO) support the routine use of postmastectomy radiation therapy for women with stage 3 or T3 disease or who have 4 or more involved axillary lymph nodes.

Current recommendations There is no clearly defined role for postmastectomy irradiation in patients with small (T1 or T2) primary tumors and negative nodes.

For patients with four or more positive lymph nodes, with or without a large primary tumor, postmastectomy radiation therapy should be considered to lower the rate of local relapse and improve disease-free survival. For patients with T1 or T2 tumors and one to three positive nodes, postmastectomy radiation therapy may have a benefit with respect to disease-free and overall survival. However, controversies and uncertainties regarding this issue remain, and individualized decision making, based on the patient's overall condition and specific risk factors, is reasonable.

Currently, an intergroup randomized trial has been activated to address the controversy of postmastectomy radiation therapy in patients with T1, T2 primary tumors with 1-3 positive nodes. All patients will be treated with standard systemic chemotherapy regimens and randomly assigned to receive postmastectomy irradiation (chest wall, internal mammary, and supraclavicular lymph nodes) vs observation. It is hoped this trial will help to define subgroups of patients who will derive the greatest benefit from postmastectomy irradiation.

Minimizing pulmonary and cardiac toxicity Early trials employing postmastectomy radiation therapy showed that the modest improvements in breast cancer mortality were offset by an excess risk of cardiovascular deaths, presumably due to the radiation treatment techniques used, which resulted in delivery of relatively high radiation doses to the heart. Recent trials employing more modern radiation therapy techniques have *not* demonstrated an excess of cardiac morbidity and, hence, have shown a slight improvement in overall survival due to a decrease in breast cancer deaths. Thus, in any patient being considered for postmastectomy radiation therapy, efforts should be made to treat the areas at risk while minimizing the dose to the underlying heart and lungs.

Radiation dose and protocol The available literature suggests that doses of 4,500-5,000 cGy should be sufficient to control subclinical microscopic disease in the postmastectomy setting. Electron-beam boosts to areas of positive margins and/or gross residual disease, to doses of ~6,000 cGy, may be considered.

In patients who have undergone axillary lymph node dissection, even in those with multiple positive nodes, treatment of the axilla does not appear to be necessary in the absence of gross residual disease. Treatment of the supraclavicular and/or internal mammary chain should employ techniques and field arrangements that minimize overlap between adjacent fields and decrease the dose to underlying cardiac and pulmonary structures.

MEDICAL TREATMENT

Medical management of local disease depends on clinical and pathologic staging. Systemic therapy is indicated only for invasive (infiltrating) breast cancers.

The sequence of systemic therapy and definitive radiation therapy in women treated with breast-conserving surgery is a subject of continued clinical research. The use of concomitant chemotherapy and irradiation is not recommended due to radiomimetic effects of chemotherapy and the potential for increased locoregional toxicity. Delaying chemotherapy up to 8-10 weeks after surgery does not appear to have a negative impact on the development of metastasis or survival.

Treatment regimens

Multiagent therapy with cyclophosphamide, methotrexate, and fluorouracil (5-FU; CMF regimen); cyclophosphamide, methotrexate, 5-FU, and prednisone (CMFP); doxorubicin and cyclophosphamide (AC); and sequential methotrexate and 5-FU (MF) have been used in node-negative patients (see Table 2 in Chapter 9). Hormonal therapy with tamoxifen ([Nolvadex], 20 mg/d PO) for 5 years has been shown to be of value in women ≥ 50 years of age with estrogen–receptor-positive tumors.

Epirubicin HCl (Ellence) recently received FDA approval for use in combination with cyclophosphamide and 5-FU (CEF regimen) in the adjuvant treatment of patients with early-stage, node-positive breast cancer who have undergone resection. In a pivotal trial conducted by the National Cancer Institute of Canada that compared CEF with CMF in 716 premenopausal women, CEF lowered the relative risk of breast cancer recurrence by 24% and the relative risk of death by 29%. Estimated 5-year disease-free survival rates were 62% and 53% in the CEF and CMF groups, respectively, and estimated 5-year overall survival rates were 77% and 70%, respectively.

Recently, data from a large international study (the ATAC trial), which randomly assigned over 9,000 postmenopausal women with invasive (primarily T1 and T2) breast cancer to receive 5 years of oral anastrozole (Arimidex; 1 mg), tamoxifen (20 mg), or a combination of both agents following surgery ± radiation therapy ± chemotherapy, demonstrated that disease-free survival and the incidence of contralateral breast cancer were significantly better in the anastrozole alone arm of the study. Patients who received tamoxifen experienced fewer bone fractures and musculoskeletal complications, whereas patients treated with anastrozole had a lower incidence of hot flashes, weight gain, vaginal bleeding, and venous thromboembolic events. Although encouraging, follow-up is not sufficiently long to determine the effect of anastrozole on overall survival or for a complete analysis of the long-term side-effect profile in this setting. However, an ASCO expert panel currently does not recommend the use of aromatase inhibitors as part of adjuvant therapy programs outside of a clinical trial.

The role of the taxanes, ie, paclitaxel and docetaxel (Taxotere), in adjuvant therapy is being investigated in clinical trials.

Stage II disease

All patients with stage II breast cancer should be considered for systemic adjuvant therapy.

Age ≤ 49 years old Among women 49 years of age or younger, multiagent chemotherapy affords the greatest benefit with respect to reductions in the risk of recurrence and death from breast cancer. Reductions of 25%-50% in the odds of death from breast cancer have been reported for patients treated with CMF, A-CMF (Adriamycin [doxorubicin], cyclophosphamide, methotrexate, and 5-FU), FAC (5-FU, Adriamycin, and cyclophosphamide), or CAF (cyclophosphamide, Adriamycin, and 5-FU).

Recent preliminary data from a Cancer and Leukemia Group B (CALGB) study indicated that the addition of four cycles of paclitaxel to four cycles of the AC regimen may modestly improve disease-free and overall survival in patients with estrogen–receptor-negative, axillary node-positive breast cancer. This study did not show any substantial benefit from dose escalation of doxorubicin or for the addition of paclitaxel in estrogen–receptor-positive patients. Thus, the recent NCI consensus conference suggested that the role of the taxanes in this setting remains to be elucidated by ongoing clinical trials.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial showed that preoperative doxorubicin-based chemotherapy decreases tumor size by > 50% in approximately 90% of operable breast cancers. This results in a greater frequency of lumpectomy but has no reported survival advantage.

In addition, data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview analyses demonstrated a significant advantage afforded by the addition of tamoxifen to the adjuvant therapy regimen of women of all ages with estrogen–receptor-positive tumors. Sequential tamoxifen (20 mg/d PO) for 5 years is recommended.

The dosages, schedules, and frequencies of these combination regimens are detailed in Table 1. These and other chemotherapy regimens for breast cancer are also listed in the Addendum following Chapter 11. Doxorubicin-containing regimens are being used with greater frequency and have been shown to be of greater value, ie, decreasing disease recurrence and improving survival, in patients treated in the adjuvant setting. Risk reductions for polychemotherapy are proportionately the same in patients with node-negative and node-positive disease.

Recent results suggest, furthermore, that patients with HER-2/*neu*-expressing breast cancers that are associated with axillary lymph node metastases benefit significantly from intensive, doxorubicin-containing adjuvant chemotherapy.

The optimal duration of systemic therapy is unknown, but four to six cycles are considered to be the minimum length of therapy for providing benefit. Chemotherapy cycles are repeated every 21-28 days or as soon as hematologic recovery (absolute granulocyte count ≥ 1,500/μL) permits.

Age ≥ 50 years old Treatment for women ≥ 50 years of age is similar in content to that for women ≤ 49 years old.

TABLE 1: Adjuvant chemotherapy regimens in node-positive breast cancer[a]

Regimen	Dose and frequency
CMF	
Cyclophosphamide	100 mg/m^2 PO on days 1-14
Methotrexate	40 mg/m^2 IV on days 1 and 8
5-FU	600 mg/m^2 IV on days 1 and 8
Repeat every 28 days	
or	
Cyclophosphamide	600 mg/m^2 IV on day 1
Methotrexate	40 mg/m^2 IV on days 1 and 8
5-FU	600 mg/m^2 IV on day 1
Repeat every 21-28 days	
FAC	
5-FU	500 mg/m^2 IV on days 1 and 8
Adriamycin	50 mg/m^2 IV by continuous 72-h infusion on days 1-3
Cyclophosphamide	500 mg/m^2 IV on day 1
Repeat at 21-day intervals if hematologic recovery occurs	
TAC	
Taxotere	75 mg/m^2 IV on day 1
Adriamycin	50 mg/m^2 IV on day 1
Cyclophosphamide	500 mg/m^2 IV on day 1
Repeat every 21 days	
CAF	
Cyclophosphamide	600 mg/m^2 IV on day 1
Adriamycin	60 mg/m^2 IV on day 1
5-FU	600 mg/m^2 IV on day 1
Repeat every 21-28 days	
AC	
Adriamycin	60 mg/m^2 IV on day 1
Cyclophosphamide	600 mg/m^2 IV on day 1
Repeat every 21-28 days depending on hematologic recovery	
AC → T	
Adriamycin	60 mg/m^2 IV on day 1
Cyclophosphamide	600 mg/m^2 IV on day 1 × 4 cycles
followed by	
Taxol (paclitaxel)	175 mg/m^2 IV by 3-h infusion q3wk × 4 cycles
FEC (CEF)[a]	
Cyclophosphamide	75 mg/m^2 PO on days 1-14
Epirubicin	60 mg/m^2 IV on days 1 and 8
5-FU	500 mg/m^2 IV on days 1 and 8 every month × 6
A-CMF	
Adriamycin	75 mg/m^2 IV on day 1
Repeat every 3 weeks for 4 courses	
Cyclophosphamide	600 mg/m^2 IV on day 1
Methotrexate	40 mg/m^2 IV on days 1 and 8
5-FU	600 mg/m^2 on day 1
Repeat every 3 weeks for 8 courses	

[a]Doses from Levine MN, Bramwell VH, Pritchard KI, et al: J Clin Oncol 16:2651–2658, 1998.

Estrogen–receptor-positive tumors In women with estrogen–receptor-positive tumors (estrogen receptor ≥ 10 fmol), the estrogen agonist/antagonist tamoxifen (20 mg/d PO) for 5 years has been shown to reduce the risk of recurrence and death from breast cancer. An overview analysis showed a reduction in risk of death of ~20% for women treated with tamoxifen. The benefit of tamoxifen is independent of menstrual status and has been demonstrated in women from 50 to > 70 years of age. Long-term follow-up from the NSABP conclusively demonstrates that there is no benefit to continuing tamoxifen therapy beyond 5 years. Recent data from the EBCTCG indicate that the use of combination chemotherapy adds significant benefit in reducing the risk of recurrence and affords a survival advantage in this group of women. Recent results from a large intergroup trial demonstrated that adjuvant tamoxifen should be used after the completion of CAF to optimize disease-free survival.

Estrogen–receptor-negative tumors Systemic therapy for women ≥ 50 years of age with hormone–receptor-negative tumors consists of a chemotherapy program, as outlined above for women ≤ 49 years of age. Very limited data are available from randomized trials regarding women ≥ 70 years of age. However, in the absence of comorbidity, such as heart or renal disease, systemic adjuvant therapy can be offered for women ≥ 70 years old.

High-dose chemotherapy Because of the higher rate of recurrence in patients with stage IIB breast cancer, high-dose chemotherapy can also be considered as part of a clinical trial. See chapter 11 for a discussion of the current status of this approach.

Toxic effects of medical therapy

Chemotherapy The most frequent acute toxicities are nausea/vomiting, alopecia, and hematologic side effects, such as leukopenia and thrombocytopenia. Neutropenia, with its attendant risk of infection, is a potentially life-threatening

TABLE 2: Follow-up recommendations for asymptomatic long-term breast cancer survivors

Intervention	Interval
History and physical examination	Every 6 months or annually
Mammogram	Annually
Chest x-ray	?Annually
Liver function tests	?Annually
Bone scan	Not routinely recommended
Tumor markers	Not routinely recommended
Liver imaging	Not routinely recommended
Brain imaging	Not routinely recommended

complication that requires prompt medical attention and broad-spectrum antibiotics until hematologic recovery occurs.

Other toxicities may include amenorrhea, cystitis, stomatitis, myocardial failure, and nail/skin changes. Amenorrhea is drug- and dose-related and is often permanent in women over 40 years of age. Recent evidence demonstrates, furthermore, that chemotherapy-induced ovarian failure in the adjuvant chemotherapy setting is associated with a very high risk of rapid bone demineralization in the first 6-12 months after treatment. Thus, premenopausal women undergoing adjuvant chemotherapy must be closely evaluated to prevent the development of early osteoporosis. Cardiac failure, although rare, is potentially life-threatening and may be irreversible.

Tamoxifen Toxicities of tamoxifen include hot flashes, weight gain, menstrual irregularities, thrombophlebitis, and endometrial hyperplasia or cancer.

Follow-up of long-term survivors

There is no consensus among oncologists as to the appropriate and optimal follow-up routine for long-term breast cancer survivors. Recommendations for follow-up testing are quite variable. The vast majority of relapses, both locoregional and distant, occur within the first 3 years, when surveillance is the most intensive. After this initial period, the frequency of follow-up visits and testing is reduced (Table 2).

History and physical examination Surveillance methods include a detailed history and physical examination at each office visit. Patients who have been treated by mastectomy can be seen in the office annually after they have been disease-free for 5 years. Patients who were treated with breast-conserving surgery and radiotherapy can be followed at 6-month intervals until they have been disease-free for 6-8 years and then annually.

Approximately 71% of breast cancer recurrences are detected by the patients themselves, and they will report a change in their symptoms when questioned carefully. In patients who are asymptomatic, physical examination will detect a recurrence in another 15%. Therefore, a patient's complaint on history or a new finding on physical examination will lead to the detection of 86% of all recurrences.

Mammography should be performed annually in all patients who have been treated for breast cancer. The risk of developing a contralateral breast cancer is approximately 0.5%-1.0% per year. In addition, approximately one-third of ipsilateral breast tumor recurrences in patients who have been treated by conservation surgery and radiotherapy are detected by mammography alone. As the time interval between the initial therapy and follow-up mammogram increases, so does the likelihood that a local breast recurrence will develop elsewhere in the breast rather than at the site of the initial primary lesion.

Chest x-ray Routine chest radiograms detect between 2.3% and 19.5% of recurrences in asymptomatic patients and may be indicated on an annual basis.

Liver function tests detect recurrences in relatively few asymptomatic patients, and their routine use has been questioned. However, these tests are relatively inexpensive, and it may not be unreasonable to obtain them annually.

Tumor markers The use of tumor markers, such as carcinoembryonic assay (CEA) and CA-15-3, to follow long-term breast cancer survivors is not recommended.

Bone scans Postoperative bone scans are also not recommended in asymptomatic patients. In the NSABP B-09 trial, in which bone scans were regularly performed, occult disease was identified in only 0.4% of patients.

Liver and brain imaging Imaging studies of the liver and brain are not indicated in asymptomatic patients.

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CHAPTER 11

Stages III and IV breast cancer

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This chapter addresses the diagnosis and management of locally advanced, locally recurrent, and metastatic breast cancer, ie, stages III and IV disease.

Approximately 20%-25% of patients present with locally advanced breast cancer. Inflammatory breast cancer is a particularly aggressive form of breast cancer that falls under the heading of locally advanced disease and accounts for 1%-3% of all breast cancers.

Locoregional recurrence of breast cancer remains a major clinical oncologic problem. Rates of locoregional recurrence may vary from $< 10\%$ to $> 50\%$, depending on initial disease stage and treatment.

Metastatic disease is found at presentation in 5%-10% of patients with breast cancer. The most common sites of distant metastasis are the lungs, liver, and bone.

The optimal therapy for stage III breast cancer continues to evolve. Recently, the use of neoadjuvant chemotherapy has been very effective in downstaging locally advanced breast cancer prior to surgical intervention. The optimal neoadjuvant chemotherapeutic regimens continue to evolve, and studies are being performed to evaluate new agents and delivery methods.

Diagnosis

Locally advanced disease

Patients with locally advanced breast cancer do not have distant metastatic disease and are in this group based on tumor size and/or nodal status. Such patients often present with a large breast mass or axillary nodal disease, which is easily palpable on physical examination. In some instances, the breast is diffusely infiltrated with disease and no dominant mass is evident.

Patients with inflammatory breast cancer often present with erythema and edema of the skin of the breast (peau d'orange) and may not have a discrete mass within the breast. These patients often are treated with antibiotics unsuccessfully for presumed mastitis.

Mammography is beneficial in determining the local extent of disease in the ipsilateral breast, as well as in studying the contralateral breast.

Fine-needle aspiration (FNA) or biopsy The diagnosis of breast cancer can be confirmed by either FNA cytology or core biopsy. When FNA is utilized to establish the diagnosis, material can be sent for determination of hormone-receptor status.

Search for distant metastasis The presence of distant metastatic disease should be ruled out by physical examination, chest radiography, CT of the liver, bone scan, and CT of the chest.

Locoregional recurrence

Biopsy or FNA Locoregional recurrence of breast cancer can be diagnosed by surgical biopsy or FNA cytology. Whichever modality is appropriate, material should be sent for hormone-receptor studies, since there is only an 80% concordance in hormone-receptor status between the primary tumor and recurrent disease. When the suspected recurrent disease is not extensive, the biopsy procedure of choice is a negative margin excisional biopsy. For an extensive recurrence, an incisional biopsy can be used.

Search for distant metastasis Prior to beginning a treatment regimen for a patient with locoregional recurrence, an evaluation for distant metastasis should be instituted, since the findings may alter the treatment plan.

Distant metastasis from the breast

Metastatic breast cancer may be manifested by bone pain, shortness of breath secondary to a pleural effusion, parenchymal or pulmonary nodules, or neurologic deficits secondary to spinal cord compression or brain metastases. In some instances, metastatic disease is identified after abnormalities are found on routine laboratory or radiologic studies.

Assessment of disease extent by radiography, CT, and radionuclide scanning is important. Organ functional impairment may be determined by blood tests (liver/renal/hematologic) or may require cardiac and pulmonary function testing. Biopsy may be required to confirm the diagnosis.

Metastasis to the breasts

The most common source of metastatic disease to the breasts is a contralateral breast primary. Metastasis to the breasts is more commonly seen in women. The average age at diagnosis ranges from the late 30s to 40s. Treatment depends on the status and location of the primary site.

Mammographic findings Mammography in patients with metastatic disease to the breast most commonly reveals a single lesion or multiple masses with distinct or semidiscrete borders. Less common mammographic findings include skin thickening or axillary adenopathy.

FNA or biopsy FNA cytology has been extremely useful in establishing the diagnosis when the metastatic disease has cytologic features that are not consistent with a breast primary. When cytology is not helpful, open biopsy may be necessary to distinguish a primary breast cancer from metastatic disease.

Treatment

TREATMENT OF LOCALLY ADVANCED DISEASE

The optimal treatment for patients with locally advanced breast cancer has yet to be defined, due to the heterogeneity of this group. There are approximately 40 different substage possibilities with the different combinations of tumor size and nodal status. Between 66% and 90% of patients with stage III breast cancer will have positive lymph nodes at the time of dissection, and approximately 50% of patients will have four or more positive nodes.

Patients with locally advanced breast cancer have disease-free survival rates ranging from 0% to 60%, depending on the tumor characteristics and nodal status. In general, the most frequent type of treatment failure is due to distant metastases, and the majority of them appear within 2 years of diagnosis.

With the increased utilization of multimodality therapy, including chemotherapy, radiation therapy, and surgery, survival for this patient population has improved significantly.

Neoadjuvant systemic therapy

Neoadjuvant therapy with cytotoxic drugs permits in vivo chemosensitivity testing, can downstage locally advanced disease and render it operable, and may allow breast-conservation surgery to be performed. Preoperative chemotherapy requires a coordinated multidisciplinary approach to plan for surgical and radiation therapy. A multimodality treatment approach can provide improved control of locoregional and systemic disease. When neoadjuvant therapy is used, accurate pathologic staging is not possible.

Active regimens Preoperative chemotherapy regimens reported to result in high response rates (partial and complete responses) include CAF (cyclophosphamide, doxorubicin [Adriamycin], and fluorouracil [5-FU]), FAC (5-FU, Adriamycin, and cyclophosphamide), CMF (cyclophosphamide, methotrexate, and 5-FU), and CMFVP (cyclophosphamide, methotrexate, 5-FU, vincristine, and prednisone). Combination chemotherapy with an anthracycline-based regimen—FAC or AC—is used most often. Recently published data suggest that the AT regimen of Adriamycin and docetaxel (Taxotere) given concomitantly may produce equivalently high response rates. Although not yet definitive, recent data indicate that enhancing dose density may increase the pathologic complete response rate for women with locally advanced disease. The doses of these combination chemotherapy regimens are given in Table 1.

Neoadjuvant chemotherapy results in complete response rates ranging from 20%-53% and partial response rates (≥ 50% reduction in bidimensionally measurable disease) ranging from 37%-50%, with total response rates ranging from 80%-90%. Patients with large lesions are more likely to have partial responses. Pathologic complete responses do occur and are more likely to be seen in patients with smaller tumors.

TABLE 1: Chemotherapy regimens commonly used for locally advanced breast cancer

Regimen	Dose and frequency
FAC	
5-FU	500 mg/m^2 IV on days 1 and 8
Adriamycin	50 mg/m^2 IV on day 1
Cyclophosphamide	500 mg/m^2 IV on day 1
Repeat every 21-28 days depending on hematologic recovery	
or	
Cyclophosphamide	600 mg/m^2 on day 1
Adriamycin	60 mg/m^2 on day 1
5-FU	600 mg/m^2 on day 1
Repeat every 21-28 days depending on hematologic recovery	
AC	
Adriamycin	60 mg/m^2 on day 1
Cyclophosphamide	600 mg/m^2 on day 1
Repeat every 21-28 days depending on hematologic recovery	
AT	
Adriamycin	50 mg/m^2 on day 1
Taxotere	75 mg/m^2 on day 1
Repeat every 21 days for 4 cycles depending on hematologic recovery	

Patients should be followed carefully while receiving neoadjuvant systemic therapy to determine treatment response. In addition to clinical examination, it may also be helpful to document photographically the response of ulcerated, erythematous, indurated skin lesions. Physical examination and mammography are best for assessing primary breast tumor response, whereas physical examination and sonography of axillary nodes are optimal for determining regional nodal disease response.

Multimodality approach

A multimodality treatment plan for locally advanced breast cancer (stage IIIA and IIIB, M1 supraclavicular nodes) is shown schematically in Figure 1. This approach has been shown to result in a 5-year survival rate of 84% in patients with stage IIIA disease and a 44% rate in those with stage IIIB disease. The most striking benefit has been seen in patients with inflammatory breast cancer, with 5-year survival rates of 35%-50% reported for a multimodality treatment approach including primary chemotherapy followed by surgery or radiation therapy and additional adjuvant systemic therapy. The same chemotherapy drugs, doses, and schedules used for single-modality therapy are employed in the multimodality approach.

Surgery Traditionally, the surgical procedure of choice for patients with locally advanced breast cancer has been mastectomy. In recently published studies,

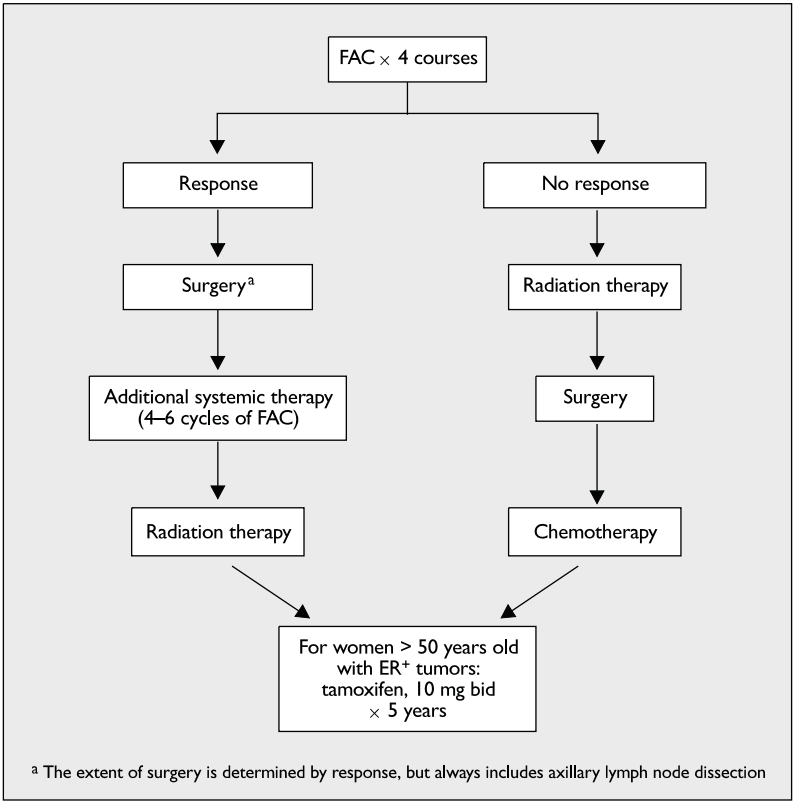

FIGURE 1: Multimodality approach to locally advanced breast cancer

some patients with locally advanced breast cancer who responded to treatment with neoadjuvant chemotherapy became candidates for breast-conservation therapy and were treated with limited breast surgery and adjuvant breast irradiation. Patients who have been downstaged using neoadjuvant chemotherapy should be evaluated very carefully before proceeding with conservative treatment.

The role of sentinel node biopsy in the treatment of breast cancer after neoadjuvant chemotherapy has yet to be defined. Studies have shown that pathologically positive axillary lymph nodes can be sterilized when neoadjuvant chemotherapy is utilized. There are other biologic concerns with sentinel node biopsy after neoadjuvant chemotherapy. The lymphatics may undergo fibrosis or may become obstructed by cellular debris, making the mapping procedure unreliable, with false-negative rates of up to 25%. The rate of conversion from positive to negative nodes can be enhanced when four cycles of a doxorubicin-based regimen is followed by four cycles of docetaxel. Sentinel node biopsy

will only be accurate then if the metastatic deposits within the axilla respond in a similar fashion to chemotherapy.

Radiation therapy remains an integral component of the management of patients with locally advanced breast cancer. For patients with operable breast cancer undergoing mastectomy, radiation therapy to the chest wall and/or regional lymph nodes (to a total dose of 5,000-6,000 cGy) is usually employed, as discussed in chapter 10. Recent randomized trials suggest that postmastectomy patients with any number of positive nodes derive a disease-free and/or overall survival benefit from postmastectomy irradiation.

Available data do not suggest a problem in delaying radiation therapy until the completion of systemic chemotherapy. Even in patients undergoing high-dose chemotherapy with autologous bone marrow or stem-cell transplantation, irradiation is generally indicated following mastectomy for patients with locally advanced disease (primary tumors ≥ 5 cm and/or ≥ 4 positive axillary nodes).

For patients whose disease is considered to be inoperable, radiation therapy may be integrated into the management plan prior to surgery.

High-dose chemotherapy Patients with locally advanced breast cancer and those with multiple positive nodes may be candidates for protocol treatment with high-dose chemotherapy plus autologous stem-cell support. Preliminary results from three prospective, randomized trials of high-dose chemotherapy with autologous stem-cell support in women with high-risk primary breast cancer were recently presented. All three trials are summarized in Table 2, and two of the trials are discussed in more detail below.

In the largest trial yet reported, investigators from all of the bone marrow transplant centers in the Netherlands randomly assigned 885 women with stage II and III breast cancer with four or more tumor-positive nodes to a standard therapy arm of five courses of FEC (5-FU, epirubicin, and cyclophosphamide) followed by radiation therapy and tamoxifen [Nolvadex] or an investigational treatment arm of four cycles of FEC followed by high-dose chemotherapy with cyclophosphamide, thiotepa (Thioplex), and carboplatin (Paraplatin) with peripheral blood stem-cell support followed by radiation therapy and tamoxifen. For an initial group of approximately 200 patients who had more than 3 years

TABLE 2: Randomized studies of high-dose chemotherapy in primary breast cancer

Investigators	Number of patients	Follow-up (median)	Survival benefit?	*P* value
Rodenhuis et al	885	36 mo	Yes	$P < .05$
Peters et al	783	36 mo	No	NS
Scandinavian Breast Cancer Study Group	525	20 mo	No	NS

of median follow-up, there were an absolute improvement in relapse-free survival in excess of 10% and a significant survival benefit. The Rodenhuis trial is now positive overall but will not be published until the 2003 American Society of Clinical Oncology (ASCO) proceedings are released.

The second largest trial evaluating high-dose chemotherapy was conducted by the Cancer and Leukemia Group B (CALGB) in patients with stage II or III breast cancer involving 10 or more axillary lymph nodes. This trial examined the value of consolidation high-dose therapy with cyclophosphamide, cisplatin (Platinol), and carmustine (BiCNU) with autologous stem-cell support following adjuvant therapy with cyclophosphamide, doxorubicin, and 5-FU. Preliminary results of this study, with 783 participants, showed a reduction in relapse frequency of over 30% in patients receiving high-dose chemotherapy; a 3-year survival rate of 68% was observed in patients treated with high-dose chemotherapy vs a 64% rate in those who received intermediate-dose consolidation therapy with the same drugs. However, follow-up is not yet long enough to define the ultimate benefit of this approach. Moreover, toxicity to date has been significantly higher and the relapse rate significantly lower in the high-dose group.

Nonrandomized studies of high-dose chemotherapy plus autologous stem-cell support have shown a disease-free survival of ~70%, as compared with historical data showing a 30% 5-year disease-free survival rate with conventional-dose chemotherapy.

To date, the results of available clinical trials have not all shown improved disease-free and overall survival in patients treated with dose-intensive regimens. However, trial design, power, and strategy have all been questioned. Outside of the context of a clinical trial, high-dose chemotherapy cannot be recommended for patients with primary or metastatic breast cancer.

PRIMARY CHEMORADIATION THERAPY

Several studies have evaluated the role of primary chemotherapy (neoadjuvant chemotherapy), followed by irradiation of the intact breast, as initial treatment in patients with newly diagnosed breast cancer. At present, this approach should be considered experimental in patients with early-stage disease and should be reserved for patients with more advanced disease who are not candidates for surgery due to comorbidity or metastatic disease.

TREATMENT OF LOCOREGIONAL RECURRENCE AFTER EARLY INVASIVE CANCER OR DCIS

When a patient develops a local failure after breast-conservation treatment for early invasive cancer or ductal carcinoma in situ (DCIS), it is generally in the region of the initial primary tumor. The risk of ipsilateral breast tumor recurrence after conservative treatment in patients with early invasive cancer ranges from 0.5%-2% per year, with long-term local failure rates plateauing at about 15%-20%. Local failure rates after wide excision alone for DCIS vary from 10%-63%, as compared with rates between 7% and 21% after wide excision

plus radiation therapy. Most patients whose disease recurs after conservative treatment for DCIS can be treated with salvage mastectomy. In one study, 14% of patients who developed a local recurrence had synchronous distant metastatic disease.

The optimal treatment of a local or regional recurrence after mastectomy has yet to be defined. Locoregional recurrences are associated with initial nodal status and primary tumor size. Appropriate treatment may result in long-term control of locoregional disease. In many instances, these patients develop simultaneous distant metastasis, or distant disease develops some time after the locoregional recurrence manifests itself.

Recurrence of invasive cancer after breast conservation

Recurrence after wide excision and breast irradiation For patients with early invasive cancer who have undergone conservative surgery followed by irradiation and whose cancer recurs in the ipsilateral breast, salvage mastectomy is the most common treatment modality. The same is true for ipsilateral recurrence (of invasive or in situ disease) after conservative treatment for DCIS, when there is no evidence of distant metastatic disease.

Some studies with limited follow-up have reported acceptable results with repeat wide local excision for ipsilateral breast tumor relapses following conservative surgery and radiation therapy. Selection criteria for this approach are unclear, however, and use of this salvage procedure remains controversial. Although the use of limited-field reirradiation has been reported, selection criteria for this management option and long-term follow-up data are lacking.

Recurrence after wide excision alone In patients initially treated with wide local excision alone who sustain an ipsilateral breast tumor recurrence, small series with limited follow-up suggest that wide local excision followed by radiation therapy to the intact breast at the time of local recurrence may be a reasonable treatment alternative. In this situation, standard radiation doses would be employed.

Recurrent disease in the chest wall after mastectomy

In general, patients who develop minimal recurrent disease in the chest wall after a long disease-free interval may be treated by excision alone, although this approach is controversial and may not be ideal. Locoregional control obtained by radiation therapy alone is related to the volume of residual disease and may not be durable. When possible, disease recurring in the chest wall or axillary nodes should be resected and radiation therapy should be delivered to aid in local control.

Radiation treatment techniques are generally similar to those employed for patients treated with standard postmastectomy irradiation and consist of photon- and/or electron-beam arrangements directed at the chest wall and adjacent lymph node regions. Treatment planning should strive for homogeneous dose distributions to the target areas while minimizing the dose to the underlying cardiac and pulmonary structures.

Radiation dose and protocol Conventional fractionation of 180-200 cGy/d to the area of locoregional recurrence and immediately adjacent areas at risk, to a total dose of 4,500-5,000 cGy, is indicated. A boost to the area of recurrence or gross residual disease, to a dose of approximately 6,000 cGy, results in acceptable long-term locoregional control.

Radical chest wall resection A select group of patients with local chest wall recurrence secondary to breast cancer may be candidates for a radical chest wall resection, which may include resection of skin, soft tissue, and bone. Flap coverage or prosthetic chest wall reconstruction is required. Appropriate candidates would include patients who do not have distant metastases and who have persistent or recurrent chest wall disease after chest wall irradiation and patients who present with a chest wall recurrence after a long disease-free interval.

ADJUVANT SYSTEMIC THERAPY FOR LOCOREGIONAL RECURRENCE

Ipsilateral breast tumor recurrence

Limited data support the use of adjuvant systemic therapy at the time of ipsilateral breast tumor recurrence. Retrospective studies have suggested a 20%-50% risk of systemic metastases in patients who sustain an ipsilateral breast tumor recurrence. A recent study conducted at Yale University found that ipsilateral breast tumor recurrence was a significant predictor of distant metastases, particularly among women who relapsed within 4 years of the original diagnosis; these women had a rate of distant metastasis of approximately 50%. Similar findings were noted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) investigators.

These data suggest that women whose tumors recur in the ipsilateral breast within the first few years following the original diagnosis may be considered for adjuvant systemic therapy. Given the lack of prospective, randomized data, specific treatment recommendations for these women remain highly individualized.

Regional nodal recurrence and postmastectomy recurrence of disease in the chest wall

Although there are limited data addressing the use of adjuvant systemic therapy at the time of locoregional relapse following mastectomy, given the high rate of systemic metastasis in this population, these patients may be considered for adjuvant systemic therapy. A recently reported randomized trial demonstrated a disease-free survival benefit with the use of adjuvant tamoxifen following radiation therapy at the time of postmastectomy recurrence of disease in the chest wall in estrogen–receptor-positive patients. The 5-year disease-free survival rate was increased from 36% to 59%, and median disease-free survival was prolonged by > 4.5 years.

FIGURE 2: Treatment approach to metastatic breast cancer

Patients with estrogen–receptor-negative tumors and aggressive locoregional recurrences may also be considered for systemic cytotoxic chemotherapy, given their relatively poor prognosis and high rate of metastasis.

MEDICAL TREATMENT OF METASTATIC BREAST CANCER

Patients with metastatic cancer can be divided into two groups: those with stage IV disease at presentation and those who develop metastases after primary treatment. The management of stage IV disease depends on the site and extent of metastases, comorbid conditions, and clinical tumor characteristics.

Patients with delayed metastatic disease can be divided into two groups, ie, so-called low risk and intermediate or high risk, based on the biological aggressiveness of the disease. As shown schematically in Figure 2, the management approach to these two groups differs.

Low-risk patients

The low-risk group includes patients who develop metastatic disease after a long disease-free interval (ie, a long disease-free interval from primary breast cancer diagnosis to presentation with metastasis), those whose tumors are positive for hormone receptors (estrogen and progesterone), those with bone-only disease, and those without extensive visceral organ involvement.

Hormone therapy Low-risk patients may be treated with a trial of hormone therapy.

First-line hormonal therapy consists of an aromatase inhibitor, with careful serial assessment of clinical and disease responses.

TABLE 3: Doses and schedules of hormonal agents commonly used in patients with metastatic breast cancer

Agent	Dose and schedule
Postmenopausal	
Tamoxifen	20 mg PO qd
or	
Toremifene	60 mg PO qd
Anastrozole	1 mg PO qd
or	
Letrozole	2.5 mg PO qd
or	
Exemestane	25 mg PO qd
Fulvestrant	250 mg IM every month
Megestrol acetate	40 mg PO qid
Fluoxymesterone	10 mg PO tid
Aminoglutethimide	250 mg PO qid
Premenopausal	
Tamoxifen	20 mg PO qd
Luteinizing-hormone–releasing-hormone analogs	7.5 mg IM depot q28d
Megestrol acetate	40 mg PO qid
Fluoxymesterone	10 mg PO tid

TABLE 4: Doses and schedules of chemotherapy agents commonly used in patients with metastatic breast cancer

Drug/combination	Dose and schedule
FAC	
5-FU	500 mg/m^2 IV on days 1 and 8
Adriamycin	50 mg/m^2 IV on day 1
Cyclophosphamide	500 mg/m^2 IV on day 1
Repeat every 3-4 weeks	
TAC	
Taxotere	75 mg/m^2 IV on day 1
Adriamycin	50 mg/m^2 IV on day 1
Cyclophosphamide	500 mg/m^2 IV on day 1
Repeat every 21 days	
Paclitaxel	175 mg/m^2 by 3-h IV infusion every 3 weeks or 80-100 mg/m^2/week
Docetaxel	60-100 mg/m^2 by 1-h IV infusion every 3 weeks or 40 mg/m^2/week
Repeat if hematologic recovery has occurred (ie, absolute granulocyte count ≥ 1,500/μL and platelet count ≥ 100,000/μL)	
Capecitabine	2,500 mg/m^2 PO bid (divided dose, AM and PM) for 14 days
Repeat after 7-day rest	
Vinorelbine	15-25 mg/m^2 by IV infusion weekly (for heavily pretreated patients)
Repeat weekly for 4-6 weeks; resume cycle after 1-2 week rest if hematologic recovery has occurred (as defined above)	

Hormone therapy may be associated with a "flare" response, a temporary worsening of signs and symptoms of disease within the first few weeks of treatment. This response generally means clinical benefit will follow.

If the tumor initially responds to first-line hormone therapy and then progresses, a second hormonal manipulation is warranted. Various hormonal agents are available (Table 3). They may be used sequentially and may provide disease palliation for prolonged periods in some patients.

Recent randomized trials suggest an advantage resulting from decreased toxicity for the initial use of aromatase inhibitors rather than tamoxifen in patients with hormone receptor-positive advanced breast cancer.

Second-line hormonal agents The most commonly used second-line hormonal agents had been progestational drugs, such as megestrol acetate (Megace). Recent randomized trials have indicated that the aromatase inhibitors, such as anastrozole (Arimidex), letrozole (Femara), fulvestrant (Faslodex), and exemestane (Aromasin), are equally effective for palliation of metastatic disease, have less toxicity, and may provide a survival advantage compared with megestrol acetate. Therefore, they are the drugs of choice for second-line therapy following tamoxifen administration. Tamoxifen may also be considered as second-line therapy for patients initially treated with an aromatase inhibitor.

Hormonal therapy continues until evidence of disease progression or drug-related toxicity precludes further therapy with the same agent. If a partial or

complete response to the first hormonal treatment is documented at the time of disease progression, a second hormonal agent may provide further palliation of symptoms and avoid the initiation of systemic chemotherapy. However, subsequent hormonal responses tend to be of shorter duration, and, ultimately, the disease will become refractory to hormone treatment.

Cytotoxic agents Hormone-refractory disease can be treated with systemic cytotoxic therapy. FAC, paclitaxel, TAC (docetaxel [Taxotere], doxorubicin [Adriamycin], cyclophosphamide), or docetaxel may be used in this situation. (For a more detailed discussion of these agents, see section on Intermediate- or high-risk patients." For doses, see Table 4.)

Intermediate- or high-risk patients

Intermediate- or high-risk patients include those with rapidly progressive disease or visceral involvement, as well as those with disease shown to be refractory to hormonal manipulation by a prior therapeutic trial.

Anthracycline-containing combinations, such as FAC (see Table 4), are preferred for these patients. However, newer combinations of doxorubicin and a taxane are gaining favor for use in patients who have not received > 450 mg/m^2 of an anthracycline and whose relapse has occurred more than 12 months after the completion of adjuvant therapy.

Single agents Many single cytotoxic drugs have shown some activity in metastatic breast cancer (Table 4). They include vinblastine (Velban), mitomycin (Mutamycin), thiotepa, capecitabine (Xeloda), vinorelbine (Navelbine), and gemcitabine (Gemzar).

Paclitaxel One of the most active agents is paclitaxel. It has demonstrated antitumor activity in patients with anthracycline-resistant disease, as well as in those who have received three or more prior chemotherapy regimens for metastatic disease.

High-dose paclitaxel (250 mg/m^2 over 3 hours) has not been shown to be superior to 175 mg/m^2 over 3 hours. The higher-dose regimen is associated with greater hematologic and neurologic toxicity.

Docetaxel, approved by the FDA for anthracycline-resistant locally advanced or metastatic breast cancer, has demonstrated overall response rates of 41% in doxorubicin-resistant disease. It has been shown to be superior to mitomycin/vinblastine in patients whose disease progressed after an anthracycline-based chemotherapy regimen.

The recommended starting dose of docetaxel—100 mg/m^2 as a 1-hour IV infusion—requires premedication with dexamethasone to avoid fluid retention and the capillary leak syndrome. The usual regimen of dexamethasone is 8 mg bid for a total of 3 days, beginning 24 hours prior to the administration of docetaxel.

Although 100 mg/m^2 is the dose of docetaxel approved by the FDA, many recent trials have demonstrated a high rate of grade 4 hematologic toxicity at this dose level; a dose of 60-70 mg/m^2 may achieve equivalent therapeutic

benefit with improved safety. As with paclitaxel, the docetaxel dosage must be modified in patients who have hepatic impairment, manifested by elevated transaminase or alkaline phosphatase levels.

Capecitabine, an orally active fluorinated pyrimidine carbonate, has been shown to have substantial antitumor effect in patients whose disease has recurred or progressed after prior anthracycline chemotherapy or after taxane therapy. Prolonged survival, limited toxicity, and response in visceral as well as soft-tissue disease add to the benefit of capecitabine. Toxicities include diarrhea, stomatitis, and hand-foot syndrome.

New approaches Multiple new approaches to treating metastatic breast cancer are being explored. Weekly schedules of docetaxel and paclitaxel have been reported to produce high response rates and lower toxicity than 3-week schedules. Combinations of doxorubicin with paclitaxel or docetaxel have also shown substantial antitumor activity, as have combinations of capecitabine and docetaxel, carboplatin and paclitaxel, and gemcitabine and cisplatin. These newer combinations need to be compared with standard AC or FAC (CAF) regimens in phase III trials. Recent studies also suggest that sequential weekly chemotherapy may be as effective as more intensive combinations with respect to overall survival in patients with metastatic breast cancer.

Monoclonal antibody therapy

Trastuzumab (Herceptin), a humanized monoclonal antibody to the HER-2/*neu* protein, has been approved for use as a single-agent in second- and third-line therapy for metastatic breast cancer and in combination with paclitaxel as first-line therapy in this setting. A randomized trial consisting of 469 women showed that the combination of trastuzumab with chemotherapy yielded a 45% overall response rate, as compared with a 29% rate with chemotherapy alone—a 55% increase. The addition of trastuzumab had the greatest impact on response when combined with paclitaxel. Among the study group as a whole, 79% of women treated with trastuzumab chemotherapy were alive at 1 year, as compared with 68% of those given chemotherapy alone.

A recent update of those data has shown a superior median overall survival with chemotherapy plus trastuzumab compared with chemotherapy alone (25.4 vs 20.9 months). The survival advantage was seen with both AC plus trastuzumab and paclitaxel plus the monoclonal antibody.

In another single-arm trial involving 222 women who had not responded to prior chemotherapy, trastuzumab shrunk tumors by 50% in 14% of women, with a median duration of response of 9 months. Overall, trastuzumab was well tolerated in both trials. Due to an increased risk of cardiac dysfunction observed in women treated with trastuzumab plus an anthracycline, trastuzumab should not be used in combination with this drug class.

It is important to point out that trastuzumab also produces cardiac toxicity when administered by itself, particularly in patients who have had extensive prior exposure to an anthracycline. Finally, essentially all of the clinical benefit

TABLE 5: Randomized studies of high-dose chemotherapy in metastatic breast cancer

Investigators	Number of patients	Median follow-up (yr)	Survival rate (%)		*P* value
			High-dose treatment	Standard treatment	
Stadtmauer et al	553	3	32.0	38.0	NS
Lotz et al	61	5	29.8	18.5	NS

of trastuzumab (alone or in combination) is confined to patients whose breast cancer expresses high (3+) levels of the HER-2/*neu* oncoprotein.

High-dose chemotherapy

Patients who present with or subsequently develop distant metastasis may be candidates for high-dose intensive chemotherapy programs with autologous stem-cell support. Multiple feasibility and phase II studies of this approach have been undertaken. The majority of programs include the use of multiple alkylating agents. The role of high-dose chemotherapy in metastatic disease remains controversial, and analysis and observation of ongoing clinical trials continue to be important.

The results from multiple centers indicate an overall 5-year disease-free survival rate of 25% in patients with metastatic disease treated with high-dose chemotherapy. However, it must be remembered that these results were obtained in a select patient population—generally individuals < 60 years of age with good performance status, chemotherapy-sensitive disease, and normal cardiac, pulmonary, renal, and hepatic function. The use of intensive supportive outpatient care, such as colony-stimulating factors and antibiotics, has significantly reduced the morbidity and mortality associated with the high-dose chemotherapy approach.

In recently presented randomized trials of high-dose chemotherapy in patients with metastatic breast cancer (Table 5), it appears that most of the benefit occurs in women with low-bulk disease, especially those in complete clinical remission. A recent meta-analysis with longer follow-up also demonstrated a benefit for the addition of high-dose therapy to standard, anthracycline-containing chemotherapy for advanced disease in the setting of patients in complete clinical remission. This therapeutic modality remains investigational for patients with stage IV disease, however; women referred for high-dose therapy should be enrolled in a clinical trial.

Adjunctive bisphosphonate therapy

Multiple published reports have now confirmed the benefit of bisphosphonates, such as IV pamidronate (Aredia) or zoledronic acid (Zometa), as an adjunct to chemotherapy and hormonal therapy for metastatic breast cancer with osteolytic

disease of bone. A significant reduction in skeleton-related events, including bone pain, pathologic fracture, and the need for radiation therapy to bone, occurs in patients treated with chemotherapy and pamidronate for metastatic disease. Long-term data showed that this benefit persists beyond 24 months of pamidronate treatment.

The standard dose of pamidronate is 90 mg in 250 mL of 5% dextrose and water infused IV over 2 hours. This dose is repeated every 3-4 weeks, depending on the schedule of chemotherapy or hormone therapy.

Minimal toxicity has been reported in patients treated with pamidronate, but bone pain, fever, and conjunctivitis may be seen occasionally. Symptomatic hypocalcemia, although relatively rare, requires frequent monitoring of calcium and phosphate levels during treatment.

ROLE OF RADIATION THERAPY IN METASTATIC DISEASE

Irradiation remains an integral component of the management of metastatic breast carcinoma. Although bone metastases are the most commonly treated metastatic sites in patients with breast cancer, brain metastases, spinal cord compression, choroidal metastases, endobronchial lung metastases, and metastatic lesions in other visceral sites can be effectively palliated with irradiation.

Radiation dose and schedule Depending on the disease site and volume of the radiation field, fractionation schedules ranging from 20 Gy in 5 fractions to 30 Gy in 10 fractions are used most commonly. In some situations, more protracted courses using lower daily doses may be indicated.

Bone metastasis For patients with widespread bone metastasis, hemibody irradiation (6-7 Gy in one fraction to the upper body or 8 Gy to the lower body) has been shown to be effective. Strontium-89 (Metastron) and other systemic radionuclides also provide effective palliation for widespread bone disease.

Consolidation after high-dose chemotherapy Since patients with metastatic disease treated with high-dose chemotherapy and autologous bone marrow or stem-cell transplantation often develop progressive disease in previously involved sites, studies have suggested the use of "consolidative radiation therapy" for patients undergoing high-dose chemotherapy. Although this approach appears to be well tolerated and preliminary data are encouraging, whether it will affect survival remains to be determined.

ROLE OF SURGERY IN METASTATIC DISEASE

There are selected indications for surgical intervention in patients with metastatic breast cancer, and the role of surgery at this point is generally palliative. Most commonly, palliative surgery is offered to patients with brain metastases, spinal cord compression, fractures, or symptomatic pleural or pericardial effusions not controlled by other means. It is also used for GI complications stemming from metastatic deposits. The curative benefit of surgery in the treatment of metastatic disease to the lungs or liver is not proven, but, in highly selected cases, surgery may be beneficial.

Spinal cord compression Patients with cord compression who have progressive symptoms during irradiation, disease recurrence after irradiation, or spinal instability or who require diagnosis are candidates for surgery.

Solitary brain metastasis Patients with a long disease-free interval and solitary brain metastasis may be candidates for resection. Evidence suggests an improved disease-free survival, overall survival, and quality of life in this subset of patients when treated with surgery combined with postoperative cranial irradiation, as compared with radiation therapy alone.

Chest wall resection It is extremely rare for a patient with distant metastatic disease to be a candidate for chest wall resection; however, patients with symptomatic recurrence of disease in the chest wall who have limited distant disease and a life expectancy of > 12 months may be appropriate candidates.

Follow-up of long-term survivors

For recommendations on the type and timing of follow-up evaluations, see chapter 10.

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CHAPTER 12

Esophageal cancer

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While still relatively uncommon in western countries, esophageal cancer is fatal in the vast majority of cases. In the United States, an estimated 13,900 new cases will be diagnosed in the year 2003, and 13,000 deaths will result from the disease. This high percentage of deaths rivals that of pancreatic cancer and is more than four times that of rectal cancer.

The esophagus extends from the cricopharyngeal sphincter to the gastroesophageal (GE) junction and is commonly divided into the cervical, upper to mid-thoracic, and thoracic portions. This can be important, as histology and optimal treatment approaches may vary considerably based on the site of the cancer. It may not be possible to determine the site of origin if the cancer involves the GE junction itself.

Epidemiology

Gender Esophageal cancer is 7 times more common and slightly more lethal in men than in women.

Age Adenocarcinoma of the esophagus (now more common in the United States than the squamous cell type) has a median age at diagnosis of 69 years. The incidence of squamous cell cancer of the esophagus increases with age as well and peaks in the seventh decade of life.

Race The incidence of squamous cell esophageal cancer is three times higher in blacks than in whites, while adenocarcinomas are more common in white men.

Geography Evidence for an association between environment and diet and esophageal cancer comes from the profound differences in incidence observed in different parts of the world. Esophageal cancer occurs at a rate 20-30 times higher in China than in the United States. An esophageal "cancer belt" extends from northeast China to the Middle East.

Survival While the overall outlook for patients diagnosed with esophageal cancer has improved in the last 30 years, most patients still present with advanced disease and their survival remains poor. One third to one half of patients treated with either chemoradiation or chemoradiation plus surgery are alive at 2 years, without recurrence of esophageal cancer.

Disease site The rate of cancer of the distal esophagus is about equal to that of the more proximal two thirds. In general, squamous cell carcinoma is found in the body of the esophagus, whereas adenocarcinoma predominates in lesions closer to the GE junction.

Etiology and risk factors

Cigarettes and alcohol Squamous cell carcinomas of the esophagus have been associated with cigarette smoking and/or excessive alcohol intake. Furthermore, cigarette smoking and alcohol appear to act synergistically, producing very high relative risks in heavy users of tobacco and alcohol. Esophageal adenocarcinoma is increased two-fold in smokers.

Diet High-fat, low-protein, and low-calorie diets have been shown to increase the risk of esophageal cancer. Exposure to nitrosamines has been proposed as a factor in the development of both squamous cell carcinoma and adenocarcinoma of the esophagus.

Barrett's esophagus and other factors Gastroesophageal reflux disease (GERD) and Barrett's esophagus (adenomatous metaplasia of the distal esophagus) have been linked to adenocarcinoma of the esophagus. Tylosis, Plummer-Vinson syndrome, history of head and neck cancer, and achalasia have also been associated with a higher-than-normal risk of developing squamous cell cancer of the esophagus.

Signs and symptoms

Because symptoms do not alert the patient until the disease is advanced, few esophageal cancers are diagnosed at an early stage.

Dysphagia The most common presenting complaint is dysphagia, which generally is not noted until the esophageal lumen is narrowed to one-half to one-third of normal, due to its elasticity.

Weight loss is common and has a significant role in prognosis ($>$ 10% of total body weight as poor prognosis).

Cough that is induced by swallowing is suggestive of local extension into the trachea with resultant tracheo-esophageal fistula.

Odynophagia and pain Pain with swallowing (odynophagia) is an ominous sign. Patients who describe pain radiating to the back may well have extra-esophageal spread. Supraclavicular or cervical nodal metastases may be appreciated on examination.

Hoarseness may be a sign of recurrent laryngeal nerve involvement due to extra-esophageal spread.

Metastatic disease may present as malignant pleural effusion or ascites. Bone metastasis can be identified by pain involving the affected site or by associated hypercalcemia. The most common metastatic sites are retroperitoneal or celiac lymph nodes.

Sixty-four patients underwent preoperative endoscopic ultrasonography (EUS) and pathologic staging. Thirty-three patients had EUS only and 31 patients underwent EUS plus fine-needle aspiration (FNA) of lymph nodes > 5 mm in width. The sensitivity for lymph node staging was 63% for EUS alone, vs 93% for EUS-FNA. Specificity was 81% vs 100% and accuracy 70% vs 93%, respectively *(Vazquez-Sequeiros E, Norton ID, Clain JE, et al: Gastrointest Endosc 53:751-757, 2001).*

The American College of Surgeons conducted a study utilizing its national cancer database to study the presentation, stage distribution, and treatment of patients diagnosed with esophageal cancer between 1994 and 1997 (n = 5,044). The most common presenting symptoms were dysphagia (74.0%), weight loss (57.3%), reflux (20.5%), odynophagia (16.6%), and dyspnea (12.1%). Fifty percent of patients had tumors located in the lower third of the esophagus. Squamous cell histology was found in 51.6%, and 42.0% had adenocarcinomas. Barrett's esophagus was found in 39.0% of those patients with adenocarcinoma. Patients undergoing initial surgical resection had the following stage distribution: stage I (13.3%), II (34.7%), III (35.7%), and IV (12.3%).

Diagnosis

In western countries, the diagnosis of esophageal cancer is generally made by endoscopic biopsy of the esophagus. In the Far East, cytologic evaluation is frequently utilized.

Endoscopic ultrasound (EUS) is extremely accurate (> 90%) in establishing the depth of tumor invasion (T stage), but less accurate (70%-80%) in determining nodal involvement (N stage) unless combined with fine needle aspiration (FNA) of the involved nodes. EUS is not reliable in determining extent of response to neoadjuvant treatment.

Endoscopy and barium x-rays Endoscopy allows for direct visualization of abnormalities and directed biopsies. Barium x-rays are less invasive and provide a good assessment of the extent of esophageal disease.

Bronchoscopy should be performed to detect tracheal invasion in all cases of esophageal cancer except adenocarcinoma of the distal third of the esophagus.

CT scan Once a diagnosis has been established and careful physical examination and routine blood tests have been performed, a CT scan of the chest, abdomen, and pelvis should be obtained to help assess tumor extent, nodal involvement, and metastatic disease.

PET A prospective trial designed to evaluate the utility of PET vs CT and EUS was performed by obtaining these studies in 48 consecutive patients prior to esophagectomy. PET achieved a 57% sensitivity, 97% specificity, and 86% accuracy compared with CT, which was 18% specific, 99% sensitive and 78% accurate. In terms of nodal staging, PET was correct in 83% of cases as compared to 60% for CT and 58% for EUS ($P = .006$). This analysis suggests the improved accuracy of PET in the staging work-up of esophageal cancer patients.

Numerous studies report the accuracy of PET scanning in determining the presence of metastatic disease, with sensitivity approaching 90% and specificity over 90%. As PET becomes more widely available, its use will probably become an important part of the preoperative evaluation of these patients. PET is being evaluated to determine response to neoadjuvant chemoradiation.

Bone scan A bone scan should be obtained if the patient has bone pain or an elevated alkaline phosphatase level.

Thoracoscopy/laparoscopy Investigators have recently begun to examine the role of surgical staging prior to definitive therapy. These procedures are designed to allow pathologic review of regional lymph nodes and the accurate assessment of extraesophageal tumor spread by direct visualization. A recently completed multi-institution trial (CALGB 9380) found these procedures to be feasible in over 70% of patients; they resulted in the upstaging of patients in 38% of cases reviewed. Further investigations need to be completed to determine the appropriate use of these tools in treatment algorithms for esophageal cancer patients.

Warning Staging studies should be undertaken only if management will change on the basis of specific findings.

Screening and surveillance

HIGH-RISK PATIENTS

Adenocarcinoma The role of screening patients with gastroesophageal reflux disease and surveillance of patients with Barrett's esophagus by upper GI endoscopy remains under investigation. In 833 patients studied by endoscopy, there was a 13% incidence of intestinal metaplasia (Barrett's esophagus). Dysplasia or cancer was seen in 31% of patients with long segment Barrett's esophagus, 10% in short segment Barrett's esophagus, and in 6.4% of GE-junction intestinal metaplasia.

Squamous cell carcinoma Mass screenings in the high-risk areas of China and Japan are considered appropriate.

Pathology

Adenocarcinoma The incidence of esophageal adenocarcinoma involving the GE junction has risen 4%-10% per year since 1976 in the United States and Europe. As a result, adenocarcinoma is now the predominant histologic subtype of esophageal cancer. The distal one-third of the esophagus is the site of origin of most adenocarcinomas.

Squamous cell carcinomas occur most often in the proximal two-thirds of the esophagus. Squamous cell carcinoma is still the most prevalent histologic subtype worldwide.

Other tumor types Other, less frequently seen histologic subtypes include mucoepidermoid carcinoma, small-cell carcinoma, sarcoma, adenoid cystic

TABLE 1: 1983 and 2002 AJCC TNM staging systems for esophageal cancer

1983 Classification (clinical)		2002 Classification (pathologic)
Primary tumor (T)		
Tis	Carcinoma in situ	Same
T1	Tumor involves ≤ 5 cm of esophageal length, produces no obstruction, and has no circumferential involvement	Tumor invades lamina propria or submucosa
T2	Tumor involves > 5 cm of esophageal length, causes obstruction, or involves the circumference of the esophagus	Tumor invades muscularis propria
T3	Extraesophageal spread	Tumor invades adventitia
T4	Not applicable	Tumor invades adjacent structures
Regional lymph nodes (N)		
Nx	Regional nodes cannot be assessed	Same
N0	No nodal metastases	No regional nodal metastasis
N1	Unilateral, mobile, regional nodal metastases (if clinically evaluable)	Regional nodal metastasis
N2	Bilateral, mobile, regional nodal metastases (if clinically evaluable)	Not applicable
N3	Fixed nodes	Not applicable
Distant metastases (M)		
M0	No distant metastases	Same
M1	Distant metastases	Distant metastases Tumors of lower thoracic esophagus: M1a Metastasis in celiac lymph nodes M1b Other distant metastasis Tumors of midthoracic esophagus: M1a Not applicable M1b Nonregional lymph nodes and/or other distant metastasis Tumors of upper thoracic esophagus: M1a Metastasis in cervical nodes M1b Other distant metastasis

Stage grouping						
Stage I	T1	N0 or NX	M0	T1	N0	M0
Stage II	T2	N0 or NX	M0			
Stage IIA				T2-3	N0	M0
Stage IIB				T1-2	N1	M0
Stage III	T3	Any N	M0	T3	N1	M0
				T4	Any N	M0
Stage IV	Any T	Any N	M1	Any T	Any N	M1
Stage IVA				Any T	Any N	M1a
Stage IVB				Any T	Any N	M1b

TABLE 2: Treatment options and survival by stage in esophageal cancer

Stage[a]	Standard treatment	5-Year survival rate (%)
Stage 0 (Tis N0 M0)	Surgery	> 90
Stage I (T1 N0 M0)	Surgery	> 70
Stage IIa (T2-3 N0 M0)	Surgery, chemoradiation, or combination	15-30
Stage IIb (T1-2 N1 M0)	Surgery, chemoradiation, or combination	10-30
Stage III (T3 N1 M0 or T4 Any N M0)	Chemoradiation Palliative resection of T3a tumors	< 10
Stage IV (Any T Any N M1)	Radiation therapy ± intraluminal intubation and dilation ± chemotherapy	Rare

[a] According to the AJCC TNM system definitions (see Table 1)

Note: Surgical results are based on the pathologic staging system, whereas patients treated with combined-modality therapy or neoadjuvant chemoradiation are clinically staged.

leiomyosarcoma, and primary lymphoma of the esophagus. Occasionally, metastatic disease from another site may present as a mass in the esophagus or a mass pressing on the esophagus.

Metastatic spread The most common sites of metastatic disease are the regional lymph nodes, lungs, liver, bone, adrenal glands, and diaphragm. Adenocarcinoma can also metastasize to the brain.

Staging and prognosis

Based on data demonstrating that the depth of penetration has important prognostic significance, the American Joint Committee on Cancer (AJCC) TNM staging system for esophageal cancer was changed from a clinical one (1983) to a pathologic one in 1997. Both the clinical and pathologic staging systems are shown in Table 1, as patients may be cured without an operation. Although pathologic information obtained from an esophagectomy specimen is of prognostic importance, postoperative therapy to improve prognosis has not been rigorously tested. Moreover, recurrence rates for stage I (30%) and stage II (70%) cancers suggest early systemic spread undetected by current noninvasive staging.

Pathologic information obtained from an esophagectomy specimen is of significant prognostic importance. Immunohistochemical analysis of the initial biopsy specimen may also have prognostic relevance. Clinical staging has also been shown to be of prognostic importance, particularly in patients managed with primary radiotherapy or chemoradiation.

Histology and grade Neither histology nor grade has been shown to be of prognostic importance in esophageal carcinoma.

Other prognostic factors Patient age, performance status, and degree of weight loss are of prognostic importance. The prognostic implications of tumor-suppressor genes and oncogenes are an area of active investigation.

Treatment

Treatment options for the various disease stages are given in Table 2, along with 5-year survival rates.

TREATMENT OF LOCALIZED DISEASE

Only 40%-60% of patients with esophageal cancer present with clinically localized disease. National Comprehensive Cancer Network (NCCN) guidelines state that patients with clinically localized disease may be treated with resection or chemotherapy plus radiation (Tables 3, 4). The overall 5-year survival rates for either surgery alone or combined chemotherapy and radiation appear equivalent.

Chemoradiation as primary management of localized or locoregionally confined esophageal cancer has been shown to be superior to radiation alone. A series of randomized trials have demonstrated that adjuvant postoperative chemoradiation does not offer a survival advantage to patients with esophageal cancer. Adequate patient selection, tumor staging, and treatment standardization will be required before we will be able to determine the optimal therapeutic modalities in these patients.

One hundred-fifty patients with superficial esophageal cancer were treated with either endoscopic mucosal resection (EMR) or radical esophagectomy. Seventy-two patients had mucosal cancer; 35 underwent EMR and 37 had surgery. Lymphatic spread or nodal metastasis was observed in 1% of the mucosal cancer patients. Seventy-eight patients had invasion of the submucosa; 33 underwent EMR and 45 had surgery. Local recurrence and nodal metastases were seen in 30% of cases with submucosal invasion. There is no evidence of difference between surgery or EMR in prognosis or survival rates in patients with superficial mucosal esophageal cancers, whereas in patients with submucosal invasion, the recurrence was lower and the survival rates were higher in patients who underwent surgery *(Fujita H, Sueyoshi S, Yamana H, et al: World J Surg 25:424-431, 2001).*

Surgery

Preoperative medical evaluation helps determine the patient's risk of developing postoperative complications and mortality. In addition to the staging and nutritional status, it should include an evaluation of the pulmonary, cardiac, renal, and hepatic functions.

Extent of surgical resection The extent of the resection depends on the location of the primary tumor, histology of the tumor, and nature of the procedure (palliative vs curative). For tumors of the intrathoracic esophagus (squamous cell carcinomas) and tumors with extensive Barrett's esophagus (adenocarcinomas), it is necessary to perform a total esophagectomy with cervical anastomosis in order to achieve a

complete resection. For distal lesions of the abdominal esophagus (adenocarcinomas) and cardia, it is often possible to perform an intrathoracic esophageal anastomosis above the azygous vein, although many surgeons would prefer to perform a total esophagectomy.

The resected esophagus may be replaced with tubularized stomach in patients with tumors of the intrathoracic esophagus or with a colon interposition in patients with tumors involving the proximal stomach, since such involvement makes this organ unsuitable for esophageal reconstruction. The esophageal replacement is usually brought up through the posterior mediastinum, although the retrosternal route is often used in palliative procedures.

Patient selection The indications for esophagectomy in esophageal cancer vary from center to center within the United States.

Clearly, patients with distant metastases, evidence of nodal metastases in more than one nodal basin, or tumor extension outside of the esophagus (airway, mediastinum, vocal cord paralysis) are candidates for palliative therapy. Patients with disease limited to the esophagus and no evidence of nodal metastases (stages I and IIa) may be treated with esophagectomy, although these patients can also be considered for definitive treatment with chemoradiation.

Esophagectomy following chemoradiation Considerable controversy exists regarding the need for esophagectomy following chemoradiation. To date, no randomized study has compared patients treated with chemoradiation alone vs those treated with chemoradiation followed by surgery. The incidence of residual disease in patients who have a complete clinical response to chemoradiation is 40%-50%. Patients with complete response following chemoradiation have the best survival rates with surgery.

A randomized trial evaluated 220 patients with adenocarcinoma of the esophagus treated with either transhiatal esophagectomy or transthoracic en bloc esophagectomy with extended lymphadenectomy. With a median follow-up of 4.7 years, there is a trend toward an improvement in long-term 5-year overall survival: 39% for the transthoracic approach vs 27% for the transhiatal approach. As expected, the transhiatal approach had a lower morbidity *(Hulscher JB, van Sandick JW, de Boer AG, et al: 347:1705-1709, 2002).*

Method of resection Considerable controversy exists among surgeons regarding the method of resection. To date, two randomized studies have compared transhiatal esophagectomy (without thoracotomy) with the Ivor-Lewis (transthoracic) esophagectomy (with thoracotomy). These studies failed to show differences between the two procedures with regard to operative morbidity and mortality. A meta-analysis failed to show differences in 5-year survival rates.

Considerable controversy exists regarding the need for pyloric drainage (pyloroplasty) following esophagectomy. A meta-analysis of nine randomized trials that included 553 patients showed a trend favoring pyloric drainage in improving gastric emptying and nutritional status, whereas bile reflux was better in the nondrainage group. The gastric emptying time evaluated by scintigraphy was twice as long in the nondrainage group than in the pyloric drainage groups.

Lymphadenectomy Considerable controversy exists regarding the need for radical lymphadenectomy in esophageal disease. Much of the controversy is due to the fact that different diseases are being compared.

Japanese series include mostly patients with squamous cell carcinomas of the intrathoracic esophagus, with 80% of the tumors located in the proximal and middle sections of the esophagus. Americans report combined series, with at least 40%-50% of patients with distal esophagus adenocarcinomas. Skinner and DeMeester favor en bloc esophagectomy with radical (mediastinal and abdominal) lymphadenectomy, based on 5-year survival rates of 40%-50% in patients with stage II disease, as compared with rates of 14%-22% in historical controls.

In a retrospective study, Akiyama found a 28% incidence of cervical node metastases in patients with squamous cell carcinomas located in the middle and distal portions of the esophagus, as opposed to 46% in those with tumors of the proximal third. Overall survival at 5 years was significantly better in patients who underwent extended lymphadenectomy (three fields) than in those who had conventional lymphadenectomy (two fields); this was true in patients with negative nodes (84% and 55%, respectively) and in those with positive nodes (43% and 28%, respectively). Extended lymphadenectomy afforded no survival advantage in patients with tumors in the distal third of the esophagus.

In a study of 1,000 patients with esophagogastric junction adenocarcinomas, the tumors were classified according to the location of the center of the tumor mass in adenocarcinomas of the distal esophagus, cardia, and subcardia. The tumors located in the cardia and subcardia regions spread primarily to the paragastric and left gastric vessel nodes and did not benefit from extended esophagectomy.

Chemoradiation

Preoperative chemoradiation Initial trials of preoperative chemoradiation reported unacceptably high operative mortality (~26%). Subsequent trials reported 4%-11% operative mortality, median survival as long as 29 months, and 5-year survival rates as high as 34%. In general, 25%-30% of patients have no residual tumor in the resected specimen, and this group tends to have a higher survival rate than those who have a residual tumor discovered by the pathologist.

The superiority of preoperative chemoradiation over surgery alone in esophageal adenocarcinoma has been demonstrated in a prospective trial. This trial included 113 patients with adenocarcinoma of the esophagus. These patients were randomized either to preoperative chemoradiation (2 courses of 5-FU and cisplatin given concurrently with 40 Gy of radiotherapy in 15 fractions) or to surgery alone. Median survival was statistically superior in the combined-modality arm than in the surgery-alone arm (16 vs 11 months). Rates of 3-year survival again statistically favored the combined-modality arm (32% vs 6%). Although toxicity was not severe, the short survival in the surgery control arm has minimized the impact of these results in the United States.

TABLE 3: Chemotherapy regimens for esophageal carcinoma

Drug/combination	Dose and schedule
Cisplatin/fluorouracil/radiation therapy	
Fluorouracil	1 g/m²/d IV infused continuously on days 1-4 of weeks 1, 5, 8, and 11
Cisplatin	75 mg/m² IV on day 1 of weeks 1, 5, 8, and 11
Radiation therapy	200 cGy/d 5 days per week (total regional treatment, 3,000 cGy), followed by a 2,000-cGy boost field (total, 5,000 cGy) in 5 weeks
Give chemotherapy concurrently with radiation therapy	

Adapted from: Herskovic A, Martz K, Al-Sarraf M, et al: N Engl J Med 326:1593–1598, 1992.

Table prepared by Ishmael Jaiyesimi, DO

A trial performed at the University of Michigan enrolled 100 patients and randomized them between surgery alone and preoperative chemoradiation (cisplatin 20 mg/m²/d), fluorouracil (5-FU) (300 mg²/d), and vinblastine (1 mg/m²/d) and radiotherapy (45 Gy/1.5 Gy bid). With a median follow-up of 8.2 years, the 3-year survival was 16% (surgery alone) vs 30% (induction chemoradiation). This difference did not reach statistical difference, as the study was designed to detect a relatively large increase in median survival from 1 to 2.2 years (Urba SG, Orringer MB, Turrisi A, et al: J Clin Oncol 19:305-313, 2001).

Primary chemoradiation Patients with locally advanced esophageal cancer (T1-4 N0-1 M0) may be cured with definitive chemoradiation. Randomized trials have demonstrated a survival advantage for chemoradiation over radiotherapy alone in the treatment of esophageal cancer. In a Radiation Therapy Oncology Group (RTOG) randomized trial involving 129 esophageal cancer patients, radiation (50 Gy) with concurrent cisplatin and 5-FU provided a significant survival advantage (27% vs 0% at 5 years) and improved local control over radiation therapy alone (64 Gy). Median survival also was significantly better in the combined-therapy arm than in the radiation arm (14.1 vs 9.3 months).

A recently completed randomized intergroup trial was designed to investigate the role for high-dose radiation in conjunction with systemic therapy. This study compared doses of 50.4 Gy with 64.8 Gy. Both treatment arms of the study administered concurrent 5-FU and cisplatin. This trial was stopped after an interim analysis revealed no statistically significant difference in survival between the two groups. The authors concluded that higher-dose radiation therapy did not offer any survival benefit compared with the 50.4 Gy dose.

Patient selection Patients with disease involving the mid- to proximal esophagus are excellent candidates for definitive chemoradiation. This is because resection in this area can be associated with greater morbidity than resection of more distal tumors.

TABLE 4: Chemotherapy regimens for gastric esophageal cancer

Dose/combination	Dose and schedule
Adjuvant fluorouracil/leucovorin/radiation therapy for gastric and gastroesophageal junction adenocarcinoma	
Fluorouracil	425 mg/m^2 IV on days 1-5
Leucovorin	20 mg/m^2 IV on days 1-5 immediately before fluorouracil for one cycle then 3-4 weeks later
Followed by	
Radiation therapy	4,500 cGy (180 cGy a day) given concurrently with
Fluorouracil	400 mg/m^2 IV on days 1-4 and on the last 3 days of radiation therpay
Leucovorin	20 mg/m^2 IV on days 1-4 and on the last 3 days of radiation therapy
One month after completion of radiation therapy:	
Fluorouracil	425 mg/m^2 IV on days 1-5
Leucovorin	20 mg/m^2 IV on days 1-5 immediately before fluorouracil
Repeat cycle every 28 days for 2 cycles	

Adapted from: Macdonald JS, Smalley S, Benedetti J, et al: Proc Am Soc Clin Oncol 19:1a, 2000.

Table prepared by Ishmael Jaiyesimi, DO

Most of the trials demonstrating the efficacy of chemoradiation have had a high proportion of patients with squamous cell cancers. Chemoradiation has thus become a standard treatment of locoregionally confined squamous cell cancer of the esophagus. It is essential that chemotherapy be given concurrently with radiation when this approach is chosen as primary treatment for esophageal cancer. A typical regimen is 50-60 Gy over 5-6 weeks with cisplatin (75 mg/m^2) and 5-FU (1 g/m^2/24 h for 4 days) on weeks 1, 5, 8, and 11.

A Patterns of Care Study examined the records of patients with esophageal cancer treated with irradiation throughout the United States between 1992 and 1994. This study revealed that 75% of patients received chemotherapy and irradiation. Multivariate analysis identified the addition of chemotherapy to be a predictor of improved overall survival. This study documented the use of definitive chemoradiation as an established treatment within the national standards of practice and confirmed the results of previously reported clinical trials.

The most recent Patterns of Care Study examined patients treated between 1996 and 1999. This study revealed a statistically significant increase in the use of EUS in the pretreatment work-up of patients as compared to the original survey. There was also a significant rise in the use of concurrent chemoradiation prior to planned surgical resection as compared to the original survey (27% vs 10%, $P = .0007$). Paclitaxel use as part of the chemoradiation strategy also significantly increased during this time period *(.2% vs 22%, $P = .0001$) Suntharalingam M, Moughan J, Coia LR, et al: Int J Radiat Oncol Biol Phys [in press]).*

The literature also supports offering patients with adenocarcinoma primary surgery, preoperative chemoradiation, or primary chemoradiation with surgical salvage if necessary. Entering these patients on protocols will allow us to further define standard treatment.

Radiotherapy

Although radiotherapy alone is inferior to chemoradiation in the management of locoregionally confined esophageal cancer, it may offer palliation to patients with advanced local disease too frail for chemotherapy.

Preoperative radiotherapy has been shown to be of little value in converting unresectable cancers into resectable ones or in improving survival. However, it decreases the incidence of locoregional recurrence.

Postoperative radiotherapy (usually to 50 or 60 Gy) can decrease locoregional failure following curative resection but has no effect on survival.

Brachytherapy Intraluminal isotope radiotherapy (intracavitary brachytherapy) allows high doses of radiation to be delivered to a small volume of tissue. Retrospective studies suggest that a brachytherapy boost may result in improved rates of local control and survival over external-beam radiotherapy alone. This technique can be associated with a high rate of morbidity if not used carefully.

A multi-institution prospective trial was conducted by the RTOG to determine the feasibility and toxicity of chemotherapy, external-beam radiation, and esophageal brachytherapy in potentially curable esophageal cancer patients. Nearly 70% of patients were able to complete external-beam radiation, brachytherapy and at least two cycles of 5-FU/cisplatin. The median survival was 11 months, and the 1-year survival was 49%. Because of the 12% incidence of fistula formation, the investigators urged caution in the routine application of brachytherapy as part of a definitive treatment plan.

Preoperative chemotherapy

The frequency of metastatic disease as the cause of death in esophageal cancer patients has resulted in exploration of the early application of systemic therapy in the treatment of esophageal cancer. The first of the two large studies was intergroup study 113. A total of 440 patients were treated with surgical resection alone or preceded by 3 cycles of cisplatin and 5-FU. Objective responses to chemotherapy were reported in only 19% of patients receiving chemotherapy. No difference in resectability, operative mortality, median survival (14.9 months with chemotherapy vs 16.1 months with surgery alone), or 2-year survival (35% vs 37%) was reported.

However, the Medical Research Council evaluated 802 patients with resectable esophageal cancer in a similar study. Patients randomized to receive chemotherapy were administered 2 cycles of cisplatin (80 mg/m^2) and 5-FU (1 g/m^2/d as a continuous infusion for 4 days). Microscopically complete resections were performed more frequently in patients receiving chemotherapy, with no difference found in postoperative complications or mortality. Moreover, patients re-

ceiving neoadjuvant chemotherapy had significantly longer median survival (16.8 months vs 13.3 months) and 2-year survival (43% vs 34%) than patients treated with surgery alone. The reasons for the differences in the outcomes are unclear, but may be related to the chemotherapy regimen and schedule employed in the intergroup study, patient population, or study design. As a result, the role of neoadjuvant chemotherapy remains in question but is promising, especially with the potentially more efficacious newer generation of chemotherapy agents.

TREATMENT OF ADVANCED DISEASE

The goal of esophageal cancer treatment is generally palliative for patients with bulky or extensive retroperitoneal lymph nodes or distant metastatic disease. Therapeutic approaches should temper treatment-related morbidity with the overall dismal outlook.

Local treatment In patients with a good performance status, the combination of 5-FU/mitomycin, or 5-FU/cisplatin, and radiotherapy (50 Gy) results in a median survival of 7-9 months. This regimen usually renders patients free of dysphagia until death.

Photodynamic therapy (PDT) Porfimer sodium (Photofrin) and an argon-pumped dye laser can provide effective palliation of dysphagia in patients with esophageal cancer. A prospective, randomized multicenter trial comparing PDT with neodymium/yttrium-aluminum-garnet (Nd:YAG) laser therapy in 236 patients with advanced esophageal cancer found that improvement of dysphagia was equivalent with the two treatments.

A recent review of 119 patients treated with endoluminal palliation reported a significant improvement in dysphagia scores and an increased ability to relieve stenosis caused by tumor when photodynamic therapy was used in conjunction with laser therapy and radiation.

Other approaches include external-beam radiotherapy with or without intracavitary brachytherapy boost, simple dilatation, placement of stents, and laser recannulization of the esophageal lumen.

Chemotherapy Recently published phase I and II studies have demonstrated moderate response rates to taxanes in esophageal cancer. Taxanes in combination with platinum compounds and fluoropyrimidines are being tested in regimens with radiation.

Although chemotherapy alone may produce an occasional long-term remission, there is no standard regimen for patients with metastatic cancer. Patients with advanced disease should be encouraged to participate in well-designed trials exploring novel agents and chemotherapy combinations.

Palliative resection for esophageal cancer is rarely warranted, although it does provide relief from dysphagia in some patients.

CHEMOTHERAPY IN ADVANCED ESOPHAGEAL CANCER

Advances have been made in the treatment of lower gastrointestinal malignancies with new chemotherapeutic agents, particularly irinotecan

TABLE 5: Single-agent chemotherapy

Agent	Response rate (%)
Cisplatin	6-35
Carboplatin	0-7
Fluorouracil	15-18
Paclitaxel	15-32
Docetaxel	20-30
Irinotecan	15
Vinorelbine	20
Etoposide	0-20

(Camptosar) and oxaliplatin (Eloxatin). Progress has been slower, however, for treatment of upper gastrointestinal malignancies. Given the different etiologies of the predominant forms of esophageal cancer, one problem in assessing the efficacy of chemotherapy in this disease is the fact that it remains uncertain whether squamous cell carcinomas and adenocarcinomas respond differently to chemotherapy. To date, both histologies appear to respond similarly to chemotherapy.

Limited data from randomized studies are available regarding the use of chemotherapy in metastatic esophageal cancer. Most current data come from phase II studies, making treatment recommendations difficult. In light of the limited efficacy of current chemotherapeutic agents and available data about the newer agents, no standard therapy for advanced esophageal carcinoma presently exists.

Through the mid-1990s, the mainstay of therapy for advanced esophageal cancer has been cisplatin, which produces responses in approximately 15%-35% of patients, with a median survival of about 4-6 months. With the addition of 5-FU as a 5-day continuous infusion (in a manner similar to squamous cell carcinoma of the head and neck), a modest increase in response rates to approximately 25%-35% occurs, but with no clear improvement in survival rates.

In Britain, the ECF regimen, a combination of cisplatin (60 mg/m^2), epirubicin (50 mg/m^2) both repeated every 21 days, with continuous infusion of 5-FU (200 mg/m^2/d), is considered to be a standard regimen for advanced esophagogastric cancers. Several phase III studies have been performed and consistently demonstrated objective responses in about 40% of patients, with a median survival of 9 months and 1-year survival of 36%-40%. The main severe toxicities of this regimen are neutropenia, in about one-third of patients (32%-36%), lethargy (18%), and nausea and vomiting (11%-17%).

With the advent of many new chemotherapeutic agents (the taxoids, paclitaxel and docetaxel, irinotecan, and gemcitabine) with varying mechanisms of activity, further studies have been conducted, and each of these drugs has demonstrated activity, with responses achieved in approximately 15%-30% of patients (Table 5).

TABLE 6: Combination chemotherapy

Agents	Response rate (%)	Survival
Cisplatin/fluorouracil	19-40	Median = 7 months, 1 year = 27%
Cisplatin/paclitaxel	37-43	Median = 6-9 months
Cisplatin/gemcitabine	47	Median = > 8.7 months
Cisplatin/irinotecan	57	Median = 14.6 months
Cisplatin/vinorelbine	33	Median = 6.8 months
Cisplatin/etoposide	45-48	Median = 8-10 months, 1 year = 26%-41%
Epirubicin/cisplatin/ fluorouracil	40-42	Median = 9 months, 1year = 36%-40%
Cisplatin/fluorouracil/ paclitaxel	48	Median = 10.8 months, 1 year = 38%

However, the primary route of investigation for these new agents has been in combination with cisplatin and/or 5-FU. The results available to date suggest promising activity, with response rates often around 50% in phase II studies. Irinotecan (65 mg/m^2) and cisplatin (30 mg/m^2) administered weekly for 4 weeks every 6 weeks have also been quite active, with responses in 20 of 35 patients (57%) and an impressive 14.6 month median survival. Paclitaxel (180 mg/m^2 over 3 hours) and cisplatin (60 mg/m^2 over 3 hours) administered every 14 days have been extensively evaluated in Europe and were reported to produce objective responses in 43% of 51 patients, including 2 complete responses, and 43% of patients were alive 1 year after initiation of therapy (Table 6).

Oxaliplatin may also have a role in the treatment of esophageal cancer, both as a radiosensitizer and an agent in advanced disease. A preliminary report from ASCO 2002 demonstrated objective responses in 48% of 29 evaluable patients treated with oxaliplatin, 5-FU, and leucovorin according to the FOLFOX 4 schedule (oxaliplatin 85 mg/m^2 on day 1, leucovorin 500 mg/m^2 over 2 hours on days 1 and 2, and 5-FU 400 mg/m^2 bolus, then 600 mg/m^2 over 22 hours on days 1 and 2, repeated every 14 days).

The primary toxicity of these regimens is severe neutropenia, occurring in about 40%-70% of patients. Severe diarrhea, nausea, and vomiting occur in ~10%-15% of patients in many studies. Fatigue and asthenia also were significant side effects with both therapies.

Novel agents are also being actively investigated, with great hope for the future. For example, at the 2001 ASCO meeting, a preliminary report involving the combination of paclitaxel with bryostatin, a protein kinase C inhibitor, noted responses in five of seven patients. The combination of paclitaxel with the cyclin-dependent kinase inhibitor flavopiridol has also demonstrated promising activity in patients with esophageal cancer. A phase I study of this combi-

nation reported one complete, one partial, and one minor response in seven patients treated with this combination. It is hoped that other new agents with novel mechanisms or other targeted therapies may have a role in the treatment of this malignancy.

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CHAPTER 13

Gastric cancer

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Gastric cancer is more common than esophageal cancer in western countries but is less fatal. An estimated 22,400 new cases of gastric cancer will be diagnosed in the United States in the year 2003, with 12,100 deaths attributable to this cancer. Worldwide, stomach cancer is the second most common neoplasm, representing approximately 558,400 new cases and accounting for 405,200 deaths. The incidence and mortality of gastric cancer have been declining in most developed countries, including the United States; the age-adjusted risk (world estimate) fell 5% from 1985-1990.

Gastric cancer is defined as any malignant tumor arising from the region extending between the gastroesophageal (GE) junction and the pylorus. It may not be possible to determine the site of origin if the cancer involves the GE junction itself, a situation that has become more common in recent years.

Epidemiology

Gender Gastric cancer occurs more frequently in men, with a male-to-female ratio of 2.3:1.0; mortality is approximately doubled in men.

Age The incidence of gastric cancer increases with age. In the United States, most cases occur between the ages of 65 and 74 years, with a median age of 70 for males and 74 for females.

Race Gastric cancer occurs 2.2 times more frequently in American blacks than whites; in black males, it tends to occur at a younger age (68 years).

Geography Evidence of an association between environment and diet and gastric cancer comes from the profound differences in incidence seen in various parts of the world. Almost 40% of cases occur in China, where it is the most common cancer, but age-adjusted incidence rates are highest in Korea.

Survival Most patients still present with advanced disease, and their survival remains poor. From 1989-1995, only 20% of patients with gastric cancer presented with localized disease. The relative 5-year survival rate for gastric cancer of all stages is 22%.

Incidence Significant increases in age-adjusted incidence rates for tumors arising in the gastric cardia have been seen in males. Rates for other gastric adenocarcinomas either have not significantly changed (black males) or have declined (white males). Overall, rates of gastric adenocarcinoma rose for white females between 1974 and 1994.

Etiology, risk factors, and prevention

Diet and environment Studies of immigrants have demonstrated that high-risk populations (eg, Koreans) have a dramatic decrease in the risk of gastric carcinoma when they migrate to the West and change their dietary habits. Low consumption of vegetables and fruits and high intake of salts, nitrates, and smoked or pickled foods have been associated with an increased risk of gastric carcinoma. Conversely, the increasing availability of refrigerated foods has contributed to the decline in incidence rates. Recent laboratory data from Japan suggest that oolong tea may contain a substance that can kill stomach cancer cells.

Occupational exposure in coal mining and processing of nickel, rubber, and timber has been reported to increase the risk of gastric carcinoma. Cigarette smoking may also increase the risk.

Ethnicity alone does not appear to explain the differences in outcome between Asian and non-Asian gastric cancer patients. A review of 2,043 patients with gastric cancer revealed that Asian patients tended to present at a younger age than non-Asian patients. Asian patients were also more likely to have cancer in the distal stomach and signet cell histology. Multivariate analysis, however, revealed that race alone was not an independent predictor of outcome *(Gill S, Shah A, Le N, et al: Proc Am Soc Clin Oncol [abstract} 21:136a, 2002).*

Intestinal metaplasia, a premalignant lesion, is common in locations where gastric cancer is common and is seen in 80% of resected gastric specimens in Japan.

Individuals with blood group A may have a greater risk of gastric carcinoma than do individuals with other blood groups. The risk appears to be for the infiltrative type of gastric carcinoma (rather than the exophytic type).

Gastric resection Although reports have suggested that patients undergoing gastric resection for benign disease (usually peptic ulcer disease) are at increased risk of subsequently developing gastric cancer, this association has not been definitely proven. Gastric resection may result in increased gastric pH and subsequent intestinal metaplasia in affected patients.

Pernicious anemia Although it has been widely reported that pernicious anemia is associated with the subsequent development of gastric carcinoma, this relationship also has been questioned.

Genetic abnormalities The genetic abnormalities associated with gastric cancer are still poorly understood. Abnormalities of the tumor-suppressor gene TP53 (alias p53) are found in over 60% of gastric cancer patients and the adenomatous polyposis coli *(APC)* gene in over 50%. The significance of these findings is not clear at present.

Overexpression, amplification, and/or mutations of oncogenes c-Ki-*ras*, HER-2/*neu (aka* c-*erb*-b2), and c-*myc* most likely play a role in the development of some gastric neoplasms. A high S-phase fraction has been associated with an increased risk of relapse as well.

Germline E-cadherin gene mutations strongly predispose patients to gastric cancer. Prophylactic gastrectomy has been described as a preventive and therapeutic option.

Family history Family members of a patient with gastric cancer have a twofold to threefold higher risk of stomach cancer vs the general population.

Prevention Overexpression of the enzyme cyclooxygenase II (COX-2) increases proliferation of gastric cancer cell lines. Agents that specifically inhibit COX-2 slow the growth of stomach cancer xenografts in nude mice. Regular users of nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit both COX-1 and COX-2, have a marked reduction in the incidence of stomach cancer. Future trials will assess the role of COX-2 inhibitors in gastric cancer prevention.

Helicobacter pylori infection is associated with gastric lymphomas and adenocarcinomas. The overall risk of developing malignancy in the presence of infection is low; however, more than 40%-50% of gastric cancers are linked with *H pylori*. The bacterium has been designated a class I carcinogen. Antibiotics alone can cure localized, node-negative MALT (mucosa-associated lymphoid tissue) lymphomas in some patients.

Signs and symptoms

Most gastric cancers are diagnosed at an advanced stage. Presenting signs and symptoms are often nonspecific and typically include pain, weight loss, vomiting, and anorexia.

Hematemesis is present in 10%-15% of patients.

Physical findings Peritoneal implants to the pelvis may be palpable on rectal examination (Blumer's shelf). Extension of disease to the liver may be appreciated as hepatomegaly on physical examination. Nodal metastases can be found in the supraclavicular fossa (Virchow's node), axilla, or umbilical region. Ascites can accompany advanced intraperitoneal spread of disease.

Screening and diagnosis

Routine screening for gastric cancer is generally not performed in western countries because the disease is so uncommon. However, screening appears more effective in high-incidence areas. Mass screening, as has been practiced in Japan since the 1960s, has probably contributed to the 2.5-fold improvement in long-term survival compared with western countries, though differences in biology may also play a role.

Endoscopy and barium x-rays The diagnosis of gastric cancer in a patient presenting with any constellation of the symptoms described above revolves around the use of upper endoscopy or double-contrast barium x-rays. The advantage of endoscopy is that it allows for direct visualization of abnormalities and directed biopsies. Barium x-rays do not facilitate biopsies but are less invasive and may provide information regarding motility.

CT scan Once a diagnosis has been established and careful physical examination and routine blood tests have been performed, a CT scan of the chest, abdomen, and pelvis should be obtained to help assess tumor extent, nodal involvement, and metastatic disease. CT may demonstrate an intraluminal mass arising from the gastric wall or focal or diffuse gastric wall thickening. It is not useful in determining the depth of tumor penetration unless the carcinoma has extended through the entire gastric wall. Direct extension of the gastric tumor to the liver, spleen, or pancreas can be visualized on CT, as can metastatic involvement of celiac, retrocrural, retroperitoneal, and porta hepatis nodes. Ascites, intraperitoneal seeding, and distant metastases (liver, lungs, bone) can also be detected.

Endoscopic ultrasonography (EUS) is a staging technique that complements information gained by CT. Specifically, depth of tumor invasion, including invasion of nearby organs, can be assessed more accurately by EUS than by CT. Furthermore, perigastric regional nodes are more accurately evaluated by EUS, whereas regional nodes farther from the primary tumor are more accurately evaluated by CT. Specific ultrasonographic features may aid in the diagnosis and staging of patients with gastric lymphomas.

Laparoscopy Laparoscopic staging procedures are being used more commonly, especially in patients being considered for preoperative chemoradiation therapy.

Bone scan A bone scan should be obtained if the patient has bony pain or an elevated alkaline phosphatase level.

PET scan A PET scan can be particularly helpful in assessing response to neoadjuvant treatment (see box). PET scanning may play a role in future staging of gastric cancer patients.

Pathology

Adenocarcinoma is the predominant form of gastric cancer, accounting for approximately 95% of cases. Histologically, adenocarcinomas are classified as intestinal or diffuse; mixed types occur but are rare. Intestinal-type cancers are characterized by cohesive cells that form glandlike structures and are often preceded by intestinal metaplasia. Diffuse-type cancers are composed of infiltrating gastric mucous cells that infrequently form masses or ulcers.

Primary lymphoma of the stomach is increasing in frequency and, occasionally, may be difficult to distinguish from adenocarcinoma.

Stromal tumors Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors of the GI tract, most commonly arising from the stomach. These tumors share an ancestor with

PET scanning may play a role in future staging of gastric cancer patients. A prospective evaluation of 44 consecutive patients with locally advanced gastric cancer treated with neoadjuvant chemotherapy was performed by German researchers. They found that a PET scan, performed after 2 weeks of therapy, had positive and negative predictive values of 77% and 90%, respectively, when correlated with final surgical pathology. In addition, patients with PET response had a much higher 2-year survival rate than those without metabolic change (89% vs 26%) *(Ott K, Weber WA, Becker K, et al: Proc Am Soc Clin Oncol [abstract] 21:131a, 2002).* Ongoing clinical trials evaluate the role of imatinib in the adjuvant treatment of high-risk GISTs after complete resection.

GISTs most commonly arise in the stomach. The overwhelming majority of patients undergoing resection of localized tumors experience recurrence, and metastatic disease has historically been resistant to treatment with systemic chemotherapy. KIT mutation leads to constitutive activation and transformation in the majority of these tumors. Imatinib mesylate inhibits the KIT tyrosine kinase receptor, which is a promising target in GISTs. A recent phase II study reported 63% of GIST patients treated with imatinib responded, and another 20% experienced prolonged stable disease. Imatinib was approved by the FDA for use in advanced GIST in 2002 (*Demetri GD, von Mehren MD, Blanke CD, et al: N Engl J Med 347:472-480, 2002; von Mehren M, Blanke C, Joensuu H, et al: Proc Am Soc Clin Oncol [abstract] 21:403a, 2002*). Ongoing clinical trials are evaluating the role of imatinib in the adjuvant treatment of high-risk GISTs after complete resection.

the interstitial cells of Cajal (the pacemaker cells of the gut), since they both express KIT (CD117), a transmembrane tyrosine kinase receptor (see box).

Other histologic types Infrequently, other histologic types are found in the stomach, such as squamous cell carcinomas, small-cell carcinomas, and carcinoid tumors. Metastatic spread of disease from primaries in other organs (eg, breasts and malignant melanoma) is also seen occasionally.

Metastatic spread Gastric carcinomas spread by direct extension (lesser and greater omentum, liver and diaphragm, spleen, pancreas, transverse colon); regional and distant nodal metastases; hematogenous metastases (liver, lungs, bone, brain); and peritoneal metastases. Multicentricity characterizes up to 20% of gastric cancers.

Staging and prognosis

At present, gastric cancers are most commonly staged by the TNM system. The most recent update of this staging system (Table 1) allows for a more precise nodal classification based on the number of lymph nodes involved.

A more detailed Japanese staging system has been shown to have prognostic importance in gastric cancer. However, these results have not yet been duplicated in the United States, and this system is not widely used around the world.

Prognostic factors Aneuploidy may predict a poor prognosis in patients with adenocarcinoma of the distal stomach. High plasma levels of vascular endothelial growth factor (VEGF) and the presence of carcinoembryonic antigen (CEA) in peritoneal washings predict poor survival in surgically resected patients. As with colorectal cancer, intratumoral levels of dihydropyrimidine dehydrogenase (DPD) may be prognostic of gastric cancer. Low levels appear to predict better response to fluorouracil (5-FU)– based chemotherapy and longer survival. The prognostic implications of tumor-suppressor genes and oncogenes are an area of active investigation. Patients with cancers of the diffuse type fare worse than those with intestinal-type lesions.

TABLE 1: TNM staging system for gastric cancer

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria or subserosa[a]
T2a	Tumor invades muscularis propria
T2b	Tumor invades subserosa
T3	Tumor penetrates the serosa (visceral peritoneum) without invasion of adjacent structures[b,c]
T4	Tumor invades adjacent structures[b,c]
Regional lymph nodes (N)	
Nx	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-6 regional lymph nodes
N2	Metastasis in 7-15 regional lymph nodes
N3	Metastasis in > 15 regional lymph nodes
Distant metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Stage grouping	
See Table 2	

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

[a] *Note:* A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified as T2. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified as T3.

[b] *Note:* The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidneys, small intestine, and retroperitoneum.

[c] *Note:* Intramural extension of disease to the duodenum or esophagus is classified by the depth of greatest invasion in any of these sites, including the stomach.

Treatment

PRIMARY TREATMENT OF LOCALIZED DISEASE

Management of gastric cancer relies primarily on surgical resection of the involved stomach, with reconstruction to preserve intestinal continuity, as resection provides the only chance for cure. Radiotherapy and chemotherapy have been tested as adjuncts to surgery and in patients with unresectable tumors. Preoperative chemoradiation therapy is an active area of current investigation.

Surgery

The objectives of operative treatment for potentially curable gastric cancers are confirmation of resectability, performance of a complete resection, facilitation of appropriate pathologic staging, and reestablishment of GI continuity and function.

Peritoneal lavage cytology and reverse transcriptase polymerase chain reaction-based CEA detection have been shown to be strong predictors of tumor recurrence in the peritoneal cavity and overall survival *(Kodera Y, Nahanishi H, Ito Y, et al: Ann Surg 235:499-506, 2002).*

Confirmation of resectability Laparoscopy has emerged as an excellent tool to assess the extent of disease and resectability before the surgeon performs an open laparotomy. Laparoscopy adds to the accuracy of preoperative imaging primarily in cases of peritoneal spread or small liver metastases. As a result, morbidity, hospital stay, and costs have been reduced significantly in patients with unresectable lesions. In addition, peritoneal washings can be obtained.

The initial experience with laparoscopic ultrasonography has shown that its value lies in identifying lesions with a high risk of recurrence (T3-4), for which a preoperative chemotherapy protocol may be available.

Extent of resection The extent of gastric resection depends on the site and extent of the primary cancer. Subtotal gastrectomy is preferred over total gastrectomy, since it leads to comparable survival but lower morbidity. A 5-cm margin of normal stomach appears to be sufficient in proximal and distal resections. For lesions of the GE junction or the proximal third of the stomach, proximal subtotal gastrectomy can be performed. If total gastrectomy is necessary, transection of the distal esophagus and proximal duodenum is required, and omentectomy is performed. In Japan, surgeons routinely resect lesions that appear confined to the mucosa (by EUS). If pathology confirms disease is only in the mucosa, radical surgery is not performed.

Extent of lymphadenectomy The extent of lymph node resection, including the number removed at the time of gastrectomy, continues to be controversial. Preferably, lymphadenectomy includes the lymphatic chains along the celiac, left gastric, splenic, and hepatic arteries, which allows for more precise lymph node staging. The exact level designation of lymph nodes varies with the site and intragastric location of the primary tumor. Based on the TNM staging criteria, 15 or more lymph nodes should be obtained and examined for an accurate N classification. Dissection of the second-echelon lymph nodes has been termed D2 lymphadenectomy. Accordingly, D1 dissection would include only the removal of pericardial or perigastric lymph nodes.

Improved long-term survival rates for Japanese patients had been attributed to the extended lymphadenectomies routinely performed in this country. Because the improvement in survival after gastrectomy during recent decades was usually associated with the performance of extended lymph node dissections (D2 dissections or greater), this practice appeared to be sensible if performed with acceptable complication rates. Retrospective data had shown that D2 lymphadenectomies are safe and do not increase morbidity.

Isolated locoregional recurrences after D2 gastrectomy are rare in western patients (6%). Most recurrences are diffuse and are predicted by T3-4 category (intraperitoneal) or advanced nodal involvement (distant) *(Schwarz RE, Zegala-Nevarez K: Ann Surg Oncol 9:394-400, 2002).*

On the other hand, at least two European randomized trials showed no significant differences in long-term survival between D1 and D2 dissection groups. The recent multicenter trials also compared complication rates for limited (D1) with those for extended (D2) lymphadenectomy and found that higher postoperative morbidity and mortality occurred in the D2 group, largely due to a higher rate of splenectomy and/or partial pancreatectomy performed with those dissections. Extended lymphadenectomies should primarily be performed in specialized centers by experienced surgeons, and splenectomy and pancreatectomy should be avoided; for adequate staging, at least 15 lymph nodes should be removed and analyzed.

Reconstruction methods After distal gastrectomy, Billroth I gastroduodenostomy or, more commonly, Billroth II gastrojejunostomy is an appropriate method for reconstruction. Reflux esophagitis is a common problem when the gastric reservoir is too small. After total or subtotal gastrectomy, a Roux-en-Y esophagojejunostomy is commonly performed.

Resection of extragastric organs may be required to control T4 disease. Such a resection can be associated with long-term survival. Splenectomy should be avoided unless indicated by direct tumor extension, as it significantly increases the rate of complications.

NEOADJUVANT THERAPY

Prompted by the promising results and acceptable toxicity of preoperative (neoadjuvant) chemoradiation therapy in other parts of the GI tract (ie, esophagus, rectum), there is growing interest in neoadjuvant therapy for gastric cancer. Neoadjuvant treatment may be performed in an attempt to convert an initially unresectable cancer to resectable status, or it may be used in advanced but resectable disease.

Results of neoadjuvant therapy are preliminary but encouraging. Several trials have been reported, using radiation therapy plus paclitaxel, 5-FU, and/or docetaxel (Taxotere). Other studies have suggested a benefit from neoadjuvant chemotherapy alone. Further randomized trials are needed to confirm the utility of preoperative chemoradiation therapy in advanced gastric carcinoma.

ADJUVANT THERAPY

The 5-year survival rate after "curative resection" for gastric cancer is only between 30% and 40% (Table 2). Treatment failure stems from a combination of local or regional recurrence and distant metastases. Investigators have studied adjuvant therapy in the hope of improving treatment results. A North American Intergroup trial randomizing resected patients to receive chemoradiation therapy or observation showed significant improvements in relapse-free and overall survival with the adjuvant therapy.

Chemoradiation therapy

Patients with T3-T4 any N M0 tumors are at highest risk of locoregional recurrence after potentially curative surgery (surgery in which all macroscopic tumor has been resected with no evidence of metastatic disease) for gastric cancer. Even patients with node-negative disease (T3 N0) have a gastric cancer-related mortality of about 50% within 5 years. Mortality is significantly worse in node-positive patients.

The potential for patients with these adverse features to benefit from postoperative treatment has been evaluated in a recent American Intergroup trial. Patients in this trial were randomized to receive chemoradiation therapy or observation following resection of stage IB-IV (M0) adenocarcinoma of the stomach. Chemoradiation therapy following resection of these high-risk patients significantly improved both disease-free and overall survival. Because of the apparent benefit of reducing locoregional recurrences, but not distant re-

TABLE 2: Treatment and survival by stage in gastric carcinoma patients

Stage			Treatment	5-Year overall survival rate[a] (%)
Stage 0 (in situ)			Surgery	> 90%
Tis	N0	M0		
Stage IA			Surgery	60%-80%
T1	N0	M0		
Stage IB			Surgery ±	50%-60%
T1	N1	M0	CRT	
T2a/b	N0	M0		
Stage II			Surgery +	30%-50%
T1	N2	M0	CRT	
T2a/b	N1	M0		
T3	N0	M0		
Stage IIIA			Surgery +	~20% (distal tumors)
T2a/b	N2	M0	CRT	
T3	N1	M0		
T4	N0	M0		
Stage IIIB			Same as for stage IIIA	~10%
T3	N2	M0	Consider preoperative CRT	
Stage IV			Palliative chemotherapy,	< 5%
T4	N1-2	M0	radiation therapy, and/or	
Any T	N3	M0	surgery, neoadjuvant	
Any T	Any N	M1	CRT	

Sources of data: American College of Surgeons Commission on Cancer and American Cancer Society

[a] Some American centers are reporting superior 5-year survival rates to those presented above. Confirmation of these results on a national level may be forthcoming.
CRT = chemoradiation therapy

currences, it is possible that more routine use of D2 lymphadenectomy may modify this recommendation in the future. D2 lymphadenectomy was performed in only 10% of the patients in this trial. Subgroup analysis revealed that outcome did not differ based upon the type of lymphadenectomy ($P = .80$). Still, since only a small percentage of patients underwent the recommended D2 dissection, further research is necessary before firm conclusions can be made in this area.

Radiotherapy

Radiotherapy can decrease the rate of locoregional failure but has not been shown to improve survival as a single postoperative modality. Postoperative radiotherapy may be appropriate in patients who are not candidates for chemotherapy.

Chemotherapy

Chemotherapy alone as a surgical adjunct does not have a defined role in the United States. Randomized trials of chemotherapy plus surgery vs resection alone have showed no survival advantage, with the possible exception of patients with widespread nodal involvement who may do better with chemotherapy. In one smaller Italian multicenter trial of node-positive patients, there was a significant survival benefit at 5 years (30% vs 13%) after receiving epirubicin, 5-FU, and leucovorin. In a recent Korean study, postoperative intraperitoneal mitomycin C (Mitomycin) and 5-FU led to a significant survival benefit (54% vs 38%), with an apparently greater benefit for patients with serosal disease involvement or lymph node metastasis.

Unresectable tumors

Patients with unresectable gastric cancers and no evidence of metastatic disease can be expected to survive 6-10 months without any treatment.

Palliative resection Palliative resection or bypass may be appropriate for some patients with obstructive lesions. Palliative resection may also be suitable for patients with bleeding gastric cancers that are not resectable for cure. Generally, resection appears to offer better palliative results than bypass.

Gastrectomy, peritomectomy, and intraoperative hyperthermia peritoneal perfusion chemotherapy represent an aggressive multimodality therapy for patients with advanced locoregional disease and peritoneal seeding. Although no prospective randomized data exist to support this approach, in phase II trials selected patients have shown superior median and long-term survival *(Sugarbaker PH, Yonemura Y: Hepato-Gastroenterol 48:1238-1247, 2001).*

Radiotherapy Radiation therapy alone can provide palliation in patients with bleeding or obstruction who are not operative candidates. Radiotherapy may convert unresectable cancers to resectable tumors.

Chemoradiation therapy Patients with locally advanced disease may be appropriately treated with chemoradiation therapy. This approach can provide relatively long-lasting palliation and may render some unresectable

cancers resectable. Older studies have shown that postoperative chemoradiation therapy can reduce relapse rates and prolong survival in patients with incompletely resected stomach cancer.

Oral fluoropyrimidines have been tested in advanced gastric cancer patients, with potential improvement in quality of life when compared with IV drugs. Capecitabine and UFT (uracil/tegafur) both have single-agent activity. Capecitabine has been successfully combined with cisplatin and epirubicin, and UFT has been combined with a number of drugs, including cisplatin, mitomycin, etoposide, and doxorubicin *(Kim TW, Kang YK, Ahn JH, et al: Ann Oncol 13:1893, 2002).*

MEDICAL TREATMENT OF ADVANCED GASTRIC CANCER

When possible, all newly diagnosed patients with disseminated gastric cancer should be considered candidates for clinical trials, and those with good performance status should be offered chemotherapy. Even though cure is not expected with chemotherapy, such treatment may provide palliation in selected patients and sometimes durable remissions. At least four randomized chemotherapy trials have suggested improvement in survival and probably quality of life vs best supportive care alone.

Single-agent therapy

Compared with other disease sites, the list of agents with established activity in gastric cancer is short: 5-FU, cisplatin (Platinol), mitomycin, etoposide, and the anthracyclines. 5-FU and cisplatin have been used most commonly. The responses seen with single-agent chemotherapy have been traditionally partial and mostly short-lived, with little, if any, impact on overall survival.

Recently, additional agents alone or in combination have demonstrated significant activity in gastric cancer. They include the taxanes, oral fluoropyrimidines, such as S-1, oxaliplatin (Eloxatin), and irinotecan (Camptosar). Novel agents recently tested in patients with advanced gastric cancer include the epidermal growth factor receptor inhibitor OSI-774.

TABLE 3: Chemotherapy regimen for gastric cancer

Drug/combination	Dose and schedule
ECF	
Epirubicin	50 mg/m^2 IV on day 1
Cisplatin	60 mg/m^2 IV on day 1
Repeat the cycle every 3 weeks to a maximum of 8 cycles	
5-FU	200 mg/m^2/d as a continuous IV infusion for up to 6 months

Webb A, Cunningham D, Scarffe HJ, et al: J Clin Oncol 15:261–267, 1997

Table prepared by Ishmael Jaiyesimi, DO

TABLE 4: Chemotherapy regimens for gastric-esophageal cancer

Dose/combination	Dose and schedule
Adjuvant 5-FU/leucovorin/radiation therapy for gastric and gastroesophageal junction adenocarcinoma	
5-FU	425 mg/m^2 IV on days 1-5
Leucovorin	20 mg/m^2 IV on days 1-5 immediately before 5-FU for one cycle then 3-4 weeks later
Followed by	
Radiation therapy	4,500 cGy (180 cGy a day) given concurrently with
5-FU	400 mg/m^2 IV on days 1-4 and on the last 3 days of radiation therapy
Leucovorin	20 mg/m^2 IV on days 1-4 and on the last 3 days of radiation therapy
One month after completion of radiation therapy:	
5-FU	425 mg/m^2 IV on days 1-5
Leucovorin	20 mg/m^2 IV on days 1-5 immediately before 5-FU
Repeat cycle every 28 days for 2 cycles	

Macdonald JS, Smalley S, Benedetti J, et al: Proc Am Soc Clin Oncol 19:1A, 2000.

Table prepared by Ishmael Jaiyesimi, DO

Another promising combination recently completed phase II testing. Ajani and associates treated 38 patients with advanced disease with cisplatin (30 mg/m^2) and irinotecan (65 mg/m^2 weekly x 4 every 6 weeks). The overall response rate was 58% (including 11% achieving a complete remission), and median survival was 9 months. Dose delays due to toxicity most commonly occurred at week 3 or 4, so the authors suggested modifying the schedule (with or without changing the doses) to weekly x 2 every 3 weeks *(Ajani JA, Baker J, Pisters PWT, et al: Cancer 94:641, 2002)*.

Combination chemotherapy

Response rates are consistently higher when combination chemotherapy regimens are used in gastric cancer. Therefore, despite no demonstrated survival advantage, combination therapy has been generally preferred over single agents (Tables 3 and 4).

In the 1980s, the combination of 5-FU, doxorubicin, and mitomycin (FAM) was considered the standard regimen in the treatment of advanced gastric cancer. However, the North Central Cancer Treatment Group (NCCTG) randomly compared this regimen with 5-FU plus doxorubicin and single-agent 5-FU and found no difference in survival among the patients treated with the three regimens.

Several different regimens, including FAMTX (5-FU, doxorubicin, and methotrexate) and ELF (etoposide, leucovorin, and 5-FU), have been tested. Most regimens show markedly better response rates and longer survival in early trials than in phase III studies. No combination has been confirmed as superior. However, the combination of epirubicin, cisplatin, and infusional 5-FU

(ECF) approaches standard of care in Canada and some parts of Europe. This regimen has proven superior to FAMTX in terms of objective response rate and survival and superior to the mitomycin, cisplatin, 5-FU (MCF) regimen in terms of toxicity. The search for the optimal combination regimen continues, with the promising newer agents being introduced in combination regimens.

Gastric cancer patients should be encouraged to participate in well-designed clinical trials. Outside of experimental regimens, the recommended therapy for patients with good performance status is a 5-FU– or cisplatin-based regimen.

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CHAPTER 14

Pancreatic, neuroendocrine GI, and adrenal cancers

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PANCREATIC CANCER

Pancreatic cancer is the fifth leading cause of cancer death in the United States. In the year 2003, an estimated 30,700 new cases will be diagnosed, and 30,000 deaths will be ascribed to this cancer.

Incidence and epidemiology

Gender The incidence of pancreatic cancer is slightly higher in males than in females. These gender differences are most prominent among younger individuals.

Age The peak incidence of pancreatic carcinoma occurs in the seventh decade of life. Two-thirds of new cases occur in people > 65 years old.

Race The incidence is higher in the black population, with an excess risk of 40%-50% over whites. Perhaps more importantly, black males probably have the highest risk of pancreatic cancer worldwide.

Survival Cancer of the pancreas is a highly lethal disease historically, with few reports of 5-year survivors. However, more recent series have shown a decrease in both operative mortality and overall morbidity. There has also been a significant increase in 5-year survival after curative resection (21%-25%). Factors that appear to be important in predicting long-term survival after resection include clear surgical margins, negative lymph nodes, and reduced perioperative mortality.

Adenocarcinoma of the pancreas, the most common histologic type, has a median survival of 9-12 months and an overall 5-year survival rate of 3% for all stages. At the time of diagnosis, over 50% of patients with pancreatic adenocarcinoma have clinically apparent metastatic disease. Among patients whose disease is considered to be resectable, 50% will die of recurrent tumor within 2 years.

Etiology and risk factors

The specific risk factors for pancreatic cancer are not as striking as those for other GI malignancies, such as esophageal and gastric carcinomas. There does, however, appear to be a significant relationship between pancreatic cancer and environmental carcinogens.

Cigarette smoking Cigarette smoke is one of the carcinogens directly linked to the causation of pancreatic malignancies. Heavy cigarette smokers have at least a twofold greater risk of developing pancreatic carcinoma than nonsmokers. In Japan, cigarette smoking carries an even greater risk, which can be as much as 10-fold in men smoking one to two packs of cigarettes daily.

N-nitroso compounds, found particularly in processed meat products, reliably induce pancreatic cancer in a variety of laboratory animals. No study has directly linked dietary carcinogens to pancreatic cancers in humans.

Caffeine The contribution of caffeine consumption to the development of pancreatic carcinoma is controversial. A case-controlled study showed a correlation between caffeine consumption and pancreatic cancer. However, other studies have been unable to confirm this relationship.

Alcohol A clear-cut relationship between alcohol use and pancreatic carcinoma has not been shown.

Diabetes does not seem to be a risk factor for pancreatic cancer. However, 10% of all patients with pancreatic carcinoma present with new-onset diabetes.

Genetic factors Cancer of the pancreas is a genetic disease. To date, more than 80% of resected pancreatic cancers have been found to harbor activating point mutations in K-*ras*. In addition, the tumor-suppressor genes *p16, p53,* and *DPC4* are all frequently inactivated in this cancer.

Familial pancreatic carcinoma has been associated with the following genetic syndromes: hereditary pancreatitis, ataxia-telangiectasia, hereditary nonpolyposis colorectal cancer (HNPCC), familial atypical mole melanoma (FAMM) syndrome, Peutz-Jeghers syndrome, and familial breast cancer. Families with *p16* germline mutations may be at higher risk of developing pancreatic cancer than those without these mutations.

Signs and symptoms

The initial clinical features of pancreatic carcinoma include anorexia, weight loss, abdominal discomfort or pain, and new-onset diabetes mellitus or thrombophlebitis. The vague nature of these complaints may delay diagnosis for several months.

Pain Specific symptoms usually relate to localized invasion of peripancreatic structures. The most common symptom is back pain, which stems from tumor invasion of the splanchnic plexus and retroperitoneum or pancreatitis. This pain is described as severe, gnawing, and radiating to the middle of the back. Pain can also be epigastric or in the right upper quadrant if bile duct obstruction is present.

Jaundice In a majority of cases, patients with pancreatic cancer present with epigastric or back pain and/or jaundice. True painless jaundice occurs with early lesions near the intrapancreatic bile duct.

GI symptoms Invasion of the duodenum or gastric outlet may give rise to nausea or vomiting as a presenting symptom. This symptom is rare early in the course of the disease. Changes in bowel habits related to pancreatic insufficiency may also be present, along with associated steatorrhea.

Glucose intolerance Recent onset of glucose intolerance in an elderly patient associated with GI symptoms should alert physicians to the possibility of pancreatic carcinoma.

A palpable gallbladder occurring in the absence of cholecystitis or cholangitis suggests malignant obstruction of the common bile duct until proven otherwise. This so-called Courvoisier's sign is present in about 25% of all pancreatic cancer patients.

Other physical findings include Trousseau's syndrome (migratory superficial phlebitis), ascites, Virchow's node (left supraclavicular lymph node), or a periumbilical mass (Sister Mary Joseph's node).

Screening and diagnosis

Early diagnosis of pancreatic carcinoma is difficult but essential if surgical resection and cure are to be improved. Defining early lesions at a resectable stage remains a diagnostic challenge. To date, leading medical organizations have not recommended routine screening of asymptomatic individuals for pancreatic cancer.

Serum markers The use of serologic tumor markers for pancreatic carcinoma, such as CA19-9, was originally thought to be appropriate as a screening tool. However, since the prevalence of pancreatic carcinoma in the general population is extremely low (0.01%), many false-positive screening results are generated. Nevertheless, CA19-9 may be a useful marker for screening patients at high risk, such as smokers, recent-onset diabetics, those with familial pancreatic cancer, or those with unexplained weight loss or diarrhea. This marker also is useful in following disease and in assessing the adequacy of resection or therapy.

No currently available serum marker is sufficiently accurate to be considered reliable for screening asymptomatic patients.

Laparoscopy is useful for staging patients with pancreatic carcinoma and for formulating treatment plans. Approximately 10%-20% of patients thought to have resectable disease are found to have distant metastases at laparoscopy. The false-negative rate of laparoscopy is $< 10\%$. The strongest indications for laparoscopy are locally advanced disease and tumors of the body and tail of the pancreas.

Peritoneal cytology also is being explored for the diagnosis of pancreatic carcinoma. Cytology is positive in ~15% of patients who are thought to have

localized disease. However, the clinical/prognostic value of this test is not yet known.

Imaging techniques

Imaging for pancreatic carcinoma is best performed with conventional ultrasonography and CT.

Ultrasonography The limit of sonographic resolution for early pancreatic carcinoma is a diameter on the order of 1.0-1.5 cm. A mass located in the pancreatic head will produce dilatation of the common bile duct. The actual sensitivity of ultrasonography in the diagnosis of pancreatic carcinoma is ~70%.

CT provides better definition of the tumor and surrounding structures than does ultrasonography and is operator-independent. CT correctly predicts unresectable tumors in 85% of patients and resectable tumors in 70% of patients. Findings of tumor unresectability on CT scanning include distant lymphadenopathy, encasement or occlusion of the superior mesenteric artery (SMA) or celiac artery, occlusion of the portal vein or superior mesenteric vein (SMV), and distant metastases.

The use of positron emission tomography with 18 fluorodeoxyglucose (FDG-PET) in the evaluation of patients with pancreatic cancer is expanding. A recent study of 126 patients with focal, malignant, or benign pancreatic lesions showed high sensitivity of FDG-PET for detection of small pancreatic neoplasms. Lack of focal glucose uptake excludes pancreatic neoplasms (sensitivity 85.4%, specificity 60.9%) *(Wiedenmann B, Bohmig M, Amthauer H, et al: Proc Am Soc Clin Oncol 20:154a [abstract], 2001).*

Spiral CT More recently, spiral CT has emerged as a preferred technique for increasing the accuracy of detecting pancreatic carcinoma in general and vessel encasement in particular. This technique permits rapid data acquisition and computer-generated three-dimensional (3D) images of the mesenteric arterial and venous tributaries in any plane. Spiral CT is quicker and less expensive and uses less contrast medium than angiography.

MRI At present, MRI is not as accurate as CT in diagnosing and staging pancreatic carcinoma.

Endoscopic ultrasonography (EUS) is a newer modality for the diagnosis of pancreatic carcinoma, with an overall diagnostic accuracy rate of approximately 85%-90%. For the assessment of regional lymph node metastases, the accuracy of EUS is 50%-70%. This technique is also important in the evaluation of portal vein involvement by tumor. In addition, EUS-guided fine-needle cytology of periampullary tumors may yield new information with respect to the diagnosis of pancreatic cancer.

In a comparison of EUS and spiral CT, both techniques showed comparable efficacy in detecting tumor involvement of lymph nodes and the SMVs and portal veins. However, EUS is less helpful in the evaluation of the SMA.

Endoscopic retrograde cholangiopancreatography (ERCP) may someday be supplanted as a diagnostic tool by EUS, although, at present, ERCP is

used in many clinics. Also, if a patient presents with jaundice and the CT scan reveals dilatation of the common bile duct without an obvious mass, ERCP may be complementary to spiral CT. ERCP findings of pancreatic cancer include an abrupt or tapered cutoff of both the main pancreatic and common bile ducts.

Magnetic resonance cholangiopancreatography (MRC) is being used to evaluate bile and pancreatic duct pathology. As yet, MRC is not a standard test for the diagnosis of pancreatic carcinoma, but it may become helpful in the future.

Pathology

Adenocarcinoma arising from the exocrine gland ductal system is the most common type of pancreatic cancer, accounting for 95% of all cases. Two-thirds of these cancers originate in the pancreatic head, and the remainder arise in the body or tail. Most ductal carcinomas are mucin-producing tumors and usually are associated with a dense desmoplastic reaction.

Although most pancreatic adenocarcinomas arise from the ductal epithelium, pancreatic acinar carcinomas and cancers arising from mucinous cystic neoplasms are also found.

Multicentricity, which is usually microscopic, is not unusual.

Metastatic spread Perineural invasion occurs in the majority of patients with pancreatic carcinoma. In addition, pancreatitis distal to and surrounding the tumor is usually present. Most patients present with lymph node metastases in the region of the pancreaticoduodenal drainage basins. Subpyloric and inferior pancreatic head, SMA**,** and para-aortic lymph node groups also may be involved.

Staging and prognosis

Pancreatic adenocarcinoma is staged according to local spread of disease, nodal status, and distant metastatic involvement using the American Joint Committee on Cancer (AJCC) TNM system (Table 1). The T staging of the primary tumor includes an analysis of direct extension of disease to the duodenum, bile duct, or peripancreatic tissues. A T4 advanced cancer may extend directly to the SMA or celiac axis, meaning that the cancer is unresectable.

Independent prognostic factors Lymph node metastases and tumor size and differentiation have independent prognostic value in patients with pancreatic carcinoma. Significantly improved survival is seen in patients with smaller lesions, lymph node-negative tumors, and tumors in which the surgical margins are not involved.

Lymph node and margin status Prior to the age of adjuvant therapy, lymph node status was the most dominant prognostic factor. It is now rivaled by sur-

TABLE 1: TNM staging of pancreatic tumors

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of a primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to the pancreas, ≤ 2 cm in diameter
T2	Tumor limited to the pancreas , > 2 cm in diameter
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
Regional lymph nodes (N)	
N0	No involved regional lymph nodes
N1	Any involved regional lymph nodes
Distant metastases (M)	
Mx	Presence of distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases

Stage grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1-3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

From Fleming ID, Cooper JS, Henson DE, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

gical margin status in series where surgical margins have been meticulously examined.

Treatment

SURGICAL TREATMENT OF RESECTABLE DISEASE

The rate of resection for curative intent ranges from 10% to > 75%, with the higher percentage resulting from both a more aggressive approach and better preoperative staging for resectability. Also, there is growing evidence that patients with potentially resectable pancreatic cancer have a shorter hospital stay, reduced surgical mortality, and an overall better outcome if the surgery is performed at "high-volume" medical centers staffed by experienced surgeons (approximately 16 operable cases per year).

Extended resections may include portal or superior mesenteric vessels, colon, adrenal, or stomach. If resection of adjacent organs or tissues results in the

conversion of a positive to a negative resection margin, it is of great potential benefit to the patient.

Determination of resectability

The initial approach to surgery for pancreatic carcinoma includes a determination of resectability. This determination should be first made preoperatively with high-quality CT or MRI and perhaps endoscopic ultrasonography. Operative determination of resectability includes careful examination of the liver, porta hepatis, and portal and superior mesenteric vessels. The head of the pancreas and uncinate process are mobilized by an extensive Kocher maneuver to evaluate the head of the pancreas and its relationship to the SMA and SMV. The hepatic artery and celiac trunk are examined to make certain there is no vascular encasement.

Criteria for unresectability include distant metastases and involvement of the SMA and celiac axis.

An analysis of 200 patients who underwent resection of pancreatic adenocarcinoma in the era prior to adjuvant therapy found that the most important factors influencing long-term survival were the diameter of the primary tumor, status of the resected lymph nodes, and status of the resected margins. Patients with tumors < 3 cm in diameter had significantly longer median survival and 5-year survival rates (21 months and 28%, respectively) than those with tumors ≥ 3 cm (11.5 months and 15%). Patients with no lymph node involvement had a 5-year survival rate of 36%, as compared with $< 5\%$ for those with positive nodes. Patients who underwent resections with negative margins had a 5-year survival rate of 26%, vs 8% for those with positive margins. The type of resection (pylorus-preserving vs standard Whipple procedure) did not influence survival.

Extent of resection

Whipple vs pylorus-preserving procedure If the tumor is deemed to be resectable, a standard pancreaticoduodenectomy (Whipple procedure) or pylorus-preserving Whipple procedure (PPW) is performed. The PPW theoretically eliminates the nutritional problems caused by a reduced gastric reservoir and gastric dumping, but this finding has not been shown definitively. If there is any doubt about cancer proximity or blood supply to the pylorus, an antrectomy should be performed. If the tumor approaches the pylorus or involves the subpyloric nodes, classic antrectomy is preferred.

Intraoperative biopsy Most patients with resectable periampullary tumors can successfully undergo pancreaticoduodenectomy without an intraoperative biopsy. A time-consuming frozen section interpretation may not be informative, and histologic confirmation may be impossible with small lesions associated with peritumoral pancreatitis. Most large series of pancreaticoduodenectomy for carcinoma include resections of benign pathology based on clinical judgment. A negative fine-needle cytology should not deter an experienced surgeon from proceeding with resection.

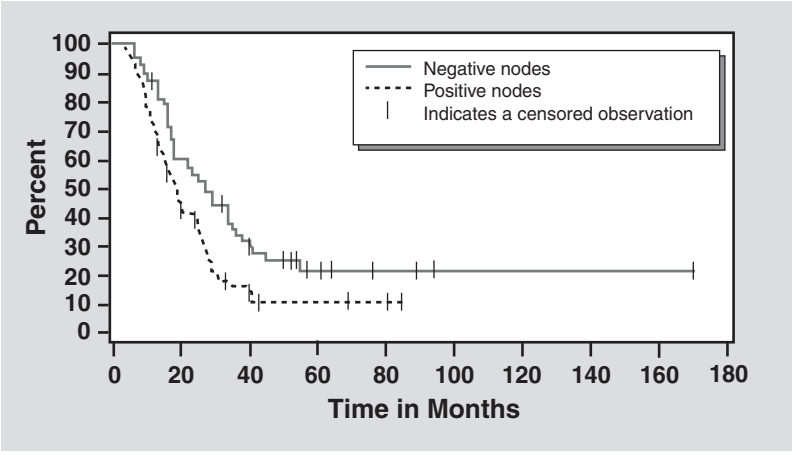

FIGURE 1: Actuarial survival as a function of regional lymph node status in patients with pancreatic cancer.

Reconstruction technique The most common reconstruction technique after a Whipple resection requires a single retrocolic jejunal loop to complete the pancreaticojejunostomy, which is followed by a hepaticocholangiojejunostomy and gastrojejunostomy. A duct-mucosal anastomosis is preferred to the pancreatojejunostomy. Pancreaticogastrostomy is also an effective and safe means of creating the anastomosis.

Postsurgical complications Operative mortality of pancreaticoduodenectomy is currently < 6% in major surgical centers. The leading causes of postoperative mortality include postoperative sepsis, hemorrhage, and cardiovascular events. Most of the septic complications arise from pancreaticojejunostomy leaks.

In many series, early delayed gastric emptying is the leading cause of morbidity for pylorus-preserving procedures. The number-two cause of morbidity, seen in 5%-15% of all patients, is a leak or fistula from the pancreatic anastomosis. Today, most fistulas close spontaneously with the addition of somatostatin analog treatment and adequate drainage. Pancreatic fistulas heal with conservative measures in approximately 90% of patients.

SURGICAL PALLIATION

Surgical palliation is also considered in patients undergoing exploration with curative intent. Jaundice, gastric obstruction, and pain may be alleviated by surgical palliation.

Biliary tract obstruction Either a choledochojejunostomy or cholecystojejunostomy can be used to bypass the biliary obstruction. Recurrent jaundice and cholangitis are less likely to develop when the common duct is used for decompression.

Duodenal obstruction Although duodenal obstruction is rare as a presenting symptom, duodenal involvement may occur eventually in 25% of patients. Some authors believe that prophylactic bypasses are safe and should be performed in all patients. One phase III trial supports prophylactic bypass, but another does not.

Pain relief Severe back pain may be an incapacitating symptom. Pain relief may be achieved by chemoablation of the celiac plexus or by alcohol injection, which may be performed intraoperatively or percutaneously. An intraoperative injection of 25 mL of ethanol (95%) on both sides of the celiac axis will ablate tumor pain. (For further discussion of these techniques, see chapter 39 on pain management.)

NEOADJUVANT AND ADJUVANT THERAPY

Radiation therapy

Even with apparently adequate surgical resection, pancreatic cancer has a high risk of locoregional recurrence. Moreover, most lesions are unresectable, even when there is no apparent distant metastatic disease. Thus, there is a theoretical rationale for the adjunctive use of radiation therapy, either before or after surgery, in almost all patients. Preoperative (neoadjuvant) radiation may help render locally advanced lesions resectable with negative margins (RO resection). Postoperative (adjuvant) radiation may help eliminate suspected residual microscopic disease in the tumor bed and/or regional lymphatics.

With an effective chemotherapeutic agent, there is greater potential for adequate locoregional cytotoxicity—as well as control of subclinical distant disease—than could be obtained with limited doses of adjuvant radiation therapy alone.

A Radiation Therapy Oncology Group (RTOG)/Southwest Oncology Group (SWOG)/Eastern Cooperative Oncology Group (ECOG) intergroup trial, the largest of its kind, is comparing infusional 5-FU to gemcitabine, both agents given before and after chemoradiation therapy, in patients with resected pancreatic cancer. Radiation is being administered without a treatment break and is being given with continuous-infusion 5-FU in both arms. End points include quality of life as well as survival. This study has met its accrual and is now closed. Results are pending.

Preoperative chemoradiation Several single-institution studies have evaluated the role of preoperative irradiation in conjunction with fluorouracil (5-FU)- and gemcitabine (Gemzar)-based chemotherapy. In these studies, 60%-80% of the lesions were completely resected 1.0-1.5 months after the completion of chemoradiotherapy. Median survival has ranged from 16 to 25 months, but no phase III trials have been conducted to evaluate preoperative therapy vs postoperative sequencing.

Preoperative radiation therapy, to 4,500-5,000 cGy, in conjunction with chemotherapy should be considered for patients with pancreatic adenocarcinoma who are medically fit but who have marginally resectable disease. There are research initiatives to further address the role of neoadjuvant chemotherapy. For example, a proposed ECOG study will evaluate gemcitabine plus radiotherapy vs gemcitabine, 5-FU, and cisplatin (Platinol) followed by

radiotherapy and 5-FU for patients with locally advanced disease. Another phase II study involves high-dose gemcitabine, with short-term radiation therapy to locally advanced but potentially resectable cancer.

Postoperative chemoradiation A small Gastrointestinal Tumor Study Group (GITSG) trial demonstrated a significant prolongation of survival (median survival increase, from 11 to 20 months) among patients with pancreatic adenocarcinoma who received irradiation plus bolus 5-FU chemotherapy after curative resection, as compared with those given no adjuvant treatment. An improvement in the long-term cure rate was also observed among those given chemoradiation therapy.

The European Organization for Research and Treatment of Cancer (EORTC) completed a trial of 104 patients similar to that of the GITSG but without maintenance chemotherapy. Reported data suggest no significant difference between split-course radiation with bolus 5-FU and observation only after curative resection (two-tailed P value = .099). The European trial is difficult to interpret because 20% of patients randomized to receive postoperative treatment were not treated.

The GITSG study utilized 4,000 cGy of radiation delivered in a split-course fashion—with a planned 2-week break midway through the treatment. However, single-institution studies indicate that 4,500-5,000 cGy can be safely delivered in 5.0-5.5 weeks without a treatment break.

Careful attention to field size is important. The GITSG allowed portals as large as 20×20 cm. However, ports that are approximately 12×12 cm are usually sufficient to cover the tumor bed with a 2- to 3-cm margin. The use of multiple beams and high-energy photons is also important.

A total of 541 patients were enrolled in a trial conducted by the European Study Group for Pancreatic Cancer (ESPAC). This study evaluated the benefits of adjuvant therapy. The design was complex, attempting to evaluate several options. They included no further therapy after surgery, chemoradiation therapy (bolus 5-FU with split-course radiotherapy), chemotherapy (5-FU with leucovorin), and chemoradiation therapy followed by chemotherapy.

Interpretation of the results is confounded by the fact that some institutions opted for a full 2×2 randomization (all four options), whereas others allowed only two options (no further therapy vs chemotherapy or no further therapy vs chemoradiation therapy). Patients in these two options could also have therapy other than that prescribed in the randomization. Furthermore, no data were collected regarding time to recurrence or whether treatment was given after recurrence.

Only the 5-FU leucovorin arm would be considered a state-of-the-art approach, and it was demonstrated to improve survival significantly ($P = .0005$). This finding would suggest a strong benefit to postoperative chemotherapy. If radiation therapy is included, it would probably best be given after 1-2 months of full-dose chemotherapy. Most practitioners would recommend continuous-course radiation therapy rather than split-course treatment.

ESPAC is now conducting a postoperative trial comparing various chemotherapy regimens with a control group. In the United States, the findings of several phase II trials of postoperative regimens will be available soon.

In summary, the best run trial is also the smallest and oldest, but does demonstrate the superior value of adjuvant chemoradiation compared with surgery alone.

TREATMENT OF UNRESECTABLE DISEASE

Irradiation can prolong and/or improve quality of life in some patients with unresectable adenocarcinoma of the pancreas. It is better combined with chemotherapy. Long-term survival is, unfortunately, highly unusual.

Chemoradiation therapy The addition of chemotherapy to radiation therapy has been shown to improve the survival of patients with unresectable pancreatic adenocarcinoma, with moderate doses of radiation only slightly less effective than higher doses. In a GITSG trial of unresectable disease, moderate-dose radiation (4,000 cGy) with 5-FU chemotherapy significantly improved survival, as compared with higher doses of radiation (6,000 cGy) and no chemotherapy (median survival, 9.6 vs 5.2 months). The GITSG has also compared chemotherapy plus irradiation with chemotherapy alone and demonstrated a significant improvement with combined-modality therapy (median survival, 42 vs 32 weeks).

Based on these data, except in a protocol setting, the palliative management of a patient with unresectable pancreatic adenocarcinoma who has significant local symptoms should probably consist of moderate doses of radiation (4,000-5,000 cGy) in conjunction with 5-FU–based chemotherapy. As in adjuvant treatment, carefully shaped portals approximately 12 × 12 cm in size should be used.

Approaches under investigation At present, numerous trials are exploring a variety of chemoradiation therapy approaches, including single-agent or combination therapy with oral or infusional 5-FU, paclitaxel (Taxol), cisplatin, gemcitabine, docetaxel (Taxotere), and oxaliplatin. Trials with combined gemcitabine and irradiation are of particular interest due to the activity of this drug in pancreatic cancer and because it is a potent radiosensitizer. The benefit of irradiation for patients with locally advanced disease, however, remains a research question because of toxicity concerns and the relatively brief survival rates. Therefore, a new ECOG trial will evaluate gemcitabine alone vs gemcitabine and irradiation for this group of patients.

If gemcitabine is given either before or after a course of radiation therapy, full doses of 1,000 mg/m^2 are possible. If irradiation and gemcitabine are given concurrently, doses of either modality must be sharply reduced.

Presently, the RTOG is conducting a phase II evaluation of gemcitabine (75 mg/m^2/wk), paclitaxel (40 mg/m^2/wk), and irradiation (5,040 cGy) followed by the farnesyl transferase inhibitor R11577 for locally advanced pancreatic cancer. When given weekly with conventional fields, the maximum tolerated dose for gemcitabine with RT is 400 mg weekly. If fields are reduced to a 2-cm margin around the target, 500 mg over 50 minutes weekly can safely be given.

TABLE 2: Chemotherapy regimens for pancreatic cancer

Drug/combination	Dose and schedule
Fluorouracil/radiation therapy (GITSG regimen)	
Fluorouracil	500 mg/m^2/d IV bolus for 3 consecutive days once every 4 weeks during radiation therapy
Radiation	Two courses of 2,000 cGy each, separated by 2 weeks (total dose, 4,000 cGy)
Gastrointestinal Tumor Study Group: Cancer 59:2006–2010, 1987.	
Infusional 5-FU with radiation therapy	
Concurrent radiation therapy and chemotherapy phase:	
Fluorouracil	150-250 mg/m^2/d, 24 hours/day during radiation therapy
Radiation	Median dose of 4,500 cGy/25 fractions (range 4,000 cGy/ 20 fractions to 5,040 cGy/28 fractions)
Fisher B, Perera F, Kocha W, et al: Int J Radiat Oncol Biol Phys 45:291-295, 1999.	
SINGLE-AGENT REGIMEN	
Gemcitabine	1,000 mg/m^2 IV infused over 30 minutes once a week for 7 weeks, followed by a 1-week rest period
Subsequent cycles once a week for 3 consecutive weeks out of every 4 weeks	
Burris HA, Moore MJ, Andersen J, et al: J Clin Oncol 15:2403–2413, 1997.	

Table prepared by Ishmael Jaiyesimi, DO

A current phase II trial is combining "full-dose" gemcitabine (1,000 mg/m^2) with irradiation directed at the primary tumor alone (36 Gy in 15 fractions).

TREATMENT OF METASTATIC ADENOCARCINOMA

Pancreatic adenocarcinoma is still one of the most frustrating, resistant solid neoplasms to treat, and therapy for metastatic disease remains palliative. Few agents have demonstrated activity of > 10%. Moreover, most of the reported series have been small, and not all encouraging results have been duplicated.

Chemotherapy

As metastatic pancreatic carcinoma is incurable, the anticipated risks of chemotherapy, which are often substantial, must be balanced against the gains that may be achieved; unfortunately, they are few. Patients who are debilitated due to their underlying or comorbid disease should not be offered chemotherapy, as their likelihood of deriving any benefit is exceedingly slim. However, patients who desire therapy and who, while symptomatic, still have a good performance status may be offered "standard" chemotherapy (Table 2) or, if possible, should be encouraged to participate in a clinical trial.

5-FU Historically, single-agent 5-FU has been associated with a response rate of 25% in pancreatic cancer. FAM (5-FU, Adriamycin [doxorubicin], and

mitomycin) and 5-FU plus doxorubicin offer no advantage over 5-FU alone. 5-FU plus leucovorin appears to be ineffective.

Gemcitabine is indicated for the treatment of locally advanced or metastatic pancreatic adenocarcinoma. Gemcitabine was compared with 5-FU in a group of 126 previously untreated patients and showed a small, but statistically significant, improvement in response rate. Median survival in the gemcitabine group was 5.7 months, with 18% of patients alive at 12 months, as compared with a median survival of 4.4 months in the group receiving 5-FU, with 2% of patients alive at 12 months. Perhaps more important, clinical benefit response (a composite measurement of pain, performance status, and weight) occurred in 23.8% of the gemcitabine-treated group, as compared with 4.8% of the 5-FU–treated group. Due to its palliative potential, gemcitabine has become the standard of care for patients with unresectable pancreatic adenocarcinoma.

A recent randomized, phase II trial of dose-intense gemcitabine administered by standard infusion vs a fixed-dose rate (10 mg/m^2/min) suggested an improved 1-year survival with the fixed-dose rate.

Promising combinations and single agents Promising combinations include irinotecan (CPT-11, Camptosar), irinotecan + gemcitabine, cisplatin + gemcitabine, cisplatin + 5-FU, and oxaliplatin (Eloxatin)-containing combinations. For example, a recent French phase II study of gemcitabine (10 mg/m^2/minute [100 minutes]) infusion followed by oxaliplatin (100 mg/m^2) included patients with locally advanced and stage IV disease. The overall response rate was similar for both groups ($>$ 30%), with a median overall survival of 9.2 months. The investigational drug 9-nitro-20(S)-camptothecin-9NC (RFS 2000) has demonstrated significant activity in metastatic pancreatic adenocarcinoma and is under further evaluation in three randomized, phase III clinical trials.

Agents with marginal activity include mitomycin, doxorubicin, ifosfamide (Ifex), streptozocin (Zanosar), and docetaxel (Taxotere). To date, monoclonal antibody therapy and hormonal manipulation have been ineffective. A phase II study of antiepidermal growth factor receptor–antibody IMC-C2259 (Cetuximab) combined with gemcitabine has shown a 12% partial response and 39% stable disease in advanced pancreatic cancer. Side effects included rash/folliculitis and fatigue. A phase III trial of the combination is planned. Other "targeted" therapies are under investigation.

A randomized trial of the Eastern Cooperative Oncology Group (ECOG) has completed a comparison of gemcitabine with or without 5-FU: 5.4 vs 6.7 month median survival for gemcitabine vs the combination, respectively. The difference was not statistically significant. Both regimens were well tolerated (*Berlin JD, Catalano PD, Thomas J, et al: J Clin Oncol 20:3270-3275, 2002*).

Novel approaches A progressively better understanding of the molecular biology of pancreatic cancer has revealed numerous new therapeutic targets. Areas of active current research include attempts to replace tumor-suppressor genes (ie, *p53*) and to inhibit K-*ras* protein function.

A recent randomized trial comparing marimastat, a broad-spectrum matrix metalloproteinase inhibitor, and gemcitabine did not demonstrate any significant difference

between the survival curves. Similarly, in randomized trials exploring the efficacy of the long-acting somatostatin analog SMS 201-995 pa LAR (octreotide pamoate LAR, Oncolar), no significant activity was demonstrated.

Many patients seek "complementary" or "alternative" treatment strategies. The NCI (National Cancer Institute) has activated a phase III study of gemcitabine vs intensive pancreatic proteolytic enzyme therapy with ancillary nutritional support for pancreatic cancer patients based on phase II data.

ECOG is conducting a new large randomized phase III trial comparing standard dose gemcitabine vs fixed-dose rate infusions of gemcitabine vs fixed-dose rate infusion gemcitabine and oxaliplatin. Another randomized phase III trial is comparing gemcitabine alone with gemcitabine in combination with the topoisomerase I inhibitor exatecan mesylate.

Pancreatic endocrine tumors

Pancreatic endocrine tumors (PETs) cover a spectrum of neoplasms, many, although not all, of which originate from the pancreatic islets of Langerhans.

Islet-cell neoplasms are not rare. Autopsy studies have documented an incidence as high as 1.5%. Most of these lesions are clinically silent.

The normal islet contains α, β, γ cells, and enterochromaffin cells, which primarily secrete glucagon, insulin, somatostatin, and serotonin, respectively. All of these hormones may be secreted in excess by islet-cell neoplasms. Other hormones that may be secreted by these tumors include vasoactive intestinal peptide (VIP), gastrin, pancreatic polypeptide (PP), and calcitonin. The aggressiveness of an islet-cell lesion in terms of its metastatic potential appears to be due to the cell of origin.

Types of tumors

Insulinomas are β-cell tumors of the pancreatic islets that produce insulin. Four-fifths of insulinomas occur as a solitary lesion, and < 10% of these tumors demonstrate malignant potential (in terms of invasiveness or the development of metastases). In patients with the multiple endocrine neoplasia type 1 (MEN-1) syndrome, insulinomas are multicentric (10% of patients). In addition, a small group of insulinomas are associated with diffuse islet-cell hyperplasia or nesidioblastosis.

Gastrinomas are gastrin-secreting tumors associated with the Zollinger-Ellison syndrome (ZES). These tumors can be either sporadic or familial. Sporadic gastrinomas do not have associated endocrinopathies, whereas hereditary gastrinomas occur in patients with MEN-1 syndrome. Patients with the sporadic form of ZES may have single or multiple gastrinomas. This finding contrasts with patients with hereditary MEN-1 islet-cell tumors, who generally have a more diffuse tumor process within the pancreas.

It is known that 80%-90% of gastrinomas are located within the "gastrinoma triangle," defined as the junction of (1) the cystic and common duct, (2) the

second and third portions of the duodenum, and (3) the neck and body of the pancreas. Although tumors most characteristically are located within the pancreas, a significant percentage of patients with ZES demonstrate primary tumors of the duodenal wall. Extrapancreatic and extraintestinal locations occur in approximately 10% of patients.

More than 90% of gastrinomas are malignant. The spectrum of clinical progression includes localized tumors, regional lymph node metastases, and widespread metastatic disease.

Other types Approximately three-quarters of VIPomas and approximately half of all glucagonomas and somatostatinomas are malignant.

"Nonfunctional" tumors Although many islet-cell carcinomas cause considerable morbidity due to the inappropriately elevated levels of the hormones that they secrete, even "nonfunctional" islet-cell carcinomas, ie, those without an associated demonstrable hormone-related syndrome (such as PPomas, neurotensinomas, and nonsecretory islet-cell carcinomas), may be aggressive. Nonfunctional tumors account for up to 30% of all islet-cell carcinomas. Two-thirds of these nonfunctional tumors will demonstrate metastatic lesions at some point during the patient's lifetime.

Signs and symptoms

The symptom complex that is observed depends on which hormone or hormones are secreted in excess.

Insulinomas are associated with symptoms of recurrent hypoglycemia. Diagnosis of these tumors is made by the demonstration of inappropriately elevated levels of insulin, proinsulin, and C peptide at the time of hypoglycemia and an elevated insulin-glucose ratio (> 0.3).

Approximately 20% of patients with ZES develop the syndrome in the setting of the MEN-1 syndrome. MEN-1 is inherited as an autosomal-dominant trait and is characterized by tumors of multiple endocrine organs, including the pituitary, pancreas, and parathyroid. The gene for MEN-1, which has been localized to the long arm of chromosome 11, was recently identified and named *MENIN*.

Gastrinomas Symptoms of gastrinoma-ZES are due to the effect of elevated levels of circulating gastrin. Ulceration of the upper GI tract is seen in $> 90\%$ of patients. Diarrhea is the second most common symptom. Approximately 25% of gastrinomas occur in the context of MEN-1 and are associated with parathyroid hyperplasia and hypercalcemia.

The diagnosis of ZES is established by the demonstration of hypergastrinemia (fasting serum gastrin concentration $>$ 1,000 pg/mL) and gastric acid hypersecretion in a patient with ulcer disease.

VIPomas VIP excess causes a profuse, watery diarrhea, hypokalemia, hypophosphatemia, and hypochlorhydria (WDHA syndrome).

Glucagonomas are associated with a rash (described as a necrotizing migratory erythema), glossitis, cheilosis, constipation and ileus, venous thrombosis,

and hyperglycemia. Not all of these manifestations are secondary to elevated glucagon levels alone. The etiology of these signs and symptoms remains unknown, but some patients respond to supplemental zinc and amino acid infusions.

Somatostatinomas, which are quite rare, are associated with elevated blood glucose levels, achlorhydria, cholelithiasis, and diarrhea.

Tumor localization

Insulinomas Ultrasonography, CT, MRI, and selective arteriography with portal vein sampling have been utilized for the preoperative localization of insulinomas. The sensitivity of these preoperative imaging tests ranges from approximately 30% to 60%. This is because 40% of insulinomas are ≤ 1 cm and two-thirds of these tumors are < 1.5 cm.

Because the success of preoperative localization tests is disappointing and 90% of these tumors will be found and successfully resected by an experienced endocrine surgeon, there is a general trend toward performing fewer tests. Some centers utilize preoperative ultrasonography if the patient has not undergone prior pancreatic surgery. Other centers still routinely employ portal vein catheterization and angiography.

More recently, intraoperative sonography has been shown to aid the surgeon. In one series, 84% of tumors not localized preoperatively were correctly located by surgical exploration and intraoperative sonography. Many lesions not discovered by surgical palpation may be found by this technique. At present, there is much less reliance on blind distal resection than was previously advocated. Obviously, the technique of intraoperative ultrasonography may not be as helpful in the MEN-1 syndrome, in which multiple small insulinomas may be found.

Gastrinomas CT, ultrasonography, selective abdominal angiography, selective venous sampling of gastrin, intraoperative ultrasonography, endoscopic ultrasonography, and intraoperative endoscopy have all been reported to be useful in localizing gastrinomas. More recently, somatostatin receptor scintigraphy (SRS) has become a valuable tool for PET localization. Several studies have suggested greater sensitivity and specificity when compared with other diagnostic tests.

Treatment

Surgery for insulinomas

For larger insulinomas in the body or tail of the pancreas, a distal pancreatectomy may be preferable to enucleation. For tumors in the head of the pancreas, enucleation of the tumor is usually possible. Patients with MEN-1 or islet hyperplasia may benefit from an 80% distal pancreatectomy. If the insulinoma is not found at surgery, a blind pancreatectomy is not warranted. Further imaging and venous sampling studies may reveal the exact location of the tumor.

A surgical cure results in normal values on subsequent provocative testing, during which blood insulin and glucose concentrations are measured simultaneously. Some insulinoma recurrences actually represent persistent disease after incomplete tumor excisions or overlooked secondary multiple tumors.

Surgery for gastrinoma-ZES

The ideal treatment for gastrinoma-ZES is surgical excision of the gastrinoma. However, this approach is possible in only 20% of patients, most of whom have a sporadic tumor. With the development of effective antisecretory agents and preoperative localization with octreotide scanning, the majority of patients demonstrating widespread metastatic disease can be identified and spared from surgical exploration. In addition, some series report that patients with nonmetastatic sporadic gastrinoma may have a higher incidence of extrapancreatic sites than was previously thought. One series has reported that two-thirds of gastrinomas are extrapancreatic.

Patients with sporadic gastrinoma All patients with sporadic gastrinoma should undergo localization studies and be considered for exploratory laparotomy, with the goal of potential cure of ZES. Recent evidence suggests that resection of primary gastrinoma decreases the incidence of liver metastases and ZES. Overall, surgery produces complete remission in approximately 60% of patients with sporadic ZES, and subsequent survival is excellent.

Patients with ZES and MEN-1 Some experts believe that surgery should not be used in the management of patients with MEN-1 and ZES. Instead, they recommend treatment with antisecretory medications. This approach is somewhat controversial, as some authors believe that all patients without demonstrated liver metastases should undergo surgery to remove duodenal and pancreatic gastrinomas.

Moreover, since many patients with ZES and MEN-1 die of metastatic gastrinoma at a young age, a surgical approach may be warranted. Surgery should be performed only if imaging studies localize the tumor. Although radical surgery may not provide a cure, removal of large tumors may decrease metastatic potential and increase survival.

Surgical procedure During surgery, the entire pancreas should be mobilized and scanned ultrasonographically to permit a thorough examination of the pancreatic head, duodenum, stomach, mesentery, liver, and splenic hilum. Intraoperative endoscopy with transillumination of the bowel wall may also be useful in identifying duodenal lesions. In general, enucleation is the treatment of choice, except for lesions within the duodenal wall, which may require pancreaticoduodenectomy. If no tumor is found, blind distal pancreatectomy should be avoided, since 90% of gastrinomas are located within the gastrinoma triangle.

Surgical resection of liver metastases is controversial. However, several authors have demonstrated meaningful survival in patients with small, isolated lesions. The use of ablative techniques, with open, laparoscopic, or percutaneous techniques, can reduce the neurohormonal tumor burden.

Radiation therapy for islet-cell tumors

Adjuvant therapy The role of adjuvant radiation in the treatment of islet-cell carcinomas of the pancreas is unclear. Because of the rarity of these lesions and their often indolent behavior, the role of this therapy will probably never be demonstrated. However, postoperative irradiation can be considered for patients with positive nodes or microscopically close margins. Concurrent chemotherapy with such agents as 5-FU and/or streptozocin also can be considered. Radiation doses are the same as are used in adjuvant treatment of pancreatic cancer.

Palliative therapy Anecdotal reports indicate that pancreatic islet-cell tumors can respond to palliative doses of irradiation. Long-term control of unresectable disease has been reported.

Chemotherapy for islet-cell tumors

Islet-cell carcinomas are more sensitive to chemotherapy than carcinoid tumors.

Single agents Agents that have demonstrated antitumor activity include recombinant human interferon alfa-2a and alfa-2b (Intron A, Roferon-A), 5-FU, doxorubicin, dacarbazine (DTIC), and streptozocin.

Combination regimens Combination chemotherapy is often more effective than monotherapy. For example, in an ECOG study, the combination of 5-FU and streptozocin demonstrated a higher response rate than streptozocin alone (63% vs 36%) in islet-cell tumors, as well as a better complete response rate (33% vs 12%) and median survival duration (26 vs 16.5 months). Therapy with doxorubicin plus streptozocin was superior to both 5-FU plus streptozocin and single-agent chlorozotocin in terms of response and survival and is the combination most widely used in the United States. Etoposide combined with cisplatin is active in poorly differentiated neuroendocrine malignancies but is marginally effective in well-differentiated lesions.

TREATMENT OF SYMPTOMS

Octreotide acetate

Octreotide (Sandostatin) is often successful in palliating symptoms in patients with islet-cell carcinomas, although this success depends somewhat on the cell type. For example, insulinomas are marginally responsive to octreotide, whereas gastrinomas and VIPomas often respond. However, compared with carcinoid tumors, the median duration of response of islet-cell neoplasms to octreotide is significantly shorter (~10 weeks).

As discussed more fully in the section on carcinoid tumors below, a promising experimental approach for patients whose tumors express somatostatin receptors is the use of octreotide conjugated to a therapeutic radioisotope.

Other agents

Omeprazole (Prilosec), an inhibitor of the function of the parietal cell hydrogen pump, is more effective than H_2-receptor antagonists in blocking gastric acid production and is useful in the symptomatic management of gastrinomas.

Other agents available for symptomatic treatment of insulinoma include diazoxide (Hyperstat), an insulin-release inhibitor, and, more recently, glucagon by continuous infusion through a portable pump. Both of these agents are used in conjunction with frequent high-carbohydrate meals.

Patients with the glucagonoma syndrome are treated symptomatically with insulin, high-protein meals, supplemental zinc, amino acid infusions, and anticoagulants.

Hepatic arterial embolization

Hepatic arterial embolization, with or without chemotherapy (chemoembolization), is an alternative palliative therapy for patients with either carcinoid tumors or an islet-cell carcinoma who have predominant liver metastases or who are symptomatic. Embolization is best reserved for patients with $< 75\%$ tumor involvement of the liver, bilirubin level < 2 mg/dL, and an ECOG performance status of ≤ 2.

CARCINOID TUMORS OF THE GI TRACT

Carcinoid tumors typically arise from components derived from the primitive gut and lungs, and, rarely, the gonads. Approximately 85% of all carcinoids originate from the gut, predominantly the appendix, followed by the small bowel and rectum.

These tumors have the propensity to cause considerable morbidity by virtue of creating a syndrome of hormonal excess. For example, although the majority of carcinoids are hormonally inert, these neoplasms may produce excessive amounts of serotonin (from dietary tryptophan), prostaglandins, kinins (secondary to kallikrein release), and a variety of other hormones, which may account for the "carcinoid syndrome."

Signs and symptoms

Flushing The most common sign of the carcinoid syndrome is flushing, which is often triggered by alcohol, catecholamines, or emotional stress. It ranges in severity from a minor annoyance to profound vasodilatation with near syncope and hypotension.

Diarrhea is also common and is due to GI hypermotility. It usually occurs after meals and is rarely voluminous, bulky, or foul-smelling.

Abdominal cramps Diarrhea may be associated with crampy pain, although other etiologies for the pain must be considered, including bowel obstruction due to tumor or mesenteric fibrosis.

Bronchospasm Patients may also develop bronchospasm, which may be mediated by histamine. This problem is often associated with (although less common than) flushing.

Valvular heart disease A late finding is right-sided valvular heart disease, although left-sided lesions may be noted occasionally. The fibrous deposits may lead to tricuspid insufficiency and/or pulmonary stenosis. Valve replacement is rarely necessary, however.

Symptom triad If there is sufficient shunting of dietary tryptophan from niacin to serotonin synthesis, patients may develop diarrhea, dermatitis, and dementia, although this symptom triad is quite rare if patients maintain adequate intake of a balanced diet.

Diagnosis

Diagnostic studies include CT/MRI of the abdomen and a 24-hour urine test for 5-hydroxyindoleacetic acid (5-HIAA). Some radiologists prefer to obtain a triple-phase CT scan of the liver to detect these highly vascular liver metastases.

Octreotide scanning [Indium-111]-octreotide scintigraphy (Octreoscan) has been shown to have a higher sensitivity for detecting pancreatic tumors and is superior to CT or MRI for detecting metastatic disease, particularly extrahepatic disease. One study suggests that [indium-111]-octreotide scintigraphy can reduce costs by avoiding unnecessary surgeries. Also, a positive scan may predict which patients may benefit from treatment with somatostatin analogs (eg, octreotide acetate). Initial studies with a new peptide tracer, [indium-111]-DOTA-lanreotide, suggest high tumor uptake and a more favorable dosimetry than is seen with [indium-111]-DTPA-D-Phel-octreotide.

Prognosis

Site and size of tumor The site of tumor origin is potentially prognostic, as most appendiceal carcinoids (75%) are < 1 cm when found and are usually cured by resection. Similarly, rectal carcinoids are usually small and completely resectable for cure.

In contrast, small bowel carcinoids tend to present at a more advanced stage, and approximately one-third have multicentric primary lesions. However, if the disease is completely resectable, patients have a 20-year survival rate of 80%; patients with unresectable intra-abdominal or hepatic metastases have median survival durations of 5 and 3 years, respectively.

Treatment

The management of carcinoid tumors focuses not only on treating the bulk disease, in common with other solid malignancies, but also on managing the complications of hormonal excess.

TREATMENT OF BULKY DISEASE

Surgery

Appendiceal carcinoids For tumors that are found incidentally in the appendix and that are probably between 1 and 2 cm, appendectomy is the treatment of choice. For tumors > 2 cm, a right hemicolectomy and lymph node dissection are appropriate.

Small intestine and rectal carcinoids should be resected with a wedge lymphadenectomy to evaluate nodal disease. Duodenal lesions should be locally excised if small (< 2 cm), with radical resection reserved for larger tumors.

Tumor debulking Liver resection or ablation of liver metastases with cryotherapy or radiofrequency techniques is useful in patients with limited extrahepatic disease and/or asymptomatic carcinoid syndrome. Tumor debulking can protect liver functional reserve and improve quality of life.

Liver transplantation may be of benefit in selected patients without extrahepatic disease whose disease progresses after other therapeutic interventions.

Radiation therapy

Carcinoid tumors are responsive to radiation therapy and frequently are well palliated with this modality. Overall, treatment with higher radiation doses (29-52 Gy) has been associated with higher response rates (40%-50%) than have been seen with lower doses (10%).

Chemotherapy

Since carcinoid tumors tend to be resistant to most chemotherapeutic agents, there are no standard regimens for the treatment of unresectable tumors.

Single agents Agents that have reported activity include 5-FU, doxorubicin, and recombinant human interferon alfa -2a and alfa-2b. However, the response rate with these agents is in the range of 10%-20%, the response duration is < 6 months, and complete remission is rare.

Combination regimens Combination chemotherapy regimens represent little improvement over single-agent therapy, with response rates ranging from 25% to 35%, response durations < 9 months, and rare complete remissions.

TREATMENT OF SYMPTOMS

Somatostatin analogs

Octreotide The most active agent is the somatostatin analog octreotide acetate. Even though native somatostatin is effective in controlling many symptoms, due to its short half-life (< 2 minutes), this agent would have to be administered via continuous infusion to be clinically useful. However, octreotide may be administered subcutaneously every 8-12 hours, facilitating outpatient therapy. The initial dose of octreotide is 100-600 μg/d in 2-4 divided doses, although the effective dose varies between patients and must be titrated to the individual patient's symptoms.

Octreotide not only is useful in managing the chronic problems of the carcinoid syndrome but also is effective in treating carcinoid crisis (volume-resistant hypotension), which may be precipitated by surgery or effective antitumor treatment.

Octreotide is well tolerated, although chronic treatment may be associated with cholelithiasis, increased fecal fat excretion, fluid retention, nausea, and glucose intolerance. Occasional objective antitumor responses have been observed in patients who have received octreotide; the median duration of symptomatic improvement is 1 year. One report evaluating the cost-effectiveness of octreotide suggested that it may double survival time.

SMS 201-995 pa LAR is a long-acting somatostatin analog that allows for monthly dosing, avoiding the need for three daily injections. This new agent improves quality of life while apparently maintaining the same activity seen with daily octreotide. The usual monthly dose is 20 or 30 mg.

Patients who demonstrate disease resistance with somatostatin analog treatment alone may benefit from combination therapy with interferon-α and the somatostatin analog.

Radiolabeled somatostatin analogs A promising experimental treatment approach involves the use of octreotide or other somatostatin analogs conjugated to radioisotopes (eg, indium-111 or yttrium-90) in patients whose tumors express somatostatin receptors (eg, those with a positive Octreoscan). This approach allows targeted in situ radiotherapy by taking advantage of internalization of the radioligand into the cell to produce DNA damage and cell death, with little effect on normal tissue. Initial reports have shown favorable results with this technique.

Other agents

Other agents that have been used for symptomatic management include H_1- and H_2-receptor antagonists, methoxamine (Vasoxyl), cyproheptadine (Periactin), and diphenoxylate with atropine. The symptom complex of diarrhea, dermatitis, and dementia may be prevented or treated with supplemental niacin.

Hepatic arterial embolization

Hepatic arterial embolization with such agents as Ivalon or Gelfoam, with or without chemotherapy (chemoembolization), is an option for patients with either a carcinoid tumor or an islet-cell carcinoma who have predominant liver metastases or who are symptomatic. These lesions often are hypervascular, and, thus, peripheral hepatic embolization may provide symptomatic relief in some patients. It is unclear whether this therapy has any effect on patient survival.

ADRENOCORTICAL CARCINOMA

Adrenocortical carcinoma is a rare, highly malignant neoplasm that accounts for about 0.2% of cancer deaths. Long-term survival is dismal overall; the survival rate is 23% at 5 years and 10% at 10 years.

Etiology

The etiology of adrenocortical cancer is unknown, but some cases have occurred in families with a hereditary cancer syndrome.

Signs and symptoms

Approximately half of adrenocortical neoplasms produce hormonal and metabolic syndromes of hormone hypersecretion (such as Cushing's syndrome, virilizing or feminizing syndromes, and hyperaldosteronism). In children, Cushing's syndrome is rare but is often due to adrenal carcinoma. Mixed syndromes, such as Cushing's syndrome and virilization, strongly suggest adrenal carcinoma. The combination of hirsutism, acne, amenorrhea, and rapidly progressing Cushing's syndrome in a young female is a typical presentation. In men, estrogen-secreting tumors are associated with gynecomastia, breast tenderness, testicular atrophy, impotence, and decreased libido.

Often the diagnosis of adrenocortical carcinoma is not evident until the discovery of metastases or until the primary tumor becomes large enough to produce abdominal symptoms. Smaller tumors may be discovered incidentally, when unrelated abdominal complaints are investigated radiographically.

Treatment

Surgery

Complete surgical resection is the treatment of choice in patients with localized disease, as it offers the best chance of extending the disease-free interval and survival.

Medical therapy

Mitotane (Lysodren) is one of only a few effective agents; it exerts a specific cytolytic effect on adrenocortical cells and has been used to treat unresectable or metastatic adrenocortical carcinoma. Only 15%-30% of patients experience objective tumor regression, with a median duration of about 7 months. Mitotane is given at a dose of 4-8 g/d as tolerated, although the dose is variable.

Chemotherapy Doxorubicin has been of benefit in a limited number of patients, and combination chemotherapy is under investigation.

Suramin (Metaret), a sulfonated drug that is cytotoxic to human adrenocortical carcinoma cell lines, has been evaluated but has not proven useful in inop-

erable adrenocortical cancer. Innovative chemotherapy programs are clearly needed for this disease.

Controlling hormone hypersecretion Hormone hypersecretion can be controlled medically in most cases. Agents that are effective in reducing steroid production and in palliating associated clinical syndromes include the antifungal drug ketoconazole (Nizoral), 800 mg/d; aminoglutethimide (Cytadren), 1-2 g/d; and metyrapone (Metopirone), 1-4 g/d or higher as needed to control cortisol levels. These agents may be used alone or with mitotane.

PHEOCHROMOCYTOMA

Pheochromocytomas are catecholamine-secreting tumors that arise from chromaffin cells in the adrenal medulla or extra-adrenal sympathetic ganglia. These tumors constitute a surgically correctable cause of hypertension in 0.1%-1% of hypertensive persons.

Only about 10% of pheochromocytomas are considered to be malignant. The vast majority (90%) of pheochromocytomas are found in the adrenal medulla, and 97% are located below the diaphragm. Approximately 10% each of pheochromocytomas are bilateral, malignant, multifocal, extra-adrenal, found in children, or associated with a familial syndrome.

Pheochromocytomas in patients with familial syndromes, such as MEN-2 and von Hippel-Lindau syndrome (VHL), are less likely to be malignant than other adrenal lesions. In contrast, pheochromocytomas in patients with a family history of malignant pheochromocytoma are more apt to be malignant.

Epidemiology and etiology

Pheochromocytomas occur in all age groups, but the incidence peaks in the third to fifth decades of life. Most pheochromocytomas (90%) are sporadic. Approximately 10% of cases are inherited as an autosomal-dominant trait, either independently or as a part of the MEN-2 syndrome; bilateral tumors are more common in this setting.

Both MEN-2A and MEN-2B include medullary thyroid carcinoma and pheochromocytoma. MEN-2A includes hyperparathyroidism, whereas MEN-2B includes ganglioneuromas and marfanoid habitus. In MEN-2 families, pheochromocytoma occurs in 5.5%-100% (mean, 40%), depending on the kindred studied. Bilateral medullary hyperplasia is almost always present. Pheochromocytomas are bilateral in 70% of cases and usually multicentric, but they are rarely extra-adrenal or malignant.

Signs and symptoms

Patients can present with various symptoms, ranging from mild labile hypertension to hypertensive crisis, myocardial infarction, or cerebral vascular accident, any of which can result in sudden death. The classic pattern of

paroxysmal hypertension occurs in 30%-50% of cases; sustained hypertension may also occur and resembles essential hypertension. A characteristic presentation includes "spells" of paroxysmal headaches, pallor or flushing, tremors, apprehension, palpitations, hypertension, and diaphoresis.

Diagnosis

The diagnosis of pheochromocytoma relies on an appropriate history and documentation of excessive catecholamine production.

Catecholamine measurements Measurement of 24-hour urinary catecholamines and their metabolites, vanillylmandelic acid and metanephrine, is commonly used; the metanephrine level is considered to be the most specific single test. Serum catecholamine measurements are more susceptible to false elevations due to stress-related physiologic fluctuations. The evaluation of serum catecholamines after clonidine suppression, however, provides a useful diagnostic tool that is more convenient than urine collections. Dynamic provocative tests are rarely indicated.

Radiologic studies Almost all pheochromocytomas are localized in the abdomen, mostly in the adrenal medulla; other locations include the posterior mediastinum or any distribution of the sympathetic ganglia. After the diagnosis is established biochemically, radiologic methods may be needed for preoperative localization of the lesion; CT and MRI are most widely used. Iodine methyl-iodobenzyl guanidine (MIBG) and SRS provide a "functional" image; they are most helpful in the detection of occult contralateral or extra-adrenal lesions.

Differentiating benign from malignant tumors The histologic differentiation between benign and malignant lesions is extremely difficult and often impossible to make; this distinction may require the development of lymph node, hepatic, bone, or other distant metastases. Recurrent symptoms of pheochromocytoma, often emerging many years after the original diagnosis, are suggestive of malignancy. Biochemical confirmation of recurrent catecholamine hypersecretion and localization of metastatic lesion(s) with iodine-131-MIBG scan constitute diagnostic proof.

Treatment

PREOPERATIVE MEDICAL MANAGEMENT

Phenoxybenzamine (Dibenzyline), an oral, long-acting, noncompetitive α-adrenoceptor blocker, is a widely used, very helpful first drug; it is given at a dose of 10-40 mg/d. Propranolol, a β-blocker (20-80 mg/d), is usually added after a few days to prevent tachycardia or arrhythmias. The use of β-blockers alone is hazardous because they may precipitate a paradoxical rise in blood pressure. The tyrosine hydroxylase inhibitor metyrosine (Demser) may be added in patients whose blood pressure is not well controlled with the combination of an α-blocker and a β-blocker.

SURGERY

The principles of pheochromocytoma resection are complete tumor resection, avoidance of tumor seeding, and minimal tumor manipulation. Adrenalectomy can be performed by means of an open anterior transabdominal, open posterior retroperitoneal, laparoscopic lateral transabdominal, or laparoscopic posterior retroperitoneal approach. In the past, an open anterior approach was the standard because it allowed for complete exploration and inspection for potential tumor foci. However, with the improved accuracy of preoperative imaging and increased experience with laparoscopic procedures, there is little need for exploration in areas in which a tumor has not been identified.

Except for tumors < 6 cm, the laparoscopic approach to pheochromocytoma is probably the technique of choice. In the absence of obvious local tumor invasion or metastatic disease, a laparoscopic procedure is acceptable to many experienced endocrine surgeons.

The most critical intraoperative aspect of surgery is control of blood pressure immediately after removal of the tumor, when all agonistic effects are abolished and the effects of α- and β-blockers are still present. Close cooperation with the anesthesiologist to expand fluid volume and prepare the appropriate infusions of agonists to support vascular stability is critical.

TREATMENT OF METASTATIC MALIGNANT PHEOCHROMOCYTOMA

The treatment of choice for metastatic malignant pheochromocytoma remains problematic.

Medical and radiation therapy

Medical therapy with α- or β-blockers, as well as metyrosine, is almost always required to maintain hemodynamic stability. Chemotherapy utilizing streptozocin-based regimens or the combination of cyclophosphamide (Cytoxan, Neosar), vincristine, and dacarbazine has yielded promising responses. Treatment with iodine-131-MIBG or (in Europe) with radiolabeled somatostatin has met with only limited success. In most cases, uncontrolled catecholamine hypersecretion eventually escapes biochemical blockade, and fatal hypertensive crisis ensues.

Surgery

In those cases in which limited and resectable lesions can be identified, surgery can effect complete and lasting remission of the disease.

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CHAPTER 15

Liver, gallbladder, and biliary tract cancers

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HEPATOCELLULAR CANCER

Hepatocellular carcinoma is one of the most common malignancies in the world, with approximately 1 million new cases recorded annually.

EPIDEMIOLOGY

Gender Hepatocellular carcinoma is the most common tumor in males worldwide, with a male-to-female ratio of 5:1 in Asia and 2:1 in the United States.

Geography Tumor incidence varies significantly, depending on geographical location. In the United States, hepatocellular carcinoma represents $< 2\%$ of all tumors, whereas in the Far East and sub-Saharan Africa, this neoplasm occurs at an incidence of 150 per 100,000 population and comprises almost 50% of all diagnosed tumors. A study analyzing SEER (Surveillance, Epidemiology, and End Results) data has shown that the incidence of hepatocellular carcinoma is rising in both white and black populations in the United States, with a current incidence of about 3.4 cases per 100,000 in whites and 5.6 per 100,000 in blacks.

Age The incidence of hepatocellular cancer increases with age. The mean age at diagnosis is 53 years in Asia and 67 years in the United States.

Race The incidence of hepatocellular tumors is higher in Asian immigrants and blacks.

Survival In patients who undergo curative resection, the 5-year survival rate is approximately 20%. Recurrence is common, with metastases arising in the remaining liver, lungs, bone, kidneys, and heart. Most patients present with unresectable disease, although patients with unimpaired liver function who can undergo resection may experience significantly longer survival.

ETIOLOGY AND RISK FACTORS

Hepatitis B The close geographic relationship between hepatitis B incidence and hepatocellular carcinoma rates is well recognized. In endemic areas of hepatitis B, approximately 90% of all patients with hepatocellular carcinoma

are positive for hepatitis B surface antigen (HBsAg). The presence of the hepatitis B "e" antigen has been found to increase risk ninefold. The most compelling epidemiologic evidence of a causal relationship between hepatitis B infection and hepatocellular carcinoma is the observation of a significant decline in the incidence of childhood hepatocellular carcinoma after the introduction of a national immunization program in Taiwan. The hepatitis B "x" gene, which can interact with p53, has been a focus of recent study into the pathogenesis of hepatocellular carcinoma.

Hepatitis C has also been implicated in hepatocellular carcinoma development. The molecular mechanisms of hepatitis C virus infection and carcinogenesis are poorly understood. Unlike patients with hepatitis B infection, hepatocellular carcinoma patients infected with hepatitis C usually have cirrhotic livers at diagnosis; this finding suggests an extended period of infection (or hepatic damage) before malignancy develops. There is currently a discrepancy in the rate of development of hepatocellular carcinoma in these patients; the rate appears to be higher in Japanese than in western studies.

Alcohol Patients with alcoholic cirrhosis are at risk for hepatocellular carcinoma, but the addition of hepatitis C virus infection increases that risk dramatically.

Other possible etiologies include aflatoxin, hemochromatosis, hepatic venous obstruction, thorotrast (a contrast agent no longer used for radiologic procedures), androgens, estrogens, and α_1-antitrypsin deficiency.

Signs and symptoms

Nonspecific symptoms Patients usually present with abdominal pain and other vague symptoms, including malaise, fevers, chills, anorexia, weight loss, and jaundice.

Physical findings An abdominal mass is noted on physical examination in one-third of patients. Less common findings include splenomegaly, ascites, abdominal tenderness, muscle wasting, and spider nevi. Up to 10% of patients may present with an acute abdomen due to a ruptured tumor.

Screening and diagnosis

Presently, no organization recommends routine screening of average risk, asymptomatic adults for liver, gallbladder, and biliary tract cancers.

α-Fetoprotein is produced by 70% of hepatocellular carcinomas. The normal range for this serum marker is 0-20 ng/mL, and a level $>$ 400 ng/mL is diagnostic for hepatocellular cancer in the absence of chronic, active hepatitis B infection. In the presence of active hepatitis B infection, the cutoff should be considered to be at least 1,000 ng/mL to 4,000 ng/mL. In the setting of hepatitis C infection, the cutoff for diagnosis of hepatocellular carcinoma has not been well studied. False-positive results may be due to acute or chronic hepatitis, germ-cell tumors, or pregnancy.

Hepatitis B and C Given the association between hepatitis B and C and hepatocellular cancer, blood should be sent for hepatitis B and C antigen and antibody determinations.

Imaging The initial diagnostic test in the symptomatic patient may be ultrasonography, as it is noninvasive and can detect lesions as small as 1 cm. Ultrasound findings should be followed up with more specific imaging.

Triple-phase, high-resolution CT and contrast-enhanced MRI are the primary imaging modalities used to diagnose and stage hepatocellular carcinoma. Recent reports have documented a high number of false-positive results with CT angioportography (CTAP) and CT hepatic angiography (CTHA). CT scan predicts resectability in only 40%-50% of cases and does not accurately determine the functional extent of cirrhosis. Major difficulties arise when the liver parenchyma is not homogeneous and the lesions are smaller than 1 cm.

Laparoscopy is useful for the evaluation of small tumors, the extent of cirrhosis, peritoneal seeding, and the volume of noninvolved liver and, therefore, may be used prior to open laparotomy for resection. Laparoscopic or intraoperative ultrasonography should be used to confirm preoperative imaging tests. In selected patients, the laparoscopic results may change surgical management in up to one-third of patients.

High-risk patients should be screened for hepatocellular carcinoma using ultrasonography and serum α-fetoprotein levels. At present, however, there is no standard screening interval, and screening has not been shown to affect survival. Data suggest that, for screened patients, there is an increase in the proportion of cancers that are resectable.

Pathology

Three morphologic patterns of hepatocellular carcinoma have been described: nodular, diffuse, and massive. Diffuse and massive types account for > 90% of cases. The nodular type usually has multiple lesions in both lobes.

Histologic arrangements Several histologic arrangements have been identified: trabecular, compact, pseudoglandular or acinar, clear cell, and a fibrolamellar variant, which is associated with a relatively favorable prognosis.

Staging and prognosis

The staging system for hepatocellular cancer is based on the number and size of lesions and the presence or absence of vascular invasion (Table 1). The Okuda staging system accounts for the degree of liver dysfunction and may better predict prognosis than the TNM stage. However, the Okuda staging system does not adequately predict resectability. Because of the limited value of standard staging, the most important factors determining survival are technical resectability of lesions and degree of dysfunction of the normal liver.

TABLE 1: TNM staging of liver and intrahepatic bile duct tumors

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor without vascular invasion
T2	Solitary tumor with vascular invasion or multiple tumors none > 5 cm
T3	Multiple tumors > 5 cm or tumor involving a major branch of the portal or hepatic vein(s)
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or perforation of the visceral peritoneum
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IIIC	Any T	N1	M0
Stage IV	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

Groups in Italy and China have created prognostic indices that may prove useful for making treatment decisions.

Of the 5%-30% of patients who can undergo resection, factors associated with improved survival include curative resection, small tumor size, well-differentiated tumors, and normal performance status. Cirrhosis, nodal metastases, and an elevated prothrombin time are indicative of a poor prognosis, as are male sex, age > 50 years, poor performance status, duration of symptoms < 3 months, tumor rupture, aneuploidy, high DNA synthesis rate, hypocalcemia, vascular invasion, and a high serum α-fetoprotein level.

Treatment

SURGERY

Surgery is the form of treatment that offers the greatest potential for cure, even though only a small minority of patients will actually be cured. Unfortunately, many patients whose disease is thought to be resectable are clinically understaged preoperatively.

Only stage I or II tumors have a significant likelihood of being resectable for cure. However, a large tumor may still be potentially resectable for cure. Moreover, contiguous involvement of large vessels (including the portal vein and inferior vena cava) or bile ducts does not automatically mitigate against a resection, especially in patients with a fibrolamellar histology, although such resections are considerably more difficult.

Bilobar disease may be addressable with formal resection, tumor ablation techniques (eg, cryoablation, radiofrequency ablation, and ethanol injection ablation), or a combination of the two modalities.

Contraindications to resection include imminent clinical hepatic failure (jaundice in the absence of biliary obstruction), hypoalbuminemia, ascites, renal insufficiency, hypoglycemia, prolongation of the prothrombin and partial thromboplastin times, main portal vein involvement, extrahepatic metastatic disease, or other comorbid diseases that would preclude surgery of any kind.

Noncirrhotic vs cirrhotic patients Resection should be performed in all noncirrhotic patients when feasible. Resection of hepatocellular carcinoma in the presence of cirrhosis is more controversial due to its increased morbidity in this setting. This has been a major deterrent to resection in western nations. Resectability rates vary from 0% to 43% for cirrhotic patients, whereas up to 60% of patients without cirrhosis undergo resection. Use of the modified Child's-Pugh classification of liver reserve may guide the surgeon in preoperative assessment of liver function status and may aid in the selection of operable patients.

When resection is performed in the presence of cirrhosis, Child's class A patients fare better than Child's class B or C patients. Survival rates at 5 years following resection vary from 4% to 36%, with noncirrhotic patients living longer than cirrhotic patients.

Transplantation Owing to the risk of hepatic failure following resection in cirrhotic patients, transplantation has become an option for patients with hepatocellular cancer

The transplant group at Mount Sinai has looked at multimodality therapy for patients with tumors > 5 cm consisting of selective TACE, perioperative IV doxorubicin, and postoperative IV doxorubicin. In this group of 37 patients (43 other patients enrolled in the trial never underwent transplantation), some of whom had tumors > 7 cm, 5-year survival was 44%. Patients with tumors > 7 cm had a worse prognosis, but those with tumors 5-7 cm had a 55% recurrence-free survival. This regimen warrants further investigation in a multicenter setting *(Roayaie S, Frischer JS, Emre SH, et al: Ann Surg 235:533-539, 2002).*

and cirrhosis. In a study of 181 patients with hepatocellular carcinoma, Starzl and Iwatsuki found similar overall 5-year survival rates in patients treated with transplantation vs resection (36% vs 33%). Survival rates were similar in the two groups when tumors were compared for TNM stage. However, survival was significantly improved in patients with concomitant cirrhosis if they were treated with transplantation. Tumor recurrence rates for stage II and III tumors were significantly lower after transplantation than after resection, but no differences were seen for stage IV tumors.

Patients with cirrhosis and single tumors < 5 cm or multiple tumors (up to 3 with none > 3 cm) can be considered for transplantation. Larger tumors may be treated with resection when feasible or chemoembolization followed by transplantation. The use of transplantation is significantly limited by the scarcity and lack of immediate availability of donor organs.

ADJUVANT AND PALLIATIVE THERAPIES

Given the high risk of recurrence after resection, the multifocal nature of hepatocellular carcinoma, and its association with chronic liver disease, nonresectional therapies can play an important role in management. A number of prognostic factors have been identified for patients with unresectable hepatocellular carcinoma. These factors, taken alone, can have a great effect on survival rates, making cross-treatment comparisons more difficult because considerable selection bias may be present in any nonrandomized trial.

Radiation therapy

Adjuvant treatment Intrahepatic recurrence has been observed in up to two-thirds of patients treated with partial hepatectomy for hepatocellular carcinoma. Such a recurrence may represent growth at the resected edge, metastatic disease, or a new primary tumor. There is no evidence, however, that adjuvant radiation therapy can reduce this risk.

Unresectable disease Whole-liver radiation therapy can provide palliation in patients with unresectable tumors but is limited to a total dose of ≤ 30 Gy due to the risk of radiation-induced liver disease. Whole-liver irradiation has been combined with chemotherapy and chemoembolization, with objective response rates of approximately 40%-50% and median survival rates of about 18 months. Patients with tumor regrowth after chemoembolization may respond to radiotherapy.

Radiation therapy has also been delivered using yttrium-90 microspheres infused via the hepatic artery. This approach has encouraging response rates, a low toxicity profile, and may be complementary with other forms of therapy.

There is recent evidence that three-dimensional conformal radiation therapy treatment planning can allow patients with nondiffuse disease to be safely irradiated to doses well above the whole-liver tolerance dose. In a phase I

trial, a dose of up to 90 Gy has been safely given in selected patients.

The use of radioprotectors infused systemically or via the portal vein has been reported in rats to protect hepatocytes from radiation damage.

A randomized controlled trial using a sequential design to compare arterial embolization vs chemoembolization vs conservative treatment of unresectable hepatocellular carcinoma was stopped after only 112 of a planned 903 patients were enrolled due to a statistically significant survival benefit (63% vs 27% at 2 years) for chemoembolization compared with conservative treatment *(Llovet JM, Real MI, Vilana R, et al: Proc Am Soc Clin Oncol 21:132a [abstract], 2002).*

Hepatic artery embolization and chemoembolization

Normal hepatocytes receive most of their blood supply from the portal vein, whereas tumors create new blood vessels from branches of the hepatic arterial system. This target is exploited by embolization of the hepatic artery with any number of substances, resulting in radiographic response rates in about 50% of patients and evidence of tumor liquefaction in over two-thirds of patients. Embolization is accomplished by advancing a catheter within the tumor-feeding branch of the hepatic artery. Materials injected have included Gelfoam powder, polyvinyl alcohol, iodized oil (Lipiodol), collagen, and autologous blood clot. Chemo-embolization should be reserved for symptomatic tumors, to reduce tumor size for resection or ablation, or as a bridge while awaiting transplant.

Randomized trials have shown mixed results. On meta-analysis chemoembolization significantly reduced the overall 2-year mortality ratio compared with nonactive treatment, but without evidence of superiority vs transarterial embolization alone.

Intratumoral ethanol injection

The direct injection of 95% ethanol into a neoplastic lesion causes cellular dehydration and coagulation necrosis. Intratumoral ethanol ablation is employed via a percutaneous route under ultrasound guidance. Percutaneous intratumoral ethanol injection is best suited for use in patients with few lesions, each < 5 cm, although larger lesions may be injected multiple times.

Although intratumoral ethanol injection appears to be an effective palliative modality in certain patients, its effect on patient survival is unclear.

CRYOTHERAPY AND RADIOFREQUENCY ABLATION

Similar to ethanol ablation, cryotherapy and radiofrequency ablation (RFA) techniques are suitable for treatment of localized disease. Cryotherapy has been used intraoperatively to ablate small solitary tumors outside a planned resection (ie, in patients with bilobar disease). Cryotherapy must be performed using laparotomy, which limits its use in the palliative setting. Radiofrequency

A meta-analysis has been performed that includes randomized trials of adjuvant chemotherapy in the postresection setting. This analysis revealed a *decrement* in survival for patients treated with postoperative chemotherapy. Unfortunately, even a meta-analysis of this question is small in size, comprising only 108 patients *(Ono T, Yamanoi A, Nagasue N: Cancer 91:2378-2385, 2001).*

ablation can be performed either via laparotomy or percutaneously and has limitations similar to those of ethanol ablation. As with ethanol ablation, there are no data about a survival advantage with these therapies, which may prove to be most useful for temporary tumor control in patients awaiting liver transplants.

A cautionary note regarding percutaneous RFA has been raised by publication of a report from Barcelona, citing 4 of 32 patients in a series who developed needle-track tumor seeding relating to subcapsular tumor location and poorly differentiated tumors.

Chemotherapy

Systemically administered chemotherapy has, for the most part, been disappointing in hepatocellular carcinoma patients. This fact relates both to low rates of response to available agents and to difficulty with toxicity for modestly active agents because of liver dysfunction. Agents with partial response rates near or above 10% include doxorubicin (Adriamycin), fluorouracil (5-FU), and cisplatin (Platinol).

An interesting abstract at the ASCO 2002 meeting explores an alternative schedule of 5-FU with very low-dose cisplatin as a modulator in Japanese patients with hepatocellular carcinoma. 5-FU was given by continuous infusion at 170 mg/m^2/d and CDDP was given over half an hour daily, 5 days per week at a dose of 3 mg/m^2/d. Thirty-seven patients with advanced hepatocellular carcinoma were evaluable in this abstract. Forty-seven percent experienced a PR, with only one reported grade 3 or 4 toxicity. This schedule may be worth repeating in further clinical trials *(Rai K, Tsuji A, Morita S, et al: Proc Am Soc Clin Oncol [abstract] 21:164a, 2002).*

Intra-arterial chemotherapy (HIA) Use of HIA, principally floxuridine (fluorodeoxyuridine [FUDR]), has good biologic rationale but is hampered by high rates of biliary complications and the requirement for surgical pump placement in patients who are generally poor surgical candidates.

Biologic therapy Interferon-alfa (IFN-α) has been shown to have potential beneficial effects in prevention of hepatocellular carcinoma, however, recent randomized studies have failed to show a benefit in patients with preexisting cirrhosis and advanced cancers. Adjuvant interferon, however, was associated with a reduction of recurrence in two very small randomized trials. This finding needs to be confirmed in a much larger trial. Moderate-to-high doses of interferon are poorly tolerated by patients with frankly cirrhotic livers.

Retinoid therapy In one Japanese randomized trial, polyprenoic acid has been shown to significantly decrease the rate of recurrence of hepatocellular carcinoma after curative resection. A survival advantage was also demon-

strated with long-term follow-up. Unfortunately, this compound has been unavailable for further study.

Hormone therapy A small trial reported a survival benefit at 1 year for patients treated with medroxyprogesterone (Provera). This result needs to be validated.

In one randomized study, people with variant estrogen receptors had a significant improvement in median survival from 7 to 18 months when megestrol (Megace) was given.

Biochemotherapy Recent results of combination biochemotherapy in a study of 154 patients by Leung et al have been encouraging. Using a combination of cisplatin, interferon-α-2a (Roferon), doxorubicin, and 5-FU for 4 days out of 28, they have shown a response rate of around 20%. Moreover, 10% of patients whose tumors were initially felt to be unresectable subsequently underwent complete resection. Eight of these patients had documented pathologic complete remissions. The question of whether this regimen can be used routinely in the neoadjuvant setting will be the subject of further study. Of note, all patients in this series had hepatitis B-associated HCC.

BILIARY TRACT CANCERS

Malignancies of the biliary tract are uncommon in the United States, with approximately 6,800 cases reported annually; nearly two-thirds of these cancers arise in the gallbladder, whereas the remainder (cholangiocarcinoma) originate from the bile ducts and periampullary region.

Gallbladder carcinoma is diagnosed approximately 5,000 times a year in the United States, making it the most common biliary tract tumor and the fifth most common GI tract cancer. Approximately 4,500 cases of bile duct tumors occur each year in the United States.

Epidemiology

GALLBLADDER CANCER

Gender Women are more commonly afflicted with gallbladder cancer than are men, with a female-to-male ratio of 1.7:1.

Age The median age at presentation of gallbladder cancer is 73 years.

Race An incidence five to six times that of the general population is seen in southwestern Native Americans, Mexicans, Hispanics, and Alaskans.

BILE DUCT CANCER

Gender Bile duct tumors are found in an equal number of men and women.

Age Extrahepatic bile duct tumors occur primarily in older individuals; the median age at diagnosis is 70 years.

Etiology and risk factors

GALLBLADDER CANCER

The risk of developing gallbladder cancer is higher in patients with cholelithiasis or calcified gallbladders and in typhoid carriers.

BILE DUCT CANCER

Ulcerative colitis is a clear risk factor for bile duct tumors. Patients with ulcerative colitis have an incidence of bile duct cancer that is 9-21 times higher than that of the general population. This risk does not decline after total colectomy for ulcerative colitis.

Other risk factors Primary sclerosing cholangitis, congenital anomalies of the pancreaticobiliary tree, and parasitic infections are also associated with bile duct tumors. No association of bile duct cancer with calculi, infection, or chronic obstruction has been found.

Signs and symptoms

GALLBLADDER CANCER

Early disease In the early stages, gallbladder cancer is usually asymptomatic.

Late disease Later, symptoms similar to those of benign gallbladder disease arise; they include right upper quadrant pain, nausea, vomiting, fatty food intolerance, anorexia, jaundice, and weight loss. This nonspecificity of symptoms delays presentation for medical attention and contributes to the low curability of gallbladder cancer.

Physical findings may include tenderness, an abdominal mass, hepatomegaly, jaundice, fever, and ascites.

BILE DUCT CANCER

Jaundice is the most frequent symptom found in patients with high bile duct tumors; it is present in up to 98% of such patients.

Nonspecific signs and symptoms Patients who do not present with jaundice have vague complaints, including abdominal pain, weight loss, pruritus, fever, and an abdominal mass.

Diagnosis

GALLBLADDER CANCER

Gallbladder carcinomas are often diagnosed at an advanced stage, such that by the time symptoms have developed, most tumors are unresectable.

Laboratory values in patients with gallbladder carcinoma are nonspecific but may include anemia, leukocytosis, and an elevated bilirubin level.

Ultrasonography is useful for defining a thickened gallbladder wall and may show tumor extension into the liver.

CT is more helpful than ultrasonography in assessing adenopathy and spread of disease into the liver, porta hepatis, or adjacent structures. MRI may be used to evaluate intrahepatic spread.

Endoscopic retrograde cholangiopancreatography (ERCP) or transhepatic cholangiography (THC) may be useful in the presence of jaundice to determine the location of biliary obstruction and involvement of the liver.

BILE DUCT CANCER

Cholangiocarcinoma may present earlier than gallbladder cancer by virtue of the development of biliary obstruction with jaundice, which may be painless. Tissue confirmation of suspected bile duct cancer can be difficult. The goals of the diagnostic evaluation include the determination of the level and extent of obstruction, the extent of local invasion of disease, and the identification of metastases.

Many patients with cholangiocarcinoma are thought to have metastatic adenocarcinoma of an unknown primary, although occasionally the metastatic lesion may produce biliary dilatation without the primary lesion itself being radiographically visualized.

Ultrasonography It is generally accepted that ultrasonography should be the first imaging procedure in the evaluation of the jaundiced patient.

CT is a complementary test to ultrasonography, but both tests are accurate for staging in only 50% of patients and for determining resectability in $< 45\%$ of patients.

Cholangiography is essential to determine the location and nature of the obstruction. Percutaneous transhepatic cholangiography (PTC) is used for proximal lesions and ERCP for distal lesions. Magnetic resonance cholangiopancreatography (MRCP) may replace invasive studies in the near future. Histologic confirmation of tumor can be made in 45%-85% of patients with the use of exfoliative or brush cytology during cholangiography.

Pathology

GALLBLADDER CANCER

Histologic types Over 85% of gallbladder neoplasms are adenocarcinomas and the remaining 15% are squamous cell or mixed tumors.

TABLE 2: TNM staging of gallbladder cancer

Primary tumor (T)		
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma in situ
T1		Tumor invades the lamina propria or muscle layer
	T1a	Tumor invades the lamina propria
	T1b	Tumor invades the muscle layer
T2		Tumor invades perimuscular connective tissue; no extension beyond the serosa or into the liver
T3		Tumor perforates the serosa (visceral peritoneum), and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4		Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures
Regional lymph nodes (N)		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
Distant metastasis (M)		
MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis

Stage grouping			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

Route of spread The major route of spread of gallbladder cancer is locoregional rather than distant, with 25% of patients having lymphatic involvement and 70% having direct extension of disease into the liver.

BILE DUCT CANCER

Adenocarcinoma Morphologically, more than 90% of bile duct tumors are adenocarcinomas. Three macroscopic appearances have been identified: The

TABLE 3: Staging of bile duct tumors

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor confined to the bile duct histologically		
T2	Tumor invades beyond the wall of the bile duct		
T3	Tumor invades the liver, gallbladder, pancreas, and/or ipsilateral branches of the portal vein (right or left) or hepatic artery (right or left)		
T4	Tumor invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures, such as the colon, stomach, duodenum, or abdominal wall		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

papillary and nodular types occur more frequently in the distal bile duct, whereas the sclerosing type is found in the proximal bile duct. Patients with papillary lesions have the best prognosis.

Other histologic types Unusual malignant diseases of the biliary tract include adenosquamous carcinoma, leiomyosarcoma, and mucoepidermoid carcinoma.

Route of spread Most bile duct tumors grow slowly, spreading frequently by local extension and rarely by the hematogenous route. Nodal metastases are found in up to one-third of patients.

Staging and prognosis

GALLBLADDER CANCER

Gallbladder cancer is staged primarily at the time of surgery, and staging is determined by lymphatic involvement and extension of disease into adjacent structures (Table 2).

Stage Survival of gallbladder carcinoma is directly related to disease stage. The 5-year survival rate is 83% for tumors that are confined to the gallbladder mucosa; this rate decreases to 33% if the tumor extends through the gallbladder. For patients who have involvement of the lymph nodes or metastatic disease, 5-year survival rates range from 0% to 15%.

Type of therapy Median survival is also improved in patients who have undergone a curative resection, as compared with those who have had palliative procedures or no surgery (17 months vs 6 and 3 months, respectively).

BILE DUCT CANCER

Over 70% of patients with cholangiocarcinoma present with local extension, lymph node involvement, or distant spread of disease. The AJCC (American Joint Committee on Cancer) staging system for extrahepatic tumors is shown in Table 3.

Stage Survival for these patients is poor and is directly related to disease stage. Median survival is 12-20 months for patients with disease limited to the bile ducts and ≤ 8 months when the disease has spread.

Tumor location Survival is also related to tumor location, with patients with distal lesions doing better than those with mid or proximal tumors.

Success of therapy Curative resections and negative margins result in improved survival.

Treatment

In the absence of polyps identified on ultrasound and confirmed by CT during the work-up of suspected cholelithiasas, relatively few patients with gallbladder cancer are diagnosed prior to surgery. Only 1%-2% of cholecystectomy specimens are found to contain malignancy.

SURGERY FOR GALLBLADDER CANCER

Surgical management of gallbladder carcinoma is based on the local extension of the tumor.

Early-stage disease Tumors that invade the mucosa, those that do not penetrate the muscularis, and those that penetrate full thickness but do not abut the liver or muscularis require cholecystectomy alone. If there is direct

extension of disease to or through the serosa, the resection should include the gallbladder bed (segments IVb and V) and a porta hepatis lymphadenectomy. Disease that involves the gallbladder node is particularly curable and should be resected. Nodal disease beyond the pericholedochal nodes defines the surgically incurable patient.

SURGERY FOR BILE DUCT CANCER

The rate of resectability is 15%-20% for high bile duct tumors and up to 70% for distal lesions.

Assessing resectability Higher resolution CT or MRI with biliary reconstruction may be supplemented with hepatic arteriography, portal venography, or duplex imaging preoperatively to assess resectability.

Preoperative treatments Three randomized trials have shown no benefit to preoperative decompression of the biliary tree in patients with obstructive jaundice. Some authors advocate the preoperative placement of biliary stents to facilitate dissection of the hilus. This procedure should be performed immediately prior to resection to reduce the risk of cholangitis and maintain the duct at its maximally dilated size.

Proximal tumors Local excision is often possible for proximal lesions. Hepatic resection is indicated for high bile duct tumors with quadrate lobe invasion or unilateral intrahepatic ductal or vascular involvement. Resection is not indicated in situations in which a clear surgical margin cannot be obtained.

Mid-ductal and distal tumors Mid-ductal lesions can often be removed by resection of the bile duct with associated portal lymphadenectomy. Distal or mid-ductal lesions that cannot be locally excised should be removed by pancreaticoduodenectomy.

Reconstruction techniques Biliary-enteric continuity is usually reconstructed with a Roux-en-Y anastomosis to the hilum for high lesions and in a standard drainage pattern following pancreaticoduodenectomy.

Liver transplantation has been attempted for unresectable tumors, but early recurrence and poor survival have prevented the widespread application of this approach.

Surgical bypass For patients found to have unresectable disease at surgical exploration, operative biliary bypass may be performed using a variety of techniques. Bypass results in excellent palliation and obviates the need for further intervention.

ADJUVANT RADIATION THERAPY FOR BILIARY TRACT CANCER

Local recurrence after cholecystectomy for gallbladder cancer has been reported to occur in 86% of patients, who die within 5 years after surgery. Resected bile duct tumors have a 25% to 40% rate of local recurrence.

Despite these observations, there are no good prospective data to define the role of adjuvant radiation or chemoradiation treatment. Retrospective studies suggested that a radiation therapy dose of > 54 Gy may result in improved local control of gallbladder cancer. For bile duct tumors, a review of 192 patients found that a benefit from adjuvant chemoradiation therapy was more evident in distal tumors than in intrahepatic or perihilar tumors. Another retrospective review, however, found that on multivariate analysis, only the lymph node status was prognostically significant.

To answer the question whether combined therapy improves the response rate over single-agent 5-FU, the EORTC (European Organization for Research and Treatment of Cancer) performed a randomized phase II trial that was presented at ASCO 2002. The trial compared high-dose 5-FU (infusional) alone vs 5-FU with leucovorin and cisplatin. The response rate was higher in the combined therapy arm (7% vs 19%). The study was small but also showed an increase in median survival of ~2.5 months (*Mitry E, Van Cutsem E, Van Laethem JL, et al: Proc Am Soc Clin Oncol [abstract] 21:175a, 2002*).

TREATMENT OF UNRESECTABLE DISEASE

Like pancreatic adenocarcinoma, unresectable biliary tract carcinoma has a poor prognosis.

Stenting

Many patients with unresectable disease, particularly those with pain, nausea, or pruritus, will benefit from nonsurgical percutaneous or endoscopic stenting.

Radiation therapy

There are little data on radiation therapy for unresectable gallbladder cancer, other than reports of intraoperative radiation therapy. External-beam radiation therapy would be anticipated to provide a palliative benefit.

There is considerable experience using brachytherapy alone or combined with external-beam radiation for unresectable bile duct tumors. Median survival ranges from 10 to 24 months and 5-year survival rates are approximately 10% with these approaches.

Chemotherapy

Because biliary tract malignancies are uncommon cancers, the number of clinical trials and the number of patients in those trials are limited. Generally speaking, responses to chemotherapy are infrequent and brief in duration. However, newer drugs and drug combinations are better tolerated and stand to improve on past results.

5-FU has historically been the most active single agent, with single-agent response rates in the 10%-20% range.

Capecitabine (Xeloda), a prodrug of 5-FU (see chapter 16), produced responses in 4 of 8 gallbladder cancers but in only 1 of 18 cholangiocarcinomas in a phase II study presented by Hassan et al from M. D. Anderson Cancer Center at ASCO 2001.

Gemcitabine (Gemzar) shows promise in the treatment of biliary tract cancers. A phase II trial recently reported responses in 7 of 19 patients. At ASCO 2001, a South American group documented responses to single-agent gemcitabine in 14 of 39 evaluable patients, most of whom had gallbladder cancer. The addition of cisplatin has been studied and awaits confirmation of superiority.

Other agents with reported activity in biliary tract malignancies include docetaxel (Taxotere), mitomycin (Mutamycin), doxorubicin, and the nitrosureas. Combination regimens do not clearly improve on the results of single-agent chemotherapy and as such remain investigational. The combination of 5-FU, leucovorin, and mitomycin has resulted in objective responses in 5 of 20 patients.

Hepatic arterial chemotherapy There is limited experience with hepatic arterial chemotherapy for biliary tract neoplasms, but there are case reports of responses to floxuridine in the literature.

Treatment recommendations In the absence of a clinical trial, patients should be offered gemcitabine or 5-FU (or capecitabine), with or without leucovorin. Other agents, such as doxorubicin or cisplatin, may be added, but, as noted, there is no evidence that combination chemotherapy produces any substantial benefits in terms of improving a patient's quality of life or survival.

SUGGESTED READING

ON HEPATOCELLULAR CARCINOMA

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CHAPTER 16

Colorectal and anal cancers

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COLORECTAL CANCER

Despite the existence of excellent screening and preventive strategies, colorectal carcinoma remains a major public health problem in western countries. An estimated 147,500 new cases are diagnosed in the United States each year, and 57,100 people die of the disease.

Colorectal carcinoma is the third leading cause of death from cancer in both males and females. It also is the third most common malignancy in both men (after prostate and lung cancers) and women (after breast and lung cancers).

Colon cancer is more than 2.4 times as common as rectal cancer. Rectal cancer is defined as cancer arising below the peritoneal reflection, up to approximately 12-15 cm from the anal verge. Because it has a different natural history, colon cancer is treated and reported separately from rectal cancer.

Epidemiology

Gender The overall incidence of colorectal cancer is nearly identical in men and women; tumors of the colon are slightly more frequent in women than in men (1.2:1), whereas rectal carcinomas are more common in men than in women (1.7:1).

Age The risk of developing colorectal tumors begins to increase at age 40 years and rises with age. In the United States, the median age at presentation is 72 years.

Race The incidence of colon carcinomas has increased by 30% in blacks since 1973 and is now higher than in whites.

Geography The incidence of colorectal carcinoma is higher in industrialized regions (the United States, Canada, the Scandinavian countries, northern and western Europe, New Zealand, Australia) and lower in Asia, Africa (among blacks), and South America (except Argentina and Uruguay).

Disease site Colon carcinomas constitute approximately 70% of all cancers in the large bowel, with occurrence in the proximal colon becoming more common.

TABLE 1: Five-year survival in colorectal cancer[a]

Time of detection	5-year survival rate (%)
In early, localized stage	90
After spread to adjacent organs or lymph nodes	64
After spread to distant sites	8

[a] Source: Cancer Facts & Figures—2002. Atlanta, American Cancer Society, 2002.

Survival Five-year survival rates (Table 1) for patients with stage I, II, and III colorectal carcinomas have improved in recent years. This fact may be due to wider surgical resections, modern anesthetic techniques, and improved supportive care. In addition, better pathologic examination of resected specimens, preoperative staging, and abdominal exploration reveal clinically occult disease and allow treatment to be delivered more accurately. Survival also has improved through the use of adjuvant chemotherapy for colon cancer and adjuvant chemoradiation for rectal cancer.

Etiology and risk factors

The specific causes of colorectal carcinoma are unknown, but environmental, nutritional, genetic, and familial factors, as well as preexisting diseases, have been found to be associated with this cancer.

Environment Asians, Africans, and South Americans who emigrate from low-risk areas assume the colon cancer risk for their adopted country, suggesting the importance of environmental factors in colorectal cancer. Smoking and alcohol intake (more than one drink per day) increase the risk of colorectal cancer.

Diet Diets rich in fat and cholesterol have been linked to an increased risk of colorectal tumors. Dietary fat causes endogenous production of secondary bile acids and neutral steroids and increases bacterial degradation and excretion of these acids and steroids, thereby promoting colonic carcinogenesis. Historically, diets rich in cereal fiber or bran and yellow and green vegetables are said to have protective effects, although recent studies have failed to prove a risk reduction with increasing dietary fiber intake. A protective role also has been ascribed to calcium salts and calcium-rich foods, because they decrease colon-cell turnover and reduce the cancer-promoting effects of bile acid and fatty acids.

Inflammatory bowel disease Patients with inflammatory bowel disease (ulcerative colitis, Crohn's disease) have a higher than normal incidence of colorectal carcinoma. The risk of colorectal carcinoma in patients with ulcerative colitis is associated with the duration of active disease, extent of colitis, development of mucosal dysplasia, and duration of symptoms.

The risk of colorectal cancer increases exponentially with the duration of colitis, from approximately 3% in the first decade to 20% in the second decade to

TABLE 2: Hereditary polyposis syndromes

Adenomatous polyposis

Familial adenomatous polyposis (FAP)

Characterized by hundreds or thousands of sessile or pedunculated polyps, each < 1 cm, throughout the large intestine; histologic examination reveals microscopic adenomas; average age at onset of polyps, 25 years; at onset of symptoms, 33 years; at diagnosis, 36 years; at diagnosis of colon cancer, 42 years; extracolonic features include mandibular osteomas, upper GI polyps, and congenital hypertrophy of the retinal pigment epithelium

Gardner's syndrome

Same colonic manifestations as FAP; extracolonic features more evident and varied, including osteomas of the skull, mandible, and long bones; desmoid tumors; dental abnormalities; neoplasms of the thyroid, adrenal glands, biliary tree, and liver; upper GI polyps; and congenital hypertrophy of the retinal pigment epithelium; fibromatosis of the mesentery is a potentially fatal complication (8%-13% of patients)

Turcot's syndrome

This rare syndrome is characterized by malignant colon and brain tumors. Two different types of Turcot's have been identified: one characterized by an adenomatous polyposis coli (APC) mutation resulting in colon cancer and malignant glioblastoma; the second characterized by a mismatch repair gene mutation resulting in colon cancer and astrocytoma

Hamartomatous polyposis

Peutz-Jeghers syndrome

In infancy and childhood, melanin deposits manifest as greenish-black to brown mucocutaneous pigmentation (which may fade at puberty) around the nose, lips, buccal mucosa, hands, and feet; polyps (most frequent in small intestine; also found in stomach and colon) are unique hamartomas with branching bands of smooth muscle surrounded by glandular epithelium; may produce acute and chronic GI bleeding, intestinal obstruction, or intussusception; 50% of patients develop cancer (median age at diagnosis, 50 years); ovarian cysts and unique ovarian sex-cord tumors reported (5%-12% of female patients)

Juvenile polyposis

Three forms: familial juvenile polyposis coli (polyps limited to the colon), familial juvenile polyposis of the stomach, and generalized juvenile polyposis (polyps distributed throughout the GI tract); polyps are hamartomas covered by normal glandular epithelium, found mostly in the rectum in children and sometimes in adults; may produce GI bleeding, obstruction, or intussusception; mixed juvenile/adenomatous polyps or synchronous adenomatous polyps may lead to cancer, but gastric cancer has not been reported in patients with familial juvenile polyposis of the stomach

Cowden's disease (multiple hamartoma syndrome)

Multiple hamartomatous tumors of ectodermal, mesodermal, and endodermal origin; mucocutaneous lesions are prominent and distinctive; also reported: breast lesions ranging from fibrocystic disease to cancer (50% of patients), thyroid abnormalities (10%-15%), cutaneous lipomas, ovarian cysts, uterine leiomyomas, skeletal and developmental anomalies, and GI polyps; no associated risk of cancer in GI polyps; probably does not warrant clinical surveillance

> 30% in the third decade. Colorectal cancer risk also is increased in patients with Crohn's disease, although to a lesser extent.

Adenomatous polyps Colorectal tumors develop more often in patients with adenomatous polyps than in those without polyps. There is approximately a 5% probability that carcinoma will be present in an adenoma; the risk correlates with the histology and size of the polyp. The potential for malignant transformation is higher for villous and tubulovillous adenomas than for tubular adenomas. Adenomatous polyps < 1 cm have a slightly greater than 1% chance of being malignant, in comparison with adenomas > 2 cm, which have up to a 40% likelihood of malignant transformation.

Cancer history Patients with a history of colorectal carcinoma are at increased risk of a second primary colon cancer or other malignancy. Women with a history of breast, endometrial, or ovarian carcinoma also have an increased chance of developing colorectal cancer.

Prior surgery Following ureterosigmoidostomy, an increased incidence of colon cancer at or near the suture line has been reported. Cholecystectomy also has been associated with colon cancer in some studies but not in others.

Genetic factors The risk of developing colorectal cancer is significantly increased in several forms of inherited susceptibility (Table 2). The lifetime risk of colorectal cancer increases to 8% for a person with one first-degree relative and to 17% when two first-degree relatives are affected. There are also other forms of inherited susceptibility, including both polyposis and nonpolyposis-type syndromes.

Familial adenomatous polyposis (FAP) is inherited as an autosomal-dominant trait with variable penetrance. Patients characteristically develop pancolonic and rectal adenomatous polyps. Approximately 50% of FAP patients will develop adenomas by 15 years of age and 95% by age 35. Left untreated, 100% of patients with FAP will develop colorectal cancer, with an average age at diagnosis ranging from 34 to 43 years. Prophylactic total colectomy is the preventive treatment of choice in this group of patients. The familial adenomatous polyposis coli *(APC)* gene has been localized to chromosome 5q21. Currently, it is possible to detect mutations in the *APC* gene in up to 82% of families with FAP. Mutations in the *APC* gene combined with mutational activation of proto-oncogenes, especially K-*ras*, occur sequentially in the neoplastic transformation of bowel epithelium in patients with FAP.

Hereditary nonpolyposis colorectal cancer (HNPCC) is not characterized by a profusion of polyps, and no obvious clinical phenotype is apparent until a cancer develops. The Amsterdam criteria were proposed in 1991 as a way to help identify patients at risk of HNPCC. In 1999, they were revised (Amsterdam II) to recognize extracolonic manifestations as part of the family history. The criteria include the following factors:

- three or more relatives with a histologically verified HNPCC-associated cancer (colorectal, endometrial, small bowel, ureter, or renal pelvis), one of whom is a first-degree relative of the other two (FAP should be excluded)

- colorectal cancer involving at least two generations
- one or more colorectal cancers diagnosed before the age of 50

The Bethesda criteria were developed based upon an analysis of high-risk patients who did not meet the Amsterdam criteria but still demonstrated germline mutations in either *MSH2* or *MLH1* gene. These criteria are much less restrictive than the Amsterdam criteria and serve to help identify those individual patients at risk of HNPCC who might benefit from further evaluation, such as the following:

- individuals with cancer in families who meet the Amsterdam criteria.
- individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers of associated extracolonic cancers; endometrial, ovarian, gastric, hepatobiliary, small bowel, or transitional cell carcinoma of the renal pelvis or ureter
- individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma; one of the cancers diagnosed at age younger than 45 years; and the adenoma diagnosed at age younger than 40 years
- individuals with colorectal cancer or endometrial cancer diagnosed at age < 45 years
- individuals with right-sided colorectal cancer with an undifferentiated pattern (solid/cribriform) on histology diagnosed at age < 45 years
- individuals with signet-ring cell-type colorectal cancer diagnosed at age < 45 years
- individuals with colorectal adenomas diagnosed at age < 40 years

Mutations in the DNA mismatch repair genes *MSH1* or *MLH2* can be found in approximately 40% of individuals who meet these criteria. Genetic evaluation for HNPCC should be considered in families that meet the Amsterdam criteria, in affected individuals who meet the Bethesda criteria, and in first-degree relatives of those individuals with known mutations. For situations in which HNPCC is suspected but the first three Bethesda criteria are not met, microsatellite instability (MSI) testing may be considered. Over 90% of HNPCC colorectal cancers will demonstrate MSI, compared with 15%-20% of sporadic colorectal cancers, and thus a negative result in the absence of compelling clinical criteria usually excludes the diagnosis of HNPCC.

Chemoprevention

Chemoprevention aims to block the action of carcinogens on cells before the appearance of cancer. The most well-studied agents in the prevention of colorectal cancer include the antioxidants β-carotene, vitamin C, and vitamin E; calcium; and nonsteroidal anti-inflammatory drugs (NSAIDs). End points

evaluated include changes in adenomatous polyps, alterations in mucosal proliferation, and colorectal cancer incidence.

Antioxidants and calcium Controlled trials of vitamins C and E and calcium have produced mixed results. In two randomized studies, β-carotene did not demonstrate a protective effect.

NSAIDs inhibit colorectal carcinogenesis, possibly by reducing endogenous prostaglandin production through cyclooxygenase inhibition. Sulindac (Clinoril) has induced regression of large bowel polyps in patients with FAP. Controlled studies have shown a reduction in the incidence of colorectal cancer with regular, long-term use of aspirin.

The expression of cyclooxygenase-2 (COX-2) messenger RNA is enhanced in tissue obtained from human colorectal adenomas and adenocarcinomas. The American Food and Drug Administration (FDA) has approved celecoxib (Celebrex), a COX-2 inhibitor, for the chemoprevention of polyps in FAP.

Signs and symptoms

Early stage During the early stages of colorectal cancer, patients may be asymptomatic or complain of vague abdominal pain and flatulence, which may be attributed to gallbladder or peptic ulcer disease. Minor changes in bowel movements, with or without rectal bleeding, are also seen; they are frequently ignored and/or attributed to hemorrhoids or other benign disorders.

Left colon Cancers occurring in the left side of the colon generally cause constipation alternating with diarrhea; abdominal pain; and obstructive symptoms, such as nausea and vomiting.

Right colon Right-sided colon lesions produce vague, abdominal aching, unlike the colicky pain seen with obstructive left-sided lesions. Anemia resulting from chronic blood loss, weakness, weight loss, and the abdominal mass may also accompany carcinoma of the right side of the colon.

As part of a cooperative colorectal cancer screening study, 2,885 Veterans Affairs patients submitted 3 specimen cards for fecal occult blood testing. They then underwent complete colonoscopy for identification of advanced neoplasia lesions. Only 23.9% of men with advanced neoplasia had a positive fecal occult blood test. Examination of the sigmoid colon and rectum identified only 75.8% of subjects with advanced neoplasia. This study underscores the need for complete colonoscopy to adequately screen for colonic cancers (*Lieberman DA, Weiss DG: N Engl J Med 345:555-560, 2001*).

Rectum Patients with cancer of the rectum may present with a change in bowel movements; rectal fullness, urgency, or bleeding; and tenesmus.

Pelvic pain is seen at later stages of the disease and usually indicates local extension of the tumor to the pelvic nerves.

Screening and diagnosis

Screening

Fecal occult blood testing Guaiac-based fecal occult blood tests are, in themselves, in-

expensive but have been associated with many false-positive and false-negative results. Almost all colonic polyps and > 50% of all colorectal carcinomas go undetected because they are not bleeding at the time of the test. The newer fecal occult blood tests, including a guaiac-based product called Hemoccult SENSA and immunochemical tests for hemoglobin (HemeSelect), appear to have better sensitivity than the older tests without sacrificing specificity. Three large randomized controlled clinical trials have demonstrated decreased colorectal cancer mortality associated with detection of earlier-stage cancer and adenomas by fecal occult blood testing. Recently, results from the Minnesota trial also showed a decreased incidence of colorectal cancer associated with fecal occult blood testing, largely because of increased use of polypectomy resulting from diagnostic endoscopy following positive tests.

Digital rectal examination is simple to perform and can detect lesions up to 7 cm from the anal verge.

TABLE 3: American Cancer Society guidelines on screening and surveillance for the early detection of colorectal adenomas and cancer—Average risk

Test	Interval (beginning at age 50)	Comment
FOBT and flexible sigmoidoscopy	FOBT annually and flexible sigmoidoscopy every 5 years	Flexible sigmoidoscopy together with FOBT is preferred over FOBT or flexible sigmoidoscopy alone. All positive tests should be followed up with colonoscopy[a]
Flexible sigmoidoscopy	Every 5 years	All positive tests should be followed up with colonoscopy[a]
FOBT	Annually	The recommended take-home multiple sample method should be used. All positive tests should be followed up with colonoscopy[a,b]
Colonoscopy	Every 10 years	Colonoscopy provides an opportunity to visualize, sample, and/or remove significant lesions
Double-contrast barium enema	Every 5 years	All positive tests should be followed up with colonoscopy

[a] If colonoscopy is unavailable, not feasible, or not desired by the patient, double-contrast barium enema (DCBE) alone or the combination of flexible sigmoidoscopy and DCBE is an acceptable alternative. Adding flexible sigmoidoscopy to DCBE may provide a more comprehensive diagnostic evaluation than DCBE alone in finding significant lesions. A supplementary DCBE may be needed if a colonoscopic exam fails to reach the cecum, and a supplementary colonoscopy may be needed if a DCBE identifies a possible lesion, or does not adequately visualize the entire colorectum.

[b] There is no justification for repeating FOBT in response to an initial positive finding.

FOBT = Fecal occult blood test

Adapted with permission from Smith RA, von Eschenbach AC, Wender R, et al: CA Cancer J Clin 51(1):38-75, 2001.

TABLE 4: American Cancer Society guidelines on screening and surveillance for the early detection of colorectal adenomas and cancer—Increased or high risk

Risk category	Age to begin	Practice
Increased risk		
A single, small (< 1 cm) adenoma	3-6 years after initial polypectomy	Colonoscopy[a]
If the exam is normal, the patient can thereafter be screened as per average-risk guidelines.		
A large (> 1 cm) adenoma, multiple adenomas, or adenomas with high-grade dysplasia or villous change	Within 3 years after the initial polypectomy	Colonoscopy[a]
If the exam is normal, repeat examination in 3 years; if the exam is normal then, the patients can thereafter be screened as per average-risk guidelines.		
Personal history of curative-intent resection of colorectal cancer	Within 1 year after cancer resection	Colonoscopy[a]
If the exam is normal, repeat examination in 3 years; if the exam is normal then, repeat examination every 5 years.		
Either colorectal cancer or adenomatous polyps in any first-degree relative before age 60 or in two or more first-degree relatives at any age (if not a hereditary syndrome)	Age 40, or 10 years before the youngest case in the immediate family	Colonoscopy[a]
Every 5-10 years. Colorectal cancer in relatives more distant than first-degree relatives does not increase risk substantially above the average-risk group.		
High risk		
Family history of familial adenomatous polyposis (FAP)	Puberty	Early surveillance with endoscopy and counseling to consider genetic testing
If the genetic test is positive, colectomy is indicated. These patients are best referred to a center with experience in the management of FAP.		
Family history of hereditary nonpolyposis colorectal cancer (HNPCC)	Age 21	Colonoscopy and counseling to consider genetic testing
If the genetic test is positive or if the patient has not had genetic testing, every 1-2 years until age 40, then annually. These patients are best referred to a center with experience in the management of HNPCC.		
Inflammatory bowel disease, chronic ulcerative colitis, Crohn's disease	Cancer risk begins to be significant 8 years after the onset of pancolitis or 12-15 years after the onset of left-sided colitis	Colonoscopy with biopsies for dysplasia
Every 1-2 years. These patients are best referred to a center with experience in the surveillance and management of inflammatory bowel disease.		

[a] If colonoscopy is unavailable, not feasible, or not desired by the patient, double-contrast barium enema (DCBE) alone or the combination of flexible sigmoidoscopy and DCBE is an acceptable alternative. Adding flexible sigmoidoscopy to DCBE may provide a more comprehensive diagnostic evaluation than DCBE alone in finding significant lesions. A supplementary DCBE may be needed if a colonoscopic exam fails to reach the cecum, and a supplementary colonoscopy may be needed if a DCBE identifies a possible lesion or does not adequately visualize the entire colorectum.

Adapted with permission from Smith RA, von Eschenbach AC, Wender R, et al: CA Cancer J Clin 51(1):38-75, 2001.

Sigmoidoscopy Flexible proctosigmoidoscopy is safe and more comfortable than examination using a rigid proctoscope. Almost 50% of all colorectal neoplasms are within the reach of a 60-cm sigmoidoscope. Even though flexible sigmoidoscopy visualizes only the distal portion of the colorectum, the identification of adenomas can lead to colonoscopy. When we add the percentage of colorectal neoplasms in the distal 60 cm of the colorectum to the percentage of patients with distal polyps leading to complete colonoscopy, 80% of those individuals with a significant neoplasm anywhere in the colorectum can be identified.

Colonoscopy provides information on the mucosa of the entire colon, and its sensitivity in detecting tumors is extremely high. Colonoscopy can be used to obtain biopsy specimens of adenomas and carcinomas and permits the excision of adenomatous polyps. Colonoscopy is the best follow-up strategy for evaluating patients with positive guaiac-based fecal occult blood tests and the best screening modality for high-risk patients.

Limitations of colonoscopy include its inability to detect some polyps and small lesions because of blind corners and mucosal folds and the fact that sometimes the cecum cannot be reached. A supplementary double-contrast barium enema may be needed if a colonoscopic exam fails to reach the cecum.

Barium enemas can accurately detect colorectal carcinoma; however, the false-negative rate associated with double-contrast barium enemas ranges from 2% to 61% because of misinterpretation, poor preparation, and difficulties in detecting smaller lesions. A supplementary colonoscopy may be needed if double-contrast barium enema does not adequately visualize the entire colon.

Recommendations for average-risk individuals Adults at average risk should begin colorectal cancer screening at age 50. The American Cancer Society (ACS) guidelines on screening and surveillance for the early detection of colorectal adenomatous polyps and cancer were updated in 2001 and provide five options for screening average-risk individuals: annual fecal occult blood test; flexible sigmoidoscopy every 5 years; annual fecal occult blood test plus flexible sigmoidoscopy every 5 years; double-contrast barium enema every 5 years; or colonoscopy every 10 years (Table 3).

For those individuals who elect fecal occult blood test alone, or in combination with flexible sigmoidoscopy, a single test of a stool sample in the clinical setting (as, for instance, is often performed with the stool sample collected on the fingertip during a digital rectal examination) is not an adequate substitute for a full set of samples using the take-home card system. Because combining flexible sigmoidoscopy with fecal occult blood test can substantially increase the benefits of either test alone, the ACS regards annual fecal occult blood test accompanied by flexible sigmoidoscopy every 5 years as a better choice than either fecal occult blood test or flexible sigmoidoscopy alone. In a recent review of the current status of emerging technologies for colorectal cancer screening, the ACS modified their guidelines for FOBT to include immunochemical tests. The ACS concluded that in comparison with guaiac-based tests for the detection of oCcult blood, immunochemical tests are more patient-friendly, and are likely to equal or better in sensitivity and specificity.

The choice of colonoscopy or double-contrast barium enema for screening may depend on factors such as personal preference, cost, and the local availability of trained clinicians to perform a high-quality examination. For those who elect either colonoscopy or double-contrast barium enema for screening, there is no need for annual fecal occult blood test. Digital rectal examination should be performed at the time of the sigmoidoscopy or colonoscopy.

Recommendations for increased-risk and high-risk individuals Individuals at increased risk of colorectal cancer have a personal or family history of adenoma(s) or colorectal cancer. Risk of colorectal cancer is even higher among individuals with one of two hereditary syndromes. Individuals with a history of inflammatory bowel disease of significant duration involving most of the colorectum are also at increased risk.

Individuals who have been diagnosed as having adenomatous polyps or a personal history of curative-intent resection of colorectal cancer should undergo a colonoscopy to remove all polyps from the colorectum, after which a colonoscopic exam should be repeated at an interval to be determined on the basis of the size, multiplicity, and histologic appearance of the adenoma(s) (Table 4). If colonoscopy is not available, or not feasible, flexible sigmoidoscopy followed by double-contrast barium enema may be used for surveillance.

A family history of either colorectal cancer or colorectal adenomas increases the risk of developing colorectal cancer. Risk is higher for individuals with a family history involving first-degree relatives, with family members with younger age of onset, and with multiple affected family members. Individuals with a single first-degree relative diagnosed with colorectal cancer or an adenomatous polyp after age 60, or with affected relatives who are more distant than first-degree relatives, can be considered to be at "average risk." People with a family history of either colorectal cancer or colorectal adenomas that occurred in a first-degree relative before age 60, or in multiple first-degree relatives of any age, if not a hereditary syndrome, should have a colonoscopy. Subsequent colonoscopy should be repeated at intervals to be determined on the basis of the initial examination. If a colonoscopy is not available or not feasible, flexible sigmoidoscopy followed by a double-contrast barium enema can be used.

FAP is a genetic condition that is caused by a mutation in the *APC* gene on chromosome 5. People with FAP develop hundreds of colorectal polyps and will almost certainly develop colorectal cancer unless the colon is removed. HNPCC is an inherited genetic condition that can also cause colorectal cancer among many people in a family, even though multiple polyps are not present. HNPCC is caused by mutations in mismatch repair genes located on chromosomes 2, 3, or 7. Since genetic tests are now available to detect the mutations that lead to FAP and HNPCC, genetic counseling should be offered to individuals with family histories suggestive of FAP or HNPCC. Individuals at elevated risk due to the known or likely presence of FAP or HNPCC should begin surveillance at an early age with endoscopic examinations (Table 4). Therefore, the opportunity to make decisions about surveillance regimens or prophylactic colectomy can be made at an appropriate time if clinically indicated.

TABLE 5: TNM staging of colorectal cancer

TNM stage	Primary tumor[a]	Lymph node metastasis[b]	Distant metastasis[c]	Modified Astler-Coller
Stage 0	Tis	N0	M0	
Stage I	T1	N0	M0	A
	T2	N0	M0	B1
Stage IIA	T3	N0	M0	B2
IIB	T4	N0	M0	B3
Stage IIIA	T1-2	N1	M0	C1[d]
IIIB	T3-4	N1	M0	C2-3[d]
IIIC	Any T	N2	M0	C1-3[d]
Stage IV	Any T	Any N	M1	D

[a] Tis = carcinoma in situ; T1 = tumor invades submucosa; T2 = tumor invades muscularis propria; T3 = tumor invades through the muscularis propria into the subserosa or into nonperitoneal pericolic or perirectal tissues; T4 = tumor perforates the visceral peritoneum or directly invades other organs or structures

[b] N0 = no regional lymph node metastasis; N1 = metastases in one to three pericolic or perirectal lymph nodes; N2 = metastases in four or more pericolic or perirectal lymph nodes

[c] M0 = no distant metastasis; M1 = distant metastasis

[d] C1 = T2 N1, T2 N2 C2 = T3 N1, T3 N2 C3 = T4 N1, T4 N2

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th Ed. New York, Springer-Verlag, 2002.

Individuals with a history of extensive inflammatory bowel disease affecting the colon should begin colonoscopic surveillance with biopsy for dysplasia every 1-2 years after 8 years of symptoms. Prophylactic colectomy should be considered in the presence of persistent dysplasia.

Diagnosis

Initial work-up An initial diagnostic work-up for patients suspected of having colorectal tumors should include:

- digital rectal examination and fecal occult blood test
- colonoscopy
- biopsy of any detected lesions

Adequate staging prior to surgical intervention requires:

- chest x-ray
- CT scan of the abdomen and pelvis
- CBC with platelet count
- liver and renal function tests

- urinalysis
- measurement of carcinoembryonic antigen (CEA) level

FDG-PET scanning FDG(18fluorodeoxyglucose)-PET scanning has emerged as a highly sensitive study for the evaluation of patients who may be candidates for resection of isolated metastases from colorectal cancer. Although not usually recommended in the evaluation of primary disease, this modality can aid in the staging of recurrence. FDG-PET scanning appears to be more sensitive and more specific than CEA scintigraphy.

Pathology

Adenocarcinomas constitute 90%-95% of all large bowel neoplasms. These tumors consist of cuboidal or columnar epithelium with multiple degrees of differentiation and variable amounts of mucin.

Mucinous adenocarcinoma is a histologic variant characterized by huge amounts of extracellular mucus in the tumor and the tendency to spread within the peritoneum. Approximately 10% of colorectal adenocarcinomas are mucinous. It is more commonly seen in younger patients.

Signet-ring–cell carcinoma is an uncommon variant, comprising 1% of colorectal adenocarcinomas. These tumors contain large quantities of intracellular mucinous elements (causing the cytoplasm to displace the nucleus) and tend to involve the submucosa, making their detection difficult with conventional imaging techniques.

Other tumor types Squamous cell carcinomas, small-cell carcinomas, carcinoid tumors, and adenosquamous and undifferentiated carcinomas also have been found in the colon and rectum. Nonepithelial tumors, such as sarcomas and lymphomas, are exceedingly rare.

Metastatic spread Colorectal carcinoma has a tendency for local invasion by circumferential growth and for lymphatic, hematogenous, transperitoneal, and perineural spread. Longitudinal spread is usually not extensive, with microscopic spread averaging only 1-2 cm from gross disease, but radial spread is common and depends on anatomic location.

By the time they are diagnosed, some 25% of colon cancers will have extended through the bowel wall, whereas cancers of the rectum will have spread through the wall in 50%-70% of patients and metastasized to lymph nodes in 50%-60%.

The most common site of extralymphatic involvement is the liver, with the lungs the most frequently affected extra-abdominal organ. Other sites of hematogenous spread include the bones, kidneys, adrenal glands, and brain.

Staging and prognosis

The TNM staging classification, which is based on the depth of tumor invasion in the intestinal wall, the number of regional lymph nodes involved, and the

A large, prospective, randomized trial from The Netherlands indicates that the local failure rate following total mesorectal excision for resectable rectal cancer is 8.2% at 2 years. Preoperative irradiation significantly decreased the 2-year rate of local failure to 2.4%, but did not improve survival (*Kapiteijn E, Marijnen CA, Nategaal ID, et al: N Engl J Med 345:638-646, 2001*).

presence or absence of distant metastases, is largely replacing the older Dukes' classification scheme (Table 5).

Pathologic stage is the single most important prognostic factor following surgical resection of colorectal tumors. The prognosis for early stages (I and II) is favorable overall, in contrast to the prognosis for advanced stages (III and IV). However, there appears to be a superior survival for patients with stage III disease whose disease is confined to the bowel wall (ie, ≤ T2, N+).

Histologic grade may be correlated with survival. Five-year survival rates of 56%-100%, 33%-80%, and 11%-58% have been reported for grades 1, 2, and 3 colorectal tumors, respectively.

Other prognostic factors (such as age at diagnosis, presurgical CEA level, gender, presence and duration of symptoms, site of disease, histologic features, obstruction or perforation, perineural invasion, venous or lymphatic invasion, ploidy status, and S-phase fraction) have not consistently been correlated with overall disease recurrence and survival. Furthermore, the size of the primary lesion has had no influence on survival. Elevated expression of thymidylate synthase and allelic loss of chromosome 18 have been correlated with a poor prognosis.

Treatment

PRIMARY TREATMENT OF LOCALIZED DISEASE

Management of colorectal carcinoma relies primarily on resection of the bowel with the adjacent draining lymph nodes. The need for adjuvant systemic or local chemotherapy or immunotherapy, with or without concurrent irradiation, depends on tumor location (colon vs rectum) and stage of disease.

Surgery

Colon The primary therapy for adenocarcinoma of the colon is surgical extirpation of the bowel segment containing the tumor, the adjacent mesentery, and draining lymph nodes. The type of resection depends on the anatomic location of the tumor. Right, left, or transverse hemicolectomy is the surgical treatment of choice in patients with right, left, or transverse colonic tumors, respectively. Tumors in the sigmoid colon may be treated with wide sigmoid resection. The length of colon resected depends largely on the requirement for wide mesenteric nodal clearance.

Rectum For rectal carcinoma, the distal surgical margin should be at least 2 cm, although some investigators have suggested that a smaller but still negative margin may be adequate. The resection should include the node-bearing mesorectum surrounding the rectum. This procedure, which is termed total

mesorectal excision (TME), is accomplished using a sharp dissection technique (see Figure 1).

Posteriorly, the mesorectal dissection is carried out along the presacral fascia. Anteriorly, the dissection follows the posterior vaginal wall in females or Denonvilliers' fascia in males, both of which may be resected in the presence of an anterior wall rectal cancer. Reported rates of local recurrence following TME for rectal cancer have generally been < 10%, compared with rates of recurrence up to 30% prior to the advent of TME. Selective use of radiation therapy can improve upon the results of TME alone (see above).

Sphincter-sparing approaches New technologies (eg, circular stapling devices) and the application of newer surgical techniques, such as coloanal anastomosis and creation of intestinal pouches, are employed to maintain anal sphincter function for tumors in the lower one-third of the rectum. If the tumor is located proximally between 6 and 15 cm from the anal verge, a low anterior resection with end-to-end anastomosis may be performed.

Abdominoperineal resection, removing the anus and sphincter muscle with permanent colostomy, may be necessary if the tumor is located in the distal rectum and other characteristics of the tumor (eg, bulky size, proximity to the sphincter musculature) preclude an oncologically adequate sphincter-sparing approach. An alternative procedure for tumors 2-5 cm from the anal verge is to resect the entire rectum, sparing the anoderm and anal sphincter musculature, and to perform a coloanal anastomosis. Either procedure can be performed with autonomic nerve preservation, minimizing bladder and sexual function morbidity.

Local excision alone may be indicated for selected patients who have small (< 3-4 cm), T1, well to moderately differentiated rectal cancers without histologic evidence of lymphovascular involvement, provided that a full-thickness negative margin can be achieved. For T2 or T3 tumors, the standard therapy remains a transabdominal resection because of the risk of mesorectal nodal spread. Preoperative transrectal ultrasonography is useful in defining lesions that can be resected by local excision alone. A trial sponsored by the CALGB (Cancer and Leukemia Group B) demonstrated reasonable results for patients with T2 rectal cancer undergoing negative margin local

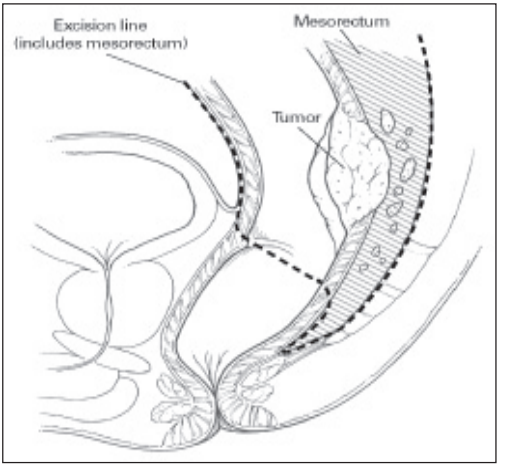

FIGURE 1: Mesorectal excision
Adapted with permission from N Engl J Med 345(9):690-692, 2001.

excision followed by fluorouracil (5-FU) and external-beam radiation therapy. The locoregional recurrence rate at 6 years was only 14%.

Neoadjuvant therapy For rectal cancers approaching the anal sphincter, preoperative (neoadjuvant) irradiation or the combination of chemotherapy and irradiation will significantly reduce the size of the majority of tumors. This approach allows for sphincter-preserving surgery in many patients. In addition, the long-term morbidity of radiation therapy for rectal cancer may be reduced if it is administered prior to surgery. The use of preoperative chemotherapy and radiation therapy is particularly important for patients presenting with locally advanced, unresectable rectal cancer, as the disease of the majority will be rendered resectable following neoadjuvant therapy. One additional role of neoadjuvant therapy may be in facilitating transanal excision of T2 and T3 rectal cancers in poor surgical risk patients. A number of investigators have reported good results wth transanal excision of T2 and T3 tumors following a complete response to neoadjuvant therapy. However, this cannot be considered the current standard of care.

Laparoscopy-assisted colectomy has been the subject of a number of prospective randomized trials. A Spanish trial including 219 patients demonstrated a shorter hospital stay, lower morbidity, and a trend toward an improved survival in patients undergoing laparoscopy-assisted colectomy compared with open colectomy *(Lacy AM, Garcia-Valdecasas JC, Delgado S, et al: Lancet 359:2224-2229, 2002)*. In contrast, the short-term analysis of an American prospective randomized trial involving 449 patients demonstrated few differences between laparoscopy-assisted colectomy and open colectomy with respect to quality-of-life indicators. Survival and recurrence-free survival have not yet been reported *(Weeks JC, Nelson H, Gelber S, et al: JAMA 287:321-328, 2002)*.

Laparoscopic colonic resection The use of laparoscopic colonic resection is being evaluated as an oncologically acceptable method of treating cancers of the colon. The potential advantages include shorter hospital stay, reduced postoperative ileus, and decreased time away from work. The potential disadvantages compared to open transabdominal resection include incomplete resection (inadequate nodal resection), longer operative time, higher operative costs, inability to palpate intra-abdominal organs, and technical considerations related to operative skills.

Patterns of failure

The natural history and patterns of failure following "curative" resection are different for colon and rectal carcinomas. Locoregional failure as the only or major site of recurrence is common in rectal cancer, whereas colon cancer tends to recur in the peritoneum, liver, and other distant sites, with a lower rate of local failure. As a result, local therapy, such as irradiation, may play a significant role in the treatment of rectal tumors but is not used routinely for colon cancers.

ADJUVANT THERAPY FOR COLON CANCER

Approximately 75% of all patients with colorectal carcinoma will present at a stage when all gross carcinoma can be surgically resected. Nevertheless, de-

TABLE 6: Chemotherapy regimens for colorectal adenocarcinoma

Drug/combination	Dose and schedule
Adjuvant fluorouracil/ levamisole for colon cancer	
Fluorouracil (5-FU)	450 mg/m^2 IV on days 1-5, then weekly beginning on day 28
Levamisole	150 mg/d (50 mg every 8 hours) PO on days 1-3, repeated every other week
Begin chemotherapy 3-5 weeks following surgery and continue for 52 weeks	
Moertel CG, Fleming TR, Macdonald JS, et al: Ann Intern Med 122:321–326, 1995. Moertel CG, Fleming TR, Macdonald JS, et al: N Engl J Med 322:352–358, 1990.	
Adjuvant low-dose leucovorin/fluorouracil	
Leucovorin	20 mg/m^2 IV bolus on days 1-5 immediately before fluorouracil
Fluorouracil	425 mg/m^2/d IV bolus on days 1-5
Repeat cycle at 4 weeks, 8 weeks, and then every 5 weeks	
Poon MA, O'Connell MJ, Moertel CG, et al: J Clin Oncol 7:1407–1418, 1989.	
Adjuvant high-dose leucovorin/fluorouracil	
Leucovorin	500 mg/m^2 IV infused over 2 hours every week for 6 weeks
Fluorouracil	500 mg/m^2 IV infused over 1 hour after the start of leucovorin every week for 6 weeks
Repeat cycle every 8 weeks for 6 cycles	
Wolmark N, Rockette H, Mamounas EP, et al: Proc Am Soc Clin Oncol 15:205, 1996.	
Fluorouracil + leucovorin as an irradiation enhancer	
Concurrent chemotherapy and irradiation phase:	
Irradiation	1.8-Gy fractions 5 days per week (total dose, 45-54 Gy over 5.5-6 weeks)
Fluorouracil	400 mg/m^2 IV bolus within 2 hours of irradiation on days 1-4 during the first and fifth weeks of irradiation
Leucovorin	20 mg/m^2/d IV bolus immediately before each fluorouracil dose on days 1-4 during the first and fifth weeks of irradiation
Maintenance phase following irradiation:	
Fluorouracil	425 mg/m^2 IV bolus on days 1-4 starting 4 weeks following irradiation and on days 1-5 starting 9 weeks after irradiation
Leucovorin	20 mg/m^2 IV bolus immediately before each fluorouracil dose on days 1-4 starting 4 weeks following irradiation and on days 1-5 starting 9 weeks after irradiation
Moertel CG, Gunderson LL, Mailliard JA, et al: J Clin Oncol 12:21–27, 1994.	

Drug/combination	Dose and schedule
Fluorouracil/leucovorin/oxaliplatin	
Fluorouracil	300 mg/m^2 IV bolus daily for 5 days
Leucovorin	20 mg/m^2 IV bolus daily for 5 days
Oxaliplatin	130 mg/m^2 IV on day 1
Repeat cycle every 21 days	
Ravaiolo A, Marangolo M, Pasquini E, et al: J Clin Oncol 20:254–2550, 2002.	
Irinotecan/leucovorin/fluorouracil	
Irinotecan	125 mg/m^2 IV infused over 90 minutes once a week for 4 weeks
Leucovorin	20 mg/m^2 IV bolus once a week for 4 weeks
Fluorouracil	500 mg/m^2 IV bolus once a week for 4 weeks
Repeat cycle every 6 weeks: ie, give all of the drugs once a week for 4 weeks, followed by 2 weeks rest, and then start the cycle again	
Saltz LB, Locker PK, Pirotta N, et al: Proc Am Soc Clin Oncol 18:898A, 1999.	
Saltz LB, Cox JV, Blanke C, et al: N Engl J Med 343:905–914, 2000.	
Irinotecan/oxaliplatin + continuous infusion fluorouracil/leucovorin	
Irinotecan	150 mg/m^2 IV infusion over 30 minutes on day 1
Leucovorin	200 mg/m^2 IV infusion over 2 hours on day 2
Followed by	
Oxaliplatin	65 mg/m^2 IV 2-hour infusion on day 2 in parallel with leucovorin but using different lines
Repeat cycle every 2 weeks	
Souglakos J, Mavroudis D, Kakolyris s, et al: J Clin Oncol 20:2651–2657, 2002.	
Single-agent irinotecan	
Irinotecan	125 mg/m^2 IV infused over 90 minutes once a week for 4 weeks, followed by a 2-week rest
Pitot HC, Wender DB, O'Connell MJ, et al: J Clin Oncol 15:2910–2919, 1997.	
Irinotecan	350 mg/m^2 IV infused over 90 minutes
Repeat cycle every 3 weeks	
NOTE: Patients with performance status of 2 or age ≥ 70 years should receive 300 mg/m^2 IV infused over 90 minutes.	
Cunningham D, Pyrhonen S, James RD, et al: Proc Am Soc Clin Oncol 17:1A, 1998.	
Single-agent capecitabine	
Capecitabine	1,250 mg/m^2 twice a day orally for 14 days (total of 2,500 mg/m^2 a day)
Repeat cycle every 3 weeks (2 weeks of treatment followed by a 1-week rest period)	
Hoff PM, Ansari R, Batist G, et al: J Clin Oncol 19:2282–s2292, 2001.	

Table prepared by Ishmael Jaiyesimi, DO

TABLE 7: Five-year overall survival in Patterns of Care (PCS) study vs the National Cancer Data Base (NCDB), Gastrointestinal Tumor Study Group (GITSG), and Mayo/North Central Cancer Treatment Group (Mayo/NCCTG) studies

Study	5-year survival	
Bimodality vs trimodality	S + RT	S + RT + CT
Stage II		
PCS	61%	81%
NCDB	55%	62%
Stage III		
PCS	33%	65%
NCDB	39%	42%
Postop CRT vs postop RT	Postop RT	Postop CRT
GITSG (7175)	52%	59%
Mayo/NCCTG (7945)	48%	57%
PCS	50%	69%

S = surgery; RT = radiation therapy; CT = chemotherapy; CRT = concurrent irradiation and chemotherapy

Adapted from Coia LR, Gunderson LL, Haller D, et al: Cancer 86:1952-1958, 1999.

spite the high resectability rate, almost half of all patients with colorectal adenocarcinoma die of metastatic disease, primarily because of residual disease that is not apparent at the time of surgery. These individuals are candidates for adjuvant local or systemic therapies.

Systemic chemotherapy

Systemic combined chemotherapy is the principal adjuvant therapy for colon cancer (Table 6). The administration of single-agent 5-FU or floxuridine (fluorodeoxyuridine [FUDR]) in patients with stage II or III tumors following surgical resection has failed to show a survival advantage over postoperatives observation.

5-FU plus levamisole (Ergamisol) 5-FU combined with levamisole, an antihelminthic agent with nonspecific immunostimulating properties, was the first adjuvant regimen to demonstrate a decrease in the recurrence rate and an increase in disease-free and overall survival in patients with stage III colon cancer. This combination is given over 1 year. It has largely been replaced by 5-FU and leucovorin, a combination with equivalent activity that can be given over 6 months.

5-FU plus leucovorin Studies have demonstrated the benefits of 5-FU plus leucovorin (folinic acid) in the adjuvant treatment of colon carcinomas. Acceptable adjuvant regimens of 5-FU plus leucovorin for colon cancer include:

- a "low-dose" leucovorin (Mayo Clinic) regimen, consisting of leucovorin (20 mg/m^2) immediately followed by 5-FU (425 mg/m^2), both

given by rapid IV injections daily for 5 consecutive days, with courses repeated every 4 weeks for 6 months

- a "high-dose" weekly leucovorin regimen, consisting of 5-FU (500 mg/m^2) by rapid IV injection given at 1 hour during a 2-hour infusion of leucovorin (500 mg/m^2) weekly for 6 weeks, with courses repeated every 8 weeks for 6 cycles

An analysis of survival data from patients with stage II or III disease treated in four consecutive National Surgical Adjuvant Breast and Bowel Project (NSABP) adjuvant chemotherapy trials showed similar relative reductions in disease recurrence and mortality as well as similar improvements in overall survival in stage II and III patients.

5-FU and leucovorin plus other agents The addition of other agents to 5-FU and leucovorin is currently being assessed.

Monoclonal antibody 17 1A (Edrecolomab) A recent randomized study of 17 1A antibody in patients with stage III colon cancer showed it to be inferior to 5-FU and leucovorin. Its addition to 5-FU and leucovorin did not improve disease-free or overall survival. A trial of the antibody in stage II colon cancer recently completed accrual. No results are yet available from this trial.

Irinotecan (CPT-11, Camptosar) The addition of irinotecan to 5-FU and leucovorin is being assessed in a phase III trial. (See discussion of irinotecan under treatment of advanced colon cancer.)

Radiation therapy

Postoperative irradiation to the tumor bed should be considered in patients with T3 node-positive and T4 (B3 or C3) tumors located in retroperitoneal portions of the colon because more than 30% of these patients develop a local recurrence. Retrospective studies suggest improved local control with irradiation, particularly in patients with positive resection margins. However, an underpowered intergroup trial recently failed to show a benefit to adjuvant chemotherapy and irradiation compared with adjuvant chemotherapy alone in selected patients with T3 node-positive and T4 disease.

ADJUVANT THERAPY FOR RECTAL CANCER

Local recurrence alone or in combination with distant metastases occurs in up to 50% of patients with rectal carcinoma. Nodal metastases and deep bowel wall penetration are significant risk factors for locoregional failure.

In the absence of nodal metastases, the rate of local recurrence may be as low as 5%-10% for stage I rectal cancer and 15%-30% for stage II tumors. In stage III disease, the incidence of pelvic failure increases to 50% or more.

Local recurrence in the pelvis is complicated by involvement of contiguous organs, soft and bony tissue, and deep nodal disease. Presenting symptoms vary from vague pelvic fullness to sciatica related to mass effect in the fixed space of the bony pelvis and invasion of the sciatic nerve.

Because local recurrence in the absence of metastatic disease is more common in rectal cancer than in colon cancer, aggressive resections, such as pelvic exenteration (anterior and posterior), sacral resection, and wide soft-tissue and pelvic floor resection, have been employed to treat these recurrences. Modern techniques of pelvic floor reconstruction, creation of continent urinary diversion, and vaginal reconstruction may be required for functional recovery.

The recent findings of the NSABP R-02 trial indicated postoperative adjuvant chemotherapy resulted in similar survival rates to postoperative chemoradiation therapy but was associated with significantly higher rate of locoregional failure.

Radiation therapy alone

Radiation therapy has been used to reduce the locoregional recurrence rate of rectal tumors. Preoperative radiation therapy has been demonstrated to reduce local tumor recurrence, even in patients undergoing TME surgery. However, with the exception of one recent study, preoperative therapy has not affected overall survival in patients with stage II or III rectal cancer. An improvement in local control also has been observed with postoperative irradiation, but again with no benefit with regard to disease-free or overall survival.

Chemoradiation

Postoperative chemoradiation Clinical trials of surgical adjuvant treatment indicate that postoperative radiation therapy with concurrent chemotherapy (chemoradiation) is superior to postoperative radiation alone or surgery alone. Postoperative chemoradiation is a standard of care for patients with stage II or III rectal cancer based largely on the findings of the North Central Cancer Treatment Group (NCCTG) and Gastrointestinal Tumor Study Group (GITSG) trials. A summary of the 5-year survival results of the Patterns of Care Study (PCS) of the American College of Radiology and the results of the National Cancer Data Base (NCDB), both of which are representative of American national averages, is shown in Table 7.

The most effective combination of drugs, optimal mode of administration, and sequence of irradiation and chemotherapy still need to be determined. Radiation doses of 45-55 Gy are recommended in combination with 5-FU–based chemotherapy. Postoperative bolus 5-FU administration with irradiation is inferior to protracted venous infusion, resulting in lower 3-year rates of both overall survival (68% vs 76%) and disease-free survival (56% vs 67%).

An adjuvant treatment-combining chemotherapy and pelvic irradiation in patients with stage II or III disease used the following regimen: 5-FU, 500 mg/m^2/d administered as a rapid IV infusion on days 1-5 and 450 mg/m^2/d on days 134-138 and days 169-173. Patients received a protracted IV infusion of 5-FU, 225 mg/m^2/d, by portable ambulatory infusion pump during the entire period of pelvic irradiation. Pelvic radiation therapy began on day 64 with a multiple-field technique to the tumor bed and nodal groups. A total of 4,500 cGy in 180-cGy fractions was administered over a 5-week period. Patients received a minimal boost dose of 540 cGy to the entire tumor bed, adjacent nodes, and 2 cm of adjacent tissue. A second boost dose of 360 cGy was allowed in se-

The optimal time to administer chemoradiotherapy for operable rectal cancer is not clear. A recent trial randomized 267 rectal cancer patients to receive either preoperative chemoradiotherapy followed by resection or rectal resection followed by postoperative chemoradiotherapy. At 1 year following randomization, 44% of the preoperative chemoradiotherapy patients with sphincter-saving surgery had no evidence of disease vs only 34% of those in the postoperative chemoradiotherapy group. At 1 year, there was no statistical difference in disease-free survival. Long-term follow-up of this important study will help to clarify the role of preoperative multimodality therapy in rectal cancer patients *(Roh MS, Petrelli N, Weiand S: Proc Am Soc Clin Oncol [abstract] 20:123a, 2001)*.

lected patients with excellent displacement of the small bowel.

Preoperative vs postoperative chemoradiation Preoperative chemoradiation may be preferred to postoperative adjuvant treatment, particularly in patients with T3 or T4 lesions. Such treatment may enhance resectability and may be associated with a lower frequency of complications compared with postoperative treatment. The relative value of preoperative vs postoperative treatment is being examined in a number of randomized trials.

TREATMENT OF ADVANCED COLON CANCER

Surgery

Local recurrences from colon cancers usually occur at the site of anastomosis, in the resection bed, or in the contiguous and retroperitoneal (para-aortic, paracaval) lymph nodes. Anastomotic recurrences heralded by symptoms are the most curable, followed by local soft-tissue recurrences. Regional and retroperitoneal lymph node recurrences portend a poor prognosis and systemic disease.

Metastasectomy Metastases to the liver and lungs account for most cases of non-nodal systemic disease in colorectal cancer. Resection of metastases, or metastasectomy, has gained recognition as a viable treatment. Resection of liver metastases results in cure rates of 5%-60%, depending on the number of metastases and stage of disease. Resection of solitary metastases in patients with stage I or II disease results in a 5-year survival rate of ~40%.

Adjuvant therapy after resection of hepatic metastases has been assessed in several randomized trials. Intra-arterial administration of floxuridine, using a hepatic artery catheter, alternating with systemic 5-FU and leucovorin, improves overall survival and reduces the risk of recurrence within the liver.

Chemotherapy The development of chemotherapy for colorectal cancer has become a very active field (Table 6). After decades of 5-FU–based treatment, and of little clinical gains, the arrival of new, effective agents has significantly changed the way this cancer is treated. Although 5-FU remains the backbone of most regimens, the new agents irinotecan (Camptosar) and oxaliplatin (Eloxatin) are rapidly becoming an important part of front-line treatment of this disease in the United States and abroad. The rapid development of newer agents, such as the molecular-targeted agents, holds the promise that progress will continue in chemotherapy for colorectal cancer.

5-FU, synthesized by Heidelberger in 1957, remains an important agent in the treatment of advanced colon carcinoma. 5-FU may be administered as a bolus injection either weekly or daily for 5 days, every 4-5 weeks. With these regimens, response rates have been approximately 10%-15%. The development of permanent venous access devices and portable infusion pumps has permitted the continuous infusion of 5-FU on an outpatient basis. Commonly used continuous infusion regimens of 5-FU are 750-1,000 mg/m^2/d for 5 days. Protracted infusions have administered 5-FU at 200-400 mg/m^2/d for up to 12 weeks.

The pattern of 5-FU toxicity differs depending on whether it is administered as a bolus or continuous infusion than by other methods. Bolus administration has pronounced myelotoxic effects, whereas the dose-limiting toxic effects of continuous infusion 5-FU are mucositis and diarrhea. Palmar-plantar erythrodysesthesia (hand-foot syndrome) has been reported with protracted infusions.

Overall, the incidence of side effects is significantly lower when 5-FU is delivered by continuous infusion. A meta-analysis of more than 1,200 patients treated with either continuous infusion or bolus regimens of 5-FU demonstrated superior response rates and a small survival advantage for the continuous infusion regimens.

Two large randomized trials recently demonstrated improved response rates and overall survival for the combination of 5-FU plus leucovorin and irinotecan (discussed later in this chapter).

Biochemical modulation of 5-FU Interest in the biochemical modulation of 5-FU by leucovorin is based on preclinical studies demonstrating that leucovorin raises the level of N_5,N_{10}-methylenetetrahydrofolate and, thus, forms a stable tertiary complex of thymidylate synthase (TS), the folate coenzyme, and 5-FU (in the form of 5-fluorodeoxyuridine). The use of 5-FU with leucovorin results in higher response rates than 5-FU alone and may prolong survival.

Although there is no agreement as to the optimal dose of leucovorin, two dosing schedules have been approved by the FDA:

- "low-dose" leucovorin regimen, consisting of leucovorin, 20 mg/m^2/d, immediately followed by 5-FU, 425 mg/m^2/d
- "high-dose" leucovorin regimen, consisting of leucovorin, 200 mg/m^2/d, immediately followed by 5-FU, 370 mg/m^2/d

With both schedules, leucovorin and 5-FU are administered by rapid IV injections daily for 5 consecutive days. Courses of both schedules are repeated at 4 weeks, 8 weeks, and every 5 weeks thereafter. There is no survival difference between these two regimens.

Irinotecan, a novel topoisomerase I inhibitor synthesized from *Camptotheca acuminata,* a tree that is native to China, has significant clinical activity in metastatic colorectal cancer patients whose disease has recurred or spread after standard chemotherapy. Its approval was based on two phase III trials showing that irinotecan (350 mg/m^2 once every 3 weeks) significantly increased survival, compared with best supportive care and infusional 5-FU, respectively, in patients

with recurrent or progressive cancer following first-line 5-FU therapy. Irinotecan increased median survival by 27% and 41%, respectively, in the two trials.

Irinotecan is active in patients whose disease progressed while they were receiving 5-FU. Reproducible 15%-20% response rates in this patient population led to the approval of irinotecan for use in patients with 5-FU–refractory disease. The dosage schedules most commonly used are 125 mg/m^2 weekly for 4 weeks, followed by a 2-week rest period (United States), and 350 mg/m^2 every 3 weeks (Europe).

The primary toxicities of irinotecan are diarrhea and neutropenia. Intensive loperamide is important in the management of the former complication. An initial 4-mg loading dose is given at the first sign of diarrhea, followed by 2-mg doses every 2 hours until diarrhea abates for at least a 12-hour period.

5-FU plus leucovorin and irinotecan The results of two large randomized trials comparing the combination of 5-FU plus leucovorin and irinotecan vs 5-FU plus leucovorin in the first-line treatment of metastatic colorectal cancer have been reported. Both trials demonstrated improved response rates and overall survival for the three-drug combination. The two trials used different schedules and were conducted in different locations, yet their results were remarkably consistent. The response rates for the three-drug combination ranged from 35%-40%, and the median time to disease progression was approximately 7 months.

Molecular changes in colorectal neoplasms, such as microsatellite instability, may influence response to chemotherapy. Further studies are needed to better define the importance of these changes *(Ribic CM, Sargent DJ, Moore MJ, et al: Proc Am Soc Clin Oncol [abstract] 21:128a, 2002).*

This combination of irinotecan, 5-FU, and leucovorin is one option for patients with metastatic colorectal cancer. Based on its superior activity, compared with 5-FU and leucovorin, the FDA approved this combination as first-line treatment for patients with metastatic colorectal cancer in 2000.

A portion of patients receiving bolus infusions of irinotecan, 5-FU, and leucovorin will develop severe and life-threatening diarrhea and neutropenia shortly after the initiation of therapy. Careful monitoring and prompt intervention are essential with the initiation of this combination.

Capecitabine (Xeloda) is an oral fluorinated pyrimidine recently approved for use in advanced colon cancer. It is converted to 5-FU through a three-step process after ingestion. In a recent phase III trial of previously untreated patients with metastatic colon cancer, capecitabine produced higher response rates than 5-FU and leucovorin. Overall survival and time to disease progression were similar (noninferior) to those with 5-FU and leucovorin. The recommended dose of capecitabine is 2,500 mg/m^2 each day, given as a twice-daily dose, for 14 days followed by a 1-week rest period. The side effects of capecitabine tend to be similar to those seen with prolonged infusion of 5-FU, with hand and foot syndrome being the most common.

Oxaliplatin (Eloxatin) is a new diaminocyclohexane platinum that has undergone clinical investigation in Europe and the United States. Oxaliplatin has

TABLE 8: NCCN recommendations for post-treatment surveillance/monitoring

- Physical examination, including digital rectal examination with stool occult blood test, every 3 months for 2 years, then every 6 months to 5 years[a]
- CBC plus chemistries every 3 months for 2 years, then every 6 months to 5 years[a]
- If the CEA level was elevated at diagnosis or within 1 week of colectomy, repeat CEA measurement every 6 months for 2 years, then annually for 5 years[a]
- Chest x-ray[a]:
  Every 12 months for 5 cycles if stage B2 or C *or*
  Every 6 months for 10 cycles if resected liver or abdominal metastases *or*
  Every 3 months for 20 cycles if resected lung metastases
- Abdominal CT[a]:
  Every 6 months for 4 cycles, then annually for 3 years if resected liver or abdominal metastases *or*
  Every 6 months for 4 cycles, then annually for 3 years if resected rectal tumor
- Chest CT[a] every 6 months for 4 cycles if resected lung metastases
- Colonoscopy[a] in 1 year; repeat in 1 year and every 3 years if:
  Negative for multiple synchronous polyps *or*
  Patient with new polyp on surveillance colonoscopy

Reprinted with permission from NCCN colorectal cancer practice guidelines. Oncology 10(11;suppl):140–175, 1996.

[a] Recommendations are somewhat controversial

CEA = carcinoembryonic antigen; NCCN = National Comprehensive Cancer Network

demonstrated activity in patients with pretreated, 5-FU–resistant colorectal cancer when used alone (10% response rate) or in combination with 5-FU (45% response rate). In patients with untreated metastatic colon cancer, response rates of 27% have been reported with oxaliplatin alone and rates as high as 57% have been noted when the drug is combined with 5-FU. Patients receiving oxaliplatin, infusional 5-FU, and leucovorin have achieved overall survivals of $>$ 20 months in several recently reported trials. However, many of these patients have received second- and even third-line therapies at the time of disease progression. Oxaliplatin's toxicity profile includes nausea/vomiting and cumulative, reversible peripheral neuropathy. Patients may also develop a reversible, cold-induced, acute pharyngolaryngeal neuropathy.

Oxaliplatin combined with infusional 5-FU and leucovorin was approved by the FDA in 2002 as second-line therapy for patients with disease progression after treatment with irinotecan, 5-FU, and leucovorin. Approval was based on an improved time to disease progression compared with that of either oxaliplatin alone or infusional 5-FU and leucovorin. A recently reported multicenter, randomized phase III study (ASCO 2002) showed improved outcome with regard to response rate, time to disease progression, and overall survival for patients receiving first-line therapy for metastatic colorectal cancer with oxaliplatin, infusional 5-FU, and leucovorin, compared with irinotecan, 5-FU, and leucovorin. At the time of the presentation, the time to disease progression for the oxaliplatin combination was 8.8 months, compared with 6.9 months for the

TABLE 9: TNM classification of anal canal tumors

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm in greatest dimension
T2	Tumor > 2 cm but not > 5 cm in greatest dimension
T3	Tumor > 5 cm in greatest dimension
T4	Tumor of any size that invades adjacent organs (eg, vagina, bladder, urethra, bladder)[a]
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in perirectal lymph node(s)
N2	Metastasis in unilateral internal iliac and/or inguinal lymph node(s)
N3	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes
Distant metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Grade (G)	
Gx	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Stage groupings			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage IIIA	T1-3	N1	M0
	T4	N0	M0
Stage IIIB	T4	N1	M0
	Any T	N2-3	M0
Stage IV	Any T	Any N	M1

[a] Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4.

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th Ed. New York, Springer-Verlag, 2002.

irinotecan combination. Based on the results of this trial, FDA approval for first-line therapy is now being sought.

The expression of COX-2 is associated with worse prognosis compared to tumors without such expression. Use of a COX-2 inhibitor, along with chemotherapy, appears to be beneficial. Phase III studies evaluating the potential benefit of COX-2 inhibitors combined with chemotherapy are in development. *(Blanke CD, Benson AB, Dragovich T, et al: Proc Am Soc Clin Oncol [abstract]21:127a, 2002).*

Intrahepatic floxuridine administration Renewed interest in regional delivery of floxuridine into the liver has followed the introduction of effective implantable infusion pumps. These pumps allow chemotherapeutic agents to be delivered in higher concentration directly into the hepatic artery.

Randomized trials have shown a considerably higher therapeutic response rate with intrahepatic administration (IA) of floxuridine than with systemic therapy. A recent meta-analysis of studies comparing IV vs IA fluorinated pyrimidines in patients with unresectable, liver-confined, metastatic disease has indicated a small advantage for IA therapy.

Intrahepatic chemotherapy is costly and associated with gastroduodenal mucosal ulceration, hepatitis, and sclerosing cholangitis. The addition of dexamethasone to floxuridine infusions appears to decrease biliary sclerosis.

Molecular-targeted agents are currently being investigated. The VEGF (vascular endothelial growth factor) receptor inhibitor SU5416 and the monoclonal antibodies C225 and rhuMAb-VEGF have reached later stages of development and been commonly combined with more conventional chemotherapy agents and regimens.

TREATMENT OF ADVANCED RECTAL CANCER

Radiation therapy

Radiation therapy is moderately effective in palliating advanced rectal cancer symptoms. Pain is decreased in 80% of irradiated patients, although only 20% report complete relief. Bleeding can be controlled in over 70% of patients. Obstruction cannot be reliably relieved by irradiation, and diverting colostomy is recommended. Only 15% of patients with recurrent rectal cancers achieve local disease control with irradiation, and median survival is < 2 years.

Chemoradiation may be useful to convert fixed unresectable lesions into resectable lesions. These regimens have generally used protracted infusions of 5-FU (200-250 mg/m^2/d) delivered via a portable infusion pump during pelvic radiation therapy (450 cGy over 5 weeks).

Intraoperative radiotherapy (localized irradiation given to the tumor or tumor bed at the time of resection) is under active investigation in advanced and locoregionally recurrent rectal cancer.

Laser photoablation

Laser photoablation is occasionally employed for temporary relief of obstructive rectal cancer in patients who are not surgical candidates because of the presence of distant metastases, surgical comorbidity, or extensive intra-abdominal disease.

TABLE 10: Chemotherapy regimens for anal canal cancer

Drug/combination	Dose and schedule
Fluorouracil/mitomycin/radiation therapy	
Fluorouracil (5-FU)	1 g/m^2/d IV infused continuously on days 1-4 and days 29-32
Mitomycin	15 mg/m^2 IV on day 1
Irradiation	200 cGy/d for 5 days per week (total dose, 3,000 cGy)
Give chemotherapy concurrently with irradiation; start both modalities on the same day	
Leichman L, Nigro ND, Vaitkevicius VK, et al: Am J Med 78:211–215, 1985.	
Fluorouracil/cisplatin/radiation therapy	
Fluorouracil	1 g/m^2/d IV infused continuously for 4 days
Cisplatin	25 mg/m^2/d IV on days 2-5 following standard hydration
Give chemotherapy concurrently with irradiation, except in elderly or frail patients	
Wagner JP, Mahe MA, Romestaing P, et al: Int J Radiat Oncol Biol Phys 29:17–23, 1994.	

Table prepared by Ishmael Jaiyesimi, DO

Follow-up of long-term survivors

Patients who have completed therapy for colorectal cancer require monitoring for potential treatment-related complications, recurrent disease, and new metachronous cancers. Specific follow-up recommendations for these patients are quite controversial at present. Guidelines for post-treatment surveillance/monitoring adopted by the National Comprehensive Cancer Network (NCCN), a consortium of 19 American cancer centers, are shown in Table 8.

ANAL CANAL CARCINOMA

Epidemiology, etiology, and risk factors

In the United States, anal canal carcinoma occurs more frequently in women than men. More than 80% of anal canal tumors occur in individuals > 60 years of age. Recent epidemiologic studies suggest that receptive anal intercourse is strongly related to anal cancer.

The incidence rate of anal cancer for single men is reported to be six times that for married men. In people < 35 years old, anal carcinoma is more common in men than women. A history of genital warts has been observed, suggesting that papillomavirus may be an etiologic factor.

Signs and symptoms

The diagnosis of anal canal carcinoma is usually delayed because the symptoms (bleeding, pain, and sensation of mass) are so often attributed to benign anorectal disorders, such as hemorrhoids or anal fissures.

Diagnosis

Evaluation should include a careful rectal examination, endoscopic examination with description of lesion size, and assessment of whether there is invasion of disease into adjacent organs (vagina, urethra, or bladder). Reexamination under general anesthesia may be necessary. A diagnostic incisional biopsy is required.

Pelvic CT is suggested to evaluate pelvic nodes. Although distant metastases are uncommon at diagnosis, a chest x-ray and liver function tests are recommended. Suspicious inguinal nodes discovered on physical examination must be assessed pathologically. The incidence of inguinal nodal metastases at diagnosis varies from 13% to 25%. The presence of perirectal, inguinal, and pelvic lymph node involvement correlates with tumor size and is unusual for tumors < 2 cm in diameter. Formal groin dissection is not advised; needle aspiration should be performed, with limited surgical biopsy if results of aspiration are inconclusive.

Pathology

Squamous cell carcinomas Most anal canal malignancies are squamous cell carcinomas. They have been classified as cloacogenic carcinomas, basaloid carcinomas, transitional cell carcinomas, or mucoepidermoid carcinomas. However, there is little difference in the natural history of these various types.

Unusual tumors arising in the anal canal include small-cell carcinomas, anal melanomas, lymphomas, and adenocarcinomas.

Small-cell carcinomas of the anal canal are aggressive neoplasms similar in natural history to bronchogenic small-cell carcinomas. If such a histology is identified, the clinician should be alerted to the possibility of early distant metastases, and treatment should include chemotherapeutic regimens used in bronchogenic small-cell carcinomas.

Anal melanomas Although advanced anal melanomas generally are associated with a dismal survival, prognosis may be related to the depth of disease penetration. Early anal melanomas < 2.0 mm in depth can be cured with wide excision. Abdominoperineal resection is indicated only rarely in the management of anal melanoma.

Adenocarcinomas are uncommon cancers associated with a poor prognosis. Treatment should be aggressive and based on a multimodality approach. The rarity of this tumor precludes the development of specific clinical trials.

Staging

Size of the primary tumor is the most important clinical predictor of survival for patients with anal carcinomas. Both the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) have agreed on a unified staging system (Table 9). The TNM classification distinguishes between anal canal carcinoma and anal margin tumors, since the latter exhibit biological behavior similar to that of other skin cancers and are staged as skin cancers.

Treatment

Surgery

In selected individuals with small superficial tumors, local excision has achieved adequate local control and survival. However, most studies of local excision have been retrospective, with small numbers of patients. Prior to the advent of primary radiotherapy and combined-modality treatment (see below), abdominoperineal resection was considered to be the conventional treatment for patients with invasive anal canal cancer. Unfortunately, even with radical surgical procedures, local recurrences are frequent. Currently, radical extirpative surgery is indicated only after the failure of combined-modality treatment.

Radiation therapy

Trials of primary external-beam radiotherapy in patients with anal canal carcinomas have used doses varying between 4,500 and 7,550 cGy. Local control rates of 60%-90%, with 5-year survival rates of 32%-90%, are similar to the results of surgical series when the trials are controlled for tumor size.

Interstitial radiation therapy alone has been used primarily in Europe for early-stage lesions. A relatively high radiation dose is delivered to a small volume. This modality carries a high potential for radiation necrosis and fails to incorporate treatment of the inguinal nodes.

Combined-modality treatment

Chemotherapy given concurrently with irradiation is the preferred therapy for most patients with anal canal cancer (Table 10). Investigators from Wayne State University pioneered the use of simultaneous pelvic irradiation and chemotherapy in the treatment of patients with anal canal carcinomas. They demonstrated that the majority of such patients could be treated with this combination, obviating the need for an abdominoperineal resection. The original study design used 3,000 cGy over 3 weeks with 5-FU (1,000 mg/m^2/d) as a continuous infusion on days 1-4 and then repeated on days 29-32. Mitomycin (Mutamycin), 15 mg/m^2, was administered as an IV bolus on day 1. A total of 4 to 6 weeks after the completion of therapy, patients had a deep muscle biopsy of the anal canal scar.

An updated analysis of this experience demonstrated that 38 of 45 patients (84%) were rendered disease free after chemotherapy and irradiation. Individuals who had positive biopsies underwent an abdominoperineal resection.

Because of the success of the above experience, other investigators have attempted to implement infusional 5-FU and mitomycin with irradiation as definitive therapy. Most studies have used similar schedules of 5-FU and mitomycin but have used higher doses of pelvic irradiation (4,500-5,700 cGy). Five-year survival rates > 70% have been reported.

A randomized trial from the Radiation Therapy Oncology Group (RTOG) showed that the use of mitomycin with irradiation and 5-FU increased complete tumor regression and improved colostomy-free survival over irradiation and 5-FU alone. At 4 years, the colostomy-free survival rate was higher in the mitomycin arm than in the 5-FU–alone arm (71% vs 59%), as was the disease-free survival rate (73% vs 51%).

Several investigators have compared the results of irradiation alone vs irradiation plus chemotherapy. Cummings et al found that with identical irradiation doses and techniques, the local control rate for cancers > 2 cm rose from 49% with radiation therapy alone to 85% when 5-FU and mitomycin were combined with irradiation. Papillon and Montbarbon found an increase in the rate of local control with a combined-modality approach, as compared with pelvic irradiation alone (81% vs 66%). Two recent randomized studies have shown improved local control with chemoradiation over irradiation.

A complete response to combined chemotherapy and radiation therapy is expected in 80%-90% of patients with anal cancer. It is important to evaluate the response of therapy with a careful examination and biopsy of the anal canal after treatment. Anal canal cancers can continue to regress for up to 3 or more months after completion of treatment. For this reason, it is recommended that a biopsy be performed no sooner than 3 months after the completion of treatment. If localized persistent disease is identified after initial treatment, or if subsequent recurrence is diagnosed, abdominoperineal resection is expected to yield long-term disease control and survival in 40%-50% of patients.

Chemotherapy

Reports of other chemotherapeutic agents in anal cancer have been relatively anecdotal, with limited phase II studies. Because of the activity of cisplatin (Platinol) in other squamous cell carcinomas, this agent has been employed as a single agent or combined with infusional 5-FU in advanced disease.

SUGGESTED READING

ON COLORECTAL CARCINOMA

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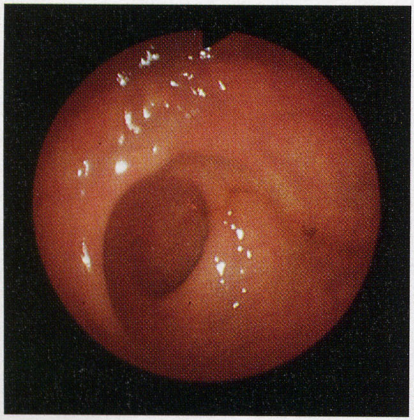
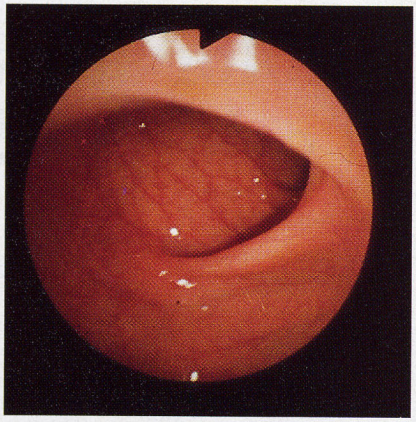
Allal AS, Laurencet FM, Reymond MA, et al: Effectiveness of surgical salvage therapy for patients with locally uncontrolled anal carcinoma after sphincter-conserving treatment. Cancer 86:405–409, 1999.

A color atlas of colorectal lesions

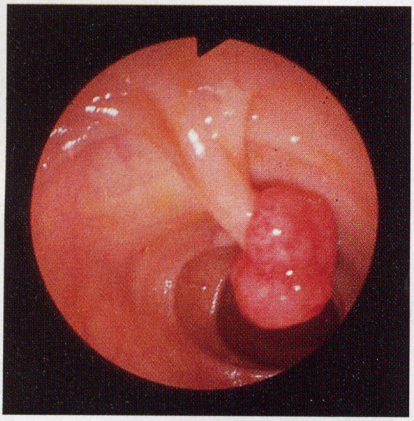
Compiled by Lawrence B. Cohen, MD
Department of Gastroenterology
Mount Sinai School of Medicine
New York, New York



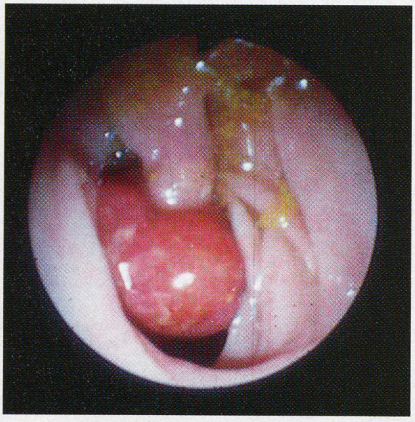
Normal rectal mucosa



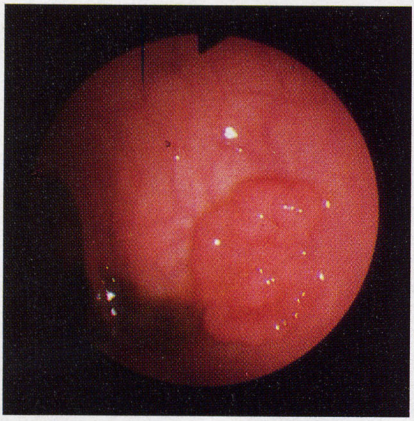
Normal sigmoid colon



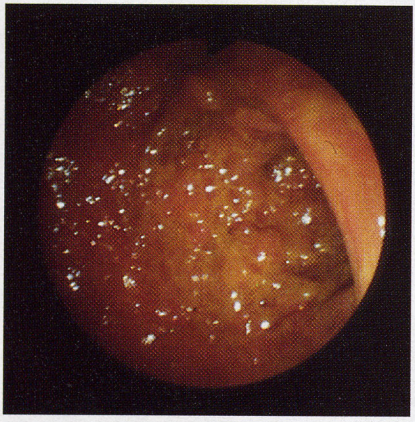
Adenomatous polyp with long pedicle



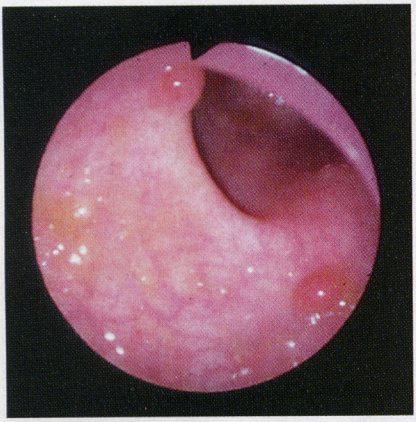
Another polyp



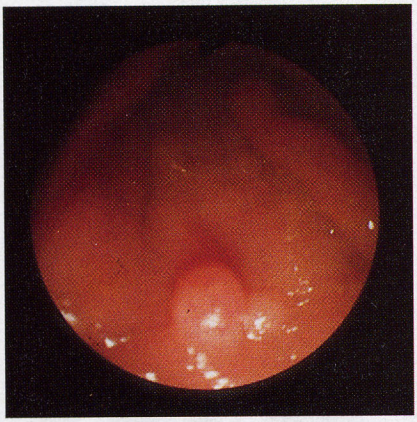
Another adenomatous sessile polyp



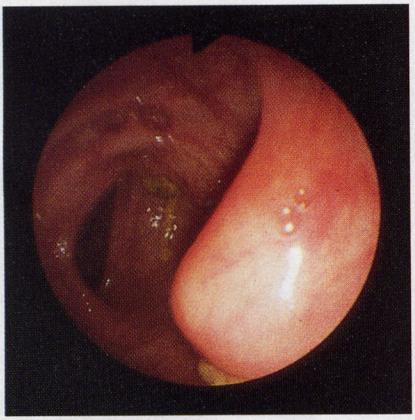
"Carpet"-like polyps



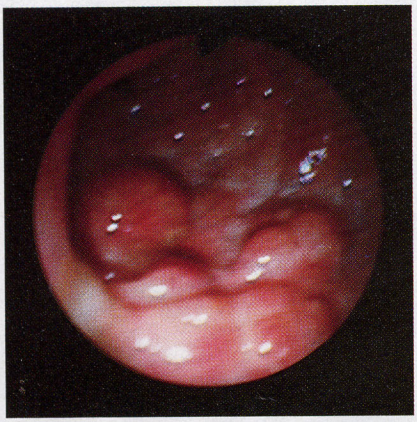
Small adenomas



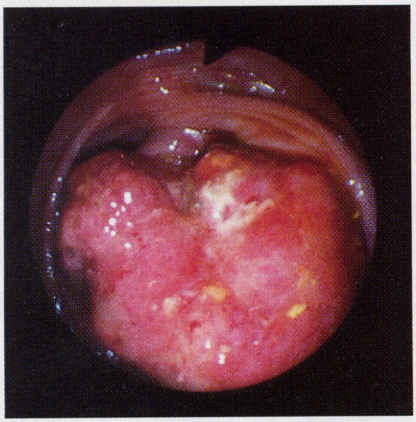
Nonadenomatous hyperplastic polyp



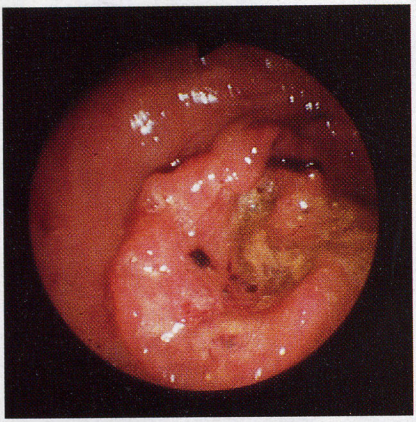
Lipoma



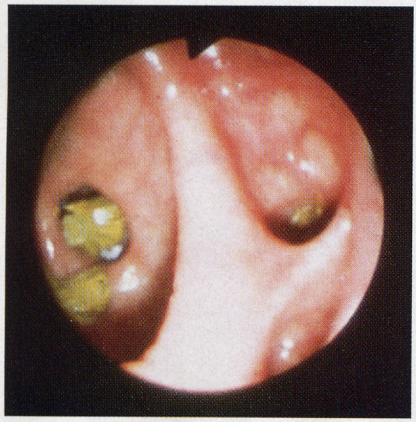
Pneumatosis cystoides



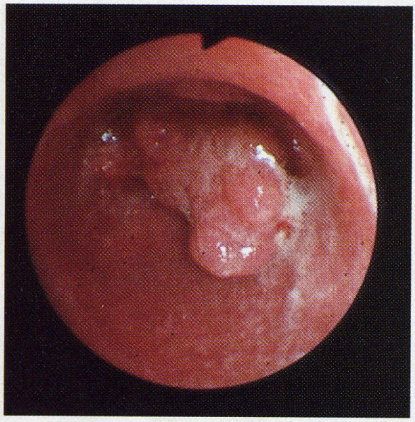
Bulky, polypoid adenocarcinomas



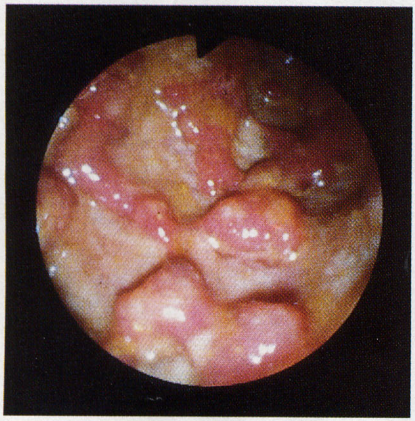
Flat, ulcerated adenocarcinoma



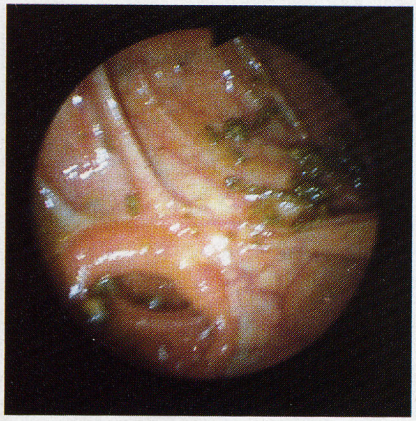
Diverticula



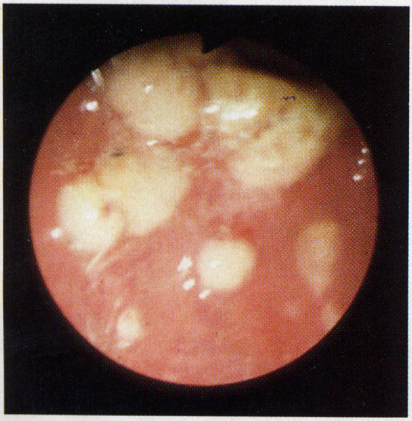
Scattered pseudopolyps



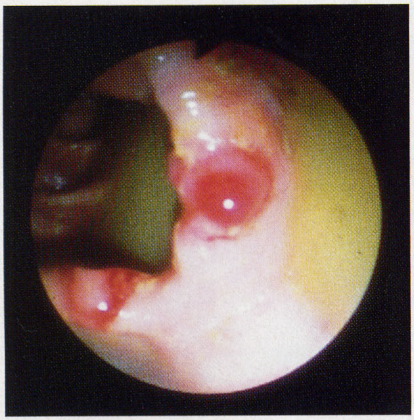
Clustered pseudopolyps



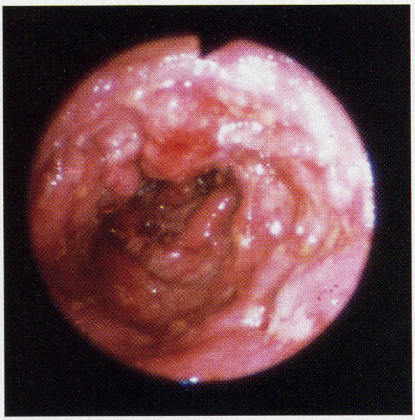
Surgical anastomosis



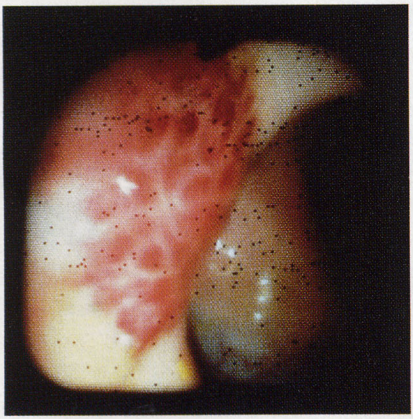
Antibiotic-associated colitis



Colonic manifestations of AIDS-cytomegalovirus colitis



Excavating ulcers of CMV infection



Submucosal Kaposi's sarcoma

Endoscopic photography courtesy of Lawrence B. Cohen, MD, Department of Gastroenterology, Mount Sinai School of Medicine, New York, New York

CHAPTER 17

Prostate cancer

Kenneth J. Pienta, MD, Howard Sandler, MD, Javid Javidan, MD, and Martin G. Sanda, MD

Prostate cancer is the most common cancer in US men. Despite the fact that this cancer will be diagnosed in an estimated 220,900 US men in the year 2003 and will lead to the death of over 28,900 men, there is no universally agreed-upon strategic plan for its diagnosis and management.

Epidemiology

Age The risk of developing prostate cancer begins to increase at age 50 years in white men who have no family history of the disease and at age 40 years in black men and those who have a first-degree relative (father, brother) with prostate cancer. Risk increases with age but, unlike other cancers, prostate cancer has no "peak" age or modal distribution.

Race The highest incidence of prostate cancer in the world is found in US black men, who have approximately a 9.8% lifetime risk of developing this cancer. This is slightly higher than the 8% lifetime risk for US white men. Black men have an incidence of prostate cancer that is 1.6 times that of whites.

The Japanese and mainland Chinese populations have the lowest rates of prostate cancer. Interestingly, although Japanese immigrants to the United States have a higher incidence of prostate cancer than Japanese living in Japan, their rate is still about half that of US whites.

Socioeconomic status appears to be unrelated to risk of prostate cancer, and the explanation for racial variability is unknown.

Geography The incidence of prostate cancer is highest in Scandinavian countries (22 cases per 100,000 population) and lowest in Asia (5 per 100,000). Risk may be inversely related to ultraviolet light exposure, as the incidence increases the farther one lives from the equator.

Etiology and risk factors

Age and race Autopsy series indicate that approximately 60% of men develop prostate cancer over time. The strongest risk factors seem to be age, being a member of the black race, and a family history of prostate cancer.

Family history Men who have a first-degree relative with prostate cancer have approximately a two-fold increased risk of developing prostate cancer during

their lifetime. An individual who has two first-degree relatives with prostate cancer has a nine-fold increase in lifetime risk.

True hereditary prostate cancer occurs in a very small number of men and tends to develop at a very early age (< 55 years old).

Dietary fat Studies have suggested that dietary fat may increase the risk of prostate cancer. However, no definitive proof of its role has yet been found.

Vasectomy Several large epidemiologic studies suggest that vasectomy may increase the relative risk of prostate cancer by as much as 1.85. However, these same studies do not report an increased risk of dying from prostate cancer associated with vasectomy but do indicate a statistically increased risk of dying from *lung* cancer. These findings argue against an association between vasectomy and prostate cancer. Currently, this association is unproven and does not constitute grounds for fundamental changes in the use of vasectomy.

Sexual activity/sexually transmitted disease There is no association between sexual activity in a man or sexually transmitted diseases and the incidence of prostate cancer.

Signs and symptoms

Early-stage disease Men with organ-confined prostate cancer often are completely asymptomatic. Men with a large component of benign prostatic hyperplasia often present with bladder outlet obstruction unrelated to their prostate cancer.

Locally advanced disease Bladder outlet obstruction is the most common sign of locally advanced prostate cancer. A few men with locally advanced disease present with hematuria, urinary tract infections, and irritative voiding symptoms secondary to bladder outlet obstruction.

Advanced disease Rarely, men with bulky lymph node metastasis may present with bilateral lower extremity edema. Men with bony metastasis often present with bone pain and, uncommonly, with lower extremity weakness or paralysis from spinal cord compression.

Screening and diagnosis

Prostate cancer screening with prostate-specific antigen (PSA) and digital rectal examination has resulted in not only an increase in prostate cancer detection but also a stage shift. More cancers are now being detected at earlier stages when they are potentially curable. Prior to screening efforts, most prostate cancers were detected when they produced local symptoms or distant metastases, at which point treatment for cure often was impossible.

Digital rectal examination Prostate biopsy prompted by abnormal findings on digital rectal exam (DRE), such as nodularity or induration of the prostate, leads to a diagnosis of prostate cancer in only 15%-25% of cases. This compares with a prostate cancer prevalence of < 5% among men of similar age

without abnormal DRE. Although neither accurate nor sensitive for prostate cancer detection, abnormal DRE is associated with a five-fold increased risk of cancer present at the time of screening.

PSA has revolutionized prostate cancer screening. PSA is a serine protease produced by the prostatic epithelium and secreted in the seminal fluid in large quantities. Prostatic disease changes the cellular barriers that normally keep PSA within the ductal system of the prostate and thereby alters serum levels. The level of PSA in serum is increased by inflammation of the prostate, urinary retention, prostatic infection, benign prostatic hyperplasia, prostate cancer, and prostatic manipulation. Although PSA has good sensitivity, it is not an optimal test because an elevated PSA level is neither specific to prostate cancer, nor does it distinguish aggressive prostate cancers from those that are biologically benign. Of those patients with a PSA of $>$ 4.0 ng/mL, approximately 15%-25% will have a diagnosis of prostate cancer.

Ross et al recently used computer modeling to evaluate different PSA screening strategies. They found that testing at ages 40 and 45 years followed by testing every other year after age 50 was more effective and less resource-intensive than annual testing beginning at age 50.

Current screening recommendations The American Cancer Society recommends that the PSA test and the DRE should be offered annually beginning at age 50 to men who have a life expectancy of at least 10 years. Men at high risk should begin testing at age 45. Prior to testing, men should have an opportunity to learn about the benefits and limitations of testing for early prostate cancer detection and treatment. Men who ask the clinician to make the testing decision on their behalf should be tested. A clinical policy of not offering testing, or discouraging testing in men who request early prostate cancer detection tests, is inappropriate.

Rather than recommending that all men $>$ 50 years old should be screened for prostate cancer, most organizations recommend that physicians should be prepared to discuss testing for prostate cancer detection with their patients, and that men should have an opportunity to make an informed decision about testing after a discussion about the current uncertainty regarding benefits and risks associated with testing and treatment. High-risk groups include men of African descent (specifically, sub-Saharan African descent) and men with a first-degree relative diagnosed at a younger age. Risk increases with the number of first-degree relatives affected by prostate cancer. The ACS recommends that these men begin testing for early prostate cancer detection at age 45. Men at appreciably higher risk of prostate cancer due to multiple first-degree relatives who were diagnosed with prostate cancer at an early age should be informed regarding possible risks and benefits of screening and may begin testing at age 40.

Men (45-80 years of age) who registered on the Quebec electoral roll were randomized between screening and no screening for prostate cancer. A total of 7,286 men underwent screening; a control group comprised 15,263 men, of whom 1,080 were screened. Over 10 years, the screened cohort experienced a 52% decline in prostate cancer mortality, showing the benefits of screening.

Biopsy When indicated, prostate biopsy usually is performed as an office procedure by transrectal ultrasound guidance using an automated 18-gauge biopsy gun. The procedure is done with, at most, local anesthesia and carries a risk of significant infection of only 1 in 200. Additional side effects of hematuria and hematochezia are common for 2-3 days following the biopsy. Hematospermia may last for up to 2-3 weeks.

TABLE 1: Staging of prostate cancer

Modified Whitmore system		TNM system[a]	
Localized disease			
A1	≤ 5% transurethral resection chips with cancer; no grade 4, 5 chips	T1a	Tumor incidental histologic finding in ≤ 5% of resected tissue; not palpable
A2	> 5% transurethral resection chips with cancer; any grade 4, 5 chips	T1b	Tumor incidental histologic finding in > 5% of resected tissue
B0	PSA level > 4.0 ng/mL (normal digital rectal examination)	T1c	Tumor identified by needle biopsy (eg, because of elevated PSA level)
B1	One lobe, ≤ 2 cm nodule	T2a	Tumor involves one-half of one lobe or less
		T2b	Tumor involves more than one-half of one lobe but not both lobes
B2	Both lobes or any nodule > 2 cm	T2c	Tumor involves both lobes
Local extension			
C1	Penetration of capsule	T3a	Extracapsular extension (unilateral or bilateral)
C2	Margin positive	T3b	Tumor invades seminal vesicle(s)
C3	Seminal vesicle involvement	T4	Bladder invasion, fixed to pelvic side wall, or invasion of adjacent structures
Metastatic disease			
D0	Organ confined, elevated prostatic acid phosphatase		
D1	Positive lymph nodes all below aortic bifurcation	N1	Positive regional lymph nodes
D2	Positive lymph nodes above aortic bifurcation; bony metastasis	M1	Distant metastasis
D3	Disease psrogression on hormonal therapy		

[a] Adapted from Greene FI, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

If the biopsy is negative, these men are typically followed conservatively with serial PSA levels and DRE repeated annually. Repeat biopsy is performed only when PSA levels rise at abnormal rates (> 0.8 ng/mL/year) or if DRE findings show new nodularity or induration. Men in whom high-grade prostatic intraepithelial neoplasia is found on biopsy may undergo repeat biopsy, since about one-third will be found to have prostate cancer.

One caveat to PSA screening is its lack of specificity when the value lies between 4 and 10 ng/mL, since many men with benign prostatic hyperplasia have PSA levels in this range. There have been several attempts to increase testing specificity, including the development of age-specific ranges, trends in PSA increase over time (PSA velocity), and calculations of the PSA density based on the volume of the prostate gland. A commonly employed test to increase testing specificity in this "indeterminate zone" is the percent-free PSA. Currently, biopsy is recommended in men whose percent-free PSA (ratio of free to total PSA) is < 10%, while biopsy is not necessary when percent-free PSA is > 25%.

Pathology

Adenocarcinomas make up the vast majority of prostate carcinomas. A total of 70% of prostate adenocarcinomas occur in the peripheral zone, 20% in the transitional zone, and approximately 10% in the central zone.

Other tumor types are relatively rare and include ductal adenocarcinoma, which occurs in the major ducts and often projects into the urethra; and mucinous adenocarcinoma, which secretes abundant mucin and does not arise from the major ducts. Transitional carcinoma of the prostate occurs within the ducts and, to a lesser extent, in the prostatic acini. Typically, primary transitional carcinomas are aggressive cancers that have a poor prognosis. Similarly, neuroendocrine (small-cell) tumors are rare and aggressive, have a poor prognosis, and typically require aggressive surgical management.

Histologic grade The grading system developed by Gleason from data accumulated by the Veterans Administration Cooperative Urologic Research Group appears to provide the best prognostic information in addition to clinical stage, and is the predominant grading system in widespread use.

Metastatic spread Adenocarcinoma of the prostate may spread locally through direct extension into periprostatic fat or via the ejaculatory ducts into seminal vesicles; lymphatically to regional lymph nodes, including the hypogastric and obturator lymph nodes; and hematogenously to bone. The most common sites of bony metastases are the lumbosacral spine (probably related to venous drainage of the prostate through Baston's plexus) and the axial skeleton, but any bone, including the skull and ribs, can be involved. Rare sites of metastatic spread include the liver and lungs.

Staging systems The most widely used and universally accepted staging system for prostate cancer is the TNM system. The previously used Whitmore

TABLE 2: Risk of dying from clinically localized prostate cancer without definitive locoregional therapy

Gleason score	Age			
	55-59	60-64	65-69	70-74
2-4	4%	5%	6%	7%
5	6%	8%	10%	11%
6	18%	23%	27%	30%
7	70%	62%	53%	42%
8-10	87%	81%	72%	60%

Adapted from Albertsen PC, Hanley JA, Gleason DF, et al: JAMA 280:975–980, 1998.

system, although now modified to include PSA-detected tumors, does not distinguish metastatic spread from the degree of local extension (Table 1) and is used less frequently. Briefly, in the TNM system, T1 and T2 tumors are confined to the gland, whereas T3 and T4 tumors have local extension.

Prognosis and natural history

Prognosis of untreated prostate cancer Survival depends on patient age at diagnosis, overall health, and tumor grade and stage at diagnosis. The natural history of prostate cancer is becoming increasingly better understood as long-term data become available.

Among untreated patients with clinically localized prostate cancer, those with a low Gleason score (2-4) have a very small risk of dying of their cancer within 15 years (4%-7%), regardless of their age at diagnosis. Those with poorly differentiated tumors (Gleason score 8-10) have a greater risk of dying from prostate cancer than from any other cause, even when the cancer is diagnosed in the eighth decade of life. Indeed, a 55- to 59-year-old man diagnosed with a clinically localized, Gleason score 8-10 prostate cancer has an 87% risk of succumbing to the disease within 15 years if untreated (Table 2).

Treatment

Treatment needs to be individualized. Decisions regarding treatment options are often based on the disease stage and grade, pretreatment PSA, and rate of PSA rise, as well as the patient's age and life expectancy. In particular, physiologic age (ie, the presence or absence of other significant medical problems) is of greater importance than chronologic age, and patients with short life expectancy (eg, $<$ 10 years) may well be observed if they have early prostate cancer.

For the sake of simplicity, we have chosen to discuss treatment according to clinical T stage. However, the risk of subclinical disease being located outside

of the prostate depends on the PSA and Gleason score. Many clinicians choose to further categorize patients with a T1 or T2 tumor according to their likelihood of extraprostatic disease: the "low-risk" group would consist of those with a PSA ≤ 10 ng/mL and a Gleason score ≤ 6; the "intermediate-risk" group, those with a PSA of 10-20 ng/mL *or* a Gleason score of 7; and the "high-risk" group, those with a PSA > 20 ng/mL *or* a Gleason score of 8-10.

TREATMENT OF CLINICALLY LOCALIZED DISEASE (T1, T2)

Radical prostatectomy

Radical prostatectomy can be performed retropubically through a lower midline incision—an approach that includes pelvic lymph node dissection. Alternatively, some urologists prefer the perineal approach, which is done through a vertical midline perineal incision. With the latter approach, a separate incision is required if lymph node removal is desired.

Although the morbidity of radical prostatectomy was a major concern in the past, major improvements were made during the 1980s. The hazards of anesthesia, risk of blood loss, and hospital stay have all been minimized. Nationwide, Medicare data suggest that surgical outcomes are significantly better at centers performing > 40 prostatectomies per year as compared to hospitals with lower surgical volume.

Transfusion is usually unnecessary, and treatment-related mortality is < 0.05% at leading prostate cancer centers. The average hospital stay of a man undergoing radical prostatectomy is now approximately 3 days at leading US referral centers and several institutions routinely discharge patients within 24 hours. Although urinary incontinence is common in the first few months after prostatectomy, most men recover urinary control; at some leading centers, 90%-95% of men report very little or no long-term urinary problems.

In 2002, results were published from a Swedish trial designed to determine whether radical prostatectomy for localized disease was associated with a survival advantage over expectant management. Holmbey and colleagues randomized 695 men with localized prostate cancer between 1989 and 1999 to receive either radical prostatectomy or watchful waiting. After an average of 6.2 years of follow-up, there was a statistically significant difference in the rate of distant metastases and disease-specific mortality favoring the radical prostatectomy group over those who underwent watchful waiting *(Holmberg L, Bill-Axelson A, Helgesen F, et al: N Engl J Med 347:781-789, 2002).*

Nerve-sparing radical prostatectomy is appropriate for men with small-volume disease. It offers those men with good potency prior to surgery the possibility of recovering that function following the operation. By permitting better visualization of Santorini's dorsal venous plexus, the apical prostate, the urethra, and the striated urethral sphincter, the nerve-sparing technique also reduces blood loss and improves recovery of urinary continence.

Referral centers have reported that approximately 50% of patients who are fully potent prior to surgery recover erections following a nerve-sparing procedure, but the quality of these recovered erections may be compromised compared with preoperative erections. Erection recovery rates can be higher than 50% in pa-

tients < 60 years of age, and lower in older men. Potency may return anywhere from 2-24 months following surgery. Regardless of potency, sensation of the penis is not changed after this procedure, and men may still experience orgasm.

Laparoscopic radical prostatectomy

Laparoscopic radical prostatectomy was initially described in the early 1990s, as an alternative method to radical retropubic prostatectomy. The goal was to achieve similar or improved results via a laparoscopic approach. However, this technique did not become popular until recently, due to the exceedingly long operative time required to perform the operation. In the past 3 years, several European teams succeeded in elaborating standardized surgical procedures, leading to significant shortening of operative time, and allowing its introduction into clinical practice in the United States. Long-term results of laparoscopic radical prostatectomy regarding impotence, incontinence, and cancer control are still not available. Prospective multicenter studies will be required to determine the relative value of laparoscopic radical prostatectomy in the management of localized carcinoma of the prostate.

As of March, 2003 a total of 400 laparoscopic radical prostatectomies have been completed at the City of Hope. Median hospital stay was 1.5 days, only five patients have required a blood transfusion and the median length of time with the Foley catheter was 6 days. Overall positive margin rate was 20% with only a 2% positive margin rate for patients with pT2a, Gleason score 6 disease. Return to urinary continence, defined as ≤ one small pad per day, was about twice as fast as open prostatecomy series with 65% continent at 1 month, 84% at 3 months, 90% at 6 months, and 99% at 1 year from surgery. Nerve sparing and potency recovery results are not yet available *(Wilson TG, Kawachi MH, Ramin SA, et al: J Urol [abstract], in press).*

Pelvic lymph node dissection Studies now indicate that regional pelvic lymph node dissection may not be necessary for patients with stage T1c disease if the total Gleason score is < 7 and PSA is < 10.0 ng/mL. However, pelvic node dissection can be justified on the basis that it allows for more accurate assessment of prognosis.

Neoadjuvant hormonal therapy

Approximately 35% of men who undergo radical prostatectomy for clinical stage T2 prostate cancer will be found to have pathologic T3 disease following surgery. This led some investigators to evaluate the efficacy of neoadjuvant androgen deprivation therapy in prospective clinical trials. Early data from these trials suggested that neoadjuvant hormonal therapy led to a reduction in positive surgical margins. However, these findings need to be considered in a technical context: Androgen deprivation therapy causes artifactual changes in prostate morphology that cause difficulties for the pathologic identification of prostate cancer foci.

Indeed, more recent data from prospective studies have shown no benefit of neoadjuvant therapy with regard to progression-free survival. At present, therefore, it appears that neoadjuvant hormonal therapy does not improve the curative potential of radical prostatectomy, but instead, is associated with morphologic alterations that complicate the prognostic utility of standard pa-

Salvage radiotherapy for rising PSA levels following radical prostatectomy can result in long-term cures and should be used prior to noncurative strategies. Recently, DeWeese et al reported the outcome of a series of patients treated with salvage radiotherapy. Although all patients had a detectable PSA level (median, 0.8 ng/mL) at some point after radical prostatectomy and before radiotherapy, 40% of patients had undetectable PSA values 4 years following radiotherapy, with rare failures thereafter. Those with a PSA level < 1.0 ng/mL had a better outcome, indicating that earlier salvage therapy is optimal *(Song DY, Thompson TL, Ramakrishnan V, et al: Urology 60:281-287, 2002).*

thology. Consequently, neoadjuvant hormonal therapy should be reserved for evaluation as an experimental modality in the context of clinical trials.

Adjuvant therapy post-prostatectomy

The potential indications for adjuvant therapy following radical prostatectomy in patients with clinical T1 or T2 malignancy, include pathologic evidence of T3 disease, positive nodes, and a rising PSA, among others. Possible adjunct treatments include radiation therapy and androgen deprivation with or without radiation therapy.

Radiation therapy Men with pathologic T3 disease following radical prostatectomy are candidates for adjuvant therapy. However, to date, no prospective randomized trials have demonstrated a survival benefit from adjuvant radiotherapy in patients with pathologic T3 adenocarcinoma of the prostate. Large studies are underway to investigate this issue.

A trial comparing two doses of radiotherapy was recently updated. Pollack randomized patients with prostate cancer to receive either 70 Gy given conventionally or 78 Gy with a conformal therapy boost. A total of 305 patients were entered and there was an advantage in freedom-from-failure for the higher dose arm at 6 years (70% vs 64%, $P = .03$). The benefit was most notable for those patients with a pretreatment PSA level > 10 ng/mL (62% vs 43%, $P = .01$), and no benefit was detected for those with a PSA level < 10 ng/mL. Toxicity was modest in the two arms, although it was somewhat higher in the higher dose arm. This important, but relatively small, trial provides some of the strongest data supporting dose intensification. A larger randomized trial has been launched by the RTOG. This trial, P0126, will accrue 1,520 cases and is likely to provide definitive information regarding a beneficial effect on mortality with higher doses of radiotherapy, if such a benefit exists *(Pollack A, Zagars G, Starkschall G, et al: Int J Radiat Oncol Biol Phys 53:1097-1105, 2002).*

Hormonal therapy Significant controversy exists within the academic community as to the timing of initiating androgen deprivation following radical prostatectomy. Clinical trials have documented a benefit only for those patients with nodal involvement.

Treatment recommendations for post-prostatectomy recurrence

Following a radical prostatectomy, it is expected that serial PSA levels will become undetectable. Any detectable PSA (> 0.2 ng/mL) following surgery indicates possible recurrent disease and indicates a need for restaging and for discussion of possible salvage therapies with the patient, including radiation or hormonal therapy, experimental protocols, or observation. However, some patients can develop low levels of detectable PSA after prostatectomy without developing a cancer recurrence even if no additional treatment is administered.

Definitive radiation therapy

External-beam treatment Traditional external-beam irradiation techniques are designed to encompass the prostate and, for those at high risk of regional metastasis, the pelvic lymph nodes. A four-field axial box arrangement with customized shielding of normal structures is commonly used. A recently presented study suggests that treatment of regional lymphatics may be beneficial in patients at risk for harboring lymph node metastases (Roach M, Lu JD, Lawton C: Int J Radiat Oncol Biol Phys [abstract] 51[suppl 1]:3, 2001).

Conformal external-beam therapy creates three-dimensional representations of target structures (ie, the prostate) and designs highly tailored treatment portals using unconventional treatment directions to create a volume of high radiation dose that conforms to the target shape. The anatomic information used to define the target is generally derived from CT images obtained while the patient is placed in the precise treatment position.

Early results using conformal therapy showed a reduction in acute and early morbidity. Also, conformal therapy has permitted the use of doses far above traditional levels without significant increases in serious morbidity. The current standard radiotherapy dose is 70 Gy given over 7-8 weeks. Dose-escalation studies are exploring the feasibility of increasing the dose to near 80 Gy. Patients with relatively low-risk disease (ie, PSA ≤ 10 ng/mL and Gleason score ≤ 6) generally have a 5-year freedom-from-progression rate of ~85% when treated with conformal external-beam radiation.

Intensity-modulated radiotherapy (IMRT) is becoming widely used for prostate cancer treatment. This refinement of conformal therapy employs highly nonuniform beam intensity profiles to create more conformal dose distributions. Although it is likely that IMRT will have a greater benefit in the treatment of nonprostate neoplasms (ie, head and neck cancers), there is emerging evidence that prostate cancer therapy is also an appropriate site for IMRT treatment.

Interstitial radiotherapy In the 1970s, the use of permanently placed radioactive iodine implants produced initial results as good as other available radiotherapy techniques and posed a small risk of impotence and other morbidity when compared with conventional external-beam radiotherapy and radical prostatectomy. However, ultimate control rates were unacceptable. The technique used (freehand placement during laparotomy) was found to distribute the radioactive seeds unevenly throughout the gland and, thus, cold regions may have contributed to the relatively poor outcome.

The use of transrectal ultrasound to guide seed placement from a transperineal approach has corrected the problem of poor seed placement. Also, radioactive palladium seeds have been developed to increase the dose rate. (Palladium has a shorter half-life than iodine.) Currently, both iodine and palladium implants are used, sometimes in conjunction with external-beam therapy.

Long-term results with improved implant techniques are becoming available and early results are encouraging for a select population. A large multi-institution trial compared the results of radical prostatectomy, radiation therapy, and

interstitial radiotherapy in men with low-, intermediate-, and high-risk prostate cancer. Brachytherapy was equivalent to the two traditional modalities in terms of PSA recurrence rates for low-risk patients. However, the rates of recurrence were significantly higher in those men with intermediate- and high-risk cancers; specifically, men with a Gleason score ≥ 7 or a PSA level > 10 ng/mL. A typical dose used for interstitial iodine therapy is 145 Gy delivered to the periphery of the prostate. The dose is lower for palladium implants due to the higher dose rate.

High–dose-rate (HDR) devices Besides permanent implants, which deliver low-dose-rate (LDR) radiotherapy, brachytherapy for prostate cancer has been delivered using temporary high-dose-rate devices, usually in patients with locally advanced disease. In this technique, a high dose (minimum, approximately 5 Gy) is delivered to the prostate over ≤ 1 hour by remotely inserting a highly radioactive source into catheters placed into the prostate under ultrasound guidance while the patient is under anesthesia. Several treatments are given on separate occasions, and external-beam radiation is used for approximately 5 weeks as well.

As prostate cancer is increasingly associated with favorable survival outcomes, the basis for patient selection of primary therapy has shifted toward consideration of health-related quality of life (HRQOL). Madalinska et al found poorer levels of general and bowel HRQOL after EBRT, whereas RP was associated with more prevalent urinary incontinence and erectile dysfunction *(Madalinska JB, Essink-Bot ML, de Koning HJ, et al: J Clin Oncol 20:1619-1628,2001).* Wei et al showed that urinary irritative and hormonal HRQOL concerns are more prevalent after brachytherapy or external radiation than after prostatectomy (urinary incontinence, bowel, and sexual HRQOL in this study were affected similarly as in previous reports). These results provide a greater understanding about potential outcomes and long-term treatment complications to help guide patients in determining their therapy choices *(Wei JT, Dunn RL, Sandler HM, et al: J Clin Oncol 20:557-566, 2002).*

The long-term consequences for normal tissue of delivering large doses per fraction using this technique are unclear. Also, long-term outcome data on tumor control are not yet available.

Medications and devices to manage impotence after prostatectomy, external radiation, or brachytherapy

Treatments for post-prostatectomy impotence Treatment for post-prostatectomy impotence include: (1) sildenafil (Viagra), a phosphodiesterase inhibitor that is taken orally; and (2) prostaglandin E_1, administered as a urethral suppository (MUSE); (3) intercavernosal injection (Caverject, Edex); or (4) vacuum-pump erection aids that are useful for improving erections in men who have poor erectile function after prostatectomy, radiation therapy, or brachytherapy. These therapies are effective in 15%-40% of men with post-prostatectomy impotence. Insertion of a penile prostheses is typically offered to patients only after unsuccessful trials with the above less invasive interventions.

DETECTION AND TREATMENT OF RECURRENCE

Significance and definition of a rising PSA postradiation

The use of PSA following definitive therapy (either radiotherapy or radical prostatectomy) can detect very early recurrences that may be amenable to salvage treatment. A rising PSA profile following radiotherapy is unequivocal evidence of the presence of a residual prostatic neoplasm. However, the definition of a rising PSA after radiation therapy varies in the literature. A 1996 consensus conference recommended that PSA failure be considered to have occurred after three consecutive PSA rises, with the rate of failure defined as halfway between the first rise and the previous PSA level.

A prospective trial of pelvic EBRT interdigitated with dose-escalating conformal HDR prostate brachytherapy was performed on patients with intermediate-risk prostate cancer by Martinez and others. A total of 207 patients were treated with pelvic EBRT and increasing HDR brachytherapy boost doses (5.50-11.5 Gy/fraction) during 5 weeks. A recently reported analysis divided these patients into 2 dose levels: low-dose biologically effective dose < 93 Gy (58 patients) and high-dose biologically effective dose > 93 Gy (149 patients). With median follow-up of 4.4 years, the actuarial 5-year biochemical control rate was 74%. The 5-year biochemical control rate for the low-dose group was 52%; the rate for the high-dose group was 87% ($P < .001$), although the follow-up time was shorter for the high-dose group. This study shows that HDR prostate brachytherapy in combination with pelvic EBRT can deliver substantial freedom from failure rates. Randomized trials would be useful to compare this modality with other prostate cancer treatments *(Martinez A, Gustafson G, Gonzalez J, et al: Int J Radiat Oncol Biol Phys 53:316-327, 2002).*

Moreover, patients with a rising PSA after irradiation may be a heterogeneous group, including patients with truly localized failure, as well as those with metastatic disease. Also, certain patients will have a slowly rising PSA after radiation and may not require additional treatment. In patients who do not receive androgen ablation, the 5-year actuarial risk of distant metastasis from the time that the PSA begins to rise is ~50%.

Treatment recommendations for recurrence postirradiation

In general, men who have clear evidence of a rising PSA level 2 years after definitive radiotherapy for localized prostate cancer should be advised about the options of either hormonal therapy (see "Treatment of locally advanced disease [T3, T4]" below), salvage surgery, observation, or experimental therapy.

If patients have minimal comorbidity, good life expectancy, and only local evidence of disease recurrence, salvage surgery is an option but should be preceded by a bone scan, CT scan, cystoscopy, and extensive counseling because urinary difficulties after salvage prostatectomy are substantial and highly prevalent.

TREATMENT OF LOCALLY ADVANCED DISEASE (T3, T4)

The treatment of patients with locally advanced prostate cancer is radiation therapy (EBRT with or without HDR interstitial therapy), androgen ablation plus external radiation, or radical prostatectomy with or without androgen deprivation.

EBRT± HDR interstitial therapy For patients with locally extensive prostate cancer, local failure remains a potential problem after EBRT. This has prompted investigations into alternative means to intensify therapy.

One strategy has been to deliver large fractions of radiotherapy using HDR interstitial techniques in combination with external-beam radiation treatment. The large interstitial fractions, which may be on the order of 5 Gy, deliver a high dose to the prostate but spare normal tissues, due to the rapid dose fall-off outside of the implanted volume. Early experience with this strategy is encouraging, but long-term data on outcome, particularly in patients with locally extensive disease, and on morbidity, are awaited.

Patients with locally advanced prostate cancer probably are not good candidates for permanent prostate implants. Patients with stage T3-T4 tumors are at high risk of gross extraprostatic involvement, and this localized therapy may not offer adequate dosimetric coverage of extraprostatic disease.

Androgen ablation + external radiation therapy Recently, two potential benefits of the use of transient androgen ablation prior to external radiotherapy have been identified. First, there may be some synergy between the apoptotic response induced by androgen deprivation and radiotherapy that may increase local control.

Second, androgen deprivation results in an average 20% decrease in prostate volume. This volume reduction not only may reduce the number of target cells, and thereby improve tumor control, but also may shrink the prostate and, thus, diminish the volume of rectum and bladder irradiated during conformal therapy. Complete androgen blockade can be achieved with the luteinizing hormone–releasing hormone (LHRH) agonists leuprolide acetate (Lupron) or goserelin acetate (Zoladex) plus flutamide (Eulexin), bicalutamide (Casodex), or nilutamide (Anadron, Nilandron).

In addition, since distant metastases are the first manifestation of disease recurrence in many patients with prostate cancer, the use of early androgen deprivation may possibly delay, or even prevent, the development of metastatic disease.

Whether the combination of androgen ablation and radiation therapy affords a survival advantage in patients with locally advanced disease has not been definitively established (see box).

The RTOG has published mature data comparing 4 months of androgen ablation and radiation therapy with irradiation alone (RTOG 86-10). Significant improvements were seen in the combined-modality group at 8 years with respect to multiple clinical end points. A significant benefit in overall survival has not yet been observed, although the trend favors the combined approach (51% vs 43% at 8 years) *(Pilepich MV, Winter K, Roach M, et al: Proc Am Soc Clin Oncol [abstract] 17:308a, 1998).* The results of a recent RTOG trial 99-02, presented at the 2000 ASCO meeting, compared patients treated with EBRT and 4 months of androgen ablation with an experimental arm that employed an additional 24 months of androgen ablation. This large trial of over 1,500 patients revealed an improvement in the 5-year survival rate with long-term androgen ablation (80% vs 69%, $P = .02$) for patients with poorly differentiated prostate cancer *(Hanks G, Lu J, Machtay M, et al: Proc Am Soc Clin Oncol [abstract] 19:327a, 2000).*

Radical prostatectomy ± adjuvant therapy

Surgical monotherapy can be considered a reasonable option for patients with locally advanced prostate cancer. Stage T3 disease can be successfully treated with low morbidity and significant reductions in risk of local recurrence, with clinical overstaging (up to 26%) reported by Yamada et al (Am J Clin Oncol, 1994). Well- and moderately differentiated cancers have cancer-specific survival rates of 76% at 10 years, comparable with that of other treatment modalities.The Mayo Clinic has one of the largest radical prostatectomy series for T3 disease, consisting of over 1,000 patients. In this population, of whom 34% received adjuvant therapy, 15-year cancer-specific survival and local recurrence rates were 77% and 21%, respectively. Ninety-eight men who were found to have nodal metastases following radical prostatectomy and pelvic lymphadenectomy were randomized to receive immediate androgen deprivation or be followed until clinical disease progression. At a median follow-up of 7 years, 18 of 51 men in the observation group had died, compared with only 4 of 47 in the treatment group ($P = .02$).

Treatment of node-positive disease

Until recently, the standard of care had been to perform frozen-section pathologic analysis on pelvic lymph nodes at the time of radical prostatectomy, prior to removal of the prostate. If this analysis revealed micrometastases, radical prostatectomy was thought to be contraindicated. Although retrospective in nature, recent data from several US centers, including one large study from the Mayo Clinic, have reported a survival benefit in men who undergo radical prostatectomy despite the presence of micrometastases to regional pelvic lymph nodes. These men tend to do better and survive longer when started on early hormonal therapy, either with orchiectomy or an LHRH agonist.

Radiation therapy Whether any local treatment adds to overall survival duration in patients with known nodal involvement is debatable. Some data from M. D. Anderson indicate a benefit from pelvic and prostate radiotherapy plus androgen ablation compared to androgen ablation alone. This matter deserves further study. However, the addition of radiotherapy may be indicated in many situations, especially in young men.

TREATMENT OF ADVANCED SYSTEMIC DISEASE

First-line therapies for advanced disease

The medical treatment of prostate cancer begins when a patient has either not responded to local treatment efforts or presents with advanced disease that cannot be treated effectively with surgery or radiation therapy.

First-line therapy for advanced disease is surgical or medical castration.

Bilateral orchiectomy The testes normally produce approximately 95% of the testosterone in human males, and bilateral orchiectomy reduces plasma testosterone levels by approximately 93%. Although there are other ways besides castration to lower serum testosterone (primarily through the estrogen

action of LHRH analogs; see below), bilateral orchiectomy has distinct advantages. These include the lack of compliance problems or the need to adjust dose to the patient's metabolic state, and the absence of the potentially fatal cardiovascular complications that are often seen with high-dose estrogen therapy (Table 3). Medical treatment also must be maintained for life and can be very costly. The psychological impact of castration is severe, however, and many men opt for medical therapy if given a choice.

LHRH analogs LHRH agonists, such as leuprolide acetate (7.5 mg SC monthly) and goserelin acetate (3.6 mg SC monthly), regulate the release of LH and thereby produce chemical castration. These agents spare the patient the psychological trauma of an orchiectomy and also are devoid of the cardiovascular side effects associated with estrogen treatment (Table 3).

Because LHRH analogs can cause a transient increase in testosterone and induce a "flare" response, an antiandrogen, such as flutamide, bicalutamide, and nilutamide, is utilized during the first month of LHRH therapy.

Antiandrogens block the effects of androgens at the prostate tissue level. These compounds appear to interfere with the binding of the active metabolite of testosterone, dihydrotestosterone, to its receptor within the prostate.

In the United States, the most commonly used antiandrogens are flutamide, bicalutamide, and nilutamide. Ketoconazole (Nizoral), an antifungal agent, is also used. As mentioned above, antiandrogens are added to LHRH analogs to block any transient stimulation of testosterone by these agents or to directly block any remaining androgens that may affect the prostate.

Combined androgen blockade Surgical or medical castration decreases circulating testosterone by 90%-95%. It has been demonstrated that the remaining androgens result from peripheral conversion of adrenal steroids. Several investigators have suggested that complete androgen blockade (CAB) or total androgen blockade (TAB), achieved by adding flutamide (250 mg PO tid), bicalutamide (50 mg PO daily), or nilutamide (150 mg PO daily) to castration, results in better disease control.

Although controversial, CAB is most likely beneficial only in patients with minimal symptoms and minimal disease on bone scan. Patients who present with widespread advanced disease and/or poor performance status do not appear to benefit from this approach.

DES Estrogen administration, in the form of diethylstilbestrol (DES), also produces chemical castration. DES inhibits prostate growth, primarily through inhibition of the hypothalamic-pituitary-gonadal axis, which blocks testicular synthesis of testosterone and thus lowers plasma testosterone. Since doses over 3 mg/d cause significant cardiovascular mortality, DES has fallen out of favor as a first-line therapy to induce castration.

Treatment recommendations A patient who presents with advanced prostate cancer requires medical or surgical castration. Although this has not definitely been demonstrated to increase the patient's life-span, the quality-of-life benefits gained from disease control are unquestioned. Controversy exists over

TABLE 3: Hormonal approaches to the treatment of metastatic prostate cancer

Method	Mechanism of action	Side effects
Surgical castration	Removes testicular androgens	Hot flashes (50%), psychological effects
Diethylstilbestrol (DES)	Inhibition of gonadotropin secretion	Gynecomastia, cardiovascular risks at high doses
LHRH analogs (goserelin, leuprolide)	Inhibition of gonadotropin secretion	Hot flashes (50%), less gynecomastia than DES, fatigue
Antiandrogens (bicalutamide, flutamide, nilutamide)	Block binding of dihydrotestosterone to its receptor	Abnormal liver function studies, diarrhea (10%)

LHRH = luteinizing hormone-releasing hormone

whether to start treatment early, when a patient is still asymptomatic, or to wait until symptoms develop. However, it is generally accepted that treatment should begin early. The primary goal of early androgen deprivation should be prolongation of survival or prevention of catrastrophic consequences of advanced disease (Table 4).

In patients with minimal bone involvement (usually defined as fewer than five lesions) and minimal symptoms, CAB is the treatment of choice. This can be accomplished by orchiectomy or the use of depot injections of leuprolide (7.5 mg SC monthly) or goserelin (3.6 mg SC monthly). Further androgen blockade is accomplished by the addition of an antiandrogen, such as flutamide (250 mg PO tid), bicalutamide (50 mg PO daily), or nilutamide (150 mg PO daily).

Patients presenting with widespread bone or soft-tissue disease can be treated with surgical castration alone. If medical castration therapy is used, treatment with an antiandrogen for 1 month after the initiation of castration therapy is recommended. This can be accomplished with flutamide, bicalutamide, nilutamide, or ketoconazole (400 mg PO tid).

Recently, the efficacy of bicalutamide monotherapy (150 mg/d) compared with flutamide + goserelin was tested in a randomized study of patients with histologically proven C or D disease. Fewer patients in the bicalutamide group experienced loss of libido ($P = .01$) and of erectile dysfunction ($P = .002$). Significant trends also were noted in the bicalutamide-treated patients with respect to their quality of life and social functioning, vitality, emotional well-being, and physical capacity. Bicalutamide monotherapy may represent a major advance in the treatment of hormone-naïve advanced prostate cancer.

Second-line hormonal therapies

Initial hormone ablation controls symptoms for 18 months to 2 years in the average patient. In the past, patients typically presented with new urinary symp-

TABLE 4: The incidence of complications from advanced prostate cancer with immediate vs deferred androgen deprivation

Complication	Immediate	Deferred
Pathologic fracture	2.3%	4.5%
Cord compression	2.0%	5.0%
Ureteric obstruction	7.0%	11.8%
Extraskeletal metastases	7.9%	11.8%

toms or new bone pain while receiving castration treatment, but with the advent of PSA determinations, most of these patients can be identified by a rising PSA prior to symptom onset. It is unclear whether these patients should be treated immediately or whether therapy should be delayed until the onset of symptoms.

Several strategies have been employed as secondary hormonal treatments. In general, responses are seen in about 20% of patients and usually last approximately 6 months.

Addition or subtraction of an antiandrogen If a patient has been receiving monotherapy, an antiandrogen is typically added, but responses are seen in only about 10% of patients. In patients who have been treated with CAB, omitting the antiandrogen from the regimen can cause a paradoxical shrinkage of measurable disease, a decrease in serum PSA, and/or a lessening of symptoms in 10%-25% of patients. Thus, the addition or subtraction of the antiandrogen has become the next step for patients in whom initial hormone therapy is ineffective. If this measure fails, another second-line agent is often employed.

Aminoglutethimide (Cytadren) and hydrocortisone have been widely used. Aminoglutethimide is started at a dose of 125 mg PO qid and increased to 250 mg PO qid. It is associated with significant side effects, including lethargy, weakness, rash, and fever.

Hydrocortisone (20 mg PO bid) alone affords significant pain relief, as well as occasional objective tumor responses.

Ketoconazole, with or without hydrocortisone, is also used. Ketoconazole is started at a dose of 200 mg PO tid and then escalated to a total dose of 400 mg tid. The 1,200-mg daily dose is associated with nausea and vomiting, however, and can result in severe liver injury. Patients receiving high-dose ketoconazole need to be monitored carefully for signs and symptoms of liver damage, and the drug should be stopped immediately if liver enzymes become elevated.

Chemotherapy for hormone-refractory disease

Despite the effectiveness of initial hormonal therapy, metastatic prostate cancer is an incurable disease, with patients surviving a median of 9-12 months after the development of androgen insensitivity.

TABLE 5: Chemotherapy regimens for prostate cancer

Drug/combination	Dose and schedule
Estramustine/etoposide	
Estramustine	15 mg/kg/d PO on days 1-21
Etoposide	50 mg/m^2/d PO on days 1-21
Repeat cycle every 28 days	
Pienta KJ, Redman B, Hussain M, et al: J Clin Oncol 12:2005–2012, 1994.	
Mitoxantrone/prednisone	
Mitoxantrone	12 mg/m^2 IV on day 1
Prednisone	5 mg PO bid
Repeat cycle every 21 days	
Tannock IF, Osoba D, Stockler MR, et al: J Clin Oncol 14:1756–1764, 1996.	
Leuprolide/flutamide	
Leuprolide	1 mg/d SC
Flutamide	250 mg PO tid
NOTE: Leuprolide, 7.5 mg depot IM every 28 days, is usually given instead of the daily SC injections.	
Crawford ED, Eisenberger MA, McLeod DG, et al: N Engl J Med 32:419–424, 1987.	
Goserelin/flutamide	
Goserelin	3.6 mg SC every 28 days
Flutamide	250 mg PO tid
Jurincic CD, Horlbeck R, Klippel KF: Semin Oncol 18(suppl 6):21–25, 1991.	
Taxotere/estramustine/prednisone (TEP)	
Docetaxel (Taxotere)	70 mg/m^2 IV 1-hour infusion on day 2
Estramustine	280 mg PO tid on days 1-5, 7-11
Prednisone	10 mg PO one daily continuously
Warfarin	2 mg PO given daily to all patients
Dexamethasone	20 mg PO 12 hours, 6 hours, and immediately prior to each docetaxel infusion may also be given to patients
Oudard S, Beuzeboc P, Dourthe LM, et al: Proc Am Soc Clin Oncol 21:177a, 2002.	

Table prepared by Ishmael Jaiyesimi, DO

One very recent advance is the acceptance of PSA as a surrogate marker for response in hormone-refractory prostate cancer. Currently, a PSA decline of $< 50\%$ from pretreatment baseline, which persists for at least 4 weeks, is considered a partial response in clinical trials. Although not proven in a phase III setting, utilization of PSA levels has helped identify new, potentially active chemotherapy regimens for use in patients with advanced androgen-independent disease (Table 5).

Mitoxantrone plus prednisone The combination of mitoxantrone (Novantrone) and prednisone has been approved for use in patients with hormone-refractory prostate cancer who are experiencing pain. Mitoxantrone

(12 mg/m^2 IV) is administered every 3 weeks. Prednisone is given as a 10-mg oral daily dose (5 mg bid). Toxicities of the combination include leukopenia and thinning of the hair.

Estramustine (Emcyt) is a chemohormonal agent that combines an estrogen molecule with a nitrogen mustard molecule. This unique agent binds to the nuclear matrix and to microtubule-associated proteins in the cytoplasm. In so doing, it synergizes the effects of the topoisomerase II inhibitor etoposide (acting within the nucleus) as well as the vinca alkyloids and taxanes (inhibiting microtubule formation in the cytoplasm). Several active regimens have been developed based on these properties; all of them have response rates of approximately 50%, as measured by PSA decline or a 50% decrease in the size of soft-tissue disease:

Estramustine (280 mg tid) and vinblastine ([Velban] 4-6 mg/m^2/wk IV) for 6 weeks every 8 weeks. Toxicities include nausea and leukopenia.

Estramustine (280 mg tid PO × 3 d) and paclitaxel ([Taxol] 90 mg/m^2/IV on day 2) for 6 weeks every 8 weeks. Toxicities include leukopenia.

Estramustine (280 mg tid PO × 5 d) and docetaxel ([Taxotere] 60 mg/m^2/IV on day 3) every 21 days. Toxicities include nausea, fatigue, and leukopenia.

Bisphosphonates for advanced prostate cancer

Bisphosphonates inhibit osteoclast activation. In a recent study, it was demonstrated that zoledronic acid (Zometa) significantly decreased pain associated with bone metastases as well as fractures in patients undergoing chemotherapy for hormone refractory prostate cancer. Zoledronic acid has been approved for use in patients with skeletal metastases and hormone refractory prostate cancer.

Radiation therapy for palliating bone metastasis

Radiotherapy is very effective in controlling local pain associated with skeletal prostate metastasis. In general, a treatment regimen of 30 Gy over 10 treatments results in rapid and durable local symptom control and a reduced dependence on analgesics.

For patients with more extensive bone involvement causing pain that may be practically difficult to address with localized external-beam techniques, alternatives include wide-field irradiation (ie, hemibody radiation) or systemic administration of radioactive bone-seeking isotopes that can deliver therapeutic doses to skeletal metastatic disease. Radioactive isotopes used in this fashion include strontium-89 chloride (Metastron) and samarium SM 153 lexidronam (Quadramet). A more detailed discussion of these approaches can be found in chapter 39.

TREATMENT OF MEDICAL EMERGENCIES

There are few medical emergencies in patients with prostate cancer. However, because of the predilection of this cancer to metastasize to the spine, the danger of spinal cord compression is always present. Patients with cord compres-

sion typically present with minimal symptoms; back pain or sciatic-type pain are the most common complaints. Paresthesias and sensory loss may occur but are usually mild. Loss of sphincter control or motor function are typically late signs.

Patients with suspected cord compression should have their spinal cord visualized by MRI or CT myelography. If there is to be any delay in visualizing the spinal cord, administration of steroids, usually in the form of dexamethasone (4-6 mg q6-8h) can avert the development of paralysis. The steroids can then be tapered rapidly if no compression is present. Confirmed spinal cord compression is treated with steroids, followed by irradiation (usually 30 Gy in 10 fractions) to the affected area.

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CHAPTER 18

Testicular cancer

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Testicular cancer, although an uncommon malignancy, is the most frequently occurring cancer in young men. In the year 2003, an estimated 7,600 cases of testicular cancer will be diagnosed in the United States. For unknown reasons, the incidence of this cancer has increased since the turn of the century, from 2 cases per 100,000 population in the 1930s, to 3.7 cases per 100,000 population from 1969 to 1971, to 5.4 cases per 100,000 population from 1995-1999.

Most testicular tumors are of germ-cell origin. These cancers are uniquely sensitive to chemotherapy and are considered the model for the treatment of solid tumors. Perhaps the most controversial area in the management of germ-cell tumors is the proper approach to early-stage disease; ie, surveillance vs primary lymphadenectomy (for nonseminoma germ-cell tumors) or radiation therapy (for seminomas). In advanced disease, chemotherapy plays an essential role, but novel treatment regimens are currently being evaluated through multi-institution clinical trials.

Epidemiology

Age Testicular cancer can occur at any age but is most common between the ages of 15 and 35 years. There is a secondary peak in incidence after age 60. Seminoma is the most common histology in the older population but is rare in those younger than age 10.

Race Testicular cancer is rare in African-Americans, occurring at a rate of 1.4 per 100,000 population. Incidence of this cancer has increased in whites during the 20th century but has remained flat in African-Americans.

Geography Denmark has the highest incidence of testicular cancer; the Far East has the lowest.

Primary site Germ-cell tumors present most commonly in the testis (90%) and only infrequently in extragonadal sites (10%). The most common extragonadal sites (in decreasing order of frequency) are the retroperitoneum, mediastinum, and pineal gland. Many patients presumed to have a primary retroperitoneal germ-cell tumor may have occult germ-cell tumors of the testicle. This possibility should be evaluated with testicular ultrasonography, especially when the retroperitoneal tumor is predominantly one-sided.

Survival The 5-year survival rate for all patients with a germ-cell tumor is ~95%. Cure rates are highest for early-stage disease, which is treated primarily

TABLE 1: Anticipated cure rates in patients with germ-cell tumors, according to disease stage

Stage	Incidence at presentation (%)	Cure rate (%)
I (testis alone)	40	100
II (extension to retroperitoneal lymph nodes)	40	98
III (disseminated disease)	20	80

with surgery or radiation therapy (early seminoma), and lower for advanced disease, for which chemotherapy is the primary therapy (Table 1).

Etiology and risk factors

The specific cause of germ-cell tumors is unknown, but various factors have been associated with an increased risk of this malignancy.

Prior testicular cancer Perhaps the strongest risk factor for germ-cell tumors is a previous history of testicular cancer. Approximately 1%-2% of patients with testicular cancer will develop a second primary in the contralateral testis over time. This represents a 500-fold increase in incidence over that in the normal male population.

Cryptorchidism Patients with cryptorchidism have a 20- to 40-fold increased risk of developing germ-cell tumors compared with their normal counterparts. Orchiopexy, even at an early age, appears to reduce the incidence of germ-cell tumor only slightly (if at all). Of note, in ~10% of patients with cryptorchidism who develop germ-cell tumors, the cancer is found in the normally descended testis. Biopsies of nonenlarged cryptorchid testes demonstrate an increased incidence of intratubal germ-cell neoplasm, a presumed precursor lesion.

Genetics Klinefelter's syndrome (47XXY) is associated with a higher incidence of germ-cell tumors, particularly primary mediastinal germ-cell tumors. For first-degree relatives of individuals affected with 47XXY, approximately a 6- to 10-fold increased risk for germ-cell tumors has been observed. In addition, patients with Down syndrome have been reported to be at increased risk for germ-cell tumors. Also thought to be at greater risk are patients with testicular feminization, true hermaphrodites, individuals with persistent müllerian syndrome, and persons with cutaneous ichthyosis.

Family history Although familial testicular cancer has been observed, the incidence among first-degree relatives remains low. One investigator, however, reported a sixfold increased risk among male offspring of a testicular cancer patient.

Environment Numerous industrial occupations and drug exposures have been implicated in the development of testicular cancer. Although exposure to di-

ethylstilbestrol (DES) in utero is associated with cryptorchidism, a direct association between DES and germ-cell neoplasm is weak at best.

At least two reports have suggested an increased risk of testicular cancer among individuals exposed to exogenous toxins, such as Agent Orange and solvents used to clean jets.

Prior trauma, elevated scrotal temperature (secondary to use of thermal underwear, jockey shorts, and electric blankets), and recurrent activities, such as horseback riding and motorcycle riding, do not appear to be related to the development of testicular cancer.

No supporting findings substantiate a viral etiology.

Fertility An increased risk of infertility exists for men with unilateral testicular cancer successfully treated with orchiectomy. For example, 40% of patients have subnormal sperm counts, and by 1 year, 25% continue to have subnormal sperm counts.

Signs and symptoms

Local disease

Scrotal mass The most common complaint of patients on presentation is a painless scrotal mass, which, on physical examination, cannot be separated from the testis. Not infrequently, the mass may be painful and thus mimic epididymitis or testicular torsion.

Hydrocele Approximately 20% of patients with germ-cell tumors have an associated hydrocele.

Inguinal adenopathy Patients generally do not have inguinal adenopathy in the absence of prior scrotal violation.

Other symptoms include low back pain (from retroperitoneal adenopathy) and gynecomastia (usually bilateral). In cases of massive retroperitoneal lymphadenopathy, abdominal pain, nausea, vomiting, and constipation may be reported.

Disseminated disease

Patients with disseminated germ-cell tumors usually present with symptoms from lymphatic or hematogenous dissemination. Mediastinal adenopathy may be associated with chest pain or cough. Supraclavicular lymphadenopathy may also be present.

Hematogenous spread to the lungs may be associated with dyspnea, cough, or hemoptysis. Infrequently, patients with extensive disease may present with signs and symptoms of CNS metastases or bone pain from osseous metastases (most common in patients with seminoma).

Metastases to the liver are not uncommon and may manifest as fullness in the upper abdomen or vague abdominal discomfort. More likely, they will be iden-

The cumulative 10-year risk of developing metachronous testicular cancer for patients with extragonadal germ cell tumors is 10.3%. Patients with extragonadal tumors of the retroperitoneum and nonseminomatous cell type have a 14.3% 10-year risk for the development of metachronous testicular cancer *(Hartman JT, Fossa SD, Nichols CR, et al: J Natl Cancer Inst 93:1733-1738, 2001).*

tified on CT scan in an otherwise asymptomatic patient.

Primary mediastinal germ-cell tumors

Primary mediastinal germ-cell tumors are associated with several unique syndromes, including Klinefelter's syndrome and acute megakaryocytic leukemia. In addition, mediastinal tumors have a great propensity for the development of non–germ-cell malignant histology as a major component of the tumor (eg, embryonal rhabdomyosarcoma, adenocarcinoma, and peripheral neuroectodermal tumor).

Screening and diagnosis

Screening

Self-examination Testicular self-examination is both simple to learn and safe to perform. The rarity of this disease, however, calls into question the value of routine aggressive screening procedures.

Testicular biopsy Testicular biopsy of a suspicious lesion is not recommended. Approximately 95% of patients with a mass within the testicle have a malignancy. Orchiectomy is the preferred treatment for patients with a testicular mass.

Carcinoma in situ (CIS) appears to be the precursor lesion for most testicular germ-cell tumors, except spermatocytic seminoma. Most patients harboring CIS can be expected to develop testicular cancer but with a latency period of a decade or more. The incidence of CIS in infertile men is about 0.6%. In patients with prior testicular cancer, biopsy will reveal CIS in the contralateral testis at a rate of ~5%-6%. Men with a history of cryptorchidism and presumed extragonadal germ-cell tumor are at greater risk for CIS. Some investigators suggest routine biopsy of the contralateral testis in men with CIS.

Diagnosis

Ultrasonography can reliably identify masses within the testis. In virtually all patients, ultrasonography can distinguish a testicular from an extratesticular mass and may detect lesions that are not palpable on physical examination. Ultrasonographic findings cannot consistently differentiate benign from malignant tumors of the testis (95% of such masses are malignant). Most patients with testicular cancer, especially seminoma, have hypoechoic lesions compared to adjacent tissue. Nonseminomatous tumors, however, may have mixed signals, including hyperechoic masses, which are commonly seen with teratoma.

Virtually all adult patients with germ-cell tumors have increased copies of isochromosome 12p, usually as i(12p). This is a useful marker in patients with undifferentiated tumors who fit the clinical profile of patients with germ-cell malignancy.

Serum markers Serum levels of β-subunit human chorionic gonadotropin (β-hCG) and α-fetoprotein (AFP) are elevated in ~80%-85% of patients with extensive germ-cell tumors. Patients with pure seminoma may have elevated levels of β-hCG but not AFP (a significantly elevated AFP level usually indicates the presence of nonseminomatous germ-cell elements). False-positive β-hCG levels can be seen in patients who have hypogonadism (cross-reactivity with luteinizing hormone) or who pursue the use of marijuana; AFP levels may be elevated in patients with liver dysfunction or hepatitis.

Inguinal orchiectomy When a testicular mass is discovered, the patient should undergo an orchiectomy through an inguinal incision.

Trans-scrotal incisions or biopsies should not be performed, as they ultimately lead to aberrant lymphatic drainage from the tumor.

Staging evaluation

The principal objective of the staging evaluation is to ascertain whether the patient has early-stage disease (which is amenable to local therapy, such as retroperitoneal lymphadenectomy [for nonseminoma] or radiation therapy [for seminoma]) or disseminated disease (which requires chemotherapy).

Chest radiograph A chest x-ray can determine whether or not a patient has gross supradiaphragmatic metastases, which would mandate initial chemotherapy.

Chest CT In patients with a normal chest x-ray, chest CT is recommended in both patients with seminoma and those with nonseminoma when abdominal adenopathy is found, to rule out occult metastases within the lungs or mediastinum. If such metastases are present, the patient should be treated with primary chemotherapy.

Abdominopelvic CT provides important information about the retroperitoneal lymph nodes. Usually, periaortic adenopathy is noted on the ipsilateral side of the primary tumor. Patients with primary retroperitoneal germ-cell tumors often show an enlarged retroperitoneal mass in the midline. Although hepatic metastases are infrequent, at present CT is the most viable method of determining these metastatic lesions.

Other scans In the absence of symptoms or signs, a CT scan (or MRI) of the head and radionuclide bone scan are unnecessary. A lymphangiogram is rarely used today to identify microscopic nodal involvement in patients with stage I disease who choose to undergo surveillance.

Pathology

Germ-cell tumors are classified into two broad histologic categories: seminoma and nonseminomatous germ-cell tumor. Patients with seminoma who have increased AFP levels or any focus of nonseminomatous germ-cell tumor components (including teratoma) are considered to have a nonseminomatous germ-cell tumor.

Seminoma

Seminoma is the most common single histology, accounting for ~30% of all germ-cell tumors. Up to 10% of seminomas have focal syncytiotrophoblast cells, thought to be the source of β-hCG in some cases.

Spermatocytic seminoma, a rare subset of germ-cell tumors, often grows to large size, occurs almost exclusively in men older than 50, and rarely, if ever metastasizes.

Nonseminoma

Embryonal carcinoma is composed of large pleomorphic cells with different architectural patterns. This tumor may be associated with an elevation in the serum levels of β-hCG and/or AFP.

Endodermal sinus tumor (yolk sac carcinoma) is the most common testicular tumor seen in infants and young children. Like embryonal carcinoma, yolk sac tumor has a variety of architectural patterns. This tumor is associated with an elevated serum level of AFP.

Choriocarcinoma, as a pure entity, is one of the least common germ-cell tumors. These tumors have a great propensity for hematogenous spread, often skipping the retroperitoneum. Choriocarcinoma is associated with an increased serum level of β-hCG.

Teratoma is a generally benign tumor with elements from each of the germ layers (ectoderm, mesoderm, and endoderm). Teratoma is uncommonly seen as the sole histology in primary tumors, but it is frequently associated with

TABLE 2: Staging systems for testicular cancer

Royal Marsden system	TNM system	Description
I	N0	Disease confined to the testis and peritesticular tissue
II	N1, N2a	Fewer than six positive lymph nodes without extension into retroperitoneal fat; no node > 2 cm (infradiaphragmatic)
A < 2 cm B 2-5 cm C > 5-10 cm D > 10 cm		
	N2b	Six or more positive lymph nodes, well-encapsulated and/or retroperitoneal fat extension; any node > 2 cm
	N3	Any node > 5 cm
III	M+	Supradiaphragmatic and infradiaphragmatic adenopathy (no extralymphatic metastasis)
IV		Disseminated disease (lung, liver, bone)

other histologic elements, including those previously mentioned. Of patients with residual disease following chemotherapy for nonseminomatous germ-cell tumor, ~45% have teratoma in resected specimens.

A subset of patients with immature teratoma that contains non–germ-cell histologies (eg, sarcoma, adenocarcinoma) has been reported. In contrast to most teratomas, these tumors may grow locally and can be lethal. In addition, late recurrences of both teratoma and carcinoma have been reported in patients with teratoma. Serum markers are normal in patients with pure teratoma.

Pattern of spread

Testicular cancer spreads in a fairly predictable fashion: from the testicle to the retroperitoneal lymph nodes and later hematogenously to the lungs or other visceral sites. Only 10% of patients present with hematogenous metastases (usually in the lungs) in the absence of discernible retroperitoneal adenopathy.

Staging systems

Clinical staging systems (Royal Marsden and TNM systems) for testicular cancer are outlined in Table 2. These staging systems help define the population for appropriate primary therapy.

Good- and poor-risk subgroups For patients with nonseminomas who are candidates for chemotherapy, other staging systems (such as those by Indiana University and Memorial Sloan-Kettering Cancer Center) were developed to segregate patients into good- and poor-risk categories. More recently, the International Germ Cell Collaborative Group Consensus Conference formulated a classification that more clearly defines good- and poor-risk disease (Table 3), and it is currently being used to stratify patients in ongoing trials.

Treatment

SURGICAL TREATMENT OF STAGE I OR II DISEASE

Initial intervention for testicular cancer is radical inguinal orchiectomy. Orchiectomy may be deferred temporarily in patients with advanced-stage disease in whom the diagnosis of nonseminomatous germ-cell tumor can be made on clinical grounds (elevated markers). In such patients, an orchiectomy must be performed sooner or later, as there is incomplete penetration of chemotherapy into the testes.

Further therapy hinges on the pathologic diagnosis. In general, pure seminomas (normal AFP level with or without an elevated β-hCG level) are treated with radiotherapy and/or chemotherapy, whereas most nonseminomas are treated with surgery and/or chemotherapy.

TABLE 3: International Germ Cell Collaborative Group Consensus Conference criteria for good- and poor-risk testicular cancer patients treated with chemotherapy

NONSEMINOMA

Good prognosis

All of the following:

- AFP < 1,000 ng/mL, hCG < 5,000 IU/L, and LDH < 1.5 × upper limit of normal
- Nonmediastinal primary
- No nonpulmonary visceral metastasis

Intermediate prognosis

All of the following:

- AFP = 1,000-10,000 ng/mL, β-hCG = 5,000-50,000 IU/L, or LDH = 1.5-10 × normal
- Nonmediastinal primary site
- No nonpulmonary visceral metastasis

Poor prognosis

Any of the following:

- AFP > 10,000 ng/mL, hCG > 50,000 IU/L, or LDH > 10 × normal
- Mediastinal primary site
- Nonpulmonary visceral metastasis present

SEMINOMA

Good prognosis

- No nonpulmonary visceral metastasis

Intermediate prognosis

- Nonpulmonary visceral metastasis present

Inguinal orchiectomy

In addition to removal of the testis, the spermatic cord is dissected high into the retroperitoneum. The vas deferens is isolated from the testicular vessels and ligated separately with a permanent suture. Also, the testicular vessels are freed from the peritoneum and carefully ligated with a permanent suture.

Retroperitoneal lymphadenectomy (nonseminomas)

For patients with nonseminomatous testicular cancer and either no evidence or a small volume of disease on CT (stage I [N0] or stage II [N1, N2a, N2b] disease), retroperitoneal lymphadenectomy (RLND) is generally indicated because it (1) accurately and definitively defines the presence or absence of retroperitoneal metastases and (2) removes the retroperitoneum as a site of recurrence, thus obviating the need for surveillance with CT.

RLND can be accomplished transperitoneally or retroperitoneally through a thoraabdominal approach. The thoracoabdominal approach is more technically difficult but eliminates the risk of postoperative small bowel obstruction and usually requires a shorter hospital stay.

With the advent of laparoscopic techniques, Janetschenk et al recently reported successful results in 73 patients who underwent unilateral nerve-sparing retroperitoneal lymph node dissection. After a steep learning curve, ejaculation was preserved in all patients with no recurrences due to surgical failure. Patients with positive lymph nodes, however, routinely receive chemotherapy *(Janetschenk G, Hobisch A, Peschel R, et al: J Urol 163:1793-1796, 2000).*

Nerve-sparing surgery Regardless of the approach, urologic oncologists recommend a unilateral, nerve-sparing procedure. For right-sided tumors, the medial border of the template is the midpoint of the aorta, and for left-sided tumors, the medial border is the midpoint of the inferior vena cava (IVC). The sympathetic trunks responsible for normal bladder neck closure during ejaculation course lateral to the aorta on the left side and behind the IVC on the right side. Below the inferior mesenteric artery, both sympathetic trunks send branches to the region anterior to the aorta. The branches coalesce and then pass to the bladder neck.

Critical aspects of nerve-sparing surgery include preservation of the ipsilateral sympathetic nerve trunk and bilateral preservation of branches below the level of the inferior mesenteric artery. In our experience and that of other authors, it is possible to maintain normal ejaculatory function in virtually all patients using this technique.

SURVEILLANCE (NONSEMINOMAS)

In patients with clinical stage I disease (normal serum markers and normal CT scans of the chest and abdomen), surveillance is a reasonable option. In patients with nonseminomatous germ-cell tumors, the risk of recurrence is approximately 25%. Thus, close follow-up with chest x-ray, serum markers (ß-hCG and AFP), and physical exam should be performed monthly during the first year, every 2 months during the second year, and every 3-4 months during the next several years. Similarly, abdominal CT scans should be performed every 2 months during the first year and every 4 months during the second year.

When followed up in this way, most (not all) patients will be detected with low volume disease. If recurrence occurs, these cases should be curable with three cycles of BEP (bleomycin, 30 IU/wk × 9; etoposide, 100 mg/m^2 on days 1-5 and 29-34; and Platinol [cisplatin]) or four cycles of EP (etoposide plus Platinol at the same doses) (see Table 4). About 10% of patients whose disease does recur present with higher volume disease and are not cured. Thus, diligent follow-up is crucial.

RADIATION THERAPY FOR STAGE I OR II SEMINOMAS

Seminomas of the testes are exquisitely sensitive to radiation. This characteristic, combined with their predictable lymphatic spread, makes these cancers amenable to radiotherapy. Since low radiation doses are used, acute and late side effects are few.

TABLE 4: Chemotherapy regimens for testicular cancer

Drug/combination	Dose and schedule
BEP	
Bleomycin	30 U IV bolus on days 2, 9, and 16
Etoposide	100 mg/m^2 IV infused over 30 minutes on days 1-5
Platinol (cisplatin)	20 mg/m^2 IV infused over 15-30 minutes on days 1-5
Repeat cycle every 21 days for 3 or 4 cycles.	
NOTE: Treat patients every 21 days on schedule, regardless of the granulocyte count. Reduce etoposide dose by 20% in patients who previously received radiotherapy or had granulocytopenia with fever/sepsis during the previous cycle. Patients receiving 4 cycles of BEP should get pulmonary function tests at baseline and at 9 weeks.	
Williams SD, Birch R, Einhorn LH, et al: N Engl J Med 316:1435–1440, 1987.	
EP	
Etoposide	100 mg/m^2 IV infused over 30 minutes on days 1-5
Platinol (cisplatin)	20 mg/m^2 IV infused over 15-30 minutes on days 1-5
Repeat cycle every 21 days for 4 cycles.	
NOTE: Treat patients every 21 days on schedule, regardless of the granulocyte count. Reduce etoposide dose by 20% in patients who previously received radiotherapy or had granulocytopenia with fever/sepsis during the previous cycle.	
de Wit R, Roberts JT, Wilkinson PM, et al: J Clin Oncol 19:1629–1640, 2001.	
VeIP	
Vinblastine	0.11 mg/kg/d on days 1 and 2
Ifosfamide	1.2 g/m^2/d IV on days 1-5
Platinol (cisplatin)	20 mg/m^2/d IV on days 1-5
Mesna	400 mg/m^2 IV bolus prior to first ifosfamide dose, then 1.2 g/m^2/d IV infused continuously for 5 days
Repeat cycle every 21 days for 4 cycles.	
Loehrer PJ, Lauer R, Roth BJ, et al: Ann Intern Med 109:540–546, 1988.	
Miller KD, Loehrer PJ, Gonin R, et al: J Clin Oncol 15:1427–1431, 1997.	
VIP	
VePesid (etoposide)	75 mg/m^2/d IV on days 1-5
Ifosfamide	1.2 g/m^2/d IV on days 1-5
Platinol (cisplatin)	20 mg/m^2/d IV on days 1-5
Mesna	400 mg IV bolus prior to the first ifosfamide dose, then 1.2 g/m^2/d IV infused continuously on days 1-5
Repeat cycle every 21 days for 4 cycles.	
Loehrer PJ, Lauer R, Roth BJ, et al: Ann Intern Med 109:540–546, 1988.	

Table prepared by Ishmael Jaiyesimi, DO

Stage I disease

Prophylactic radiotherapy vs chemotherapy vs surveillance Primary lymphatic drainage of the testes is to the para-aortic lymph nodes from the level of the renal vessels to the bifurcation of the aorta. Although ipsilateral pelvic nodal failures and, to a much lesser extent, inguinal failures occur following tumor resection by inguinal orchiectomy in patients with stage I disease, these sites are at a much lower risk of failure than the para-aortic region. Based on surveillance data, the overall incidence of disease failure without radiotherapy is 15%-27% (median, 20%), whereas only 2%-5% (median, 3%) of patients who are treated with radiotherapy relapse. Relapse rates with surveillance appear to be lower in patients with < 6 cm tumors, age > 34 years, and no lymphatic-vascular invasion.

Reiter and colleagues reported 100% of stage I seminoma cases were free of disease relapse after 2 cycles of carboplatin (400 mg/m^2). Median follow-up was 74 months *(Reiter WJ, Brodowicz T, Alavi S, et al: J Clin Oncol 19:101-104, 2001).*

Although surveillance appears to be a reasonable approach for patients with stage I disease, since 80% of these patients will be treated unnecessarily, follow-up is problematic because disease progression usually is not associated with symptoms until the tumor burden is large. Surveillance requires frequent abdominopelvic CT scans and chest x-rays for 4-5 years. Despite excellent salvage rates reported in patients who relapse while undergoing surveillance (initial salvage rates of approximately 90%, with ultimate salvage rates after relapse of approximately 95%), most groups have discontinued surveillance protocols in lieu of prophylactic radiotherapy to the draining lymphatics or chemotherapy. Those patients who do develop a recurrence usually receive four cycles of EP.

Several phase II trials have evaluated one to two cycles of carboplatin (Paraplatin) for prophylactic treatment of stage I seminomas. The preliminary results are comparable to those with radiotherapy in terms of recurrence rates, particularly when two cycles are used. Late toxicity data are lacking; thus, prophylactic carboplatin therapy is not considered to be a standard approach in this country.

Radiation fields and doses The radiotherapy portals typically include the para-aortic lymph nodes from T10-L5 and the ipsilateral hemipelvis, including the inguinal scar. However, recent studies that reduced the size of para-aortic fields and omitted hemipelvis radiation in selected patients (eg, those who have not undergone prior orchiopexy or other pelvic, inguinal, or scrotal surgery) are encouraging. Pelvic and/or inguinal failures occurred in $< 5\%$ of these patients. The smaller treatment volume reduces the dose to the remaining testicle and probably the risk of secondary malignancy.

The hemiscrotum is usually treated if the tumor penetrated the tunica albuginea, a trans-scrotal incision was performed, or orchiopexy was performed for cryptorchidism. Although treatment of the hemiscrotum for these reasons remains a standard practice, it has been questioned since the incidence of scro-

tal failure is low, even in the presence of these risk factors. In fact, some surgeons advocate trans-scrotal exploration to rule out benign lesions.

The sites listed above are treated with 25-30 Gy over 3-3.5 weeks, although some data suggest that 20 Gy is sufficient. The 5-year actuarial rate of disease freedom using such techniques is 97%, and the rate of overall survival is nearly 100% since the availability of platinum-based chemotherapy for salvage. A recent study by Fossa and colleagues randomized 478 men with stage I seminomas to receive irradiation of the para-aortic fields only. The actuarial rate of 3-year freedom from relapse was about 96% for both groups, although there were more pelvic relapses in patients given para-aortic radiation therapy only. The few failures observed following radiotherapy most often occur in the next echelon of lymph node drainage sites, such as the mediastinum or left supraclavicular fossa.

Side effects The acute side effects of radiotherapy are limited to nausea, vomiting, and infrequently diarrhea, all of which usually can be readily controlled with medication. Late toxicities are rare, although peptic ulcers (~5%) and marginally higher rates of second malignancies have been reported.

Permanent infertility from scattered radiation to the contralateral testis is uncommon, whereas prolonged aspermia for more than 1 year may occur, especially with irradiation of the hemiscrotum. Nevertheless, sperm banking is recommended for patients concerned about childbearing.

Stage II disease

The majority of patients with infradiaphragmatic para-aortic and/or pelvic adenopathy < 5 cm are treated with radiotherapy alone. Those with larger lymph node metastases are typically treated with platinum-based chemotherapy. Among patients who are candidates for radiotherapy, it is essential that renal function be preserved in case chemotherapy is necessary for salvage treatment. Recent preliminary evidence indicates that the 5-year freedom-from-failure rates may be improved to 97% by administration of neoadjuvant carboplatin combined with radiotherapy.

Radiation fields The radiotherapy fields are similar to those used for stage I disease except that the fields are widened to include any para-aortic or pelvic adenopathy with a 2- to 3-cm margin. In the past, mediastinal and supraclavicular treatment was standard in patients with stage II disease. However, data from several series revealed only a 3% rate of mediastinal/supraclavicular relapse. In addition, late cardiac toxicity has been reported. Although treatment to supradiaphragmatic sites has largely been abandoned in these cases, one report indicates that the rate of failures in the left supraclavicular fossa is higher than was previously believed.

The actuarial rate of freedom from disease at 5 years for patients with para-aortic adenopathy < 5 cm is ~90%, vs 85% for those with adenopathy > 5 cm and < 10 cm. Most of the data on the latter group of patients are from older studies in which patients often received prophylactic mediastinal and supraclavicular irradiation, and outcome may be poorer without such treatment.

Radiation doses The involved areas are usually treated with 30-35 Gy and the uninvolved areas, with 20-25 Gy. There is no evidence of a dose-response effect above 20 Gy for uninvolved areas and above 30 Gy for involved areas. Failures within the irradiated volume are anecdotal.

MEDICAL TREATMENT OF STAGE II NONSEMINOMAS

Over the past several years, the threshold for primary surgery in patients with stage II disease on CT scans has changed. At present, masses > 3 cm in greatest cross-sectional diameter are generally handled primarily with chemotherapy. For patients with tumor sizes ≤ 3 cm, primary RLND is considered the standard approach. It should be noted that up to 25% of patients with enlarged lymph nodes on CT scans will be found to have pathologic stage I (false-positive) disease by RLND.

Adjuvant chemotherapy for nonseminomas

The risk of systemic recurrence is 5%-10% in patients with pathologic stage I nonseminomas, 15%-30% in those with completely resected stage IIA (N2a) disease, and 30%-50% in those with stage IIB (N2b) disease. Recurrence usually occurs in the lungs within the first 24 months after surgery. The risk of retroperitoneal recurrence in patients with stage I, IIA, or IIB disease is < 1% after a properly performed RLND.

Following RLND, patients with complete resection of stage II disease can be considered candidates for adjuvant chemotherapy.

The decision of whether or not to prescribe adjuvant therapy following lymph node dissection is somewhat arbitrary and often depends on the patient's social circumstances and likelihood of adhering to close follow-up. A patient with completely resected carcinoma who undergoes RLND has a 70% chance for cure; thus, the majority of patients will never need chemotherapy. However, these patients must be monitored carefully with chest x-rays and serum marker determinations every month for 1 year, every 2 months for an additional year, and then every 6 months for the next 3 years. (CT scanning is not performed routinely unless clinically indicated.) The 30% of patients followed in such a manner who do develop a recurrence will present with a tumor of low volume (eg, small pulmonary metastases or elevated serum markers); nearly 100% of these patients should be cured with appropriate systemic therapy.

However, some patients with resected stage II disease elect to receive adjuvant chemotherapy to minimize the risk of cancer recurrence. For such therapy, two cycles of BEP (bleomycin, 30 IU/wk × 8; etoposide, 100 mg/m^2 on days 1-5 and 29-34; and Platinol, 20 mg/m^2 on days 1-5 and 29-34) are recommended (Table 4). It should be emphasized that in a patient who agrees to close follow-up, the chance of dying of cancer should be negligible in either scenario. For patients who have persistently elevated or increasing serum markers following RLND or who have undergone incomplete lymph node dissection, three cycles of BEP are indicated.

In a study of 75 patients with stage I nonseminomatous germ-cell tumors, compliance with clinical examinations was 61.5% in year 1 and 35.5% in year 2, whereas compliance for obtaining abdominal/pelvic CT was only 25% and 11.8% in years 1 and 2, respectively. Careful selection of highly motivated patients for surveillance is indicated.

TREATMENT OF STAGE III DISEASE

Seminomas

Chemotherapy is the treatment of choice for patients with stage III seminomas (see Table 4). The management of patients with bulky disease after chemotherapy (residual mass > 3 cm) is somewhat controversial. Investigators at Memorial Sloan-Kettering Cancer Center suggest that such patients require consolidation with radiotherapy or surgical removal of radiographically evident disease. More recent data from the Royal Marsden Hospital report a relapse rate of 10%-15% in patients with residual masses with or without postchemotherapy surgery or radiotherapy, supporting the practice of observation in patients with residual masses following chemotherapy.

Nonseminomas

As mentioned above, patients with nonseminomas being treated with chemotherapy can be classified as having good- or poor-risk disease (see Table 3).

Good-risk nonseminomas In patients with good-risk nonseminomas, three cycles of BEP given every 3 weeks or, alternatively, four cycles of etoposide plus Platinol without bleomycin (EP; at the same dosages) appear to yield equivalent results. More than 90% of good-risk patients should be cured with these therapies.

Two prospective randomized trials comparing cisplatin with carboplatin in good-risk patients with disseminated germ-cell tumors have demonstrated inferior results for carboplatin-containing regimens.

Postchemotherapy resection If a patient has persistent radiographic disease with normal serum markers 4-6 weeks following chemotherapy for a nonseminomatous germ-cell tumor, surgical resection should be performed when possible.

Postresection chemotherapy Histologic examination of residual disease will reveal necrotic fibrous tissue in ~45% of such cases, benign teratoma in ~45%, and persistent carcinoma in ~10%-15%. If persistent carcinoma is detected in the resected specimen, two additional cycles of cisplatin plus etoposide should be administered. For patients with complete resection of mature and immature teratoma or necrosis, no additional therapy is needed.

Poor-risk nonseminomas A cohort of patients with disseminated germ-cell tumors present with very advanced or poor-risk disease. "Poor risk" has been variously defined (see Table 3) but represents a patient population with a cure rate of ≤ 50% with standard cisplatin-based combination chemotherapy. Radiation is useful in the treatment of metastatic nonseminomas to the brain.

Chemotherapy During the past few years, several trials have evaluated a variety of combination regimens in patients with poor-risk disease (Table 4). They include the use of high-dose therapy, sequential therapy, and VIP (VePesid [etoposide], ifosfamide [Ifex], and Platinol). VIP appears therapeutically equivalent to BEP; however, for most patients with advanced disease, BEP is the preferred regimen because it produces less myelosuppression. In patients with underlying pulmonary dysfunction, VIP is preferred.

In a study by Bhatia et al, 65 patients with recurrent testicular cancer were treated with tandem cycles of high-dose etoposide plus carboplatin followed by peripheral stem-cell transplantation as initial salvage therapy. With a median follow-up of 39 months, 37 patients (57%) remain continuously disease-free with 3 additional patients (5%) disease-free with subsequent surgery. There was no treatment-related mortality.

Because of its success, high-dose chemotherapy and bone marrow transplantation (BMT) are currently being evaluated in a prospective intergroup trial comparing four cycles of BEP with two cycles of BEP followed by 2 tandem courses of high-dose chemotherapy plus BMT in previously untreated patients with poor-risk disease.

Postchemotherapy resection The ultimate goal of combination chemotherapy in these patients is resolution of all radiographically visible disease and normalization of tumor markers. If residual radiographic abnormalities persist in the lungs and/or abdomen, surgical resection of residual disease is indicated.

A postchemotherapy retroperitoneal lymph node resection must clear the region of residual disease. In general, postchemotherapy resections are extremely difficult, and incomplete resections are unacceptable. After the retroperitoneum is cleared of persistent radiographic disease, persistent pulmonary lesions are resected. In cases with residual disease in the retroperitoneum and thorax, RLND should be performed first. If necrosis is found, the disease within the chest can be observed. If teratoma or cancer is noted, the supradiaphragmatic disease should be resected.

Complicating factors associated with postchemotherapy resections include the risk of oxygen toxicity secondary to bleomycin, as well as intense fibrosis and adherence of residual disease to the aorta and other vital retroperitoneal organs. Inspired oxygen levels must remain below 35% to prevent bleomycin-related acute respiratory distress syndrome, which has a fatality rate $\geq 50\%$.

After successful resection, the only visible structures remaining should include the back muscles, nerves, anterior spinous ligament, aorta, IVC, renal vessels, kidneys, and ureters. Up to 20% of patients with advanced abdominal disease may require resection of a kidney or even the IVC. Operative mortality in centers with experience performing resections of these advanced-stage tumors should be $< 2\%$.

Postresection chemotherapy As mentioned, two additional cycles of chemotherapy are indicated for patients with persistent viable carcinoma in the resected

specimen. For patients with resected teratoma of nonviable necrotic tissue, no additional chemotherapy is warranted.

Salvage chemotherapy

Approximately 20%-30% of patients with disseminated germ-cell tumors do not attain a complete remission with induction chemotherapy or relapse after such therapy. These patients may be candidates for salvage chemotherapy. It should be noted that occasional patients may be erroneously classified as having recurrent disease based on false-positive markers or abnormal radiographic findings. Some of these false-positive results may be due to a growing teratoma, pseudonodules from bleomycin-induced pulmonary disease, or elevated markers from other causes, such as an elevated β-hCG level from marijuana usage, or cross-reactivity with luteinizing hormone or an elevated AFP level associated with hepatitis or liver dysfunction. Another cause of persistently elevated markers is a tumor sanctuary site (eg, in the testes or brain). Assuming that false disease progression has been ruled out, several approaches to salvage therapy are being used. When possible, autologous BMT is preferred. It can achieve slightly more durable response rates.

In a study of 32 patients with disease progression after high-dose platinum-based chemotherapy and hematopoietic stem-cell support, subsequent treatment outcomes were retrospectively reviewed. Surgical resection of all masses was the most effective; chemotherapy had marginal activity, and radiotherapy had no obvious benefit *(Fléchon A, Rivoire M, Biron P, et al: J Urol 165:1920-1926, 2001).*

VeIP Ifosfamide is one of a few drugs (including etoposide, gemcitabine [Gemzar], and paclitaxel [Taxol]) that has clinical activity in patients with cisplatin-refractory disease. As second-line therapy, VeIP (Velban [vinblastine], 0.11 mg/kg on days 1 and 2 (total dose = .22 mg/kg), plus ifosfamide, 1.2 g/m^2 [plus mesna (Mesnex)], plus Platinol, 20 mg/m^2; both on days 1-5) produces durable complete remissions in ~30% of patients previously treated with BEP chemotherapy (Table 4). Toxicity is primarily hematologic, which can be minimized with the use of colony-stimulating growth factor.

Seminoma Patients with recurrent seminoma appear to be more sensitive to salvage therapy. In a study by Miller et al, 24 patients with seminoma were treated with VeIP as second-line therapy (following relapse after cisplatin-etoposide combination therapy). Of the 24 patients, 20 (83%) achieved a complete response and 13 (54%) are long-term survivors, including 4 of 6 with extragonadal primary sites. Thus, initial salvage therapy in these patients should be VeIP (Table 4) rather than high-dose chemotherapy with bone marrow rescue.

High-dose chemotherapy with bone marrow rescue High-dose chemotherapy with tandem courses of carboplatin and etoposide plus autologous bone marrow rescue produces durable complete remission in 5%-10% of patients whose disease is overtly refractory to cisplatin. When this approach is used in patients with recurrent, but not cisplatin-refractory, disease, improved response rates are observed; ~50% of patients with recurrences of testicular cancer (excluding extragonadal recurrences) will be cured.

Surgery Some patients with recurrent disease appear to have localized or minimally metastatic disease. In such cases, "desperation" surgery may achieve a durable complete remission. A 25% cure rate was seen in a select group of patients with elevated serum markers who underwent such surgery at Indiana University. These patients had completely resected viable carcinoma without chemotherapy following surgery.

Other agents Few drugs besides etoposide and ifosfamide have activity in patients with cisplatin-refractory disease. Oral etoposide given in a chronic schedule (50 mg/m^2/d for 21 days) has produced objective responses in ~20% of patients who were previously treated with IV etoposide. Paclitaxel has a similar response rate in minimally pretreated patients (< six cycles). Gemcitabine produces a response rate of ~15% in patients with cisplatin-refractory disease. The Eastern Cooperative Oncology Group conducted a phase II trial of gemcitabine (1,000 mg/m^2) plus paclitaxel (110 mg/m^2) every week × 3 given every 4 weeks in patients with recurrent germ-cell tumor not thought to be curable with standard chemotherapy or surgery. Of 28 evaluable patients, 6 responded, including 3 complete responses (2 of whom are free of disease at 15+ and 25+ months).

Follow-up of long-term survivors

Delayed toxicity from systemic therapy

Delayed toxicity from systemic therapy for germ-cell tumors has been well characterized. In the absence of signs and symptoms, specific monitoring for these late effects is not generally warranted. A number of late effects have been observed.

Fertility problems and fetal malformation Fertility problems, manifested by azoospermia or oligospermia at or beyond 2 years, occur in 45%-55% of treated patients. No increased risk of fetal malformation has been observed in the offspring of men treated with chemotherapy for testicular cancer.

Cardiovascular disease The risk of hypertension or other cardiovascular disease may be increased in patients with testicular cancer who received chemotherapy, but this theory is controversial. The only exception is Raynaud's phenomenon, which occurs at a rate directly proportional to the number of cycles of cisplatin-based chemotherapy.

Renal and pulmonary toxicity Although renal and pulmonary dysfunction can occur acutely during therapy, long-term consequences from therapy are uncommon. A similar percentage of patients may suffer a late recurrence of the primary tumor. These late recurrences typically occur over 5 years (longest 32+ years) after primary therapy, and frequently present with an elevated serum level of AFP, and are particularly resistant to salvage chemotherapy. Thus, surgical resection of disease is the primary treatment strategy.

Secondary malignancies

Perhaps of greatest concern is the development of secondary malignancies.

Testicular cancer Approximately 1%-2% of patients may develop a second primary testicular cancer.

Other cancers Papers by Travis et al discuss testicular cancer patients' increased risk of many secondary cancers. They include acute leukemia, melanoma, as well as GI and GU cancers.

The contribution of chemotherapy and/or radiation therapy to the development of these other malignancies, as opposed to a natural propensity toward their development, is unknown. However, in several series, etoposide has been shown to pose an increased risk for the development of secondary leukemia (dose-related). In one paper by Travis and colleagues, both increased dosages of radiation therapy and cisplatin were associated with an increased risk for acute leukemia. Although these risks are real, they still are low compared with the risk of death caused by testicular cancers. Nonetheless, indiscriminate use of chemotherapy for early-stage disease should be tempered by the recognition of the long-term hazards of therapy.

Follow-up for relapse

Because the relapse rate is low, patients with pathologically confirmed stage I nonseminomatous germ-cell tumors require no further therapy, and follow-up can be accomplished easily with chest x-ray, tumor markers, and physical examination. Similarly, for patients who have stage II disease and receive adjuvant chemotherapy, the risk of relapse is low. For patients with either of these two clinical scenarios, follow-up tests (chest x-ray, serum markers) should be performed every 2 months for 1 year, every 4 months for the second year, every 6 months for years 3 through 5, and annually thereafter.

In patients with resected, stage II, nonseminomatous germ-cell tumors who do not receive adjuvant chemotherapy, the follow-up tests are the same as those listed above. However, in these patients, follow-up tests are performed every month for 1 year, every 2 months for 2 years, every 6 months for years 3 through 5, and then annually.

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CHAPTER 19

Urothelial and kidney cancers

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UROTHELIAL CANCER

In the year 2003, an estimated 57,400 new cases of urothelial cancer will be diagnosed in the United States, and approximately 12,500 patients will die of this disease.

Urothelial cancers encompass carcinomas of the bladder, ureters, and renal pelvis; these cancers occur at a ratio of 50:3:1, respectively. Cancer of the urothelium is a multifocal process. Patients with cancer of the upper urinary tract have a 30%-50% chance of developing cancer of the bladder at some time in their lives. On the other hand, patients with bladder cancer have a 2%-3% chance of developing cancer of the upper urinary tract. The incidence of renal pelvis tumors is decreasing.

Epidemiology

Gender Urothelial cancers occur more commonly in men than in women (3:1) and have a peak incidence in the seventh decade of life.

Race Cancers of the urothelial tract are also more common in whites than in blacks (2:1).

Etiology and risk factors

Cigarette smoking The major cause of urothelial cancer is cigarette smoking. A strong correlation exists between the duration and amount of cigarette smoking and cancers at all levels of the urothelial tract. This association holds for both transitional cell and squamous cell carcinomas.

Analgesic abuse Abuse of compound analgesics, especially those containing phenacetin, has been associated with an increased risk of cancers of the urothelial tract. This risk appears to be greatest for the renal pelvis, and cancer at this site is usually preceded by renal papillary necrosis. The risk associated with analgesic abuse is seen after the consumption of excessive amounts (5 kg).

Chronic urinary tract inflammation also has been associated with urothelial cancers. Upper urinary tract stones are associated with renal pelvis cancers.

Chronic bladder infections can predispose patients to cancer of the bladder, usually squamous cell cancer.

Occupational exposures have been associated with an increased risk of urothelial cancers. Workers exposed to arylamines in the organic chemical, rubber, and paint and dye industries have an increased risk of urothelial cancer similar to that originally reported for aniline dye workers.

Balkan nephropathy An increased risk of cancer of the renal pelvis and ureters occurs in patients with Balkan nephropathy. This disorder is a familial nephropathy of unknown cause that results in progressive inflammation of the renal parenchyma, leading to renal failure and multifocal, superficial, low-grade cancers of the renal pelvis and ureters.

Genetic factors There are reports of families that have a higher risk of transitional cell cancers of the urothelium, but the genetic basis for this familial clustering remains undefined.

Signs and symptoms

Hematuria is the most common symptom in patients presenting with urothelial tract cancer. It is most often painless, unless obstruction due to clot or tumor and/or deeper levels of tumor invasion have already occurred.

Urinary voiding symptoms of urgency, frequency, and/or dysuria are also seen in patients with cancers of the bladder or ureters but are uncommon in patients with cancers of the renal pelvis.

Vesical irritation without hematuria can be seen, especially in patients with carcinoma in situ of the urinary bladder.

Symptoms of advanced disease Pain is usually a symptom of more advanced disease, as is edema of the lower extremities secondary to lymphatic obstruction.

Diagnosis

Initial work-up The initial evaluation of a patient suspected of having urothelial cancer consists of excretory urography, followed by cystoscopy. In patients with upper tract lesions, retrograde pyelography can better define the exact location of lesions. Definitive urethroscopic examination and biopsy can be accomplished utilizing rigid or flexible instrumentation.

At the time of cystoscopy, urine is obtained from both ureters for cytology, and brush biopsy is obtained from suspicious lesions of the ureter. Brush biopsies significantly increase the diagnostic yield over urine cytology alone. Also at the time of cystoscopy, a bimanual examination is performed to determine whether a palpable mass is present and whether the bladder is mobile or fixed.

Evaluation of a primary bladder tumor In addition to biopsy of suspicious lesions, evaluation of a bladder primary includes biopsy of selected mucosal sites to detect possible concomitant carcinoma in situ. Biopsies of the primary

lesion must include bladder wall muscle to determine whether there is invasion of muscle by the overlying carcinoma.

CT For urothelial cancers of the upper tract or muscle invasive bladder cancers, a CT scan of the abdomen/pelvis is performed to detect local extension of the cancer and involvement of the abdominal lymph nodes.

Bone scan For patients with bone pain or an elevated alkaline phosphatase level, a radioisotope bone scan is performed.

A chest x-ray completes the staging evaluation.

Pathology

Transitional cell carcinomas constitute 90%-95% of urothelial tract cancers.

Squamous cell cancers account for 3%-7% of urothelial carcinomas and are more common in the renal pelvis and ureters.

Adenocarcinomas account for a small percentage (< 3%) of bladder malignancies and are predominantly located in the trigone region. Adenocarcinomas of the bladder that arise from the dome are thought to be urachal in origin.

Carcinoma in situ In approximately 30% of newly diagnosed bladder cancers, there are multiple sites of bladder involvement, most commonly with carcinoma in situ. Although carcinoma in situ can occur without macroscopic cancer, it most commonly accompanies higher disease stages.

When carcinoma in situ is associated with superficial tumors, rates of recurrence and disease progression (development of muscle invasion) are higher (50%-80%) than when no such association is present (10%). Carcinoma in situ involving the bladder diffusely without an associated superficial tumor is also considered an aggressive disease. Most patients with this type of cancer will develop invasive cancers of the bladder.

Staging and prognosis

Staging system Urothelial tract cancers are staged according to the American Joint Committee on Cancer (AJCC) TNM classification system (Table 1). Superficial bladder cancer includes papillary tumors that involve only the mucosa (Ta) or submucosa (T1) and flat carcinoma in situ (Tis). The natural history of superficial bladder cancer is unpredictable, and recurrences are very common. Most tumors recur within 6-12 months and are of the same stage and grade, but 10%-15% of patients with superficial cancer will develop invasive or metastatic disease.

Prognostic factors For carcinomas confined to the bladder, ureters, or renal pelvis, the most important prognostic factors are T stage and differentiation pattern. The impact of associated carcinoma in situ on Ta and T1 lesions is discussed above (see section on "Pathology"). Less-differentiated Ta-T1 lesions also are associated with higher recurrence and progression rates. Patients with well-differentiated Ta lesions without carcinoma in situ have a

TABLE 1: TNM staging of urothelial cancers

Primary tumor (T)		
Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Ta		Noninvasive papillary tumor
Tis		Carcinoma in situ: "flat tumor"
T1		Tumor invades subepithelial connective tissue
T2		Tumor invades muscle
	pT2a	Tumor invades superficial muscle (inner half)
	pT2b	Tumor invades deep muscle (outer half)
T3		Tumor invades perivesical tissue
	pT3a	Microscopically
	pT3b	Macroscopically (extravesical mass)
T4		Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
	T4a	Tumor invades prostate, uterus, vagina
	T4b	Tumor invades pelvic wall, abdominal wall
Regional lymph nodes (N)		
Nx		Regional lymph nodes cannot be assessed
N0		No regional node involvement
N1		Metastasis in a single node, ≤ 2 cm in greatest dimension
N2		Metastasis in a single node, > 2 cm but ≤ 5 cm in greatest dimension; or multiple lymph nodes, none > 5 cm in greatest dimension
N3		Metastasis in a lymph node, > 5 cm in greatest dimension
Distant metastasis (M)		
Mx		Distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis

Stage grouping			
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1-N3	M0
	Any T	Any N	M1

From: Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

95% survival rate, whereas those with high-grade T1 lesions have a 10-year survival rate of 50%.

Muscle invasive carcinoma carries a 5-year survival rate of 20%-50%. When regional lymph nodes are involved, the 5-year survival rate is 0%-20%.

Treatment

TREATMENT OF LOCALIZED DISEASE

Surgical approaches to superficial bladder cancer

Transurethral resection Most patients with superficial bladder cancer can be treated adequately with transurethral resection (TUR). Such procedures preserve bladder function, entail minimal morbidity, and can be performed repeatedly. Survival rates > 70% at 5 years are expected. Although TUR removes existing tumors, it does not prevent the development of new lesions. Patients should be followed closely.

Laser The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser has achieved good local control when used in the treatment of superficial bladder tumors. However, it has not been adopted for general use because of its limitations in obtaining material for staging and grading of tumors.

Partial cystectomy is an infrequently utilized treatment option for patients whose tumors are not accessible or amenable to TUR.

Radical cystectomy is generally not used for the treatment of superficial bladder tumors. The indications for radical cystectomy include:

- Unusually large tumors that are not amenable to complete TUR, even on repeated occasions
- Some high-grade tumors
- Multiple tumors or frequent recurrences that make TUR impractical
- Symptomatic diffuse carcinoma in situ (Tis) that proves unresponsive to intravesical therapy
- Prostatic stromal involvement

Intravesical therapy The indications for intravesical therapy include:

- Stage T1 tumors, especially if multiple
- Multifocal papillary Ta lesions, especially grade 2 or 3
- Diffuse carcinoma in situ (Tis)
- Rapidly recurring Ta, T1, or Tis disease

In the United States, four intravesical agents are commonly used: thiotepa (Thioplex), an alkylating agent; bacillus Calmette-Guérin (BCG), an immune modulator/stimulator; and mitomycin (Mutamycin) and doxorubicin, both antibiotic chemotherapeutic agents. The dose of BCG varies with the strain

(50 mg [Tice] or 60 mg [Connaught]). Mitomycin doses range from 20 to 40 mg. Although all four agents reduce the tumor recurrence rate, BCG is the most effective. For the treatment of papillary Ta and T1 lesions, BCG and mitomycin have the greatest efficacy (complete response rate, approximately 50%). For the treatment of carcinoma in situ (Tis), BCG is extremely effective.

Surgical approaches to invasive bladder cancer

Radical cystectomy Invasive bladder cancer (stage II or higher) is best treated by radical cystectomy. Candidates for radical cystectomy include:

- Patients with muscle-invasive tumor (depth of invasion is not important, merely its presence), regardless of grade
- Patients with high-grade, invasive, lamina propria tumors with evidence of lymphovascular invasion, with or without carcinoma in situ (Tis)
- Patients with diffuse carcinoma in situ or recurrent superficial cancer who do not respond to intravesical therapy

In men, radical cystectomy includes en bloc pelvic lymph node dissection and removal of the bladder, seminal vesicles, and prostate. In women, radical cystectomy entails en bloc pelvic lymph node dissection and anterior exenteration, including both ovaries, fallopian tubes, uterus, cervix, anterior vaginal wall, bladder, and urethra.

Partial cystectomy is an infrequently utilized treatment option and should only be considered when there is a solitary lesion in the dome of the bladder and random biopsies from remote areas of the bladder and prostatic urethra are negative.

Urethrectomy is routinely included in the anterior exenteration performed in female patients. Urethrectomy in male patients is performed if the tumor grossly involves the prostatic urethra or if prior TUR biopsy of the prostatic stroma is positive. Delayed urethrectomy for positive urethral cytology or biopsy is required in about 10% of male patients.

Urinary reconstruction may involve any one of the following: intestinal conduits (eg, ileal, jejunal, or colonic), continent cutaneous diversion (eg, Indiana pouch, Kock pouch), or orthotopic reconstruction (in both male and female patients).

Surgical approaches to ureteral and renal pelvic tumors

Optimal surgical management of urothelial malignancies of the ureter and renal pelvis consists of nephroureterectomy with excision of a bladder cuff. Some tumors may respond well to local resection, and tumor specifics may allow for a more conservative intervention.

Upper ureteral and renal pelvic tumors (because of similar tumor behavior and anatomic aspects) may be considered as a group, whereas lower ureteral tumors may be considered as a separate group.

Upper ureteral and renal pelvic tumors are best treated with nephroureterectomy. Solitary, low-grade upper tract tumors may be considered for segmental excision or ureteroscopic surgery, if close surveillance is feasible. Care should be exercised, however, as multicentricity is more probable and the risk of recurrence is greater than for lower ureteral lesions.

Lower ureteral lesions may be managed by nephroureterectomy, segmental resection, and neovesical reimplantation or by endoscopic resection. A 15% recurrence rate is seen after segmental resection or endoscopic excision. Careful follow-up is mandatory. Disease progression, the development of a ureteral stricture precluding periodic surveillance, or poor patient compliance are indications to abandon conservative management and perform nephroureterectomy.

ROLE OF RADIATION THERAPY

Radiation therapy for bladder cancer

Primary radiation or chemoradiation therapy Radiation therapy, either alone or in conjunction with chemotherapy, is the modality of choice for patients whose clinical condition precludes surgery, either because of extensive disease or poor overall status. Recent trials have shown that patients treated with irradiation and cisplatin with or without fluorouracil (5-FU) have improved local control, as compared with patients treated with irradiation alone.

Other studies suggest that TUR followed by radiation therapy combined with cisplatin or 5-FU chemotherapy, with cystectomy reserved for salvage, provides survival equivalent to that achieved with initial radical cystectomy while allowing for bladder preservation in many patients. The extent of TUR and the absence of hydronephrosis are important prognostic factors in studies of bladder-conserving treatment. Recent updates from institutions in Europe and the United States on over 600 patients with long-term follow-up support the durability of outcomes previously reported.

A randomized, phase III study of bladder preservation with or without neoadjuvant chemotherapy following TUR, conducted by the Radiation Treatment Oncology Group (RTOG), revealed no advantage to the use of MCV (methotrexate, cisplatin, and vinblastine) before radiation therapy and concurrent cisplatin. The favorable outcome without neoadjuvant chemotherapy may make bladder preservation a more acceptable option for a wider range of patients.

Preoperative irradiation may improve survival in patients undergoing radical cystectomy. Its use is limited due to concern over complications occurring with the urinary diversions currently utilized.

Radiation dose and technique Initially, a pelvic field is treated to 4,500 cGy utilizing a four-field box technique, with 180 cGy delivered daily. The bladder tumor is then boosted to a total dose of 6,480 cGy utilizing multifield techniques, with 180 cGy delivered daily.

TABLE 2: Chemotherapy regimens for bladder carcinoma

Drug/combination	Dose and schedule
CISCA	
Cisplatin	100 mg/m^2 IV on day 2
Adriamycin (doxorubicin)	50 mg/m^2 IV on day 1
Cyclophosphamide	650 mg/m^2 IV on day 1
Repeat cycle every 21-28 days	
Sternberg JJ, Bracken RB, Handel PB, et al: JAMA 238:2282–2287, 1977.	
M-VAC	
Methotrexate	30 mg/m^2 IV on days 1, 15, and 22
Vinblastine	3 mg/m^2 IV on days 2, 15, and 22
Adriamycin (doxorubicin)	30 mg/m^2 IV on day 2
Cisplatin	70 mg/m^2 IV on day 2
NOTE: Reduce doxorubicin dose to 15 mg/m^2 in patients who have received prior pelvic irradiation. On days 15 and 22, methotrexate (30 mg/m^2) and vinblastine (3 mg/m^2) are given only if the WBC count is > 2,500 cells/mL and the platelet count is > 100,000 cells/mL.	
Repeat cycles every 28-32 days even if the interim dose is withheld due to myelosuppression or mucositis	
Loehrer PJ Sr, Einhorn LH, Elson PJ, et al: J Clin Oncol 10:1066–1073, 1992.	
Paclitaxel/carboplatin	
Paclitaxel	200 mg/m^2 IV infused over 3 hours
Carboplatin	Dose calculated by the Calvert formula to an area under the curve (AUC) of 5 mg/mL/min IV infused over 15 minutes after paclitaxel
Repeat cycle every 21 days	
PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; as well as ranitidine, 50 mg IV, and diphenhydramine, 50 mg IV, both 30-60 minutes prior to paclitaxel.	
Redman B, Smith D, Flaherty L, et al: J Clin Oncol 16:1844–1848, 1998.	
Gemcitabine/cisplatin	
Gemcitabine	1 g/m^2 IV on days 1, 8, and 15
Cisplatin	75 mg/m^2 IV on day 1
Repeat cycle every 28 days	
Kaufman D, Stadler W, Carducci M, et al: Proc Am Soc Clin Oncol 17:320a, 1998.	

Radiation therapy for renal pelvic/ureteral cancer

In patients with renal pelvic and ureteral lesions who have undergone nephroureterectomy, postoperative local-field irradiation is offered if there is periureteral, perirenal, or peripelvic extension or lymph node involvement. A dose of approximately 4,500-5,040 cGy is delivered utilizing multifield techniques.

Palliative irradiation

Palliative radiation therapy is effective in controlling pain from local and metastatic disease and in providing hemostatic control. A recent randomized study

Drug/combination	Dose and schedule
PCG	
Paclitaxel	200 mg/m^2 IV infused over 3 hours on day 1
Carboplatin	Dose calculated on AUC of 5, 15-minute IV infusion on day 1
Gemcitabine	800 mg/m^2 30-minute IV on days 1 and 8
Repeat cycle every 21 days	
PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; diphenhydramine, 50 mg IV, 30 minutes prior to paclitaxel; and either cimetidine, 300 mg IV, or ranitidine, 50 mg IV, 30 minutes prior to paclitaxel.	
Hussain M, Vaishampayan U, Du W, et al: J Clin Oncol 19:2527–2533, 2001.	
Paclitaxel/cisplatin	
Paclitaxel	135 mg/m^2 IV infused over 3 hours
Cisplatin	70 mg/m^2 IV infused over 2 hours
Repeat cycle every 3 weeks until progression or for a maximum of 6 cycles	
PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; as well as ranitidine, 50 mg IV, or cimetidine, 300 mg IV, prior to paclitaxel, and diphenhydramine, 50 mg IV, 30 minutes prior to paclitaxel.	
Burch PA, Richardson RI, Cha SS, et al: Proc Am Soc Clin Oncol 18:1266A, 1999.	
TCG	
Taxol (paclitaxel)	80 mg/m^2 IV infused over 1 hour on days 1 and 8
Cisplatin	70 mg/m^2 on day 1
Gemcitabine	1 g/m^2 IV on days 1 and 8
Repeat cycle every 21 days	
PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; as well as diphenhydramine, 50 mg IV, 30 minutes prior to paclitaxel, and either cimetidine, 300 mg IV, or ranitidine, 50 mg IV, 30 minutes prior to paclitaxel.	
Vaishampayan U, Smith D, Redman B, et al: Proc Am Soc Clin Oncol 18, 1282A, 1999.	
Table prepared by Ishmael Jaiyesimi, DO	

comparing 3,500 cGy in 10 fractions vs 2,100 cGy in 3 hypofractionated treatments revealed high rates of relief of hematuria, frequency, dysuria, and nocturia with either regimen. In selected cases of bladder cancer, aggressive palliation to approximately 6,000 cGy may be warranted to provide long-term local control. Concurrent chemotherapy, such as cisplatin, should be considered.

CHEMOTHERAPY FOR ADVANCED DISEASE

Treatment of advanced metastatic urothelial cancer is palliative. Cisplatin, paclitaxel, and gemcitabine (Gemzar) have all demonstrated single-agent ac-

A multicenter randomized trial evaluated neoadjuvant chemotherapy (M-VAC) administered before surgery vs surgery alone in patients with locally advanced transitional cell carcinoma of the bladder (T2-4a N0 M0). Overall survival was 6.2 years for patients receiving chemotherapy/surgery vs 3.8 years for patients receiving surgery alone, with a median follow-up of 7.1 years. Though this trial supports the use of neoadjuvant M-VAC, its report created a great deal of discussion and does not confirm a benefit for adjuvant chemotherapy *(Natale RB, Gossman HB, Blumenstein B, et al: Proc Am Soc Clin Oncol [abstract] 20:2a, 2001).*

tivity for the systemic treatment of this disease. A randomized trial showed an advantage for a regimen of M-VAC (methotrexate, vinblastine, Adriamycin [doxorubicin], and cisplatin) over cisplatin alone with regard to progression-free and overall surival. Combination regimens with cisplatin or carboplatin (Paraplatin), usually with paclitaxel or gemcitabine or in combination with methotrexate and vinblastine with or without doxorubicin, produce response rates of 40%-60% in patients with advanced disease, with a median survival of 12 months (Table 2). The role of combination chemotherapy in the adjuvant treatment of resected urothelial cancer remains undetermined and an area of clinical research.

KIDNEY CANCER

Approximately 31,900 new cases of renal cell carcinoma will be diagnosed in the year 2003 in the United States, with an associated 11,900 deaths. There has been a steady increase in the incidence of renal cell carcinoma that is not explained by the increased use of diagnostic imaging procedures. Mortality rates have also shown a steady increase over the past 2 decades.

Epidemiology

Gender and age This malignancy is twice as common in men as in women. Most cases of renal cell carcinoma are diagnosed in the fourth to sixth decades of life, but the disease has been reported in all age groups.

Ethnicity Renal cell carcinoma is more common in persons of northern European ancestry than in those of African or Asian descent.

Etiology and risk factors

Renal cell carcinoma occurs most commonly as a sporadic form and rarely as a familial form. The exact etiology of sporadic renal cell carcinoma has not been determined. However, smoking, obesity, and renal dialysis have been associated with an increased incidence of the disease.

Genetic factors More recently, a genetic basis has been sought for this disease.

Von Hippel-Lindau disease, an autosomal-dominant disease, is associated with retinal angiomas, CNS hemangioblastomas, and renal cell carcinoma.

Chromosomal abnormalities Deletions of the short arm of chromosome 3 (3p) occur commonly in renal cell carcinoma associated with von Hippel-Lindau

disease. In the rare familial forms of renal cell carcinoma, translocations affecting chromosome 3p are uniformly present. Sporadic renal cell carcinoma of the nonpapillary type is also associated with 3p deletions.

Associated malignancy Two recent studies from large patient databases have reported a higher than expected incidence of patients with both kidney cancer and lymphoma. No explanation for this association has been found.

Signs and symptoms

Renal cell carcinoma has been associated with a wide array of signs and symptoms. The classic triad of hematuria, flank mass, and flank pain occurs in only 10% of patients and is usually associated with a poor prognosis. With the routine use of CT scanning for various diagnostic reasons, renal cell carcinoma is being diagnosed more frequently as an incidental finding.

Hematuria More than half of patients with renal cell carcinoma present with hematuria.

Other common signs/symptoms Other commonly associated signs and symptoms of renal cell carcinoma include normocytic/normochromic anemia, fever, and weight loss.

Less common signs/symptoms Less frequently occurring, but often described, signs and symptoms include polycythemia, hepatic dysfunction not associated with hepatic metastasis, and hypercalcemia. Although not a common finding at the time of diagnosis of renal cell carcinoma, hypercalcemia ultimately occurs in up to 25% of patients with metastatic disease.

Diagnosis

Contrast-enhanced CT scanning has virtually replaced excretory urography and renal ultrasonography in the evaluation of suspected renal cell carcinoma. In most cases, CT imaging can differentiate cystic from solid masses and also supplies information about lymph nodes and renal vein/inferior vena cava (IVC) involvement.

Ultrasonography is useful in evaluating questionable cystic renal lesions if CT imaging is inconclusive.

Venography and MRI When IVC involvement by tumor is suspected, either IVC venography or MRI is needed to evaluate its extent. MRI is currently the preferred imaging technique for assessing IVC involvement at most centers.

Renal arteriography is not used as frequently now as it was in the past in the evaluation of suspected renal cell carcinoma. In patients with small, indeterminate lesions, arteriography may be helpful. It is also used by the surgeon as part of the preoperative evaluation of a large renal neoplasm.

Percutaneous cyst puncture is used in the evaluation of cystic renal lesions that are thought to be potentially malignant on the basis of ultrasonography or

CT imaging. Percutaneous cyst puncture permits the collection of cyst fluid for analysis, as well as the evaluation of cyst structure via instillation of contrast medium after fluid removal. Benign cyst fluid is usually clear to straw-colored and low in protein, fat, and lactate dehydrogenase (LDH) content, whereas malignant fluid is usually bloody with high protein, fat, and LDH content.

Evaluation of extra-abdominal disease sites includes a chest x-ray. In the face of a normal chest x-ray, CT imaging of the chest adds no further helpful information. A bone scan is required if a patient has symptoms suggestive of bone metastasis and/or an elevated alkaline phosphatase level.

Pathology

Renal cell carcinoma arises from the proximal renal tubular epithelium. Histologically, renal cell carcinoma can be of various cellular types: clear cell, granular cell, and sarcomatoid (spindle) variant. The majority of these tumors are mixtures of clear and granular cell types. Approximately 1%-6% of renal cell carcinomas are of the sarcomatoid variant type, which is a more aggressive malignancy that has a worse prognosis.

Staging and prognosis

Staging system The preferred staging system for renal cell carcinoma is the TNM classification (Table 3).

Prognostic factors The natural history of renal cell carcinoma is highly variable. However, approximately 30% of patients present with metastatic disease at diagnosis, and one-third of the remainder will develop metastasis during follow-up.

Five-year survival rates after nephrectomy for tumors confined to the renal parenchyma (T1/2) are $>80\%$. Renal vein involvement without nodal involvement does not affect survival. Lymph node involvement and/or extracapsular spread is associated with a 5-year survival of 10%-25%. Patients with metastatic disease have a median survival of 1 year and a 5-year survival rate of 0%-20%.

Nephrectomy in metastatic kidney cancer may be of value in patients being treated with interferon. In a randomized trial, those patients who had a nephrectomy followed by interferon α-2b had a median survival of 11.1 months, whereas those patients treated with interferon alone had a median survival of 8.1 months ($P = .05$). This benefit was most evident in patients with a performance status of 0 *(Flanigan RC, Salmon SE, Blumenstein BA, et al: N Engl J Med 345:1655-1659, 2001).*

Treatment

Surgery

Radical nephrectomy is the established therapy for localized renal cell carcinoma. At surgery, the kidneys, adrenal gland, and perirenal fat (structures bound by Gerota's fascia) are removed. Also, limited regional lymph node dissection is often performed for staging purposes. Partial nephrectomy is considered in patients in whom a radical nephrectomy would result in permanent dialysis.

TABLE 3: TNM staging of renal cell carcinoma

Primary tumor (T)		
Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1		Tumor ≤ 7 cm in greatest dimension, limited to the kidneys
	T1a	Tumor ≤ 4 cm in greatest dimension, limited to the kidneys
	T1b	Tumor > 4 cm but not > 7 cm in greatest dimension, limited to the kidneys
T2		Tumor > 7 cm in greatest dimension, limited to the kidneys
T3		Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
	T3a	Tumor directly invades adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota's fascia
	T3b	Tumor grossly extends into renal vein or its segmental (muscle-containing) branches, or vena cava below diaphragm
	T3c	Tumor grossly extends into vena cava above diaphragm or invades the wall of the vena cava
T4		Tumor invades beyond Gerota's fascia
Regional lymph nodes (N)		
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in a single regional lymph node
N2		Metastasis in more than one regional lymph node
Distant metastasis (M)		
Mx		Distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis

Stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3a	N0-N1	M0
	T3b	N0-N1	M0
	T3c	N0-N1	M0
Stage IV	T4	N0-N1	M0
	Any T	N2	M0
	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

Since complete resection is the only known cure for renal cell carcinoma, even in locally advanced disease, surgery is considered if the involved structures can be safely removed. In the presence of metastatic disease, surgery is generally considered for palliation only.

Radiation therapy for renal cell carcinoma

Primary radiation therapy Radiation therapy may be considered for palliation as the primary therapy for renal cell carcinoma in patients whose clinical condition precludes surgery, either because of extensive disease or poor overall condition. A dose of 4,500 cGy is delivered, with consideration of a boost up to 5,500 cGy.

Postoperative radiation therapy is controversial. However, it may be considered in patients with perinephric fat extension, adrenal invasion, or involved margins. A dose of 4,500 cGy is delivered, with consideration of a boost.

Palliation Radiation therapy is commonly used for palliation for metastatic and local disease.

Systemic therapy of advanced disease

Metastatic renal cell carcinoma is resistant to chemotherapeutic agents. An extensive review of currently available agents concluded that the overall response rate to chemotherapy is 6%.

Interleukin-2 The only FDA-approved treatment for metastatic renal cell carcinoma is high-dose interleukin-2 (IL-2, aldesleukin [Proleukin]; Table 4).

High-dose regimen High-dose IL-2 (720,000 IU/kg IV piggyback every 8 hours for 14 doses, repeated once after a 9-day rest) results in a 15% remission rate (7% complete responses, 8% partial responses). The majority of responses to IL-2 are durable, with a median response duration of 54 months.

An initial report of a randomized trial of high-dose IL-2 vs a low-dose outpatient IL-2/IFN regimen has shown a trend toward improved quality responses in the high-dose arm (25% vs 12%). Further follow-up will be needed to report on overall survival *(McDermott D, Flaherty L, Clark J, et al: Proc Am Soc Clin Oncol [abstract] 20:685, 2001).*

The major toxicity of high-dose IL-2 is a sepsislike syndrome, which includes a progressive decrease in systemic vascular resistance and an associated decrease in intravascular volume due to "capillary leak." Management includes judicious use of fluids and vasopressor support to maintain blood pressure and intravascular volume and at the same time to avoid pulmonary toxicity due to noncardiogenic pulmonary edema from the capillary leak. This syndrome is totally reversible.

Other doses and schedules Because of the toxicity of high-dose IL-2, other doses and schedules have been and are being evaluated. Several trials of low-dose IL-2 (3-18 $\times$ 10^6 IU/d), either alone or combined with interferon alfa (Intron A, Roferon-A), and with or without 5-FU, have reported durable response rates similar to those achieved with high-dose IL-2. Patients should be encouraged to participate in ongoing clinical trials of metastatic renal cell carcinoma.

TABLE 4: Chemotherapy regimens for renal cell carcinoma

Dose and schedule
High-dose IL-2
IL-2: 600,000 or 720,000 IU/kg IV infused over 15 minutes every 8 hours until toxicity develops; or 14 consecutive doses for 5 days
After a 5- to 9-day rest period, an additional 14 doses of IL-2 are administered over a 5-day period. If patients show evidence of tumor regression or stable disease, 1-2 more courses of treatment may be given.
Fyfe G, Fisher RI, Rosenberg SA, et al: J Clin Oncol 13:688–696, 1995.
Low-dose IL-2
IL-2: 72,000 IU/kg by IV bolus every 8 hours to a maximum of 15 doses every 7-10 days for 2 cycles
NOTE: The cycles represent one course of therapy. Patients who are stable or responding after one course of therapy receive a second course. Third and fourth courses are given only if patients demonstrate further tumor regression.
Yang JC, Topalian SL, Parkinson D, et al: J Clin Oncol 12:1572–1576, 1998.

Table prepared by Ishmael Jaiyesimi, DO

Immunotherapy New immunotherapeutic approaches under investigation for the treatment of advanced kidney cancer include the use of peripheral blood stem-cell transplantations, dendritic cell-based vaccines, and monoclonal antibodies. Early reports on the use of allogeneic stem-cell transplantation from HLA-matched donors to invoke a graft-vs-tumor reaction have shown encouraging preliminary results that warrant further investigation. A humanized monoclonal antibody against the G250 antigen found on all clear cell, and the majority of non-clear cell, renal cell carcinomas is also in clinical trials.

Other areas of promising therapeutic clinical research in advanced kidney cancer are the use of dendritic cell-based vaccines and the evaluation of antiangiogenic factors. Most renal cell carcinomas are highly vascular tumors, and inhibition of tumor neovascularity holds new promise for better treatments.

SUGGESTED READING

ON UROTHELIAL CANCER

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ON KIDNEY CANCER

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Stodlen WM, Vogelzang NJ: Low-dose interleukin-2 in the treatment of metastatic renal cell carcinoma. Semin Oncol 22:67–73, 1995.

CHAPTER 20

Cervical cancer

Dennis S. Chi, MD, Rachelle M. Lanciano, MD, and Andrzej P. Kudelka, MD

The overall incidence of invasive cervical carcinoma has declined steadily since the mid-1940s. Of the predominant gynecologic cancers, cervical cancer is the least common, with only 12,200 new cases anticipated in the United States in the year 2003. Nevertheless, approximately 4,100 women die of invasive cervical carcinoma annually in the United States.

Epidemiology

Age The peak age of developing cervical cancer is 47 years. Approximately 47% of women with invasive cervical cancer are < 35 years old at diagnosis. Older women (> 65 years) account for another 10% of patients with cervical cancer. Although these older patients represent only 10% of all cases, they are more likely to die of the disease due to their more advanced stage at diagnosis.

Socioeconomic class Carcinoma of the uterine cervix primarily affects women from the lower socioeconomic class and those with poor access to routine medical care.

Geography Although invasive cervical carcinoma is relatively uncommon in the United States compared to the more common cancers in women (breast, endometrial, and ovarian cancers), it remains a significant health problem for women worldwide. In many developing countries, not only is cervical carcinoma the most frequently occurring cancer among middle-aged women, but also it is a leading cause of death. This is due, in part, to poor access to medical care and the unavailability of routine screening in many of these countries.

Etiology and risk factors

Sexual activity Invasive cervical carcinoma can be viewed as a sexually transmitted disease. If a woman is never sexually active, it is extremely unlikely that she will ever develop this cancer. Conversely, any woman who has been sexually active is at risk for invasive cervical carcinoma.

Human papillomavirus An important cofactor in the etiology of invasive cervical carcinoma is the human papillomavirus (HPV). Worldwide, it is estimated that approximately 90%-100% of all invasive cervical carcinomas are related to HPV infection. Of the wide variety of HPV subtypes, several (ie, subtypes 16, 18, 31, 33, and 35) are associated with invasive carcinoma.

Age of onset of sexual activity Population studies of women with invasive cervical carcinoma have demonstrated that early age of onset of sexual activity also plays a role in the later development of the cancer. It is postulated that during the time of menarche in early reproductive life, the transformation zone of the cervix is more susceptible to oncogenic agents, such as HPV. Women who begin sexual activity before 16 years of age or who are sexually active within 1 year of beginning menses are at a particularly high risk of developing invasive cervical carcinoma (Table 1).

Other risk factors include multiple sexual partners and a history of genital warts.

Cigarette smoking has been identified as a significant risk factor for cervical carcinoma. The mechanism may be related to diminished immune function secondary to a systemic effect of cigarette smoke and its by-products or a local effect of tobacco-specific carcinogens.

Oral contraceptives may also play a role in the development of invasive cervical carcinoma, although this theory is more controversial. Given that most women who use oral contraceptives are more sexually active than women who do not use oral contraceptives, this may represent a confounding factor rather than a true independent risk factor. The exception may be adenocarcinoma of the cervix. This relatively uncommon histologic subtype may be related to previous oral contraceptive use.

Immune system alterations In recent years, alterations in the immune system have been associated with an increased risk of invasive cervical carcinoma, as exemplified by the fact that patients who are infected with the human immunodeficiency virus (HIV) have increased rates of both preinvasive and invasive cervical carcinoma. These patients also are at risk for other types of carcinoma, including Kaposi's sarcoma, lymphomas, and other squamous cell carcinomas of the head and neck and the anogenital region. (For further discussion of AIDS-related malignancies, see chapter 29.)

Data suggest that patients who are immunocompromised due to immunosuppressive medications also are at risk for both preinvasive and invasive cervical carcinoma. This association is probably due to the suppression of the normal immune response to HPV, which makes patients more susceptible to malignant transformation.

Signs and symptoms

Common symptoms The classic symptom of cervical carcinoma is intermenstrual bleeding in a premenopausal patient. Other commonly reported symptoms include heavier menstrual flows and metrorrhagia. The patient may also complain of postcoital bleeding.

Less common presentations Less commonly, patients present with signs of advanced disease, such as bowel obstruction and renal failure due to urinary tract obstruction. Only rarely are asymptomatic patients (normal screening

TABLE 1: Relative risk of cervical carcinoma posed by selected factors

Risk factor	Relative risk
Age at coitarche (years)	
< 16	16
16-19	3
> 19	1
Years from menarche to coitarche	
< 1	26
1-5	7
6-10	3
> 10	1
Total number of sexual partners	
> 4 partners (vs no or 1 partner)	3.6
Number of sexual partners before age 20 years	
> 1 partner (vs no partner)	7
Genital warts	
Any (vs none)	3.2
Smoked > 5 cigarettes daily	
> 20 years (vs < 1 year)	4

Adapted, with permission, from Morrow CP, Curtin JP, Townsend DE (eds): Synopsis of Gynecologic Oncology, 5th ed. New York, Churchill Livingstone, 1998; data from Peters RK, Thomas D, Hagen DC, et al: J Natl Cancer Inst 77:1063, 1986.

Pap smear) found to have a lesion on the cervix, which leads to a diagnosis of invasive cervical carcinoma.

Screening and diagnosis

Screening

Pap smear The paradigm for a cost-effective, easy-to-use, reliable screening test is the cervical cytology screen, or Pap smear. In every population studied, the introduction of the Pap smear has resulted in a significant reduction in the incidence of invasive cervical carcinoma, as well as a shift toward earlier-stage disease at the time of diagnosis. The success of cervical cytology, as measured by the lowered incidence of cervical cancer, ironically has led to some controversy regarding the most effective application of this screening tool. With the marked reduction in the incidence of cervical carcinoma, more patients are screened and greater costs incurred in order to detect each additional case of cervical carcinoma.

Current screening recommendations The current recommendation of the American College of Obstetricians and Gynecologists (ACOG) is that all women who are 18 years of age or older and are sexually active be screened. If the

patient has three consecutive annual cervical cytology smears that are normal, she may be safely screened at a less frequent interval of perhaps 2-3 years. There are no data to support screening patients on a less frequent basis. Any patient who has a history of cervical dysplasia should be screened, at a minimum, on a yearly basis.

The American Cancer Society (ACS) revised guidelines for cervical cancer screening in 2002 as follows: Cervical cancer screening should begin ~3 years after the onset of vaginal intercourse but no later than age 21. Cervical screening should be performed every year with conventional cervical cytology smears, or every 2 years using liquid-based cytology until age 30, after which time screening may continue every 2-3 years for those women who have had three consecutive, technically satisfactory normal tests. Women who are > 70 years old with an intact cervix and who have had three or more documented, consecutive, technically satisfactory normal cervical cytology tests and no abnormal cytology tests within the 10-year period prior to age 70 may elect to cease cervical cancer screening. Women with a history of cervical cancer, in utero exposure to diethylstilbestrol (DES), and/or who are immunocompromised (including HIV+) should continue cervical cancer screening for as long as they are in reasonably good health and do not have a life-limiting chronic condition. Women > 70 years old should discuss their need for cervical cancer screening with a health care professional and make an informed decision about continuing screening based on its potential benefits, harms, and limitations.

Women who have had a subtotal hysterectomy should continue cervical cancer screening as per current guidelines. Cervical cancer screening following total hysterectomy (with removal of the cervix) for benign gynecologic disease is not indicated. Women with a history of CIN2/3 or for whom it is not possible to document the absence of CIN2/3 prior to or as the indication for the hysterectomy should be screened until three documented, consecutive, technically satisfactory normal cervical cytology tests and no abnormal cytology tests (within a 10-year period) are achieved. Women with a history of in utero DES exposure and a history of cervical carcinoma should continue screening after hysterectomy for as long as they are in reasonably good health and do not have a life-limiting chronic condition.

Three new techniques designed to improve the sensitivity of the Pap smear (Thin Prep system, Autopap, and Papnet) were recently approved by the FDA. However, no large, population-based, prospective studies have been completed to determine whether any of these techniques lowers the incidence of invasive cervical cancer or improves the survival rate. Consequently, in a committee opinion, ACOG has stated that the appropriate use of these techniques requires further investigation and that "they currently are not the standard of care."

Diagnosis

The diagnosis of invasive cervical carcinoma can be suggested by either an abnormal Pap smear or an abnormal physical finding.

Colposcopy In the patient who has an abnormal Pap smear but normal physical findings, colposcopy is indicated. Colposcopic findings consistent with inva-

sive cervical carcinoma include dense white epithelium covering the ectocervix, punctation, mosaicism, and, especially, an atypical blood vessel pattern.

Biopsy If the colposcopic findings are suggestive of invasion, biopsies are obtained from the ectocervix and endocervix. If these biopsies demonstrate only precancerous changes but not an invasive carcinoma, the patient should undergo an excisional biopsy of the cervix. In most current clinical settings, the loop electrosurgical excision procedure (LEEP) is the most expedient method for performing an excisional biopsy. This can be easily accomplished in the office under local anesthesia and provides adequate tissue for diagnosis. Once the diagnosis of either a microinvasive or an invasive carcinoma has been established, the patient can be triaged accordingly.

Patients with signs/symptoms of advanced disease The patient with signs/symptoms of advanced invasive cervical carcinoma requires a cervical biopsy for diagnosis and treatment planning. In this setting, a Pap smear is superfluous and may be misleading.

Pathology

Squamous cell carcinoma The most common histology associated with invasive cervical carcinoma is squamous cell carcinoma, which accounts for approximately 80% of all carcinomas of the uterine cervix. For the most part, the decline in the annual incidence of invasive cervical carcinoma has been seen primarily among patients with this subtype.

Adenocarcinoma In the past, adenocarcinoma was relatively uncommon as a primary histology of cervical cancer. As a result of the decrease in the overall incidence of invasive squamous cell cancer and, probably, an increase in the baseline incidence of adenocarcinoma of the uterine cervix, this histology now accounts for approximately 20% of all cervical cancers.

There is controversy over whether patients with adenocarcinoma of the cervix have a worse prognosis than those with the more common squamous cell histology. The poorer prognosis associated with adenocarcinoma may be due to the relatively higher frequency of late stage at the time of diagnosis among patients with this histologic type. In several series in which patients were stratified by stage and tumor size, the outcome of cervical adenocarcinoma appeared to be similar to that of squamous lesions of the cervix.

Aggressive subtypes Among the various subtypes of adenocarcinoma, certain types are particularly aggressive and are associated with a poor prognosis. Among these are the small neuroendocrine tumors, which have a poor prognosis even when diagnosed at an early stage.

Rare tumor types More rare lesions of the cervix include lymphoma, sarcoma, and melanoma. These histologic subtypes account for $< 1\%$ of all cervical cancers.

TABLE 2: FIGO staging for carcinoma of the uterine cervix

Stage	Description
0	Carcinoma in situ, intraepithelial carcinoma (Cases of stage 0 should not be included in any therapeutic statistics for invasive carcinoma.)
I	Carcinoma strictly confined to the cervix (Extension to the corpus should be disregarded.)
IA	Invasive cancer identified only microscopically. All gross lesions even with superficial invasion are stage IB cancers. Invasion is limited to measured stromal invasion with maximum depth of 5.0 mm and no wider than 7.0 mm
IA1	Measured invasion of stroma no greater than 3.0 mm in depth and no wider than 7.0 mm
IA2	Measured invasion of stroma greater than 3.0 mm and no greater than 5.0 mm and no wider than 7.0 mm
IB	Clinical lesions confined to the cervix or preclinical lesions greater than stage IA
IB1	Clinical lesions no greater than 4.0 cm
IB2	Clinical lesions greater than 4.0 cm
II	Carcinoma extends beyond the cervix but has not extended onto the pelvic wall. Carcinoma involves the vagina, but not as far as the lower third
IIA	No obvious parametrial involvement
IIB	Obvious parametrial involvement
III	Carcinoma has extended onto the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and pelvic wall. Tumor involves the lower third of the vagina. All cases with hydronephrosis or nonfunctioning kidney should be included, unless they are due to other causes
IIIA	No extension onto the pelvic wall, but involvement of the lower third of the vagina
IIIB	Extension to the pelvic wall or hydronephrosis or nonfunctioning kidney
IV	Carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum
IVA	Spread to adjacent organs
IVB	Spread to distant organs

FIGO = International Federation of Gynecology and Obstetrics

Staging and prognosis

Clinical staging

The widely accepted standard for staging of cervical carcinoma is the staging system outlined by the International Federation of Gynecology and Obstetrics (FIGO). This is primarily a clinical staging system based on histology for the earlier stage I cancers and tumor size (Table 2). For the more advanced tumors, staging is based on extension of the disease in the pelvis.

Radiographic examination allowed under the FIGO staging system includes chest x-ray and barium enema, as well as IV pyelography. However, where available, CT scanning or MRI is the preferred diagnostic study. MRI is superior to the CT scan in evaluating extent of disease in the pelvis. Lymphangiography may be helpful in evaluating the pelvic and para-aortic lymph nodes. In the United States, barium enema and IV pyelography are rarely indicated. For advanced disease, cystoscopy and/or sigmoidoscopy may be indicated. Additional clinical information can be gathered by pelvic examination under anesthesia.

A recent modification of the FIGO system has clarified the description of patients with microinvasive cervical carcinoma. This better differentiation between stages IA1 and IA2 followed the lead established by the Society of Gynecologic Oncologists (SGO) in their staging of microinvasive carcinoma.

In addition, the modified FIGO system now stages patients with lesions that are clinically confined to the cervix (stage IB) according to the size of the primary tumor.

Surgical staging

Clinical staging of cervical carcinoma, although widely utilized, is not without controversy. When compared to surgical staging carried out by large cooperative groups, clinical staging is frequently inaccurate in predicting locoregional spread. For many cooperative groups, including the Gynecologic Oncology Group (GOG), surgical staging may be required for patients who are entering prospective, randomized clinical protocols.

The most common method used to stage patients with advanced disease is extraperitoneal sampling of the pelvic and aortic lymph nodes. This approach minimizes the risk of subsequent radiation injury to the small bowel due to surgical adhesions and, in patients with advanced disease, allows for individualized treatment planning.

Work-up for advanced disease The standard work-up of a patient with advanced cervical carcinoma who is not considered a candidate for radical surgery includes an abdominopelvic CT scan with both renal and GI contrast. If there is evidence of aortic lymph node metastases, the patient should undergo fine-needle aspiration (FNA) of these enlarged lymph nodes. If the FNA confirms that there is aortic lymph node metastasis, treatment should be individualized and extended-field radiation should be considered as part of the primary treatment regimen.

If the scalene lymph nodes are negative on clinical examination and the patient is known to have positive metastatic disease to the aortic lymph nodes, consideration can be given to performing a scalene lymph node biopsy; the incidence of positive scalene nodes when aortic lymph nodes are known to be positive ranges from 0.0% to 17%. The rationale for biopsying the scalene nodes is that if there is disease outside of the radiation therapy field, chemotherapy is appropriate.

If the fine-needle aspirate is negative, or if the abdominopelvic CT scan does not demonstrate enlarged aortic lymph nodes, the patient can be considered for surgical staging.

Recent data regarding the use of PET scan in cervical cancer reveal that tumor volume can be accurately measured by PET and can separate patients into prognostic groups. In a series of 51 consecutive patients with advanced cervical cancer, 63% had positive lymph nodes on PET, which correlated with decreased survival following chemoradiation.

Surgical staging of locally advanced or recurrent cervical cancer via a laparoscopic extraperitoneal approach was recently reported in 98 patients. Infrarenal aortic and common iliac lymph node dissection yielded a mean node count of 18 per patient, with 23 of 98 patients (24%) having positive nodes. Five patients (5%) required a second procedure under anesthesia, with two (2%) undergoing an operative procedure for complications. This approach combines the benefits of laparoscopy and the extraperitoneal approach to identify patients who may benefit from extended-field radiation therapy while minimizing associated toxicities secondary to adhesions *(Sonoda Y, Leblanc E, Papageorgiou TC, et al: Gynecol Oncol [abstract] 84:490, 2002).*

Pros and cons of surgical staging The advantage of surgical staging is that patients with microscopic disease in the aortic lymph nodes can be treated with extended-field radiation therapy and, possibly, chemotherapy and potentially benefit in terms of long-term survival. The controversy regarding surgical staging stems from the fact that a very small number of patients will actually benefit from the procedure; the majority of patients who undergo it either will be found not to have metastatic disease and will receive the same treatment as planned prior to surgical staging or, if they are found to have metastatic disease, will be unlikely to benefit from extended-field radiation therapy. Because of this controversy, the GOG considers surgical staging to be optional for patients with advanced-stage cervical cancer.

Laparoscopic surgery In more recent years, the introduction of minimal-access surgery has allowed surgeons to accurately stage patients via the laparoscope prior to initiation of radiation therapy. However, the safety and efficacy of laparoscopic surgical staging are areas of ongoing investigation.

Work-up for early-stage disease For patients who have early-stage disease for which surgery is contemplated, only a minimal diagnostic work-up is indicated prior to surgery. At most institutions, this would include a two-view chest x-ray. Patients who have stage IA cervical carcinoma (microinvasive carcinoma) do not require preoperative CT scanning prior to hysterectomy. For patients with a small IB carcinoma of the cervix, a CT scan of the abdomen and pelvis has a low yield and is unlikely to change the treatment plan.

Prognostic factors

Clinical stage The most important determinant of prognosis remains clinical stage. The overall 5-year survival rate ranges from 95% to 100% for patients with stage IA cancer and from 75% to 90% for those with stage IB disease. Patients with stage IV disease have a ≤ 5% chance of surviving 5 years after diagnosis.

Patients with early disease For patients with early invasive carcinoma (stage IB), the size of the lesion, percentage of cervical stromal invasion, histology, tumor grade, and lymphovascular space involvement are important local factors that predict prognosis. In general, good prognostic signs are lesions that are ≤ 2 cm in diameter, superficially invasive, and well differentiated with no lymphovascular space involvement.

For patients who have undergone a radical hysterectomy for early cervical carcinoma, poor prognostic factors, in addition to the local factors mentioned above, include positive vaginal or parametrial margins and metastasis to the pelvic lymph nodes. For stage IB patients with positive pelvic nodes, the 5-year survival rate drops from approximately 75%-85% to 50%.

Patients with advanced disease For patients with advanced-stage disease (stages II through IV), the primary determinants of prognosis are histology and size of the primary lesion. Survival is significantly higher for patients with small stage IIB cervical carcinomas and minimal parametrial involvement than for patients with large bulky tumors and bilateral parametrial involvement. Disease extension beyond the pelvis to the aortic nodes is associated with a significant decrease in overall survival rate. With regard to histology, a better prognosis is associated with a large-cell nonkeratinizing squamous cell cancer of the cervix, as opposed to a poorly differentiated adenocarcinoma.

Other prognostic factors Other factors that may predict outcome include the patient's general medical and nutritional status. Patients who are anemic may respond poorly to radiation therapy, as compared with those with normal hemoglobin levels. Patients with significant alterations in their immune system may not respond as well; this is becoming increasingly apparent with regard to patients who are HIV-seropositive.

A recent retrospective review of 605 patients from seven institutions in Canada treated with radiation for cervical cancer described average weekly nadir Hgb levels as significant prognostic factors for survival, second only in importance to tumor stage. These data would suggest that Hgb levels should be kept ≥ 120 g/L for successful radiotherapy and disease-free survival.

Treatment

SURGICAL TREATMENT OF EARLY-STAGE DISEASE

The standard management of patients with early cervical carcinoma is surgical removal of the cervix. The extent of resection of surrounding tissue depends on the size of the lesion and depth of invasion.

Stage IA1 disease

Simple hysterectomy Patients who have a microinvasive squamous carcinoma of the cervix with ≤ 3 mm of invasion, ≤ 7 mm of lateral extent, and no lymphovascular space involvement (stage IA1) can be treated with a simple hysterectomy. Vaginal and abdominal hysterectomy are equally effective.

Cone biopsy Although simple hysterectomy is considered the standard therapy for patients with microinvasive cervical carcinoma, there are some patients in whom preservation of future fertility is a strong consideration. A cone biopsy entails removal of the cervical transformation zone. Provided that the biopsy margins are free of dysplasia and microinvasive carcinoma, cone biopsy is probably a safe treatment for such patients who meet the criteria of having superficial invasion < 3 mm, minimal lateral extension, and no lymphovascular space involvement.

Since there is a small risk of recurrence among this population of patients treated by cone biopsy alone, they should be followed closely. Follow-up includes a Pap smear every 3 months for 2 years and then twice a year. An abnormal Pap smear is an indication for a repeat colposcopy. If such a patient is successful in achieving pregnancy and has no evidence of recurrent squamous cell carcinoma, there is no need to proceed with hysterectomy at the completion of her planned childbearing.

Laparoscopic radical hysterectomy with aortic and pelvic lymphadenectomy was recently reported in 78 patients with stage IA2 and IB cervical cancer. All but five procedures were completed laparoscopically. The average lymph node count was 34 (range 19-68) and 9 patients (11.5%) had positive nodes. All margins were macroscopically negative, but three patients had microscopically positive and/or close margins. One patient developed a ureterovaginal fistula that required reoperation. There have been four documented recurrences (5.1%) with a minimum 3-year follow-up. With appropriate surgical expertise, this procedure can be successfully completed with acceptable morbidity and efficacy (*Spirtos NM, Eisenkop SM, Schlaerth JB, et al: Am J Obstet Gynecol 187:340-348, 2002*).

Stages IA2, IB1, and nonbulky IIA disease

Radical hysterectomy A standard treatment for patients with small cervical carcinomas (tumor ≤ 4 cm) confined to the uterine cervix or with minimal involvement of the vagina (stage IIA) is radical hysterectomy (removal of the uterus, cervix, and parametrial tissue), pelvic lymphadenectomy, and aortic lymph node sampling. The overall success of this treatment is similar to that of radiation therapy, and for patients with early lesions, radical hysterectomy may provide an improved quality of life. The benefits of surgical excision include rapid treatment, less time away from normal activities, and preservation of normal ovarian and vaginal function.

A recent randomized trial for patients with early-stage cervix cancer, reported no difference in survival between radical hysterectomy and definitive radiation. Because a significant percentage of patients following radical hysterectomy required postoperative pelvic radiotherapy, the morbidity was increased in the surgery arm. Therefore, patients selected for radical hysterectomy should have small-volume disease so adjuvant pelvic radiation is unnecessary.

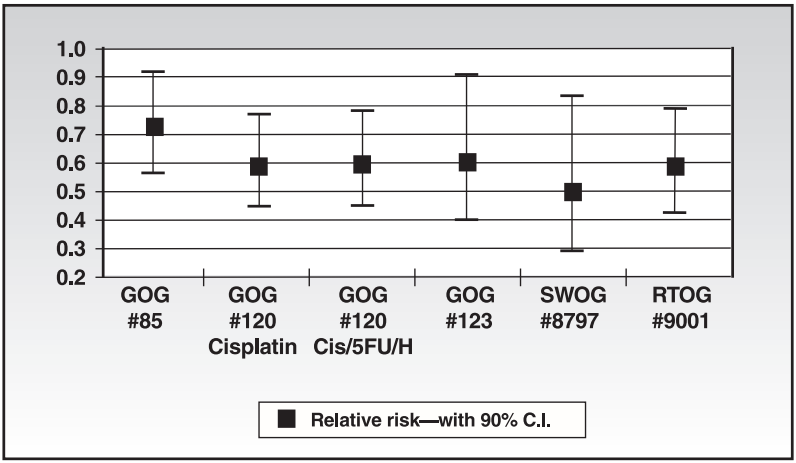

FIGURE 1: Relative risk estimate of survival from five phase III randomized, controlled clinical trials of chemoradiation in women wih cervical cancer. A relative risk of 1 would indicate no difference in outcome between the treatment arms. A risk of < 1 indicates a benefit for the experimental treatment. A relative risk of 0.6, for example, would indicate that the treatment has reduced the risk of death by 40%. The relative risks of survival for all five trials, with 90% confidence intervals shown, range from 0.70-0.50, indicating that the concurrent chemoradiation decreased the risk of death by 30%-50%.

Currently, there are no specific contraindications to radical hysterectomy. Several studies have demonstrated that patients ≥ 65 years old tolerate this procedure well, and age alone should not be considered a contraindication. Obesity also is not a contraindication to radical hysterectomy.

Alternatives to radical hysterectomy Recent reports have described the use of laparoscopically assisted radical vaginal hysterectomy and laparoscopic abdominal radical hysterectomy as less invasive alternatives to traditional radical hysterectomy. The use of fertility-preserving surgery by means of laparoscopic pelvic lymphadenectomy followed by radical vaginal trachelectomy (removal of the uterine cervix) has also been evaluated. Successful pregnancies after this procedure have been reported. However, further data is needed to adequately assess the safety and efficacy of fertility-preserving surgery. The role of laparoscopic sentinel lymph node detection is an area of active investigation.

Complications Due to improved surgical techniques, as well as the use of prophylactic antibiotics and prophylaxis against deep-vein thrombosis, the morbidity and mortality associated with radical hysterectomy have declined significantly over the past several decades. The currently accepted complication rate for radical hysterectomy includes approximately a 0.5%-1.0% incidence of urinary tract injury, a 0.5%-1.0% incidence of deep-vein thrombosis, and an overall mortality of < 1.0%.

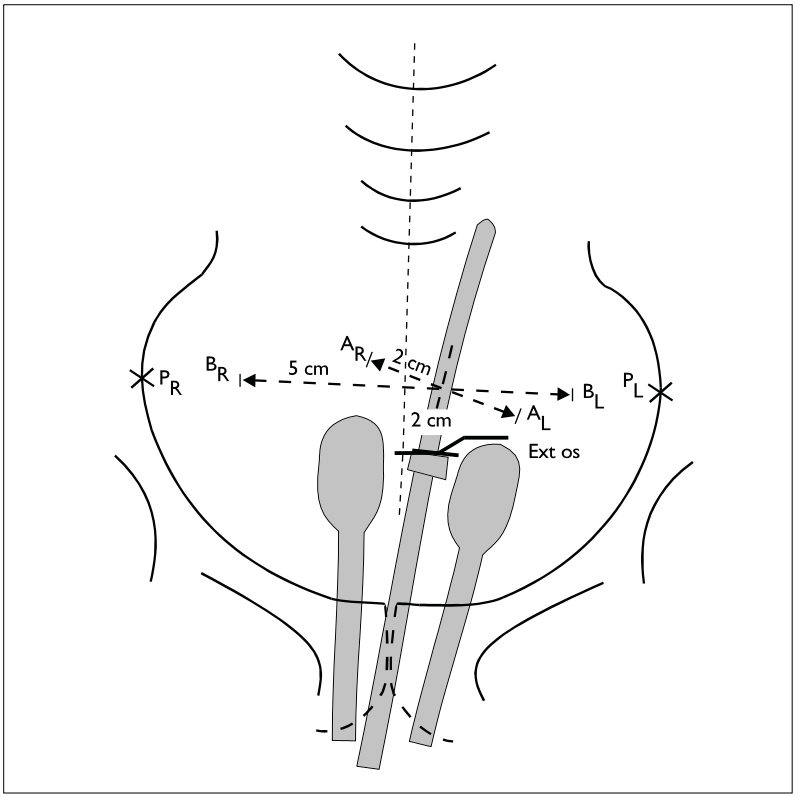

FIGURE 2: GOG definitions of points A, B, and P.

The increased awareness of the risks associated with blood transfusion is reflected in the fact that, in many cases, no transfusions are administered. The need for heterologous blood transfusion also can be decreased by encouraging autologous blood donation prior to radical hysterectomy or by using intraoperative hemodilution.

The average hospital stay for patients undergoing a radical hysterectomy is between 4 and 7 days. Follow-up should include a vaginal Pap smear every 3 months for 2 years, twice a year for 3 years, and yearly thereafter.

Stages IB2 and bulky IIA disease

Numerous studies have demonstrated that patients with early-stage "bulky" lesions (tumor > 4 cm) have a worse prognosis than those with nonbulky tumors. Therefore, patients who have undergone radical hysterectomy and pelvic lymphadenectomy for early-stage bulky cervical cancer have traditionally received postoperative adjuvant pelvic radiation therapy. However, a recent randomized trial from Italy demonstrated that radical hysterectomy plus radiotherapy does not improve overall or disease-free survival in patients with

early-stage bulky tumors, as compared with radiation therapy alone, but does significantly increase morbidity.

Furthermore, a recent GOG trial demonstrated the benefit of the addition of cisplatin chemotherapy to pelvic radiation followed by extrafascial hysterectomy in this group of patients (Figure 1). Therefore, many experts feel that patients with stage IB2 and bulky IIA cervical cancer should be treated initially with chemoradiation followed by adjuvant extrafascial hysterectomy.

RADIATION THERAPY FOR STAGES I-IV DISEASE

The role of curative surgery diminishes once cervical cancer has spread beyond the confines of the cervix and vaginal fornices. Intracavitary radiation for central pelvic disease and external-beam radiation therapy for lateral parametrial and pelvic nodal disease are typically combined to encompass the known patterns of disease spread with an appropriate radiation dose while sparing the bladder and rectum from receiving full doses. The addition of intracavitary radiation to external-beam radiation is associated with improved pelvic control and survival over external radiation alone, as the combination can achieve high central doses of radiation.

Radiation techniques

Intracavitary brachytherapy Radioactive isotopes, such as cesium-137, can be introduced directly into the uterine cavity and vaginal fornices with special applicators. The most commonly used applicator is the Fletcher-Suit intrauterine tandem and vaginal ovoids.

Calculating dose rates With the advent of computerized dosimetry, the dose rate to a number of points from a particular source arrangement can be calculated. Adjustments in the strength or positioning of the sources can then be made to yield a selected dose rate to one or more points.

Quantification of acceptable implant geometry was recently described by Katz et al after review of 808 implants performed in 396 cervical cancer patients treated with radiation at M. D. Anderson Cancer Center. These guidelines set the standard for high-quality tandem and ovoid insertions.

Points of interest usually include the maximum rectal and bladder dose, as well as the dose to three standard pelvic points: A, B, and P (see Figure 2). Point A is located 2 cm cephalad from the cervical os and 2 cm lateral to the uterine canal. Anatomically, it represents the medial parametrium/lateral cervix, the approximate point at which the ureter and uterine artery cross. Point B is 5 cm lateral to the center of the pelvis at the same level as point A and approximates the region of the obturator nodes or lateral parametrium. Point P is located along the bony pelvic sidewall at its most lateral point and represents the minimum dose to the external iliac lymph nodes.

LDR vs HDR brachytherapy Standard dose rates at point A are typically 50-70 cGy/h; this is considered low-dose-rate (LDR) brachytherapy. The applicator is placed into the uterus while the patient is under anesthesia in the operating room, and the patient must stay in bed in the hospital for 2-3 days during the

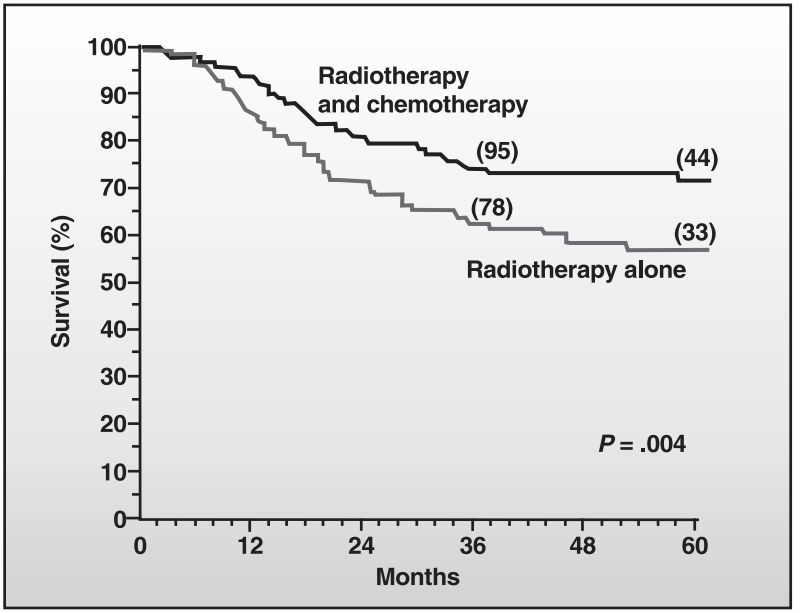

FIGURE 3: Improvement in survival for chemoradiation for advanced cervix cancer compared with radiation alone (RTOG).

Numbers in parentheses are the numbers of patients alive and included in a follow-up assessment at 3 and 5 years.

Reprinted, with permission, from Morris M, Eifel PJ, Lu J, et al: Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 340(15):1137-1143, 1999. *Copyright 1999, Massachusetts Medical Society. All rights reserved.*

implant. One or two implants are usually placed. Despite the fact that two insertions may allow time for regression of disease between placements, there are no data indicating that two insertions improve pelvic control or survival rates over one insertion.

Whereas LDR brachytherapy has been used successfully for decades in the treatment of carcinoma of the cervix, the use of high-dose-rate (HDR) brachytherapy has been increasing in the United States over the last decade. Dose rates are typically 200-300 cGy/min, with short treatment times allowing for stable position of the applicator.

The major benefit of HDR brachytherapy is that the procedure can be performed on an outpatient basis with less radiation exposure to personnel. The major disadvantage is biological: large single fractions of radiation (5-10 Gy) are used with 3-10 insertions per patient, which may increase the rate of late complications.

Several series have cited comparable disease control and complication rates with HDR and LDR brachytherapy. HDR brachytherapy is an alternative to

LDR brachytherapy in the current GOG and Radiation Therapy Oncology Group (RTOG) advanced cervical cancer trial.

Guidelines have been recently published for HDR brachytherapy for cervical cancer by the American Brachytherapy Society.

External-beam pelvic radiation therapy is used in conjunction with intracavitary radiotherapy for stages IA2 disease and above when the risk of pelvic lymph node involvement is significant. The amount of external-beam radiation delivered and the timing of its administration relative to intracavitary radiation is individualized. For example, the presence of a large exophytic cancer that distorts the cervix would initially preclude successful placement of intracavitary brachytherapy. External-beam radiotherapy would be administered first, and after significant regression of disease, could be followed by intracavitary radiotherapy.

Various techniques have been developed to optimize external-bean radiation including CT simulation, conformal blocking, and more recently, intensity-modulated radiation therapy (IMRT). These techniques reduce the volume of normal tissue having full-dose radiation while coverage of the target is not compromised.

Advanced tumors require relatively more external radiation due to the inability of central radioisotope sources to effectively irradiate disease in the lateral parametrium. Typically, external pelvic doses of 4,000-5,000 cGy are followed by 4,000-5,000 cGy to point A with intracavitary brachytherapy, for a total dose of 8,000-9,000 cGy to point A. A parametrial boost completes treatment to the lateral pelvis, for a total dose to point B or P of 6,000 cGy from external-beam radiation and brachytherapy, depending on the extent of disease.

External-beam para-aortic radiation therapy may be used in addition to external-beam pelvic radiation when para-aortic disease is confirmed or suspected. An RTOG trial found that external-beam para-aortic radiation conferred a survival benefit in patients with advanced cervical cancer (stage IB > 4 cm, stage IIA, and stage IIB) over external-beam pelvic therapy alone. Although external-beam radiation therapy can successfully sterilize microscopic disease, its value in the treatment of gross para-aortic disease is limited, as the tolerance

TABLE 3: Relationship between tumor size and outcome in patients with tumors ≥ 5 cm treated with radiation alone[a]

Tumor size (cm)	Number of patients	Central pelvic control rate (%)	Total pelvic control rate (%)	DSS (%)
5-5.9	200	93	85	69
6-6.9	99	92	79	69
7-7.9	55	90	81	58
≥ 8	48	69	57	40

[a] Excludes patients who underwent adjuvant hysterectomy DSS = disease-specific survival

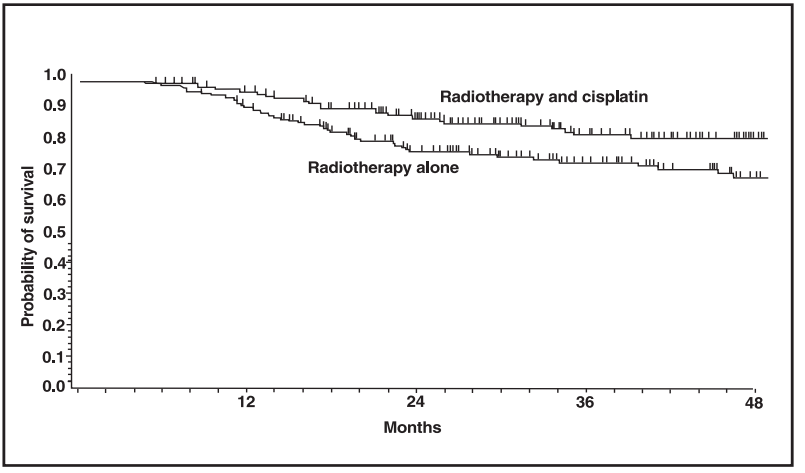

FIGURE 4: Improvement in survival for chemoradiation compared with radiation alone for bulky IB cervical cancer (GOG).

The rate of survival was significantly higher among patients in the combined-therapy group ($P = .008$). Tick marks indicate patients who died.

Adapted, with permission, from Keys HM, Bundy BN, Stehman FB, et al: Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 340(15):1154-1161, 1999. *Copyright 1999, Massachusetts Medical Society. All rights reserved.*

of surrounding organs (bowel, kidney, spinal cord) precludes the delivery of sufficiently high doses to the para-aortic region.

In multivariate analysis, treatment factors associated with improved pelvic control for cervical cancer include the use of intracavitary brachytherapy, total point A dose > 8,500 cGy (stage III only), and overall treatment time < 8 weeks.

Definitive radiation therapy

CIS, stage IA disease Carcinoma in situ (CIS) and microinvasive cervical cancer (stage IA) are not associated with lymph node metastases. Therefore, intracavitary brachytherapy alone, delivering approximately 5,500 cGy to point A, can control 100% of CIS and stage IA disease and is an acceptable alternative to surgery for patients who cannot undergo surgery due to their medical condition.

Stage IB disease The most important prognostic factor associated with pelvic tumor control and survival following radiation therapy for stage IB cervical cancer is tumor size. The central pelvic control rate with radiotherapy alone is excellent for tumors < 8 cm (97%), with total pelvic control and survival rates of 93% and 82%, respectively. Therefore, many experts have argued that adjuvant hysterectomy is unnecessary for cervical cancer < 8 cm. For bulky cervical cancers ≥ 8 cm, pelvic control and survival rates decrease to 57% and 40%, respec-

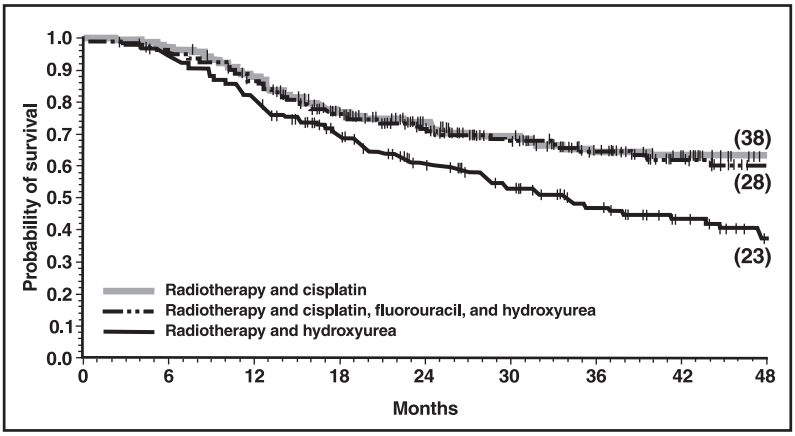

FIGURE 5: Improvement in survival for chemoradiation with either weekly cisplatin or cisplatin, 5-FU, and hydroxyurea compared with radiation and hydroxyurea for advanced cervical cancer (GOG).

Tick marks indicate patients who died. Numbers in parentheses are the numbers of patients at risk at 4 years.

Adapted, with permission, from Rose P, Bundy BN, Watkins EB, et al: Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 340(15):1144-1153, 1999. *Copyright 1999, Massachusetts Medical Society. All rights reserved.*

tively, with irradiation alone, and adjuvant hysterectomy may potentially improve local control and survival rates (Table 3).

A recently completed RTOG trial (RTOG 9001) for advanced cervical cancer (stage IB or IIA with tumor ≥ 5 cm or with biopsy-proven pelvic lymph node involvement and stage IIB-IVA) compared external-beam pelvic radiation plus concurrent fluorouracil (5-FU) and cisplatin with external-beam pelvic and para-aortic radiation; in both arms, these therapies were followed by intracavitary radiation. The addition of chemotherapy to radiation improved 5-year survival from 58% to 73% and disease-free survival from 40% to 67% by reducing rates of both local recurrence and distant metastases (Figures 1 and 3).

Five national phase III trials of concurrent chemotherapy and irradiation have reported improved survival vs irradiation alone for stages IB2-IVA cervical cancer.

A previous trial by the GOG attempted to define the best local therapy (radiation therapy alone or radiation followed by extrafascial hysterectomy) in bulky stage IB2 cervical disease (defined as > 4 cm). The results of this trial suggested that adjuvant hysterectomy reduces the risk of pelvic recurrence but does not affect overall survival.

A subsequent GOG trial (GOG 123) randomized similar patients to either local treatment alone (external and intracavitary radiation followed by hysterec-

tomy) or local therapy plus weekly cisplatin. The combination of concurrent weekly cisplatin and radiation significantly reduced the relapse rate and improved survival by 50%. The 3-year survival rate was significantly improved from 74% to 83% with the use of chemotherapy; this was primarily due to a reduced risk of local recurrence (21% vs 9%) (Figures 1 and 4). The current GOG trial (GOG 0201) for stage IB2 cervical cancer randomizes patients to undergo radical hysterectomy and tailored postoperative chemoradiation vs primary chemoradiation without surgery.

Current treatment recommendations Concurrent radiotherapy and chemotherapy (usually cisplatin-based) with or without adjuvant hysterectomy are standard treatments for bulky IB2 cervical cancer.

The use of adjuvant hysterectomy is controversial for small (< 8 cm) stage IB2 cervical cancer, since dose-intense external pelvic and intracavitary radiation plus chemotherapy may obviate the need for adjuvant surgery. The GOG trial suggests that adjuvant hysterectomy reduces the recurrence rate but does not affect survival.

The use of weekly cisplatin × 6 cycles or 5-FU and cisplatin every 3 weeks × 2 cycles concurrent with radiotherapy is the standard treatment approach for bulky IB cervical cancer.

Stage IIA-IVA disease The most important prognostic factor associated with pelvic tumor control and survival is the bulk of pelvic disease within each stage. For stage IIB, bulky disease is variously defined as bilateral or lateral parametrial infiltration or central bulky disease > 5 cm in diameter. For stage IIIB, bulky disease is defined as bilateral sidewall involvement, lower third vaginal involvement, or hydronephrosis.

In the previous GOG experience, in which para-aortic lymph node staging had been mandated, multivariate analysis testing revealed para-aortic lymph node involvement to be the most powerful negative prognostic factor, followed by pelvic lymph node involvement, larger tumor diameter, young age, advanced stage, and lower performance status for patients with negative para-aortic lymph nodes. Five-year survival rates for radiotherapy alone vary from 80% for stage I, 60% for stage II, and 35% for stage III disease, with corresponding pelvic control rates of 90%, 80%, and 50%, respectively.

Chemoradiation Attempts by cooperative groups to improve upon these results have generally included concurrent chemotherapy with standard radiation therapy. The GOG has completed a phase III trial (GOG 85) randomizing stage IIB-IVA patients with pathologically negative para-aortic lymph nodes to pelvic external-beam radiation plus hydroxyurea (Hydrea) vs pelvic external-beam radiation plus 5-FU and cisplatin followed, in both arms, by intracavitary radiotherapy. Compared with hydroxyurea, the use of 5-FU and cisplatin was associated with a significant improvement in survival, as well as a decrease in relapse (Figure 1).

A subsequent GOG phase III trial (GOG 120) compared standard pelvic external-beam radiation/intracavitary brachytherapy plus hydroxyurea vs weekly

cisplatin vs hydroxyurea, 5-FU, and cisplatin. Both the weekly cisplatin and the 5-FU-cisplatin-hydroxyurea arms produced significantly improved survival and relapse rates compared to hydroxyurea alone. Two-year progression-free survival rates were significantly improved from 47% to 67% and 64% with weekly cisplatin-radiation and 5-FU-cisplatin-hydroxyurea-radiation compared with hydroxyurea and radiotherapy (Figures 1 and 5). The improved outcome was due to reduced rates of pelvic failure and lung metastases. Because of an improved therapeutic ratio, weekly cisplatin is the favored regimen.

A recently completed GOG trial (GOG 165) compared standard radiation therapy plus concurrent weekly cisplatin vs concurrent protracted venous infusion 5-FU (225 mg/m^2/d over 5 weeks) as radiation sensitizers. In this study, the dose of radiation to point A had been increased by 500 cGy, and the pelvic fields redefined to improve the dose intensity and accuracy of radiotherapy.

A recent meta-analysis of 4,580 randomized patients described a 16% absolute benefit in progression-free survival and 12% benefit in overall survival rates for concomitant chemotherapy and radiation for stage IB-IVA cervical cancers. In contrast, the NCI of Canada recently reported no advantage to weekly cisplatin concurrent with irradiation for advanced cervical cancer over irradiation alone.

As mentioned above, the RTOG study (RTOG 9001) of advanced cervical cancer compared pelvic and para-aortic external-beam radiotherapy to pelvic radiation plus 5-FU/cisplatin-based chemotherapy, both followed by intra-cavitary radiation (see previous page).

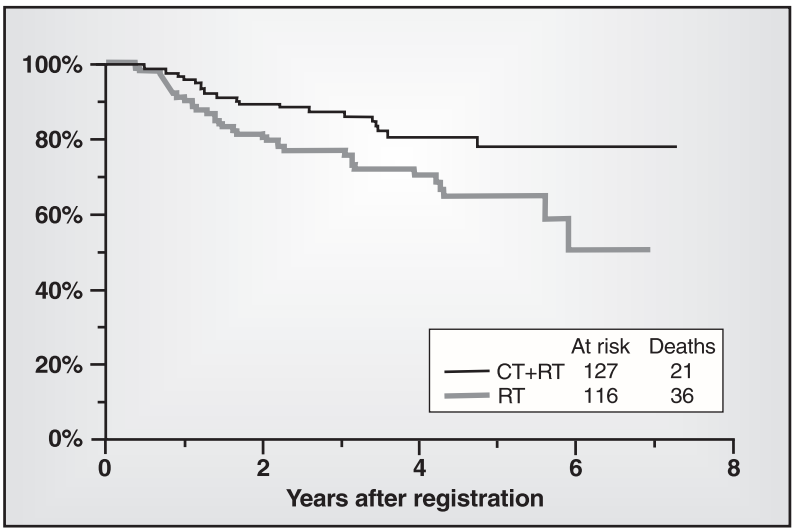

FIGURE 6: Improvement in survival for patients with positive nodes following radical hysterectomy for cervical cancer with combined chemoradiation compared with pelvic irradiation alone.

Reprinted, with permission, from Peters WA, Liu PY, Barrett RJ, et al: J Clin Oncol 18(8):1606-1613, 2000.

The current phase II RTOG trial (RTOG 0128) for advanced cervical cancers (IB/IIA and tumor size > 5 cm or IIB-IVA) and negative para-aortic lymph nodes is studying the benefit of celecoxib (Celebrex) and chemoradiation with 5-FU and cisplatin.

For patients with advanced cervical cancer and positive para-aortic lymph nodes, the RTOG phase I/II study (RTOG 9210) is studying the benefit of amifostine in addition to extended-field radiation with weeky cisplatin. The GOG phase III study (GOG 0191) for advanced cervical cancer and negative para-aortic lymph nodes is being conducted to determine the benefit of epogen/transfusion in addition to chemoradiation with weekly cisplatin for patients with Hgb < 130 g/L.

Current treatment recommendations For patients without para-aortic lymph node metastases, pelvic external radiation (4,000-5,000 cGy) should be used, followed by intracavitary brachytherapy (4,000-5,000 cGy) to point A, for a total dose of 8,000-9,000 cGy to point A.

In view of the multiple randomized trials documenting a survival benefit with concurrent chemoradiation, the use of concurrent weekly cisplatin or cisplatin-5-FU every 3 weeks with radiation is standard therapy for stages IB2-IVA cervical cancer (Figure 1, Table 4). Determination of the benefit of protracted infusional 5-FU administered concurrently with radiotherapy awaits analysis of the recently closed GOG trial.

Adjuvant radiotherapy following radical hysterectomy

Node-negative patients Local failure rates approach 20% following radical hysterectomy and pelvic lymphadenectomy when pelvic lymph nodes are not involved but the primary tumor has high-risk characteristics (primary tumor > 4 cm, outer third cervical stromal invasion, and capillary-lymphatic space invasion). A recently completed GOG trial randomized these intermediate-risk, node-negative patients to receive pelvic external-beam radiation therapy (5,100 cGy/30 fractions) or no further therapy following radical hysterectomy-pelvic lymphadenectomy. Postoperative radiation produced a significant 44% reduction in recurrence; the recurrence-free rate at 2 years was 88% with radiation vs 79% without it. Survival analysis awaits further follow-up.

Node-positive patients For patients with positive pelvic lymph nodes following radical hysterectomy–pelvic lymphadenectomy, pelvic radiotherapy reduces the pelvic failure rate from approximately 50% to 25% but does not affect survival since distant metastases are still seen in 30% of patients. A recently reported GOG/Southwest Oncology Group (SWOG 8797) trial randomized these high-risk, node-positive patients (or patients with positive surgical margins) to pelvic external-beam radiation (4,930 cGy/29 fractions) vs pelvic external-beam radiation plus concurrent 5-FU and cisplatin for 4 cycles following radical hysterectomy–pelvic lymphadenectomy. A significant improvement in progression-free and overall survival was seen for concurrent 5-FU-cisplatin and radiation therapy compared with radiation therapy alone (4-year survival, 81% vs 71%) (Figures 1 and 6).

Current treatment recommendations At present, the use of adjuvant pelvic radiotherapy should be considered for patients with negative nodes who are at risk for pelvic failure, and remains the standard postoperative treatment for patients with positive lymph nodes. Treatment consists of external pelvic radiation (45-50 Gy), with specific sites boosted with further external-beam or intracavitary radiation as needed.

Since the combination of radical surgery and irradiation has greater morbidity than either modality alone, complete preoperative assessment is crucial to minimize the need for both.

Since concurrent chemoradiation following radical hysterectomy provides a significant benefit in node-positive high-risk cervical cancer, it should be part of the postoperative treatment plan. The current GOG trial for stage IB2 cervical cancer mandates postoperative chemoradiation following radical hysterectomy for patients with positive margins or parametria, involved pelvic or paraortic lymph nodes, ≥ middle-third stromal invasion, and lymphovascular space invasion in tumors ≥ 5 cm.

SURGICAL MANAGEMENT OF RECURRENT OR METASTATIC DISEASE

Recurrent advanced disease

Pelvic exenteration For patients whose disease fails to respond to primary radiation therapy or those with early invasive cervical carcinoma whose disease recurs after surgery or radiation therapy, pelvic exenteration offers the possibility of cure. Patients should be considered for pelvic exenteration only if they have locoregional disease that can be completely removed by this radical surgical procedure. In most cases, patients will require surgical removal of the bladder, uterus, cervix, vagina, and rectum.

Of all patients who are considered candidates for pelvic exenteration, only about half will be found to have resectable disease at the time of exploratory laparotomy. For patients who successfully undergo pelvic exenteration, 5-year survival rates range from 25% to 50%.

When the patient has a central recurrence of squamous cell or adenocarcinoma of the cervix, the initial evaluation includes a complete physical examination, as well as an abdominopelvic CT or MRI scan and, usually, a chest CT scan. Evidence of extrapelvic disease is a contraindication to pelvic exenteration. If no evidence of disease beyond the pelvis is found, the patient can be prepared for pelvic exenteration.

Preparation for exenteration includes complete bowel preparation, a visit with the stoma therapy nurse, and counseling regarding the radical nature of the surgery and the anticipated changes in body image after the operation. In most cases, we counsel the patient that vaginal reconstruction should be done at the time of pelvic exenteration, both for maintenance of body image and improved healing.

Surgical procedure During surgery, a careful exploration is carried out to confirm that there is no evidence of unresectable disease beyond the pelvis. The pelvic sidewall spaces are opened and resectability is determined. An en bloc resection is usually carried out; in some cases, especially when the recurrent tumor involves the lower vagina, a two-team approach can expedite the procedure. The actual exenterative portion of the procedure may take several hours and is usually accompanied by significant blood loss. In cases where surgical margin status may be questionable, the use of intraoperative radiation therapy is considered.

Reconstruction Following the exenterative procedure, the reconstructive portion of the procedure begins. We currently recommend to nearly all patients that they consider a continent urinary diversion. While this may add approximately ½-1 hour to the surgical procedure, the improvement in quality of life is significant.

In patients who have undergone a supralevator pelvic exenteration, we frequently attempt a stapled reanastomosis of the colon. Unless there is excessive tension on the anastomosis or other problems, a diverting colostomy is not routinely indicated. About one-third of these patients suffer anastomotic breakdown in the postoperative period. At that time, a diverting colostomy can be performed. Unfortunately, Hatch et al found no benefit to the earlier use of colostomy.

Lung metastasis

For the rare patient who presents with a single isolated lung metastasis after treatment of invasive cervical carcinoma, pulmonary resection may offer the possibility of long-term disease-free survival or even cure in selected cases. For patients who have multiple lung metastases or unresectable pelvic disease, surgery offers little or no hope and produces significant morbidity and mortality.

RADIATION THERAPY FOR RECURRENT OR METASTATIC DISEASE

Local recurrence after radical hysterectomy

Local recurrence confined to the pelvis and para-aortic lymph nodes following radical hysterectomy for cervical cancer can be treated with radiotherapy with curative intent. An experience with 5-FU-based chemotherapy and concurrent pelvic external-beam radiation resulted in a 58% complete response rate and a 45% no-evidence-of-disease rate at a median follow-up of 57 months. The total pelvic external-beam dose was 5,280 cGy plus a boost to sites of recurrence with twice-daily 160-cGy fractions during the 5-FU infusion. Therefore, radiotherapy, with or without chemotherapy, can provide durable local control, with better results attainable for small, central recurrences, for which brachytherapy is possible.

Local recurrence after definitive radiation

Local recurrence confined to the pelvis following definitive radiation therapy rarely can be cured with exenteration. In a series of patients treated with de-

TABLE 4: Chemotherapy regimens for advanced cervical carcinoma

Drug/combination	Dose and schedule
BIC	
Bleomycin	30 U IV on day 1
Ifosfamide	2,000 mg/m^2 IV on days 1-3
Mesna	400 mg/m^2 IV 15 minutes prior to ifosfamide, then 400 mg/m^2 IV 4 and 8 hours following ifosfamide (800 mg/m^2 of mesna may be given PO according to the same schedule)
Carboplatin	200 mg/m^2 IV on day 1
Repeat cycle every 21 days	
Murad AM, Santiago FF, Triginelli SA: Proc Am Soc Clin Oncol 11:229, 1992.	
Fluorouracil/cisplatin concurrently with pelvic irradiation—for high-risk patients	
Radiation therapy	1.8 Gy per fraction (total dose, 45 Gy) to the pelvic and para-aortic lymph nodes
Cisplatin	75 mg/m^2 IV infused over 4 hours
Followed by	
Fluorouracil	4 g/m^2 infused continuously over 96 hours
Give chemotherapy 16 hours after the administration of the first radiation fraction (days 1-5 of radiation therapy). Repeat chemotherapy every 21 days for additional 2 cycles	
Morris M, Eifel PJ, Lu J, et al: N Engl J Med 340:1137–1143, 1999.	
Cisplatin-based chemotherapy/radiation therapy—for locally advanced cervical cancer	
Radiation therapy	24 fractions totaling 40.8 Gy or 30 fractions totaling 51.0 Gy to the whole pelvis, followed, 1 to 3 weeks later, by intracavitary brachytherapy
Cisplatin	40 mg/m^2 IV infused over 4 hours per week for 6 weeks before irradiation (ie, at weeks 1 to 6 of irradiation)
or	
Cisplatin	50 mg/m^2 IV on days 1 and 29 of irradiation
Fluorouracil	4 g/m^2 given as an IV infusion continuously over 96 hours on days 1 and 29 of irradiation
Hydroxyurea	2 g/m^2 PO twice weekly 2 hours before irradiation at weeks 1-6
Give chemotherapy concurrently with radiation therapy	
Rose PG, Bundy BN, Watkins EB, et al: N Engl J Med 340:1144–1153, 1999.	

Table prepared by Ishmael Jaiyesimi, DO

finitive radiotherapy, 21% (80/376) of recurrences were isolated to the pelvis. Only 29% (23/80) of these localized pelvic recurrences were explored for curative exenteration, and for the 43% (10/23) of patients deemed operable, the 5-year survival rate was 16%.

TABLE 5: Single-agent chemotherapy for cervical cancer

Drug	Number of responses (%)	Drug	Number of responses (%)
Alkylating agents		**Antimetabolites**	
Cyclophosphamide	38/251 (15)	5-FU	29/142 (20)
Chlorambucil	11/44 (25)	Methotrexate	17/96 (18)
Melphalan	4/20 (20)	Hydroxyurea	0/14 (0)
Ifosfamide	39/126 (31)	Gemcitabine[a]	5/45 (11)
Dibromodulcitol	16/55 (29)		
		Camptothecins	
		Irinotecan (CPT-11)	20/97 (21)
		Topotecan	4/21 (19)
Heavy metal complexes		**Plant alkaloids**	
Cisplatin	182/785 (23)	Vincristine	10/55 (18)
Carboplatin	56/301 (19)	Vinblastine	2/20 (10)
Iproplatin	31/217 (14)	Vindesine	5/49 (10)
		Etoposide	0/31 (0)
		Teniposide	3/22 (14)
Antitumor antibiotics		**Taxanes**	
Doxorubicin	33/205 (16)	Paclitaxel	
Bleomycin	19/176 (11)	CCOP[b]	9/33 (27)
Mitomycin	6/52 (12)	GOG[c]	9/52 (17)
		Docetaxel[d]	6/32 (19)
Miscellaneous agents			
Hexamethylmelamine	12/64 (19)		

Adapted from Thigpen T, Vance RB, Khansur T: Carcinoma of the uterine cervix: Semin Oncol 21(suppl 2):45, 1994; Vermorken JB: Int J Gynaecol Cancer 3:130, 1993; Rose PG: Chemotherapy of cervical cancer, in Depp G, Baker VV (eds): Gynecologic Oncology-Principles and Practice of Chemotherapy, pp 150-184. Arnold, London, 1999.

CCOP = Community Clinical Oncology Program; GOG = Gynecologic Oncology Group

[a] Goedhals L, Bezwoda WR: Proc Am Soc Clin Oncol 15:296 (abstract 819), 1996.

[b] Kudelka AP: Personal communication, December 2001.

[c] McGuire WP, Blessing JA, Moore D, et al: J Clin Oncol 14:792–795, 1996.

[d] Kudelka AP: Personal communication, December 2001.

Palliation of metastatic disease

Palliative radiation therapy to sites of metastatic cervical cancer is effective. The most common sites of metastasis are distant lymph nodes, bone, and lung. Reirradiation of the pelvis is possible in selected patients to control local symptoms, such as bleeding, but carries an increased risk of bowel complications.

TABLE 6: Combination chemotherapy for advanced or recurrent cervical carcinoma

Chemotherapy regimen	Number of evaluable patients	Prior radiation therapy (%)	Complete response rate (%)	Overall response rate (%)
Bleomycin/ifosfamide/cisplatin	49	86	20	69
Bleomycin/ifosfamide/carboplatin	21	49	23	60
Vinblastine/bleomycin/cisplatin	33	66	18	67
5-FU/doxorubicin/vincristine/ cyclophosphamide	31	87	9	58
Paclitaxel/cisplatin[a]	130	91	–	36
Paclitaxel/carboplatin[b]	32	–	22	72
Gemcitabine/cisplatin[c]	32	69	25	63
Irinotecan/cisplatin[d]	27	–	4	37

From Lopez A, Kudelka AP, Edwards CL, et al: Carcinoma of the uterine cervix, in Pazdur R (ed): Medical Oncology: A Comprehensive Review, 2nd ed. Melville, New York, PRR, 1996.

[a]Moore DH (abstract 801); [b]Mickiewicz E (abstract 825); [c]Mahfouf H (abstract 824); [d]Garin A (abstract 826): Proc Am Soc Clin Oncol 20: 201a-207a, 2001.

For previously unirradiated sites of metastatic disease, 3,000 cGy in 10 fractions provides palliation of symptoms in the majority of patients.

CHEMOTHERAPY FOR ADVANCED/RECURRENT DISEASE

Chemotherapy has traditionally been used for the palliative management of advanced or recurrent disease that can no longer be managed by surgery or radiation therapy (see Table 4). Various factors complicate the use of chemotherapy in such patients, however. Prior radiation treatment can affect the blood supply to the involved field, which may result in decreased drug delivery to the tumor site. Pelvic irradiation also reduces bone marrow reserve, thus limiting the tolerable doses of most chemotherapeutic agents. Moreover, radiation may produce its cytotoxic effect, in part, through a mechanism similar to that of alkylating agents; thus, it is thought to be cross-resistant with some chemotherapeutic agents. A significant number of patients with advanced disease may also have impaired renal function, further limiting the use of certain chemotherapeutic regimens.

Single agents

Among the chemotherapeutic agents used for cervical cancer, cisplatin and ifosfamide (Ifex) have shown the most consistent activity as single agents (Table 5). The duration of response with any single agent is brief, ranging from 4 to 6 months, with survival ranging from 6 to 9 months.

Cisplatin has been the most extensively evaluated single agent for cervical carcinoma. A dose of 100 mg/m^2 was shown to have a higher response rate

than a dose of 50 mg/m^2 (31% vs 21%), but the higher dose was associated with increased toxicity, and overall survival did not differ significantly between the two groups. A 24-hour infusion of cisplatin was tolerated better than a 2-hour infusion, with no difference in therapeutic efficacy.

Ifosfamide produces response rates ranging from 33% to 50% in various dose schedules. A dose of 1.5 g/m^2 over 30 minutes for 5 days (with mesna [Mesnex]) produced an overall response rate of 40% and a 20% complete response rate.

Lower response rates are generally seen in patients who have had prior chemotherapy. Responses also are decreased in previously irradiated sites.

Taxanes Paclitaxel and docetaxel (Taxotere) have been reported to have activity in cervical cancer. A study of paclitaxel (170 mg/m^2 over 24 hours) showed an objective response rate of 17%, and another study of paclitaxel (250 mg/m^2 over 3 hours) demonstrated an objective response rate of 27%. Docetaxel (100 mg/m^2 over 1 hour) has yielded a response rate of 19%.

Camptothecins Irinotecan (CPT-11 [Camptosar]), and topotecan (Hycamtin) semisynthetic camptothecins, have shown activity in patients with cervical cancer, even in patients who did not respond to prior chemotherapy and prior radiation therapy. The reported objective response rates were 21% and 19%, respectively.

Combination regimens

Various combination chemotherapy regimens have been evaluated in phase II trials, and high response rates ($>$ 50%) were noted even in patients who had received prior radiation therapy. The results of some of these trials are summarized in Table 6. In one study, a subset analysis showed a response rate of 72% with the combination of bleomycin, ifosfamide, and cisplatin as treatment for tumors located in previously irradiated sites. Neoadjuvant regimens of cisplatin combined with gemcitabine in patients with locally advanced cervix cancer demonstrated very high activity, with a clinical response rate of 95%. Neoadjuvant ifosfamide and cisplatin with or without paclitaxel reported 87% and 82% response rates, respectively, among 146 evaluable patients in a randomized study. However, no adequate phase III trial has yet determined whether polychemotherapy regimens offer a survival benefit over single-agent cisplatin.

NEOADJUVANT CHEMOTHERAPY

The use of chemotherapy in the neoadjuvant (primary) setting has also been investigated. Four randomized trials in which patients with stages IIB-IVA disease were treated either with various cisplatin-based combination chemotherapy regimens followed by radiation therapy or with radiation therapy alone failed to show any survival benefit of neoadjuvant chemotherapy. In fact, one of these studies showed increased toxicity and decreased survival in the patients given neoadjuvant therapy. Another trial also reported significantly inferior

local disease control and survival rates in the patients randomized to receive primary chemotherapy compared to those who received radiotherapy alone.

Theoretically, increased toxicity with neoadjuvant chemotherapy may prevent delivery of adequate radiation doses. As mentioned above, there also is the issue of cross-resistance between these two modalities.

Neoadjuvant chemotherapy combined with surgery may decrease lymph node involvement, as compared with historical controls. However, a randomized trial of patients with stage IB bulky disease failed to show any benefit in overall survival for patients receiving neoadjuvant cisplatin, vincristine, and bleomycin, when compared to patients receiving surgery and postoperative radiation therapy alone.

ADJUVANT CHEMOTHERAPY AFTER RADICAL HYSTERECTOMY

Adjuvant chemotherapy has shown no benefit in patients found to have pelvic lymph node involvement after a radical hysterectomy. A randomized trial failed to demonstrate any improvement in survival and relapse rates when this group of patients was treated with adjuvant cisplatin, vinblastine, and bleomycin.

INTRA-ARTERIAL CHEMOTHERAPY

The use of intra-arterial chemotherapy offers the theoretical advantage of increased drug concentration at the tumor site, as well as the possibility of decreased systemic drug delivery. Most response rates obtained with various intra-arterially administered regimens have not been superior to rates achieved with IV chemotherapy, however. Furthermore, significant drug- and catheter-related toxicity has been seen with intra-arterial chemotherapy.

BIOLOGICAL AGENTS

Retinoids and interferon The combination of 13-*cis*-retinoic acid and interferon-alfa 2a (IFN-α-2a [Roferon-A]) produced an overall response rate of 50% (12% complete response rate) in 32 previously untreated patients who had locally advanced squamous cell carcinoma of the cervix. The drugs were administered daily for at least 2 months at doses of 1 mg/kg PO for 13-*cis*-retinoic acid and 6 million units SC for IFN-α-2a. After a median response duration of 3 months, 9 of the 16 responders eventually progressed. Only minimal toxicity was seen with this regimen.

Both interferons and retinoids have antiviral as well as immunoregulatory properties, and they also modulate malignant cell differentiation and proliferation. Furthermore, they are known to inhibit angiogenesis, and serial biopsies of the responders in the study described above showed a significant reduction in the number of blood vessels.

Preliminary data from an ongoing trial of an induction regimen of 13-*cis*-retinoic acid and IFN-α-2a followed by concomitant radiobiotherapy in patients with

> stage II active cervical cancer showed this regimen to be tolerable; 70% of patients treated with this regimen were free of disease at 1 year.

Angiogenesis inhibitors Angiogenesis inhibition is a novel approach to cancer treatment. TNP-470, a fumagillin analog that inhibits angiogenesis, is being evaluated in cervical cancer. In a phase I study, a patient with metastatic disease treated with this agent has maintained a complete response for over 2 years, and three other patients have stabilization of progressive disease. A phase II study, however, failed to confirm the activity of TNP-470 in cervical cancer.

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A color atlas of cervical lesions

Compiled by John P. Curtin, MD

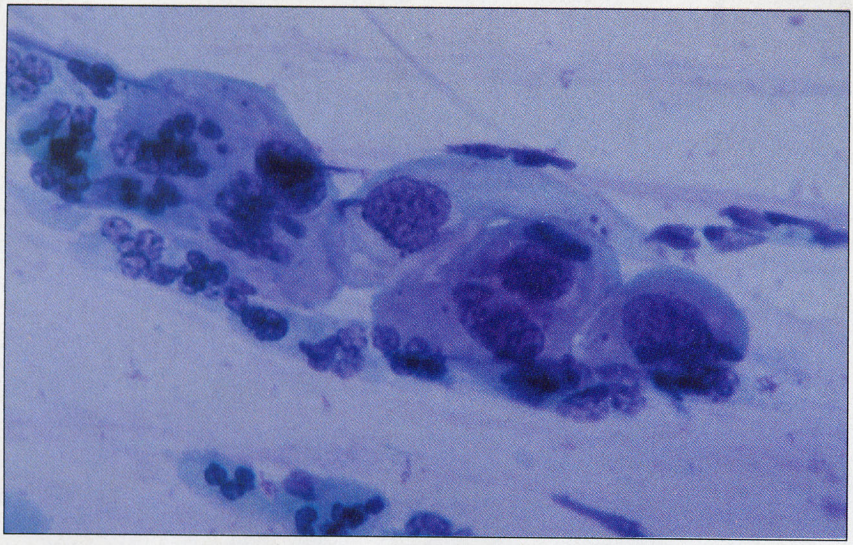

FIGURE 1: Pap smear demonstrating a high-grade squamous intraepithelial lesion.

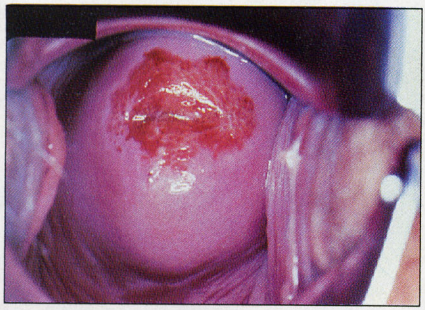

FIGURE 2: Colposcopy of a normal cervix showing the transformation zone. (Figures 1 through 6 courtesy of the American Society for Colposcopy and Surgical Pathology)

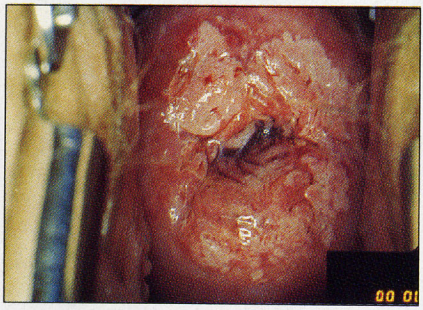

FIGURE 3: Colposcopic photograph of a cervix with a very large transformation zone. There are areas of dense white epithelium with sharp borders present, extending from ten o'clock on the interior cervix all the way across to four o'clock on the right lower quadrant.

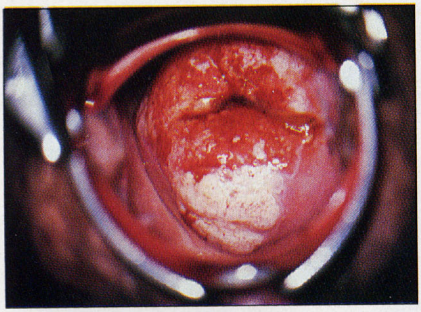

FIGURE 4: Low-power view showing area of white epithelium on the posterior lip of the cervix.

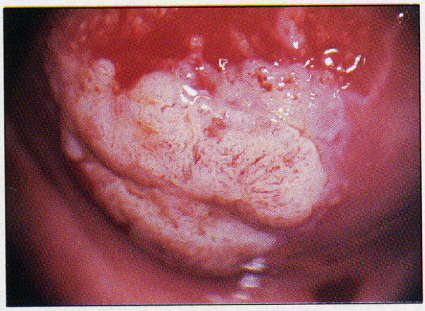

FIGURE 5: High-power view of a microinvasive lesion of the cervix, demonstrating dense white epithelium with areas of atypical blood vessels consistent with microinvasive carcinoma.

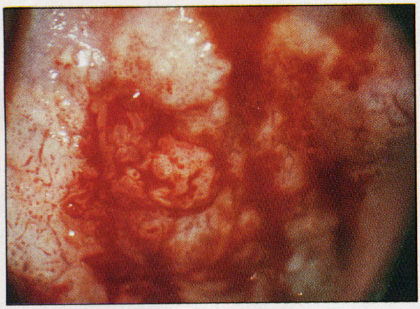

FIGURE 6: High-power view of frankly invasive squamous cell carcinoma of the cervix with areas of heaped-up ulcerative epithelium, dense white epithelium, a punctate pattern, and irregularly spaced and atypical blood vessels.

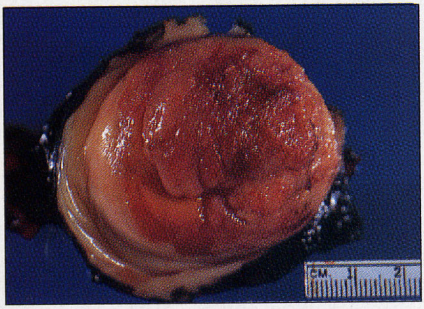

FIGURE 7: A radical hysterectomy specimen demonstrating a large stage IB2 squamous cell carcinoma of the cervix.

CHAPTER 21

Endometrial cancer

Richard R. Barakat, MD, Kathryn M. Greven, MD, and Maurie Markman, MD

Carcinoma of the epithelial lining (endometrium) of the uterine corpus is the most common female pelvic malignancy. The American Cancer Society estimates that 40,100 cases of this cancer will occur in the year 2003 in the United States. Factors influencing its prominence are the declining incidence of cervical cancer, longer life expectancy, and earlier diagnosis.

Adenocarcinoma of the endometrium, the most prevalent histologic subtype, is currently the fourth most common cancer in women, ranking behind breast, lung, and bowel cancers. Endometrial adenocarcinoma is the eighth leading cause of death from malignancy in females, accounting for 6,800 deaths each year.

Epidemiology

Age Endometrial cancer is primarily a disease of postmenopausal women, although 25% of cases occur in premenopausal patients, with 5% of cases developing in patients < 40 years old.

Geography The incidence of endometrial cancer is higher in Western nations and very low in Eastern countries.

Immigrant populations tend to assume the risks of native populations, highlighting the importance of environmental factors in the genesis of this disease. Endometrial cancers tend to be more common in urban than in rural residents. In the United States, white women have a two-fold higher incidence than black women.

Etiology and risk factors

Adenocarcinoma of the endometrium may arise in normal, atrophic, or hyperplastic endometrium. Two mechanisms are generally believed to be involved in the development of endometrial cancer. In approximately 75% of women, there is a history of exposure to unopposed estrogen, either endogenous or exogenous (type I). The tumors in these women begin as endometrial hyperplasia and progress to carcinomas, which usually are better differentiated and have a favorable prognosis.

In the other 25% of women, carcinomas appear spontaneously, are not clearly related to a transition from atypical hyperplasia, and rather arise in a background

of atrophic or inert endometrium. These neoplasms tend to be associated with a more undifferentiated cell type and a poorer prognosis (type II).

Unopposed estrogen It has been hypothesized that long-term estrogenic stimulation of the endometrium unmodified by progesterone has a role in the development of endometrial carcinoma. This hypothesis derives from observations that women who are infertile or obese or who have dysfunctional bleeding due to anovulation are at high risk for this disease, as are women with estrogen-secreting granulosa theca cell ovarian tumors. Also, the recognition that atypical adenomatous (complex) hyperplasia is a precursor of cancer, and that it is associated with unopposed estrogen in women, underscores the importance of the association among risk factors, estrogens, and cancer. In the late 1970s and early 1980s, several case-control studies demonstrated that the risk of endometrial cancer is increased 4–15-fold in long-term estrogen users, as compared with age-matched controls.

Diet The high rate of occurrence of this disease in Western societies and the very low rate in Eastern countries suggest a possible etiologic role for nutrition, especially the high content of animal fat in Western diets. There may be a relationship between high-fat diets and the higher incidence of endometrial carcinoma in women with conditions of unopposed estrogen: Endogenous estrogens rise in postmenopausal women because of increased production of androstenedione or a greater peripheral conversion of this hormone to estrone. In obese women, the extraglandular aromatization of androstenedione to estrone is increased in fatty tissue.

Obesity Phenotypically, the majority of women who develop endometrial cancer tend to be obese. Women who are 30 pounds over ideal weight have a 3-fold increased risk of developing endometrial cancer, whereas those 50 pounds or more over ideal weight have a 10-fold increased risk.

Parity Nulliparous women are at 2 times greater risk of developing endometrial cancer, females who undergo menopause after age 52 are at 2.5 times greater risk, and those who experience increased bleeding at the time of menopause are at 4 times greater risk.

Other risk factors Other known risk factors for endometrial cancer include diabetes mellitus, hypertension, endometrial hyperplasia, a family history of endometrial cancer, and use of exogenous hormones. Diabetic females have a 3-fold increased risk, and hypertensive patients have a 1.5-fold greater risk. Whereas patients found to have simple endometrial hyperplasia have a very low risk of disease progression to cancer, 29% of those with complex atypical hyperplasia, if left untreated, will develop adenocarcinoma.

Tamoxifen (Nolvadex), a nonsteroidal antiestrogen commonly used in the management of breast carcinoma, exerts its primary effect by blocking the binding of estrogen to estrogen receptors. It also exerts mild estrogenic effects on the female genital tract. This weak estrogenic effect presumably accounts for an increased frequency of endometrial carcinoma observed in women receiving prolonged adjuvant tamoxifen therapy for breast carcinoma.

Initially reported in 1985, the increased frequency of endometrial carcinoma in patients treated with tamoxifen was characterized more fully in a study of 1,846 women recorded in the Swedish Cancer Registry. This study reported a 6.4-fold increase in the relative risk of endometrial carcinoma with a daily dose of 40 mg of tamoxifen. The greatest cumulative risk was observed after 5 years of tamoxifen use.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) subsequently reported on the incidence of other cancers in 2,843 women with node-negative, estrogen-receptor–positive breast cancer treated with either tamoxifen or placebo in its B-14 randomized trial and an additional 1,220 patients treated with tamoxifen in another NSABP trial. The relative risk of endometrial carcinoma in the tamoxifen-treated patients was 7.5. The hazard rate was 0.2 case per 1,000 cases with placebo and 1.6 per 1,000 cases with tamoxifen therapy. The mean duration of tamoxifen therapy for all patients was 35 months, and 36% of the cancers had developed by 2 years after the initiation of treatment.

These data raise the question of whether tamoxifen should be used as adjuvant therapy in women at relatively low risk for breast cancer recurrence. First, it should be recognized that the endometrial cancers that develop in patients receiving tamoxifen exhibit the same stage, grade, and prognosis distribution as other endometrial cancers. There is some evidence that tamoxifen use is associated with an increased risk of uterine sarcoma; fortunately, with an annual incidence of .17/1,000 population, this risk is very low. This means that the cure rate should be high. Second, adjuvant tamoxifen reduces the cumulative rate of recurrence of breast cancer from 228 to 124 cases per 1,000 and the cumulative rate of second primary breast cancers from 40.5 to 23.5 cases per 1,000.

When all of these facts are taken into account, there is an overall 38% reduction in the cumulative hazard rate for recurrence of breast cancer in tamoxifen-treated patients. Thus, the benefits of tamoxifen outweigh the risks of endometrial cancer.

If tamoxifen is used, how should treated women be screened? The current recommendations are to educate patients about the significance of abnormal spotting, bleeding, or discharge and to investigate promptly any of these abnormalities.

Some experts have proposed that tamoxifen-treated women be screened with transvaginal ultrasound. However, recent data suggest a high false-positive rate and a low frequency of significant findings, leading to the conclusion that endometrial screening is not warranted.

Signs and symptoms

Postmenopausal women Symptoms of early endometrial carcinoma are few. However, 90% of patients complain of abnormal vaginal discharge, and 80% of these women experience abnormal bleeding, usually after menopause. In the general population, 15% of postmenopausal women presenting with abnormal bleeding will be found to have endometrial carcinoma. Signs and symptoms of more advanced disease include pelvic pressure and other symptoms indicative of uterine enlargement or extrauterine tumor spread.

Premenopausal women The diagnosis of endometrial cancer may be difficult to make in premenopausal patients. The physician must maintain a high index of suspicion in this group of patients and perform endometrial sampling in any women who complain of prolonged, heavy menstrual periods or intermenstrual spotting.

Screening and diagnosis

Screening There is no role for screening of asymptomatic patients for endometrial cancer.

Outpatient endometrial sampling procedures, such as endometrial biopsy or aspiration curettage coupled with endocervical sampling, are definitive if results are positive for cancer. The results of endometrial biopsies correlate well with endometrial curettings, and these biopsy procedures have the advantage of avoiding general anesthesia. However, if sampling techniques fail to provide sufficient diagnostic information or if abnormal bleeding persists, a formal dilation and curettage is required.

Dilation and curettage The gold standard for assessing uterine bleeding and diagnosing endometrial carcinoma is formal fractional dilation and curettage. Before dilating the cervix, the endocervix should be curetted. Next, careful sounding of the uterus is accomplished. Dilation of the cervix is then performed, followed by systematic curetting of the entire endometrial cavity. Cervical and endometrial specimens should be kept separate and forwarded for pathologic interpretation.

The American Cancer Society (ACS) recently concluded that there was insufficient evidence to recommend routine screening for endometrial cancer for average-risk women. However, the ACS recommends that at the time of menopause, all women should be informed about the risks and symptoms of endometrial cancer and strongly encouraged to report any unexpected bleeding or spotting to their physicians. Women at elevated risk for endometrial cancer from tamoxifen therapy should be informed about the risk and symptoms of endometrial cancer and strongly encouraged to report any unexpected bleeding or spotting to their physicians. In addition, results from three HNPCC (hereditary nonpolyposis colorectal cancer) registries have shown a 10-fold increased risk of endometrial cancer for women who carry the

HNPCC genetic abnormality, with a cumulative risk for endometrial cancer of 43% by age 70. Women with or at risk for HNPCC can be offered endometrial screening annually beginning at age 35, but informed decision-making after a discussion of options, including benefits, risks, and limitations of testing, is appropriate. Additional investigation is needed to determine the appropriate monitoring for endometrial cancer in HNPCC carriers.

Pathology

Adenocarcinoma Endometrioid adenocarcinoma is the most common form of endometrial carcinoma, comprising 75%-80% of cases. It varies from well differentiated to undifferentiated. The former demonstrates well-preserved glands in at least 95% of the tumor, whereas in the latter, less than half of the neoplasm shows glandular differentiation. Squamous differentiation can be seen in 30%-50% of cases.

Adenoacanthoma Adenocarcinoma with benign squamous differentiation has been termed adenoacanthoma and generally has a good prognosis.

Adenosquamous carcinoma If the squamous component resembles squamous carcinoma, the tumor is designated an adenosquamous carcinoma. These lesions tend to have a worse prognosis due to their association with a poorly differentiated glandular component.

Serous carcinoma is an aggressive form of endometrial cancer that accounts for < 10% of these tumors. Serous cancer of the endometrium closely resembles serous carcinoma of the ovaries and fallopian tubes and is usually found in an advanced stage in older women.

Clear-cell carcinomas of the endometrium closely resemble their counterparts in the cervix, vagina, and ovaries. As with serous cancers, these tumors generally occur in older women and have a poor prognosis due to their propensity for early intraperitoneal spread.

Secretory adenocarcinoma is an uncommon endometrial cancer that resembles secretory endometrium with its associated progestational changes. These cancers tend to be of low grade and have a good prognosis.

Staging and prognosis

Two large prospective Gynecologic Oncology Group (GOG) surgical staging trials reported in 1984 and 1987 helped define the prognostic factors for endometrial carcinoma and the current treatment approach. In addition to evaluating the predictive value of such factors as age, race, and endocrine status, the studies confirmed that prognosis is directly related to the presence or absence of easily determined uterine and extrauterine risk factors.

Uterine prognostic factors include histologic cell type, tumor grade, depth of myometrial invasion, occult extension of disease to the cervix, and vascular space invasion.

TABLE 1: FIGO surgical staging for endometrial cancer

Stage	grade	Characteristics
IA	G1,2,3	Tumor limited to endometrium
IB	G1,2,3	Tumor invasion to less than half of the myometrium
IC	G1,2,3	Tumor invasion to more than half of the myometrium
IIA	G1,2,3	Endocervical glandular involvement only
IIB	G1,2,3	Cervical stromal invasion
IIIA	G1,2,3	Tumor invades serosa or adnexa or positive peritoneal cytology
IIIB	G1,2,3	Vaginal metastases
IIIC	G1,2,3	Metastases to pelvic or para-aortic lymph nodes
IVA	G1,2,3	Tumor invades the bladder and/or bowel mucosa
IVB		Distant metastases, including intra-abdominal and/or inguinal lymph nodes
Histopathology—Degree of differentiation[a]		
G1		≤ 5% of a nonsquamous or nonmorular solid growth pattern
G2		6%-50% of a nonsquamous or nonmorular solid growth pattern
G3		> 50% of a nonsquamous or nonmorular solid growth pattern

FIGO = International Federation of Gynecology and Obstetrics

[a] Cases should be grouped by the degree of differentiation of the adenocarcinoma.

Extrauterine prognostic factors include adnexal metastases, intraperitoneal spread of disease to other extrauterine structures, positive peritoneal cytology, pelvic lymph node metastases, and aortic node involvement.

Uterine size was previously believed to be a risk factor and was part of the older clinical staging system. However, recent information indicates that uterine size is *not* an independent risk factor but rather relates to cell type, grade, and myometrial invasion.

Surgical staging Cell type and grade can be determined before hysterectomy, although in some series, grade, as determined by dilation and curettage, has an overall inaccuracy rate of 31% compared with grade in the hysterectomy specimen, and grade 3 tumors have an inaccuracy rate of 50%. Recognition of all of the other factors requires an exploratory laparotomy, peritoneal fluid sampling, and hysterectomy with careful pathologic interpretation of all removed tissue. This primary surgical approach led the International Federation of Gynecology and Obstetrics (FIGO) in 1988 to define endometrial cancer as a surgically staged disease, incorporating many of the prognostic factors into the staging process (Table 1).

Treatment

Surgery

Approximately 90% of patients with a diagnosis of endometrial cancer are medically able to undergo surgery. Preparation for this surgery should include evaluation of such concurrent medical problems as hypertension and diabetes, which are frequently found in patients with endometrial cancer.

Open surgical procedure The operative procedure is performed through an adequate abdominal incision that allows for thorough intra-abdominal exploration and retroperitoneal lymph node removal if necessary. On entry into the peritoneal cavity, fluid samples are obtained for subsequent cytologic determination (intraperitoneal cell washings). Next, thorough intra-abdominal and pelvic exploration is undertaken, with biopsy or excision of any suspicious lesions. In particular, the uterus should be observed for tumor breakthrough of the serosal surface. The distal ends of the fallopian tubes are clipped or ligated to prevent possible tumor spillage during uterine manipulation.

These procedures should be followed by total extrafascial hysterectomy and bilateral salpingo-oophorectomy. The excised uterus is opened away from the operating table, and the depth of myometrial penetration and the presence or absence of endocervical involvement are determined by clinical observation or microscopic frozen section. The depth of myometrial invasion can be accurately assessed in over 90% of cases.

Laparoscopic surgery An alternative method of surgically staging patients with clinical stage I endometrial cancer is gaining in popularity. This approach combines laparoscopically assisted vaginal hysterectomy with laparoscopic lymphadenectomy.

Childers and colleagues described their experience with laparoscopic surgery in 59 patients with clinical stage I endometrial carcinoma. The peritoneal cavity was thoroughly inspected, intraperitoneal washings were obtained, and a laparoscopically assisted vaginal hysterectomy was performed. Laparoscopic pelvic and aortic lymph nodes were sampled in all patients with grade 2 or 3 lesions, as well as in those with grade 1 lesions who were found to have $>$ 50% myometrial invasion on frozen-section analysis. In two patients, laparoscopic lymphadenectomy was precluded by obesity.

Six patients noted to have intraperitoneal disease at laparoscopy underwent exploratory laparotomy. Two additional patients required laparotomy for complications, including a transected ureter and a cystotomy. The mean hospital stay was 2.9 days.

Laparoscopic assisted surgical staging (LASS) is feasible in a select group of patients. However, it is not yet known whether this approach is applicable to all patients with clinical stage I disease. In particular, patients who are overweight or have intra-abdominal adhesions may not be ideal candi-

dates. Para-aortic lymphadenectomy is technically more difficult through the laparoscope. To obtain adequate exposure, it is necessary to elevate the small bowel mesentery into the upper abdomen, which becomes increasingly difficult as the patient's weight increases, especially when weight exceeds 180 pounds. The safety, efficacy, and cost savings of LASS are currently being evaluated by GOG in a prospective randomized trial comparing LASS vs staging laparotomy.

Lymph node sampling Any suspicious pelvic or para-aortic lymph nodes should be removed for pathologic evaluation. If there is no gross residual intraperitoneal tumor, pelvic and para-aortic lymph nodes should be sampled for the following indications:

- invasion of more than one-half of the outer myometrium
- presence of tumor in the isthmus-cervix
- adnexal or other extrauterine metastases
- presence of serous, clear-cell, undifferentiated, or squamous types
- visibly or palpably enlarged lymph nodes

Lymph nodes need not be sampled in patients whose tumor is limited to the endometrium, regardless of grade, because $< 1\%$ of these patients have disease spread to pelvic or para-aortic lymph nodes. The decision of whether to perform lymph node sampling is less clear-cut for patients whose only risk factor is invasion of the inner half of the myometrium, particularly if tumor grade is 1 or 2. This group has a $\leq 5\%$ chance of node positivity.

Sampling procedures When indicated, para-aortic node sampling can be performed through a midline peritoneal incision over the common iliac arteries and aorta. Alternatively, sampling can be performed on the right by mobilizing the right side of the colon medially and on the left by mobilizing the left side of the colon medially. In each case, a sample of lymphatics and lymph nodes is resected along the upper common iliac vessels on either side and from the lower portion of the aorta and vena cava. On the left side, the lymph nodes and lymphatics are slightly posterior to the aorta, and on the right side, they lie primarily in the vena caval fat bed.

In cases where pelvic lymph node sampling is indicated, a sample of lymph nodes is taken from the distal common iliac artery, the superior iliac artery and vein, and the group of nodes that lie along the obturator nerve. In a lymph node sampling procedure, it is important to try to achieve an adequate sample of nodes from each anatomic site, but no attempt is made to perform a complete lymphadenectomy.

Surgical staging After these procedures, the patient is surgically staged according to the 1988 FIGO criteria. The overall surgical complication rate after this type of staging is approximately 20%. The rate of serious complications is 6%, and they include vascular, ureteral, and bowel injuries.

TABLE 2: Results from the PORTEC Study

Parameter	Radiotherapy	Control
Locoregional recurrence	4.2%	13.7%
Distant metastasis	7.9%	7.0%
Survival	81.0%	85.0%

Adjuvant radiation therapy

Following surgical staging, adjuvant radiation therapy is offered to patients based on prognostic factors found at the time of surgery. A pelvic recurrence rate of 7%-14% is predictable for all stage I patients after surgery alone, although certain subgroups with more risk factors may have a higher incidence of recurrence of endometrial carcinoma. Well-described prognostic factors include disease extent (cervical involvement, extrauterine involvement of the serosa, adnexa, lymph nodes, peritoneal fluid, or intra-abdominal spread), as well as histologic grade of tumor, depth of myometrial penetration, pathologic subtype, and presence of lymphovascular space invasion.

Pelvic irradiation, vaginal irradiation, or both? Most adjuvant irradiation has been delivered using external-beam irradiation directed to the pelvis, which allows for treatment of the pelvic nodes.

A trial conducted by the GOG compared the results of pelvic radiation to observation following hysterectomy and lymphadenectomy. The 2-year relapse-free survival rate was significantly higher among patients treated with pelvic irradiation than among those who were observed (96% vs 88%). Overall survival rates at 3 years did not differ significantly between the two groups.

Criticism of this trial includes the fact that the majority of patients had low-grade histology, as well as shallow myometrial penetration. The predominant site of pelvic failure in these patients was the vagina (14 of 19 recurrences). Thirteen other sites of recurrence were outside the pelvis. Although this trial was presented in abstract form at a meeting, the manuscript remains unpublished.

The findings of a multicenter trial with 754 patients from the Netherlands called the Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) study recently were reported. Eligible patients had IC grade 1 tumors (21%), IB or IC grade 2 tumors (69%), or IB grade 3 tumors (10%). After total abdominal hysterectomy, without lymphadenectomy patients were randomized to receive pelvic radiotherapy (46 Gy) or no further treatment.

Pelvic irradiation decreased the incidence of locoregional recurrence but did not affect survival. Patients with grade 3 histology demonstrated the highest risk of distant metastases and death caused by endometrial cancer. Most of the locoregional relapses were located in the vagina (30 of 40 cases).

TABLE 3: Recommendations for adjuvant pelvic irradiation

	Stage		
Histologic grade	**IA**	**IB**	**IC**
G1	–	–	–
G2	–	–	+[b]
G3	+[b]	+[b]	+[b]
Vascular space invasion[a]	+	+	+

[a] Any grade; +, irradiation recommended; –, irradiation not recommended.

[b] After full lymphadenectomy, consider brachytherapy alone because of excess complications.

It is possible that vaginal brachytherapy could have prevented the majority of these cases (Table 2).

A few reports have demonstrated excellent local control with vaginal irradiation alone. Pearcey and Petereit reviewed the world literature that represented 1,800 patients with low- to intermediate-risk disease. Overall, the vaginal control rate was 99.3% following adjuvant high-dose rate vaginal brachytherapy.

In a randomized study from the Norwegian Radium Hospital, pelvic irradiation significantly decreased the incidence of locoregional recurrences compared with vaginal irradiation alone. Patients with deeply invasive, grade 3 tumors had lower death and recurrence rates when treated with pelvic plus vaginal irradiation, as compared with vaginal irradiation alone.

Many women with endometrial cancer are being treated with lymphadenectomy at the time of hysterectomy. There has been some interest in using vaginal irradiation alone to treat women who have negative nodes but deep myometrial penetration or high-grade histology. Several small retrospective reports have demonstrated excellent outcomes for such patients. However, more experience is needed to determine whether vaginal irradiation alone is adequate. Fanning reported outcomes of 66 patients, with a follow-up of 4.4 years. These patients were treated with bilateral pelvic and para-aortic lymphadenectomy with hysterectomy and oophorectomy. Brachytherapy alone was given as adjuvant therapy. There were no pelvic recurrences. Major complications occurred in 6% of patients.

In general, vaginal irradiation alone is reserved for patients at low risk for pelvic node metastasis. Because of increased rectal and vaginal sequelae, treatment of the entire length of the vagina is usually not recommended.

Pelvic and vaginal irradiation have been combined for the adjuvant treatment of some patients. Patients with cervical involvement or extrauterine disease, who may have an increased incidence of local failure, may benefit

from the two treatments combined, although there are no data to suggest that the addition of brachytherapy improves outcome over external-beam irradiation alone. Patients with uterine-confined disease have excellent local control following treatment with either type of radiation. Combining the two treatments has not been shown to benefit these patients.

Vaginal irradiation Vaginal radiation can be delivered with high-dose rate (HDR) or low-dose rate (LDR) equipment. Both techniques have resulted in excellent local control rates and low morbidity when administered by experienced practitioners. Each technique has its advantages. HDR treatments require multiple insertions, generally with one insertion performed every week for 3-6 weeks. However, hospitalization is not required, and each insertion takes only a brief amount of time. LDR treatments are delivered once but require hospitalization for 2-3 days.

Stage I disease Current recommendations for the treatment of patients with pathologic stage I disease include adjuvant pelvic irradiation for women with deep myometrial penetration, grade 2 or 3 histology, or evidence of vascular-space invasion (Table 3). Data support the use of vaginal irradiation alone for women with more superficial tumors and low-grade histology.

Radiation doses are generally 45-50 Gy with standard fractionation. The technique should include multiple fields treated daily, with attempts to protect the small bowel. Complications from adjuvant pelvic irradiation are related to technique and the extent of lymphadenectomy.

If full lymphadenectomy has been performed, the incidence of complications increases significantly with pelvic irradiation. For these patients, consideration should be given to adjuvant brachytherapy rather than pelvic irradiation.

Papillary serous histology The high rate of upper abdominal, pelvic, and vaginal recurrences in patients with uterine papillary serous cancers has led to the recommendation that they receive whole-abdominal irradiation (with doses of up to 30 Gy) and additional treatments to bring the pelvic dose to 50 Gy. A vaginal cylinder or colpostats may be used to boost the surface dose with 40 Gy. This treatment has resulted in a 5-year survival rate of 50%.

Stage II disease Patients whose endometrial cancer extends to the cervix usually represent a heterogeneous group with differing histologic grades and varying degrees of cervical involvement, myometrial penetration, and nodal involvement. Similar outcomes with preoperative and postoperative irradiation suggest that initial surgical treatment with tailored postoperative irradiation is a reasonable approach.

Current treatment recommendations frequently include adjuvant pelvic irradiation to a dose of 45-50 Gy, in addition to insertion of a vaginal cylinder or colpostats to raise the total dose to the vaginal surface to 80-90 Gy. This treatment should result in a 5-year disease-free survival rate of 80%, with a locoregional control rate of 90%. Of course, outcome varies with the extent

of myometrial penetration, degree of cervical involvement, and histologic grade of tumor.

Extensive cervical involvement Patients who have a large amount of cervical involvement that precludes initial hysterectomy are candidates for preoperative irradiation. A multiple-field technique is used to deliver a dose of 40-45 Gy with standard fractionation. A midline block may be inserted for the last 20 Gy to protect the rectum.

Intracavitary insertion with a standard Fletcher applicator, consisting of a uterine tandem and vaginal colpostats, delivers 20-25 Gy to point A (defined as 2 cm caudally and 2 cm laterally to the cervical os). Hysterectomy should follow in approximately 4-6 weeks. The expected 5-year disease-free survival rate for patients with disease that is this extensive is 70%-80%.

Stage III disease Women in whom endometrial cancer has spread outside the uterus (stage III disease) are at increased risk of death but have a wide spectrum of expected outcomes.

Isolated ovarian metastasis One subgroup found to have a relatively good prognosis includes women with isolated ovarian metastasis. Five-year disease-free survival rates ranging from 60%–82% have been reported in these women after hysterectomy and pelvic irradiation, depending on the histologic grade of tumor and the depth of myometrial penetration. Pelvic irradiation usually includes a dose of 45-50 Gy using standard fractionation. A vaginal boost with a cylinder or colpostats may add 30-35 Gy to the vaginal surface.

Extension to periaortic nodes In patients with disease extension to the periaortic nodes, the relapse-free survival rate after hysterectomy and adjuvant irradiation to the pelvis and periaortic regions is approximately 30%. It has been suggested that multiple sites of extrauterine involvement may be the single worst prognostic factor in these patients. Such women have a high recurrence rate and should be treated with extended-field irradiation. The standard treatment recommendation includes 45-50 Gy of radiation to a volume encompassing the pelvic and periaortic regions.

Whole-abdominal irradiation Because upper abdominal failures have been reported previously in patients with stage III disease, attention has focused on the role of whole-abdominal irradiation. Although subsets of patients have done well with whole-abdominal therapy, it is unclear whether this more aggressive therapy has any benefit over pelvic irradiation. The GOG has completed a trial of whole-abdominal irradiation compared with chemotherapy. Results are pending. The Radiation Therapy Oncology Group (RTOG) has investigated the combination of pelvic irradiation and chemotherapy in patients who are at risk for pelvic and distant sites of recurrence.

Definitive radiation treatment

For patients who are poor operative risks, definitive treatment with irradiation has produced excellent local control and survival rates. Such treatment is considered to be justified when the operative risk exceeds the 10%-15% uterine recurrence rate expected with irradiation alone.

A more favorable outcome with definitive irradiation is related to low clinical tumor stage, less aggressive histologic variant, and use of brachytherapy for at least part of the treatment. Five-year disease-specific survival rates as high as 87%, 88%, and 49% have been reported in patients with stages I, II, and III or IV disease, respectively. Ten-year local control rates in patients with stages I/II and III or IV disease were 84%, 87%, and 68%, respectively.

Treatment techniques with irradiation alone for patients with early-stage disease and low-grade histology consist of uterine intracavitary insertions with Heyman or Simon capsules or an afterloading intrauterine tandem. Doses for intracavitary treatment range from 40-45 Gy prescribed to point A. Patients with more advanced disease, a large uterus, or aggressive histology generally receive both an intrauterine intracavitary insertion and external pelvic irradiation. External irradiation typically delivers 40-45 Gy to the pelvis, followed by intracavitary treatment that delivers 30-35 Gy to point A.

Complication rates Rates of serious complications attributable to irradiation range from 4%-5% with intracavitary treatment alone to 10%-15% with combined external and intracavitary irradiation.

Adjuvant systemic therapy

Only a few trials of adjuvant systemic therapy have been conducted in patients with early-stage endometrial cancer. At present, we believe that such therapy should not be recommended outside the clinical trial setting.

Endocrine therapy Early uncontrolled trials suggested that progestin therapy might prolong the progression-free interval and time to recurrence in patients with stage I and II lesions treated with initial surgery and irradiation. However, at least three subsequent randomized trials failed to show any survival benefit for progestins. A recent meta-analysis has demonstrated no advantage of adjuvant progestin therapy.

Chemotherapy To date, there is also no convincing benefit for adjuvant chemotherapy. The GOG compared doxorubicin with observation in 181 patients with high-risk, early-stage, endometrial carcinoma; at 5 years, there was no difference in recurrence rates. A subsequent phase II trial suggested a better outcome for 62 high-risk patients treated with adjuvant CAP (cyclophosphamide, Adriamycin [doxorubicin], and Platinol [cisplatin]) when compared with historic controls. The RTOG and GOG currently are investigating the role of adjuvant chemotherapy for high-risk uterine-confined disease by randomizing patients following hysterectomy to receive irradiation alone or irradiation with cisplatin and paclitaxel.

TREATMENT OF RECURRENT OR METASTATIC DISEASE

Patterns of recurrence

Recurrent endometrial cancer is initially confined to the pelvis in 50% of patients. The major sites of distant metastasis are the abdominal cavity, liver, and lungs.

Following diagnosis and initial treatment, periodic evaluation, including history, physical examination, and pelvic examination, is recommended at 3-6 month intervals for the first 5 years and yearly thereafter. The use in asymptomatic patients of more extensive and more costly procedures, such as chest x-ray, CT imaging, and marker studies, is of questionable value and is unlikely to have a major impact on survival. Symptomatic patients should be evaluated as is appropriate.

Radiation therapy

After hysterectomy alone for endometrial cancer, approximately 50% of recurrences are pelvic and 50% are extrapelvic. It is clear that locoregional recurrences can develop in isolation, without distant metastasis, and salvage can be accomplished with high-dose irradiation.

Pelvic recurrences Five-year disease-specific survival rates as high as 51% have been reported in patients with isolated locoregional recurrences treated with radiation therapy. Factors that have an adverse impact on outcome are increased size of recurrence, young age, pelvic vs vaginal involvement, and treatment of the recurrence with external-beam irradiation only vs the addition of vaginal brachytherapy.

Radiation treatment for pelvic recurrence usually consists of external-beam irradiation with the addition of a brachytherapy boost that may include colpostats, a cylinder, interstitial needles, or seeds.

Treatment must be individualized based on the location and size of the recurrence and the boost method selected. The tolerance of normal tissues must be

TABLE 4: Results of a phase III, dose-response trial of progestins in advanced or recurrent endometrial carcinoma

	Oral medroxyprogesterone acetate	
Parameter	**200 mg/d (N = 145)**	**1,000 mg/d (N = 154)**
Response rate (%)	25	15
Complete response rate (%)	17	9
Median progression-free survival (mo)	3.2	2.5
Median survival (mo)	11.1	7.0

respected, but combined doses > 60 Gy have been associated with improved local control.

Extrapelvic recurrences For patients with recurrences outside the pelvis, irradiation is effective in producing responses in localized symptomatic lesions. Therefore, radiation may be effective for palliation of such lesions in the lymph nodes, brain, or bones. Doses and protocols vary, depending on the site of recurrence.

Advanced disease with abdominal involvement Whole-abdominal irradiation may also be effective palliative therapy in patients with advanced endometrial carcinoma involving the abdominal cavity. A randomized trial comparing irradiation with chemotherapy in this setting (GOG protocol 122) is currently in progress.

Pelvic exenteration for pelvic recurrences after irradiation

Isolated pelvic central recurrence after irradiation is rare. Selected patients in whom it does occur may benefit from pelvic exenterative surgery. No large series have been published, but some long-term survivors have been reported.

Barakat et al reported on 44 patients who underwent pelvic exenteration for recurrent endometrial cancer at Memorial Sloan-Kettering Cancer Center between 1947 and 1994. Primary therapy usually consisted of total abdominal hysterectomy and bilateral salpingo-oophorectomy, with most patients receiving either preoperative or postoperative radiotherapy. Prior to exenteration, 10 (23%) of 44 patients had never received any form of radiotherapy. The median interval between initial surgery and exenteration was 28 months (range, 2-189 months).

Exenteration was total in 23 patients (52%), anterior in 20 patients (46%), and limited to posterior in 1 patient. One vascular injury led to the only intraoperative death. Major postoperative complications occurred in 35 patients (80%) and included intestinal/urinary tract fistulas, pelvic abscess, septicemia, pulmonary embolism, and cerebrovascular accident. Median survival for the entire group of patients was 7.36 months, with 9 patients (20%) achieving long-term survival (> 5 years). Although the long-term survival rate after this procedure is only 20%, it remains the only potentially curative option for the few patients with central recurrence of endometrial cancer who have not responded to standard surgery and radiation therapy.

Endocrine therapy

Progestins produce complete and partial response rates of 15%-25% in patients with locoregional recurrence or distant metastases. The route, type, and dose of progestins do not appear to be related to response; hence, oral therapy is preferred.

In clinical practice, oral administration of 200 mg of medroxyprogesterone acetate or 160 mg of megestrol acetate (Megace) produces blood levels simi-

lar to those achieved with parenteral therapy (400-1,000 mg of medroxyprogesterone acetate IM weekly). A phase III trial conducted by GOG comparing 200 mg to 1,000 mg of medroxyprogesterone acetate given orally daily found no differences between the two regimens, although it is noteworthy that the trends all favored the low-dose regimen (Table 4). Doses higher than 200 mg/d of medroxyprogesterone acetate, therefore, are clearly not warranted.

Several factors are predictive of a favorable response to progestin therapy. Patients with well-differentiated lesions are more likely to respond. A related observation is that a much higher percentage of grade 1 tumors have significant levels of estrogen and progesterone receptors; data show that lesions with higher receptor levels respond much more frequently to progestins than those with lower receptor levels. Response is almost always associated with better progression-free and overall survival.

The median time to disease progression for all patients treated with progestins is 3-4 months, and the median survival is 10 months.

Tamoxifen has been utilized in the treatment of endometrial carcinoma both in the salvage setting and as a first-line systemic treatment. The largest trial, a recent GOG study involving patients who had never received systemic therapy for endometrial carcinoma, reported a 13% response rate. For all recent studies, the response rates range from 0%-13%. These data suggest that tamoxifen is not as active as progestins and is of little value as second-line therapy in patients who do not respond to progestins.

Some reports evaluate combined therapy with tamoxifen plus a progestin given sequentially in the hope that tamoxifen may increase progesterone-receptor expression and, thus, increase the likelihood of response to progestins. None of the studies suggests an advantage for such an approach.

Other hormonal agents, such as gonadotropin-releasing hormone analogs and aminoglutethimide (Cytadren), have been studied to some extent in endometrial carcinoma. These agents do not appear to have sufficient activity to warrant further study.

Chemotherapy

Single agents Chemotherapy for advanced endometrial cancer focuses on three groups of agents (anthracyclines, platinum compounds, and taxanes) with demonstrated activity.

Active agents The anthracyclines studied include doxorubicin and epirubicin. In a total of 298 patients, doxorubicin produced a 27% response rate. Epirubicin (Ellence), primarily in European studies including 27 patients, yielded a 26% response rate. Two platinum compounds have activity. Cisplatin, in 86 patients, elicited responses in 29%. Carboplatin (Paraplatin) produced a 31% response rate in 52 patients. Paclitaxel, in two studies involving 47 patients, yielded responses in 36%.

For all of these studies, the progression-free interval ranged from 4-7 months, with an overall survival range of 8-12 months. Approximately one-third of the responses were clinical complete responses with a substantially longer duration and better survival than partial responders.

Agents with limited activity Other agents studied have included alkylating agents (cyclophosphamide, ifosfamide [Ifex]), altretamine (Hexalen), fluorouracil (5-FU), methotrexate, mercaptopurine (Purinethol), vinblastine, etoposide, teniposide (Vumon), and mitoxantrone (Novantrone). All of these agents exhibited insufficient activity to warrant further study.

Combination regimens A number of phase II trials of combination regimens have been conducted. Recently, the combination of carboplatin and paclitaxel has been demonstrated to be active in advanced endometrial cancer (50%-60% response rate). Ultimately, the relative merits of combination chemotherapy must be judged in the context of a randomized trial.

Following the results of GOG protocol 107, which demonstrated the addition of cisplatin to doxorubicin resulted in a superior response rate and longer progression-free survival, but no improvement in overall survival, compared with single-agent doxorubicin, the group compared this two-drug (cisplatin [50 mg/m^2]/doxorubicin [60 mg/m^2]) regimen with a three-drug combination of cisplatin (50 mg/m^2), doxorubicin (45 mg/m^2), and paclitaxel (160 mg/m^2 as a 3-hour infusion), with G-CSF support (GOG protocol 177). The three-drug combination of the paclitaxel-containing program produced a higher response rate (57% vs 33%) and an improved 5-month progression-free survival (67% vs 50%). However, overall survival did not differ between the regimens. In addition, this program resulted in more grade 3 neuropathy (12% vs 1%) and five cases of congestive heart failure (vs none with cisplatin/doxorubicin).

Chemotherapy plus progestins Combinations of chemotherapy plus progestins have been studied in a number of phase II trials. The only large, randomized trial evaluating this approach (GOG protocol 29) allocated patients with advanced or recurrent disease to receive either cyclophosphamide, doxorubicin, cisplatin, and megestrol acetate or melphalan (Alkeran), 5-FU, and megestrol acetate. In pilot studies, these two regimens had been reported to yield response rates of 75% and 94%, respectively. The randomized trial produced response rates of 36% and 38%, respectively, with no evident advantage of either combination over prior studies of single-agent doxorubicin with regard to response rate, progression-free interval, or overall survival. These results do not suggest any advantage for the combined use of chemotherapy and progestins.

Treatment recommendations

Patients who have advanced or recurrent endometrial carcinoma should be considered for systemic therapy. Patients should first be offered the opportunity to participate in a clinical trial. Those who are ineligible or who choose not to participate should be treated according to current evidence.

Patients who have a grade 1 tumor and/or known progesterone-receptor–positive disease clearly benefit from treatment with progestins (response rate, 40%; median progression-free interval, 9 months; overall median survival, 14 months) and should be so treated. Those with a grade 2-3 tumor and/or known progesterone-receptor–negative disease do not do well with progestin therapy (response rate, 12%; median progression-free interval, 3 months; overall median survival, 10 months) and should be considered for initial treatment with single-agent chemotherapy (eg, paclitaxel, doxorubicin, carboplatin) or a combination regimen. Options include cisplatin/doxorubicin, cisplatin/paclitaxel, and carboplatin/paclitaxel. (It is difficult to justify routine use of the three-drug paclitaxel-containing regimen noted above based on the limited improvement in efficacy and substantial toxicity.) Chemotherapy should also be considered for patients who do not respond to initial hormonal therapy.

Regimens that include both chemotherapy and hormonal therapy should not be considered outside a clinical trial because of the lack of data supporting any advantage of these combinations. Likewise, sequential use of tamoxifen and progestins is not indicated because of the absence of enhanced efficacy.

Uterine sarcomas

Carcinosarcomas and other uterine sarcomas are uncommon tumors, accounting for less than 4% of all cancers of the uterine corpus. Carcinosarcomas, the most common histologic subtype, demonstrate both epithelial and stromal differentiation. Endometrial stromal sarcomas and leiomyosarcomas (LMSs) are characterized by differentiation toward one or more stromal tissues. LMSs occur at an earlier age than do carcinosarcomas, with a plateau observed in middle age. There is strong epidemiological evidence that prior exposure to pelvic radiation may increase the risk for the development of uterine sarcomas. Generally, these tumors are characterized by aggressive growth, with early lymphatic or hematogenous spread. The overall survival rate is poor, with the majority of deaths occurring within 2 years of diagnosis.

PATTERNS OF SPREAD

Lymphatic metastases are a significant route of spread for carcinosarcoma, with a reported incidence of 40%-60% occurring with stage I disease. LMS has a propensity for extra-abdominal spread often involving the lungs. For carcinosarcoma, the initial site for recurrence after surgical resection is likely to be pelvis or abdomen, whereas LMSs tend to fail to recur distantly. In a prospective surgical staging trial of GOG, the recurrence rate for early-stage carcinosarcoma was 53% and for LMS was 71%.

SURGERY

Surgery is the mainstay of treatment for uterine sarcomas. For carcinosarcoma, this usually consists of total abdominal hysterectomy and bilateral salpingo-oophorectomy with washings to be obtained for peritoneal cytology. The GOG prospective staging study reported a 17% incidence of nodal metastasis for this histologic subtype, so retroperitoneal nodes should be sampled as for poorly differentiated endometrial cancers. For patients with advanced/recurrent disease, aggressive surgical debulking does not appear to improve outcome.

Hysterectomy with oophorectomy is also standard therapy for uterine LMS. Retroperitoneal nodal sampling is not usually performed, because lymph node involvement is unusual. For late recurrences of LMS, surgery must be individualized. Five-year survival rates of 30%-50% have been reported following pulmonary resection for lung metastases. Patients with unilateral metastases have a significantly better prognosis than those with bilateral disease. Local and regional recurrences may also be amenable to surgical resection of disease.

Hysterectomy with oophorectomy is the standard of care for patients with low-grade endometrial stromal sarcomas. Removal of the ovaries is critical, as these tumors tend to have very high concentrations of estrogen and progesterone receptors and often respond to hormonal therapy. Because these tumors have a tendency to spread via the lymphatics, resection of all disease, especially extension into the parametrium, should be attempted. This may require a radical hysterectomy.

ADJUVANT IRRADIATION

Currently there are no clear data suggesting improvement in outcome for patients with uterine sarcomas treated with adjuvant pelvic irradiation. Pelvic recurrence is a pattern of failure for most uterine sarcomas; isolated pelvic recurrences are uncommon. Adjuvant irradiation can decrease local recurrence, but there is no clear evidence that this improves survival. Patients will often experience recurrence distantly and treatment failure. Pelvic irradiation may be indicated for improvement of quality of life, however, because pelvic recurrence can be associated with pain, bleeding, and intestinal obstruction.

ADJUVANT RADIOTHERAPY

Uterine sarcomas represent only 2%-5% of all uterine malignancies. These patients have a high incidence of distant, as well as pelvic, recurrences. In a nonrandomized prospective GOG study, patients with stage I and II mixed mesodermal sarcomas and leiomyosarcomas had fewer pelvic recurrences following irradiation than did those patients who did not undergo pelvic irradiation. No difference in overall or disease-free survival was noted.

Several retrospective reports have suggested improved pelvic control rates following pelvic irradiation for stage I and II uterine sarcomas. Decreasing pelvic recurrences may improve symptom-free survival for these patients.

Currently, GOG has an open randomized study for patients with stage I-IV mixed mesodermal sarcomas. Following resection of gross disease, patients are randomized to receive whole abdominal irradiation (30 Gy) with a pelvic boost (1,980 cGy) or chemotherapy alone with cisplatin, ifosfamide, and mesna.

ADJUVANT CHEMOTHERAPY

There is no proven role for adjuvant chemotherapy in stage I disease following complete surgical resection. A GOG study looking at adjuvant doxorubicin vs no further therapy showed no differences in recurrence rate, progression-free survival, or overall survival.

For patients with advanced/recurrent disease, single-agent chemotherapy can be used with a palliative intent. For carcinosarcomas, ifosfamide or paclitaxel appears to be the agent of choice, whereas doxorubicin is the drug of choice for LMSs. Hormonal agents, specifically progestins, are the treatment of choice for advanced/recurrent stromal sarcomas.

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CHAPTER 22

Ovarian cancer

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Despite the fact that it is highly curable if diagnosed early, cancer of the ovaries kills more American women each year than all other gynecologic malignancies combined. An estimated 25,400 new cases of this cancer will be diagnosed in the United States in 2003, and about 14,300 women will succumb to the disease.

Although the number of deaths from ovarian cancer continues to increase, notable advances in chemotherapy and surgery over the past several decades have begun to translate into improved survival. Long-term survival data reflecting these recent advances are expected to show further increases. According to American Cancer Society data, the overall 5-year survival rate from ovarian cancer has increased significantly, from 36% in the mid-1970s to 53% in the mid-1990s. Recent data from the National Cancer Institute show a similar increase in stage-specific survival.

This chapter will focus on epithelial cancers of the ovaries, which account for about 90% of ovarian malignancies.

Epidemiology

Age Ovarian cancer is primarily a disease of postmenopausal women, with the large majority of cases occurring in women between 50 and 75 years old. The incidence of ovarian cancer increases with age and peaks at a rate of 61.5 per 100,000 in the 75–79-year-old age group.

Race The incidence of ovarian cancer appears to vary by race, although the effects of race are difficult to separate from those of environment related to culture, geography, and socioeconomic status. In the United States, the age-adjusted rate of ovarian cancer for Caucasians is estimated to be 17.9 per 100,000 population, which is significantly higher than 11.9 per 100,000 for the African-American population.

Geography There are distinct geographic variations in the incidence of ovarian cancer, with the highest rates found in the industrialized countries and the lowest rates seen in underdeveloped nations. Japan, with an incidence of only about 3.0 per 100,000 population, is a notable exception to this observation. It has been postulated that geographic variations in the incidence of ovarian cancer are related, in part, to differences in family size.

Some of the highest rates are seen in European-born Jews, who have an estimated incidence of 17.2 per 100,000, a probable result of the relatively high frequency of *BRCA1* and *BRCA2* mutations in this population.

Etiology and risk factors

The cause of epithelial ovarian cancer remains unknown. Although it now appears likely that, at the cellular level, ovarian cancer results from the accumulation of multiple discrete genetic defects, the mechanism(s) by which these defects develop have yet to be determined. Epidemiologic studies have identified a number of factors that may increase or decrease the risk of the disease. In addition, a small proportion of ovarian cancers, ~5%-10%, result from inherited defects in the *BRCA1* gene or other genes, including *BRCA2* and the hereditary nonpolyposis colorectal cancer *(HNPCC)* genes.

Diet It has been suggested that numerous dietary factors increase the risk of ovarian cancer.

Fat Countries with a higher per capita consumption of animal fat tend to have higher rates of ovarian cancer.

Lactose Populations with a high dietary intake of lactose who lack the enzyme galactose-1-phosphate uridyltransferase have been reported to be at increased risk.

Coffee Conflicting reports have been published regarding the role of coffee consumption and the risk of ovarian cancer.

Environmental factors Various environmental risk factors also have been suggested.

Talc Exposure to talc (hydrous magnesium trisilicate) used as dusting powder on diaphragms and sanitary napkins has been reported in some studies to increase the risk of ovarian cancer, although other studies have failed to find an association.

Radiation Data on the association between exposure to ionizing radiation and the risk of ovarian cancer are also conflicting.

Viruses Several studies have examined the effect of viral agents, including mumps, rubella, and influenza viruses, on the risk of ovarian cancer. No clear relationship has been demonstrated.

Hormonal and reproductive factors In contrast to the conflicting data on dietary and environmental factors, some clear associations have been drawn between certain hormonal and reproductive factors and the risk of developing ovarian cancer.

Low parity and infertility Several analyses have documented that women with a history of low parity or involuntary infertility are at increased risk of ovarian cancer.

Ovulation-inducing drugs Recent evidence suggests that treatment with ovulation-inducing drugs, particularly for prolonged periods, may be a risk factor.

Hormone replacement therapy Although the data are not consistent, some studies have shown an association between the use of postmenopausal hormone replacement and the development of ovarian cancer.

Oral contraceptives Several large case-controlled studies have documented a marked protective effect of oral contraceptives against ovarian cancer. Women

who have used oral contraceptives have approximately half the risk of ovarian cancer as do nonusers, and the protective effect of oral contraceptives appears to persist for years after their discontinuation. It is estimated that the routine use of oral contraceptives may prevent nearly 2,000 cases of ovarian cancer yearly in the United States.

Hereditary cancer syndromes There has been a fascinating evolution in our understanding of the role of hereditary factors in the development of ovarian cancer. It has been recognized for many years that women with a family history of cancer, particularly cancer of the ovaries or breasts, are themselves at increased risk of ovarian cancer. More recently, Lynch and colleagues have refined these observations by delineating several apparently distinct syndromes of hereditary cancer involving the ovaries, including breast-ovarian cancer syndrome, site-specific ovarian cancer syndrome, and Lynch II syndrome (HNPCC).

Epidemiologically, these syndromes appear to be inherited as an autosomal-dominant trait with variable penetrance. During the past several years, the specific genes responsible for HNPCC and for most cases of hereditary ovarian cancer have been identified, allowing fundamental observations to be made regarding their molecular pathophysiology.

BRCA *mutations* The *BRCA1* gene is classified as a tumor suppressor, since mutations in this gene increase the risk of breast and ovarian cancers. Definitive identification of the function of the protein translated from this gene remains to be elucidated, although recent evidence suggests that it plays a role in the repair of oxidative damage to DNA. Part of the protein appears to contain a DNA-binding domain, suggesting that it also functions as a transcriptional regulator.

The frequency of *BRCA1* mutations in the general population is estimated at approximately 1 in 800 and in Jewish women of eastern European descent, 1 in 100.

Women carrying a germline mutation of *BRCA1* have a significantly elevated risk of both breast and ovarian cancers compared with the general population. The average population risk of developing breast cancer is about 12.5% (1 in 8) and for developing ovarian cancer, 1.5%. However, in the presence of a germline *BRCA1* mutation and a strong family history of cancer, these risks rise to about 90% and 40% for breast and ovarian cancers, respectively.

It is important to recognize that these risk estimates are derived from families identified with multiple cases of breast and/or ovarian cancer. The risk for women with *BRCA1* mutations from families with less impressive family histories is probably lower, perhaps in the range of 15%-20%, for ovarian cancer.

Although the presence of germline mutations in *BRCA1* is not limited to women with a strong family history of breast cancer, data from several laboratories suggest that *BRCA1* mutations usually are not a feature of sporadic ovarian cancer. Mutations in this gene appear to play a role in the development of approximately 50% of familial breast cancer cases and appear to account for the majority of hereditary ovarian cancers. Recent evidence suggests that

BRCA1-related ovarian cancers may have a less aggressive clinical course than do sporadic ovarian cancers.

HNPCC *or* BRCA2 *mutations* Hereditary ovarian cancers not related to *BRCA1* may be related to the *HNPCC* genes or the *BRCA2* gene.

Signs and symptoms

Early-stage disease In the early stages, ovarian cancer may be an insidious disease, producing essentially no symptoms or symptoms that are nonspecific. A study by Goff et al surveyed 1,725 women diagnosed with ovarian cancer, and 95% reported symptoms most commonly categorized as abdominal (77%), gastrointestinal (70%), pain (58%), constitutional (50%), or other. These symptoms often do not lead to the diagnosis of ovarian cancer before stage III or IV disease, and these cancers may grow to a size of about 10-12 cm before impinging on adjacent organs and producing more typical symptoms of urinary frequency and rectal pressure.

Early ovarian cancer may be detected as a pelvic mass noted fortuitously at the time of a routine pelvic examination. Imaging with sonography, CT, or MRI will confirm the presence of a mass. The size, internal architecture, and blood flow of the mass can be used to make an educated guess as to whether it is benign or malignant, but imaging findings are not diagnostic in this regard. About half of patients with early ovarian cancers have an elevated serum CA-125 level.

Advanced-stage disease Patients may complain of abdominal bloating or swelling if ascites is present, and large pelvic masses may produce bladder or rectal symptoms. Occasional patients may have respiratory distress as a result of a large pleural effusion, which is more common on the right side. Infrequently, there may be a history of abnormal vaginal bleeding.

Most patients with advanced disease have ascites detectable by physical examination or imaging. Complex pelvic masses and an omental tumor cake may be present, and nodules can frequently be palpated in the pelvic cul-de-sac on rectovaginal examination. It should be noted that some patients with advanced ovarian cancer have essentially normal-sized ovaries.

Screening and diagnosis

Screening Unfortunately, no effective strategy exists for screening of the general population for ovarian cancer. Imaging techniques, including abdominal and transvaginal sonography, have been studied extensively, as has the serum marker CA-125. None of these techniques, alone or in combination, is specific enough to serve as an appropriate screening test, even in populations targeted by age.

Both the National Institutes of Health Consensus Conference (see NIH guidelines on the next page) and the American College of Obstetricians and Gynecologists have issued statements advising against routine screening for ovarian cancer, which, due to its high false-positive rate, leads to an unacceptable amount of invasive interventions in women without significant disease.

The NIH Prostate, Lung, Colon, and Ovarian (PLCO) Screening Trial has accrued its full complement of 152,000 patients. Half are female and half are male. For the ovarian cancer segment of the trial, half of the women will be screened via physical examination, CA-125, and vaginal ultrasonography and the other half, via standard medical care. Since patients will be followed for 13 years or more, it will be many years before results are available.

A recent study using serum proteomics to screen for early ovarian cancer has yielded promising results.

High-risk patients Management of women from families with hereditary ovarian cancer is controversial. Recent evidence suggests that surveillance of such women with serum markers and sonography is of benefit in early detection of ovarian cancer. Most experts would recommend prophylactic excision of the ovaries after age 35 years if the woman has completed childbearing, as several studies have shown that it willl dramatically reduce the risk of ovarian cancer. Recent evidence suggests that prophylactic oophorectomy may also lower the risk of breast cancer in women from high-risk families.

Exploratory laparotomy The diagnosis of ovarian cancer is generally made by histopathologic study following exploratory laparotomy. The stage of the disease can only be determined by surgery, as discussed below.

Preoperative evaluation Patients with suspected ovarian cancer should undergo a thorough evaluation prior to surgery. This assessment should include a complete history and physical examination and serum CA-125 level determination. In women younger than age of 30 years, determinations of β-human chorionic gonadotropin (β-HCG) and α-fetoprotein (AFP) levels are useful, as germ-cell tumors are more common in this age group.

Abdominal CT and MRI In apparent early-stage cases, abdominal scanning by CT or MRI adds little to the diagnostic evaluation, and, thus, these studies are not routinely necessary. CT and MRI may be useful in providing a preoperative assessment of disease extent in probable advanced-stage cases.

Preoperative endometrial sampling Women with abnormal vaginal bleeding should have preoperative endometrial sampling.

Preoperative cytologic or histologic evaluation of effusions or tumor masses is neither necessary nor desirable. Often, patients with ascites and large pelvic masses, for whom exploration is necessary, are subjected to paracentesis or needle biopsy. These procedures only delay definitive management and may lead to seeding of tumor cells along needle tracts.

NIH GUIDELINES ON SCREENING FOR OVARIAN CANCER

Until clinical trials gather enough information, no evidence supports routine screening for ovarian cancer in women without first-degree relatives affected by the disease, according to a consensus development panel convened by the NIH.

The panel did recommend that physicians take a comprehensive family history of their female patients. The panel also advised women to undergo routine annual rectovaginal pelvic examinations.

There are no conclusive data that screening is beneficial, even for women with two or more first-degree relatives with ovarian cancer, the panel stated. However, these women have a significant chance of having a hereditary ovarian cancer syndrome and should be counseled by a gynecologic oncologist or other qualified specialist regarding their individual risk.

Patients with hereditary ovarian cancer syndrome

Patients with hereditary ovarian cancer syndrome (assuming autosomal-dominant inheritance with 80% penetrance) have a 40% lifetime risk of developing ovarian cancer. Recent data suggest that screening these women reduces their mortality from ovarian cancer.

High-risk women

The three known hereditary syndromes that place a woman at exceedingly high risk are familial site-specific ovarian cancer syndrome, breast-ovarian cancer syndrome, and breast-ovarian-endometrial-colorectal cancer syndrome. Annual rectovaginal pelvic examinations, CA-125 level determinations, and transvaginal ultrasonography are recommended for these women until their childbearing is completed or until age 35 years, at which time prophylactic bilateral oophorectomy is recommended.

Prophylactic oophorectomy performed in women undergoing abdominal surgery for other indications, such as benign uterine disease, is also associated with a significant reduction in the risk of ovarian cancer. The appropriateness of hormonal replacement therapy is not straightforward given that many of these women are at higher risk for breast cancer. In addition, the recent report from the study by the Women's Health Initiative in postmenopausal women raised questions regarding the role of long-term hormonal replacement, particularly showing no benefit in terms of cardiovascular risk reduction. Women should discuss the potential for estrogen replacement vs other agents for the prevention of osteoporosis, for example, with their health care provider.

Other panel recommendations

Women with ovarian masses who have been identified preoperatively as having a significant risk of ovarian cancer should be advised to have their surgery performed by a gynecologic oncologist.

Aggressive attempts at cytoreductive surgery as the primary management of ovarian cancer will improve the chances for long-term survival.

Women with stage IA and IB, grade 1 ovarian cancer do not require postoperative adjuvant therapy, although many remaining stage I patients do require chemotherapy. Subsets of stage I must be fully defined and ideal treatment determined.

Second-look laparotomy should not be employed as routine care for all patients but should be performed for patients enrolled in clinical trials or for patients in whom the surgery will affect clinical decision-making and the clinical course.

From Ovarian cancer: Screening, treatment and follow-up. NIH Consensus Statement. 12:1–30, 1994.

Pathology

The ovaries are notable for their ability to give rise to a large variety of neoplasms with distinct embryologic origins and differing histologic appearances.

Epithelial adenocarcinoma Approximately 90% of all ovarian malignancies are of epithelial origin, arising from the cells that invest the surface of the ovaries. These cells give rise to a variety of adenocarcinomas, including serous, mucinous, endometrioid, and clear-cell types. These tumors have benign counterparts of similar histologic appearance and can also exist as "borderline" cancers, also known as "tumors of low malignant potential." There is some prognostic significance to the cell type of the tumor, with clear-cell and mucinous varieties tending to be especially virulent.

Histologic differentiation Pathologists also classify adenocarcinomas according to the degree of histologic differentiation. Those tumors retaining clear-cut glandular features are considered grade 1, or well differentiated, whereas those that are largely composed of solid sheets of tumor are considered grade 3, or poorly differentiated. Tumors showing both glandular and solid areas are assigned to grade 2. The histologic grade seems to correlate roughly with biologic aggressiveness.

Stromal and germ-cell tumors Malignancies can also arise from the ovarian stroma or the primordial germ cells contained within the ovaries. Stromal tumors are often hormone-producing, and include such types as the granulosa tumor, Sertoli-Leydig tumor, and several variants. Germ-cell tumors, which tend to be highly aggressive, include the dysgerminoma, endodermal sinus tumor, malignant teratoma, embryonal carcinoma, and rare primary choriocarcinoma of the ovaries.

Staging and prognosis

Staging system

The staging system for ovarian cancer shown in Table 1, developed by the International Federation of Gynecology and Obstetrics (FIGO), is used uniformly in all developed countries. It is based on the results of a properly performed exploratory laparotomy, a fact that bears emphasis, since inadequate surgical staging has been and continues to be a significant problem.

Surgical staging The surgical staging of ovarian cancer is based on an understanding of the patterns of disease spread and must be conducted in a systematic and thorough manner. It should include a complete evaluation of all visceral and parietal surfaces within the peritoneal cavity, omentectomy, and biopsy of aortic and pelvic lymph nodes. It generally includes removal of the internal reproductive organs as well.

The issue of adequate surgical staging becomes particularly acute in just the patient population likely to be operated upon by individuals with no specialized training in gynecologic oncology: patients with adnexal masses that are not obvious cancers on preoperative evaluation. At the time of exploration, if the mass is

TABLE I: FIGO staging system for ovarian cancer

Stage	Characteristics
I	Growth limited to the ovaries
IA	Growth limited to one ovary; no ascites; no tumor on the external surfaces, capsule intact
IB	Growth limited to both ovaries; no ascites; no tumor on the external surfaces, capsule intact
IC	Tumor either stage IA or IB but on the surface of one or both ovaries; capsule ruptured; ascites containing malignant cells present ; or positive peritoneal washings
II	Growth involving one or both ovaries with pelvic extension of disease
IIA	Extension of disease and/or metastases to the uterus and/or fallopian tubes
IIB	Extension of disease to other pelvic tissues
IIC	Tumor either stage IIA or IIB but on the surface of one or both ovaries; capsule(s) ruptured; ascites containing malignant cells present; or positive peritoneal washings
III	Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes; superficial liver metastasis equals stage III; tumor is limited to the true pelvis but with histologically verified malignant extension to the small bowel or omentum
IIIA	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
IIIB	Tumor of one or both ovaries; histologically confirmed implants on abdominal peritoneal surfaces, none > 2 cm in diameter; nodes negative
IIIC	Abdominal implants > 2 cm in diameter and/or positive retroperitoneal or inguinal nodes
IV	Growth involving one or both ovaries with distant metastases; if pleural effusion is present, there must be positive cytologic test results to allot a case to stage IV; parenchymal liver metastasis equals stage IV

FIGO = International Federation of Gynecology and Obstetrics

shown to be malignant on frozen section and there is no obvious metastatic disease, a complete staging operation is essential to search for occult metastatic spread, which may be present in 20%-30% of such cases. Also, if the tumor is documented to be stage IA by thorough staging and the patient wishes to preserve the potential for future fertility, it may be appropriate to conserve the uterus and uninvolved ovaries and fallopian tube–an option often overlooked by the inexperienced surgeon.

The elements of surgical staging for apparent early ovarian cancer are listed in Table 2.

Prognostic factors

The prognosis of epithelial ovarian cancer depends on a number of factors.

Disease stage Of primary importance is disease stage, which, when properly determined, is of strong prognostic significance. The distribution of ovarian

TABLE 2: Procedures for surgical staging of apparent early ovarian cancer

Vertical incision
Multiple cytologic washings
Intact tumor removal
Complete abdominal exploration
Removal of remaining ovaries, uterus, fallopian tubes[a]
Omentectomy
Lymph node sampling
Random peritoneal biopsies, including the diaphragm

[a] May be preserved in selected patients who wish to preserve fertility

cancer cases by stage follows: stage I, 26%; stage II, 15%; stage III, 42%; stage IV, 17%. For patients with advanced ovarian cancer, the amount of residual tumor at the conclusion of the initial operation is of major importance. Patients with stage III disease who have minimal or no residual tumor may have a 30%-50% chance of 5-year survival, whereas those stage III patients left with a bulky tumor have a 5-year survival rate of only about 10%.

Histologic grade and type Most studies have found the histologic grade of the tumor to have prognostic significance; the histologic cell type of the tumor is of lesser importance, although patients with clear cell and possibly mucinous tumors may have a worse prognosis.

Molecular markers In recent years, a great deal of effort has been devoted to the identification of molecular markers of prognosis in ovarian cancer. Studies of HER-2 *p53, ras*, and other oncogenes and tumor-suppressor genes have had varying results relative to prognostic significance. Currently, the assessment of molecular markers of prognosis has no clinical utility, although much work continues in this promising area.

Predictors of chemosensitivity Similarly, after 25 years of investigations assessing in vitro and in vivo methods to predict the sensitivity or resistance of ovarian cancers to various chemotherapeutic drugs, the clinical usefulness of such an approach remains under investigation.

Treatment

Surgery plays a crucial role in all phases of the management of ovarian cancer and, when applied as part of a multidisciplinary approach, affords patients the highest likelihood of a favorable outcome. For most patients with ovarian carcinoma, surgery is not curative due to dissemination of tumor cells throughout the abdominal cavity. Therefore, successful management generally requires additional treatment.

The use of postoperative chemotherapy is standard for all patients with advanced-stage disease and for many patients with early-stage disease. Adjunctive chemotherapy significantly prolongs survival, with most current data supporting the use of platinum- and taxane-based regimens.

Despite a long history of the use of radiation therapy in ovarian carcinoma, opinions on its utility differ widely. Presumably, this controversy is due to the limited amount and adequacy of data comparing radiotherapy with modern chemotherapy regimens. Similarly, the role of radiotherapy as part of up-front combined-modality therapy, salvage treatment following chemotherapy, and palliative therapy remains unclear.

TREATMENT OF EARLY DISEASE

Clearly, comprehensive surgical staging is necessary to properly identify patients with stages I and II ovarian carcinoma. Beyond surgery, the need for adjuvant treatment with chemotherapy has been recently supported, with the exception of patients with stage I disease and well-differentiated histology.

Surgery

Suspicious adnexal masses should be excised intact and submitted for frozen section. If a malignancy is confirmed and there is no obvious metastatic spread, complete surgical staging should be undertaken. As discussed earlier (see section on "Staging and prognosis"), it is of critical importance that surgical staging be performed in a systematic and complete manner. Inadequate staging may result in inappropriate postoperative treatment that can severely compromise the chances for cure.

Data from the American College of Surgeons community hospital-based tumor registry show that almost 75% of the primary surgeries for ovarian cancer performed in this country are performed without the involvement of a gynecologic oncologist. This finding is particularly unfortunate given the fact that, with physical examination, measurement of CA-125 levels, and appropriate imaging tests, the majority of cases of ovarian cancer can be identified preoperatively. Results from other studies suggest that when a gynecologic oncologist is not present at the initial operation, staging is more often inadequate, cytoreduction is more often suboptimal, and long-term survival is poorer.

Reproductive organ conservation In a woman of reproductive age with cancer limited to one ovary, it may be possible to conserve the uterus and opposite fallopian tube and ovary if she wishes to maintain the option of future fertility. To facilitate such intraoperative decision-making, it is essential that the surgeon's preoperative discussion with the patient and her family address the possibility of malignancy and review the surgical options for both benign and malignant diseases.

Operative laparoscopy Recent advances in the instrumentation for operative laparoscopy have led to an increase in the proportion of adnexal masses being managed with this technique. Physicians should exercise caution in se-

lecting patients with adnexal masses for operative laparoscopic approaches. Unless the surgeon's laparoscopic skills are extraordinary, suspicious masses are best managed by laparotomy. For masses that are approached laparoscopically, the same surgical principles of removal without spill and complete surgical staging apply.

Systemic chemotherapy

The current management of patients with early-stage disease focuses on comprehensive surgical staging and the identification of high-risk features. Patients with stage IA or IB tumors with well-differentiated histology have excellent 5-year survival rates, and adjuvant chemotherapy is generally not used in such patients. High-risk features include moderately to poorly differentiated tumors, stage IC or II disease, and clear-cell histology.

The reported survival rates of 60%-80% in patients who have early-stage tumors with high-risk features suggested a potential role for adjuvant therapy. The Italian Inter-Regional Cooperative Group conducted two randomized trials to evaluate the role of adjuvant therapy in patients with stage I disease. The first trial compared cisplatin (Platinol), 50 mg/m^2 q28d × 6, to observation in 85 patients with stage IA or IB, grade 2-3 disease. The 5-year disease-free survival rate was higher in patients treated with cisplatin than in those who were observed (83% vs 63%), but the 5-year overall survival rate was similar in the two groups (88% vs 82%).

The second trial compared cisplatin (same dose) to phosphorus-32 (P-32) administration in 161 patients with stage IA-IB, grade 2 or stage IC disease. The 5-year disease-free survival rate again favored the platinum arm (85% vs 65%), but the 5-year overall survival rate was unchanged and similar to that reported in the previous trial.

More recent preliminary data have provided support for a survival benefit to the immediate use of adjuvant chemotherapy in patients with early-stage disease. The results of the ACTION (European Organization for Research on the Treatment of Cancer [EORTC] Adjuvant Treatment in Ovarian Neoplasm) and International Collaborative on Ovarian Neoplasm (ICON) trials were combined and reported at the 2001 American Society of Clinical Oncology (ASCO) meeting. A 5-year survival rate improvement of 7% was reported for those receiving immediate chemotherapy compared with reserving chemotherapy for those who relapsed (75% vs 82%).

Improvements in the systemic chemotherapy of advanced ovarian cancer with associated improvements in survival are relevant to the design of regimens for early-stage disease. A recently completed Gynecologic Oncology Group trial (GOG 157) evaluated three vs six cycles of paclitaxel and carboplatin (Paraplatin) in patients with stage IA or IB, grade 2-3; stage IC; or stage II disease. The trial completed accrual in 1995, and final results are not available. The GOG replacement trial is evaluating three cycles of paclitaxel plus carboplatin with or without additional weekly paclitaxel (40 mg/m^2) in patients with early-stage disease.

In the absence of additional data, taxane- and platinum-based systemic chemotherapy should be considered the standard approach for patients who have early-stage disease with high-risk features. The optimum number of cycles is currently unclear, but three cycles were considered the standard arm in the GOG 157 trial.

Radiation therapy

Past GOG trials have established that patients with stages IA and IB, well-differentiated or moderately differentiated tumors have a 5-year survival rate of 90%-98%, which does not seem to improve with adjuvant chemotherapy. However, patients with less favorable neoplasms by virtue of higher grade or stage have poorer outcomes (80% 5-year survival rate among treated patients).

Although reasonable therapy, the use of P-32 in intermediate-prognosis patients remains subject to question, as do all adjuvant therapies, particularly in stage I disease. Patients with stage II disease, particularly those with macroscopic residual disease following surgery, have relapse rates that require consideration of adjuvant therapy.

Whole-abdominal irradiation Externally administered whole-abdominal irradiation (WAI) has a number of theoretical and practical advantages over P-32 therapy. They include improved homogeneity of radiation dose, treatment of pelvic and para-aortic lymph nodes, better coverage of all peritoneal surfaces, and lack of treatment restrictions due to postoperative adhesions.

However, late toxicity has been a legitimate concern. A retrospective study found that patients who received six cycles of cisplatin and cyclophosphamide (Cytoxan, Neosar) with WAI administered between the third and fourth cycles had significantly better outcomes than those given single-agent cisplatin. The difference was particularly evident in patients with stage I or II, grade 3 tumors without gross residual disease.

A recent study by Hepp et al found WAI to be an effective adjuvant therapy in patients with optimally debulked tumors. In a series of 60 patients, the 5-year survival rate was 55%, with a median follow-up of 96.5 months. Patients who received chemotherapy (n = 41) fared slightly worse than those who received radiation therapy only. The abdominal control rate was 83%, and the grade 3 and 4 late toxicity rates were 7% and 3%, respectively.

The findings indicate that 5- and 10-year survival rates obtained with WAI are at least equivalent to results obtained using modern systemic agents. However, in view of the recognized limitations of these trials, more rigorously gathered data will be required to establish the role of WAI in these patients.

Collectively, existing data suggest that WAI should be studied further as a primary adjuvant treatment modality in patients thought to require treatment. Appropriate patients for trials including WAI are intermediate-risk patients, as defined by Dembo. The entire abdomen should be treated with an open-field technique using 100-150 cGy/d, to a total dose of 2,200-2,500 cGy. The utility of routine pelvic boosts is questionable in patients with completely debulked tumors.

TREATMENT OF ADVANCED DISEASE

Surgery

Typically, surgeons operating on patients with ovarian cancer find obvious evidence of widespread metastatic disease. Ascites is often present, with diffuse peritoneal tumor studding and extensive omental involvement. In such cases, it is still important to document the surgical stage (usually a substage of stage III) and carefully evaluate and describe the extent and location of tumor identified at both the beginning and conclusion of surgery.

Optimal cytoreduction The primary function of surgery in patients with advanced ovarian cancer is cytoreduction or debulking. When surgery is performed by experienced gynecologic cancer surgeons, at least 50% of patients with stage III ovarian cancer can be left with "optimal" residual tumor (ie, < 1 cm). The morbidity associated with such surgery is low, and operative mortality is rare.

Several benefits accrue to patients who can be left with optimal residual disease. These patients have an increased likelihood of achieving a complete clinical response to chemotherapy, and among those who achieve a complete response and have a second-look operation, a greater proportion will have no tumor detectable. In addition, the risk of relapse after negative second-look surgery is reduced in patients left with small-volume residual disease at the conclusion of their primary operation. Disease progression-free interval, median survival, and long-term survival are all improved in patients who have optimal cytoreduction.

Even among patients with suboptimal residual disease (> 1 cm) after primary surgery, those left with smaller tumor volumes (1-2 cm) have a survival advantage over those with a larger residuum. It is thus clear that aggressive surgical cytoreduction, if successful in reducing tumor to small volumes, improves several measures of outcome.

Interval cytoreduction In an EORTC trial, 299 patients with suboptimal advanced ovarian cancer were randomized to receive 6 cycles of cisplatin plus cyclophosphamide with or without interval surgical cytoreduction after the third cycle. Median survival for patients who underwent interval debulking surgery was 27 months, vs 19 months for patients who did not have interval debulking ($P = .01$). The GOG has recently completed accrual to a randomized trial of interval cytoreduction using a cisplatin-paclitaxel chemotherapy regimen. These results are reported in abstract form currently, and, to date, no benefit for interval cytoreduction has been shown (median overall survival; 32 vs 33 months). The introduction of taxane-based therapy, or more standardized aggressive initial debulking, in the GOG trial has been offered as a possible explanation for the discordant outcomes. Final results are pending.

Chemotherapy

Primary treatment The results of two randomized trials support a survival advantage for patients treated with combinations of IV platinum and paclitaxel,

TABLE 3: Chemotherapy regimens for ovarian carcinoma

Drug/combination	Dose and schedule
Paclitaxel/cisplatin	
Paclitaxel	135 mg/m^2 IV infused continuously over 24 hours
Cisplatin	75 mg/m^2 IV on day 1
Repeat cycle every 21 days	
PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours before paclitaxel; as well as diphenhydramine, 50 mg IV, and ranitidine, 50 mg IV, both 30-60 minutes before paclitaxel	
McGuire WP, Hoskins WJ, Brady MF, et al: N Engl J Med 334:1–6, 1996.	
Paclitaxel/carboplatin	
Paclitaxel	175 mg/m^2 IV infused over 3 hours on day 1
Carboplatin	Dose calculated by the Calvert formula to an AUC between 5.0 and 7.5 mg/mL/min IV infused over 30 minutes. Carboplatin is given after paclitaxel.
Repeat cycle every 21 days for 6 courses	
PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; as well as diphenhydramine, 50 mg IV, and ranitidine, 50 mg IV, both 30-60 minutes prior to paclitaxel.	
Coleman RL, Bagnell KG, Townley PM: Cancer J Sci Am 3:246–253, 1997.	
Single-agent topotecan	
Topotecan	1.5 mg/m^2 IV over 30 minutes daily for 5 days
Repeat cycle every 21 days	
Iva B, Ondrej B, Milan B, et al: Proc Am Soc Clin Oncol 19:1570a, 2000.	
Single-agent liposomal doxorubicin[a]	
Liposomal doxorubicin	50 mg/m^2 IV on day 1
Repeat cycle every 4 weeks	
[a]**NOTE:** Clinical experience is accumulating to suggest that liposomal doxorubicin (at doses of 40 mg/m^2 q 4 weeks) and topotecan (at 1.0 mg/m^2/d × 5 days) are equally efficacious and better tolerated than these agents at initial phase II doses. Definitive trials are ongoing.	
Muggia FM, Hainsworth JD, Jeffers S, et al: J Clin Oncol 15:987–993, 1997.	

Table prepared by Ishmael Jaiyesimi, DO

as compared with those given a platinum plus cyclophosphamide. McGuire et al found a 37- vs 24-month median survival advantage for the platinum-paclitaxel arm. Similarly, an analysis of the intergroup trial by Piccart et al showed an improvement in median survival from 25 to 35 months ($P = .001$) in favor of the paclitaxel arm. In contrast, the initial analysis of the ICON 3 trial evaluating a control arm (carboplatin or CAP [cyclophosphamide, doxorubicin, cisplatin] chemotherapy) vs paclitaxel and carboplatin has failed to show a survival advantage for the taxane-containing arm. Many factors in the study have been proposed to explain this difference, and for the present, taxane, and platinum-based therapy remains the standard.

A randomized trial (GOG 158) comparing paclitaxel (175 mg/m^2 via a 3-hour infusion) plus carboplatin (dosed to achieve an area under the curve [AUC] of

7.5) vs the standard regimen of paclitaxel (135 mg/m^2 via a 24-hour infusion) plus cisplatin (75 mg/m^2) in patients with optimally debulked disease showed the shorter schedule with carboplatin to be as effective as the older regimen. Due to its lesser toxicity and ease of administration, the shorter schedule with carboplatin is the preferred treatment.

In addition, preliminary results from the SCOTROC trial suggested that, as primary treatment, docetaxel (Taxotere) and paclitaxel have similar efficacy when combined with carboplatin and that docetaxel produces less neuropathy.

A five-arm international randomized study of the primary therapy for patients with stage III or IV disease is under way by the GOG. This study will determine the optimal primary chemotherapy regimen among currently available standard agents (Table 3). It uses carboplatin and paclitaxel as the control arm and evaluates two triplets (carboplatin + paclitaxel with either gemcitabine [Gemzar] or liposomal doxorubicin [Doxil]) and two sequential doublets (topotecan [Hycamtin]/carboplatin + carboplatin/paclitaxel or carboplatin/gemcitabine + carboplatin/paclitaxel).

Recurrent disease Patients who respond to primary chemotherapy with paclitaxel and platinum agents and who relapse ≥ 6 months after the completion of treatment often have additional responses of limited duration when retreated with the same agents. Response rates to repeat treatment with carboplatin are ~30% in those patients who relapse 12 months after primary therapy and 57% if the relapses occur > 24 months after primary therapy. In addition, a plethora of new agents have demonstrated modest phase II activity in patients with refractory disease.

Topotecan has FDA approval for the treatment of patients with refractory disease (Table 3). An oral preparation is in phase III trials.

An open, randomized study compared topotecan (1.5 mg/m^2/d for 5 days) with paclitaxel (175 mg/m^2 q21d) in 226 women whose ovarian cancer had recurred after first-line platinum therapy. There were no statistically significant differences between the treatment groups with respect to response rate (20.5% vs 14.0%), response duration (25.9 vs 21.6 weeks), or median survival (63 vs 53 weeks).

Topotecan has efficacy comparable to that of paclitaxel in this setting and is being evaluated in combination with platinum and other agents.

Liposomal doxorubicin also has received FDA approval for the treatment of patients with metastatic platinum- and paclitaxel-refractory disease (Table 3). A randomized trial by Gordon et al compared liposomal doxorubicin with topotecan in this setting; similar response rates, time to disease progression, and overall survival (60.0 vs 56.7 weeks) were seen with these two agents.

Other agents Recent phase II trials have demonstrated the activity of other agents in patients with recurrent ovarian cancer. They include gemcitabine, vinorelbine (Navelbine), oral altretamine (Hexalen), and oral etoposide. In general, these agents have similar response rates, ranging from 10%-15% in patients with plati-

num-resistant disease and 30% in patients with platinum-sensitive disease, with a median duration of response ranging from 4 to 8+ months.

For many patients, ovarian cancer becomes a chronic disease characterized by a series of relapses followed by partial or complete remission. With the judicious selection and dosing of available agents to keep symptoms from disease and treatment to a minimum, a good quality of life can be maintained throughout much of the disease course.

High-dose chemotherapy

Currently, there is no role for high-dose chemotherapy in the standard management of patients with epithelial ovarian cancer.

In a trial conducted largely in patients with platinum-resistant (66%) and bulky disease (61%), the median progression-free and overall survival intervals were short (7 and 13 months, respectively) in patients treated with high-dose chemotherapy and stem-cell support. Based on these and other similar data, patients with platinum-resistant, bulky disease should not receive high-dose chemotherapy.

Intraperitoneal chemotherapy

A randomized, phase III study conducted by the Southwest Oncology Group (SWOG), Eastern Cooperative Oncology Group (ECOG), and GOG compared IV cisplatin (75 mg/m^2) and paclitaxel (135 mg/m^2 over 24 hours) with IV carboplatin (dosed to an AUC of 9) followed by IV paclitaxel (135 mg/m^2 over 24 hours) and intraperitoneal cisplatin (100 mg/m^2) in patients with optimally debulked disease. Results indicated superior recurrence-free survival in the patients treated with intraperitoneal cisplatin (27.6 vs 22.5 months; $P = .020$), as well as an improvement in overall survival duration that was of borderline statistical significance (52.9 vs 47.6 months; $P = .056$). This trial is criticized because of the asymmetry of the experimental arms.

A more recent phase III study in patients with optimally debulked disease compared IV paclitaxel plus IV cisplatin as the standard treatment arm with IV paclitaxel plus intraperitoneal cisplatin and intraperitoneal paclitaxel as the investigational arm. The preliminary results were presented at the 2002 ASCO meeting and showed the relative risk of recurrence was 0.73 in favor of the intraperitoneal arm. Toxicity was considerably greater using the intraperitoneal approach. The role of intraperitoneal therapy in patients with optimally debulked disease remains a debated topic.

Treatment recommendations and unresolved issues

For advanced ovarian cancer, current frontline management should incorporate a taxane with platinum-based therapy.

Recent results of the GOG 132 trial showed no statisically significant differences among three treatment groups regarding the appropriate primary regimen for advanced ovarian cancer. This trial compared three arms: IV cisplatin (100 mg/m^2), IV paclitaxel (200 mg/m^2), and IV cisplatin (75 mg/m^2) plus

paclitaxel (135 mg/m^2). The overall survival was the same in all three arms, whereas the tolerability and ability to complete therapy were best in the combination arm. Upon final analysis, approximately 50% of the patients in each group were crossed over to the alternate therapy prior to objective disease progression. This crossover may have blurred any survival advantage between the treatments. The standard for primary therapy still remains paclitaxel and platinum-based chemotherapy.

Issues that remain to be resolved follow: (1) the role of intraperitoneal therapy in primary treatment and persistent disease following initial systemic chemotherapy; (2) the role of the multiple new agents with documented phase II activity, both in combination and as single agents in primary treatment; and (3) the optimal use of platinum vs nonplatinum/taxane agents in recurrent disease.

Radiation therapy as a single modality

In a 1975 study from M. D. Anderson Hospital, 5-year survival rates with WAI and chemotherapy were similar, although toxicity and cost seemed to be lower with oral melphalan (Alkeran) than radiation therapy. A subsequent trial from Toronto randomized patients with advanced disease to receive either pelvic radiotherapy plus chlorambucil (Leukeran) or WAI. Although surgical staging and chemotherapy were less aggressive than current protocols, the survival advantage and altered failure patterns seen with the Canadian WAI regimen were quite provocative.

No prospective, randomized trial has compared WAI, performed with modern techniques and equipment, with a modern chemotherapy regimen. However, published series document treatment outcomes with WAI that are at least comparable, if not superior, to outcomes with platinum-based chemotherapy regimens. The comparability of WAI to chemotherapy regimens including paclitaxel also is unknown. In view of the encouraging data reported, WAI should be studied further using current concepts and techniques.

Large-volume disease The ability of WAI to sterilize macroscopic deposits of ovarian carcinoma is limited. Patients with any site of residual disease $>$ 1 cm have compromised outcomes, no matter what therapy they receive. However, given the limited radiation tolerance of the abdominal organs, patients with larger volumes of disease are not candidates for WAI as sole adjuvant treatment.

Chemotherapy plus radiation therapy

It is possible to identify patients for whom chemotherapy or radiotherapy is unlikely to be curative because of unfavorable histologic subtype, grade, and amount of residual disease following surgical cytoreduction. Combined-modality therapy incorporating various combinations and sequences of chemotherapy and radiation therapy has been studied in these patients.

Chemotherapy plus WAI Sequential combined-modality therapy (CMT) employing chemotherapy and irradiation has been shown to be feasible. There are a number of important differences between sequential CMT and salvage irradiation: (1) Planned sequential CMT permits the omission of second-look

surgery in selected patients, possibly limiting late toxicity. (2) Clinical studies of CMT have often incorporated a reduction in chemotherapy duration, providing improved tolerance to radiation therapy; this approach permits appropriate radiation doses to be given and potentially limits the emergence of platinum-radiation therapy cross-resistance. (3) With CMT, many patients will have no demonstrable disease but are at high risk of recurrence, whereas with salvage WAI, all patients have clinical or pathologic evidence of disease.

In a recent European study, 64 of 94 patients with stage IC-IV disease who had undergone "radical" surgery and had no evidence of gross residual disease after 6 courses of chemotherapy (carboplatin, epirubicin [Ellence], and prednimustine [Sterecyt]) were randomized to receive either consolidation WAI (30 Gy), followed by a boost to the para-aortic region and pelvis (12.0 and 21.6 Gy, respectively) or no further therapy. Relapse-free survival rates were significantly higher in patients who received adjuvant chemoradiation therapy than in those who received adjuvant chemotherapy only (2- and 5-year relapse-free survival rates, 68% vs 56% and 49% vs 26%, respectively); the same was true of overall survival rates (2- and 5-year overall survival rates, 87% vs 61% and 59% vs 33%, respectively). The differences between the two treatment groups were more pronounced in patients with stage III disease (2- and 5-year relapse-free survival rates, 77% vs 54% and 45% vs 19%, respectively; 2- and 5-year overall survival rates, 88% vs 58% and 59% vs 26%, respectively).

Einhorn et al, from the Karolinska Hospital in Stockholm, treated 75 patients with stages IIB-IV ovarian carcinoma with combined surgery, chemotherapy, and WAI to 40 Gy, utilizing a "six-field" approach. Outcomes were compared with those of 98 patients treated in subsequent years with only surgery and chemotherapy. After different prognostic factors were controlled statistically, it was found that patients who received WAI had a significantly better survival rate than those who did not. The authors suggest that, given the results of this and other studies combined with the very limited success of modern combina-

TABLE 4: Possible prognostic factors for salvage radiation therapy following chemotherapy

Residual tumor before WAI	Lymph node status
Location of residual disease	Chemotherapy duration
Initial FIGO stage	Type of prior chemotherapy
Histologic grade	Completion of WAI
Disease bulk at diagnosis	Response to chemotherapy
Patient age	Histologic type
Disease-free interval from initial treatment to relapse	CA-125 level
	CA-125 level trend
Performance status	Parameters of WAI
Number of sites of residual disease	Interval debulking/second-look surgery

FIGO = International Federation of Gynecology and Obstetrics; WAI = whole-abdominal irradiation

tion chemotherapy regimens, the role of abdominal radiation therapy should be further investigated in a prospective fashion.

Salvage and palliative radiotherapy after chemotherapy

Patients in whom microscopic disease is detected at surgical reassessment have been reported to have median overall and progression-free survival times of 27 and 19 months, respectively. Unfortunately, residual or recurrent disease following first-line chemotherapy is frequent, and salvage rates are dismal.

Patients with residual tumor detected at a planned surgical reassessment have a spectrum of disease, ranging from isolated positive cytology and/or microscopic serosal involvement to gross residual disease. In contrast, relapsing patients generally present with abdominal symptoms from advanced larger-volume recurrences. The latter clinical situation is not particularly amenable to salvage radiotherapy. However, in the setting of small-volume residual disease detected immediately following chemotherapy, two radiotherapy approaches, external-beam irradiation and intraperitoneal radioisotopes, have been used with variable success. Most likely, this variability is related to significant differences in prognostic factors among treated patients. Unfortunately, there are only limited data that can be used to define subgroups who may or may not benefit from salvage WAI. Given the number of possible prognostic variables (Table 4), a clear consensus on this issue is unlikely to be reached.

Chemotherapy-refractory disease Favorable experiences with salvage radiation therapy in chemotherapy-refractory ovarian carcinomas continue to be reported. Sedlacek et al described 27 patients who had not responded to aggressive cytoreductive surgery followed by multiple-drug platinum-based chemotherapy and who received WAI (30-35 Gy at 100-150 cGy/fraction, with a pelvic boost to a total dose of 45 Gy). The 5-year survival rate was 15%. Extent of residual disease at the initiation of radiation therapy strongly correlated with length of survival.

Baker et al analyzed the efficacy of salvage WAI in 47 patients with ovarian cancer who had not responded to one or more chemotherapy regimens. Actuarial 4-year survival and disease-free survival rates were 48% and 37%, respectively, in patients with microscopic residual disease, vs 11% and 5%, respectively, in patients with macroscopic residual disease. In addition, patients with disease limited to the pelvis after laparotomy (including gross disease) had a 4-year actuarial survival rate of 60% and disease-free survival rate of 54%, as compared with 16% and 4%, respectively, in patients with upper abdominal involvement.

This finding was confirmed by Firat and Erickson, who described their experience with selective radiotherapy in 28 patients with recurrent or persistent disease involving the vagina and/or rectum. Pelvic radiotherapy was uniformly successful in palliating vaginal bleeding. Furthermore, there were eight long-term survivors (five with no evidence of disease), implying that pelvic radiotherapy alone can be effective salvage therapy, particularly when there is no extrapelvic disease.

Fujiwara and colleagues reported high rates of objective and symptomatic responses using local radiotherapy in 20 patients (42 evaluable lesions) with recurrent ovarian cancer following chemotherapy. Lymph node metastases appeared to be particularly responsive.

Tinger et al reported an overall response rate of 73% in 80 patients with advanced and recurrent disease treated with palliative intent. Responses were maintained until death in all but 10 patients. Toxicity was limited, and there was no grade 4 toxicity. It was suggested that response rate, survival, and toxicity with palliative radiotherapy compared favorably with those of second- and third-line chemotherapy.

Based on these and other studies, certain treatment guidelines can be suggested:

- Patients with any site of residual disease > 0.5 cm will fare poorly with salvage WAI. However, salvage WAI can be considered in selected patients with microscopic residual disease following first-line chemotherapy.
- Irradiation-related morbidity can be minimized by limiting the abdominal dose to 25 Gy and abandoning WAI in patients who require treatment breaks of more than 1-2 weeks. In fact, randomized clinical trial data from Fyles et al show no benefit from WAI doses > 22.5 Gy.
- Patients with limited gross residual disease confined to the pelvis may constitute a prognostically favorable group in whom pelvic boosts or pelvic radiation therapy alone may be warranted.
- Localized radiation therapy to areas of symptomatic (and, in some cases, asymptomatic) recurrent disease is associated with high rates of durable responses with limited toxicity. In some cases, extended survival is possible.

The relative merits of salvage WAI compared with other treatments, such as intraperitoneal chemotherapy, second-line chemotherapy, and high-dose chemotherapy/bone marrow transplantation, can only be determined in a prospective, randomized, controlled trial.

SUGGESTED READING

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CHAPTER 23

Gestational trophoblastic tumors

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Gestational trophoblastic tumors (GTTs) encompass a spectrum of neoplastic disorders that arise from placental trophoblastic tissue after abnormal fertilization. GTTs are classified histologically into four distinct groups: hydatidiform mole (complete and partial), chorioadenoma destruens (invasive mole), choriocarcinoma, and placental site tumor. Most commonly, GTT results in a hydatidiform "molar" pregnancy characterized by the lack of a fetus, trophoblastic hyperplasia, edematous chorionic villi, and a loss of normal villous blood vessels.

Most molar pregnancies spontaneously resolve after uterine evacuation with no further sequelae. However, at any time during or after gestation, malignant transformation may occur in approximately 10%-20% of molar pregnancies. Nearly two-thirds of these cases have an invasive mole confined to the uterus (chorioadenoma destruens). Choriocarcinoma characterized by distant metastatic spread develops in one-third of patients. Placental site tumors are uncommon neoplasms derived from intermediate trophoblast cells of the placenta, which are identified by cellular secretion of placental lactogen and small amounts of β-subunit human chorionic gonadotropin (β-hCG).

In the United States, GTTs account for less than 1% of gynecologic malignancies. However, knowledge of the natural history and management of GTTs is important because of this tumor's potential for cure with appropriate therapy. Forty years ago, women with choriocarcinoma had a 95% mortality rate. Today, with the advent of effective chemotherapy and the development of a reliable tumor marker (β-hCG), the cure rate for choriocarcinoma is 90%-95%.

Epidemiology and etiology

A hydatidiform mole develops in approximately 1 in 1,000-2,000 pregnancies in the United States. Molar pregnancies are reported in approximately 3,000 patients per year, and malignant transformation occurs in 6%-19% of these cases. Complete molar pregnancies occur in 1 in 40 molar pregnancies, 1 in 15,000 abortions, and 1 in 150,000 normal pregnancies. Overall, approximately 80% of cases of GTTs are hydatidiform moles, 15% are chorioadenoma destruens, and 5% are choriocarcinomas. Choriocarcinoma is associated with an antecedent mole in 50% of cases, a history of abortion in 25%, term delivery in 20%, and ectopic pregnancy in 5%.

Pathology

Hydatidiform moles, invasive moles, and choriocarcinomas have distinct morphologic features. Moles are described as partial or complete (classic) based on their morphologic, karyotypic, and clinical features. Complete moles are distinguished by the complete absence of normal villi and by chromosomal material that is virtually always of paternal origin. Partial moles are characterized grossly by an admixture of normal and hydropic villi, a triploid karyotype, and the presence of both maternal and paternal chromosomal material.

Choriocarcinomas have a unique histology that is distinct from that of the moles. The tumor is grossly red and granular and exhibits extensive necrosis and hemorrhage. Microscopically, the neoplasm is composed of a disordered array of syncytiotrophoblastic and cytotrophoblastic elements, frequent mitoses, and multinucleated giant cells. Vascular invasion occurs early, with resultant metastases to the lungs, vagina, brain, kidneys, liver, and gastrointestinal tract.

Clinical presentation

Complete mole

The classic signs of a molar pregnancy include the absence of fetal heart sounds, physical evidence of a uterus that is larger than expected for gestational age, and vaginal bleeding. Although an intact fetus may coexist with a partial mole, this occurs in fewer than 1 in 100,000 pregnancies.

The most common presenting symptom of molar pregnancy is vaginal bleeding, reported in up to 97% of patients. Intrauterine clots may undergo oxidation and liquefaction, producing pathognomonic prune juice–like fluid. Rarely, spontaneous expulsion of grape–like villi will provide the diagnosis of hydatidiform mole. Prolonged or recurrent bleeding may result in iron-deficiency anemia. Symptoms of anemia occur in approximately 50% of patients at the time of diagnosis.

Early toxemia (hypertension, proteinuria, and edema) presenting during the first or second trimester is common (20%-30%) in molar pregnancy. Very rarely, eclamptic convulsions may occur in this setting.

Hyperemesis gravidarum—protracted nausea and vomiting during pregnancy—is observed in approximately 10% of women with GTT. The mechanism is not well understood.

Hyperthyroidism is seen clinically in approximately 7% of molar pregnancies. An elevation of triiodothyronine (T3) and thyroxine (T4) levels is observed more commonly than are the manifestations of tachycardia, sweating, weight loss, and tremor. These hormonal elevations are presumed to be secondary to the structural similarity of hCG to thyroid-stimulating hormone (TSH).

Partial mole

Patients with partial mole have different clinical features than those with complete mole. Fewer than 10% of patients with partial mole have uterine enlargement. Patients with partial mole do not have prominent theca-luteal cysts, hyperthyroidism, or respiratory insufficiency. They experience toxemia only rarely. The diagnosis of partial mole is usually made after histologic review of curettage specimens.

Metastatic trophoblastic disease

Metastatic GTT is reported in 6%-19% of patients after molar evacuation. Metastases sometimes have an identical histology to that of molar disease, but the vast majority are choriocarcinomas. Metastatic spread is hematogenous. Because of its extensive vascular network, metastatic GTT often produces local, spontaneous bleeding. Berkowitz et al at the New England Trophoblastic Disease Center (NETDC) reported that the common metastatic sites of GTT are the lungs (80%); vagina (30%); pelvis (20%); liver (10%); brain (10%); and bowel, kidneys, and spleen (5% each).

Pulmonary metastases are quite common (80% of patients with metastatic disease) and occur when trophoblastic tissue enters the circulation via uterine venous sinuses. The radiologic features may be protean or subtle and include alveolar, nodular, and miliary patterns. Pleural effusions may also be present. Pulmonary metastases can be extensive and can cause respiratory failure and death.

Right upper-quadrant pain has been observed when hepatic metastases stretch Glisson's capsule. Gastrointestinal lesions may result in severe hemorrhage or in perforation with peritonitis, both of which require emergency intervention. Vaginal examination may reveal bluish metastatic deposits; these and other metastatic sites should not undergo biopsy because severe uncontrolled bleeding may occur.

Central nervous system (CNS) involvement from metastatic GTT suggests widespread disease and has a poor prognosis. CNS metastases are clinically evident in 7%-28% of patients with metastatic choriocarcinoma. Bakri and colleagues reported a 17% incidence of patients with GTT metastatic to the brain. All patients had concurrent pulmonary metastases. Cerebral metastases tend to respond favorably to both radiotherapy and chemotherapy.

DIAGNOSTIC STUDIES

Although the clinical presentation may suggest a diagnosis of GTT, certain laboratory studies, particularly a determination of the patient's β-hCG level, and radiographic studies are needed to confirm this diagnosis.

Laboratory studies

Thyroid function studies should be performed in all patients with a clinical history or physical examination suggestive of hyperthyroidism. Abnormal thyroid function, manifested as an elevated T4 level, is common in GTT. Meta-

static deposits in the kidneys or gastrointestinal tract may reveal themselves by hematuria or hematochezia.

Tumor markers A well-characterized glycoprotein hormone secreted by the syncytiotrophoblast, hCG is essential to maintaining normal function of the corpus luteum during pregnancy. This hormone has an α-subunit identical to the α-subunit of the pituitary hormones and a β-subunit (β-hCG) that confers the hormone's unique biologic activity. The presence of hCG appears approximately 8 days after ovulation, and its concentration doubles every 2-4 days, until it peaks at 10-12 weeks of gestation; thereafter, β-hCG levels decline steadily. Because all trophoblastic tumors secrete β-hCG, this hormone serves as an excellent marker for tumor activity in the nonpregnant patient.

Serial β-hCG levels should be monitored during therapy to ensure adequate treatment. The level of β-hCG is roughly proportional to the tumor burden and inversely proportional to therapeutic outcome. The approximately 10%-20% of patients with hydatidiform mole who are not cured by local therapy or do not achieve a spontaneous remission can be identified by a rising or plateauing β-hCG titer on serial determinations after the evacuation of a mole. These patients are considered to have persistent trophoblastic disease and require additional therapy.

NOTE: In an occasional patient the current β-hCG assays may result in a false elevation. This may be secondary to a nonspecific cross–reaction between antibodies in the patient's serum and in the immunoassay kit. A positive urine pregnancy test (urine β-hCG) will confirm a true positive serum β-hCG. Most commonly these are human antimouse antibodies (HAMA). As always in medicine, if the laboratory result does not fit the clinical picture it needs to be verified using alternative methods.

RADIOLOGIC STUDIES

A chest x-ray should always be performed because 70%-80% of patients with metastatic GTT have lung involvement. Although this x-ray usually demonstrates nodular metastases, the patterns of metastatic disease can range from atelectatic areas to subtle pleural abnormalities. A CT scan is often helpful in evaluating these nonspecific findings.

Since it has been demonstrated that 97%-100% of patients with CNS disease from choriocarcinoma have concomitant pulmonary metastases, a CNS work-up in asymptomatic patients with normal chest x-rays is not routinely warranted. If the chest x-ray is abnormal, or if β-hCG levels plateau or rise during treatment, a more thorough evaluation for metastatic disease is indicated. Magnetic resonance imaging (MRI) of the brain, brain stem and cerebellum, CT scans of the abdomen and pelvis should be performed to evaluate other likely sites of metastatic spread. The presence of intrauterine or ovarian disease also may be detected by MRI of the pelvis.

Ultrasonography is a reliable, safe, economical, and relatively simple method for confirming the diagnosis of intrauterine GTT. It is also useful in identifying embryonic remnants.

TABLE 1: Proposed FIGO 2000 scoring system for gestational trophoblastic disease

Prognostic factor	Score[a] 0	1	2	4
Age (yr)	≤ 39	> 39		
Antecedent pregnancy	Hydatidiform mole	Abortion	Term	
Interval (mo)[b]	< 4	4-6	7-12	> 12
hCG (IU/L)	< 1,000	1,000-10,000	10,000-100,000	>100,000
Largest tumor	< 3 cm	3-4 cm	≥ 5 cm	
Site(s) of metastases	Lungs	Spleen, kidneys	GI tract, liver	Brain
Number of metastases		1-3	4-8	> 8
Prior chemotherapy			Single drug	Two or more drugs

[a] The total score for a patient is obtained by adding the individual scores of each prognostic factor: 4 or less = low risk; 5-7 = intermediate risk; > 7 = high risk.

[b] Time between end of antecedent pregnancy and start of chemotherapy.

Adapted, with permission, from Kohorn EI, Goldstein DP, Hancock BW, et al: Int J Gynaecol Cancer 10:84–88, 2000.

The proposed FIGO 2000 anatomic staging system is a straightforward system based on anatomic criteria. In GTT, stage I disease is confined to the uterus; stage II disease is outside the uterus but limited to the genital structures. Stage III disease extends to the lungs with or without known genital tract involvement, whereas stage IV disease includes all other metastatic sites. The FIGO 2000 scoring system (Table 1) is based on a method (adapted from WHO) to identify patients at high risk for treatment failure. With the FIGO 2000 scoring system, patients are classified as being in a low-, middle-, or high-risk category. A total score of up to 4 is considered low risk; 5-7, middle risk; and 8 or greater, high risk. (Some centers recommend a low-risk score of 6 or less, a high-risk score of 7 or greater, and no middle-risk score.)

TREATMENT

Although the treatment strategy for GTT must be individualized for each patient, Figure 1 summarizes the general diagnostic and therapeutic approaches used at The University of Texas M. D. Anderson Cancer Center. The stratification of risk groups enables physicians to direct an appropriate treatment strategy. Low-risk disease responds readily to single-agent chemotherapy and is virtually 100% curable. High-risk disease is not likely to be cured with single-agent therapy and therefore requires multidrug regimens.

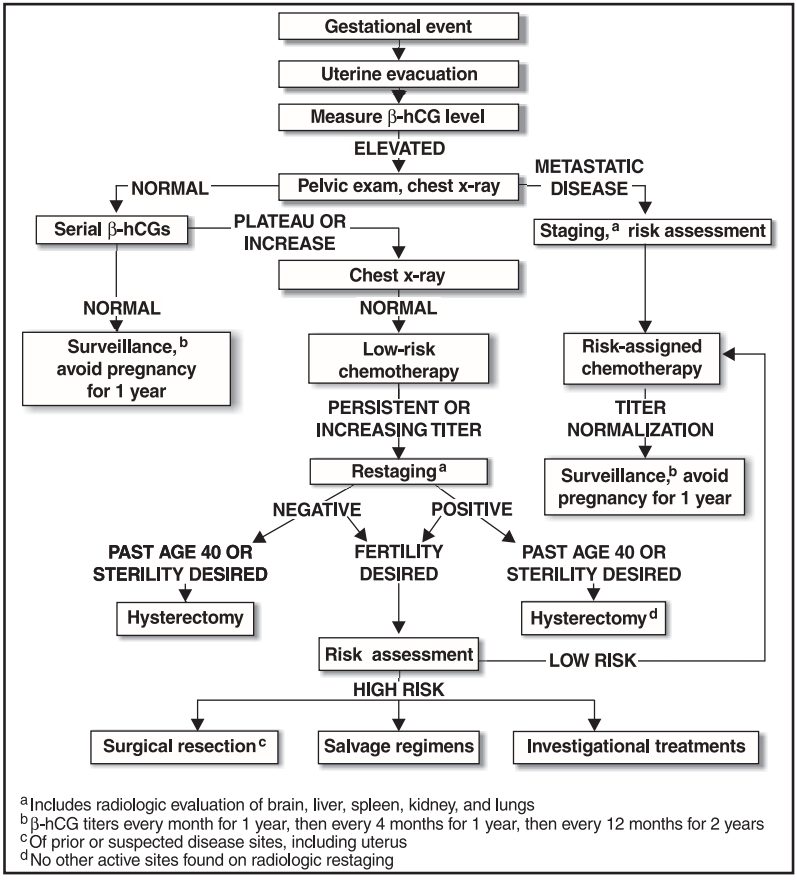

FIGURE 1: Diagnostic and therapeutic approaches to gestational trophoblastic disease, as practiced at the M. D. Anderson Cancer Center.

Molar pregnancy

For patients with complete or partial hydatidiform mole, evacuation of the mole by suction and sharp curettage should be performed. Oxytocics also are given to produce uterine involution and to control bleeding. However, these agents should be used judiciously as they may cause hyponatremia and fluid overload. A baseline chest x-ray and β-hCG measurement should be obtained prior to surgery.

After molar evacuation, 80% of patients will need no further intervention. However, these patients' weekly serum β-hCG levels must be diligently monitored until they return to normal. Although normal β-hCG levels typically return within 8 weeks of surgery, in a minority of patients it takes 14-16 weeks for levels to return to normal. Sometimes transient plateaus are observed before the β-hCG level returns to baseline. An increased or prolonged plateau of

β-hCG titers implies persistent trophoblastic disease or metastatic spread and requires additional therapy.

Chemotherapy is indicated when there is a plateau or increase in β-hCG levels on consecutive measurements, failure to reach normal titers by 16 weeks, or metastatic disease. Such patients are usually at low risk and will respond to single-agent chemotherapy. Methotrexate is the most commonly initiated single agent (Table 2). Therapy is continued for one to two courses after a normal β-hCG level is achieved.

Follow-up As mentioned previously, all patients with molar disease should obtain a baseline chest x-ray. Serial β-hCG levels should be obtained every 1-2 weeks until the level is normal for three consecutive assays. Complete remission is defined by three consecutive normal β-hCG levels. Once this has occurred, β-hCG levels should be checked monthly for 12 months, every 4 months for the following year, and then yearly for 2 years.

Although the use of oral contraceptives during the surveillance period remains controversial, strict contraception is required, because pregnancy would obviate the usefulness of β-hCG as a tumor marker. In general, once a 12-month surveillance establishes a disease-free status, conception is acceptable. These women are always at high risk for future molar disease and will require close observation during future pregnancies. A pelvic ultrasound examination should be performed during the first trimester of all subsequent pregnancies to confirm that gestation is normal.

LOW-RISK METASTATIC DISEASE

In more than 30 years of experience, single-agent chemotherapy with methotrexate has produced a high cure rate in patients with low-risk GTT. Likewise, methotrexate plus folinic acid (leucovorin) induces remission in 90% of patients with low-risk metastatic disease with low toxicity. The use of dactinomycin in methotrexate-resistant patients increased the cure rate to more than 95%.

TABLE 2: Chemotherapy regimens for low-risk[a] gestational trophoblastic disease

Drug	Administration	Cycle[b]
Methotrexate *and* Folinic acid	1 mg/kg (up to 70 mg) IM or IV days 1, 3, 5, 7 0.1 mg/kg IM or IV days 2, 4, 6, 8	14 days
Methotrexate	0.4 mg/kg IM or IV daily for 5 days	14 days
Methotrexate	30 to 50 mg/m² IM	7 days
Dactinomycin	10 μg/kg (up to 0.5 mg) IV daily for 5 days	14 days
Dactinomycin	1.25 mg/m² IV single dose	14 days

[a] Therapy based on FIGO 2000 risk criteria (see Table 1).

[b] Withhold treatment for marrow recovery if necessary.

Suggested therapeutic regimens for low-risk GTT are outlined in Table 2. The regimen of intramuscular methotrexate plus leucovorin is preferred because it obviates intravenous access problems, allows the therapeutic administration at home or work, minimizes the interruption of the patient's life, and is the least toxic of the regimens listed. These patients are usually treated for two to three courses after attaining a normal β-hCG level.

If single-agent therapy with methotrexate or dactinomycin fails to achieve remission, multidrug chemotherapy must be attempted. This is necessary in nearly 40% of patients with low-risk metastatic GTT. Despite resistance to first-line chemotherapy, a cure rate of almost 100% is achieved with further combination chemotherapy.

HIGH-RISK METASTATIC DISEASE

The discovery that etoposide is an effective agent against trophoblastic disease led to the development of the EMA-CO regimen (etoposide, methotrexate, actinomycin D [dactinomycin], cyclophosphamide, Oncovin [vincristine]) by Bagshawe, who reported a survival rate of 83% in patients with high-risk choriocarcinoma. This regimen has been confirmed to be highly effective at several centers, including the Brewer Trophoblastic Disease Center, where a 100% cure rate has been achieved over the past 5 years.

EMA-CO (Table 3) is the preferred regimen for high-risk GTT. We also utilize this regimen for patients with middle-risk GTT, as defined by the FIGO 2000 criteria. EMA-CO is generally well tolerated, with no life-threatening toxic effects. Alopecia occurs universally, and anemia, neutropenia, and stomatitis are mild. Reproductive function is preserved in approximately 75% of patients.

Within hours of receiving chemotherapy, patients with a significant tumor burden are at risk of hemorrhage into tumors and surrounding tissues. Thus, any acute organ toxicity that begins shortly after the induction of chemotherapy should be considered as possibly related to this phenomenon. Some researchers have advocated a reduction in dosage at the beginning of therapy in patients with large-volume disease to minimize these sequelae.

SALVAGE THERAPY

Unfortunately, about 25% of women with high-risk metastatic disease become refractory to EMA-CO and fail to achieve a complete remission. Currently, there is no standard salvage chemotherapy regimen for patients not responding to EMA-CO. However, salvage regimens that combine cisplatin (Platinol), etoposide, vinca alkaloids, and bleomycin (Blenoxane) have been administered.

Because of significant nephrotoxicity, cisplatin-containing regimens are withheld as primary therapy for GTT. Early studies show cisplatin-based regimens to be an effective salvage therapy in GTT. A recent dose-intensive regimen, EMA-CE, utilizes cisplatin (100 mg/m^2) and etoposide (200 mg/m^2) combined with EMA, with favorable results.

Another alternative is to give cisplatin in the EMA-POMB regimen (Platinol [cisplatin], Oncovin [vincristine], methotrexate, bleomycin). POMB is admin-

TABLE 3: Chemotherapy regimens for middle- and high-risk[a] gestational trophoblastic regimens

Drug regimen		Administration
EMA-CO[b] (preferred regimen)		
Course 1 (EMA)		
Day 1	Etoposide	100 mg/m² IV over 30 min
	Methotrexate	100 mg/m² IV bolus
	Methotrexate[c]	200 mg/m² IV as 12-h continuous infusion
	Dactinomycin	0.5 mg IV bolus
Day 2	Etoposide	100 mg/m² IV over 30 min
	Folinic acid[c]	15 mg IV/IM/PO every 6 h for 4 doses, beginning 24 h after start of methotrexate
	Dactinomycin	0.5 mg IV bolus
Course 2 (CO)		
Day 8	Cyclophosphamide	600 mg/m² IV over 30 min
	Vincristine	1 mg/m² (up to 2 mg) IV bolus

[a] Therapy based on FIGO 2000 risk criteria (see Table 1).
[b] Repeat each regimen in sequence every 14 days as toxicity permits.
[c] In case of CNS metastasis, increase the dose of infused methotrexate to 1,000 mg/m² IV over 12 h after having alkalinized the urine. Increase the number of folinic acid doses to 8, given every 6 h. This regimen is called "high-dose methotrexate EMA-CO."

istered as vincristine, 1 mg/m² IV, and methotrexate, 300 mg/m² IV (day 1); bleomycin, 15 mg IV over 24 h by continuous infusion (CI), and folinic acid, 15 mg bid for four doses (day 2); bleomycin, 15 mg IV over 24 h CI (day 3); and cisplatin, 120 mg/m² IV (day 4).

A new PEBA regimen (Platinol [cisplatin], etoposide, bleomycin, Adriamycin [doxorubicin]) was recently reported from China and was found to be effective in EMA-CO-resistant disease. A complete remission (CR) was achieved in 96% of the women, and 73% had a sustained CR that lasted at least 1 year. In a small study, ifosfamide (Ifex) alone and combined in the VIP regimen (VePesid [etoposide], ifosfamide, and Platinol [cisplatin]) showed promise as being an effective salvage drug in GTT.

Another consideration in the treatment of refractory GTT is the use of high-dose chemotherapy with autologous bone marrow transplantation. In this setting, Lotz et al treated five women with refractory GTT with high-dose ifosfamide, carboplatin (Paraplatin), and etoposide (ICE). Only one of the five women attained a durable CR (68+ months). The risk and benefits of high-dose chemotherapy in the treatment of GTT are still under investigation.

PULMONARY METASTASES

At the time of diagnosis, pulmonary metastases can be extensive and may cause respiratory failure and death.

In patients with extensive pulmonary metastases, reduced doses of initial chemotherapy (eg, 50%) have been suggested to diminish the risk of respiratory failure. However, reduction of the initial chemotherapy dose did not uniformly protect against pulmonary failure and death. Because of the increased risk of pulmonary decompensation, women with extensive pulmonary metastases should be observed in an intensive care setting during induction chemotherapy.

CNS CHORIOCARCINOMA

Brain metastases pose a significant threat to the survival of patients with GTT, especially if the metastases appear while the patient is receiving chemotherapy. Although cerebral disease is observed clinically in only 7%-28% of patients with choriocarcinoma, postmortem examinations demonstrate CNS involvement in as many as 40% of cases. This subset represents a significant fraction of patients who die of the disease.

In 1983, Athanassiou et al reported results of a 23-year experience with choriocarcinoma involving the CNS at Charing Cross Hospital. Overall, 8.8% of 782 patients with choriocarcinoma who received chemotherapy had CNS metastases. Of these patients, 48% presented with CNS disease prior to treatment. Although 49% of patients who presented with CNS metastases enjoyed long-term survival, only 6% of the patients who developed CNS disease while on therapy survived. Radiotherapy did not appear to benefit patients whose disease was resistant to chemotherapy.

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CHAPTER 24

Melanoma and other skin cancers

Kim A. Margolin, MD, and Vernon K. Sondak, MD

The skin is the most common site of cancer development in humans. More than 1 million new skin cancer cases will be diagnosed in the United States in the year 2003, compared with about 1.3 million cases *of all other types of cancer combined*. Therefore, skin cancers will constitute fully one-half of all cancers diagnosed in 2003.

Moreover, both the incidence and mortality of skin cancers are increasing in the United States and throughout the world. The incidence of melanoma has climbed steadily since 1930; the rate of this increase is higher than that for any other type of cancer. Melanoma is now the fifth most common malignancy in men and the seventh most common malignancy in women in this country.

Although the incidence of melanoma is only about 5% of that of nonmelanoma skin cancer, melanoma accounts for more than three times as many deaths each year (7,600 vs 2,200). Because of the relatively young age at onset of most melanoma cases (see below), the toll of melanoma in terms of "years of potential life lost" is second only to leukemia among all types of malignancy in the United States.

Although this chapter will focus primarily on melanoma, some discussion of nonmelanoma skin cancers will be included.

Epidemiology

Age Melanoma affects a broad range of age groups, including many patients in their 20s and 30s, with an average age at development of 55 years. Three-quarters of all cases occur in individuals younger than 70 years of age.

Gender Melanoma is slightly more common in men than in women, with a male-female ratio of approximately 1.2:1.0. The most common site of melanoma development in females is the extremities, whereas the trunk is most frequently affected in males. Melanoma is now the most common malignancy in women 25-29 years of age and is exceeded only by breast cancer in women aged 30-35. The continuing increase in the incidence and mortality of this disease appears to be due to a complex interaction between genetics and ultraviolet (UV) radiation exposure, but recent epidemiologic observations suggest that it can be modulated by changes in sun-protection practices. Most series have found that women have a slightly better prognosis, stage for stage, than do men.

Race Skin cancer is much less common in blacks, with an annual age-adjusted incidence only 1% of that seen in whites. Asians and Hispanics are similarly at very low risk of melanoma compared with whites. It is nonetheless important to recognize that both melanoma and nonmelanoma skin cancers *do* occur in these groups.

The presentations of both categories of skin cancer differ in more deeply pigmented races. For example, most melanomas in these patients occur on the relatively nonpigmented skin of the palms and soles. Also, basal cell cancers, which are usually nonpigmented in whites, are almost always pigmented in black patients. Finally, most cases of squamous cell cancer of the skin occur on the sun-exposed skin of the head and neck or arms, but in blacks the majority of cases develop on less exposed areas, such as the legs.

Geography Melanoma is most common in parts of the world where fair-skinned whites live in a very sunny climate near the equator. Thus, Australia and Israel have among the highest melanoma incidences in the world (approximately 40 cases per 100,000 individuals per year). Whites in Hawaii and the southwestern United States also have a very high incidence of melanoma, about 20-30 cases per 100,000 individuals annually, which equals or exceeds the incidence of colorectal cancer in those regions. The incidence of melanoma in the United States decreases with increasing latitude (ie, more northerly regions); overall, about 12 cases of melanoma are seen per 100,000 American whites.

Disease sites Nonmelanoma skin cancers can occur on any part of the skin surface but are largely found on the head and neck, hands, and forearms. The vast majority (> 90%) of melanomas are cutaneous lesions, but melanomas also occur in the pigmented cells of the retina (choroidal or ocular melanomas) and on the mucous membranes of the nasopharyngeal sinuses, vulva, and anal canal. In general, these noncutaneous tumors present at a more advanced stage and are rarely curable.

Survival If detected at an early stage, most cutaneous melanomas and virtually all nonmelanoma skin cancers can be cured with surgical excision. The prognosis of patients with lymphatic dissemination of disease decreases signifi-

TABLE 1: Five-year survival rates of patients with melanoma and nonmelanoma skin cancer

	5-year survival rate (%)	
When detected	Melanoma	Nonmelanoma skin cancer
In localized stage	87	99
After spread to regional lymph nodes	35	50
After spread to distant organs	2	< 10

cantly, and few patients who develop metastatic disease survive beyond 5 years (Table 1).

Etiology and risk factors

Two melanoma susceptibility genes have been identified that involve regulation of cyclin-dependent kinases: *CDKN2A* on chromosome 9p21 (which encodes the cyclin-dependent kinase inhibitor p16) and *CDK4* on chromosome 12q14 (which encodes a cyclin-dependent kinase regulated by p16/CDKN2A). It is likely that others will be discovered as well.

Molecular genetic data implicate an interaction among the cyclin-dependent kinase N2A (CDKN2A, p16 or INK4a) and variants in the melanocortin-1 receptor (MC1R) melanocyte-stimulating receptor gene in the association of melanoma with sunlight exposure and skin and hair pigment types.

An exciting new development has been the finding that a majority of melanoma cell lines and specimens contain mutations in the B-*raf* gene, which is a key part of the Ras pathway. The Ras pathway is involved in cellular reactions to UV light exposure, raising the possibility that these B-*raf* changes may be an early manifestation of melanomagenesis as well as a potential target for new therapeutic approaches.

UV light Melanoma and nonmelanoma skin cancers share a common causative factor—exposure to the UV radiation in sunlight—although the precise mechanism of causation and the types of exposure most likely to cause each disease may vary. Most dangerous is UV B radiation (wavelength, 290-320 nm), but UV A radiation (320-400 nm) probably also has carcinogenic potential. Overall, skin cancer incidence rates are increasing, likely both because people spend more time in the sunlight and because the atmosphere's ability to screen out UV radiation has decreased (depletion of the ozone layer).

Chronic vs intermittent exposure Different types of skin cancer are associated with different patterns of sun exposure. Almost all basal and squamous cell cancers of the skin occur on chronically exposed areas of skin, such as the head, neck, and hands. There is a clear-cut association between *cumulative* sun exposure and the incidence of these nonmelanoma skin cancers.

On the other hand, exposure to intermittent solar radiation appears to be more important in most cases of melanoma. A number of studies have implicated sun exposure during childhood—particularly blistering sunburns—as a major risk factor. Melanoma is more common in indoor workers than outdoor laborers and occurs most often on parts of the body that are only occasionally exposed to the sun. The one exception to this principle is lentigo maligna melanoma, which occurs most frequently on the head and neck of older individuals with a long history of chronic sun exposure and evidence of actinic skin damage, as is the case for nonmelanoma skin cancer. Melanoma is quite rare on skin surfaces that are never exposed to the sun (the "bathing suit" or doubly covered areas).

Skin type and hair color Not everyone is at equal risk of developing skin cancer. As previously discussed, blacks are at lower risk than whites. Among whites, melanoma occurs most frequently in fair-skinned, light-haired individuals who sunburn easily and rarely or never tan.

Typical moles Typical or benign moles, also called melanocytic nevi, are small (< 6 mm), round, uniformly tan or brown, and symmetrical. They are generally raised above the skin surface, as opposed to freckles. Patients with many (> 25-50) melanocytic nevi are at increased risk of melanoma; most of these patients are also fair-skinned, light-haired individuals who burn easily and rarely tan.

Atypical moles, also called clinically atypical nevi or dysplastic nevi, are larger (generally > 6 mm), irregularly shaped, and have a pebbly surface. They are usually tan or brown but may have various shades of coloration within them.

At least 5% of the white population of the United States has at least one clinically atypical nevus. Otherwise healthy individuals with at least one clinically atypical nevus have a 6% lifetime risk of developing melanoma. This risk rises to as high as 80% in individuals who also have a family history of melanoma.

Some clinically atypical nevi eventually progress to melanoma. Even if every atypical mole is surgically removed, however, the patient remains at an increased risk of melanoma developing in the rest of the normal skin. Until such time, if ever, that genetic testing identifies those individuals with atypical moles who are at greatest risk of melanoma development, all individuals with clinically atypical nevi should be carefully followed. Close follow-up is particularly important in those with a positive family history for melanoma.

Dysplastic nevus syndrome A familial tendency to develop atypical moles has long been recognized. First termed the B-K mole syndrome (after the initials of the last names of the two families in which it was recognized), it is now most commonly referred to as the dysplastic nevus syndrome. Since most families with this syndrome also contain a number of individuals with melanoma, the name "familial atypical mole/melanoma" (FAMM) syndrome has been proposed as an alternative. The inheritance patterns and genetic markers for this familial cancer susceptibility are being actively studied.

Actinic keratoses are scaly, rough, erythematous patches that occur in chronically sun-exposed areas; they are both markers for and precursors to nonmelanoma skin cancer development. These lesions may progress to squamous cell cancers or, in some cases, regress spontaneously in response to prolonged avoidance of sun exposure. If few in number, actinic keratoses can be removed or destroyed with liquid nitrogen. For multiple lesions, topical fluorouracil (5-FU) cream has been used successfully.

Burns Squamous cell cancers occasionally arise in burns or other scars. Burn scar cancers (so-called Marjolin's ulcers) may have a more aggressive clinical course than the usual nonmelanoma skin cancer.

Giant congenital nevi Congenital nevi are pigmented lesions actually present at birth, as opposed to developing months or years later. Even among known congenital nevi, however, only the giant (> 20 cm in diameter) congenital nevus,

a very rare lesion, is a documented precursor to melanoma. Most melanomas occurring in children younger than 10 years of age arise within these lesions. Whenever the cosmetic result permits, giant congenital nevi should be excised in early childhood. If complete excision is impossible, even with staged procedures, close follow-up is indicated.

Xeroderma pigmentosum, a rare congenital disorder in which patients lack the capacity to repair UV-induced DNA damage, is associated with the development of innumerable melanoma and nonmelanoma skin cancers at a very early age.

Immunosuppression or prior hematologic malignancy Nonmelanoma skin cancers and, to a much lesser degree, melanomas are more common in patients who are immunosuppressed or have had previous hematologic malignancies. Furthermore, the aggressiveness of the skin tumors can be significantly greater in these patients.

Diagnosis

Although the vast majority of skin cancers are curable, a substantial number of skin cancer-related deaths occur each year. Since these cancers are visible on the skin, early detection should be the goal in every case.

Early diagnosis of melanoma

Differentiation from benign moles Early melanomas may be differentiated from benign moles by assessing the asymmetry, border irregularity, color, and diameter of the lesions (the so-called ABCDs; Table 2). Other signs of melanoma include itching, bleeding, ulceration, or changes in a preexisting benign mole.

Patients with clinically atypical nevi Clinically atypical nevi have some, but not all, of the features of melanoma: they are >6 mm, asymmetrical, and often show border irregularity. Significantly raised areas or regions of dark brown or black pigmentation in a known atypical nevus suggest the development of melanoma. Biopsy of any suspicious skin lesion should be carried out (see "Biopsy techniques"). Patients with too many atypical nevi to excise require careful follow-up with frequent skin examinations.

Periodic total-body skin examinations combined with photographs of any atypical nevi and, most importantly, thorough patient education on the need to watch for changes in existing moles or the development of new lesions are essential components of the management of patients with atypical moles.

Differentiating nonmelanoma skin cancers

Nonmelanoma skin cancers usually are not confused with melanomas, since most (but not all) melanomas are pigmented and most (but not all) nonmelanoma skin cancers are not. Basal and squamous cell cancers may be more difficult to distinguish from one another, but certain features are more characteristic of one type than the other. Basal cell cancers often have a pearly, trans-

TABLE 2: The 'ABCDs' for differentiating early melanomas from benign melanocytic nevi

Feature	Benign mole	Melanoma
Asymmetry	No	Yes
Border irregularity	No	Yes
Color	Uniform, tan/brown	Variegated, black
Diameter	< 6 mm	May be > 6 mm

lucent appearance with a rolled border, whereas squamous cell cancers are often keratinized or ulcerated.

Total-body skin examination

Total-body skin examination is a critical step in the initial evaluation and follow-up of a patient with a melanoma, nonmelanoma skin cancer, or clinically atypical nevus. Because of the common denominator of solar exposure in the causation of skin cancer, patients with one skin cancer are at significant risk of harboring or developing a second or even multiple skin cancers, often of a different histologic type. A complete skin examination is essential for patients with clinically atypical nevi, since they have an increased risk of developing melanoma on their entire skin surface, not just within recognized moles.

Fundamental to a thorough and complete skin examination is a well-lit room, a completely disrobed patient, and a relaxed and unhurried approach. Useful adjuncts in some cases include serial photography, both of individual lesions and whole skin areas, and special techniques of illumination and magnification, such as Wood's lamp ("black light") examination and epiluminescence microscopy (direct application of a magnifying lens to an area of the skin that has had oil applied to minimize reflectance).

Examination of lymph nodes

Lymphatic spread is the most frequently encountered type of dissemination in both melanoma and nonmelanoma skin cancers. The regional lymph nodes should be carefully examined in all skin cancer patients at the time of presentation and at each follow-up visit. Since melanoma may also disseminate hematogenously to any lymph node basin in the body, all accessible node groups should be examined in melanoma patients.

Biopsy techniques

When the decision is made to biopsy a suspicious pigmented or nonpigmented skin lesion, several factors must be taken into consideration. Foremost among them is that the pathologist must receive adequate tissue in good condition to permit assessment of all relevant histologic features. Also critical is that the biopsy should not make subsequent surgical treatment more difficult.

Techniques to avoid Shallow shave biopsies, cryosurgery, or electrodesiccation do not allow for pathologic analysis of margins and depth of invasion and should be avoided.

Complete excision Most clinically suspicious skin lesions are best biopsied by complete excision using local anesthesia, taking a 1- to 2-mm margin of normal skin and including some subcutaneous fat.

Incisional or punch biopsy Unusually large lesions or those situated in cosmetically sensitive areas, such as the face, may be biopsied by incisional or punch biopsy. In these cases, the most abnormal area(s)—generally the most elevated portion(s) of the lesion—should be sampled.

Frozen-section analysis is not routinely employed for the diagnosis of skin lesions.

Biopsy of lymph nodes Palpably enlarged lymph nodes suspected of representing melanoma metastasis are best diagnosed using fine-needle aspiration (FNA). A positive aspiration cytology is grounds for performing a full lymph node dissection. If the cytology is nondiagnostic or negative, or if the node location precludes aspiration, an open biopsy is appropriate; only the enlarged node should be removed, with minimal dissection of the surrounding tissue. In this setting, frozen-section analysis may be employed and a full node dissection carried out during the same procedure.

Sentinel lymph node biopsy Clinically normal lymph nodes harbor microscopic or even macroscopic deposits of melanoma in up to 30% of patients. A technique for identifying those lymph nodes most likely to be involved by melanoma—the so-called sentinel nodes—has been developed. This technique is described in detail (see "Selective lymphadenectomy").

Techniques for enhancing the detection of microscopic nodal metastases by applying more sensitive assay methods are under investigation. One such assay is the polymerase chain reaction (PCR) for the detection of mRNA sequences for tyrosinase, a protein that is specific for melanocytes. The prognostic and therapeutic implications of detecting micrometastases by these methods are under investigation in trials such as the Sunbelt Melanoma Trial (see page 523) *(McMasters KM, Reintgen DS, Ross MI, et al: J Clin Oncol 19:2851-2855, 2001; Palmieri G, Asciento PA, Cossu A, et al: J Clin Oncol 19:1437-1443, 2001).*

Pathology

Histologic types of nonmelanoma skin cancer

Basal cell and squamous cell carcinomas The two most common types of nonmelanoma skin cancer are basal cell carcinoma and squamous cell carcinoma. Bowen's disease is the name given to squamous cell carcinoma in situ involving the skin. Merkel's cell cancer is a rarer, more aggressive skin cancer, which presumably arises from the neuroendocrine cells of the skin.

Cancers arising in the skin appendages (eg, hair follicles, sweat glands) can be adenocarcinomas or apocrine cancers; they are exceedingly rare.

Sarcomas The most common primary sarcoma affecting the skin is dermatofibrosarcoma protuberans. Leiomyosarcoma, angiosarcoma, and malignant fibrous histiocytoma can also arise entirely within the skin.

Histologic types of cutaneous melanoma

Melanomas are classified into four major histologic categories: superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral-lentiginous melanoma.

Superficial spreading melanomas are the most common type of cutaneous melanomas. They often arise within a preexisting nevus and are surrounded by a zone of atypical melanocytes that may extend beyond the visible borders of the lesion.

Nodular melanomas represent about 10%-15% of cutaneous melanomas. They are generally dark blue-black and are more symmetrical and uniform in coloration than other melanomas. Amelanotic nodular melanomas also occur and are frequently misdiagnosed.

Lentigo maligna melanomas account for 10%-15% of cutaneous melanomas. They typically occur on the sun-exposed areas of the head, neck, and hands. Clinically, they are large (often $>$ 3 cm in diameter), flat, tan lesions with areas of dark brown or black coloration. These lesions arise from a precursor lesion known as lentigo maligna, or Hutchinson's freckle.

Acral-lentiginous melanoma is a distinct variant of melanoma that occurs in equal frequency among whites and darker-pigmented races. Because of the high incidence of other types of cutaneous melanoma in whites, acral-lentiginous melanomas account for only 2%-8% of melanomas in whites, as opposed to 40%-60% of melanomas in blacks, Hispanics, and Asians. Acral-lentiginous melanomas occur on the palms, soles, and subungual locations. Subungual melanomas can easily be confused with subungual hematomas; the presence of pigmentation in the paronychial skin is indicative of melanoma.

TABLE 3: Five-year survival rates of pathologically staged patients[a]

	IA	IB	IIA	IIB	IIC	IIIA	IIIB	IIIC
Ta: Nonulcerated	T1a	T2a	T3a	T4a	-	N1a	N1b	N3
melanoma	95%	89%	79%	67%	-	N2a	N2b	-
	-	-	-	-	-	67%	54%	28%
Tb: Ulcerated	-	T1b	T2b	T3b	T4b	-	N1a	N1b
melanoma	-	91%	77%	63%	45%	-	N2a	N2b
	-	-	-	-	-	-	-	N3
	-	-	-	-	-	-	52%	24%

[a] Adapted from Balch CM, et al: Melanoma of the skin, in Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

Growth phases of melanoma

The growth of melanoma has been characterized histologically as occurring in two distinct phases: radial and vertical.

Radial growth phase The radial growth phase is characterized by melanoma tumor cells in the epidermis and papillary dermis, with development of a raised irregular surface on the skin. Although pure radial growth phase melanomas may be fully invasive lesions, they are extremely unlikely to metastasize to the regional nodes or beyond and have a prognosis similar to that of melanoma in situ.

Vertical growth phase Vertical growth into the deeper layers of skin is associated with increasing nodularity of the lesion and a much greater potential for metastasis. As discussed in "Staging and prognosis of melanoma," the depth of invasion correlates directly with prognosis. This correlation is valid only in lesions showing vertical growth, however, because radial growth phase lesions have an excellent prognosis regardless of depth.

Staging and prognosis of melanoma

A great deal of information is available regarding factors that correlate with clinical outcome in patients with melanoma. In the absence of known distant metastatic disease, the most important prognostic factor is regional lymph node involvement. Overall, however, 85% of melanoma patients present with clinically normal lymph nodes. In clinically node-negative patients, most investigators have found the microscopic degree of invasion of the melanoma, or microstaging, to be of critical importance in predicting outcome (Tables 3 and 4).

Microstaging

Two methods have been described for microscopic staging of primary cutaneous melanomas.

Clark's levels Wallace Clark and associates devised a system to classify melanomas according to the level of invasion relative to histologically defined landmarks in the skin. Although Clark's levels correlate with prognosis (lesions with deeper levels of invasion have a greater propensity for recurrence), the inherent problem with Clark's system is that the thickness of the skin—and hence the distance between the various landmark dermal layers—varies greatly in different parts of the body. Furthermore, except for Clark's level I (melanoma in situ), there is no scientific rationale for considering these landmarks to be biological barriers to tumor growth. For example, there is no a priori reason to suspect that a lesion that reaches but does not invade the reticular dermis is inherently less aggressive than a similar melanoma that penetrates the reticular dermis in an area where the skin is thinner.

Breslow's thickness An alternative microstaging method, described by Alexander Breslow, obviates some of the problems associated with Clark's levels. In this method, the thickness of the primary tumor is measured from the top of the granular layer of the epidermis to the deepest contiguous tumor cell at the base of the lesion using a micrometer in the microscope eyepiece.

TABLE 4: TNM classification of melanoma

Primary tumor (T)	
Tx	Primary tumor cannot be assessed (eg, shave biopsy or regressed melanoma)
T0	No evidence of primary tumor
Tis	Melanoma in situ
T1	Melanoma ≤ 1.0 mm in thickness, with or without ulceration
T1a	Melanoma ≤ 1.0 mm in thickness and level II or III, no ulceration
T1b	Melanoma ≤ 1.0 mm in thickness and level IV or V or with ulceration
T2	Melanoma 1.01-2.0 mm in thickness with or without ulceration
T2a	Melanoma 1.01-2.0 mm in thickness, no ulceration
T2b	Melanoma 1.01-2.0 mm in thickness, with ulceration
T3	Melanoma 2.01-4.0 mm in thickness with or without ulceration
T3a	Melanoma 2.01-4.0 mm in thickness, no ulceration
T3b	Melanoma 2.01-4.0 mm in thickness, with ulceration
T4	Melanoma > 4.0 mm in thickness, with or without ulceration
T4a	Melanoma > 4.0 mm in thickness, no ulceration
T4b	Melanoma > 4.0 mm in thickness, with ulceration
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one lymph node
N1a	Clinically occult (microscopic) metastasis
N1b	Clinically apparent (macroscopic) metastasis
N2	Metastasis in two to three regional nodes or intralymphatic regional metastasis without nodal metastases
N2a	Clinically occult (microscopic) metastasis
N2b	Clinically apparent (macroscopic) metastasis
N2c	Satellite or in-transit metastasis without nodal metastasis
N3	Metastasis in four or more regional nodes, or matted metastatic nodes, or in-transit metastasis or satellite(s) with metastasis in regional node(s)
Distant metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis to skin, subcutaneous tissues, or distant lymph nodes
M1b	Metastasis to lungs
M1c	Metastasis to all other visceral sites or distant metastasis at any site associated with an elevated serum lactate dehydrogenase (LDH) level

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

Many investigators have documented an inverse correlation between Breslow's tumor thickness and survival. More important, several studies have demonstrated that tumor thickness conveys more prognostic information than does Clark's level of invasion. In addition, the measurement of tumor thickness is generally more reproducible and less subjective than is the determination of Clark's level.

Occasionally, usually because of technical factors related to the performance of the biopsy or the preparation of the histologic specimen, Breslow's thickness is impossible to determine and only the Clark's level is available for microstaging. These situations, which inevitably result in the loss of important prognostic information, can be largely avoided by the performance of full-thickness (not shave) biopsies and by careful attention to detail when preparing specimens.

Regional lymph node involvement

The presence of regional lymph node metastases is a grave sign regardless of the microstage of the primary lesion. There is a direct relationship, however, between the thickness of the primary lesion and the likelihood of microscopic nodal involvement in patients with clinically normal nodes.

Number of involved nodes As in other cancers, the number of involved lymph nodes in melanoma patients has an inverse correlation with survival. The 5-year survival rate for patients with multiple positive lymph nodes is about 20%-25%, whereas the rate for patients with only one or two involved lymph nodes is over 50%.

Palpable nodes In general, patients with palpable nodes fare worse than those with only microscopic involvement. Furthermore, large, matted nodes are associated with a worse prognosis.

Clinical and pathologic staging

TNM staging system The melanoma staging committee of the American Joint Committee on Cancer (AJCC) has recently revised the TNM staging system to more accurately reflect the impact of statistically significant prognostic factors that were validated on a multi-institution sample of over 17,000 melanoma patients. The new system is shown in Tables 5A and 5B.

For stages I and II (node-negative) melanoma, the most important prognostic factors are the Breslow depth (for thin melanomas < 1 mm; the Clark's level of invasion retains some prognostic value) and the presence or absence of ulceration (defined as the absence of an intact epidermis overlying a major portion of the primary melanoma). For stage III disease, the predictive factors are the number of nodes and extent of involvement (microscopic vs macroscopic), as well as the presence of satellite or in-transit deposits.

For patients with stage IV disease (distant metastases), there are few but significant differences in prognosis for disease limited to the skin, for subcutaneous and nodal sites vs visceral sites, and for levels of lactate dehydrogenase (LDH) in the serum.

TABLE 5A: 2002 version of TNM classification for cutaneous melanoma

T classification	Thickness	Ulceration status
T1	≤1.0 mm	a: without ulceration and level II/III
T1		b: with ulceration or level IV or V
T2	1.01-2.0 mm	a: without ulceration
T2		b: with ulceration
T3	2.01-4.0 mm	a: without ulceration
T3		b: with ulceration
T4	> 4.0 mm	a: without ulceration
T4		b: with ulceration
N classification	**No. of nodes**	**Nodal involvement**
N1	1 lymph node	a: micrometastasis[a] b: macrometastasis[b]
N2	2-3 lymph nodes or in-transit met(s)/satellite(s) without nodal involvement	a: micrometastasis[a] b: macrometastasis[b] c: in-transit met(s)/satellite(s) *without* metastatic nodes
N3	≥ 4 metastatic nodes, matted nodes, or in-transit met(s)/satellite(s), and metastatic node(s)	
M classification	**Site**	**Serum lactate dehydrogenase level**
M1a	Distant skin, SQ, or node mets	Normal
M1b	Lung mets	Normal
M1c	All other visceral or any distant mets	Normal Elevated

met(s) = metastases

[a] Micrometastases are diagnosed after elective or sentinel lymphadenectomy.

[b] Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when any nodal metastasis demonstrates gross extracapsular extension.

Some of the most significant changes include new cutoff points for T classification (T1 = ≤ 1.0 mm, T2 = 1.01-2.0 mm, T3 = 2.01-4.0 mm, T4 = > 4 mm), inclusion of ulceration as a factor in T stage (a: no ulceration, b: ulceration), replacement of node size with node number for N stage, inclusion of node size (microscopic vs macroscopic) as a factor in N stage, and inclusion of LDH level as a factor in M stage. When incorporated into new clinical protocols, the new system will undoubtedly improve our understanding of the impact of interventions in this disease (Tables 5A and 5B).

Other prognostic factors

Histologic type In general, nodular and acral-lentiginous melanomas are significantly thicker at the time of diagnosis than superficial spreading or lentigo maligna melanomas. Prognostic factors discussed in the rest of this section ap-

TABLE 5B: 2002 stage groupings for cutaneous melanoma

Clinical staging[a]				Pathologic staging[b]			
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III[c]	Any T	N1	M0				
		N2					
		N3					
				IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a/b	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					Any T	N3	M0
IV	Any T	Any N	Any M1	IV	Any T	Any N	Any M1

[a] Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases; by convention, it should be used after complete excision of the primary melanoma with *clinical* assessment for regional and distant metastases.

[b] Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy, except for *pathologic stage 0 or stage IA patients, who may not need pathologic evaluation of their lymph nodes.*

[c] There are no stage III subgroups for clinical staging.

Adapted from Balch CM, Buzaid AC, Soong S-J, et al: J Clin Oncol 19(16):3635-3648, 2001.

ply only to patients with melanomas in vertical growth phase, because melanomas in radial growth phase have a good prognosis regardless of all other factors. The nodular growth pattern was recently shown in multivariate analysis to have significance as an unfavorable prognostic feature.

Site of the primary Several studies have shown that patients with melanomas of the extremities have a better survival rate than those with lesions arising on the trunk or head and neck. The subset of melanomas occurring on the back, back of the upper arms, neck, and scalp—the so-called BANS area—have been thought to have a worse prognosis than primaries in other sites that are matched for thickness. A multivariate analysis of statistics in the database used to derive

the newly proposed AJCC system, however, did not find that the site of the primary lesion contributed to the prognosis.

Treatment of melanomas

SURGICAL TREATMENT OF CUTANEOUS MELANOMA

Excision of the primary lesion

Margins of excision It was recognized over a century ago that tumor cells could extend within the skin for several centimeters beyond the visible borders of a melanoma, so that the risk of local recurrence relates to the width of normal skin excised around the primary. Only much more recently was it realized that the thickness of the primary tumor influenced the likelihood of contiguous spread and that not all melanomas require the same excision margin. This realization prompted a number of randomized trials to determine the optimal excision margins for melanomas of different Breslow's thicknesses.

Initially, a "one-size-fits-all" approach of taking a 5-cm margin around all cutaneous melanomas was adopted. With such wide margins, skin grafts were required after removal of melanomas on most parts of the body. Melanomas < 1 mm thick had very low recurrence rates, however, even when less than the full 5-cm margin was excised.

A randomized trial found that when a 1-cm margin of normal skin was taken around a melanoma < 1 mm thick, the local recurrence rate was exceedingly low ($< 1\%$), and patient survival was just as good as if 3-cm margins were taken. For melanomas 1-2 mm in thickness, patient survival was the same for both margins of excision, but the local recurrence rate was slightly higher with the 1-cm margin (about 2%).

Another randomized trial compared 2- vs 4-cm margins for all cutaneous melanomas between 1 and 4 mm in thickness. In this trial, both local recurrence and survival were the same regardless of whether 2- or 4-cm margins were taken. Skin grafts were less frequent and hospital stays shorter with the narrower margin, however.

Current recommendations Based on these two landmark studies, it is now possible to make rational recommendations for excision margins for melanoma patients.

- For lesions < 1 mm in thickness, the recommended excision margin is 1 cm.
- Lesions 1-4 mm in thickness generally require a 2-cm margin.
- At least a 2-cm margin should be taken for lesions > 4 mm in thickness.

Several facts should be borne in mind regarding these recommendations:

- Regardless of the recommended margin, a histologically negative margin is necessary. Thus, if a 2-cm margin is taken and the pathology

report reveals melanoma cells or atypical melanocytic hyperplasia at the margins, further excision is indicated.

- When the anatomic location of the primary precludes excision of the desired margin (eg, on the hands and feet or the face), at least 1 cm should be taken as long as the margins are histologically negative.
- If a minor compromise in excision margin can allow primary closure without a skin graft, it is worthwhile.

Although the recommended excision margins have been reduced over the years, the importance of an adequately wide excision cannot be overstressed. When excessively narrow margins are taken, local recurrence rates inevitably rise, and local recurrence of melanoma is associated with an 85% chance of eventual death from the disease. Further refinements in these recommendations for excision margin widths will come from ongoing and proposed trials in the UK and the US evaluating 1-cm margins for melanomas $>$ 2 mm in thickness.

Management of regional lymph nodes

Clinically enlarged nodes Melanoma patients with clinically enlarged lymph nodes and no evidence of distant disease (AJCC stage III) should undergo a complete regional lymph node dissection. Depending on the number of lymph nodes found to contain melanoma, the prognosis for long-term survival is approximately 20%-40% in these patients.

Clinically normal nodes For decades, the management of melanoma patients with clinically normal lymph nodes has been controversial. It is clear that the likelihood of occult nodal involvement rises with increasing thickness of the primary tumor.

Thin melanomas Patients with thin melanomas ($<$ 1 mm) have a very low likelihood of nodal involvement ($<$ 5%) and, thus, generally require only wide excision of the primary with a 1-cm margin. These patients should undergo periodic physical examinations to detect the rare cases of nodal recurrence, as well as annual or more frequent total-body skin examinations to detect second primary melanomas and nonmelanoma skin cancers.

Intermediate-thickness melanomas Melanomas 1-4 mm in thickness are associated with about a 20%-25% chance of occult nodal involvement. To date, randomized trials have shown no significant difference in survival between patients randomized to receive immediate (elective) lymph node dissection and those randomized to receive careful follow-up with delayed (therapeutic) lymph node dissection at the time of clinical or radiographic recurrence in the nodes. Although there may be a modest survival benefit for certain subsets of patients, this benefit has not been confirmed in a prospective fashion. Elective node dissection is now obsolete with the advent of sentinel node biopsy and selective lymphadenectomy (described below).

Thick melanomas Patients with thick or ulcerated melanomas ($>$ 4 mm) have a high likelihood of nodal involvement but also have a high incidence of occult

systemic metastasis at the time of diagnosis. For this reason, even strong proponents of elective node dissection agree that patients with thick or ulcerated primaries may not benefit from *elective* removal of clinically negative lymph nodes. For patients who are candidates for clinical trials, however, surgical staging of the lymph nodes may be an important component of diagnostic, prognostic, and therapeutic decision-making.

Selective lymphadenectomy Morton and colleagues developed the technique of sentinel lymph node (SLN) evaluation based on the observation that lymphatics from any given location in the skin drained to a single node, or at most 2-3 specific nodes, within the regional basin (or basins). SLN biopsy has numerous advantages over routine performance of elective node dissection in patients with clinically negative regional nodes. There is obviously less morbidity for patients with negative nodes when they undergo a small biposy instead of a complete dissection. However, the careful lymphatic mapping used to identify the sentinel node allows the surgeon to find nodes in locations outside the formal confines of the regional basin, called interval nodes, that would be missed during a node dissection. Examples include the popliteal and epitrochlear nodes as well as nodes in soft-tissue sites like the flank, lateral back, upper arms, and mid-thighs. Most important, when the pathologist is provided with one node or a few selected nodes, as opposed to a node dissection specimen containing dozens of nodes, a more detailed histopathologic analysis is feasible and permits more accurate staging.

Because of these advantages, and because in most surgeons' hands the false-negative rates have remained under 4%, SLN biopsy has been widely adopted as the preferred staging method for patients with clinically negative nodes and melanomas ≥ 1 mm. This finding is true even though no data are as yet available as to whether SLN biopsy actually improves survival, which is the subject of a large multi-institute trial now in progress. For patients and surgeons alike, the detailed staging information and low overall morbidity make SLN biopsy a preferred option, even without proof that it independently affects survival rates. Important unresolved issues for current and future trials are to define whether there are categories of patients with melanomas < 1 mm who would benefit from SLN biopsy and to determine whether all patients with positive sentinel nodes require full node dissection and adjuvant therapy.

Several questions remain about the technique of selective lymphadenectomy, some of which will be answered by a randomized comparison to wide excision alone in a multi-institution trial now in progress. These questions include the rate of nodal recurrence in sentinel node-negative basins and, most important, whether there is any survival benefit for patients undergoing selective lymphadenectomy. Nonetheless, while these questions are being answered, the technique of selective lymphadenectomy has been adopted by a number of surgeons as an alternative to "watch-and-wait" or routine elective node dissection strategies.

Techniques of selective lymphadenectomy Two techniques are available for identifying the sentinel node draining a cutaneous melanoma.

Morton originally described the use of a blue lymphangiogram dye (either isosulfan blue [Lymphazurin]or patent blue) injected intradermally at the site of the primary lesion (or adjacent to the biopsy scar if the primary has been excised). About 5 minutes later, an incision is made over the lymph node basin, and the blue lymphatic channel or channels coursing to the sentinel node are identified and traced until a blue-stained node is identified and removed. This technique allows for identification of the sentinel node at least 80% of the time.

An alternative technique involves injection of a radiolabeled colloid solution, which can be done up to 4 hours prior to surgery, combined with intraoperative identification of the sentinel node using a handheld gamma detector.

Since the radiolabeled technique provides no visual clues to the node's location, most surgeons combine the two techniques. The combined use of blue dye plus radiolabeled colloid enables the detection of the sentinel node in $>98\%$ of cases.

Pitfalls of selective lymphadenectomy Wide excision of the primary melanoma sufficiently alters the lymphatic drainage patterns to make identification of the sentinel node unreliable. Therefore, patients who have had >1 cm of skin excised around their primary melanoma are not considered good candidates for selective lymphadenectomy.

In addition, reliable prediction of the status of the nodal basin requires careful examination of the sentinel nodes. Generally, this examination involves techniques not routinely applied to full node dissection specimens, such as serial sectioning and immunohistochemical staining of the removed nodes. Since there have been several reports of regional failure in patients whose sentinel node was considered to be "clean" by standard examination but subsequently proved to be involved on more sophisticated evaluation, the results of the Sunbelt Melanoma Trial and other investigations of more sensitive assays for nodal involvement will contribute important information to this aspect of melanoma management.

Finally, patients with melanoma metastatic to the regional nodes have multiple nodes involved at least 20% of the time. Thus, any patient in whom an involved sentinel node has been identified should undergo a full lymph node dissection, performed in a timely manner.

Isolation limb perfusion In-transit metastases—ie, cutaneous or subcutaneous

The Sunbelt Melanoma Trial was designed to further test the value of regional lymphadenectomy and adjuvant IFN-α in patients with intermediate-to-deep primary melanoma and clinically negative nodes. The two-part trial is divided into protocols A and B. Protocol A is for patients with positive sentinel node(s) detected by histology or immunohistochemistry. Patients with only a single positive sentinel node will be stratified by tumor thickness and then randomized to undergo observation or to receive IFN-α following lymphadenectomy. Protocol B is for patients with a histologically negative sentinel node biopsy. Patients whose sentinel node is positive for tyrosinase by polymerase chain reaction will be stratified by thickness and then randomized to undergo lymphadenectomy vs no further surgery in a 2:1 ratio. One-third of the patients will be observed without further surgery or adjuvant IFN-α. The other two-thirds will be randomized to receive IFN-α or no further therapy after lymphadenectomy *(McMasters KM: Ann Surg Oncol 8[suppl 9]:41-43, 2001).*

nodules arising between the primary site and the regional lymph node basin—are a well-recognized, but fairly uncommon, site of failure in cutaneous melanoma. A surgical technique developed to treat in-transit metastases, isolation limb perfusion, involves cannulating the artery and vein to an extremity and connecting the cannulas to a cardiopulmonary bypass machine. This technique effectively isolates the blood flow to that extremity and allows for prolonged perfusion with cytotoxic and/or biological agents.

Most commonly, the chemotherapeutic agent melphalan (Alkeran) has been used for isolation limb perfusion; this drug is generally heated to an elevated temperature (up to 41°C) and perfused for up to 90 minutes. Hyperthermic isolation perfusion with melphalan alone or combined with the investigational agent tumor necrosis factor-α (TNF-α) results in the regression of $>$ 90% of cutaneous in-transit metastases. This approach is useful for very limited clinical situations at centers experienced in the technique.

Hyperthermic isolation perfusion with melphalan has also been combined with wide excision in patients at high risk of recurrence of in-transit metastases. Adjuvant use of perfusion demonstrated no significant benefit in a large, international intergroup trial, however, and cannot be recommended.

SURGICAL TREATMENT OF NONCUTANEOUS MELANOMA

Noncutaneous melanomas generally present at a more advanced stage than cutaneous lesions. The site of the lesion greatly affects the approach to the primary tumor and regional lymph nodes.

Ocular melanomas generally do not have access to lymphatic channels, so the surgical principles outlined above do not apply here. However, the unique propensity to metastasize hematogenously, often to the liver after a long relapse-free interval, warrants further study of this primary site's unique biology. Advances in understanding the biology of ocular melanomas may lead to adjuvant approaches different from therapies now under investigation for cutaneous primaries.

A diagnosis of ocular melanoma with no evidence of distant disease signifies that a decision must be made as to whether or not the eye can be spared. Some small melanomas situated peripherally in the retina can be excised with minimal loss of vision, but most cannot. For larger lesions, treatment options are enucleation (total removal of the eye) or implanted radiotherapy with a radioactive gold plaque fitted to the back of the eyeball immediately behind the tumor. A multi-institution, randomized trial comparing implanted radiotherapy with enucleation for local disease control and overall survival was recently completed by the Collaborative Ocular Melanoma Study Group; it appears that both techniques provide similar outcomes for all sizes of tumor.

Melanomas of the anus and vulva pose challenges in the treatment of both the primary lesion and regional nodes. Excision of primary tumors in these areas should not be overly radical: Abdominoperineal resection or radical vulvectomy is unnecessarily deforming and is not associated with improved survival compared with wide local excision. Abdominoperineal resection, with

its attendant permanent colostomy, is indicated only for locally recurrent melanomas after prior sphincter-conserving excision or for melanomas with radiographic evidence of mesorectal node involvement.

Anal and vulvar melanomas often present with inguinal lymph node metastases; if there is no evidence of distant disease, both the primary site and regional nodes should be removed.

Nasal sinuses or nasopharyngeal melanomas Melanomas arising in the nasal or nasopharyngeal mucosa should be widely excised to include adjacent bony structures, if needed. Node dissection is reserved for patients who have proven nodal involvement. Radiation therapy should be considered for those patients whose primary tumor cannot be fully removed from this site with adequate margins.

ADJUVANT THERAPY FOR MELANOMA

The 10-year disease-free survival estimate for patients with shallow stage I cutaneous melanoma (< 1.5 mm depth) is 85%. However, fewer than half of patients with deep primaries or intermediate-level primaries with ulceration (see new proposed AJCC system) and/or regional lymph node involvement will experience long-term disease-free survival.

Development of adjuvant therapy approaches that increase survival over surgery alone has been a long-standing goal of melanoma researchers.

Interferon-α-2b (IFN-α-2b)

Results of a large, randomized, multicenter study in high-risk melanoma patients performed by the Eastern Cooperative Oncology Group (ECOG) showed significant improvements in relapse-free and overall survival with postoperative adjuvant IFN (interferon)-α-2b therapy, compared with standard observation (ECOG 1684). In this trial, 287 patients with deep primary (T4 N0) or node-positive (N1-2) melanoma were randomized to receive either (1) postoperative adjuvant treatment with IFN-α-2b, 20 mIU/m^2 IV every day, 5 days per week, for 4 weeks, followed by 10 mIU SC 3 times weekly for 48 weeks, or (2) observation.

IFN-α-2b therapy significantly increased median relapse-free survival by 9 months (1.72 years for IFN-α-2b patients vs 0.98 years for observation patients) and produced a 42% improvement in the 5-year relapse-free survival rate (37% vs 26%). In addition, IFN-α-2b therapy significantly increased median overall survival by 1 year and produced a 24% improvement in the 5-year overall survival rate (46% for IFN-α-2b patients vs 37% for observation patients). Although side effects were common, 68% of patients receiving IV induction therapy and 60% of patients receiving SC maintenance therapy were able to tolerate ≥ 80% of the recommended dose.

Based on this trial, the FDA approved IFN-α-2b as adjuvant treatment after surgical excision in patients with malignant melanoma who are free of disease but are at high risk of systemic recurrence.

Unresolved questions Several questions regarding the use of adjuvant IFN-α-2b for patients with resected intermediate- or high-risk melanoma remain under investigation.

- Is dose-intensive IV induction followed by aggressive SC maintenance therapy required for the adjuvant benefit of IFN-α?
- What is the optimal adjuvant therapy for node-negative melanoma?

Optimal IFN-α-2b regimen A report on the World Health Organization (WHO) trial of 3 years of low-dose IFN-α-2b (3 mIU SC 3 times weekly) vs observation in stage III node-positive patients showed a difference of borderline statistical significance in 2-year disease-free survival, with retrospective subgroup analysis suggesting interactions among treatment, age, and gender. On a subsequent analysis, however, overall survival did not appear to be favorably affected by the low-dose IFN-α-2b regimen.

An intergroup study comparing the high-dose regimen of 1 year of IFN-α-2b vs a more prolonged, lower-dose regimen (3 mIU SC 3 times weekly for 2 years) vs observation was recently completed (ECOG 1690). Patients with deep-primary and node-negative or node-unknown disease comprised a larger proportion of patients in this trial than in the original ECOG study (ECOG 1684). The results of this study provide additional data on node-positive patients and deep-primary, node-negative patients as well as on the lower-dose regimen in both groups of patients.

A preliminary analysis of data from the intergroup trial showed an improvement in relapse-free survival, but not overall survival, in patients treated with high-dose IFN-α-2b but not in the low-dose treatment arm. The improved results seen in the observation group, which were superior to those expected, could have been due to "crossover" to interferon therapy upon relapse, which also may have influenced the study's power to detect a survival advantage for interferon therapy.

Based on the promising immunologic responses (mainly IgM antibody) to a vaccine containing GM_2, a ganglioside found predominantly in melanoma cells, a subsequent intergroup trial (ECOG 1694) was designed to compare high-dose IFN-α-2b with GM_2 conjugated to keyhole-limpet hemocyanin, administered with the potent immunologic adjuvant QS21 in patients with resected deep-primary or node-positive melanomas. This trial was closed early (after accrual of the original number of patients but before all patients had completed therapy) based on a planned interim analysis, which demonstrated significantly superior disease-free and overall survival for IFN-α-2b.

A small percent of patients with metastatic melanoma can be rendered disease free by surgical excision of all known sites of disease. Since these patients have an extremely high likelihood of relapse, the development of effective adjuvant therapy is essential. An ongoing intergroup trial will assess the role of the immunomodulatory cytokine granulocyte-macrophage colony-stimulating factor and three melanoma antigen peptides as adjuvant therapy for melanoma patients following surgical resection of metastatic disease.

Optimal adjuvant treatment of node-negative melanoma The best adjuvant intervention for patients with intermediate-risk melanoma has not yet been identified, but the goal of avoiding toxicity and the recognition that these patients may be the ideal candidates for

immunotherapeutic interventions have justified the enrollment of these patients in trials of vaccines and low-dose IFN-α-2b. Several trials outside the United States failed to demonstrate a survival benefit using IFN-α-2b in various schedules and doses for patients with high-risk node-negative disease.

Further data on the impact of a high-dose induction period and the optimal dose and duration of lower-dose therapy with IFN-α are being evaluated in a large, recently completed phase III trial of the EORTC (European Organization for Research on the Treatment of Cancer). The current EORTC trial will assess the potential benefit of long-acting, pegylated IFN-α administered for 5 years on distant disease-free survival for patients with node-positive disease. This form of interferon requires less frequent injections and may have a lower rate of side effects, making long-term use and use in node-negative patients with intermediate risk of recurrence more feasible.

A large Southwest Oncology Group (SWOG) study of an allogeneic melanoma vaccine vs observation in patients with original AJCC stage IIA (1.5-4.0 mm deep primary with clinically or pathologically negative nodes) was recently reported (SWOG 9035). Patients randomized to receive treatment with the vaccine had improved relapse-free survival, a difference that reached statistical significance for the entire group of 689 patients. Patients randomized to receive treatment with the vaccine had a trend toward improved relapse-free survival. For the subset of patients who expressed the HLA class I antigens HLA-A2 or HLA-C3, however, treatment with the vaccine was associated with a statistically significant improvement in both relapse-free and overall survival. HLA status is known to affect how the immune system processes and presents tumor antigens. This finding raises the hope that directed therapies can be developed for certain groups of patients.

Fotemustine is a nitrosourea that has recently been shown to produce responses in one-third of patients with ocular melanoma metastatic to the liver, a disease for which other systemic therapies have been inactive *(Leyvraz S, Bosshard W, Salmon R, et al: Proc Am Soc Clin Oncol [abstract] 341a, 2002)*. This agent has also been under investigation, due to its high CNS penetration, as a treatment for melanoma with brain metastases. In the preliminary report of a recent European multicenter phase III trial, its overall antitumor activity was slightly superior to that of dacarbazine, and there appeared to be a delay in the development of brain metastases in patients randomized to receive fotemustine *(Aamdal S, Avril M, Grob JJ, et al: Proc Am Soc Clin Oncol [abstract] 341a, 2002)*. This drug has been approved in several other countries but remains investigational in the United States.

Radiation therapy

Radiation therapy is rarely employed after surgery for primary or nodal melanoma, although recent reports have demonstrated that the pessimistic impression that melanoma is a "nonradioresponsive" tumor is not justified. A study at M. D. Anderson Cancer Center suggested that postoperative radiation therapy to the neck after radical or modified radical neck dissection decreased regional recurrence rates in node-positive patients.

ECOG is performing a randomized, multi-institution trial (ECOG 3697) to evaluate the effectiveness of postoperative hypofractionated radiotherapy added

to IFN-α-2b for patients with nodal re-recurrence or extracapsular involvement at first nodal resection in cervical, axillary, or inguinal sites. If this trial confirms a significant benefit, postoperative radiation therapy may become more widely used. Until the results of this trial are available, it seems reasonable to consider the use of postoperative radiation therapy in patients with multiple (≥ 10) involved lymph nodes or gross extracapsular extension, as these patients are at high risk of regional recurrence despite adequate lymph node dissection.

Since these patients are also candidates for IFN-α-2b or investigational studies of adjuvant therapy, the optimal schedule for integrating radiation therapy with IFN-α-2b will need to be determined. In the absence of definitive data, we defer the start of radiation therapy until after the completion of the initial month of IV IFN-α-2b.

TREATMENT OF ADVANCED MELANOMA

Chemotherapy

Single agents Among the numerous available chemotherapeutic agents, only dacarbazine (DTIC), which has a 10%-15% objective response rate when given alone, is currently approved for the treatment of advanced melanoma. Most combination regimens in current use or under investigation include this agent. Temozolomide (Temodar) is an oral alkylating agent approved for the treatment of malignant gliomas that has activity comparable to that of dacarbazine in advanced melanoma. Its mechanism of action is similar to that of dacarbazine, but its high oral bioavailability and penetration into the CNS make it ideal for consideration in treatment of this disease, with a high propensity for CNS metastasis. Although there are no adequate phase III data supporting this hypothesis, temozolomide has been substituted for dacarbazine in many combination regimens and is currently under investigation in combination with radiation therapy for patients with melanoma metastatic to the brain.

Thalidomide, an anti-inflammatory agent with proven activity against several other malignancies, possibly via antiangiogenic pathways, has recently been evaluated in combination with temozolomide in patients with metastatic melanoma. This combination of oral agents has produced objective responses in about one-quarter of patients *(Hwu W-J, Krown SE, Menell JH, et al: Proc Am Soc Clin Oncol [abstract] 21:344a, 2002; Danson S, Arace A, Lorigan P, et al: Proc Am Soc Clin Oncol [abstract] 21:343a, 2002).* The Southwest Oncology Group (SWOG) is currently evaluating the antitumor activity of thalidomide plus very low-dose, twice-daily IFN-α-2b as a form of combination antiangiogenic therapy for patients with advanced melanoma.

Other drugs with sufficient single-agent activity to justify their inclusion in combination regimens are the nitrosoureas, vinca alkaloids, and cisplatin, each of which produces objective response rates of approximately 10%-15%. However, these responses are nearly always of brief duration (several months), are rarely complete (approximately 2%), and occur most often in asymptomatic patients with small-volume metastases in the soft tissue, skin, lymph nodes, or lungs.

Combination regimens The principles of combination chemotherapy and potential drug synergy have been applied with limited

TABLE 6: Randomized trials of biochemotherapy regimens in patients with metastatic melanoma

Regimen	No. of patients	No. of CRs	No. of PRs	OR rate (%)	Median survival (mo)
Falkson study					
DTIC	69	2	8	15	10
DTIC + IFN-α	68	6	8	21	9
DTIC + Tam	68	2	10	18	8
DTIC + IFN-α + Tam	66	3	10	19	10
Rosenberg study					
CDDP + DTIC + Tam	52	8	19	27	16
CDDP + DTIC + Tam ± IL-2 + IFN-α	50	6	38	44	11
Ridolfi study					
CDDP + DTIC ± BCNU	89	3	15	20	9.5
CDDP + DTIC ± BCNU + IL-2 + IFN-α	87	3	19	25	11
M. D. Anderson study					
CDDP + DTIC + Vlb	92	1	22	23	9.5
CDDP + DTIC + Vlb + IL-2 + IFN-α	91	6	38	44	11.8

BCNU = carmustine; CDDP = cisplatin; CR = complete response; DTIC = dacarbazine; IFN-α = interferon-α; IL-2 = interleukin-2; OR = overall response; PR = partial response; Tam = tamoxifen; Vlb= vinblastine

success to the treatment of advanced melanoma (Table 6). Combinations with approximately double the activity of the most active single agents have been adopted by many practitioners for routine use despite a lack of adequate data from prospective, randomized trials demonstrating a survival advantage of combination regimens over optimal single-agent therapy. Nevertheless, a three-drug regimen developed at M. D. Anderson has recently assumed "standard therapy" status.

The combination of cisplatin, vinblastine, and dacarbazine (CVD) has been extensively studied in patients with advanced melanoma and has been reported to produce a 30%-40% response rate. Although the activity of this combination has not been shown to be superior to that of single-agent chemotherapy in randomized trials, it has been used as the chemotherapeutic component of a series of biochemotherapy combinations that have shown promising activity (see "Biological agents plus chemotherapy").

Nitrosoureas have been used as a single agent and as a component of combination regimens in patients with advanced melanoma for many years. However, recent data have demonstrated that regimens containing carmustine, which cause nausea and myelosuppression, are not superior to single-agent therapy for advanced melanoma.

Biological therapies

IFN-α-2b, when used as a single agent, produces objective responses in approximately 15% of patients with metastatic melanoma. As with chemotherapy, the best responses with IFN-α-2b occur in patients with small-volume, nonvisceral metastatic disease and a good performance status.

The toxicities of IFN-α-2b are predominantly constitutional, consisting of fever and chills (which subside in most patients after the first few doses), nausea and anorexia, myalgias, and arthralgias. Fatigue, which may be progressive as therapy continues, is generally the most troublesome side effect and is often dose-limiting. CNS toxicity, ranging from mild difficulties with concentration to severe depression, is also related to the dose and duration of therapy.

The most common laboratory abnormalities consist of asymptomatic elevations in serum levels of transaminase and mild myelosuppression, as well as occasional nephrotoxicity. Virtually all of these effects are reversible and occur in a dose- and schedule-dependent pattern.

Other interferons IFN-β (Betaseron) and IFN-γ (Actimmune) have limited activity in the treatment of advanced melanoma and are not recommended, except in the investigational setting as possible immunomodulators or chemomodulators.

Interleukin-2 (IL-2, aldesleukin [Proleukin]) is the only other recombinant biological molecule with demonstrated antitumor activity against melanoma. The majority of published data come from trials of high doses of IL-2 (600,000-720,000 IU/kg IV every 8 hours for 14 doses, repeated after a 9-day rest period) given over limited treatment durations at toxicity levels requiring inpatient management. The most common toxicities, including hypotension with fluid retention, acidosis and renal insufficiency, neurotoxicity and cardiovascular complications, can be life-threatening. Mucocutaneous and constitutional toxicities including fever/chills, nausea/anorexia, and profound fatigue may also limit the number of doses tolerated by patients. The generalized capillary leak syndrome may lead to multiorgan dysfunction that requires skill and experience to administer the maximum number of doses tolerated while avoiding life-threatening toxicities. At these dose-intensity levels, objective response rates of approximately 20% have been achieved, with about half of responding patients experiencing durable complete remissions lasting in excess of 5 years. Based on these favorable results, high-dose IL-2 was approved by the FDA in 1998 for the treatment of metastatic melanoma. Recently completed phase III trials have failed to demonstrate a significant reduction in toxicities or enhancement in the therapeutic efficacy of IL-2 using modulators chosen for their selective inhibitory effects on inflammatory pathways associated with the toxic effects of IL-2.

Although the frequency of durable complete responses to IL-2 therapy appears to be higher than that reported for other single agents and combination regimens, it is important to consider that patients selected for their ability to tolerate the serious multisystem toxicities of high-dose IL-2 may represent a more favorable group with a higher a priori likelihood of tumor response.

Only limited data are available on the activity of outpatient, low-dose IL-2 regimens in patients with melanoma, and this form of therapy is not recommended outside a clinical trial.

IFN-α-2b plus IL-2 IFN-α-2b and IL-2 have been used together in the treatment of advanced melanoma, as well as other tumors. In addition to potential synergistic antitumor efficacy, the clinical advantage of this combination includes the relative lack of overlapping toxicities. Combinations of IFN-α-2b and IL-2 at maximum doses in either the inpatient or outpatient setting have not, however, achieved a higher response rate than either agent alone in patients with metastatic melanoma and are not recommended for routine use.

Melanoma vaccines Vaccines produced from allogeneic melanoma cell lines administered with one of several available nonspecific immunologic "adjuvants" (which stimulate antigen-presenting cells and enhance other aspects of immune recognition of antigens) have shown limited antitumor activity (generally ≤ 10% objective response rates in patients with limited metastatic disease). Active research in melanoma therapy involves evaluation of tumor vaccines in patients with metastatic disease, as well as in patients who have been rendered surgically free of disease but who remain at a high risk of relapse.

Tumor-specific antigens most critical to mediating an antimelanoma immune response and the relative efficacy of T-cell response vs humoral immune responses remain the subject of ongoing investigations. Peptide vaccines hthat induce T-cell immunity to precisely defined immunodominant peptides contained in melanoma protein antigens have been developed. The immune response to such peptides is restricted by the HLA system. These vaccines may work well when administered directly to patients with an immune adjuvant, such as described above, or may have enhanced immuno-stimulatory activity when administered as part of a dendritic cell vaccine. Dendritic cell-targeted therapy takes advantage of the dendritic cells' antigen-presenting function, involved in T-cell responses. Under investigation are peptides from several known melanoma antigens, including the MAGE series, gp-100, tyrosinase, MART-1/Melan-A, and NY-ESO-1. Phase III trials are ongoing to study the best immunologic adjuvant as well as combinations of peptide vaccines with cytokines (eg, GM-CSF [Leukine] and IL-2) that also enhance the T-cell response.

Gene therapy New advances in gene therapy have made possible the genetic modification of tumor cells as well as effector cells, such as dendritic cells and T cells. Some of the genetic modifications that have been studied include the transfection of genes for immunostimulatory cytokines, allogeneic HLA sequences, and accessory molecules critical for immune recognition. Continued efforts in this area will soon define the optimal system for the application of these laboratory techniques to the immunotherapy for human melanoma.

Biological agents plus chemotherapy

Several preclinical models of advanced melanoma indicate that the combination of selected chemotherapeutic agents and biological response modifiers in optimal doses and sequence have led to enhanced antitumor effects.

Randomized trials of the combination of dacarbazine and IFN-α, both active as single agents, have shown conflicting results (Table 6). The first of these phase III trials, reported by ECOG in 1998, demonstrated the lack of benefit when IFN-α-2b was added to dacarbazine with or without tamoxifen (at that time believed to enhance the antitumor effects of certain chemotherapeutic agents).

More promising findings were described in phase II trials for combinations of IL-2 plus IFN-α with chemotherapy, the so-called biochemotherapy regimens, although these regimens are more toxic than chemotherapy regimens alone. Two subsequent phase III trials failed to demonstrate a significant survival benefit with the addition of IL-2 and IFN-α to combination chemotherapy despite the higher objective response rates associated with these combinations. The preliminary results of a larger American intergroup phase III trial of CVD chemotherapy with or without IL-2 and IFN-α-2b were also recently reported; they showed no significant benefit of added biotherapy on progression-free or overall survival. The possibility of a small, but significant, difference in the rate of durable complete remissions will require longer follow-up of patients currently in remission.

The possibility that the combination of IL-2 and IFN-α-2b may enhance the activity of chemotherapy is currently being studied in randomized trials. The therapeutic potential of other cytokines (such as IL-4, GM-CSF, IL-12, and IL-18) remains under investigation.

Radiation therapy

Radiation therapy is the only treatment available for most patients with unresectable brain metastases, but meaningful responses are observed in less than 25% of treated patients. Alternative fractionation schedules have been investigated but have not proved to be superior to standard regimens of whole-brain irradiation. Recently, techniques of stereotactic radiosurgery have shown encouraging results in patients with melanoma metastatic to the CNS; this approach is currently recommended when the size, number, and location of metastases are amenable to stereotactic techniques. The median survival is only a few months. Corticosteroids are often given concomitantly with brain irradiation to minimize intracranial swelling and are tapered off rapidly after the completion of therapy. Because melanoma has limited responsiveness to radiotherapy and is often associated with intracranial hemorrhage, excision should be considered for brain metastases that can be removed safely.

Attempts to take advantage of systemic therapy using agents that cross the blood-brain barrier, such as the nitrosoureas and temozolomide, have been largely unsuccessful in the treatment of established CNS metastases; their role in the prevention of CNS metastases in patients with extracranial metastatic melanoma is currently under investigation.

Radiation therapy is occasionally of benefit in the palliative treatment of melanoma metastatic to the bone or other symptomatic sites.

Treatment of nonmelanoma skin cancer

Surgery

Margins of excision Most nonmelanoma skin cancers can be conservatively excised with much narrower margins than are required for cutaneous melanomas. Excision margins of 0.5-1.0 cm are adequate for most nonrecurrent basal and squamous cell cancers and yield local recurrence rates under 5%, provided that histologically negative margins are achieved. For most tumors in most anatomic sites, these excision margins can be achieved using standard surgical techniques with local anesthesia and primary closure.

Recurrent cancers and lesions in difficult sites More sophisticated techniques are required for recurrent skin cancers or those in cosmetically difficult areas, such as the tip of the nose or the eyelids. For these lesions, a variation of Mohs' micrographic surgery is frequently employed. Simply stated, this type of surgery is a controlled surgical excision in which the removed tissue is precisely oriented and carefully examined histologically, and serial re-excisions are performed wherever residual disease is noted.

Although Mohs' surgery may take much longer than routine surgical excision, the extra precision can be helpful for identifying the often asymmetrical extensions of skin cancers, thus minimizing the amount of normal tissue resected. After Mohs' surgery has achieved complete excision, reconstruction is performed by whatever means is appropriate but often involves skin grafts or local flaps rather than primary closure.

More aggressive histologic types of skin cancers, particularly Merkel's cell cancers and sarcomas, generally require wider excision than do the more common basal and squamous cell cancers. Margins of 2-3 cm are usually taken, similar to those for a thick melanoma. In particular, dermatofibrosarcoma protuberans may spread in an eccentric fashion, with little extension in one direction but many centimeters of subclinical tumor growth in another. Careful examination of the histologic status of the margins is essential. Mohs' surgery may be useful in some cases.

Radiation therapy

Radiation therapy is a potential treatment for skin cancers located in critical sites where surgical excision would be disfiguring. Primary basal and squamous cell cancers treated with radiation therapy have nearly identical cure rates (about 95%) to those treated with surgical excision.

Radiation therapy is also employed postoperatively to reduce local recurrence rates after excision of high-grade or recurrent sarcomas of the skin. It can also be used postoperatively in patients with basal cell or squamous cell carcinoma when margins are positive.

Topical and intralesional therapy

Topical 5-FU Occasionally, patients present with numerous skin cancers or tumors in essentially sensitive areas that would be impossible to resect com-

pletely. This scenario is particularly common in the immunosuppressed patient who is predisposed to skin cancer development. For these patients, topical chemotherapy with 5-FU cream can dramatically reduce the number of excisions required. This may also be an option for overall skin cancers.

Direct intralesional injection of IFN-α-2b has been reported to treat basal cell cancers successfully. This technique may be particularly helpful for locally recurrent lesions after surgery and/or radiation therapy.

MANAGEMENT OF RECURRENT DISEASE

Local recurrence The vast majority of nonmelanoma skin cancers are successfully treated with surgery or primary irradiation, with fewer than 5% recurring locally. Of those that do recur locally, at least 80% are cured by further local treatment. Regional lymph node metastases develop in about 5% of patients with squamous cell cancers and ≤ 1% of patients with basal cell cancers. Nodal metastasis is somewhat more common in Merkel's cell cancers but is very unusual in sarcomas of the skin.

Regardless of the histologic type, whenever clinically obvious nodal enlargement occurs, a needle biopsy should be performed and a therapeutic lymph node dissection performed if regional spread is documented. There is essentially no role for elective dissections of clinically normal nodes in any form of nonmelanoma skin cancer.

Distant metastasis occurs in about 2% of patients with squamous cell cancers and 0.1% of patients with basal cell cancers, most frequently after nodal recurrence. No effective therapy exists for metastatic nonmelanoma skin cancer, although a few reports of scattered temporary responses to chemotherapy exist. Recently, Lippman and colleagues described encouraging results with the combination of IFN-α and 13-*cis*-retinoic acid (isotretinoin [Accutane]).

SUGGESTED READING

GENERAL INFORMATION ON SKIN CANCERS

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ON BIOLOGY AND EPIDEMIOLOGY OF MELANOMA

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The ABCDs of moles and melanomas

Concept and photographs:

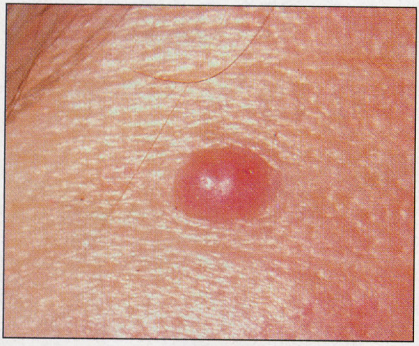
Robert J. Friedman, MD, Darrell S. Rigel, MD, Alfred W. Kopf, MD,
and the Skin Cancer Foundation

People at high risk of developing melanoma are those who have:

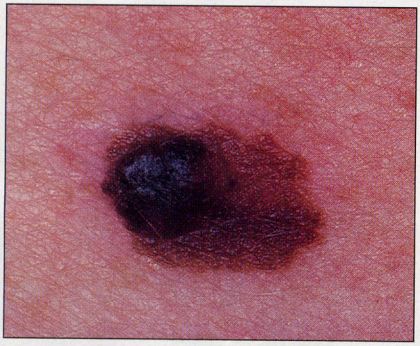
- A family history of melanoma, or who have had a melanoma in the past
- Unusual moles on the skin, or changing moles
- Fair skin, light hair and eye color, and who sunburn easily or tan with difficulty
- A record of painful or blistering sunburns as children or in their teenage years
- Indoor occupations and outdoor recreational habits

When you inspect moles, pay special attention to their sizes, shapes, edges, and color. A handy way to remember these features is to think of the A, B, C, and D of skin cancer–asymmetry, border, color, and diameter.

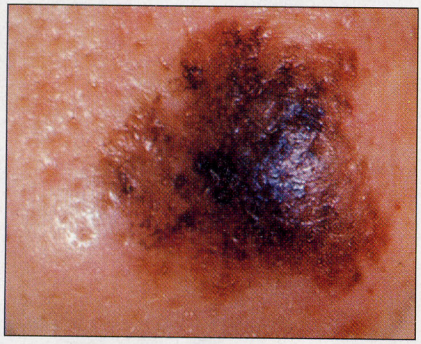
A Asymmetry



Benign — Symmetrical



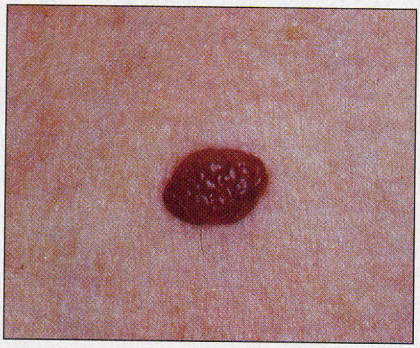
Malignant — Asymmetrical



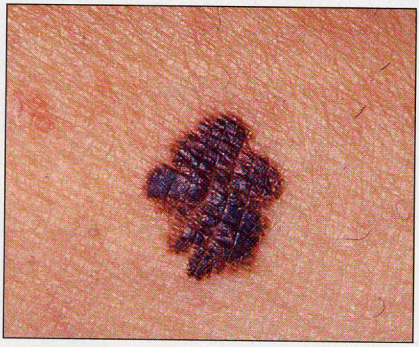
Malignant — Asymmetrical

Some forms of early malignant melanoma are asymmetrical, meaning that a line drawn through the middle will not create matching halves. Moles are round and symmetrical.

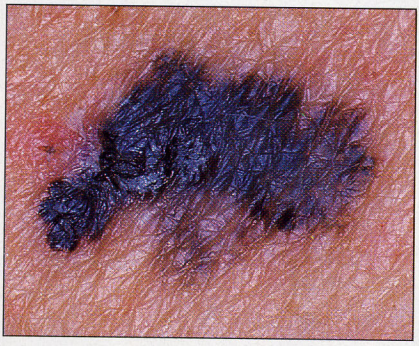
B Border



Benign — Even edges



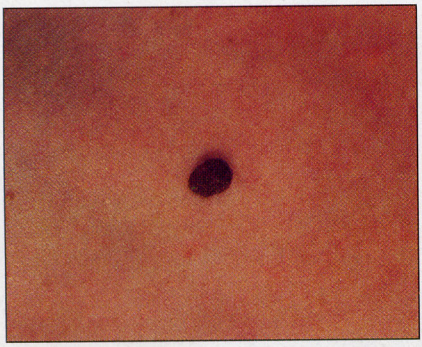
Malignant — Uneven edges



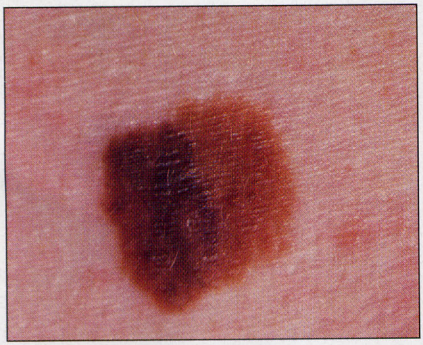
Malignant — Uneven edges

The borders of early melanomas are frequently uneven, often containing scalloped or notched edges. Common moles have smooth, even borders.

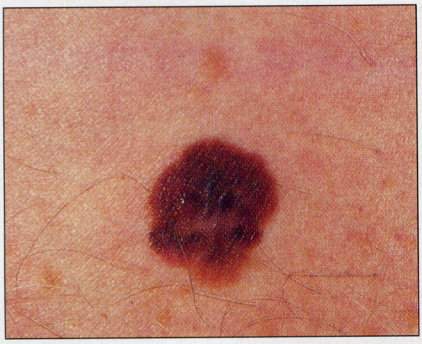
C
Color



Benign — **One shade**

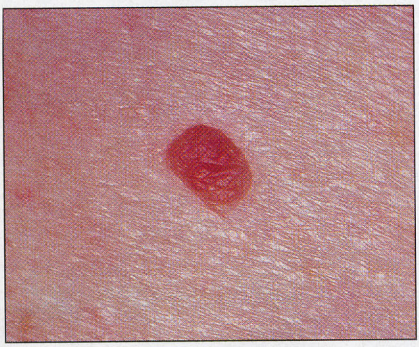


Malignant — **Two or more shades**

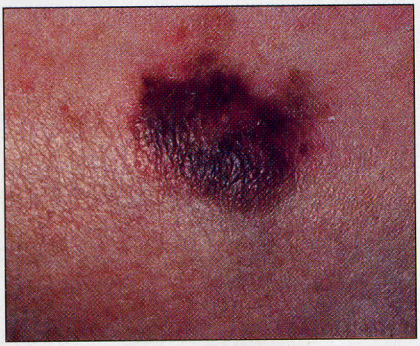


Malignant — **Two or more shades**

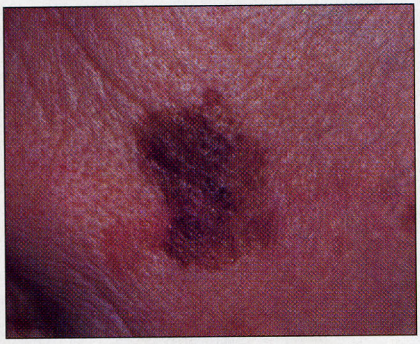
D
Diameter



Benign — **Smaller than 6 mm**



Malignant — **Larger than 6 mm**



Malignant — **Larger than 6 mm**

Different shades of brown or black are often the first sign of a malignant melanoma. Common moles usually have a single shade of brown.

Common moles are usualy less than 6 mm in diameter (1/4 in.), the size of a pencil eraser. Early melanomas tend to be larger than 6 mm.

A color atlas of skin lesions

Prepared by Howard Koh, MD, and the American Academy of Dermatology

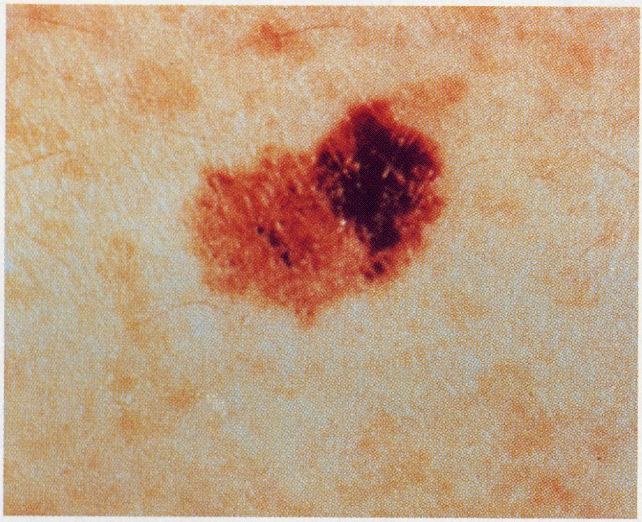


FIGURE 1: Malignant melanoma
The heterogeneous color and asymmetry of the lesion point to the diagnosis of melanoma. Particularly note the black color of the right side of the lesion. (Figures 1, 2, and 8 courtesy of the American Academy of Dermatology)

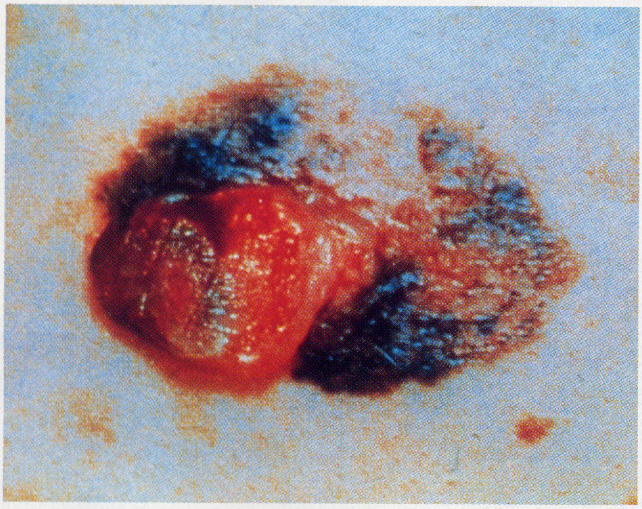


FIGURE 2: Malignant melanoma
There are several colors clearly visible in this lesion, consistent with melanoma. There are mottled black areas of the lesion, with central tumor growth that is eroded and less pigmented.

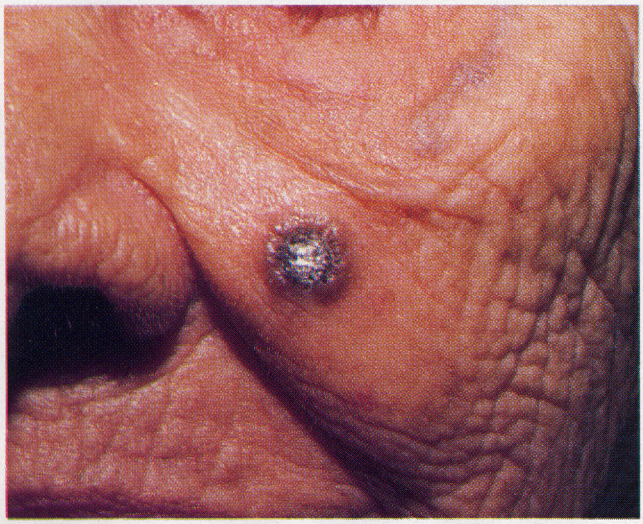


FIGURE 3: Pigmented basal cell epithelioma
While this lesion mimics melanoma, it has a slightly translucent appearance around the rim consistent with the diagnosis of basal cell cancer.

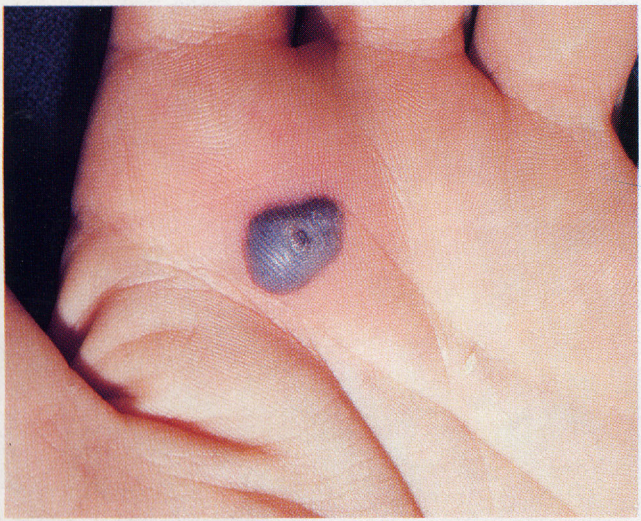


FIGURE 4: Blood blister
Although this lesion mimics melanoma, it is tense, fluid-filled, and benign. Normal skin markings are visible through much of the lesion.

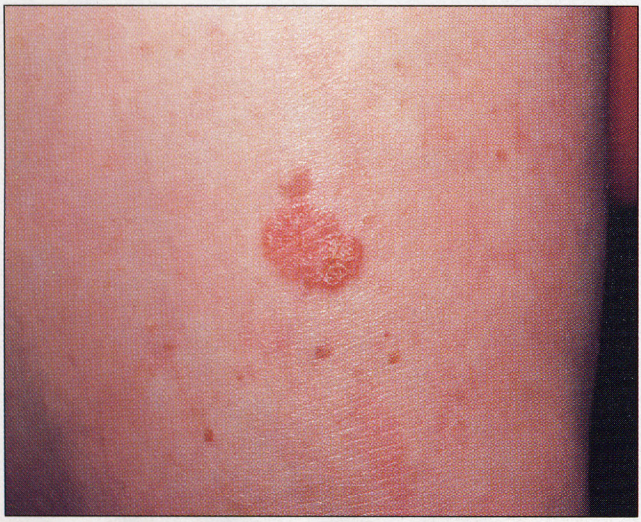


FIGURE 5: Bowen's disease
This sharply demarcated, slightly scaly plaque is typical of squamous cell cancer in situ.

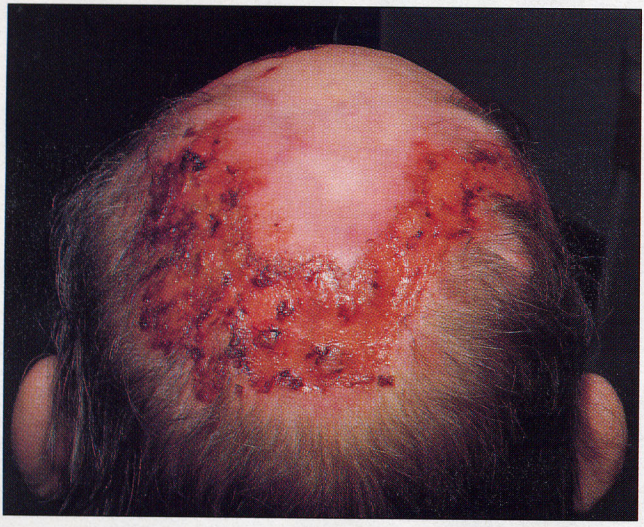


FIGURE 6: Basal cell carcinoma
This patient has extensive, ulcerative disease of the scalp. It is an unusual case that can be diagnosed only through biopsy and is associated with severe morbidity.

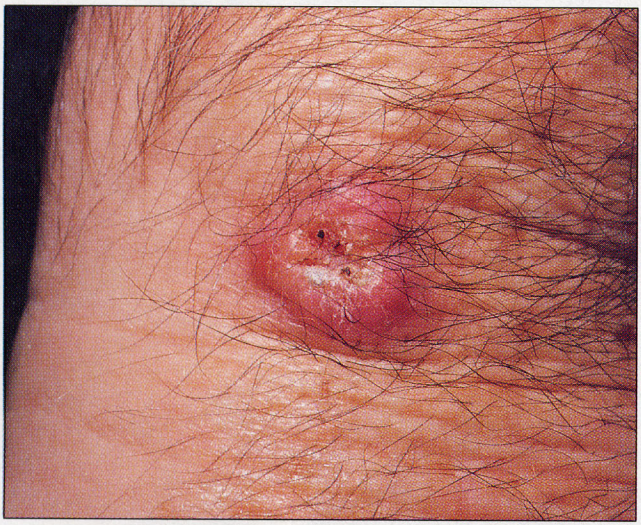


FIGURE 7: Squamous cell carcinoma
This infiltrated red plaque has central erosion and crust.

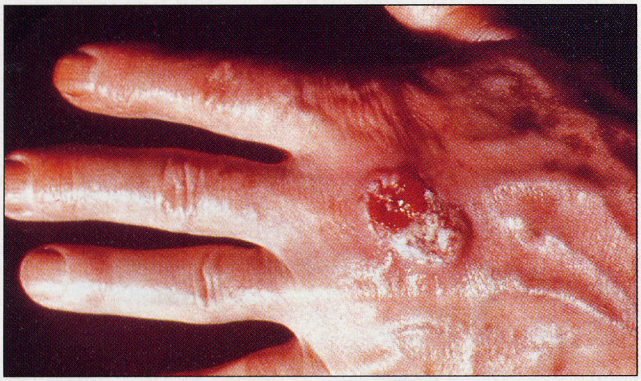


FIGURE 8: Squamous cell carcinoma
Erythematous and infiltrated lesion in a maximally sun-exposed area, with an erosive center.

CHAPTER 25

Bone sarcomas

Alan W. Yasko, MD, and Warren Chow, MD

Bone sarcomas are extremely rare neoplasms, which precludes determination of their true incidence. Approximately 2,400 new cases are identified annually in the United States. Population-based tumor registries seldom separate bone sarcomas into various histologic types.

Osteosarcoma is the most common malignant primary bone tumor (excluding multiple myeloma), comprising 30% of all such malignancies. The annual incidence of osteosarcoma is approximately 800 cases per year in the United States. Chondrosarcoma is the second most common malignant primary tumor of bone; its annual incidence is approximately half that of osteosarcoma. Ewing's sarcoma represents approximately 6% of all primary malignant bone tumors, with an annual incidence of 200 cases. Malignant fibrous histiocytoma (MFH) comprises < 1% of primary bone sarcomas.

Epidemiology

Gender The incidence of primary bone sarcomas is higher in males than in females regardless of histologic type. A low-grade variant of osteosarcoma (parosteal osteosarcoma) is observed more frequently in females.

Age Osteosarcoma and Ewing's sarcoma develop primarily in children and adolescents. A biphasic pattern of incidence of osteosarcoma has been observed that peaks in adolescents (rapid growth of long bones) and in the elderly (secondary tumors arising in association with Paget's disease or within previously irradiated tissue). Chondrosarcomas are rarely seen in skeletally immature patients. They usually develop in middle-aged and older adults. MFH is observed in adults.

Race No predilection has been noted in any particular race. However, Ewing's sarcoma is extremely rare in American and African blacks.

Disease site Any bone and any site within a given bone may be affected. Most osteosarcomas occur in the metaphyseal region of skeletally immature long bones (ie, distal femur, proximal tibia, and proximal humerus), which have the greatest growth potential. Ewing's sarcoma is classically described as a diaphyseal lesion but may arise in any region within an involved long bone. It commonly arises in the flat bones of the pelvis and scapula. Primary bone tumors of any histologic type are extremely rare in the spine and sacrum.

Survival Low-grade sarcomas are associated with the most favorable survival, which approaches 90% in patients with adequately treated tumors. With re-

gard to high-grade sarcomas, survival has improved dramatically in patients with osteosarcoma or Ewing's sarcoma due to the advent of effective multiagent chemotherapy regimens. Survival has improved from historical rates of < 20% to current rates of 50%-75% with multimodality therapy.

Etiology and risk factors

For the majority of bone sarcomas, no specific etiology has been established. A few predisposing factors have been identified.

Genetic factors Children with familial retinoblastoma have a 13q chromosome deletion and an increased incidence of osteosarcoma.

Radiation therapy Bone sarcomas constitute a rare but devastating consequence of therapeutic irradiation. Radiation-associated sarcomas develop within the radiation field, usually after a latent period of at least 3 years. The majority of these tumors are osteosarcomas. MFH and other histologies also can arise within a radiation field.

Chemotherapy Alkylating agents and anthracyclines administered for unrelated cancers have been implicated as etiologic factors in the development of second malignant neoplasms, particularly osteosarcoma.

Preexisting benign tumors/conditions Osteosarcomas can arise in association with Paget's disease and rarely in association with benign bone tumors (ie, fibrous dysplasia). Chondrosarcomas can develop in the cartilaginous component of osteochondromas (solitary and multiple hereditary exostosis) and in patients with enchondromatosis (Ollier's disease and Maffucci's syndrome). MFH can arise in association with bone infarcts.

Trauma A traumatic event often prompts medical intervention, at which time the bone sarcoma is detected. The short temporal relationship between the traumatic event and the diagnosis of the tumor usually rules out a causal relationship.

Orthopedic implants Case reports of bone sarcomas arising in the region in which a metallic prosthetic device has been implanted have been published. The rarity of these clinical situations relative to the vast number of devices implanted makes a causal relationship unlikely.

Signs and symptoms

Local symptoms Localized pain and swelling are the hallmark clinical features of bone sarcomas. The pain, which initially is insidious and transient, becomes progressively more severe and unremitting. Localized soft-tissue swelling, with or without associated warmth and erythema, may be present. A joint effusion may be observed, and range of motion of the adjacent joint may be limited and painful. Movement or weight-bearing of the involved extremity may exacerbate local symptoms.

Patients with tumors arising in the lower extremities can present with a painful limp. The neurovascular examination of the affected extremity is usually normal. Regional lymph nodes are rarely involved.

Pathologic fracture may also be a presenting sign, although a history of pain prior to fracture usually can be elicited.

Constitutional symptoms are rare in patients with bone sarcoma, but such symptoms as fever, malaise, and weight loss can be observed in those with Ewing's sarcoma.

Screening and diagnosis

Currently, there is no screening test for primary bone sarcomas. The diagnosis must be made by clinical and radiographic evaluation and confirmed by histopathologic analysis of biopsy-obtained tissue.

Physical examination should include an assessment of the local extent of the soft-tissue mass, if present, and its relationship to the adjacent joint.

Laboratory studies A CBC may demonstrate anemia and/or a leukocytosis associated with Ewing's sarcoma, but, in general, these studies fall within the normal range. Alkaline phosphatase and lactate dehydrogenase levels may be elevated in patients with osteosarcoma or Ewing's sarcoma. An abnormal glucose tolerance test may be observed in patients with chondrosarcomas.

X-rays Biplanar (AP and lateral) plain radiographs of the affected extremity provide critical information on the nature of the bone lesion. The specific site of involvement within the bone, pattern and extent of bone destruction, type of periosteal changes, presence of matrix mineralization within the tumor, and presence of soft-tissue extension may be gleaned from plain films.

CT Standard CT scans provide further delineation of many of these changes.

MRI is the imaging study of choice for the evaluation of the extent of an associated soft-tissue mass and the relationship of the tumor to the neurovascular structures, surrounding soft tissues, and the adjacent joint. The intramedullary extent of the tumor and presence of skip metastases within the bone are best demonstrated by MRI.

TABLE 1: Surgical staging of bone sarcomas

Stage	Grade	Site
IA	Low	Intracompartmental
IB	Low	Extracompartmental
IIA	High	Intracompartmental
IIB	High	Extracompartmental
III	Any regional or distant metastasis	Any

From Enneking WF, Spanier SS, Goodman MA: A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop 153:106–120, 1980.

Bone scan A bone scan is performed to screen for distant osseous metastases.

Chest radiographic studies A plain film of the chest is required in any patient suspected of having a bone sarcoma. Once the diagnosis of malignancy has been established, a CT scan of the chest is a critical part of initial staging.

Biopsy With few exceptions, a biopsy must be obtained to confirm the diagnosis. Tissue may be obtained by percutaneous (closed) or surgical (open) techniques. The biopsy should be performed by personnel expert in percutaneous biopsy techniques who are familiar with bone tumors and their treatment.

Biopsies performed at referring institutions have been reported to be associated with a higher incidence of misdiagnosis and complications, which may affect patient outcome. Optimally, the biopsy should be performed at the institution where definitive treatment will be given.

Pathology

Histologic subtypes Current histopathologic classification of bone neoplasms is based on the putative cell of origin. Malignant tumors may arise from any cellular constituent present in bone, including osteogenic (osteosarcoma), chondrogenic (chondrosarcoma), hematopoietic (multiple myeloma, lymphoma), vascular (angiosarcoma, hemangioendothelioma, leiomyosarcoma), lipogenic (liposarcoma), neurogenic (neurofibrosarcoma, chordoma), and histiocytic and fibrohistiocytic (MFH, Ewing's sarcoma) elements. Histologic subtyping is based on the predominant cellular pattern present within the tumor, degree of anaplasia, and relationship of the tumor to the bone (intramedullary vs surface).

A monoclonal antibody (CD99) has been developed that recognizes a cell-surface glycoprotein (p30/32MIC2) in human Ewing's sarcoma and peripheral neuroectodermal tumor (PNET). There is strong immunoreactivity of CD99 in Ewing's sarcoma and PNET that aids in distinguishing these tumors from other small round-cell tumors of childhood and adolescence. Additional experience with CD99, however, demonstrates that it is not exclusively specific for Ewing's sarcoma and PNET.

Dedifferentiation Primary bone sarcomas can exhibit the phenomenon of "dedifferentiation." These neoplasms demonstrate a dimorphic histologic pattern, which is characterized by the presence of a borderline malignant or low-grade malignant tumor juxtaposed against a high-grade, histologically different sarcoma. Enchondromas, low-grade chondrosarcomas, low-grade variants of osteosarcoma (surface and intramedullary), and chordomas may all develop an area of high-grade spindle-cell tumor, usually MFH.

Metastatic spread Approximately 10%-20% of patients with osteosarcoma and 15%-35% of patients with Ewing's sarcoma have evidence of metastatic disease at initial presentation. In approximately 90% of patients with bone sarcomas, the initial site of distant metastasis is the lungs. Distant osseous sites, bone marrow, and viscera may also be involved as a manifestation of advanced

disease, but involvement of these sites is less common and usually occurs after the development of pulmonary metastases. Regional lymph node involvement is rare.

Staging and prognosis

Staging system The staging system of the Musculoskeletal Tumor Society is used currently (Table 1). This system is based on tumor grade (I = low or II = high), tumor extent (A = intraosseous involvement only or B = extraosseous extension), and presence of distant metastases, regardless of the extent of local disease (III). Patients with localized tumor may have stage IA, IB, IIA, or IIB disease.

Prognostic factors Many studies have demonstrated that tumor response to preoperative chemotherapy, as determined by histologic analysis of the resected specimen, is the most powerful predictor of survival for patients with osteosarcoma. Adverse prognostic indicators, such as an axial primary or elevated lactate dehydrogenase and alkaline phosphatase levels, signal an even worse outcome.

Tumor size (low volume) and anatomic site (peripheral), absence of metastases at initial presentation, and good histologic response to chemotherapy are prognostic variables associated with better outcome in osteosarcomas and Ewing's sarcoma. The translocation t(11;22), which results in the type 1 EWS-FLI1 fusion, is also a significant positive predictor of overall survival in Ewing's sarcoma.

For low-grade malignant tumors, adequacy of surgery is the most significant predictor of outcome.

Treatment

PRIMARY TREATMENT OF BONE SARCOMAS

Surgical excision is the mainstay of treatment for patients with low-grade sarcomas. For high-grade tumors, multimodality therapy is indicated. For most high-grade bone sarcomas, excluding chondrosarcoma, preoperative multiagent chemotherapy (three to four cycles) is followed by surgical extirpation of the primary tumor. Chemotherapy is reinitiated postoperatively after wound healing has occurred (usually 2-3 weeks after surgery).

For patients with Ewing's sarcoma, the optimal therapy for local tumor control is less well defined. Historically, radiotherapy has been a mainstay of local treatment. However, there has been a recent trend toward surgery, with or without radiotherapy, to achieve local tumor control. No prospective, randomized studies have been performed to define the relative role of each of these treatment modalities, but several retrospective studies suggest improvements in local tumor control and patient survival when surgery is satisfactorily performed. Patients with unresectable tumors or microscopic or mac-

roscopic residual disease following tumor excision clearly require adjuvant radiotherapy to consolidate their local treatment.

Surgical treatment strategy

The Musculoskeletal Tumor Society recognizes wide excision, either by amputation or a limb-salvage procedure, as the recommended surgical approach for high-grade sarcomas. A wide excision removes the primary tumor en bloc along with its reactive zone and a cuff of normal tissue in all planes. Conceptually, this strategy is applicable to all high-grade sarcomas. Wide excision successfully controls local disease in ≥ 90% of patients.

The timing of surgery must be coordinated with the patient's chemotherapy schedule and with bone marrow recovery to minimize the period of systemic therapy. Generally, surgical intervention is postponed until the patient's absolute neutrophil count (ANC) has recovered to a level of ≥ 1,500/μL and platelet count, to a level of ≥ 70,000/μL.

Limb-salvage procedures

Wide tumor excision with limb preservation has supplanted amputation as the principal surgical method for eradicating local disease in patients with primary sarcomas of bone, regardless of histology or grade. Local tumor control and patient survival have not been compromised by this more conservative operative strategy. Refinements in surgical techniques and advances in bioengineering have increased the number of patients eligible for limb-salvage surgery. Currently, 75%-80% of patients may be treated with conservative surgery.

Successful limb-salvage surgery of the patient with a high-grade bone sarcoma is predicated on complete extirpation of the tumor, effective skeletal reconstruction, and adequate soft-tissue coverage. Planning for the operative procedure must begin far in advance to permit adequate time to procure the implant for reconstruction.

Types of resections Limb-sparing tumor resections fall into one of three types based on the anatomic site and extent of involved bone to be excised. Resections can involve: (1) tumor-bearing bone and adjacent joint (osteoarticular); (2) tumor-bearing bone only (intercalary); or (3) whole bone and adjacent joints (whole bone).

Since most bone sarcomas arise in the metaphysis of the long bone near the joint, the majority of procedures performed for these tumors involve resection of both the segment of tumor-bearing bone and the adjacent joint (osteoarticular resection). Most of these resections are performed through the adjacent joint (intra-articular). When the tumor extends along the joint capsule or ligamentous structures and/or invades the joint, the entire joint should be resected (extra-articular) to avoid violating areas that have tumor involvement.

Reconstruction Prosthetic arthroplasty is the most common method by which the skeletal defect and adjacent joint are reconstructed. Osteoarticular allografts, intercalary allografts, and vascularized and nonvascularized autografts are also

TABLE 2: Chemotherapy regimens for bone sarcomas

Drug/combination	Dose and schedule
T-12 regimens	
Preresection:	
Methotrexate	8-12 g/m^2 IV on day 1of week 0, 8 of week 1, 29 of week 4, and 36 of week 5
Leucovorin	10-15 mg PO every 6 hours for 10 doses beginning 20 hours after each methotrexate dose and completed when the serum methotrexate level is < 100 nmol/L. Additional leucovorin was administered if elevated serum methotrexate levels were noted or if renal toxicity was present.
BCD regimen	
Bleomycin	15 U/m^2 IV bolus × 2 (on days 15 and 16 of week 2)
Cyclophosphamide	600 mg/m^2/d IV bolus × 2 days (on days 15 and 16 of week 2)
Dactinomycin	600 µg/m^2/d IV bolus × 2 days (on days 15 and 16 of week 2)
Preoperative chemotherapy was completed in 6 weeks and followed by definitive surgery between days 43 of week 6 and 50 of week 7	
Postresection regimen for patients with primary tumor grades 1 and 2 (less necrosis):	
Doxorubicin	25 mg/m^2 IV continuous infusion over 3 days (on days 57, 58, 59 of week 8; 106, 107, 108 of week 15; 155, 156, 157 of week 22; 190, 191, 192 of week 27; and 225, 226, 227 of week 32)
Cisplatin	120 mg/m^2 IV on day 57 of week 8, 106 of week 15, 155 of week 22 , 190 of week 27, and 225 of week 32
Methotrexate	As above on day 78 of week 11, 99 of week 14, 127 of week 18, and 148 of week 21
BCD	Regimen as above on day 85 of week 12, 134 of week 19, 176 of week 25, and 211 of week 30
Postresection regimen for patients with primary tumor grades 3 or 4 (more necrosis):	
Doxorubicin	As above on days 57, 58, 59 of week 8; 106, 107, 108 of week 15; 155, 156, 157 of week 22; and 204, 205, 206 of week 29
Methotrexate	As above on day 78 of week 11, 99 of week 14, 127 of week 18, 148 of week 21, 176 of week 25, 197 of week 28, 225 of week 32, and 246 of week 35
BCD	Regimen as above on days 85 and 86 of week 12, 134 and 135 of week 19, 183 and 184 of week 26, and 232 and 233 of week 33

NOTE: Administering this protocol safely and successfully requires extensive experience and excellent supportive care

Meyers PA, Gorlick R, Heller G, et al: J Clin Oncol 16:2452–2458, 1998.

Table prepared by Ishmael Jaiyesimi, DO

used, depending on the extent of resection and requirements for successful reconstruction.

Tumors in the immature skeleton

Tumors arising in the immature skeleton pose a unique problem for the orthopedic oncologist, particularly in patients with substantial projected growth of the involved extremity. The surgical management of bone sarcomas in very young patients, with few exceptions, has entailed amputation or rotationplasty.

Custom-manufactured expandable metallic joint prostheses can be implanted to allow for skeletal growth in those children deemed candidates for limb-salvage surgery. The long-term outcome of this technique has been promising. However, multiple operative procedures should be anticipated to maintain a functional extremity.

Soft-tissue coverage

Adequate soft-tissue coverage is critical to the success of any limb-salvage procedure. Local transposition muscle flaps and free tissue transfers are extremely useful for providing a healthy, well-vascularized soft-tissue envelope to cover the reconstruction and reduce the risk of deep infection.

SURGICAL TREATMENT OF METASTATIC DISEASE

The most common site of metastatic involvement for bone sarcoma is the lungs. Patients who present with pulmonary metastases (10%-20% of patients with osteosarcoma) have a poor prognosis (5-year survival rate, < 15%). Approximately 30%-40% of patients who present with localized disease and who subsequently develop resectable pulmonary metastases can undergo salvage treatment with reinduction chemotherapy and metastasectomy (see "Treatment of advanced osteosarcoma"). Patients with extrapulmonary metastases or unresectable pulmonary metastases have a uniformly poor prognosis. The objective of any surgical intervention in these patients, therefore, would be palliative.

CHEMOTHERAPY FOR OSTEOSARCOMA

The probability of 5-year disease-free survival for patients with osteosarcoma of the extremities treated with either amputation or limb-salvage surgery alone is < 20%. Although the incidence of local recurrence is low, microscopic dissemination is likely to be present in 80% of patients at the time of diagnosis, leading to distant metastases, mostly in the lungs and bones, within the first 6-12 months. The incorporation of chemotherapy as part of the standard therapeutic plan for osteosarcoma (Table 2) has improved both relapse-free and overall survival.

Neoadjuvant/adjuvant chemotherapy

In order to achieve better systemic control and decrease the degree of functional defect following surgery, neoadjuvant (presurgical) treatment programs

have been developed by several centers. Early trials incorporated high doses of methotrexate, given weekly for 4 weeks with leucovorin rescue, prior to surgery. Subsequent modifications included the incorporation of bleomycin (Blenoxane), dactinomycin, and cyclophosphamide (Cytoxan, Neosar) into the regimen, with the further addition of doxorubicin.

The next generation of trials adjusted the adjuvant (postoperative) chemotherapeutic regimen, depending on the degree of tumor necrosis found at the time of surgery. Patients who had a good tumor response (> 90% necrosis) were treated with additional cycles of the neoadjuvant regimen; those who had a poor response received cisplatin (Platinol) and doxorubicin. It remains controversial whether altering the adjuvant chemotherapeutic regimen for patients with poor histologic response truly changes their event-free survival.

The addition of ifosfamide (Ifex) did not improve survival in pediatric osteosarcoma patients in a recent study. A Children's Oncology Group (COG) study reported no difference in outcome between a three-drug combination of cisplatin, doxorubicin, and high-dose methotrexate and a four-drug regimen of the same drugs and ifosfamide. Additionally, the European Osteosarcoma Intergroup reported no difference in histopathological response to preoperative chemotherapy and overall survival in patients randomized to receive a two-drug regimen with doxorubicin and cisplatin or a complex multidrug protocol containing doxorubicin, cisplatin, and high-dose methotrexate among other agents.

The actuarial 5-year event-free survival rate in patients presenting with localized, primarily extremity osteosarcoma is > 70%. Regardless of the multidrug therapy used, event-free survival correlates with histologic response. Patients with > 90% tumor necrosis have a > 80% probability of 5-year event-free survival. Complete responses are more likely to occur in patients with the nonchondroblastic subtype and in those whose peak serum methotrexate levels are > 700 µmol/L. Chemosensitivity also seems to be diminished in patients with metastatic disease at presentation.

Poor responders Patients with poor tumor response may represent 30%-60% of the population with extremity osteosarcoma. For these patients, more effective treatment regimens, such as dose intensification using growth factors and stem-cell support, and newer agents need to be evaluated.

Alternative approaches One alternative approach to neoadjuvant therapy is adjuvant therapy. A randomized study of the Pediatric Oncology Group (POG) demonstrated no detectable difference in event-free survival whether chemotherapy was offered before or after surgery. Additionally, intra-arterial delivery of cytotoxic agents has shown no specific benefit.

TREATMENT OF ADVANCED OSTEOSARCOMA

Axial primary tumor For the 10%-15% of patients who present with axial primary osteosarcoma, neoadjuvant chemotherapy should be considered in order to reduce the tumor burden prior to surgery or radiation therapy. With

the use of aggressive neoadjuvant and adjuvant chemotherapy, relapse is usually delayed beyond 2 years. The most frequent site of metastasis is the thorax.

Pulmonary metastasis Patients with metastatic disease to the lungs should be evaluated for resection. Following aggressive pulmonary metastasectomy, < 25% of patients will achieve prolonged relapse-free survival. Hence, these patients may also benefit from aggressive "secondary" adjuvant chemotherapy.

Chemotherapy should also be considered for patients whose pulmonary metastases are unresectable, with the intention of performing surgery in those who have a sufficient response; approximately 10% of such patients may become long-term survivors.

Extraosseous osteosarcoma is a rare, primary soft-tissue form of osteosarcoma. Radiographic and pathologic good response rates to doxorubicin-based multiagent osteosarcoma regimens are low. Extraosseous osteosarcoma should be considered clinically and therapeutically distinct from osseous osteosarcoma.

A retrospective study of patients treated on a single Memorial Sloan-Kettering Cancer Center multiagent chemotherapy trial demonstrated correlation of expression of the human epidermal growth factor receptor 2, (HER2)/*erb*B-2, with histologic response to preoperative chemotherapy and event-free survival. This finding has prompted the clinical evaluation of the recombinant humanized anti-HER2 monoclonal antibody in patients with metastatic osteosarcoma *(Gorlick R, Huvos AG, Heller G, et al: J Clin Oncol 17:2781-2788, 1999).*

Poor-risk patients or patients with recurrent disease are candidates for clinical trials that evaluate chemotherapy dose intensification or newer therapeutic agents. Alternatively, the POG demonstrated stabilization of disease in patients with recurrent or refractory osteosarcoma employing the combination of cyclophosphamide and topotecan (Hycamtin), although objective responses were rare. Interestingly, investigators at the Mayo Clinic reported significant palliation of pain in osteosarcoma patients with symptomatic bone metastases who were treated with samarium-153 ethylene diamine tetramethylene phosphonate (^{153}Sm-EDTMP), a bone-seeking radiopharmaceutical, in conjunction with stem-cell rescue. Nonhematologic side effects were minimal.

CHEMOTHERAPY FOR EWING'S SARCOMA

Prior to the availability of effective chemotherapeutic agents, < 10% of patients with Ewing's sarcoma survived beyond 5 years. The first Intergroup-Ewing's Sarcoma Study demonstrated an improved survival rate for patients receiving systemic therapy with the VACA regimen (vincristine, Actinomycin D [dactinomycin], cyclophosphamide, and Adriamycin [doxorubicin]) for the first three drugs only and for patients receiving VAC plus bilateral pulmonary irradiation. In the future, selection of a specific therapeutic regimen may be influenced by the presence of molecular markers in addition to standard clinical criteria.

In the second intergroup study, the addition of doxorubicin to VAC, when given on an intermittent schedule and at a higher dose, improved the 5-year

relapse-free survival rate to 73%; this rate was almost double that of the cohort of patients not receiving doxorubicin as part of their treatment. The worst results were observed in patients with pelvic, proximal extremity, and lumbar vertebral lesions.

The addition of ifosfamide and etoposide further improved relapse-free survival in patients with Ewing's sarcoma and PNET of the bone. In addition to biological adverse features at presentation (male sex, age, high lactate dehydrogenase levels, anemia, fever, axial locations, non-type 1 fusion transcripts, and lack of feasibility of surgical resection), independent prognostic factors also include the type of chemotherapy and degree of tumor necrosis.

CHEMOTHERAPY FOR ADVANCED EWING'S SARCOMA

Aggressive combination chemotherapy and irradiation can lead to prolonged progression-free survival, even in patients with metastatic disease. The combination of ifosfamide (1.6 g/m^2) and etoposide (100 mg/m^2 given on days 1-5) results in high response rates of $>$ 80%. Unfortunately, late recurrences are not uncommon.

Dose intensification of active chemotherapeutic compounds, including those employing autologous stem-cell rescue, has not been definitively shown to significantly improve survival of patients with poor-risk and metastatic Ewing's sarcoma and PNET. Newer therapeutic agents should be tested.

In patients with recurrent or refractory Ewing's sarcoma, the combination of cyclophosphamide and topotecan was shown to possess significant antitumor activity by the POG.

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CHAPTER 26

Soft-tissue sarcomas

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The soft-tissue sarcomas are a group of rare but anatomically and histologically diverse neoplasms. This is due to the ubiquitous location of the soft tissues and the nearly three dozen recognized histologic subtypes of soft-tissue sarcomas. In the United States, 8,300 new cases of soft-tissue sarcoma are identified annually, and 3,900 patients die of the disease each year. The age-adjusted incidence is 2 cases per 100,000 persons.

Epidemiology

Unlike the more common malignancies, such as colon cancer, little is known about the epidemiology of soft-tissue sarcomas. This, again, reflects the uncommon nature of these lesions.

Gender There is a slight male predominance, with a male-to-female ratio of 1.1:1.0.

Age The age distribution in adult soft-tissue sarcoma studies is $<$ 40 years, 20.7% of patients; 40-60 years, 27.6% of patients; $>$ 60 years, 51.7% of patients.

Race Studies in large cohorts of patients demonstrate that the race distribution of soft-tissue sarcomas mirrors that of the American population (86% Caucasian, 10% African-American, 1% Asian-American, 3% other).

Geography Studies have suggested that the incidence and mortality of soft-tissue sarcomas may be increasing in New Zealand. There are no currently available data addressing this possibility in the United States.

Etiology and risk factors

In the majority of cases of soft-tissue sarcoma, no specific etiologic agent is identifiable. However, a number of predisposing factors have been recognized.

Radiation therapy Soft-tissue sarcomas have been reported to originate in radiation fields following therapeutic irradiation for a variety of solid tumors. Frequently, they are seen in the lower-dose regions at the edge of the radiation target volume. By definition, radiation-induced sarcomas arise no sooner than 3 years after radiation therapy and often develop decades later. The majority of these sarcomas are high-grade lesions (90%), and osteosarcoma is a pre-

dominant histology. Malignant fibrous histiocytoma (MFH), angiosarcoma, and other histologic subtypes have also been reported.

Chemical exposure Exposure to various chemicals in specific occupations or situations has been linked with the development of soft-tissue sarcoma. These chemicals include the phenoxy acetic acids (forestry and agriculture workers), chlorophenols (sawmill workers), Thorotrast (diagnostic x-ray technicians), vinyl chloride (individuals working with this gas, used in making plastics and as a refrigerant), and arsenic (vineyard workers).

Chemotherapy Soft-tissue sarcomas have been reported after previous exposure to alkylating chemotherapeutic agents, most commonly after treatment of pediatric acute lymphocytic leukemia. The drugs implicated include cyclophosphamide (Cytoxan, Neosar), melphalan (Alkeran), procarbazine (Matulane), nitrosoureas, and chlorambucil (Leukeran). The relative risk of sarcoma appears to increase with cumulative drug exposure.

Chronic lymphedema Soft-tissue sarcomas have been noted to arise in the chronically lymphedematous arms of women treated with radical mastectomy for breast cancer (Stewart-Treves syndrome). Lower-extremity lymphangiosarcomas have also been observed in patients with congenital lymphedema or filariasis complicated by chronic lymphedema.

Trauma and foreign bodies Although a recent history of trauma is often elicited from patients presenting with soft-tissue sarcoma, the interval between the traumatic event and diagnosis is often short; thus, a causal relationship is unlikely. Chronic inflammatory processes, however, may be a risk factor for sarcoma. Foreign bodies, such as shrapnel, bullets, and implants, have also been implicated.

Signs and symptoms

Signs and symptoms of soft-tissue sarcoma depend, in large part, on the anatomic site of origin. Due to the ubiquitous location of the soft tissues, these malignancies may arise at any site in the body where soft tissues are located. Since 50% of soft-tissue sarcomas arise in an extremity, the majority of patients present with a palpable soft-tissue mass. Pain at presentation is noted in only one-third of cases.

Extremity and superficial trunk Extremity and superficial trunk sarcomas account for 60% of all soft-tissue sarcomas. The majority of patients present with a painless primary soft-tissue mass.

Retroperitoneum Retroperitoneal sarcomas account for 15% of all soft-tissue sarcomas. Most patients (80%) present with an abdominal mass, with 50% reporting pain at presentation. Due to the considerable size of the retroperitoneum and the relative mobility of the anterior intra-abdominal organs, these tumors often grow to substantial size before the patient's nonspecific complaints are evaluated or an abdominal mass is noted on physical examination.

Viscera Visceral soft-tissue sarcomas, which comprise 15% of all soft-tissue sarcomas, present with signs and symptoms unique to their viscus of origin. For example, GI leiomyosarcomas present with GI symptoms that are usually indistinguishable from the more common adenocarcinomas. Similarly, uterine leiomyosarcomas frequently present with painless vaginal bleeding such as that often noted in patients with more common uterine malignancies.

Head and neck Head and neck sarcomas comprise 10% of all soft-tissue sarcomas. Although generally smaller than sarcomas in other sites, they may present with important mechanical problems related to compression or invasion of adjacent anatomy (eg, orbital contents, airway, or pharynx). In addition, their proximity to critical anatomy can pose management difficulties due to compromise in the delivery of both surgery and radiotherapy.

Pathology

Histopathologic classification As a consequence of the wide spectrum of soft tissues, a variety of histologically distinct neoplasms have been characterized. The current histopathologic classification is based on the putative cell of origin of each lesion. Such classification based on histogenesis is reproducible for the more differentiated tumors. However, as the degree of histologic differentiation declines, it becomes increasingly difficult to determine cellular origin.

In addition, many of these tumors dedifferentiate. This results in a variety of overlapping patterns, making uniform classification difficult. Experienced soft-tissue pathologists frequently disagree on the cell of origin of an individual tumor. Comparative studies have demonstrated concordance in histopathologic diagnosis in only two-thirds of cases. MFH used to be the most common histologic subtype of soft-tissue sarcoma. However, in one study, reanalysis histologically, immunohistochemically, and ultrastructurally allowed reclassification in 84% of tumors to a specific line of differentiation.

Assignment of a specific histologic subtype is of secondary importance. This is because, with the possible exceptions of certain small-cell sarcomas, rhabdomyosarcoma, fibrosarcoma, and some forms of angiosarcoma, histogenesis is not directly related to biological behavior. The propensity for distant metastases and disease-related mortality are best predicted on the basis of histologic grade and tumor size.

Staging and prognosis

AJCC/UICC staging system

The relative rarity of soft-tissue sarcomas, the anatomic heterogeneity of these lesions, and the presence of more than 30 recognized histologic subtypes of variable grade have made it difficult to establish a functional system that can accurately stage all forms of this disease. The recently revised staging system (6th edition) of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is the most widely employed stag-

TABLE 1: AJCC/UICC staging system for soft-tissue sarcomas

Primary tumor (T)		
Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1		Tumor ≤ 5 cm in greatest dimension
	T1a	Superficial tumor[a]
	T1b	Deep tumor[a]
T2		Tumor > 5 cm in greatest dimension
	T2a	Superficial tumor[a]
	T2b	Deep tumor[a]
Regional lymph nodes (N)		
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
Grade (G)		
Gx		Grade cannot be assessed
G1		Well differentiated
G2		Moderately differentiated
G3		Poorly differentiated
G4		Poorly differentiated or undifferentiated (four-tiered systems only)

Stage grouping						
Stage I	T1a-T2b	N0	M0	G1,2	G1	Low
Stage II	T1a-T2a	N0	M0	G3,4	G2,3	High
Stage III	T2b	N0	M0	G3,4	G2,3	High
Stage IV	Any T	N1	M0	Any G	Any G	High or low
	Any T	N0	M1	Any G	Any G	High or low

[a] Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia or superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors.

AJCC = American Joint Committee on Cancer; UICC = International Union Against Cancer

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

ing classification for soft-tissue sarcomas (Table 1). All soft-tissue sarcoma subtypes are included, except dermatofibrosarcoma protuberans. Four distinct histologic grades are recognized, ranging from well differentiated to undifferentiated.

Histologic grade and tumor size are the primary determinants of clinical stage. Tumor size is further substaged as "a" (a superficial tumor that arises outside the investing fascia) or "b" (a deep tumor that arises beneath the fascia or invades the fascia).

The AJCC/UICC system is designed to optimally stage extremity tumors but is also applicable to torso, head and neck, and retroperitoneal lesions. It should not be used for sarcomas of the GI tract.

A major limitation of the current staging system is that it does not take into account the anatomic site of soft-tissue sarcomas. Anatomic site, however, is an

important determinant of outcome. Patients with retroperitoneal, head and neck, and visceral sarcomas have a worse overall prognosis than do patients with extremity tumors. Although site is not incorporated as a specific component of any current staging system, outcome data should be reported on a site-specific basis.

Prognostic factors

Understanding relevant clinicopathologic prognostic factors is important in treatment planning for patients with soft-tissue sarcoma. Several reports document the adverse prognostic significance of tumor grade, anatomic site, tumor size, and depth relative to the investing fascia (for extremity and body wall tumors). Patients with high-grade lesions, large (T2) sarcomas, nonextremity subsite, or deep tumor location are at increased risk for disease relapse and sarcoma-specific death.

Sarcoma-specific nomogram Kattan and colleagues from Memorial Sloan-Kettering Cancer Center have developed a sarcoma-specific nomogram for estimation of sarcoma-specific 12-year survival. The nomogram takes into account pretreatment clinicopathologic factors, including anatomic site, histologic subtype, tumor size, histologic grade, tumor depth, and patient age. The nomogram is based on prospectively collected data and has been validated in a population of 2,136 sarcoma patients. The nomogram can be found on www.nomograms.org and is available in a handheld personal digital assistant version. The sarcoma nomogram may be useful for patient stratification for clinical trials and for risk assessment and treatment planning for individual patients.

Prognostic factors for local vs distant recurrence Unlike other solid tumors, the adverse prognostic factors for local recurrence of a soft-tissue sarcoma differ from those that predict distant metastasis and tumor-related mortality. In other words, patients with a constellation of adverse prognostic factors for local recurrence are not necessarily at increased risk for distant metastasis or tumor-related death. This concept has been recently validated by an analysis of the Scandinavian Sarcoma Group prospective database. In 559 patients with soft-tissue sarcomas of the extremities and trunk treated with surgery alone, inadequate surgical margin was found to be a risk factor for local recurrence but not for distant metastasis.Therefore, staging systems that are designed to stratify patients for risk of distant metastasis and tumor-related mortality using these prognostic factors (such as the AJCC/UICC system) do not stratify patients for risk of local recurrence.

Screening and diagnosis

Currently, there are no screening tests for soft-tissue sarcomas. Since the majority of patients with soft-tissue sarcoma have lesions arising in the extremities or superficial trunk, most of the comments here apply to soft-tissue lesions in those sites. A separate algorithm is usually employed for the evaluation of a primary retroperitoneal mass or visceral sarcoma.

Physical examination should include an assessment of the size of the mass and its mobility relative to the underlying soft tissues. The relationship of the mass to the investing fascia of the extremity (superficial vs deep) and nearby neurovascular and bony structures should be noted. Site-specific neurovascular examination and assessment of regional lymph nodes should also be performed.

Biopsy Any soft-tissue mass in an adult should be biopsied if it is symptomatic or enlarging, is >5 cm, or has persisted beyond 4-6 weeks.

Percutaneous approaches Percutaneous tissue diagnosis can usually be obtained with fine-needle aspiration (FNA) for cytology or by percutaneous core biopsy for histology. The needle track should be placed in an area to be excised. In most instances, when an experienced cytopathologist and/or histopathologist examines the specimen, a diagnosis of malignant soft-tissue sarcoma can be made. Histology is usually preferred to cytology, as more tissue is obtained for accurate delineation of tumor type and grade. Percutaneous tissue diagnosis is preferred to facilitate subsequent treatment planning and to permit surgical resection to be performed as a one-stage procedure.

Open biopsy In some cases, an adequate histologic diagnosis cannot be secured by percutaneous means. Open biopsy is indicated in these instances, with the exception of relatively small superficial masses, which can be easily removed by excisional biopsy with clear margins.

Biopsies should be incisional and performed with a *longitudinal* incision parallel to the long axis of the extremity. This facilitates subsequent wide local excision of the tumor and the incisional scar with minimal difficulties in wound closure. It also facilitates inclusion of any scars within the area of the tumor in adjuvant radiation fields without the excessive morbidity of large-field radiotherapy planning. The incision should be centered over the mass at its most superficial location. Care should be taken not to raise tissue flaps. Meticulous hemostasis should be ensured after the biopsy to prevent dissemination of tumor cells into adjacent tissue planes by hematoma.

Retroperitoneal mass Biopsy of primary retroperitoneal soft-tissue masses is generally not required for radiographically resectable masses. The circumstances under which percutaneous or preoperative biopsy of retroperitoneal masses should be strongly considered include:

- tissue diagnosis for radiographically unresectable disease
- clinical suspicion of lymphoma or germ-cell tumor
- tissue diagnosis for neoadjuvant treatment
- suspected metastases from another primary tumor

Primary tumor imaging Optimal imaging of the primary tumor depends on the anatomic site. For soft-tissue masses of the extremities, MRI has been regarded as the imaging modality of choice because it enhances the contrast between tumor and muscle and between tumor and adjacent blood vessels and also provides multiplanar definition of the lesion. However, a recent study by the Radiation Diagnostic Oncology Group that compared MRI and CT

in 183 patients with malignant bone and 133 patients with soft-tissue tumors showed no specific advantage of MRI over CT from the diagnostic standpoint.

For pelvic lesions, the multiplanar capability of MRI may provide superior single-modality imaging. In the retroperitoneum and abdomen, CT usually provides satisfactory anatomic definition of the lesion. Occasionally, MRI with gradient sequence imaging can better delineate the relationship of the tumor to midline vascular structures, particularly the inferior vena cava and aorta. In the future, MRI-CT fusion techniques may facilitate treatment planning using conformal radiotherapy techniques.

More invasive studies, such as angiography and cavography, are almost never required for the evaluation of soft-tissue sarcomas.

Imaging for metastatic disease Cost-effective imaging to exclude the possibility of distant metastatic disease depends on the size, grade, and anatomic location of the primary tumor. In general, patients with low-grade or intermediate-/high-grade tumors < 5 cm in diameter require only a chest x-ray for satisfactory staging of the chest. This reflects the fact that these patients are at comparatively low risk of presenting with pulmonary metastases. In contrast, patients with high-grade tumors ≥ 5 cm should undergo more thorough staging of the chest by CT.

Patients with retroperitoneal and intra-abdominal visceral sarcomas should undergo single-modality imaging of the liver to exclude the possibility of synchronous hepatic metastases. The liver is a more common site for a first metastasis from these lesions.

Treatment

TREATMENT OF LOCALIZED DISEASE

Surgical resection is the cornerstone of therapy for patients with localized disease. Over the past 20 years, there has been a gradual shift in the surgical management of extremity soft-tissue sarcoma away from radical ablative surgery, such as amputation or compartment resection, and toward limb-sparing approaches combining wide local resection with preoperative or postoperative radiotherapy. The development of advanced surgical techniques (eg, microvascular tissue transfer, bone and joint replacement, and vascular reconstruction) and the application of multimodality approaches have allowed most patients to retain a functional extremity without any compromise in survival.

Surgery

The surgical approach to soft-tissue sarcomas depends on careful preoperative staging with MRI or CT for extremity lesions and a percutaneous histologic diagnosis and assessment of grade. In most instances, preoperative imaging studies allow for accurate prediction of resectability.

The surgical approach to soft-tissue sarcomas is based on an awareness that these lesions tend to expand and compress tissue planes, producing a pseudocapsule comprising normal host tissue interlaced with tumor fimbriae. Conser-

The Princess Margaret Hospital Sarcoma Group has reported a retrospective analysis and classification of positive resection margins for patients with extremity sarcoma. Patients were categorized into four groups: patients with low-grade liposarcoma, patients with planned positive margins prior to surgery (planned to preserve critical structures), patients who had undergone unplanned excision prior to referral with a positive margin on subsequent reexcision, and patients with unplanned positive margins occurring during primary tumor resection. Eighty-seven patients with positive microscopic surgical margins following limb-sparing surgery and adjuvant irradiation were grouped according to this grading classification system. The rates of local recurrence differed significantly among these subsets of margin-positive patients, with those in the first two low-risk groups having low-local recurrence rates of < 5% and those in the second two higher risk groups having significantly higher local recurrence rates in excess of 30% *(Gerrand CH, Wunder JS, Kandel RA, et al: J Bone Joint Surg Br 83:1149-1155, 2001).*

vative surgical approaches in which the plane of dissection is immediately adjacent to this pseudocapsule, such as intracapsular or marginal excision, are associated with prohibitive local recurrence rates of 33%-63%.

Wide local resection encompassing a rim of normal tissue around the lesion has led to improvements in local control, with local recurrence rates of approximately 30% in the absence of adjuvant therapies. However, studies indicate that carefully selected patients with localized, small (T1), low-grade soft-tissue sarcomas of the extremity can be treated by wide resection alone, with local recurrence rates of < 10%. For example, in a cohort of 56 patients with primarily subcutaneous or intramuscular lesions treated with wide local excision without adjuvant irradiation, 4 local recurrences were noted.

Further studies will be required to define which subsets of patients with primary extremity sarcoma can be treated by wide excision surgery alone. Preoperative or postoperative radiotherapy should be employed for patients with primary T1 sarcomas in whom a satisfactory gross surgical margin cannot be attained without compromise of functionally important neurovascular structures.

Limb-sparing surgery plus irradiation Limb-sparing surgery employing adjuvant irradiation to facilitate maximal local control has become the standard approach for large (T2) extremity soft-tissue sarcomas. In most centers, upwards of 90% of patients are treated with limb-sparing approaches. Amputation is reserved as a last resort option for local control and is used with the knowledge that it does not affect survival. This approach was validated in a prospective National Cancer Institute (NCI) study, in which patients with a limb-sparing surgical option were randomized to receive limb-sparing surgery with postoperative radiation therapy or amputation. Both arms included postoperative therapy with doxorubicin, cyclophosphamide, and methotrexate.

Surgical procedure The planned resection should encompass the skin, subcutaneous tissues, and soft tissues adjacent to the tumor, including the previous biopsy site and any associated drain sites. The tumor should be excised with a 2- to 3-cm margin of normal surrounding tissue whenever possible. Since good adjuvant approaches are available to facilitate local control, this ideal margin is sometimes compromised rather than attempting resection of adjacent, possibly involved bone or neurovascular structures that would result in significant func-

tional loss. In the rare circumstance of gross involvement of neurovascular structures or bone, they can be resected en bloc and reconstructed.

Metal clips should be placed at the margins of resection in order to facilitate radiation field planning, when and if external irradiation is indicated. Drain sites should be positioned close to the wound to allow inclusion in radiation therapy fields. As noted earlier, avoidance of transverse incisions greatly facilitates the ability to include the tissues at risk in radiation target volume without unduly large fields.

Regional lymphadenectomy Given the low, 2%-3%, prevalence of lymph node metastasis in adult sarcomas, there is no role for routine regional lymphadenectomy. Patients with angiosarcoma, embryonal rhabdomyosarcoma, synovial sarcoma, and epithelioid histologies have an increased incidence of lymph node metastasis and should be carefully examined and radiographically imaged for lymphadenopathy. Clinically apparent lymphadenopathy should be treated with therapeutic lymphadenectomy.

Isolated limb perfusion

Recent studies have evaluated the role of isolated limb perfusion (ILP) in the management of extremity sarcoma. These studies have generally been extrapolations from protocols initially designed to treat locally advanced melanoma.

The agents most commonly employed for ILP have been melphalan and tumor necrosis factor-alpha (TNF-α), with or without interferon-gamma (IFN-γ [Actimmune]). The results of the largest series of ILP in patients with locally advanced extremity soft-tissue sarcoma were reported by Eggermont and colleagues. TNF has now been approved in Europe for ILP in patients with locally advanced, grade 2/3 soft-tissue sarcomas of the extremities.

The National Cancer Institute of Canada Clinical Trials Group recently published 3-year median follow-up results of a randomized phase III trial comparing preoperative with postoperative radiotherapy for limb soft-tissue sarcoma. Wound complications were observed in 31 of 88 patients (35%) in the preoperative group and 16 of 94 patients (17%) in the postoperative group (difference, 18% [95% CI 5-30]; *P* = .01). Tumor size and anatomical site were also significant risk factors in multivariate analysis. Local control was identical in both arms of the trial, although overall survival was slightly better in the preoperative arm than in the postoperative arm (*P* = .0481). In addition, preoperative radiotherapy is associated with significantly lower rates of fibrosis and edema in long-term follow-up (O'Sullivan B, Davis A: Int J Radiat Oncol Biol Phys 51[suppl 1]:151-152, 2001). Because preoperative radiotherapy is associated with a greater risk of wound complications than postoperative radiotherapy, but less late fibrosis and edema, the choice of regimen for patients with soft-tissue sarcoma should take into account the timing of surgery and radiotherapy and the size and anatomical site of the tumor *(O'Sullivan B, Davis AM, Turcotte R, et al: Lancet 359:2235-2241, 2002).*

ROLE OF RADIATION THERAPY

Primary radiation therapy

Several studies on radiation therapy alone in the treatment of unresectable or medically inoperable soft-tissue sarcomas have reported 5-year survival rates of 25%-40% and local control rates of 30%. Local control depends largely on the size of the primary tumor. Radiation doses should be at least 65-70 Gy, if

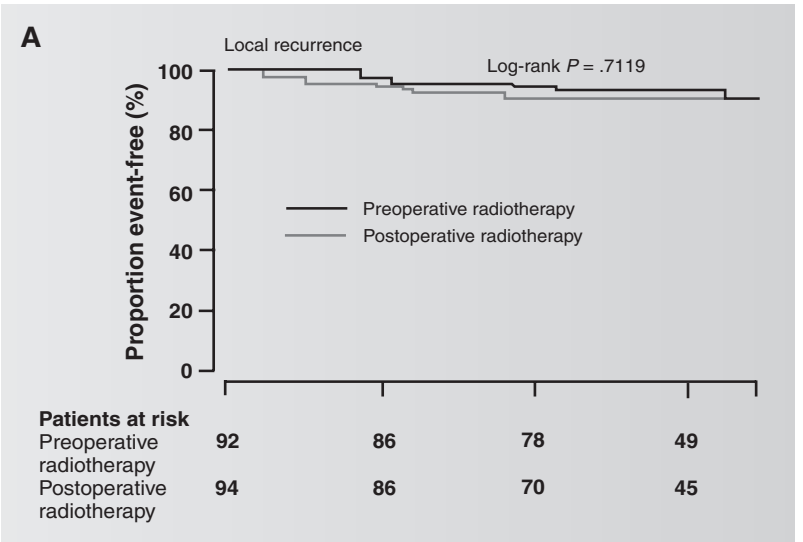

FIGURE 1A: Kaplan-Meier plots for probability of local recurrence in the National Cancer Institute of Canada Clinical Trials group phase III trial.

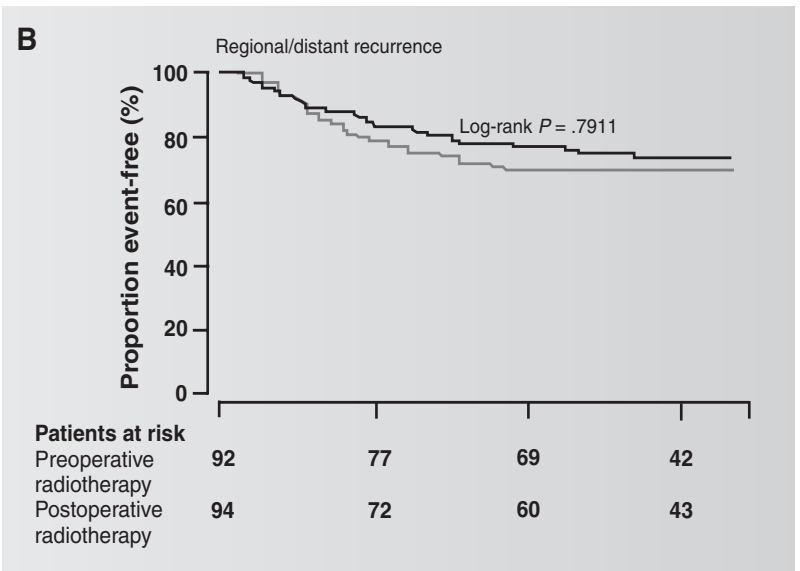

FIGURE 1B: Kaplan-Meier plots for probability of metastatic (regional and distant) recurrence in the National Cancer Institute of Canada Clinical Trials group phase III trial.

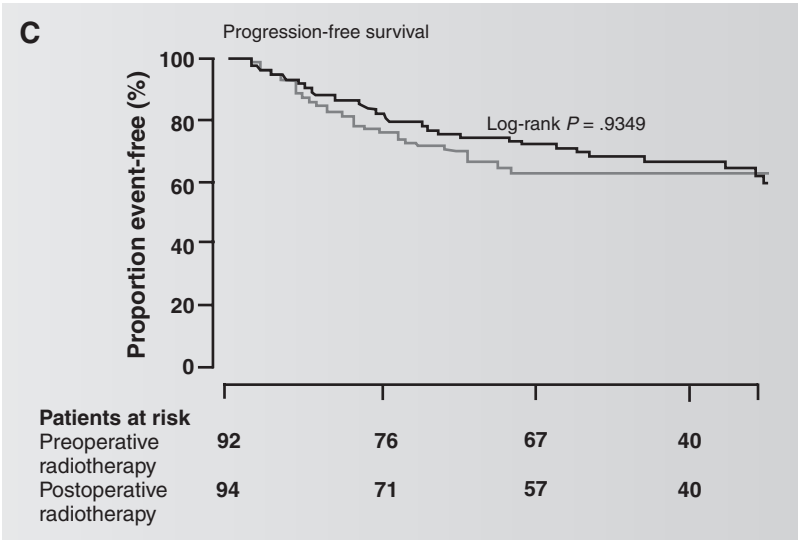

FIGURE 1C: Kaplan-Meier plots for probability of progression-free survival in the National Cancer Institute of Canada Clinical Trials group phase III trial.

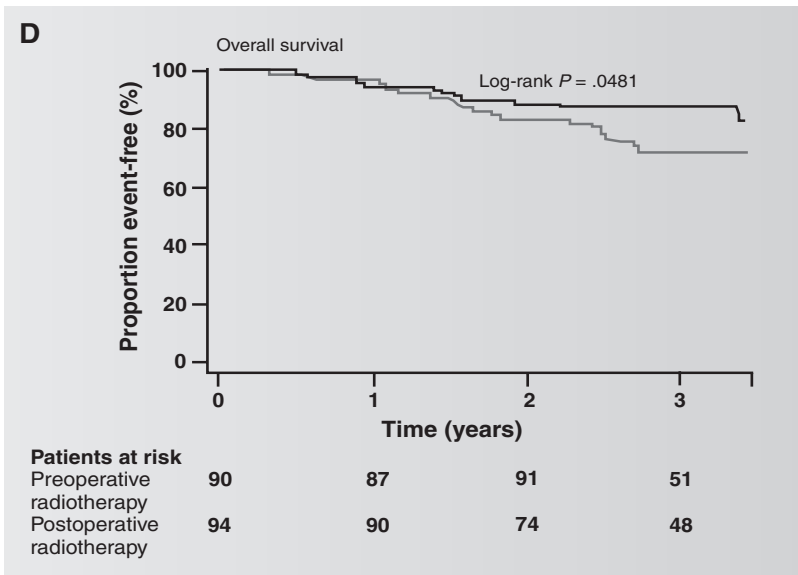

FIGURE 1D: Kaplan-Meier plots for probability of overall survival in the National Cancer Institute of Canada Clinical Trials group phase III trial.

From: O'Sullivan R, Davis AM, Turcotte R, et al: Lancet 359:2235-2241, 2002.

delivery of such doses is feasible. The tumor's location may be particularly important in determining this dose because of the potential for damage to critical structures (eg, the spinal cord) by the higher doses normally used.

Preoperative or postoperative radiation therapy

Radiation therapy is usually combined with surgical resection in the management of extremity soft-tissue sarcomas. The decision of whether to use preoperative (neoadjuvant) or postoperative (adjuvant) irradiation remains controversial and has been addressed in a phase III randomized trial.

Preoperative irradiation has a number of theoretical and practical advantages: (1) Smaller radiation portals can be utilized, as the scar, hematomas, and ecchymoses do not need to be covered. (2) Preoperative irradiation may produce tumor encapsulation, facilitating surgical resection from vital structures. (3) It is easier to spare a strip of skin and thereby reduce the risk of lymphedema. (4) The size of the tumor may be reduced, thus decreasing the extent of surgical resection. (5) Lower radiation doses can be utilized, as there are fewer relatively radioresistant hypoxic cells.

Preoperative irradiation also has several drawbacks, however. They include (1) the inability to precisely stage patients based on pathology due to downstaging and (2) increased problems with wound healing.

Studies of preoperative irradiation from the University of Florida, M. D. Anderson Cancer Center, and Massachusetts General Hospital demonstrated local control rates of 90% using doses of approximately 50 Gy. Survival depended on the size and grade of the primary tumor. Distant metastases were the primary pattern of failure.

Postoperative irradiation A number of retrospective reports, as well as a randomized trial from the NCI, have demonstrated that limb-sparing surgery plus postoperative irradiation produces local control rates comparable to those achieved with amputation. Five-year local control rates of 70%-90%, survival rates of 70%, and limb-preservation rates of 85% can be expected.

Equivocal or positive histologic margins are associated with higher local recurrence rates, and, therefore, adjuvant external-beam irradiation should be considered in all patients with extremity sarcoma with positive or close microscopic margins in whom reexcision is impractical. Postoperative doses of 60-65 Gy should be used.

Interstitial therapy with iridium-192 is used at some institutions as a radiation boost to the tumor bed following adjuvant external-beam irradiation. At Memorial Sloan-Kettering Cancer Center, 89% of patients randomized to receive adjuvant brachytherapy achieved local control, as compared with only 66% of those who had surgery alone. If an implant alone is used, the dose is 40-45 Gy to a volume that includes all margins; when a boost is combined with additional external-beam irradiation, a dose of 20-25 Gy is utilized. Some data suggest a higher rate of wound complications and a delay in healing when implants are afterloaded prior to the third postoperative day. Although some

centers load implants sooner, this must be done with caution and with strict attention to the incision site.

Over a 15-year period, 202 patients with high-grade extremity sarcoma underwent complete gross resection and adjuvant brachytherapy to a median dose of 45 Gy, delivered over 5 days. With a median follow-up of 61 months, the 5-year local control, distant relapse-free survival, and overall survival rates were 84%, 63%, and 70%, respectively. These rates compared favorably with data on external-beam irradiation. Morbidity of brachytherapy was considered acceptable, with reoperation rates of 12%, bone fractures in 3%, and nerve damage in 5%.

Comparison of irradiation techniques Comparable local control results (90%) are obtained with preoperative, postoperative, and interstitial techniques, although rates of wound complications are higher with preoperative techniques. Brachytherapy can offer a number of advantages. When brachytherapy is employed as the sole adjuvant, the entire treatment (surgery and irradiation) is completed in a 10- to 12-day period, compared with the 10-12 weeks required for typical external-beam irradiation (6-7 weeks) and surgery (4- to 6-week break before or after irradiation). Generally, smaller volumes can be irradiated with brachytherapy, which could improve functional results. However, smaller volumes may not be appropriate, depending on the tumor size, grade, and margin status.

Regardless of the technique employed, local control is a highly achievable and worthwhile end point, as demonstrated in a study of 911 patients treated by various techniques at Memorial Sloan-Kettering Cancer Center. Of the 116 patients who developed a local recurrence, 38 subsequently developed metastases and 34 died. Metastases after local recurrence were predicted in patients with high-grade or large ($>$ 5 cm) tumors.

Treatment recommendations Adjuvant radiotherapy should be employed for virtually all high-grade extremity sarcomas and larger ($\geq$ 5 cm) low-grade lesions. If small (T1) lesions can be resected with clear margins, radiotherapy can be omitted. Postoperative therapy with either external-beam irradiation (with or without an interstitial implant boost) or an implant alone will achieve a high likelihood of local control and, therefore, limb preservation. Preoperative irradiation, although equally efficacious, does carry a higher wound complication rate.

Radiation therapy in retroperitoneal sarcomas

Only 50% of patients with retroperitoneal sarcoma are able to undergo complete surgical resection. Of patients undergoing complete resection, one-half develop a local recurrence. This significant local failure rate suggests a potentially important role for adjuvant treatment in all patients with retroperitoneal sarcomas. However, the role of radiation therapy in the treatment of retroperitoneal sarcomas remains controversial due to the rarity of the tumor, the paucity of data, the retrospective nature of available studies, the low doses of radiation used in many studies, and the lack of consistent policies in determining the indications for radiation therapy.

Postoperative irradiation Two-year local control rates of 70% have been reported with the addition of postoperative irradiation. However, irradiation of the retroperitoneum/abdomen in doses that have effected local control in extremity soft-tissue sarcoma (50-65 Gy) is usually associated with significant GI toxicity. Obviously, the incidence of GI toxicity depends on the exact fields and technique used. However, as most retroperitoneal sarcomas are > 10-15 cm, the radiation fields employed are generally also quite large, and bowel is often located and/or tethered in the high-risk area. Three-dimensional treatment planning and conformal techniques can now be utilized to maximize the radiation dose to the tumor bed while minimizing the dose to the surrounding normal tissues.

Preoperative irradiation The advantages of preoperative radiotherapy have already been discussed for extremity soft-tissue sarcomas. In the retroperitoneum, an additional advantage is that bowel is frequently displaced significantly by the tumor. In contrast to the postoperative setting, the bowel being treated is also unlikely to be tethered by adhesions from prior surgery. These features significantly offset acute toxicity of large-field intra-abdominal radiotherapy (eg, nausea, vomiting, and diarrhea) as well as the potential for late-onset bowel toxicity. Conformal techniques capable of sparing normal tissues are also more easily applied in the preoperative setting, when the tumor can be visualized and the target area more readily defined.

Intraoperative irradiation In a prospective trial from the NCI, 35 patients with completely resected retroperitoneal sarcomas were randomized to receive either intraoperative electron-beam irradiation (IORT) followed by low-dose (30-40 Gy) postoperative external-beam irradiation or high-dose postoperative external-beam irradiation (35-40 Gy plus a 20-Gy boost). Absolute local recurrence rates were significantly lower in the IORT group ($P < .05$), but disease-specific and overall survival rates did not differ between the two groups.

Similarly, a nonrandomized series from the Massachusetts General Hospital has suggested improved local control with IORT for patients with retroperitoneal sarcoma. In 16 patients who underwent irradiation, complete gross resection, and IORT, overall survival and local control were 74% and 83%, respectively. These numbers diminished to 30% and 61%, respectively, in the 13 patients treated with irradiation and complete gross resection without IORT. Although these local control results are encouraging, IORT remains investigational and cannot be advocated on a routine basis at this time.

ROLE OF ADJUVANT CHEMOTHERAPY

The striking success of combined-modality therapy in children with osteogenic sarcoma, embryonal rhabdomyosarcoma, and the Ewing's sarcoma family of tumors has provided the stimulus for the use of aggressive combined-modality approaches in adult patients. The literature is replete with reports of the apparent benefit of combined-modality therapy in patients with resectable soft-tissue sarcoma. Yet most series are either retrospective or small, nonrandomized trials.

Postoperative chemotherapy

A number of published trials have compared postoperative chemotherapy with observation alone in adult patients who had undergone resection of a primary or recurrent soft-tissue sarcoma. Most of these trials included fewer than 100 patients, and even the largest trial had inadequate statistical power to detect a 15% difference in survival. Other flaws confound the interpretation of many of the studies. Some trials included low-risk patients with small and/or low-grade sarcoma. In some trials, patient ineligibility rates were as high as 20%, and in none of these trials was ifosfamide (Ifex) part of the combination evaluated.

In five of the six trials in which doxorubicin monotherapy was studied, including one study limited to patients with uterine sarcoma, a significant improvement in survival could not be demonstrated. Among the trials of combination chemotherapy, most used the combination known as CyVADIC (cyclophosphamide, vincristine, doxorubicin [Adriamycin], and dacarbazine [DTIC]). A significant survival advantage was seen only in one combination chemotherapy trial.

Nonetheless, some of the trials showed a trend or a statistically significant improvement in disease-free survival among patients given adjuvant chemotherapy, especially among those with high-grade extremity sarcoma. Analyses of the pooled results of the published literature are consistent with this observation.

SMAC meta-analysis A formal meta-analysis of individual data from 1,568 patients who participated in randomized trials of postoperative adjuvant chemotherapy vs no chemotherapy control patients was performed by the Sarcoma Meta-Analysis Collaboration (SMAC). Although not all data were available for all patients, the analysis demonstrated a significant reduction in the risk of local or distant recurrence in patients who received adjuvant chemotherapy.

The overall hazard ratio for distant relapse-free survival was 0.70; ie, the risk of distant relapse (metastasis) was reduced by 30% in treated patients. The absolute benefit at 10 years was 10%, so the recurrence-free survival rate at 10 years was improved from 60% to 70%. Also, the hazard ratio for local recurrence-free survival was 0.73 (27% reduction in the risk of local recurrence), and the absolute benefit was 6%.

The hazard ratio for overall survival, however, was 0.89, which did not meet the criteria for statistical significance. The observed survival at 10 years was 54% for patients who received chemotherapy and 50% for those who did not. Subset analysis failed to show that the effects of chemotherapy differed by primary site, although the best evidence for an effect of adjuvant chemotherapy was seen in patients with extremity sarcoma.

Ifosfamide-containing trials Only one trial included in the meta-analysis used an ifosfamide-containing regimen; that trial involved only 29 patients. An attempt to conduct a large prospective trial of postoperative chemotherapy with the MAID (mesna [Mesnex], doxorubicin [Adriamycin], ifosfamide, and dacarbazine) regimen in the United States failed because of insufficient patient accrual.

An Italian cooperative group conducted a trial in which patients 18-65 years old with high-grade (≥ 5 cm) extremity sarcoma or any recurrent extremity sarcoma were randomized to receive postoperative chemotherapy or observation alone. The treatment consisted of 5 cycles of epirubicin (Ellence), 60 mg/m^2 on days 1 and 2, plus ifosfamide, 1.8 gm/m^2 on days 1-5. Granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) was used to support the granulocyte counts during therapy.

The trial had been planned for 200 patients but was interrupted after accrual of 104 patients, when an interim analysis showed a significant survival advantage for the chemotherapy-treated group. At 36 months after the last randomization, with a median follow-up of 59 months, median overall survival among the patients who received adjuvant chemotherapy was 75 months, vs 46 months in control patients ($P = .03$; Frustaci S, Gherlinzoni F, DePaoli A, et al: J Clin Oncol 19:1238-1247, 2001).

Preoperative chemotherapy

Preoperative chemotherapy has been adopted at many centers for patients with large high-grade sarcoma. The specific regimens employed have evolved over the years but generally contain both an anthracycline and ifosfamide. Some investigators have added concurrent, sandwiched or sequential preoperative radiation therapy in nonrandomized trials. European investigators have also explored combination chemotherapy with regional hyperthermia.

Aside from theoretical considerations, there are several pragmatic reasons to favor preoperative over postoperative treatment. First, a reduction in the size of a large lesion may permit surgical resection with less morbidity. Second, compliance may be better with preoperative therapy. One observation that supports the neoadjuvant approach is that response to preoperative chemotherapy, whether pathologic or radiographic, predicts improved tumor control and survival.

Neoadjuvant chemotherapy has been explored in a prospective randomized trial initiated by the EORTC (European Organization for Research and Treatment of Cancer). The trial was open to patients who had a sarcoma measuring at least 8 cm (of any grade), a primary or recurrent intermediate- to high-grade (grade II/III) sarcoma of any size, or a locally recurrent or inadequately excised grade II/III sarcoma. In spite of these broad eligibility criteria, accrual was slow, and the trial was closed after only 150 patients entered. Patients were randomized to receive either immediate surgery, followed by radiation therapy for close or positive margins, or 3 cycles of chemotherapy with doxorubicin (50 mg/m^2 by IV bolus plus) ifosfamide (5 g/m^2 by 24-hour continuous infusion) with mesna. Among the 134 eligible patients, over 80% had extremity primaries, but only 4% had grade II/III lesions > 8 cm. Among 49 patients assessable for response, 29% had major objective responses, including 4 CRs. Only 18% had progression of disease before surgery. Chemotherapy was generally well tolerated and never prevented surgery. With a median follow-up of 7.3 years, the estimated 5-year survival among the 67 surgery-alone patients

was 64% and among the neoadjuvant chemotherapy patients was 65% ($P = .22$).

Treatment recommendations

- Multidisciplinary treatment planning should precede the initiation of any therapy. An experienced multi-disciplinary team should evaluate pathologic material and imaging studies and coordinate the integration of surgical resection, irradiation, and systemic therapy.
- Ideally, patients should be offered participation in clinical trials. Unfortunately, there are no active trials in the United States that will definitively answer the most important questions. Thus, a decision to treat must be made on an individual basis.
- Preoperative chemotherapy should be considered for fit, high-risk patients after a discussion of the risks and potential benefits. Older patients, especially those with cardiac or renal disease, are not optimal candidates for such treatment.
- Patients who do not receive preoperative chemotherapy may still be offered postoperative treatment. Adjuvant doxorubicin/ifosfamide combinations may improve relapse-free survival in carefully selected patients and can be considered for the treatment of those with tumor size > 5 cm, deep tumor location, and high histologic grade.
- For patients who opt for preoperative or postoperative chemotherapy, a regimen that includes doxorubicin (60-75 mg/m^2) or epirubicin (120 mg/m^2) plus ifosfamide (9-10 g/m^2) or the MAID regimen (see the section on "Combination chemotherapy"), given for a total of 5 cycles, would be reasonable choices.
- Outside the context of a clinical trial, concurrent chemotherapy and irradiation should be avoided.

Ecteinascidin (ET-743), a novel compound isolated from a marine organism, demonstrated antineoplastic activity during its phase I evaluation in patients with refractory soft-tissue or osteogenic sarcoma. Occasional responses have been seen in compassionate-use programs in which the drug was given as a 24-hour infusion *(Delaloge A, et al: J Clin Oncol 19:1248-1255, 2001; Ruiz-Casado A, Lopez-Martin J, Nieto A, et al: Proc Am Soc Clin Oncol [abstract] 21:408a, 2002)*. In a multicenter phase II trial involving 62 previously treated patients with soft-tissue sarcoma, the PR rate was only 5%, although 15 patients had at least stable disease for more than 3 months. Toxicity was primarily myelosuppression and hepatic enzyme elevation *(George S, Maki RG, Harmon D, et al: Proc Am Soc Clin Oncol [abstract] 21:408a, 2002)*. Partial responses were seen in 3 of 25 patients (12%) with soft-tissue sarcoma in an Italian phase II trial *(Dileo P, Casali PG, Bacci M, et al: Proc Am Soc Clin Oncol [abstract] 21:408a, 2002)*. The major toxicities are hepatic and hematologic.

TREATMENT OF LOCAL RECURRENCE

Despite optimal multimodality therapy, local recurrence develops in 10%-50% of patients, with a median local recurrence-free interval of ~24 months. Local recurrence rates are a function of the primary site and are highest for retro-

TABLE 2: Chemotherapy regimens for soft-tissue sarcoma

Drug/combination	Dose and schedule
AD (96-hour infusional)	
Adriamycin (doxorubicin)	15 mg/m^2/d for 4 days (96-hour continuous infusion), total dose of 60 mg IV over 4 days
Dacarbazine	250 mg/m^2/d for 4 days (96-hour continuous infusion), total dose of 1,000 mg/m^2 IV over 4 days
Repeat cycle every 21 days	
Antman K, Crowley J, Balcerzak SP, et al: J Clin Oncol 11:1276–1285, 1993.	
AD (bolus)	
Adriamycin	60 mg/m^2 on day 1 by rapid IV infusion
Dacarbazine	750 mg/m^2 on day 1by rapid IV infusion
Repeat cycle every 21 days	
NOTE: Bolus dosage was compared with Adriamycin at 60 mg/m^2 and dacarbazine at 750 mg/m^2 delivered by continuous IV infusion for 96 hours on days 1-4. The median survival times between the two treatment arms were equivalent, with the toxic effects being milder in the infusional dosage.	
Zalupski M, Metch B, Balcerzak S, et al: J Natl Cancer Inst 83:926–932, 1991.	
AIM	
Adriamycin	30 mg/m^2 IV on days 1 and 2 by rapid IV infusion
Ifosfamide	3,750 mg/m^2 on days 1 and 2 by IV infusion over 4 hours
Mesna	750 mg/m^2 IV infused immediately preceding and 4 and 8 hours after ifosfamide administration on days 1 and 2
Repeat cycle every 21 days	
NOTE: IV hydration at 300 mL/h beginning 3 hours before each treatment cycle and for 3 days at 100 mL/h after each day-1 ifosfamide infusion. Granulocyte colony-stimulating factor, 5 μg/kg subcutaneously, may be given starting 24-48 hours daily for 10 days or until a granulocyte count of 1,500/μL is reached. Appropriate supportive measures should be given.	
Edmonson JH, Ryan LM, Blum RH, et al: J Clin Oncol 11:1269–1275, 1993.	

peritoneal and head and neck sarcomas, for which adequate surgical margins are difficult to attain. In addition, high-dose adjuvant irradiation of these sites is often limited by the relative radiosensitivity of surrounding structures. These factors result in local recurrence rates of 40% for retroperitoneal sarcomas and up to 50% for head and neck sarcomas, which are substantially higher than the 10% proximity typically seen for extremity sarcomas.

Reoperation Following staging evaluation, patients with an isolated local recurrence should undergo reoperation. The results of reoperation in this setting are good, with two-thirds of patients experiencing long-term survival.

Adjuvant radiation therapy If no prior radiation therapy was employed, adjuvant irradiation (50-65 Gy) should be used before or following surgery for locally recurrent disease. Radiation therapy (external-beam irradiation or brachytherapy) should be considered in patients for whom previous radiation

Drug/combination	Dose and schedule
EIM	
Epirubicin	60 mg/m^2 IV infused on days 1 and 2, total dose of 120 mg/m^2 per cycle
Ifosfamide	1.8 g/m^2/d on days 1-5, total dose of 9 g/m^2 per cycle
Mesna	360 mg/m^2 IV infused immediately before and 4 and 8 hours after ifosfamide infusion
Repeat cycle every 3 weeks for a total of 5 cycles	
Granulocyte colony-stimulating factor, 300 μg subcutaneously given on days 8 through 15.	
Hydration (1,500-2,000 mL) of fluids IV given after ifosfamide.	
Frustaci S, Gherlinzoni F, De Paoli A, et al: J Clin Oncol 19:1238–1247, 2001.	
MAID	
Mesna	2.5 mg/m^2/d IV infused continuously over 24 hours on days 1-4
Adriamycin	20 mg/m^2/d IV infused continuously over 24 hours on days 1-3
Ifosfamide	2.5 g/m^2/d IV infused continuously over 24 hours on days 1-3
Dacarbazine	300 mg/m^2/d IV infused continuously over 24 hours on days 1-3
Repeat cycle every 21 dayss	
Elias A, Ryan L, Sulkes A, et al: J Clin Oncol 7:1208–1216, 1989.	

Table prepared by Ishmael Jaiyesimi, DO

doses were subtherapeutic or previous radiation field design permits additional treatment.

Reports from Memorial Sloan-Kettering Cancer Center, M. D. Anderson Cancer Center, and Princess Margaret Hospital suggest that patients who develop local recurrence following previous full-dose irradiation represent a difficult local control challenge. A report from Memorial Sloan-Kettering Cancer Center suggests that limb-sparing surgery combined with adjuvant brachytherapy may produce excellent local control and function in this group.

ILP Ongoing clinical investigations are defining the role of isolated limb perfusion in the management of patients with locally recurrent sarcoma.

TREATMENT OF LIMITED PULMONARY METASTASIS

Thoracotomy and metastasectomy The most common site of metastatic disease involvement of soft-tissue sarcoma is the lungs. Rates of 3-year survival following thoracotomy for pulmonary metastasectomy range from 23%-42%. This fact, combined with the limited efficacy of systemic therapy, is the basis

for the recommendation that patients with limited pulmonary metastases and no extrapulmonary disease should undergo thoracotomy and metastasectomy.

Appropriate patient selection for this aggressive therapeutic approach to metastatic disease is essential. The following are generally agreed upon criteria: (1) the primary tumor is controlled or controllable; (2) there is no extrathoracic metastatic disease; (3) the patient is a medical candidate for thoracotomy; and (4) complete resection of all disease appears to be possible.

Preresection chemotherapy Chemotherapy is often recommended before resection of pulmonary metastases. However, there are no convincing data to support this approach.

A randomized multicenter trial evaluated two doses of oral imatinib mesylate (Gleevec, 400 mg vs 600 mg) in 147 patients with advanced GIST. With median follow-up of 288 days, 54% had a PR, and 28% had stable disease, but there were no CRs. Response was sustained, with a median duration over 6 months. Most patients had mild grade 1 or 2 toxicity, but only 21% had severe grade 3 or 4 toxicity. GI or intra-abdominal hemorrhage occurred in 5% of patients. There was no difference in response or toxicity between the two doses *(Demetri GD, von Mehren M, Blanke CD, et al: N Engl J Med 7:472,480, 2002).*

CHEMOTHERAPY FOR UNRESECTABLE LOCALLY ADVANCED OR METASTATIC DISEASE

Single agents

Doxorubicin Early trials of doxorubicin reported major responses in approximately 30% of patients with advanced soft-tissue sarcoma. In more recent randomized series, however, the rate of response has been closer to 17%.

Subset analysis of patients with soft-tissue sarcoma from a broad phase II trial in which patients were randomized to receive various doses of doxorubicin demonstrated a steep dose-response relationship; patients treated with doses < 60 mg/m^2 rarely responded. Whether dose intensification of doxorubicin is associated with improved survival remains an open question (see section on "Intensifying chemotherapy"). Preliminary results suggest that it may be possible to overcome *p*-glycoprotein-mediated resistance to doxorubicin in some patients with VX-710.

Pegylated liposomal doxorubicin (Doxil in the United States, Caelyx in Europe) has demontrated limited activity in phase II trials, especially in patients whose disease is refractory to standard doxorubicin. In a randomized comparison among 95 previously untreated patients, however, the response rates to pegylated liposomal doxorubicin (50 mg/m^2 every 4 weeks; 10%) and to standard doxorubicin (75 mg/m^2 every 3 weeks; 9%) were similar, with no significant difference in time to disease progression or survival. Response rates improved to 14% and 12%, respectively, when GI stromal tumor (GIST) cases were excluded (Judson I, et al: Eur J Cancer 37:870-877, 2001).

Ifosfamide In a randomized phase II trial conducted by the EORTC, 18% of patients treated with ifosfamide (5 g/m^2) experienced major responses, in con-

trast to 12% of patients treated with cyclophosphamide (1.5 g/m^2), despite the greater myelosuppression with the latter agent. In a large American phase II trial, 17 of 99 patients with soft-tissue sarcoma responded to ifosfamide (8 g/m^2). All of the patients had been treated previously with doxorubicin-based therapy, suggesting a degree of non–cross-resistance.

Increasing ifosfamide dose Recent trials have focused on increasing the dose of ifosfamide. Responses to ifosfamide (≥ 12 g/m^2) have been observed in patients who progressed while receiving lower doses, supporting the concept of a dose-response relationship.

In a randomized trial, the response to 9 g/m^2 of ifosfamide (17.5%) was superior to the 3% response observed among patients treated with 5 g/m^2. The reason for the low response to the lower dose was unclear. In a subsequent trial by the same investigators, the response to 12 g/m^2 was only 14%, however.

Among 45 "assessable" patients enrolled in a Spanish phase II trial of ifosfamide (14 g/m^2 given by continuous infusion over 6 days), the response rate was 38%, but 47% of patients developed febrile neutropenia and 32%, grade 3 neurotoxicity.

At M. D. Anderson Cancer Center, ifosfamide (14 g/m^2 given by continuous infusion over 3 days) yielded responses in 29% of 37 patients with soft-tissue sarcoma and 40% of patients with bone sarcoma. Also within that report was a small cohort of patients in whom the response to the same total dose of ifosfamide was higher when the drug was given by an intermittent bolus rather than a continuous infusion; this finding led the authors to suggest that bolus therapy is more efficacious than continuous infusion. Pharmacokinetic studies, however, have shown no difference between a 1-hour infusion or bolus injection of ifosfamide with respect to the area under the curve for serum ifosfamide or its metabolites or the levels of ifosfamide metabolites in urine.

In an EORTC phase II trial, ifosfamide (12 g/m^2 given as a 3-day continuous infusion every 4 weeks) yielded a response rate of 17% among 89 chemotherapy-naive patients and 16% among 25 previously treated patients.

Ifosfamide doses as high as 14-20 g/m^2 have been given with hematopoietic growth factor support; reported response rates are high, but neurologic and renal toxicities often are dose-limiting. The available data suggest that synovial sarcoma is particularly sensitive to ifosfamide.

DTIC The activity of DTIC in soft-tissue sarcoma has been recognized since the 1970s and was confirmed in a formal phase II trial. This marginally active agent has been used mostly in doxorubicin-based combinations.

In a phase II study of 34 patients with unresectable leiomyosarcoma, mostly uterine in origin, 53% responded to a combination of gemcitabine (given by 90-minute infusion) plus docetaxel, with filgrastim support. An additional 20% had stable disease *(Hensley ML, Maki R, Venkatraman, E, et al: J Clin Oncol 20:2824-2831, 2002)*. Almost half of the patients had progressed after anthracycline-based therapy. Median time to disease progression was 5.6 months, and grade 3-4 toxicity was uncommon. This trial has been expanded to include sarcomas of various histologic types and sites. Prospective randomized trials are needed to compare this combination with gemcitabine alone and to explore its integration into anthracycline-based treatment strategies.

Other agents, including the taxanes, vinca alkaloids, and platinum compounds, have demonstrated only marginal activity in phase II trials. The taxanes appear to have unique activity in angiosarcoma. Gemcitabine (Gemzar) has demonstrated modest activity in several phase II studies, including those with previously treated patients. A novel marine compound, ecteinascidin (ET-743), has demonstrated promising activity in sarcoma during phase I and early phase II evaluations.

Targeted therapy The demonstration of the efficacy of imatinib mesylate (STI-571, Gleevec) in patients with GIST has been among the most dramatic and exciting observations in solid tumor oncology. GISTs are rare mesenchymal tumors that usually arise in the gut, although they also arise in the peritoneal cavity or retroperitoneum. Although most GISTs do not spread, metastatic GISTs may progress rapidly and are notoriously resistant to chemotherapy. GISTs express CD117, a marker of the KIT proto-oncogene product, a transmembrane receptor with tyrosine kinase activity. KIT activation occurs in all GISTS and appears to be critical in the pathogenesis of these tumors. KIT mutations are common in GIST but not essential for diagnosis.

Combination chemotherapy

Combination chemotherapy regimens have been used widely in the management of patients with soft-tissue sarcoma. High response rates have been reported in a number of single-arm phase II trials. Most combination regimens include an anthracycline (either doxorubicin or epirubicin) plus an alkylating agent, DTIC, or both agents. Overall, response rates are higher in these single-arm trials than when the same regimens are tested in larger, randomized studies.

AD and CyVADIC regimens The combination of Adriamycin plus DTIC (AD regimen) has been studied extensively (Table 2). Also, for over a decade, the CyVADIC regimen was widely accepted as the standard of care. In a prospective, randomized trial, however, CyVADIC did not prove to be superior to doxorubicin alone.

Doxorubicin (or epirubicin) plus ifosfamide Combinations of doxorubicin (or epirubicin) plus ifosfamide have consistently yielded responses in over 25% of patients in single-arm trials. In sequential trials conducted by the EORTC, doxorubicin at 75 mg/m^2 plus ifosfamide (5 g/m^2) was superior to doxorubicin at 50 mg/m^2 plus ifosfamide (5 g/m^2). A prospective randomized EORTC trial with 314 patients compared the two regimens. There was no difference in response rate or overall survival, but disease progression-free survival favored the more intensive regimen.

MAID regimen The MAID regimen (mesna, Adriamycin [60 mg/m^2], ifosfamide [7.5 g/m^2], and DTIC [900 mg/m^2], all given over 3 days; Table 2) yielded an overall response rate in 47% of patients in a large phase II trial. In a randomized comparison of AD vs MAID, the response to MAID was 32%, vs 17% with the two-drug regimen ($P < .002$). However, the price paid for the higher response was toxicity; of 8 toxic deaths reported in this trial, 7 occurred among the 170 patients treated with MAID. All treatment-related deaths occurred in patients > 50 years old. During the study, the doses of MAID were

reduced to lessen toxicity. Median survival did not differ significantly between the two regimens, although a trend favoring the AD regimen was noted.

Combination chemotherapy vs single-agent doxorubicin Combination chemotherapy has been compared with single-agent doxorubicin in eight randomized phase III trials. Two trials were limited to patients with uterine sarcoma. Some of these studies showed superior response rates with combination chemotherapy, but none of the trials found a significant survival advantage. Kaplan-Meier plots of survival are virtually superimposable within each trial and from trial to trial.

It should be emphasized that approximately 20%-25% of patients entered into such trials are alive 2 years after therapy is initiated. Complete responses are uncommon and do not appear to translate into prolonged survival.

Intensifying chemotherapy Hematopoietic growth factors have facilitated the evaluation of dose-intensive chemotherapy in patients with sarcoma. The nonhematologic toxicities (cardiac, neurologic, and renal) of the agents most active in soft-tissue sarcoma prevent dramatic dose escalation.

Phase I and II trials of dose-intense anthracycline/ifosfamide regimens with hematopoietic growth factor support have shown that doxorubicin (70-90 mg/m^2) can be used in combination with ifosfamide (10-12 g/m^2) in selected patients. Response rates as high as 69% have been reported. Although toxicity increases, often dramatically, with these relatively modest dose escalations, the clinical benefit in terms of survival or palliation in patients with metastatic disease remains uncertain.

No randomized trial has demonstrated a survival advantage for patients treated with these more aggressive regimens. In one randomized trial, however, the French Federation of Cancer Centers demonstrated that, in comparison with standard doses, a 25% escalation in doses of MAID with G-CSF support did not improve outcome.

High-dose therapy with autologous stem-cell transplantation. In one recent trial involving 30 patients with metastatic or locally advanced sarcoma, accrued over a period of 6 years, more than 20% were free of disease progression at 5 years after high-dose therapy with stem-cell rescue. Complete response to induction standard chemotherapy predicted superior 5-year survival. Based on these favorable results, the investigators suggested a prospective randomized trial examining this approach. Nonetheless, the experience with this approach is limited, and its superiority over conventional dosing remains speculative.

Prognostic factors for response to therapy Over the past 20 years, the EORTC has collected data on more than 2,000 patients with metastatic disease who participated in first-line anthracycline-based chemotherapy trials. Multivariate analysis of this data set indicated that the patients most likely to respond to chemotherapy are patients without liver metastases ($P < .0001$), younger patients, individuals with high histologic grade, and those with liposarcoma. In this Cox model, the factors associated with superior survival were good performance status, absence of liver metastases, low histologic grade, a long time to metastasis after treatment of the primary, and young age.

More recently, these same investigators have reported that the observed response rate is superior in patients who have pulmonary metastases only, as compared with those who have metastases to the lungs and other sites or to other sites only. These findings highlight the danger of reaching broad conclusions based on extrapolations from small trials that include highly selected patients. The EORTC data are also consistent with the observation that patients with metastatic GI sarcoma rarely respond to standard chemotherapy regimens. This increasingly recognized observation has been used to explain the low response rates seen in some trials.

Treatment recommendations

- For patients with rapidly progressive disease or with symptoms, combination chemotherapy with an anthracycline/ifosfamide combination is indicated. For most patients, however, sequential single-agent therapy is less toxic and not inferior in terms of survival.
- The importance of histology relevant to selection of therapy is increasingly being appreciated. It is especially important to distinguish GISTs from GI leiomyosarcomas. Patients with GIST should be referred to specialists experienced in the use of imatinib.
- Periods of watchful waiting may be appropriate for many patients with metastatic sarcoma who have no or only minimal symptoms.

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CHAPTER 27

Primary brain tumors

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Intracranial neoplasms can arise from any of the structures or cell types present in the cranial vault, including the brain, meninges, pituitary gland, skull, and even residual embryonic tissue. The overall annual incidence of primary brain tumors in the United States is 5.9 cases per 100,000 population. Over 50% of primary brain tumors are gliomas, and at least two-thirds of these tumors are clinically aggressive and high grade. Brain tumors represent 20% of all childhood malignancies and are the second most frequent cause of cancer death after leukemia in children.

Epidemiology

Gender There is a slight predominance of primary brain tumors in males.

Age Primary brain tumors have a bimodal distribution, with a small peak in the pediatric population and a steady increase in incidence with age, beginning at age 20 years and reaching a maximum of 20 cases per 100,000 population between the ages of 75 and 84 years.

Etiology and risk factors

The cause of primary brain tumors is unknown, although genetic and environmental factors may contribute to their development.

Genetic factors Clear heritable factors play a minor role in the genesis of primary brain tumors; < 5% of glioma patients have a family history of brain tumor. Several inherited diseases, such as tuberous sclerosis, neurofibromatosis type I, Turcot syndrome, and Li-Fraumeni cancer syndrome, predispose patients to the development of gliomas. However, these tumors tend to occur in children or young adults and do not account for the majority of gliomas, which appear in later life.

Molecular markers of brain tumors can predict survival and will become increasingly more important in the diagnosis and treatment of glioma.

Environmental factors Prior cranial irradiation is the only well-established risk factor for intracranial neoplasms.

Loss of heterozygosity (LOH) on chromosome 9p and 10q and p16 deletions are frequently observed in high-grade gliomas, with low-grade gliomas having the fewest molecular abnormalities (*Rasheed A, Herndon JE, Stenzel TT, et al: Cancer 94:2688-2697, 2002*). In anaplastic oligodendrogliomas, 1p + 19q LOH is associated with significantly improved survival.

Lifestyle characteristics Brain tumors are not associated with lifestyle characteristics, such as cigarette smoking, alcohol intake, or cellular phone use.

Signs and symptoms

Brain tumors produce both nonspecific and specific signs and symptoms.

Nonspecific symptoms include headache, which occurs in about half of patients, and nausea and vomiting, which are caused by an increase in intracranial pressure. Because of the widespread availability of CT and MRI, papilledema is now seen in < 10% of patients, even when symptoms of raised intracranial pressure are present.

Specific signs and symptoms are usually referable to the particular intracranial location of the tumor.

Lateralizing signs, including hemiparesis, aphasia, and visual-field deficits, are present in ~50% of patients.

Seizures are a common presenting symptom, occurring in ~25% of patients with high-grade gliomas and at least 50% of patients with low-grade tumors. Seizures may be either generalized or partial.

Stroke-like presentation Hemorrhage into a tumor may present like a stroke, although the accompanying headache and alteration of consciousness usually suggest an intracranial hemorrhage rather than an infarct. Hemorrhage is usually associated with high-grade gliomas, occurring in 5%-8% of patients with glioblastoma multiforme. However, oligodendrogliomas have a propensity to bleed, and hemorrhage occurs with 7%-14% of these low-grade neoplasms. Sudden visual loss and fatigue may be seen with bleeding from pituitary tumors, termed *pituitary apoplexy.*

Diagnosis

MRI The diagnosis of a primary brain tumor is best made by cranial MRI. This should be the first test obtained in a patient with signs or symptoms suggestive of an intracranial mass. The MRI scan should always be obtained both with and without contrast material (gadolinium).

*High-grade or malignant tumor*s appear as contrast-enhancing mass lesions that arise in white matter and are surrounded by edema (Figure 1). Multifocal malignant gliomas are seen in ~5% of patients.

Low-grade gliomas typically are nonenhancing lesions that diffusely infiltrate and tend to involve a large region of the brain. Low-grade gliomas are usually best appreciated on T2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI scans (Figure 2).

CT A contrast-enhanced CT scan may be used if MRI is unavailable. Low-grade tumors or lesions in the posterior fossa may be missed on CT scan. Calcification is often better appreciated on CT than on MRI.

FIGURE 1: T1-weighted MRI with gadolinium contrast showing a typical appearance of a glioblastoma multiforme. Non–contrast-enhanced images of this lesion (not shown) revealed the presence of some hemorrhage.

Pathology

Glial tumors arise from astrocytes, oligodendrocytes, or their precursors and exist along a spectrum of malignancy.

The astrocytic tumors are graded, using a three-tier system, into astrocytoma, anaplastic astrocytoma, and glioblastoma multiforme. Grading is based on pathologic features, such as endothelial proliferation, cellular pleomorphism, and mitoses; the presence of necrosis establishes the diagnosis of glioblastoma multiforme.

Tumor tissue expression of Ki-67, a nuclear proliferation marker, directly correlates with age, and values ≥ 5% are prognostically significant for reduced cause-specific survival. However, it is not independent of other prognostic factors and is not useful in predicting which low-grade glioma patients should receive immediate postoperative radiotherapy *(Fisher BJ, Naumova E, Leighton CC, et al: Int J Radiat Oncol Biol Phys 52:996-1001, 2002).*

Low-grade astroglial tumors (such as astrocytoma and oligodendroglioma) and mixed neuronal-glial tumors (such as ganglioglioma) grow slowly but have a propensity to transform into malignant neoplasms over time. Transformation is usually associated with progressive neurologic symptoms and the appearance of enhancement on MRI.

The high-grade gliomas include glioblastoma, gliosarcoma, anaplastic astrocytoma, and anaplastic oligodendroglioma. These tumors are extremely inva-

FIGURE 2: T2-weighted MRI demonstrating a diffusely infiltrating, low-grade oligodendroglioma involving the left frontal and temporal lobes. This lesion did not enhance with gadolinium.

sive, with tumor cells often found up to 4 cm away from the primary tumor mass.

Ependymomas Intracranial ependymomas are relatively rare, accounting for < 2% of all brain tumors. They are most frequently seen in the posterior fossa or spinal cord, although they may also arise in the supratentorial compartment. Ependymomas are typically low grade histologically, but their high rate of recurrence indicates malignant behavior.

Medulloblastomas are uncommon in adults but are one of the two most common primary brain tumors in children (the other being cerebellar astrocytomas). Medulloblastomas arise in the cerebellum and are always high-grade neoplasms.

Primitive neuroectodermal tumors (PNETs) are high-grade, aggressive tumors that usually occur in children. They include pineoblastoma and neuroblastoma. Histologically, they are identical to medulloblastomas, but their prognosis might be worse than that for medulloblastomas. Thus, their biology is different, even though they may be similar pathologically.

Extra-axial tumors The most common extra-axial tumor is the meningioma. Meningiomas are usually benign tumors that arise from residual mesenchymal cells in the meninges. They produce neurologic symptoms by compressing the underlying brain. Meningiomas rarely are malignant or invade brain tissue.

Other common extra-axial tumors include pituitary adenoma, epidermoid or dermoid tumors, and acoustic neuroma (vestibular schwannoma). Most extra-axial tumors have a benign histology but can be locally invasive.

Staging and prognosis

Staging is not applicable to most primary brain tumors because they are locally invasive and do not spread to regional lymph nodes or distant organs.

Staging with a fully enhanced spinal MRI and CSF evaluation is important for a few tumor types, such as medulloblastoma, ependymoma, and PNET, because they can disseminate via the CSF.

Prognostic factors Prognosis is inversely related to several important factors, including pathologic grade, patient age, and overall clinical condition at diagnosis. Several molecular markers that correlate well with prognosis have been recently identified, such as loss of heterozygosity (LOH) on chromosomes 1p and 19q in anaplastic oligodendroglioma.

With conventional treatment, including surgical resection, radiotherapy, and chemotherapy, median survival is 3 years for patients with an anaplastic astrocytoma and 1 year for those with a glioblastoma multiforme. In a population of patients with low-grade tumors, including astrocytoma and oligodendroglioma, median survival is 5-10 years; most of these individuals die of malignant transformation of their original tumor. Patients $\geq$ 40 years old with low-grade glioma generally have more aggressive disease; their median survival is usually $<$ 5 years. Prognosis for patients with low-grade tumors is significantly better than for those with malignant tumors, with $>$ 80% of patients experiencing long-term survival.

Treatment

Treatment of primary brain tumors consists of both initial supportive and definitive therapies.

SUPPORTIVE THERAPY

Supportive treatment focuses on relieving symptoms and improving the patient's neurologic function. The primary supportive agents are anticonvulsants and corticosteroids.

Anticonvulsants

Anticonvulsants are administered to the ~25% of patients who have a seizure at presentation. Phenytoin (300-400 mg/d) is the most commonly used medi-

cation, but carbamazepine (600-1,000 mg/d), phenobarbital (90-150 mg/d), and valproic acid (750-1,500 mg/d) are equally efficacious. Doses of all these anticonvulsants can be titrated to the appropriate serum levels to provide maximal protection.

Newer anticonvulsants, such as gabapentin (Neurontin), lamotrigine (Lamictal), and topiramate (Topamax), are also effective. Therapeutic serum levels of these drugs have not yet been established.

Prophylaxis Prospective studies have failed to show the efficacy of prophylactic anticonvulsants for patients with brain tumors who have not had a seizure. Consequently, prophylactic anticonvulsants should not be administered, except during the perioperative period, when their use may reduce the incidence of postoperative seizures. Phenytoin and carbamazepine are the agents usually used for prophylaxis.

Corticosteroids

Corticosteroids reduce peritumoral edema, diminishing mass effect and lowering intracranial pressure. This effect produces prompt relief of headache and improvement of lateralizing signs. Dexamethasone is the corticosteroid of choice because of its minimal mineralocorticoid activity. The starting dose is ~16 mg/d, but this dose is adjusted upward or downward to reach the minimum dose necessary to control neurologic symptoms.

Long-term corticosteroid use is associated with hypertension, diabetes mellitus, a nonketotic hyperosmolar state, myopathy, weight gain, insomnia, and osteoporosis. Thus, the steroid dose in brain tumor patients should be tapered as rapidly as possible once definitive treatment has begun. Most patients can stop taking steroids by the time they have completed cranial irradiation. However, older (> 65 years) patients taking corticosteroids for more than 6 weeks should be on antibiotic prophylaxis for *Pneumocystis carinii* pneumonia. Prophylaxis should continue for 1 month after the steroids have been discontinued.

DEFINITIVE THERAPY FOR INTRACRANIAL TUMORS

Definitive treatment of intracranial tumors includes surgery, radiotherapy, and chemotherapy. The first step is to devise an overall therapeutic plan, which should outline the sequence and elements of multidisciplinary therapy.

Surgery

Various surgical options are available, and the surgical approach should be carefully chosen to maximize tumor resection while preserving vital brain structures and minimizing the risk of postoperative neurologic deficits. The goals of surgery follow: (1) obtaining an accurate histologic diagnosis; (2) reducing tumor burden and associated mass effect caused by the tumor and/or peritumoral edema; (3) maintaining or reestablishing pathways for CSF flow; and (4) achieving potential "cure" by gross total removal.

Surgical tools A variety of tools are available to help the neurosurgeon achieve these goals, including stereotactic and image-based guidance systems and electrophysiologic brain mapping.

Stereotactic frames provide a rigid, three-dimensional (3D) coordinate system for accurate targeting of brain lesions identified on CT or MRI scans and is particularly well suited for obtaining tissue for biopsy from tumors located in deep structures or in other sites where aggressive tissue removal would produce unacceptable neurologic deficits. A limitation of stereotactic biopsy is that small volumes of tissue are obtained, and tissue sampling errors may result in failure to reach a correct diagnosis. Stereotactic biopsy may be nondiagnostic in 3%-8% of cases and has a surgical morbidity of approximately 5%.

Image-based guidance system "Frameless" or "image-guided" stereotactic systems use computer technology to coregister preoperative imaging studies with intraoperative head position, thereby establishing stereotactic accuracy without the need for a frame. These systems are useful for delivering maximal resections of predefined tumor volumes and minimizing surgical morbidity. Intraoperative MRI accomplishes similar goals but is limited by a requirement for specialized operating suites.

A recent multivariate analysis of 416 patients with glioblastoma demonstrates convincingly that tumor resection of 98% or more, as defined by postoperative imaging, was significantly and independently associated with longer survival. Median survival was 13 months after ≥ 98% tumor resection, compared with only 8.8 months in those who received a less complete resection *(Lacroix M, Abi-Said D, Fourney DR, et al: J Neurosurg 95:190-198, 2001).*

Brain mapping, also termed cortical mapping, uses electrical stimulation of the cortical surface to define the primary motor, sensory, or speech cortex. By pinpointing the exact location of these areas prior to tumor resection, the surgeon can avoid these structures, thereby preserving neurologic function. These tools enable the neurosurgeon to perform more complete removal of tumors with less morbidity.

Pathology-based surgical approach The surgical approach to an intracranial lesion is strongly influenced by the suspected or previously confirmed pathology. Guidelines for the management of the most common tumors are discussed below.

Meningiomas and other extra-axial tumors Benign extra-axial tumors, such as meningiomas, usually have a well-defined plane separating them from the surrounding brain parenchyma. In general, total extirpation can be achieved by open craniotomy. Firm attachment of the tumor to the dura, cranial nerves, vascular structures, or skull base may make this impossible. Subtotal resections that preserve neural or vascular structures while reducing mass effect are often favored for extensive skull base tumors.

The surgical management of other benign extra-axial tumors, such as acoustic neuroma, pineocytoma, choroid plexus papilloma, and pituitary adenoma, closely parallels that of meningiomas. Gross total resection is generally curative and should be attempted whenever safe.

Low-grade gliomas Gross total resection, whenever possible, is the goal of surgery for low-grade gliomas and mixed neuronal-glial tumors (eg, astrocytoma, oligodendroglioma, pilocytic astrocytoma, and ganglioglioma). Long-term survival is generally considered better in patients who have undergone a gross total resection than in those who have had a subtotal resection (5-year survival rates > 80% for gross total resection vs ~50% for subtotal resection).

A thorough and critical review of all papers examining the extent of resection as a factor influencing outcome for low-grade gliomas indicates that tissue diagnosis is the only well-established management standard *(Keles GE, Lamborn K, Berger MS: J Neurosurg 95:731-732, 2001).*

If a radiographically proven gross total resection is attained, postoperative irradiation or chemotherapy can often be withheld until there is evidence of tumor progression (see "Radiation therapy"). If a postoperative scan reveals a small but surgically accessible residual lesion, immediate reoperation should be considered, particularly in children.

When low-grade tumors are found in patients with medically refractory, chronic epilepsy, surgical management should be oriented toward curing the epilepsy, as well as achieving total tumor removal.

Ependymomas Gross total resection is the goal of surgery whenever possible. Because ependymomas arise in the ventricular system, they can disseminate in the CSF. Therefore, all patients should be assessed for subarachnoid metastases with complete cranial and spinal MRI performed with gadolinium.

In this retrospective analysis of 65 low-grade glioma patients treated with surgery and postoperative radiotherapy, the extent of resection was determined by postoperative imaging and correlated with survival. The 10-year overall survival was 82% for those who had a gross total resection, compared with only 32% for those who had a subtotal excision ($P = .0008$) *(Lo SS, Cho KH, Hall WA, et al: Int J Cancer 96:71-78, 2001).*

High-grade gliomas More extensive resections improve the quality of life and Karnofsky performance status (KPS) score of patients with high-grade gliomas (glioblastoma multiforme, anaplastic astrocytoma, and anaplastic oliogodendroglioma) by reducing mass effect, edema, and steroid dependence. True gross resections prolong survival relative to subtotal or partial resections, but extensive subtotal resections do not appear to confer any survival advantage over biopsy alone or limited resections. For this reason, most neurosurgeons attempt to achieve maximal resections while minimizing risk to critical areas of the brain. Stereotactic biopsy may be favored when the tumor is deep-seated, situated in eloquent cortex, or multifocal.

Recurrent or progressive tumors When a brain tumor recurs or enlarges, reoperation is often necessary to reduce mass effect. Recurrent tumor cannot be distinguished from radiation necrosis on routine MRI. Both may cause severe mass effect and edema, and resection is the optimal treatment for both. However, magnetic resonance spectroscopy can often distinguish tumor from treatment effect. Although rarely curative, these procedures can improve quality of life and modestly extend survival.

In general, reoperation is not considered in patients with a KPS score ≤ 60 or in patients who are not candidates for adjuvant therapy following initial surgery.

Initial resection or reoperation followed by intracavitary administration of chemotherapy, immunotherapy, or gene therapy is being explored but is still investigational. Carmustine (BCNU)-impregnated wafers (Gliadel) are the only form of intracavitary chemotherapy currently approved by the FDA for recurrent glioblastoma.

Radiation therapy

Radiation therapy plays a central role in the treatment of brain tumors in adults. It is the most effective nonsurgical therapy for patients with malignant gliomas and also has an important role in the treatment of patients with low-grade gliomas.

Whole-brain vs partial-brain irradiation Whole-brain irradiation is reserved for multifocal lesions and lesions with significant subependymal or leptomeningeal involvement. For the majority of patients with unifocal disease, limited-field treatment results in less morbidity and appears to produce equal, albeit poor, overall survival.

CT-based treatment planning, or 3D conformal radiation therapy, is a relatively new method of treatment planning that utilizes CT information and powerful computer technology to optimize delivery of external-beam radiotherapy to tumors. Recent studies demonstrate that the predominant failure pattern of high-grade gliomas treated with high-dose (90 Gy) conformal radiation therapy remains local. Conformal treatments do not increase the risk of marginal or distant recurrences, but they can decrease the late effects of radiotherapy by reducing the volume of normal brain irradiated.

A recent study from Duke University using iodine-131–labeled antitenascin monoclonal antibody for patients with newly diagnosed malignant gliomas was reported. In a phase II trial, 33 patients had the radioactive antibody placed directly into the surgical cavity, followed by external-beam radiotherapy and chemotherapy. Median survival was 86.7 weeks for all patients and 79.4 weeks for those with glioblastoma. Reversible neurologic toxicity was seen in 27% of patients, and 15% had histologically confirmed neurologic toxicity.

A new technology has been developed to fill a surgical cavity with an inflatable balloon. The balloon contains radioactive iodine. The temporary source of radiation appears to increase local control.

Several studies have evaluated the role of concurrent chemotherapy with cranial irradiation as a means of enhancing the efficacy of radiotherapy. A phase II trial evaluating concurrent temozolomide (Temodar) with radiotherapy for glioblastoma patients suggested enhanced survival, with a median of 16 months. A similar study evaluating concurrent topotecan (Hycamtin) failed to show improved outcome. The use of RSR-13, a synthetic allosteric modifier of hemoglobin that acts like a hypoxic cell sensitizer, showed suggestive evidence of efficacy with median survival of 12.3 months and a favorable impact on

hemoglobin oxygen saturation in newly diagnosed glioblastoma patients receiving radiotherapy.

Dose-response in low-grade gliomas Retrospective studies suggest a radiation dose-response in low-grade gliomas. However, selection bias may play a role in these studies.

Several recently completed randomized studies addressed the question of optimal timing and dose of radiotherapy in patients with low-grade gliomas. An American intergroup randomized trial compared 50.4 vs 64.8 Gy of radiation in patients with low-grade glioma. A European Organization for Research and Treatment of Cancer (EORTC) trial compared 45.0 vs 59.4 Gy of radiation in patients with low-grade astrocytoma. Both studies confirmed the superiority or equivalent efficacy of the lower radiation dose.

A second EORTC trial tested immediate vs delayed radiotherapy in individuals with low-grade glioma. Although immediate radiotherapy significantly improved 5-year progression-free survival, overall survival was identical in the two treatment arms. Furthermore, quality of life was better in patients whose radiotherapy was deferred until clinical or radiographic disease progression was evident.

Recommended treatment approach for low-grade astrocytomas The role of postoperative radiotherapy in the management of incompletely resected low-grade astrocytomas has not been firmly established. However, based on the available data, the following principles appear to be reasonable:

- A complete surgical resection of hemispheric astrocytomas should be attempted.
- If a complete surgical resection has been attained, radiation therapy can be withheld until MRI or CT studies clearly indicate a recurrence that cannot be approached surgically.
- When a complete surgical resection is not performed, postoperative irradiation may be recommended, depending upon the patients' clinical condition. Patients with controlled seizures and no neurologic deficit can be followed and radiation therapy deferred until clinical or radiographic disease progression occurs. Patients with progressive neurologic dysfunction such as language or cognitive difficulties require immediate therapy. Astrocytomas must be treated with radiotherapy, but oligodendrogliomas or mixed gliomas may benefit from chemotherapy as initial treatment (see below).
- Radiation therapy should be delivered, using a megavoltage machine, in 1.7- to 2.0-Gy daily fractions to a total dose of 50-60 Gy. The treatment fields should include the primary tumor volume only, as defined by MRI, and should not encompass the whole brain.
- In low-grade astrocytomas, radiation therapy can be expected to produce a 5-year survival rate of 50% and a 10-year survival rate of 20%. Patients with low-grade oligodendrogliomas survive longer than those with high-grade tumors.

- Cognitive impairment may develop in long-term survivors of low-grade gliomas treated with radiotherapy.

Radiation therapy for high-grade gliomas An analysis of three studies of high-grade gliomas performed by the Brain Tumor Study Group (BTSG) showed that postoperative radiotherapy doses > 50 Gy were significantly better in improving survival than no postoperative treatment and that 60 Gy resulted in significantly prolonged survival compared with 50 Gy. On the other hand, an American intergroup protocol, which randomized patients to receive 60 Gy of whole-brain irradiation, with or without a local boost of 10 Gy, demonstrated no survival benefit in the group receiving treatment with a total radiation dose of 70 Gy. These results may have been confounded by the competing morbidity of whole-brain radiotherapy when given at a dose of 60 Gy.

Based on these data, involved-field radiotherapy to 60 Gy in 30-33 fractions is standard treatment for high-grade histologies; this amount corresponds to a dose just above the threshold for radionecrosis. About half of patients with anaplastic astrocytomas exhibit radiographic evidence of response following 60 Gy of radiation, compared with 25% of patients with glioblastoma multiforme. Complete radiographic response is rare in either case.

Alternatives to conventional radiotherapy The results of standard radiation treatment in patients with malignant gliomas are poor. Patients with glioblastoma multiforme have a median survival of 9-12 months, whereas patients with anaplastic astrocytomas survive a median of 3 years. In an attempt to improve these poor results, a number of new approaches have been tried, including hyperfractionated radiotherapy (HFRT), focal dose escalation with interstitial brachytherapy, and radiosurgery. Newer experimental treatments include the use of radiosensitizers and boron neutron capture therapy (BNCT).

Brachytherapy is the placement of radioactive isotopes directly into the tumor to be treated. Stereotactic techniques are employed to place the radioactive seeds precisely and calculate the dose. The tumor receives the highest dose, and surrounding tissues are spared, due to the rapid falloff in dose with increasing distance from the sources. Two randomized trials failed to show improved survival in patients with malignant gliomas when brachytherapy was added to conventional radiotherapy.

Radiosurgery Over the past several years, there has been growing interest in the use of radiosurgery for the treatment of primary and recurrent malignant brain tumors. Radiosurgery is currently performed with one of three technologies: high-energy photons produced by linear accelerators, the Gamma Knife (AB Elekta, Stockholm, Sweden), or, less frequently, charged particles, such as protons or other ions produced by cyclotrons or synchrotrons.

The survival rates, patterns of recurrence, and rates of complications (including radionecrosis) of radiosurgery and brachytherapy are similar. Radiosurgery is more appealing than brachytherapy for the management of highly focal malignant gliomas because it is a noninvasive, single-day procedure that can usually be performed in an outpatient setting.

Radiosurgery is relatively safe, and patient age and tumor volume are highly predictive of outcome. A randomized trial to establish the efficacy of this technique is currently underway through the Radiation Therapy Oncology Group (RTOG).

Radionecrosis Both brachytherapy and stereotactic radiosurgery can induce focal radionecrosis. This complication produces symptoms of mass effect in about 50% of patients with malignant glioma, requiring resection to remove the necrotic debris. (Fewer than 5% of patients with other lesions [eg, brain metastases] require reoperation for radionecrosis.) Occasionally, treatment with corticosteroids can control the edema around the radionecrotic area, but often the patient becomes steroid-dependent, with all of the attendant complications of chronic steroid use. Radionecrosis can be a significant limitation of the focal radiotherapy techniques.

Recommended approach for extra-axial tumors Surgery alone is curative in the vast majority of patients with benign tumors. However, in certain subsets of patients, postoperative radiotherapy may control further growth of these lesions.

Pituitary adenomas For hormonally inactive pituitary adenomas that persist or recur after surgery, 45 Gy is delivered in 25 fractions to the radiographic boundaries of the tumor. For Cushing's disease and acromegaly, higher doses are required. Coronal-enhanced MRI is critical for treatment planning, since CT often does not visualize the skull base and the entire extent of disease.

The most common indications for radiotherapy are invasion of the cavernous sinus or the suprasellar space and incomplete resection of macroadenomas ($>$ 1.5 cm). Most pituitary lesions do not grow following therapy, and hormonally active tumors usually demonstrate a hormonal response with a reduction in hormone hypersecretion in 1-3 years. Following radiation therapy, 20%-50% of patients develop panhypopituitarism, requiring hormone replacement therapy. Other significant complications (ie, damage to the visual apparatus) are rare today.

Meningiomas are readily curable with complete surgical resection. However, base of skull lesions and lesions involving a patent venous sinus often cannot be resected completely. For some patients with these lesions, a course of postoperative radiotherapy is indicated. In general, 54 Gy is delivered in 30 fractions to the radiographic tumor region utilizing 3D treatment planning. Radiosurgery may also be useful in treating meningiomas, and doses of 13-18 Gy are associated with a high rate of control at 10 years following therapy.

Acoustic neuroma has classically been considered a surgical disease. Following total resection, recurrence rates are $<$ 5%. When only subtotal resection is possible, disease recurs in at least 60% of patients.

Radiosurgery has been used as an alternative to surgery for acoustic neuroma. Control rates of $>$ 80% at 20 years have been reported. For patients with useful hearing prior to radiosurgery, that function is preserved in $<$ 50%. After radio-

surgery, 10% of patients experience facial weakness and 25% trigeminal neuropathy. The risk of cranial neuropathies is related to the size of the lesion treated.

Chemotherapy

Malignant gliomas Chemotherapy has limited benefit in the treatment of patients with malignant gliomas. It does not significantly lengthen median survival in all patients, but a subgroup seems to have prolonged survival with the addition of adjuvant chemotherapy to radiotherapy. Prognostic factors (age, KPS score, and histology) do not predict which patients will benefit from chemotherapy.

Several alkylating agents have antiglioma activity. The nitrosoureas, such as BCNU or the combination of procarbazine (Matulane), lomustine (CeeNu), and vincristine (PCV), have been the traditional initial choices for the treatment of patients with malignant glioma. Their efficacy is limited, and toxicity, particularly with the PCV regimen, can be considerable. Despite initial studies suggesting the superiority of PCV over BCNU, there are now clear data demonstrating no benefit of PCV over BCNU in either glioblastoma or anaplastic astrocytoma patients. However, there is considerably more toxicity associated with the PCV regimen.

Temozolomide is a new alkylating agent recently approved by the FDA for the treatment of patients with recurrent anaplastic glioma. It has demonstrated

TABLE 1: Chemotherapeutic regimens for gliomas

Regimen	Dose	Route and frequency
Single-agent BCNU		
BCNU	200 mg/m^2 (maximum cumulative dose, 1,500 mg/m^2)	IV q8wk
Single-agent temozolomide		
Temozolomide	150-200 mg/m^2	PO on days 1-5
Repeat cycle every 28 days		
Standard PCV		
Lomustine	110 mg/m^2	PO on day 1
Procarbazine	60 mg/m^2/d	PO on days 8-21
Vincristine	1.4 mg/m^2 (maximum dose, 2 mg)	IV on days 8 and 29
Repeat cycle every 6-8 weeks, optimally for 6 cycles		
Intensified PCV[a]		
Lomustine	130 mg/m^2	PO on day 1
Procarbazine	75 mg/m^2/d	PO on days 8-21
Vincristine	1.4 mg/m^2 (no dose limit)	IV on days 8 and 29
Repeat cycle every 6 weeks		

[a] Sometimes used in patients with oligodendrogliomas

efficacy and is clearly superior to second-line procarbazine in patients with recurrent disease. A randomized phase III trial has not compared temozolomide with a nitrosourea for up-front chemotherapy, but many neuro-oncologists have switched to temozolomide as the initial treatment for all patients with malignant astrocytic neoplasms. This change is not only because temozolomide may have enhanced efficacy over a nitrosourea, but it clearly has less toxicity and is better tolerated.

Despite initial treatment, virtually all malignant gliomas recur. At relapse, patients may benefit from re-resection, focal radiotherapy techniques (such as radiosurgery), and different chemotherapeutic agents. Depending upon which chemotherapeutic agent was used at initial treatment, temozolomide, procarbazine, or a nitrosourea would be a reasonable conventional choice at recurrence. Clinical trials employing signal transduction inhibitors, anti–epidermal growth factor receptor (EGFR) antibodies, or antiangiogenic agents may also be available at tumor relapse.

There has been considerable interest in the potential use of antiangiogenic agents in malignant gliomas, but the only antiangiogenic drug tested thus far is thalidomide (Thalomid). As a single agent, it has produced few responses, but stable disease was seen in one-third of patients. Furthermore, novel approaches with a dendritic cell vaccine are showing promise.

Astrocytomas Chemotherapy has no role in the initial treatment of low-grade astrocytomas, and usually they have progressed to a malignant tumor at the time of recurrence.

Oligodendroglioma In contrast, the oligodendroglioma is now recognized as a particularly chemosensitive primary brain tumor. This finding was first observed with the anaplastic oligodendroglioma but has recently been seen with the more common low-grade oligodendroglioma. Chemosensitivity of anaplastic tumors is associated with loss of chromosomes 1p and 19q.

Several alkylating agents are active, but the best studied regimen is PCV, which produces response rates of 75% and 90% in malignant and low-grade oligodendrogliomas, respectively. Consequently, chemotherapy is an important therapeutic modality and may be used as initial treatment in patients with low-grade tumors who require therapeutic intervention. This approach defers or eliminates the late cognitive toxicity associated with cranial irradiation in patients with low-grade tumors, who can have relatively prolonged survival. Patients with malignant oligodendrogliomas require both radiotherapy and chemotherapy for initial treatment.

Patients with oligodendrogliomas are treated with standard PCV or an intensified form of the regimen (see Table 1). The intensified regimen is cycled every 6 weeks, whereas the standard regimen is cycled every 8 weeks. It is not clear which regimen has greater efficacy, but the intensive regimen is associated with more myelosuppression. Temozolomide has activity against oligodendroglial tumors either at diagnosis or recurrence, even in those previously treated with PCV.

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ON PRIMARY INTRACRANIAL TUMORS

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CHAPTER 28

Metastatic brain tumors

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Brain metastases occur in ~15% of cancer patients as a result of hematogenous dissemination of systemic cancer, and the incidence may be rising with better control of systemic disease. Lung and breast cancers are the most common solid tumors that metastasize to the CNS. Melanoma and testicular and renal carcinoma have the greatest propensity to metastasize to the brain, but their relative rarity explains the low incidence of these neoplasms in large series of patients with brain metastases.

Patients with brain metastases from nonpulmonary primaries have a 70% incidence of lung metastases. Although many physicians presume that all brain metastases are multiple, in fact, half are single and many are potentially amenable to focal therapies.

Signs and symptoms

Lateralizing signs and symptoms of brain metastasis depend on the location of the lesion(s) and are similar to the signs and symptoms of other space-occupying masses. However, a few features unique to brain metastases deserve emphasis.

Seizures Focal or generalized seizures are the presenting symptom in 15%-20% of patients with brain metastasis. Metastases from melanoma have a 50% incidence of seizures, perhaps due to their hemorrhagic nature.

Lateralizing signs More than half of patients with brain metastases have lateralizing signs, including hemiparesis, aphasia, or visual field deficits.

Headaches are seen in about half of patients but are rarely an isolated finding of metastatic disease.

Altered mental status Approximately 75% of patients with brain metastases have impairment of consciousness or cognitive function. Some patients with multiple bilateral brain metastases may present with an altered sensorium as the only manifestation of metastatic disease; this finding can be easily confused with a metabolic encephalopathy.

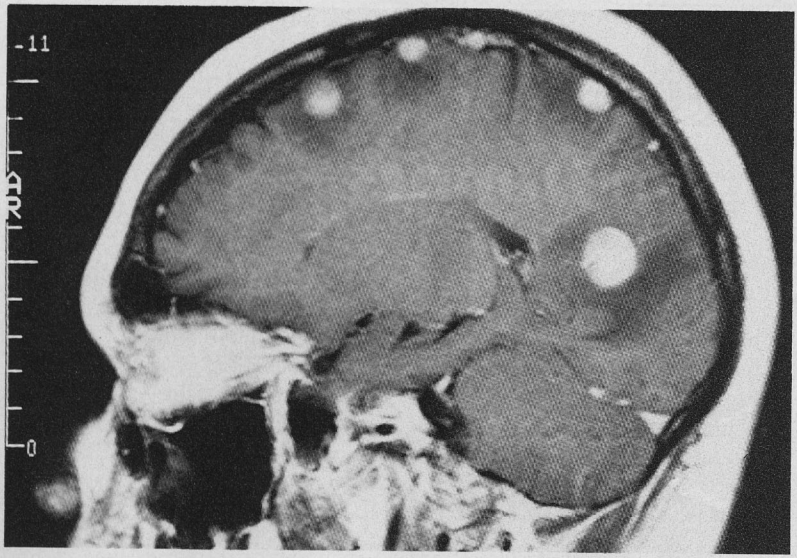

FIGURE 1: Gadolinium-enhanced MRI scan demonstrating multiple brain metastases. Note the edema surrounding each lesion.

Screening and diagnosis

Screening

Screening for brain metastases is performed in only a few clinical situations:

Lung cancer Approximately 10% of patients with small-cell lung cancer (SCLC) have brain metastases at diagnosis, and an additional 20%-25% develop such metastases during their illness. Therefore, cranial CT or MRI is performed as part of the evaluation for extent of disease.

In 25 patients with locally advanced NSCLC (stage IIB-IIIB) treated with multimodality therapy who developed brain metastases, tumor occurred within 2 years of diagnosis in all but 1 patient, and 72% of patients with isolated brain metastases died of CNS disease. These results show that brain screening in high-risk patients is most valuable within the first 2 years after diagnosis *(Ceresoli GL, Reni M, Chiesa G: Cancer 95:605-612, 2002).*

Occasionally, patients with non–small-cell lung cancer (NSCLC) undergo routine cranial CT or MRI prior to definitive thoracotomy, since the presence of brain metastases may influence the choice of thoracic surgical procedure. This approach is particularly valuable in patients with suspected stage IIB or III disease for whom thoracotomy is considered following neoadjuvant therapy.

Diagnosis

CT and MRI The diagnosis of brain metastases is established by CT or MRI. MRI is

the superior test and should be performed whenever feasible in any patient being evaluated for metastatic brain disease (Figure 1). A high-quality, contrast-enhanced MR scan should be obtained to define the number of metastatic nodules and to look for evidence of leptomeningeal disease. If MRI is unavailable, CT is adequate to exclude brain metastases in most patients, but it can miss small lesions or tumors located in the posterior fossa.

Radiographic appearance of lesions On CT or MRI, most brain metastases are enhancing lesions surrounded by edema, which extends into the white matter (Figure 1). Unlike primary brain tumors, metastatic lesions rarely involve the corpus callosum or cross the midline.

The radiographic appearance of brain metastases is nonspecific and may mimic other processes, such as infection. Therefore, the CT or MR scan must always be interpreted within the context of the clinical picture of the individual patient, particularly since cancer patients are vulnerable to opportunistic CNS infections or may develop second primaries, which can include primary brain tumors.

Thyroid transcription factor-1 (TTF-1) is expressed in lung adenocarcinomas and thyroid carcinomas but not in adenocarcinomas from other sites. TTF-1 immunohistochemical staining can identify whether a brain metastasis from an unknown primary is coming from a pulmonary or nonpulmonary source *(Srodon M, Westra WH: Hum Pathol 33:642-645, 2002).*

Pathology

The pathology of metastatic brain lesions recapitulates the pathology of the underlying primary neoplasm. This feature often enables the pathologist to suggest the primary source in patients whose systemic cancer presents as a brain metastasis. However, even after a complete systemic evaluation, the site of the primary tumor remains unknown in 5%-13% of patients with brain metastases.

Staging and prognosis

Any patient with brain metastasis has disseminated systemic cancer, and staging usually is not employed, unless the patient is being considered for surgical resection and the extent of systemic disease is unknown.

For a large proportion of patients with brain metastases, median survival is only 4-6 months after whole-brain radiotherapy. However, some patients (ie, those who are < 60 years old, have a single lesion, and have controlled or controllable systemic disease) can achieve prolonged survival, and these individuals warrant a more aggressive therapeutic approach. Furthermore, most of these patients qualify for vigorous local therapy for their brain metastases, such as surgical resection or, possibly, stereotactic radiosurgery. These approaches can achieve a median survival of 40 weeks or longer.

Treatment

Treatment for brain metastases is both supportive (see chapter 27) and definitive. Definitive treatment includes surgery, radiotherapy, and chemotherapy.

DEFINITIVE THERAPY

Surgery

Resection followed by whole-brain irradiation significantly prolongs survival compared with whole-brain irradiation alone in patients with a solitary brain metastasis, and some patients achieve long-term disease-free survival. Most patients with brain metastases have a life expectancy of < 9 months, but the majority who undergo resection of a solitary metastatic lesion followed by irradiation will die of systemic rather than intracranial disease.

If brain metastases are the presenting sign of systemic cancer and no clear primary source can be identified with routine staging, surgery may also be required to establish a tissue diagnosis and plan further therapy.

In addition, surgical removal of a brain metastasis often reverses the neurologic deficits caused by compression of local structures by tumor and reduces intracranial hypertension.

Excision of metastases is rarely curative, however, as microscopic cells may be left behind. Nevertheless, the reduced tumor burden becomes more amenable to adjuvant irradiation and/or chemotherapy.

Criteria for surgery The decision whether to recommend surgery should be based on the following factors:

Extracranial oncologic status A comprehensive work-up of the patient's extracranial oncologic status is necessary. Extensive critical organ metastases preclude surgery in favor of palliative irradiation as the sole therapy. Brain surgery should not be performed in patients with limited expected survival (3-6 weeks) based on extracranial disease.

Number of metastases In general, only patients harboring a single metastasis are considered for resection. Occasionally, a large tumor will be removed in the presence of multiple smaller nodules if the edema and mass effect of this lesion are causing a substantial neurologic deficit that could be improved by tumor removal.

Three recent studies concluded that when multiple (up to three distinct locations) metastases are resected, either with or without radiotherapy, survival times are identical to those in patients with surgically resected solitary metastases and almost twice as long as those in patients treated by radiation therapy or radiosurgery alone. These studies suggest that a more aggressive surgical approach may be justified in patients with multiple brain metastases who have stable systemic disease.

Recurrence of solitary metastases Up to 20% of solitary metastases may recur in long-term survivors. In these cases, a second operation may be war-

ranted to remove the recurrent lesion and confirm the histologic diagnosis (ie, exclude radionecrosis).

Radiation therapy

For symptomatic patients with brain metastases, median survival is about 1 month if untreated and 3-6 months if whole-brain radiation therapy is delivered, with no significant differences among various conventional radiotherapy fractionation schemes (20 Gy in 5 fractions, 30 Gy in 10 fractions, 40 Gy in 20 fractions). A more protracted schedule is used for patients who have limited or no evidence of systemic disease or for those who have undergone resection of a single brain metastasis, since these patients have the potential for long-term survival or even cure. The use of hypofractionated regimens is associated with an increased risk of late neurologic toxicity.

A recent phase III trial was completed evaluating the role of motexafingadolinium (MGd) as a radiation enhancer in patients with brain metastases. A total of 401 patients were randomized to receive either whole-brain radiotherapy alone or whole-brain radiotherapy plus MGd. There was no difference in median overall survival (5.2 months MGd and 4.9 months control) or median time to neurologic disease progression (9.5 months MGd and 8.3 months control) between the two treatment arms (*Mehta MP, Rodrigus P, Terhaard C, et al: Proc Am Soc Clin Oncol [abstract] 21:286a, 2002).*

Relief of neurologic symptoms The major result of whole-brain radiation therapy is an improvement in neurologic symptoms, such as headache, motor loss, and impaired mentation. The overall response rate ranges from 70% to 90%. Unfortunately, symptomatic relief is not permanent, and symptoms recur with intracranial tumor progression.

Solitary lesion Postoperative whole-brain radiation therapy significantly improves control of CNS disease after resection of a single brain metastasis but has no impact on overall survival. Postoperative whole-brain radiation therapy may be withheld, therefore, in selected patients, such as elderly individuals or those with highly radioresistant primaries (eg, renal cancer), because these patients are vulnerable to the toxic effects of cranial irradiation without reaping the potential benefits.

Multiple lesions Patients with multiple lesions are generally treated with whole-brain radiation therapy alone. Retreatment with a second course of whole-brain radiation therapy can provide further palliation for patients with progressive brain metastases (who have at least a 6-month or longer remission of symptoms after the initial course of cranial irradiation).

Temozolomide (Temodar) given concurrently with whole-brain radiotherapy in patients treated for brain metastates from lung or breast cancer have a higher response rate (complete plus partial responses)—96%, compared with a 66% intracranial response in those receiving whole-brain radiotherapy alone ($P = .017$). Overall survival was not affected, but temozolomide may function as an effective radiation sensitizer in this situation (*Antonadou D, Paraskevaides M, Coliarakis N, et al: Proc Am Soc Clin Oncol [abstract] 20:57a , 2001).*

Concomitant steroid therapy Since the radiographic and clinical responses to whole-brain irradiation take several weeks, patients with significant mass effect should be treated with

steroids during whole-brain radiation therapy. Dexamethasone (16 mg/d) is started prior to therapy, and the dose may be tapered as tolerated during treatment. Occasionally, higher doses are necessary to ameliorate neurologic symptoms. However, most patients can be safely tapered off corticosteroids at the completion of whole-brain radiotherapy.

Radiosurgery

Radiosurgery has been used as sole therapy, as a boost to whole-brain radiation therapy, or for recurrent lesions in patients with brain metastases. Radiosurgery has the advantage of delivering effective focal treatment, usually in a single dose, without irradiating all of the normal brain. It is particularly useful for patients who have 1-3 lesions, each < 4 cm in diameter. Patients with numerous lesions are not good candidates for radiosurgery because some of the ports may overlap, and, more importantly, these patients likely harbor other microscopic lesions in the brain that are not being effectively treated with such focal therapy.

Brain metastases are particularly amenable to treatment with radiosurgery. Metastatic tumors do not infiltrate the brain and tend to have well-circumscribed borders; therefore, they can be targeted effectively with highly focused irradiation techniques that maintain a sharp delineation between the enhancing tumor seen on neuroimaging and normal brain. Furthermore, radiosurgery does not have the operative morbidity that may be associated with resection of a brain metastasis. Consequently, it can be used safely in many patients who are not surgical candidates, and it can even treat lesions in surgically unapproachable locations such as the brainstem.

Radiosurgery can achieve crude focal control rates of 73%-98% over a median follow-up of 5-26 months. Radiosurgery was initially used primarily as a boost after treatment with whole-brain radiotherapy. Three randomized trials have reported on the value of radiosurgery in addition to whole-brain radiotherapy for patients with multiple brain metastases. Although all three studies show a local control advantage and an improvement in quality-of-life end points with the addition of a radiosurgery boost, none shows a statistical advantage in survival. For patients with multiple brain metastases, adding radiosurgery to whole-brain radiotherapy only offers an improved neurologic quality of life with no impact on survival.

Radiosurgery is often considered an alternative to standard surgical resection, but it is unclear whether they are equivalent. Some retrospective studies suggest that the two techniques produce identical results, but a case-control study demonstrated that surgery is superior to radiosurgery in the treatment of a single brain metastasis. An ongoing prospective study being conducted by the Radiation Therapy Oncology Group (RTOG) is comparing the efficacy of radiosurgery vs that of surgery plus whole-brain radiotherapy in the treatment of brain metastases.

Increasingly, radiosurgery is being used as sole therapy for one to three brain metastases. A prospective randomized trial is currently underway to deter-

mine outcome with radiosurgery ± whole-brain radiotherapy, but most investigators expect the results to be similar to those observed in the phase III trial of surgical resection of a single brain metastasis ± radiotherapy: improved local control but no survival benefit. There is growing evidence from large retrospective series that radiosurgery alone may be as effective as radiosurgery plus whole-brain irradiation for the control of CNS disease; however, some series point to a 4% incidence of brain recurrence if whole-brain radiotherapy is withheld. Radiosurgery alone substantially shortens treatment time and eliminates the risk of cognitive impairment associated with whole-brain irradiation, particularly in elderly patients.

Median survival from the time of radiosurgery is 6-15 months, and some patients can live for years without recurrence. Most patients exhibit clinical improvement and decreased steroid requirements after radiosurgery, and only 11%-25% of patients eventually die of neurologic causes.

Temozolomide has some activity against recurrent brain metastases, especially from non–small-cell lung cancer (*Abrey LE, Christodoulou C: Semin Oncol 13:34-42, 2001*).

Treatment recommendations

In patients with one to three brain metastases, aggressive local therapy (surgical resection or radiosurgery) produces superior survival and quality of life than does whole-brain radiation therapy alone. Radiosurgery may be the optimal choice for elderly patients at greater risk for surgical morbidity. Whole-brain radiotherapy does not contribute to survival after surgical resection and probably not after radiosurgery. Increasingly, we are reserving it for use at CNS recurrence and not following a complete resection or radiosurgery with routine whole-brain irradiation.

Chemotherapy

Chemotherapy usually has a limited role in the treatment of brain metastases and has not proven to be effective as an adjuvant therapy after irradiation or surgery. However, it may have some efficacy in patients with recurrent brain metastases who are not eligible for further whole-brain radiation therapy or stereotactic radiosurgery (see box above). In addition, a recent phase III trial of chemotherapy with early vs delayed whole-brain radiotherapy in NSCLC patients with brain metastases showed an identical intracranial response rate and survival. Thus, systemic chemotherapy had some efficacy against brain metastases.

Brain metastases from chemosensitive primary tumors Brain metastases from primary tumors that are chemosensitive, such as SCLC, choriocarcinoma, and breast cancer, may be responsive to systemic therapy. Single drugs or drug combinations should be selected based on their expected activity against the primary tumor.

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CHAPTER 29

AIDS-related malignancies

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Malignancies have been detected in approximately 40% of all patients with acquired immunodeficiency syndrome (AIDS) sometime during the course of their illness. These cancers have been both a primary cause of death in some patients and also a source of considerable morbidity. In the current era of protease inhibitors and highly active antiretroviral therapy (HAART), patients infected with the human immunodeficiency virus (HIV) are surviving longer than ever. HAART appears to have substantially reduced the incidence of Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) and may enhance the efficacy of treatment for those patients who do develop these tumors. Unfortunately, HAART has not shown a similar effect on the development of other types of neoplasms, and the need to care for patients who develop malignancies as part of AIDS remains a challenge. Furthermore, HAART is not available universally, with few patients in resource-poor developing countries having access to antiretroviral drugs.

A survey of the changes in cancer incidence in HIV-infected patients in North America, Europe, and Australia found that the incidence rate of Kaposi's sarcoma declined from 15.2 to 4.9 cases per 1,000 person-years and the incidence rate of non-Hodgkin's lymphoma declined from 6.2 to 3.6 cases per 1,000 person-years between 1992-1996 and 1997-1999. This decline presumably is related to the greater use of potent antiretroviral therapies. No significant changes were seen in incidence rates of Hodgkin's disease or of cervical cancer. The adjusted incidence rate for all other cancers was 1.7 and remained unchanged over this period *(J Natl Cancer Inst 92:1823-1830, 2002).*

KAPOSI'S SARCOMA

KS has been the most common tumor associated with HIV infection, but it currently develops in < 10% of homosexual men with AIDS in the United States and 1%-2% of other HIV-infected persons. The incidence of KS has declined substantially, from 4.8 per 100 person-years in 1990 to 1.5 per 100 person-years in 1997.

Epidemiology

Gender Among AIDS patients in the United States, the incidence of KS is higher in males than in females. There is also a higher incidence of KS in men than in women in Africa (male-female ratio, 2:1), despite the equal prevalence of HIV infection among men and women.

Age The age distribution of AIDS-related KS follows the distribution of HIV infection. As such, AIDS-related KS can occur in all age groups. In US adult males, the most common age of onset of AIDS-related KS is 30-40 years old. No peak age has been reported.

Race No racial or ethnic differences in the incidence of AIDS-related KS have been observed.

Geography In the United States, KS is seen in < 10% of homosexual men with AIDS. The proportion of KS among AIDS-defining diagnoses is lower in parts of Europe, where there are proportionately fewer male homosexual AIDS cases (eg, 6.8% of Italian AIDS patients), and higher in parts of Africa, where KS is endemic in the non–HIV-infected population. Among AIDS cases in the United States, the proportion of patients with KS has declined from the beginning of the AIDS epidemic, possibly as a result of changes in high-risk sexual behavior among homosexual men and the wider use of more effective antiretroviral combination regimens.

Etiology and risk factors

In the United States, the observation that KS occurs predominantly in homosexual men and the epidemiologic evidence that KS has declined among AIDS patients in parallel with the declining incidence of sexually transmitted diseases (STDs) among homosexual men are cited as support for the theory that a sexually transmitted agent may be involved in the development of AIDS-related KS.

Viruses In 1994, unique viral DNA sequences were identified in tumor tissues from patients with AIDS-related KS, which led to the identification of a new virus called KS-associated herpesvirus (KSHV) or human herpesvirus type 8 (HHV-8). HHV-8 has been found in > 90% of AIDS-KS tumors, as well as in classic KS, endemic African KS, and post-organ transplant-related KS. It has also been identified in body cavity-based lymphoma/primary effusion lymphoma, multicentric Castleman's disease, and angio-immunoblastic lymphadenopathy with dysproteinemia (AILD) in HIV-infected patients.

HHV-8 may be transmitted through sexual contact or blood products or during organ transplantation. Seroprevalence of HHV-8 in AIDS-related KS is nearly 100%. More recently, HHV-8 has been found in high concentration in saliva in KS patients, which may account for its high incidence in African children.

HHV-8 is critical in the pathogenesis of AIDS-related KS. The mechanism by which HHV-8 induces KS in susceptible individuals is the subject of intense current investigations.

Environmental and host factors Various environmental and host factors, including HIV- and HHV-8–induced cytokines, AIDS-associated infections, the host's hormonal milieu, immunosuppression, and antiretroviral therapy, may induce or suppress the development of KS and alter its growth.

Signs and symptoms

The manifestations of KS in patients with AIDS are variable and range from small innocuous-looking cutaneous lesions to symptom-producing visceral or oral lesions, which may be quite troublesome and even life-threatening. Just about every internal organ can occasionally be involved with KS in some instances. KS is rarely seen in the bone marrow or CNS.

Skin lesions KS tumors typically begin as flat or raised lesions that may progress to plaque-like or nodular tumors. Lesions vary in size and shape but are generally nonpruritic and painless. They range in color from light pink to red to deep purple. KS lesions may be cosmetically disfiguring and may result in social stigmatization that far exceeds any actual physical impairment.

Dermal and lymphatic infiltration with tumor can result in edema of the extremities, periorbital areas, and genitals and may be complicated by skin breakdown and bacterial cellulitis. Edema can be marked and may prevent patients from wearing shoes and/or walking.

Lesions on the feet can cause pain and hamper walking.

Oral lesions are often asymptomatic but can produce pain and swallowing difficulties.

GI tract involvement with KS is seen in up to 50% of patients. Most lesions are asymptomatic; however, obstruction, bleeding, or enteropathy can occur occasionally.

Pulmonary KS usually presents as dyspnea without fever and may become severely debilitating and rapidly fatal if untreated.

Screening and diagnosis

Currently, there are no screening tests for KS. Although most KS lesions are readily recognized, early lesions may be difficult to diagnose, and the lesions of other diseases (eg, bacillary angiomatosis) may mimic those of KS. Once clinically suspected, the diagnosis of KS is made by biopsy and histologic examination of skin lesions, an excised lymph node, or other tissue or by presumptive diagnosis based on the bronchoscopic or endoscopic appearance of a visceral lesion.

GI KS has a typical red, raised appearance and is difficult to diagnose by biopsy because of the submucosal location of many lesions.

Pulmonary KS In patients with pulmonary KS, chest radiographs typically demonstrate diffuse, reticular-nodular infiltrates, mediastinal enlargement, and, sometimes, pleural effusion. Bronchoscopy may reveal extensive endobronchial involvement with tumor. Definitive diagnosis requires transbronchial or open-lung biopsy. Transbronchial biopsies, however, often yield negative results. A presumptive diagnosis of pulmonary KS may be made, in the absence of fever, based on typical radiographic and endobronchial findings of KS-appearing lesions and after the exclusion of infections.

Thallium and technetium-99m scanning may help differentiate KS from other pulmonary diseases. Patients with KS have been found to have thallium- and technetium-avid scans, whereas pulmonary lymphomas and infections are more typically gallium-avid.

Pathology

Cutaneous KS is a lesion of the dermis composed of a proliferation of aberrant vascular structures lined by abnormal-appearing, spindle-shaped endothelial cells and with extravasated erythrocytes and leukocytes within the structures. These spindle cells are generally sparse in early stages but become more numerous and stack up between the vascular structures as the tumor advances. Infiltration of mononuclear leukocytes, including plasma cells, T cells, and monocytes, is more prominent in earlier lesions. The histologic appearance of KS in AIDS is similar to that seen in non–HIV-infected patients.

Cell of origin The KS tumor cell is believed to be of mesenchymal, endothelial origin. Several endothelial cell markers are positive in KS, including stains for Ulex europaeus, CD31, CD34, and EN-4. In addition, the tumor stains with factor VIIIa, CD68, and α-actin but not with PAL-E.

Staging and prognosis

Prognostic factors Although it is difficult to predict from the initial presentation which patients are most likely to have rapidly progressive tumors, several retrospective studies have shown a correlation of survival with the degree of T-cell immunodeficiency, as reflected in the absolute number of T-helper cells. Prior opportunistic infections or the presence of such symptoms as fevers, night sweats, and weight loss (B symptoms) also portend a poor prognosis. Patients who develop KS or whose tumor growth accelerates after an opportunistic infection often have a more aggressive clinical course. Patients with pulmonary involvement generally have a poor prognosis.

Staging system A tumor classification system has been proposed for AIDS-related KS by the oncology committee of the AIDS Clinical Trials Group (ACTG). This system segregates patients into good or poor prognostic groups based on tumor characteristics, immune system function, and systemic illness (the TIS system; see Table 1). A retrospective analysis of 294 patients with AIDS-related KS has shown that the TIS system is a valid predictor for survival.

Gauging response to therapy Given the heterogeneity and unpredictable growth of this tumor, it is often difficult to gauge objective responses. The peculiarities of this multicentric tumor make some subjectivity almost inevitable in gauging treatment responses.

Treatment

The treatment of AIDS-related KS requires an individualized approach, based on the extent and location of the lesions, the wishes and treatment needs of the patient, the presence of tumor-associated symptoms (eg, pain, bleeding, edema), the presence of other AIDS-associated illnesses, and the patient's tolerance of medications. Nevertheless, the following general statements can be made:

- Patients with widespread symptomatic disease or life-threatening visceral involvement require prompt, cytoreductive treatment with one or more chemotherapeutic drugs.
- Even in the absence of symptomatic visceral disease, the disfigurement and emotional distress of having these visible reminders of AIDS may mandate treatment for psychological reasons.
- For patients with asymptomatic indolent lesions, aggressive treatment is not mandatory, but these patients may derive substantial benefits from investigational therapies that are directed against HIV or HHV-8 or that may interrupt the pathogenesis of KS and/or restore immune competence.

Treatment options

With the introduction of protease inhibitors and non-nucleoside reverse transcriptase inhibitors for HIV, cases of KS regression with combination antiretroviral therapy have been reported. Because KS seems to be influenced

TABLE 1: Staging classification for AIDS-related KS[a]

Characteristic	Risk status	
	Good risk (0)	**Poor risk (1)**
	All of the following:	Any of the following:
Tumor (T)	Tumor confined to skin and/or lymph nodes and/or minimal oral disease[b]	Tumor-associated edema or ulceration; extensive oral KS; GI KS; KS in other non-nodal viscera
Immune system (I)	CD4 cells ≥ 150/mm^3	CD4 cells < 150/mm^3
Systemic illness (S)	No history of opportunistic infection or thrush; no B symptoms[c]; performance status ≥ 70 (Karnofsky)	History of opportunistic infection and/or thrush; B symptoms; performance status < 70 (Karnofsky); other HIV-related illness (eg, neurologic disease, lymphoma)

From Krown SE, Metroka C, Wernz JC: J Clin Oncol 7:1201, 1989, as modified by Krown SE, et al: J Clin Oncol 15:3085, 1997.

[a] Patients are assigned a disease state T**X**I**X**S**X**, where X corresponds to the risk designation (0 or 1) for each risk category

[b] Minimal oral disease is non-nodular KS confined to the palate

[c] B symptoms: unexplained fever, night sweats, > 10% involuntary weight loss, or diarrhea persisting for more than 2 weeks

by the state of HIV infection, we believe that all patients with AIDS-related KS should have their HIV infection under optimal control. There is no one best anti-HIV regimen, and oncologists should consult with infectious disease specialists familiar with the treatment of HIV infection. Eventually, even with good anti-HIV therapy, most patients with AIDS-related KS will require some form of treatment for their tumor.

Local treatments, including cryotherapy, topical retinoic acid, intralesional chemotherapy and other sclerosing agents, and local radiation, can produce good local control of tumors. Interferon-alfa (IFN-α [Intron A, Roferon-A]) and cytotoxic chemotherapy are effective systemic treatments for patients with more extensive or symptomatic disease. Single-agent or combination chemotherapy is effective in controlling tumors, even in patients with extensive disease and severe immune deficiencies (Table 2). The use of hematopoietic growth factors has facilitated the administration of myelosuppressive treatments, such as IFN-α and chemotherapy.

IFN-α

The first treatment licensed for AIDS-related KS was recombinant IFN-α. Tumor responses have been seen in approximately 30% of patients treated with SC interferon given either daily or 3 times weekly. Current practice is to administer IFN-α 3 times weekly by SC injection. Unmaintained response durations in trials of IFN-α monotherapy have ranged from 12 to 24 months in complete responders and from 8 to 12 months in partial responders.

Duration of therapy The optimal duration of IFN-α treatment is unknown; however, many patients relapse within a few months after discontinuation of therapy. Reinduction of second responses with IFN-α after relapse may be unreliable and often is of short duration. It is therefore generally recommended that treatment with IFN-α be continued for as long as drug tolerance and tumor responses continue.

Dose The optimal dose of IFN-α also has not been clearly established. IFN-α is generally administered at either 3 or 5 million units SC 3 times weekly, together with antiretroviral therapy.

Major dose-limiting toxicities of IFN-α include fever, chills, rigor, and other flu-like symptoms. They are dose related and often observed at the initiation of treatment but lessen somewhat with continued use. Neutropenia, transaminase elevation, depression, peripheral neuropathy, and other neuropsychiatric abnormalities may also occur, especially when IFN-α is used in combination with various antiretroviral medications.

Other side effects include headaches, cognitive impairments, paresthesias, and mild thrombocytopenia. As the subjective side effects of IFN-α are also common in HIV-related or other conditions, care must be taken to avoid ascribing all of these symptoms to drug toxicity and overlooking treatable infections and other conditions.

Factors correlating with response Factors that appear to correlate with a greater likelihood of tumor regression to IFN-α include a negative history for opportunistic infections and the absence of B symptoms.

Retinoids

Alitretinoin gel 0.1% (9-*cis*-retinoic acid [Panretin]) has received FDA approval for the topical treatment of localized cutaneous KS. This compound inhibits the growth of KS and induces apoptosis of KS cells by binding to retinoic acid receptors on the cell surface.

Phase II clinical trials comparing 3-4 times daily application of alitretinoin vs placebo gel demonstrated a 35% rate of complete and partial responses in the alitretinoin-treated patients, as compared with a rate of 18% in controls.

Median time to response to alitretinoin was 29-34 days, with a median duration of response of 12-16 weeks. Responses were seen in both previously untreated and previously treated KS patients and were not dependent on patients' CD4 cell count.

Local cutaneous adverse reactions to alitretinoin include erythema, skin irritation, skin cracking, flaking, peeling, and desquamation. The severity of these reactions can be mitigated with topical vitamin E.

TABLE 2: Chemotherapy for AIDS–related KS

Regimen	Dose	Response rate[a] (%)
Vincristine	2 mg/wk IV	20-60
Vinblastine	0.05-0.1 mg/kg/wk IV	25-30
Doxorubicin	20 mg/m² IV every other week	50-60
Etoposide	150 mg/m² IV every day × 3 q3-4wk	75
Vinorelbine	30 mg/m² IV q2wk	47
Liposomal daunorubicin	40 mg/m² IV q2-4wk	25-70
Liposomal doxorubicin	20 mg/m² IV q2-4wk	58-63
Paclitaxel	100-135 mg/m² IV over 3 h q2-4 wk	60-72
Vincristine + vinblastine	2 mg IV (vincristine) alternating with 0.1 mg/kg IV (vinblastine) every other week	45
Vincristine + bleomycin	2 mg IV (vincristine) + 10 mg/m² IV (bleomycin) q2wk	23-70
Doxorubicin + bleomycin + vincristine	10 mg/m² IV (doxorubicin) + 10 mg/m² IV (bleomycin) + 1-2 mg IV (vincristine) q2wk	87

[a] Complete responses plus partial responses

Alitretinoin should be reserved for patients who do not require systemic treatment for visceral disease. However, it may be used in conjunction with other treatments for cutaneous disease.

Oral 9-*cis*-retinoic acid has also been investigated in patients with AIDS-related KS and found to have a 37% response rate.

Bexarotene (Targretin), an oral retinoid X receptor (RXR)-selective agonist, also has been studied in patients with AIDS-related KS, with an overall response rate of 33% in one study.

Chemotherapy

For patients with more widely disseminated, rapidly progressive, or symptomatic disease, systemic chemotherapy is generally warranted. Chemotherapy drugs are included in Table 2.

Antiretroviral drugs A total of 16 anti-HIV drugs have received FDA approval, and more are in various stages of clinical development. When evaluated by an oncologist, the majority of HIV-infected individuals will be taking some anti-HIV drugs. The interactions between cytotoxic chemotherapy and the various anti-HIV drugs have not been fully studied. Thus, oncologists treating patients with AIDS-related KS should continue to monitor them frequently for side effects.

Combination regimens The two most frequently utilized combination chemotherapy regimens are Adriamycin (doxorubicin), bleomycin (Blenoxane), and vincristine (ABV), and bleomycin and vincristine (BV). These regimens were initially reported to yield tumor response rates in excess of 70%-90%, with good palliation of symptoms, including decreased edema, decreased pain, and, in patients with pulmonary KS, respiratory improvement and alleviation of obstructive symptoms. A beneficial effect of these combinations on survival has not been clearly demonstrated, however.

Early reports of a high response rate with these combination regimens have not been reproduced by later multicenter trials. A conservative response rate of 50%-60% has been reported in more contemporary phase III trials. The discrepancy in response rates most likely stems from differences in the response criteria used.

Liposomal anthracyclines (eg, liposomal doxorubicin and liposomal daunorubicin) are also very effective in inducing tumor regression in KS. Clinical trials have shown that liposomal anthracyclines as single agents can achieve a response rate equal to or better than the ABV combination regimen. As such, the liposomal anthracyclines have become the first-line chemotherapy for AIDS-related KS.

The dose-limiting toxicity is neutropenia, and many patients will require the use of granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) after several cycles of treatment. Other common side effects include nausea, fatigue, anemia, and thrombocytopenia. A palmar-plantar syndrome, characterized by acute painful erythematous swelling of the hands and feet, has been

reported with the use of liposomal doxorubicin. Once the symptoms resolved, readministration of liposomal doxorubicin did not necessarily reproduce the syndrome. Neither of the liposomal anthracyclines has been reported to depress left-ventricular function.

Paclitaxel (Taxol) has been shown to produce responses in both chemotherapy-naive KS patients and patients with refractory tumors, including those refractory to liposomal anthracyclines. Dosage is typically 100-135 mg/m^2 IV given over 3 hours every 2-4 weeks.

The dose-limiting toxicity is neutropenia. Other reported toxicities include anemia, stomatitis, alopecia, and fatigue. Neuropathy has not been a major problem with this low-dose approach.

Investigational agents Other drugs under investigation for the treatment of KS include thalidomide (Thalomid), antiviral drugs, matrix metalloproteinase inhibitors (MMPs), and several antiangiogenesis compounds. Studies of compounds that may inhibit HHV-8 are also in development or in early clinical testing in KS patients.

Radiation therapy

Although radiation therapy can easily produce sufficient regression of KS to be useful for palliation of symptomatic disease or cosmetic improvement of disfiguring lesions, this practice has become less common as HAART has changed the natural history of AIDS. More than 90% of lesions will respond (complete responses [CRs] and partial responses [PRs]). Local radiation therapy commonly alleviates pain and bleeding, lessens edema, and shrinks obstructing lesions.

Treatment technique For most superficial lesions, a single, shaped, en face beam of relatively limited penetration (approximately 100 kV) works well. A relatively low-energy electron beam (eg, 6 MeV) often can be used with shielding as an alternative to superficial x-rays.

Large lesions For very large lesions, electron beams are used more often, due to the limited penetration of kilovoltage x-ray beams and the limited width of the treatment cones attached to most superficial x-ray units. For patients with more widespread tumors of the leg with edema, parallel opposed megavoltage x-ray beams and overlying bolus material are often used to provide homogeneous irradiation to the entire area.

Dose fractionation regimens Several dose fractionation regimens have proven effective in AIDS-related KS. As this tumor is very radiosensitive, almost any dose of radiation therapy can produce some response. Interestingly, in vitro irradiation of KS cell cultures induces the cells to produce interleukin-6 (IL-6) and oncostatin M (OSM), which, in turn, make the cells more sensitive to radiation therapy.

For most cutaneous lesions, a single treatment of 800 cGy will produce a short-term response. For lesions on sensitive structures (eg, penis, hands, conjunctivae), some radiation oncologists attenuate treatment to a total dose of 2,000 cGy

administered in 300 cGy increments (accepting a 50% decrease in CR rate), whereas 3,000 cGy delivered over 2 weeks is more typically used for lesions in general.

Prospectively acquired data clearly demonstrate a dose-response relationship for radiation therapy in AIDS-related KS. A dose of 4,000 cGy delivered in 20 fractions over 4 weeks was significantly more effective than 2,000 cGy in 10 fractions or 800 cGy in 1 fraction, as measured by higher response rate, longer duration of tumor control, and the absence of residual hyperpigmentation. However, the short- and medium-term effects of moderately intense but briefer regimens, such as 3,000 cGy in 10 fractions over 2 weeks, probably are equivalent to those of higher total dose, more protracted regimens, and the moderately intense regimens require only half the time to deliver.

For patients with an anticipated survival of < 3 months, in whom the response duration may be of less overall importance, a single fraction of 800 cGy is likely to provide the same benefit as the more intensive regimens. In contrast, small lesions in patients who are expected to survive for at least 1 year should be treated with fractionated radiation therapy, such as 3,000 cGy in 10 fractions over 2 weeks.

NON-HODGKIN'S LYMPHOMA

The incidence of NHL is 60 times higher in individuals with HIV infection than in the general population. The overall occurrence of lymphoma as a manifestation of AIDS has declined somewhat as treatment of HIV has improved.

Although NHL currently comprises $< 5\%$ of all initial AIDS-defining conditions, it accounts for as many as 15% of all AIDS-related deaths. The majority of patients present with advanced-stage, high- or intermediate-grade, B-cell lymphoma and have a high frequency of extranodal involvement. Primary CNS lymphoma occurs in approximately 0.5% of patients with AIDS.

The majority of patients with AIDS-related lymphoma have advanced HIV disease. Median CD4 cell counts in patients with systemic lymphoma range from 100 to 200 cells/mm^3, whereas CD4 cell counts < 50 cells/mm^3 are found in nearly all patients with primary CNS lymphoma.

Epidemiology

At-risk groups NHL occurs with approximately equal frequency in all population groups infected by HIV, including IV drug users, homosexual-bisexual men, transfusion recipients, and patients with hemophilia.

Gender and race AIDS-related NHL is seen more frequently in men than in women and occurs more often in whites than in blacks.

Age The age distribution of AIDS-related NHL follows the distribution of HIV infection. Primary CNS lymphoma occurs with the same frequency in all age groups.

Geography Current data do not indicate any geographic differences in the incidence of AIDS-related NHL.

Etiology and risk factors

AIDS-related NHL is believed to arise as a consequence of continued stimulation of B-cell proliferation as a result of HIV, Epstein-Barr virus (EBV), and other infections, all of which occur in the setting of profound T-cell immunodeficiency. Recently, an association between the polyomavirus, simian virus 40 (SV40), and diffuse large B-cell and follicle-type lymphoma has been detected. HIV also induces the expression of a number of cytokines (eg, IL-6 and IL-10) that can further increase B-cell activation.

Small noncleaved lymphomas Genetic errors are increased in the setting of chronic B-cell proliferation, and a variety of chromosomal translocations resulting in oncogene activation can lead to polyclonal and monoclonal B-cell expression. Other molecular biological abnormalities associated with small noncleaved lymphomas include expression of an abnormal TP53 (alias p53) tumor-suppressor gene and the c-*myc* or *ras* oncogene.

Immunoblastic lymphoma The pathogenesis of AIDS-related immunoblastic lymphoma appears to be distinct from that of small noncleaved lymphoma and is more likely related to EBV infection without c-*myc* dysregulation. Clonal integration of EBV within tumor cells, with expression of various latent EBV proteins, has been demonstrated in essentially all cases of AIDS-related primary CNS lymphoma and in as many as two-thirds of systemic lymphomas.

Diffuse large cell lymphoma The specific molecular aberrations described in patients with AIDS-related diffuse large cell lymphoma appear distinct as well, with recent descriptions of abnormal *bcl*-6 expression in approximately 40% of cases.

Body cavity–based lymphoma/primary effusion lymphoma appears to be highly associated with HHV-8 and EBV. The tumor cells stain positive for CD45. The disease appears to occur predominantly in males and may coexist with KS in patients with AIDS.

Signs and symptoms

B symptoms (ie, fever, weight loss, and night sweats) are seen in approximately 80% of patients with systemic AIDS-related NHL. In these patients, it is mandatory to exclude the presence of occult opportunistic infections before ascribing B symptoms to the lymphoma itself.

Extranodal involvement Advanced-stage disease is expected in the majority of patients, with extranodal involvement reported in 60%-90% of patients in most series. Common sites of extranodal involvement include the CNS (occurring in approximately 30% of patients), GI tract (25%), and bone marrow (25%). Essentially any other site in the body can also be involved, including the rectum, soft tissue, oral cavity, lungs, and heart.

CNS lymphoma Patients with primary CNS lymphoma often present with focal neurologic deficits, seizures, and/or altered mental status. Any site in the brain

may be involved, and one to four space-occupying lesions are usually seen on MRI or CT scan.

Other sites Changes in bowel habits, GI bleeding, weight loss, pain, and hepatomegaly are common presenting symptoms in patients with GI involvement. Pancytopenia may indicate bone marrow involvement.

Primary effusion lymphoma Patients usually present with pleural or pericardial effusion without an identifiable mass. Pain, shortness of breath, and B symptoms are the main initial complaints.

Screening and diagnosis

Diagnosis of NHL in patients with AIDS requires histologic confirmation by biopsy with immunophenotypic and/or molecular gene rearrangement studies.

A complete staging evaluation should be done in all patients. This should include:

- CT or MRI of the head and chest/abdomen/pelvis
- bone marrow aspiration and biopsy
- liver function studies
- spinal fluid analysis

Assessing spinal fluid for EBV The presence of EBV DNA in CSF, as determined by polymerase chain reaction (PCR), appears to have a high specificity and sensitivity for the diagnosis of primary CNS lymphoma. The use of thallium single-photon emission computed tomography (SPECT) may further increase the diagnostic yield.

Pathology

Common tumor types Over 95% of AIDS-related NHL cases are of B-lymphocyte origin. Most AIDS-related NHL tumors are high-grade types, including the immunoblastic and small noncleaved lymphomas. Diffuse large cell lymphoma constitutes up to 30% of AIDS lymphomas.

Less common tumor types Although not considered part of the AIDS epidemic, several cases of T-cell lymphoma occurring in HIV-infected patients have been described. In addition, cases of Ki-1–positive, large cell anaplastic lymphoma have been reported in HIV-infected patients. The clinical and pathologic characteristics of these forms of lymphoma are similar to those seen in non–HIV-infected individuals.

CNS lymphomas are typically of the immunoblastic or large cell type.

GI and oral cavity lymphomas Large cell or immunoblastic lymphomas are also more likely to involve the GI tract and oral cavity than are small noncleaved lymphomas.

Primary effusion lymphoma The cells are large and pleomorphic with promi-

nent nucleoli and immunoblastic morphology. Clonal immunoglobulin DNA rearrangement demonstrates clonality of the tumor cells but not surface immunoglobulin expression.

Staging and prognosis

Staging system Staging of AIDS-related NHL is the same as that for non–AIDS-related NHL. The Ann Arbor classification system for staging of NHL is utilized (see chapter 32), and the staging work-up includes imaging studies, as well as bone marrow and CNS evaluation for lymphomas.

Prognostic factors Four factors have been shown to correlate most closely with shorter survival in patients with systemic AIDS-related NHL:

- a history of opportunistic infection prior to the lymphoma
- CD4 cell count $<$ 100 cells/mm^3
- Karnofsky performance score $<$ 70
- stage IV disease, especially if due to bone marrow or meningeal involvement

In patients without these findings, median survival is typically 11-12 months, as compared with a median survival of approximately 4-5 months in those with one or more of these adverse prognostic features.

Three factors correlate with *better* survival in patients with primary CNS lymphoma:

- Karnofsky score $>$ 70
- age $<$ 35 years
- adequate dose of radiation therapy

Type of lymphoma To date, no major differences have been seen in response or survival among the various pathologic types of systemic AIDS-related NHL. Patients with polyclonal lymphomas appear to have better tumor responses to chemotherapy and better survival. Patients with primary CNS lymphoma have an extremely poor prognosis, with a median survival of only 2-3 months despite therapy; treatment with potent antiretroviral therapy does seem to improve survival. Prognosis for patients with primary effusion lymphoma is also poor, with a median survival of only 5 months.

Treatment

TREATMENT OF SYSTEMIC NHL

Chemotherapy

The mainstay of treatment for patients with systemic AIDS-related NHL is chemotherapy. As the likelihood of dissemination is great, AIDS patients who develop NHL must be assumed to have widespread disease at presentation

TABLE 3: Chemotherapy for AIDS-related NHL

Regimen	Drugs and dosage	Cycle length	CR rate (%)	Median survival
m-BACOD	Methotrexate, 500 mg/m^2 IV on day 15, with leucovorin, 25 mg PO q6h × 4, after completion of methotrexate	q 28 d	41	35 wk
	Bleomycin, 4 U/m^2 IV on day 1			
	Adriamycin, 25 mg/m^2 IV on day 1			
	Cyclophosphamide, 300 mg/m^2 IV on day 1			
	Oncovin, 1.4 mg/m^2 IV on day 1 (maximum, 2 mg)			
	Dexamethasone, 3 mg/m^2 PO on days 1-5			
CDE	Cyclophosphamide, 800 mg/m^2/96 h IV	q 28 d	46	8.2 mo
	Doxorubicin, 50 mg/m^2/96 h IV			
	Etoposide, 240 mg/m^2/96 h IV			
EPOCH	Etoposide, 200 mg/m^2/96 h IV	q 3-4 wk	60	5.6 mo
	Oncovin, 2 mg IV on day 1			
	Doxorubicin, 40 mg/m^2/96 h IV			
	Cyclophosphamide, 187 mg/m^2 IV on day 5 (if CD4 < 100) or 375 mg/m^2 IV on day 5 (if CD4 ≥ 100)			
	Prednisone, 60 mg/m^2 PO on days 1-6			
CEOP	Cyclophosphamide, 750 mg/m^2 IV on day 1	q 3-4wk	47	10 mo
	Epirubicin, 50 mg/m^2 IV on day 1			
	Oncovin, 2 mg IV on day 1			
	Prednisone, 100 mg PO on days 1-5			
CHOP	Cyclophosphamide, 750 mg/m^2 IV on day 1	q 21d	63	9 mo
	Doxorubicin, 50 mg/m^2 IV on day 1			
	Oncovin, 1.4 mg/m^2 IV on day 1 (maximum, 2 mg)			
	Prednisone, 60 mg PO on days 1-5			

CR = complete response

and should be treated with systemic chemotherapy, even if dissemination is not confirmed on routine staging evaluation.

Some of the commonly used regimens designed for AIDS-related NHL are listed in Table 3. No regimen appears to be superior to any other, although early unconfirmed findings show that the EPOCH regimen (etoposide, prednisone, Oncovin [vincristine], cyclophosphamide [Cytoxan, Neosar], doxorubicin HCl) gives the best results to date.

CNS prophylaxis with either intrathecal cytarabine (Ara-C; 50 mg) or intrathecal methotrexate (10-12 mg) every week for 4 treatments has been shown to be effective in reducing the incidence of CNS relapse.

In an Italian study, rituximab (Rituxan), an anti-CD 20 MoAb, also has been studied in combination with CDE (cyclophosphamide, doxorubicin, etoposide) at lower doses and has been shown to have an overall response rate of 86% and an actuarial 2-year survival rate of 80%.

The importance of pathologic subtypes and other prognostic indicators for lymphoma tumor response and survival is still under evaluation. The French-Italian Cooperative Lymphoma Group has shown that patients with good prognostic factors (CD4 > 200/mm^3, no CNS or bone marrow involvement, and no B symptoms) tolerate intensive chemotherapy better, have higher response rates, and survive longer. Patients with poor prognostic features are less likely to benefit from more intensive chemotherapy regimens.

Dose intensity A randomized trial (ACTG 142) showed no differences between standard-dose m-BACOD (methotrexate, bleomycin, Adriamycin, cyclophosphamide, Oncovin, and dexamethasone) and reduced-dose m-BACOD with respect to complete response rate, time to disease progression, or overall survival. Subanalysis using a CD4 cell count of 100 cells/mm^3 as the cutoff point also showed no statistical differences in these end points in the two treatment groups. The standard-dose arm showed a statistically significant increase in toxicity, especially neutropenia. Therefore, the prudent approach for the treatment of patients with AIDS-related NHL is to use low- or standard-dose regimens, such as CHOP (cyclophosphamide, doxorubicin HCl, Oncovin, and prednisone) or m-BACOD, with myeloid growth factor support.

Certain subsets of patients with high CD4 cell counts (> 100 cells/mm^3), no B symptoms, lower disease stage at presentation (stage I or II), and good performance status (0 or 1) may enjoy prolonged survival (> 2 years) when treated with either standard-dose or intensive, high-dose regimens. However, until more data are available to clearly identify these patient subsets, the intensive, high-dose approach is not recommended outside of clinical trial settings.

Growth factor support The major dose-limiting toxic effect of multiagent chemotherapy regimens is myelosuppression. Studies of m-BACOD or CHOP chemotherapy demonstrated that coadministration of myeloid hematopoietic growth factors enhanced patient tolerance of these regimens.

Salvage chemotherapy Patients in whom initial treatment fails or who relapse after initial remission rarely achieve a prolonged second remission.

Mitoguazone (MGBG), given at a dose of 60 mg/m^2 on days 1 and 8 and then every 2 weeks, achieved a CR in 11.5% of patients with primary refractory or relapsed disease. The median survival for the whole group was 2.6 months, whereas a median survival of 21.5 months was noted in the complete responders.

Second-line chemotherapy (eg, ESHAP [etoposide, methylprednisolone, high-dose Ara-C, Platinol]) has been shown to have a CR of up to 31% and a PR of 23%, with a median survival of 7.1 months, in patients with refractory or relapsed AIDS-related NHL.

Radiation therapy

The role of radiotherapy in systemic lymphoma is limited to consolidation of the effects of chemotherapy. Treatment principles are similar to those used for aggressive NHL in the non-HIV setting and typically involve the use of involved or extended fields only.

Lymphomatous meningitis For patients with lymphomatous meningitis and/or radiographically detectable cerebral deposits, "step-brain" irradiation (including the covering meninges) is administered along with intrathecal chemotherapy to control microscopic spinal disease. Focal radiation therapy may be required for known tumor deposits in the spine. Unfortunately, many such patients develop multiple deposits anywhere along the spinal axis, either synchronously or metachronously.

Fractionated doses of 3,000-4,500 cGy may be used to control local lymphoma deposits in nodal areas. Patients who have lymphomatous meningitis typically have a poor prognosis and are best treated with regimens that do not unduly occupy their time (eg, 3,000 cGy in 10 fractions over 2 weeks).

TREATMENT OF PRIMARY CNS LYMPHOMA

A very effective therapy for patients with AIDS-related CNS lymphoma has not yet been found.

Radiation therapy

The conventional standard of treatment is step-brain irradiation, which can result in response rates of 50% and improve survival, as compared with untreated patients, even when adjusted for antiretroviral therapy, CD4 cell count, and time to diagnosis. Treatment is directed to the entire cranial contents, including the meninges down to C2.

Doses equivalent to 3,900 cGy (or more) delivered at 200 cGy/fraction appear to be associated with increased survival. Better Karnofsky performance scores and younger age at the time of treatment are also associated with longer survival. Mean survival ranges from 2 to 6 months, with death often due to complicating opportunistic infections.

HAART

By itself, HAART appears to have some activity against CNS lymphoma. Observers have reported anecdotal instances of regression of biopsy- proven, AIDS-related CNS lymphoma after institution of HAART.

Chemotherapy

As HAART has changed the biological behavior of AIDS, there has been more interest in using high-dose methotrexate, based on evidence of activity in non–AIDS-associated disease. Studies to evaluate short courses of combination chemotherapy or the use of less myelosuppressive single agents followed by whole-brain irradiation are currently in progress. Although these approaches appear to be efficacious in non–HIV-infected patients with primary CNS lymphoma, the available data do not suggest that this approach is superior to CNS irradiation alone in AIDS patients.

CERVICAL CARCINOMA

Cervical carcinoma in the setting of HIV infection has been recognized as an AIDS-defining malignancy since 1993. Unfortunately, in some women, cervical carcinoma may be the first indication that they have HIV infection.

Cervical intraepithelial neoplasia (CIN) is also seen in association with HIV infection. These premalignant lesions, also known as squamous intraepithelial lesions (SILs), may foretell a higher incidence of cervical carcinoma among HIV-infected women. SILs have been associated with human papillomavirus (HPV), particularly those subtypes with greater oncogenic potential, such as serotypes 16, 18, 31, 33, and 35.

Epidemiology

Prevalence of HIV infection and cervical abnormalities The risk of HIV infection in women with an abnormal Pap smear varies with the prevalence of HIV infection in the given population. Screening in clinics in high-prevalence areas has yielded HIV-positivity rates of between 6% and 7% (and up to 10% in parts of Africa). In such high-prevalence areas, among women under the age of 50 years with cervical carcinoma, up to 19% of women were found to be HIV positive. HIV-positive women have up to a 10-fold increased risk of abnormal cervical cytology. Several centers have reported abnormal cytology rates of 30%-60% in HIV-positive women and Pap smears consistent with cervical dysplasia in 15%-40%. The prevalence of cervical dysplasia increases with declining CD4 cell counts in HIV-infected women.

Nationwide, invasive cervical carcinoma was found in 1.3% of women with AIDS. In New York, invasive cervical carcinoma constitutes 4% of AIDS-defining illnesses in women. Recent findings from linkage studies in the US and Italy clearly have shown increased rates of cervical cancer in women with HIV.

Race and geography The prevalence of invasive cervical carcinoma among US Hispanic and black women is lower than that in white women. However, this difference may stem from a difference in access to health care. The southern and northeastern sections of the United States have a higher reported number of cases of HIV-associated invasive cervical carcinoma.

Etiology and risk factors

The severe cellular immunodeficiency associated with advanced HIV infection may allow oncogenic viruses to flourish and may also compromise the body's immunologic defenses that control the development of these tumors.

HPV There is abundant evidence that HPV infection is related to malignant and premalignant neoplasia in the lower genital tract. HPV serotypes 16, 18, 31, 33, and 35 are the most oncogenic and have been associated with invasive cervical carcinoma and progressive dysplasia. The prevalence of cervical SILs among HIV-infected women may be as high as 20%-30%, with many having higher cytologic and histologic grade lesions.

Signs and symptoms

The majority of cervical SILs are detected on routine cytologic evaluation of Pap smears in women with HIV infection.

Advanced invasive disease Postcoital bleeding with serosanguineous and/or foul-smelling vaginal discharge is usually the first symptom of more advanced invasive disease. Lumbosacral pain or urinary obstructive symptoms may indicate advanced disease.

Screening and diagnosis

Because the majority of patients with cervical dysplasia or early invasive cancer are asymptomatic, frequent cytologic screening of women at risk for HIV infection must be undertaken.

Screening of HIV-positive women Current screening recommendations call for women with HIV infection to have pelvic examinations and cytologic screening every 6 months. Pap smears indicating cervical SILs must be taken very seriously, and abnormalities justify immediate colposcopic evaluation. Although abnormalities are sometimes missed by relying solely on cytologic screening, recommendations for the use of routine colposcopy have not yet been established.

Screening of women with a history of cervical SILs For women who have a history of cervical SILs, more frequent reevaluation and cytologic screening should be undertaken. Since these women are at high risk for recurrence or development of lesions in other areas of the lower genital tract, post-therapy surveillance with repeat colposcopy also is warranted.

Work-up of women with invasive carcinoma For women with invasive carcinoma, complete staging should be undertaken; this should include pelvic examination, CT of the pelvis and abdomen, chest x-ray, and screening laboratory tests for hepatic and bone disease. In addition, full evaluation and treatment for HIV and related complications should be initiated.

Pathology

Squamous cell carcinoma Most cases of cervical carcinoma are of the squamous cell type.

Staging and prognosis

The staging classification for cervical carcinoma (see chapter 20), as adopted by the International Federation of Gynecology and Obstetrics (FIGO), also applies to AIDS patients.

Cervical dysplasia in HIV-infected women is often of higher cytologic and histologic grade. These women are more likely to have CIN II-III lesions with extensive cervical involvement, multisite (vagina, vulva, and perianal) involvement, and endocervical lesions.

HIV-infected women with cervical carcinoma typically present with more advanced disease and appear to have a more aggressive clinical course. Tumors are typically high grade with a higher proportion of lymph node and visceral involvement at presentation. Mean time to recurrence after primary treatment is short, and many patients have persistent disease after primary therapy. Median time to death in one series was 10 months in HIV-infected women, as compared with 23 months in HIV-negative patients.

Treatment

TREATMENT OF PREINVASIVE DISEASE

Cryotherapy, laser therapy, cone biopsy, and loop electrosurgical excision procedure (LEEP) have all been used to treat preinvasive disease in HIV-infected patients. Short-term recurrence rates of 40%-60% have been reported.

Determinants of recurrence Immune status of the patient seems to be the most important determining factor for recurrence. Close surveillance after initial therapy is critical, and repetitive treatment may be necessary to prevent progression to more invasive disease.

TREATMENT OF CERVICAL CARCINOMA

The same principles that guide oncologic management of the immunocompetent patient with cervical carcinoma (see chapter 20) are utilized in AIDS patients with this cancer.

Surgery can be undertaken for the usual indications, and surgical decisions should be based on oncologic appropriateness and not on HIV status.

Radiation therapy As most AIDS patients with cervical cancer present with advanced disease, radiation therapy is indicated more often than surgery. If the patient's overall physical condition permits, treatment regimens are identical to those used for the same stage disease in uninfected individuals (see chapter 20). It is important to note that the standard of care for advanced carcinoma of the cervix (stages III-IV, without hematogenous dissemination) has changed from radiation alone to a combination of radiation and concurrent cisplatin (Platinol)-based chemotherapy. At present, there is insufficient evidence to suggest that radiation or other treatments for cervical carcinoma in AIDS patients is any less effective than in similar non-HIV-infected individuals.

Chemotherapy regimens, such as cisplatin (50 mg/m^2) or carboplatin (Paraplatin; 200 mg/m^2), bleomycin (20 U/m^2; maximum, 30 U), and vincristine (1 mg/m^2), have been used in patients with metastatic or recurrent disease. Vigorous management of side effects and complications of these treatments and of AIDS itself must be provided.

ANAL CARCINOMA

Although anal carcinoma is not currently an AIDS-defining illness, the incidence of this tumor is increasing in the population at risk for HIV infection. The incidence of anal carcinoma in homosexual men in a San Francisco study was estimated at between 25-87 cases per 100,000, compared with 0.7 case per 100,000 in the entire male population.

Etiology and risk factors

HPV Precursor lesions of anal intraepithelial neoplasia (AIN), also known as anal SILs, have been found to be associated with HPV infection, typically with oncogenic serotypes, eg, types 16 and 18. Cytologic abnormalities occur in nearly 40% of patients, especially those with CD4 cell counts < 200 cells/mm^3. Abnormal cytology may predict the later development of invasive carcinoma.

Other STDs and sexual practices Individuals with a history of perianal herpes simplex, anal condylomas, or practice of anal receptive behavior with multiple sexual partners are at greater risk of developing this tumor.

Signs and symptoms

Rectal pain, bleeding, discharge, and symptoms of obstruction or a mass lesion are the most frequent presenting symptoms.

Screening and diagnosis

Studies to evaluate the usefulness of anoscopy with frequent anal cytology have been undertaken to determine whether early detection of AIN may result in interventions that would prevent the development of invasive tumors.

Work-up of patients with anal carcinoma For patients with anal carcinoma, determination of local disease extent, as well as full staging for dissemination, should be undertaken (see chapter 16).

Pathology

Squamous cell carcinoma The majority of anal carcinomas are of the squamous cell type.

Histologic grading The grading for AIN is similar to that for CIN, with AIN-1 denoting low-grade dysplasia and AIN-2 and AIN-3, higher-grade dysplastic lesions. The gross appearance of lesions on anoscopy does not predict histologic grade. Higher-grade dysplastic lesions are seen in patients with lower CD4 cell counts.

Staging and prognosis

The staging of squamous cell carcinoma of the anus in HIV-infected individuals is the same as that in non–HIV-infected patients (see chapter 16). Patients with severe immunosuppression, ie, CD4 cell counts < 50 cells/mm^3, may present with more advanced, more aggressive disease. The true natural history of this tumor in the AIDS population has yet to be defined, however.

Treatment

TREATMENT OF AIN AND CARCINOMA IN SITU

Treatment of patients with local intraepithelial neoplasia is similar to that of women with CIN. Ablative therapy may be used.

TREATMENT OF INVASIVE ANAL SQUAMOUS CELL CARCINOMA

Anal cancer can be controlled with chemotherapy and radiation therapy despite HIV infection. However, patients who have low CD4 cell counts appear to be more likely to experience severe toxicity and to require colostomy for salvage therapy. For patients with squamous cell carcinoma of the anus, chemotherapy with mitomycin (Mutamycin; 10 mg/m^2 on day 1) and fluorouracil (5-FU; 1,000 mg/m^2 by continuous infusion on days 1-4) combined with radiation therapy can produce high rates of complete remission.

Concomitant radiation therapy, 5-FU, and mitomycin C have been reported to produce complete response of AIDS-associated invasive anal carcinoma in

9 of 11 patients (median CD4 cell count at diagnosis of 209 cells/mm^3) and a 60% 2-year actuarial survival rate. Two patients remain alive more than 8 years following treatment, but severe toxicity (three grade 3 hematologic, one grade 3 dermatologic, one grade 4 and one grade 5 gastrointestinal toxicity) and one death resulted from treatment.

Recent evidence appears to suggest that 5-FU plus cisplatin may be superior to 5-FU plus mitomycin. Tolerance to treatment seen in patients who have relatively intact immune systems is similar to that seen in HIV-infected patients. However, the appropriate dose of radiation therapy for patients with anal carcinoma in the context of HIV infection remains unsettled. Patients who are unable to tolerate chemoradiation and those in whom treatment fails (defined as a positive biopsy after CR) should be considered for abdominoperineal resection.

OTHER NON–AIDS-DEFINING MALIGNANCIES

Case reports of other malignant tumors occurring in HIV-infected individuals include Hodgkin's disease, nonmelanomatous skin cancers, lung cancer, germ-cell tumors, myeloid or lymphoid leukemias, multiple myeloma, renal cell carcinoma, breast cancer, head and neck cancer, brain tumors, squamous tumor of the conjunctiva, and leiomyosarcoma in pediatric patients. Most of the case reports describe only a few affected individuals, and there are insufficient numbers of patients to confirm an increased risk of developing these malignancies among HIV-infected individuals, with the possible exceptions of Hodgkin's disease, nonmelanomatous skin cancers, lung cancer, and pediatric leiomyosarcoma.

As HIV-infected individuals are surviving longer with currently available combination anti-HIV drugs, clinicians should anticipate seeing the development of more tumors in these patients. Greater vigilance for these tumors is warranted.

Rates of other non–AIDS-defining cancers also appear to be increasing among HIV-infected individuals. In an Australian cancer data base, 196 cases of non–AIDS-defining cancers were noted in 13,067 (1.5%) individuals among 8,351 HIV infected only and 8,118 patients with AIDS *(Grulich AE, Li Y, McDonald A, et al: AIDS 16:1155-1161, 2002).*

Hodgkin's disease Most of the studies showing a possible increased incidence of Hodgkin's disease in HIV-infected individuals are from European countries, especially Italy and Spain. The most common histology is mixed cellularity and lymphocyte-depleted. Male predominance, a higher prevalence of B symptoms, and more extranodal disease on presentation are the main characteristics of Hodgkin's disease in HIV patients.

Chemotherapy is recommended for this group of patients, due to the high proportion of stage III or IV disease. Standard treatments include ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) or ABVD alternating with MOPP (mechlorethamine, Oncovin, procarbazine, and prednisone).

Radiation therapy appears useful in approximately 50% of HIV-associated Hodgkin's disease. Of 14 patients recently treated at M. D. Anderson Cancer Center (stage I: 1; stage II: 3; stage III: 4; and stage IV: 6), 1 patient received radiation therapy alone and 7 received both chemotherapy and radiation. The projected overall 5-year survival (64-month median follow-up) was 54%. A greater proportion of patients died because of other HIV-related causes than because of Hodgkin's disease.

Nonmelanomatous skin cancers As in the general population, basal cell carcinoma is more common than squamous cell carcinoma in the setting of HIV infection. The risk factors for the development of these tumors are the same as in the general population: namely, fair skin, history of sun exposure, and family history. A study from San Francisco demonstrated that these skin cancers can be treated successfully with standard local therapy, with a recurrence rate indistinguishable from that of the general population of approximately 6%.

Lung cancer Patients with HIV appear to have a higher relative risk of developing lung cancer than do age-matched controls (RR 4.5, 95% CI = 4.2-4.8). These tumors tend to present at later stages than do tumors with similar histologic distribution in the general population.

Pediatric leiomyosarcoma Cases of aggressive leiomyosarcoma developing in HIV-positive children have been reported. Leiomyosarcoma is a very rare tumor, occurring in < 2 cases per 10 million non–HIV-infected children. However, a much higher than expected frequency of leiomyosarcoma has been reported in HIV-infected children. Visceral sites are commonly involved, eg, the lungs, spleen, and GI tract.

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CHAPTER 30

Carcinoma of unknown primary site

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Carcinoma of unknown primary site is a common clinical syndrome, accounting for approximately 3% of all oncologic diagnoses. Patients in this group are heterogeneous, having a wide variety of clinical presentations and pathologic findings. A patient should be considered to have carcinoma of unknown primary site when a tumor is detected at one or more metastatic sites, and routine evaluation (see below) fails to define a primary tumor site.

Although all patients with cancer of unknown primary site have advanced, metastatic cancer, universal pessimism and nihilism regarding treatment are inappropriate. Subsets of patients with specific treatment implications can be defined using clinical and pathologic features. In addition, trials of empiric chemotherapeutic regimens incorporating new antineoplastic agents have suggested improved response rates and survival in unselected groups of patients with carcinoma of unknown primary site.

Epidemiology

Gender Unknown primary cancer occurs with approximately equal frequency in men and women and has the same prognosis in the two genders.

Age As with most epithelial cancers, the incidence of unknown primary cancer increases with advancing age, although a wide age range exists. Some evidence suggests that younger patients are more likely to have poorly differentiated histologies.

Disease sites Autopsy series performed prior to the availability of CT resulted in the identification of a primary site in 70%-80% of patients. Above the diaphragm, the lungs were the most common primary site, whereas various GI sites (pancreas, colon, stomach, liver) were most common below the diaphragm. Several frequently occurring cancers, particularly breast and prostate cancers, were rarely identified in autopsy series.

With improved radiologic diagnosis, the spectrum of unknown primary cancer has probably changed. Limited recent autopsy data suggest a lower percentage of primary sites identified, particularly in patients with poorly differentiated histology.

Signs and symptoms

Patients with unknown primary cancer usually present with symptoms related to the areas of metastatic tumor involvement.

Common sites of metastatic involvement include the lungs, liver, and skeletal system; therefore, symptoms referable to these areas are common.

Constitutional symptoms such as anorexia, weight loss, weakness, and fatigue are common.

Common physical findings include peripheral adenopathy, pleural effusions, ascites, and hepatomegaly.

Pathologic evaluation

Optimal pathologic evaluation is critical in the initial evaluation of patients with carcinoma of unknown primary site and can accomplish the following:

- identification of the primary site
- identification of other unsuspected cancer types (eg, lymphoma, sarcoma)
- identification of patient subsets (eg, patients with poorly differentiated neuroendocrine tumors) with specific treatment implications

Light microscopic examination

The initial light microscopic examination can separate patients into four categories: adenocarcinoma (65%), squamous cell carcinoma (10%), poorly differentiated carcinoma or poorly differentiated adenocarcinoma (20%), and poorly differentiated neoplasm (5%). These categories can be used to guide further evaluation.

Adenocarcinoma In general, additional pathologic study in patients with adenocarcinoma is unlikely to identify the primary site definitively. Exceptions are immunoperoxidase tissue staining for prostate-specific antigen (PSA)(quite specific for prostate cancer) and estrogen/progesterone receptors (suggestive of breast cancer). Other light microscopic features of adenocarcinoma, such as signet-ring cell formations and papillary features, are nonspecific and should not be used to infer a primary site.

Poorly differentiated carcinoma All patients with the light microscopic diagnosis of poorly differentiated carcinoma or poorly differentiated neoplasm require additional specialized pathologic evaluation. Often, a surgical biopsy rather than a needle aspiration biopsy is necessary for optimal evaluation of these patients.

Immunoperoxidase staining

All poorly differentiated carcinomas of unknown primary site should be studied further with specific immunoperoxidase stains. Anaplastic lymphoma can be reliably diagnosed with the leukocyte common antigen (LCA) stain. Other

TABLE 1: Immunoperoxidase staining in the differential diagnosis of carcinoma of unknown primary site

	Immunoperoxidase stains				
Tumor type	Cytokeratin	Leukocyte common antigen	S100 protein, HMB 45	Chromogranin, synaptophysin	Vimentin, desmin
Carcinoma	+	–	–	±	–
Lymphoma	–	+	–	–	–
Melanoma	–	–	+	±	–
Sarcoma	–	–	–	–	+
Neuroendocrine	+	–	–	+	–

tumor types (eg, melanoma, sarcoma, neuroendocrine carcinoma) can be suggested by specific immunoperoxidase staining features. Immunoperoxidase stains useful in the evaluation of poorly differentiated neoplasms of unknown primary site are listed in Table 1.

Electron microscopy

If the identity of poorly differentiated neoplasms is not established after immunoperoxidase staining, electron microscopy should be considered. Rebiopsy to obtain appropriate tissue should be considered in young patients with poorly differentiated neoplasms, since specific ultrastructural findings can result in the diagnosis of various poorly differentiated sarcomas, poorly differentiated neuroendocrine tumors, aggressive lymphoma, or melanoma.

Clinical evaluation

After a biopsy has established metastatic carcinoma, a relatively limited clinical evaluation is indicated to search for a primary site. Recommended evaluation includes a complete history, physical examination, chemistry profile, CBC, chest radiograph, and CT scan of the abdomen.

Symptomatic areas Specific radiologic and/or endoscopic evaluation of symptomatic areas should be pursued. In addition, mammograms should be performed in women with clinical features suggestive of metastatic breast cancer (eg, axillary adenopathy), and serum PSA level should be measured in men with features suggestive of prostate cancer (eg, blastic bone metastasis). In young men with poorly differentiated carcinoma, serum human chorionic gonadotropin (HCG) and alpha-fetoprotein (AFP) levels should always be measured.

Asymptomatic areas In general, radiologic or endoscopic evaluation of asymptomatic areas is not productive and should be avoided. In one small series, positron emission tomography (PET) scanning detected primary sites in 7 of 29 patients (24%); further experience is necessary before recommending

this procedure routinely. Several reports have documented that superfluous testing is frequently performed in these patients, and several thousand dollars can be spent in a futile search for the primary tumor site.

Cervical lymphadenopathy Metastatic squamous carcinoma in cervical lymph nodes usually involves upper or mid-cervical locations. All patients should undergo a thorough search for a primary site in the head and neck region, including direct endoscopic examination of the oropharynx, hypopharynx, nasopharynx, larynx, and upper esophagus. Biopsy of any suspicious areas should be taken. Fiberoptic bronchoscopy should be considered in patients with involvement of low cervical or supraclavicular nodes. This type of evaluation will identify a primary site, usually in the head and neck, in 85%-90% of these patients.

Inguinal lymphadenopathy Patients with metastatic squamous cell cancer presenting in inguinal lymph nodes almost always have an identifiable primary site in the perineal area. Women should undergo careful examination of the vulva, vagina, and cervix; men should have careful inspection of the penis. Anoscopy should be performed to exclude lesions in the anorectal area.

Treatment

Table 2 summarizes the recommended treatments for various recognized clinicopathologic subsets.

Adenocarcinoma

When evaluating patients with adenocarcinoma of unknown primary site, several clinical subsets should be identified and treated specifically. Empiric therapy for patients not included in any of these subsets is outlined in the final section of this chapter.

Women with isolated axillary adenopathy Treatment appropriate for stage II breast cancer should be administered. Mastectomy reveals an occult primary cancer in 50%-60% of these patients, even when physical examination and mammography are normal. Axillary dissection with breast irradiation is also a reasonable treatment, although there are no definitive comparisons of this approach vs mastectomy. Adjuvant systemic therapy, following standard guidelines for stage II breast cancer, is also indicated.

Women with peritoneal carcinomatosis Often, the histopathology in these patients suggests ovarian cancer (ie, serous cystadenocarcinoma or papillary adenocarcinoma). However, all women with this syndrome should be treated as if they had stage III ovarian cancer. Initial cytoreductive surgery should be followed by chemotherapy with a taxane/platinum combination, as recommended for advanced ovarian cancer. In these patients, serum CA-125 can often be used as a tumor marker.

TABLE 2: Recommended treatment for recognized clinicopathologic subsets

Histopathology	Clinical subset	Treatment
Adenocarcinoma	Women with isolated axillary adenopathy	Treat as stage II breast cancer
	Women with peritoneal carcinomatosis	Treat as stage III ovarian cancer
	Men with blastic bone metastases or elevated serum PSA level	Treat as metastatic prostate cancer
	Single metastatic site	Local excision and/or radiation therapy
Squamous cell carcinoma	Cervical adenopathy	Treat as head/neck primary (combined modality therapy)
	Inguinal adenopathy	Node dissection ± radiation therapy
Poorly differentiated carcinoma	Young men with mediastinal/ retroperitoneal mass	Treat as extragonadal germ-cell tumor
	Neuroendocrine features by immunoperoxidase staining or electron microscopy	Treat with platinum/ etoposide-based regimen
	All others with good performance status	Treat with platinum/ etoposide-based regimen

PSA = prostate-specific antigen

Men with bone metastasis Metastatic prostate cancer should be suspected and usually can be diagnosed with either elevated serum PSA level or positive tumor staining for PSA. In such patients, hormonal therapy, as recommended for prostate cancer, is often of palliative benefit.

Patients with a single metastatic site Local treatment, either with surgical excision or radiation therapy, should be administered to patients who present with clinical evidence of a single metastasis. Some of these patients have prolonged survival after local therapy, particularly those who present with a sole metastasis in an isolated peripheral lymph node group. The role of "adjuvant" systemic therapy is undetermined in these patients.

Squamous cell carcinoma

Squamous cell cancer accounts for only 10% of light microscopic diagnoses in patients with unknown primary cancer. Isolated cervical adenopathy is the most common presentation for squamous carcinoma of unknown primary site; an additional group of patients have isolated inguinal adenopathy

at presentation. Specific management is essential for both of these subgroups, since both have the potential for long-term survival following treatment.

Patients with cervical lymphadenopathy in whom no primary site is identified should be treated as if they had a primary site in the head and neck. Concurrent treatment with chemotherapy and radiation therapy has recently proven superior to local treatment alone or to the treatment modalities used sequentially. Radiation therapy doses and techniques should be identical to those used in treating patients with known head and neck primaries. In addition to the involved neck, the nasopharynx, oropharynx, and hypopharynx should be included in the radiation field.

Five-year survival rates with combined modality therapy are 60%-70% and appear superior to results with local modalities alone (30%-50%). The extent of cervical lymph node involvement is the most important prognostic factor.

Patients with inguinal lymphadenopathy Identification of a primary site in the perineal area is important in patients with inguinal lymphadenopathy, as curative therapy is available for some patients even after metastasis to inguinal lymph nodes. In the uncommon patient in whom no primary site is identified, inguinal node dissection, with or without radiation therapy, can result in long-term survival. While limited data exist on this uncommon subgroup, the demonstrated superiority of combined modality therapy vs local treatment alone for primary squamous cancers in the perineal area (eg, cervix, anus) has led to a suggestion that the addition of platinum-based chemotherapy may improve treatment results.

Poorly differentiated carcinoma

This heterogeneous group includes a minority of patients with highly responsive neoplasms and therefore requires special attention in initial clinical and pathologic evaluations. Specialized pathologic techniques can identify some patients with tumor types known to be treatable; these patients should be treated using standard guidelines for the appropriate tumor type.

In the remaining patients, several investigators have documented an increased responsiveness to platinum-based chemotherapy when compared with patients with adenocarcinoma of unknown primary site. In addition, several series have described a small cohort of long-term survivors following platinum-based treatment. Patients with poorly differentiated adenocarcinoma have usually been included in this group when making treatment decisions. Although most patients in this group should receive an empiric trial of treatment, several specific subsets can be recognized.

Men with extragonadal germ-cell cancer syndrome Young men with predominant tumor location in the mediastinum and retroperitoneum and/or high levels of serum HCG or AFP should be treated as if they had a poor prognosis germ-cell tumor (ie, four courses of chemotherapy with cisplatin/etoposide/bleomycin, followed by surgical resection of residual radiographic abnormalities).

Molecular genetic analysis can identify an i(12p) chromosomal abnormality diagnostic of a germ-cell tumor in some of these patients, even when the diagnosis cannot be made by any other pathologic evaluation. Patients with germ-cell tumors diagnosed in this manner have been shown to be as responsive to treatment as patients with extragonadal germ-cell tumors of typical histology.

Patients with poorly differentiated neuroendocrine carcinoma With the improved immunoperoxidase stains now available, neuroendocrine features are recognized more frequently in patients with poorly differentiated carcinoma. These tumors are distinct in biology and therapeutic implications from well-differentiated neuroendocrine tumors (eg, carcinoid tumors, islet-cell tumors) of unknown primary site, which almost always present with multiple liver metastases. In contrast to typical carcinoid tumors, poorly differentiated neuroendocrine tumors are difficult to recognize by light microscopic examination alone, although some of the latter tumors have neuroendocrine or "small-cell" features.

Patients with poorly differentiated neuroendocrine carcinoma of unknown primary site should receive a trial of chemotherapy with a regimen containing a platinum and etoposide(VePesid). In a group of 51 such patients, the complete response rate was 28% following treatment with cisplatin (Platinol) and etoposide, with or without bleomycin (Blenoxane); overall response rate was 71%. Eight patients (16%) had durable complete remissions.

More recently, the combination of paclitaxel (Taxol), carboplatin (Paraplatin), and etoposide has shown a high level of efficacy in the treatment of poorly differentiated neuroendocrine tumors (see "Empiric chemotherapy" below) and is better tolerated than cisplatin/etoposide.

Although the identity of most poorly differentiated neuroendocrine tumors remains unknown, this group of chemotherapy-responsive patients can be reliably identified using specialized, but widely available, pathologic evaluation.

Other patients with poorly differentiated carcinoma Most patients with poorly differentiated carcinoma do not have neuroendocrine features or clinical features of germ-cell tumor. Patients in this group should receive an empiric trial of chemotherapy, unless extremely poor performance status precludes this possibility. In a group of 220 such patients treated at a single institution with cisplatin-based regimens effective for germ-cell tumors, the overall response rate was 64%, with 27% complete responses. Median survival of this group was 20 months, and 13% of patients have been disease-free for more than 8 years and are considered cured. Although the young median age of 39 years indicates that this was a selected patient group, the extreme chemosensitivity of some patients in this large, heterogeneous group is clearly demonstrated.

Empiric chemotherapy

Systemic therapy for patients not included in any specific treatable subgroup has been difficult. Unfortunately, this group includes the majority of patients with adenocarcinoma of unknown primary site; some patients with poorly dif-

TABLE 3: Results of empiric chemotherapy for carcinoma of unknown primary site[a]

Regimen	Number of patients	Response rate (%)	Median survival (mo)
Old Regimens			
FAM	120	20	8
AM	197	29	5
CAF/CMeF	72	17	5
Cisplatin/5-FU-based	186	24	6
Other cisplatin-based	90	30	5
New Regimens			
Paclitaxel/carboplatin/etoposide	71	46	11
Paclitaxel/carboplatin	72	41	12
Docetaxel/platinum	76	24	8
Paclitaxel/carboplatin/gemcitabine	120	25	9
Gemcitabine/cisplatin	40	42	8
Paclitaxel/carboplatin/etoposide, gemcitabine/irinotecan (sequential)	54	33	9

F, 5-FU= fluorouracil; A = Adriamycin; M = mitomycin; C = cyclophosphamide; Me = methotrexate

[a] Reported series using similar regimens have been compiled; response rates and median survivals are averages.

ferentiated carcinoma and no "favorable" clinical features also respond poorly to current therapy.

'Old' regimens Table 3 summarizes results compiled from phase II trials of empiric chemotherapy. Most patients in these trials had adenocarcinoma, but 5%-10% had poorly differentiated carcinoma. In general, the most extensively tested empiric regimens have been those effective for GI malignancy and breast cancer, as well as various cisplatin-based regimens. Most tested regimens have produced response rates of 20%-35% and median survival durations of 5-8 months. There is little evidence for prolongation of median survival or long-term complete remissions with any of these regimens, and none is considered "standard treatment" in this group of patients.

Regimens incorporating new agents The recent availability of several new antineoplastic agents with broad-spectrum activity has renewed interest in the empiric therapy of carcinoma of unknown primary site. The taxanes, gemcitabine (Gemzar), and the topoisomerase I inhibitors are all agents with potential efficacy in the treatment of unknown primary cancer.

Results with taxane-based regimens are included in Table 3. Most experience with these regimens suggests higher response rates and longer median survivals than with older regimens. In addition, the toxicity of taxane/carboplatin regimens is reduced when compared with previous cisplatin-based regimens.

Long-term follow-up of patients treated with paclitaxel/carboplatin/etoposide shows actual 2-year and 3-year survivals of 20% and 14%, respectively. Recently, a gemcitabine/irinotecan combination has also shown activity, with less toxicity, but further experience is required before comparisons are possible. At present, paclitaxel/carboplatin, with or without etoposide, should be considered for empiric therapy of patients with adenocarcinoma of unknown primary site and good performance status.

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CHAPTER 31

Hodgkin's disease

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In the year 2003, approximately 7,600 new cases of Hodgkin's disease will be diagnosed in the United States. Over the past four decades, advances in radiation therapy and the advent of combination chemotherapy have tripled the cure rate of patients with Hodgkin's disease. In 2003, more than 80% of all newly diagnosed patients can expect a disease-free normal life span.

Epidemiology

Gender The male-to-female ratio of Hodgkin's disease is 1.3:1.0.

Age The age-specific incidence of the disease is bimodal, with the greatest peak in the third decade of life and a second, smaller peak after the age of 50 years. The second peak is probably an artifact of histologic misclassification, since recent studies have shown that many cases diagnosed as Hodgkin's disease in this older age group were, in fact, non-Hodgkin's lymphoma (NHL).

Race Hodgkin's disease occurs less commonly in African-Americans (2.3 cases per 100,000 persons) than in Caucasians (3.0 per 100,000 persons).

Geography The age-specific incidence of Hodgkin's disease differs markedly in different countries. In Japan, the overall incidence is low and the early peak is absent. In some developing countries, there is a downward shift of the first peak into childhood.

Etiology and risk factors

The cause of Hodgkin's disease remains unknown, and there are no well-defined risk factors for its development. However, certain associations have been noted that provide clues to possible etiologic factors.

Familial factors For example, same-sex siblings of patients with Hodgkin's disease have a 10 times higher risk for the disease. Patient-child combinations are more common than spouse pairings. Higher risk for Hodgkin's disease is associated with few siblings, single-family houses, early birth order, and fewer playmates—all of which decrease exposure to infectious agents at an early age. The monozygotic twin sibling of a patient with Hodgkin's disease has a 99 times higher risk of developing Hodgkin's disease than a dizygotic twin sibling of a patient with Hodgkin's disease. These associations suggest a genetic predisposition and/or a role for an infectious or environmental agent during childhood or early adolescence in the etiology of the disease.

Viruses Familial aggregation may imply genetic factors, but other epidemiologic findings mentioned above suggest an abnormal response to an infective agent. Both factors may play a role in the pathogenesis of the disease. The Epstein-Barr virus (EBV) has been implicated in the etiology of Hodgkin's disease by both epidemiologic and serologic studies, as well as by the detection of the EBV genome in 20%-80% of tumor specimens.

There have been no conclusive studies regarding the possible increased frequency of Hodgkin's disease in patients with human immunodeficiency (HIV) infection. However, Hodgkin's disease in HIV-positive patients is associated with an advanced stage and poor therapeutic outcome. (For further discussion of Hodgkin's disease in patients with HIV infection, see chapter 29.)

Signs and symptoms

Hodgkin's disease is a lymph node-based malignancy and commonly presents as an asymptomatic lymphadenopathy that may progress to predictable clinical sites.

Location of lymphadenopathy More than 80% of patients with Hodgkin's disease present with lymphadenopathy above the diaphragm, often involving the anterior mediastinum; < 10%-20% of patients present with lymphadenopathy limited to regions below the diaphragm. The commonly involved peripheral lymph nodes are located in the cervical, supraclavicular, and axillary areas; inguinal areas are involved less frequently. Disseminated lymphadenopathy is rare in patients with Hodgkin's disease, as is involvement of Waldeyer's ring and occipital, epitrochlear, posterior mediastinal, and mesenteric sites.

Systemic symptoms About 30% of patients experience systemic symptoms. They include fever, night sweats, or weight loss (so-called B symptoms) and chronic pruritus. These symptoms occur more frequently in older patients and have a negative impact on prognosis (see "Staging and prognosis" section).

Extranodal involvement Hodgkin's disease may affect extranodal tissues by direct invasion (contiguity; the so-called E lesion) or by hematogenous dissemination (stage IV disease). The most commonly involved extranodal sites are the spleen, lungs, liver, and bone marrow.

Diagnosis

The initial diagnosis of Hodgkin's disease can only be made by biopsy. Because reactive hyperplastic nodes may be present, multiple biopsies of a suspicious site may be necessary. Needle aspiration is inadequate because the architecture of the lymph node is important for diagnosis and histologic subclassification.

Pathology

Reed-Sternberg cell

In a biopsied lymph node, the Reed-Sternberg (R-S) cell is the diagnostic tumor cell that must be identified within the appropriate cellular milieu of lymphocytes, eosinophils, and histiocytes. Hodgkin's disease is a unique malignancy pathologically in that the tumor cells constitute a minority of the cell population, whereas normal inflammatory cells are the major cell component. As a result, it may be difficult to identify R-S cells in some specimens. Also, other lymphoproliferations may have cells resembling R-S cells.

The R-S cell is characterized by its large size and classic binucleated structure with large eosinophilic nucleoli. Two antigenic markers are thought to provide diagnostic information: CD30 (Ber-H2) and CD15 (Leu-M1). These markers are present on R-S cells and their variants but not on background inflammatory cells.

Recent studies have confirmed the B-cell origin of the R-S cell. Single-cell polymerase chain reaction (PCR) analysis of classic R-S cells shows a follicular center B-cell origin for these cells with clonally rearranged but crippled V heavy-chain genes, presumably leading to an inhibition of apoptosis. Also, high levels of the nuclear transcription factor-kappa-B (NF-κB) have been found in R-S cells; these high NF-κB levels may play a role in pathogenesis by interfering with apoptosis.

Constitutively activated nuclear factor (NF)-κB is observed in a variety of neoplastic diseases and is a hallmark of the malignant Hodgkin and Reed-Sternberg (H/R-S) cells in Hodgkin's disease. Given the distinctive role of constitutive NF-κB for H/R-S cell viability, NF-κB–dependent target genes were searched for by using adenoviral expression of the super-repressor LκBΔN. A surprisingly small but characteristic set of genes, including the cell-cycle regulatory protein cyclin D2, the antiapoptotic proteins Bfl-1/A1, c-IAP2, TRAF1, and Bcl-x(L), and the cell surface receptors CD86 and CD40 were identified. Thus, constitutive NF-κB activity maintains expression of a network of genes, which are known for frequent marker-like expression in primary or cultured H/R-S cells. NF-κB inhibition resulted in massive spontaneous and p53-independent apoptosis, which could be rescued by ectopic expression of Bcl-x(L), underscoring its dominant role in survival of H/R-S cells. Hence, NF-κB controls a signaling network in H/R-S cells, which promotes tumor cell growth and confers resistance to apoptosis (*Hinz M, Loser P, Mathas S, et al: Blood 97:2798-2807, 2001*).

Histologic subtypes

According to the Rye classification (based on the number and appearance of R-S cells, as well as the background cellular milieu), there are four histologic subtypes of Hodgkin's disease.

Nodular sclerosis, the most common subtype, is typically seen in young adults (more commonly in females) who have early-stage supradiaphragmatic presentations. Its distinct features are the presence of: (1) broad birefringent bands of collagen that divide the lymphoid tissue into macroscopic nodules and (2) an R-S cell variant, the lacunar cell.

Mixed cellularity is the second most common histology. It is more often diagnosed in males, who usually present with generalized lymphadenopathy or extranodal disease and with associated systemic symptoms. R-S cells are fre-

quently identified; bands of collagen are absent, although a fine reticular fibrosis may be present; and the cellular background includes lymphocytes, eosinophils, neutrophils, and histiocytes.

Lymphocyte-predominant Hodgkin's disease is an infrequent form of Hodgkin's disease in which few R-S cells or their variants may be identified. The cellular background consists primarily of lymphocytes in a nodular or sometimes diffuse pattern. The R-S variants express a B-cell phenotype (CD20-positive, CD15-negative). B-cell clonality has also been demonstrated by PCR of the immunoglobulin heavy-chain genes in single R-S variant cells in biopsy material from patients with lymphocyte-predominant Hodgkin's disease.

This finding has led investigators to propose that lymphocyte-predominant Hodgkin's disease is a B-cell malignancy with a mature B-cell phenotype, distinct from the other three histologic types of Hodgkin's disease. Lymphocyte-predominant Hodgkin's disease is often clinically localized, is usually treated effectively with irradiation alone, and may relapse late (a clinical feature reminiscent of low-grade lymphoma). The 15-year disease-specific survival is excellent (> 90%).

The WHO (World Health Organization) classification recognizes a new subtype of lymphocyte-rich classic Hodgkin's disease that has morphologic similarity to nodular lymphocyte-predominant Hodgkin's disease. However, the R-S cells have a classic morphology and phenotype (CD30-positive, CD15-positive, CD20-negative), and the surrounding lymphocytes are reactive T cells. This disease subtype does not show a tendency for late relapse and should be managed like other classic Hodgkin's disease histologies.

A new approach employing antibody treatment with the anti-CD20 chimeric human-mouse antibody, rituximab, in lymphocyte-predominant Hodgkin's disease was recently reported. In 19 assessable patients, roughly divided evenly between previously untreated and relapsed categories, CR was achieved in 8 (42%), CR undetermined was achieved in 2 (11%), and PR 9 (47%), respectively. Response rate was similar among untreated and previously treated patients. Yet 9 patients relapsed, and median freedom from disease progression was short, only 10 months *(Ekstrand BC, Lucas JB, Horwitz SM, et al: Proc Am Soc Clin Oncol [abstract] 21:264a, 2002).*

Lymphocyte depletion is a rare diagnosis, particularly since the advent of antigen marker studies, which led to the recognition that many such cases represented T-cell NHLs. R-S cells are numerous, the cellular background is sparse, and there may be diffuse fibrosis and necrosis. This subtype may be associated with HIV infection and is most commonly diagnosed in the elderly and in people from underdeveloped countries. Patients usually have advanced-stage disease, extranodal involvement, an aggressive clinical course, and a poor prognosis.

Correlation has been found between tissue eosinophilia and the expression of the chemokine eotaxin. Approximately 40% of patients have prominent tissue eosinophilia, a feature correlated with an unfavorable prognosis.

Staging and prognosis

Precise definition of the extent of nodal and extranodal involvement with Hodgkin's disease according to a standard staging classification system is critical for selection of the proper treatment strategy.

Staging system

The recently modified staging system is detailed in Table 1, and the anatomic regions that provide the basis for the staging classification are illustrated in Figure 1. The assignment of stage is based on:

- the number of involved sites
- whether lymph nodes are involved on both sides of the diaphragm and whether this involvement is bulky (particularly in the mediastinum)

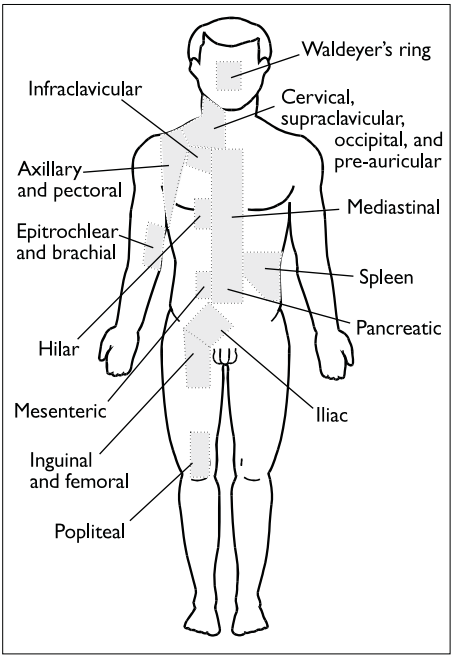

FIGURE 1: Anatomic regions for staging of Hodgkin's disease

- whether there is contiguous extranodal involvement (E sites) or disseminated extranodal disease
- whether typical systemic symptoms (B symptoms) are present

In defining the disease stage, it is important to note how the information was obtained, since this fact reflects on remaining uncertainties in the evaluation for extent of disease. Clinical staging refers to information that has been obtained by initial biopsy, history, physical examination, and laboratory and radiographic studies only. A pathologic stage is determined by more extensive surgical assessment of potentially involved sites, eg, by surgical staging laparotomy and splenectomy.

Also, various designations relating to the presence or absence of B symptoms or bulky disease (see Table 1) can be applied to any disease stage. For example, a patient with no B symptoms but with a bulky mediastinal mass and involvement of the cervical lymph nodes would be defined as having CS IIAX disease. A patient with axillary disease and fever who underwent a staging laparotomy that revealed involvement of the para-aortic lymph nodes and spleen would be staged as PS III_2B.

Most recent studies in stages I-II distinguish between favorable and unfavorable early-stage patients, according to the European Organization for Research on the Treatment of Cancer (EORTC) definitions outlined in Table 2.

TABLE 1: The Cotswald's staging classification for Hodgkin's disease

Stage	Description
I	Involvement of a single lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (ie, the mediastinum is a single site, hilar lymph nodes are lateralized). The number of anatomic sites should be indicated by a subscript (eg, II_2).
III	Involvement of lymph node regions or structures on both sides of the diaphragm:
	III_1: With or without involvement of splenic, hilar, celiac, or portal nodes
	III_2: With involvement of para-aortic, iliac, or mesenteric nodes
IV	Involvement of extranodal site(s) beyond that designated E
Designations applicable to any disease stage[a]	
A	No symptoms
B	Fever, drenching sweats, weight loss
X	Bulky disease: > 1/3 the width of the mediastinum > 10 cm maximal dimension of nodal mass
E	Involvement of a single extranodal site, contiguous or proximal to a known nodal site
CS	Clinical stage
PS	Pathologic stage

[a] For examples of how these designations are applied to disease stage, see text discussion.

Clinical staging evaluation

Disease-associated symptoms As mentioned above, disease-associated symptoms may occur in up to one-third of patients. They may include B symptoms, pruritus, and, less commonly, pain in involved regions after ingestion of alcohol. In each anatomic stage, the presence of B symptoms is an adverse prognostic indicator and may strongly affect treatment choices. B symptoms are carefully defined in the staging system. Unexplained fever should be $> 38°C$ and recurrent during the previous month, night sweats should be drenching and recurrent, and unexplained weight loss is significant only if $> 10\%$ of body weight has been lost within the preceding 6 months. Although pruritus is no longer considered to be a B symptom, the presence of generalized itching may be considered to be an adverse prognostic symptom.

Certain combinations of B symptoms are more prognostically significant than others. For example, the combination of fever and weight loss has a worse prognosis than do night sweats alone.

Physical examination should carefully determine the location and size of all palpable lymph nodes. Inspection of Waldeyer's ring, detection of spleno-

TABLE 2: EORTC prognostic definition of early-stage disease

Favorable	CS[a] I and II (maximum 3 involved areas) and < 50 years *and* ESR[b] < 50 mm/h (no B symptoms) *or* ESR < 30 mm/h (B symptoms present) *and* MT[c] ratio < 0.35
Unfavorable	CS II ≥ 4 nodal areas involved *or* age ≥ 50 years *or* ESR ≥ 50 mm/h (no B symptoms) *or* ESR ≥ 30 mm/h (B symptoms present) *or* MT ratio ≥ 0.35

EORTC = European Organization for Research and Treatment of Cancer
[a]CS = Cotswald's staging; [b]ESR = erythrocyte sedimentation rate; [c]MT = mediastinal/thoracic

megaly or hepatomegaly, and evaluation of cardiac and respiratory status are important.

Laboratory studies should include a CBC with WBC differential and platelet count, the erythrocyte sedimentation rate (ESR), tests for liver and renal function, and assays for serum alkaline phosphatase and lactate dehydrogenase (LDH). A moderate to marked leukemoid reaction and thrombocytosis are common, particularly in symptomatic patients, and usually disappear with treatment.

ESR The ESR may provide helpful prognostic information. At some centers, treatment programs for patients with early-stage disease are influenced by the degree of ESR elevation. In addition, changes in the ESR following therapy may correlate with response and relapse.

Abnormalities of liver function studies should prompt further evaluation of that organ, with imaging and possible biopsy.

Alkaline phosphatase and LDH An elevated alkaline phosphatase level may be a nonspecific marker, but it may also indicate bone involvement that should be appropriately evaluated by a radionuclide bone scan and directed skeletal radiographs. A significantly elevated LDH level has been associated with a poor prognosis in some studies.

Imaging studies Radiologic studies should include a chest x-ray and CT scan of the chest, abdomen, and pelvis with IV contrast. In most patients, PET scan will provide important information and is highly recommended. Radionuclide bone scan, MRI of the chest or abdomen, and CT scan of the neck are contributory only under special circumstances.

Evaluation for supradiaphragmatic disease The thoracic CT scan details the status of intrathoracic lymph node groups, the lung parenchyma, pericardium, pleura, and chest wall. Since the chest CT scan may remain abnormal for a long time after the completion of therapy, the evaluation of pretreatment involvement and response to therapy is assisted by the use of a PET or gallium scan. FDG(^{18}fluorodeoxyglucose)-PET scanning appears to provide more information and better resolution than does gallium scan.

Evaluation of the abdomen and pelvis A CT scan and PET are the basic imaging studies for evaluation of the abdomen and pelvis. Lymphangiography, the imag-

FDG-PET scanning has been found useful in predicting recurrences in residual masses following treatment of Hodgkin's disease. In one series, there were 10 recurrences among 22 cases with PET-positive residual masses following treatment as compared with 1 relapse among 28 cases with PET-negative residual masses. In another series, 11 of 18 relapsed cases with residual masses were PET positive as compared with 1 of 6 cases that were PET negative *(de Wit M, Bohuslaviziki KH, Buchert R, et al: Ann Oncol 12:29-37, 2001; Hueltenschmidt B, Sautter-Bihl ML, Lang O, et al: Cancer 91:302-310, 2001)*. Yet, in a recent study from Vanderbilt University, 32% of patients (6/19) with a negative FDG-PET scan after chemotherapy alone for Hodgkin's disease or NHL relapsed within the (unirradiated) original site of disease *(Lavely WC, Delbeke D, Price RR, et al: Int J Radiat Oncol Biol Phys [abstract] 54 [suppl]:141, 2002)*.

ing technique that provides information on both the size and architecture of lymph nodes, has practically disappeared from most diagnostic radiology practices and is rarely available.

Bone marrow biopsy Bone marrow involvement is relatively uncommon, but because of the impact of a positive biopsy on further staging and treatment, unilateral bone marrow biopsy should be part of the staging process of patients with stage IIB disease or higher.

Staging laparotomy

Staging laparotomy is the most definitive method for detecting occult infradiaphragmatic Hodgkin's disease. A major problem with all imaging techniques for Hodgkin's disease is their inability to identify splenic involvement. In about 30% of patients with normal-sized spleens, Hodgkin's disease is found in the resected spleen. Conversely, approximately 50% of patients with clinical or radiologic enlargement of the spleen do not have pathologic involvement at splenectomy.

Oophoropexy (ie, movement of the ovaries into a shielded area, typically behind the uterus) is also performed in females of reproductive age. Metallic clips marking the ovaries are used for identification and subsequent shielding during radiotherapy.

Complications Reviews of laparotomy series report the risk of major postoperative complications to be between 3% and 7%. Surgical mortality is rare ($< 1\%$), and many large series report no operative deaths. Because of occasional severe bacterial infections occurring after splenectomy, pneumococcal vaccine (Pneumovax, Pnu-Imune) should be administered prior to staging laparotomy.

Patient selection Although staging laparotomy remains the most precise way to determine the presence and extent of infradiaphragmatic Hodgkin's disease, it is not a routine staging procedure and is rarely practiced today. It should be considered only if the additional information may significantly alter the treatment choice. Thus, it is relevant only for patients who are potential candidates for mantle-field radiotherapy alone.

Treatment

Hodgkin's disease is sensitive to radiation and many chemotherapeutic drugs, and, in most stages, there is more than one effective treatment option. Disease

stage is the most important determinant of treatment options and outcome. All patients, regardless of stage, can and should be treated with curative intent.

TREATMENT OF STAGES I-II DISEASE

Treatment options

Subtotal lymphoid irradiation (ie, treatment of the mantle and para-aortic fields only) remains an adequate treatment of clinically or pathologically staged favorable (nonbulky and without B symptoms) early-stage Hodgkin's disease (stages I-II). In patients who underwent pathologic staging (laparotomy) and were treated with primary irradiation alone, several large series reported a 15- to 20-year survival rate of nearly 90% and relapse-free survival rate of 75%-80%. Most relapses (75%) occurred within 3 years after the completion of therapy; very late relapses were uncommon. Importantly, more than half of the patients who relapsed after radiotherapy alone were still curable with standard chemotherapy.

The long-term results of a randomized trial at the Istituto Nazionale Tumori, Milano, indicate that four cycles of ABVD followed by involved-field radiotherapy (IFRT) can achieve results comparable to those with the same regimen followed by extensive RT. The trial compared four cycles of ABVD followed by subtotal lymphoid irradiation (STLI) vs the same regimen followed by IFRT in 140 consecutive patients with clinically staged early Hodgkin's disease (I bulky and/or B; II A, A bulky, and EA). The RT dose ranged from 30 to 36 Gy delivered to uninvolved and involved sites, respectively. A total of 136 patients are evaluable with main characteristics fairly well-balanced between the two arms. After a median follow-up of 87 months, treatment outcome was as follows: CR 100% after ABVD + STLI vs 97% after ABVD + IFRT; freedom from disease progression 97% vs 94%, and total survival 93% vs 94%, respectively. After ABVD alone, CR was achieved in 88% of patients (30% within the third cycle); 14 of 15 partial responders achieved CR with RT. Apart from one case of acute leukemia in the STLI arm, acute and late toxicities were mild. This effective and safe modality can be considered the treatment of choice in early-stage Hodgkin's disease with both favorable and unfavorable presentation (*Bonfante V, Viviani S, Devizzi L, et al: Proc Am Soc Clin Oncol [abstract] 20:281a, 2001*).

Canadian and European studies have reported excellent overall survival results in patients selected for radiotherapy on the basis of clinical prognostic factors alone. Thus, irradiation alone can be safely offered to clinically staged patients with favorable prognostic factors.

When irradiation is used as the sole therapeutic modality, the standard radiation field used in patients with early-stage disease who did not undergo a staging laparotomy is subtotal lymphoid irradiation. This approach is because clinically staged patients who were irradiated to a small field had a high relapse rate. Patients in whom laparotomy was negative may be treated safely with mantle-field irradiation alone. A different approach can be used for patients with lymphocyte-predominant histology, namely, less extensive irradiation without surgical staging.

Chemoradiation An increasingly accepted alternative treatment approach used in patients with favorable early-stage disease is combined treatment with irradiation and chemotherapy. Further, combined-modality therapy is the treatment of choice for patients with unfavorable (bulky and/or with B symp-

toms, more than four sites of involvement) early-stage disease. Combined-modality therapy reduces the relapse rate but, in most studies, does not change the overall survival rate.

New strategies that combine shorter, less toxic chemotherapy regimens with irradiation to clinically involved sites are currently under evaluation. A recent randomized study from Milan documented excellent results (rate of freedom from relapse, 94%) in patients with unfavorable stages I-II disease who were treated with only four cycles of ABVD (Adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine [DTIC]) and involved-field radiotherapy (IFRT) (see box on previous page).

The German Hodgkin's Study Group and the EORTC have also reported excellent results with four cycles of chemotherapy followed by IFRT (see box).

Combination chemotherapy In two recent prospective, randomized studies, radiotherapy alone was as effective as or superior to MOPP (mechlorethamine, Oncovin [vincristine], procarbazine, and prednisone) chemotherapy in improving the survival of early-stage disease patients. Although the relapse rate after chemotherapy is similar to that after radiotherapy, conventional dose salvage chemotherapy used after failure of chemotherapy has poor results, which translates into an inferior overall survival. Other drug combinations, such as ABVD, may be more effective and less toxic than MOPP, but they have not been tested alone in early-stage Hodgkin's disease and should not be used outside a controlled clinical trial. Recent published results of the Children's Cancer Group (CCG) randomized study that evaluated the option of risk-adopted chemotherapy alone in Hodgkin's disease have demonstrated that the elimination of low-dose IFRT even after a CR to chemotherapy has resulted in an inferior event-free survival (see box).

The German Hodgkin's Study Group (GHSG) HD8 study was designed to evaluate the extent of the radiation field required in a combined-modality setting. Patients with intermediate stage Hodgkin's disease were randomized to receive two double cycles of COPP/ABVD and either 30 Gy extended-field radiation therapy + 10 Gy to bulky disease or 30 Gy IFRT + 10 Gy to bulky disease. A total of 1,066 patients were eligible for analysis at a median observation time of 64 months. The overall survival rate was 91%, freedom from treatment failure was 83%, and acute toxicities were more frequent in the extended-field arm. This study demonstrates that four cycles of chemotherapy and IFRT of 30 Gy + a boost of 10 Gy provided excellent results in early-stage disease patients with unfavorable features and in patients with stage IIIA disease *(Engert A, Schiller P, Pfistner B, et al: Blood [abstract] 98:768a , 2001).*

The EORTC H8-U randomized study also evaluated three different regimens in unfavorable early-stage Hodgkin's disease. Preliminary results indicated that the combination of four cycles of MOPP/ABV hybrid and IFRT might be sufficient to cure the majority of unfavorable early-stage Hodgkin's disease patients. With four cycles of MOPP/ABV + IFRT, the CR rate was 91%, 4-year treatment failure-free survival was 92%, and overall survival was 92%. These findings were no different from results obtained with six cycles of MOPP/ABV hybrid and IFRT or four cycles of MOPP/ABV hybrid and subtotal nodal irradiation *(Fermé C, Eghbali H, Hagenbeek A, et al: Blood [abstract] 96:576a, 2000).*

TECHNICAL ASPECTS OF RADIATION THERAPY

Radiation fields

Successful therapy with irradiation alone requires treatment of all clinically involved lymph nodes and all nodal and extranodal regions at risk for subclinical involvement. The Hodgkin's disease radiation fields were designed to conform to the philosophy of treating regions beyond the immediately involved area while accounting for normal tissue tolerance and the technical constraints of field size.

The mantle irradiation field extends from the base of the mandible to the diaphragm, covering the lymph node areas above the diaphragm, including the submandibular, cervical, supraclavicular, infraclavicular, axillary, mediastinal, and hilar nodal areas. Individually contoured Cerrobend blocks shield the lungs and cardiac apex. In addition, depending on anatomy and disease location, supplementary blocks are placed over the humeral heads, occiput, and mouth posteriorly and anteriorly. Half-value layer blocks were also inserted to shield the larynx anteriorly and the cervical cord posteriorly throughout the treatment course. If high (above the thyroid notch) cervical lymph nodes are involved, the preauricular nodes are treated prophylactically to a dose of 3,000-3,600 cGy.

The para-aortic field includes all of the para-aortic lymph nodes between the aortic bifurcation and the bottom of the mantle field. This field is normally positioned to encompass the lateral transverse processes of the lumbar vertebrae, unless imaging or surgical data indicate more extensive disease. It is also designed to encompass the spleen and splenic hilar nodes. When the spleen has been removed, only the splenic pedicle is included. Attention should be paid to the location of the kidneys, as they may be partially included in the field, and proper shielding can decrease the renal volume that is irradiated. The inferior border of the para-aortic field is placed at the bottom of the L4 vertebral body.

The CCG randomized 501 children and adolescents (< 21 years) with Hodgkin's disease who obtained a CR following risk-adopted chemotherapy involved-field radiotherapy (LD-IFRT) or no further treatment. Randomization was stopped after an interim analysis revealed a significantly higher number of relapses on the no-radiotherapy arm. The 3-year projected event-free survival was better in patients randomized to receive LD-IFRT than in those who did not receive radiotherapy. *As-treated* analysis indicated a significantly better event-free survival for the irradiated group. At present, with a short follow-up, no survival advantage has been documented *(Nachman JB, Sposto R, Herzog P, et al: J Clin Oncol 20:3765-3771, 2002).*

The pelvic field encompasses the iliac, inguinal, and femoral nodes. The superior border is at the level of L5, matched, with an appropriate gap, to the bottom of the para-aortic field. A large, customized Cerrobend block shields the midline structures that are not at risk, including the bladder, rectum, and centrally transposed ovaries in women or testes in men. Iliac wing blocks are placed to spare the bone marrow.

The inverted-Y field combines the para-aortic and pelvic fields.

Total vs subtotal lymphoid irradiation The term "total lymphoid irradiation" refers to treatment of the mantle, para-aortic, and pelvic fields (Figure 2). "Subtotal lymphoid irradiation" denotes treatment of the mantle and para-aortic fields only (Figure 2). To avoid excessive toxicity, the radiation fields are treated sequentially, the total dose is fractionated, and the irradiated volumes are carefully tailored with individualized divergent blocks. When patients require separate treatment to adjacent regions, the calculation of field separation is particularly important to avoid overlap at the spinal cord.

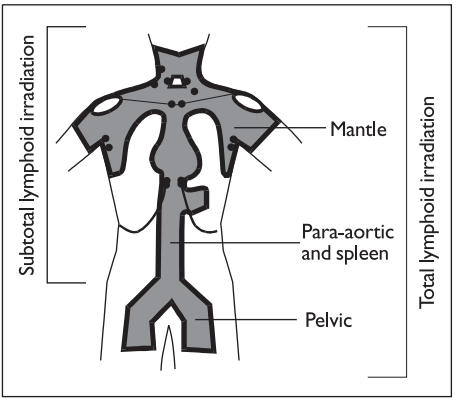

FIGURE 2: Radiation fields used for treatment of Hodgkin's disease

Involved-field irradiation In a combined-modality setting, irradiation of the involved lymph node chain, with or without adjacent sites, and tailoring of the field borders to the postchemotherapy tumor volume (in critical areas such as the mediastinum) are recommended. Recommendations for IFRT for Hodgkin's disease are detailed in an article by Yahalom and Mauch.

Dose considerations

When irradiation alone is used to treat Hodgkin's disease, the standard total dose to each field is 3,600 cGy, delivered in daily fractions of 180 cGy over 4 weeks. In addition, clinically involved areas are given a boost of 540-900 cGy in 3-5 fractions to bring the total dose to these areas up to 4,140-4,500 cGy. Patients who receive irradiation as consolidation after chemotherapy receive a total dose of 2,000-3,600 cGy in 150-180-cGy fractions. We normally use opposed anterior and posterior fields that are evenly weighted and treat both fields daily. Three-dimensional conformal radiotherapy and intensity-modulated radiation therapy (IMRT) are employed for selected cases.

SIDE EFFECTS AND COMPLICATIONS OF RADIOTHERAPY

Side effects of radiotherapy depend on the irradiated volume, dose administered, and technique employed. They are also influenced by the extent and type of prior chemotherapy, if any, and by the patient's age.

Acute effects The acute side effects of mantle-field irradiation include mouth dryness, change in taste, pharyngitis, nausea, dry cough, dermatitis, and fatigue. These side effects are usually mild and transient.

The main potential side effects of subdiaphragmatic irradiation are loss of appetite, nausea, and increased bowel movements. These reactions are usually mild and can be minimized with standard antiemetic medications.

Irradiation of more than one field, particularly after chemotherapy, can cause myelosuppression, which may necessitate treatment delays.

Delayed effects Delayed side effects may develop anywhere from several weeks to several years after the completion of radiotherapy.

Lhermitte's sign Approximately 15% of patients may note an electric shock sensation radiating down the backs of both legs when the head is flexed (Lhermitte's sign) 6 weeks to 3 months after mantle-field radiotherapy. Possibly secondary to transient demyelinization of the spinal cord, Lhermitte's sign resolves spontaneously after a few months and is not associated with late or permanent spinal cord damage.

Pneumonitis and pericarditis During the same period, radiation pneumonitis and/or acute pericarditis may occur in $< 5\%$ of patients; these side effects occur more often in those who have extensive mediastinal disease. Both inflammatory processes have become rare with modern radiation techniques.

Herpes zoster infection Patients with Hodgkin's disease, regardless of treatment type, have a propensity to develop herpes zoster infection within 2 years after therapy. Usually the infection is confined to a single dermatome and is self-limited. If the cutaneous eruption is identified promptly, treatment with systemic acyclovir (Zovirax) will limit its duration and intensity.

Subclinical hypothyroidism Mantle-field radiotherapy can induce subclinical hypothyroidism in about one-third of patients. This condition is detected by elevation of thyroid-stimulating hormone (TSH). Thyroid replacement with levothyroxine (T_4) is recommended, even in asymptomatic patients, to prevent overt hypothyroidism and decrease the risk of benign thyroid nodules.

Infertility Irradiation of the pelvic field may have deleterious effects on fertility. In most patients, this problem can be avoided by appropriate gonadal shielding. In females, the ovaries can be moved into a shielded area laterally or inferomedially near the uterine cervix. Irradiation of the mantle and para-aortic fields alone does not increase the risk of sterility.

Secondary malignancies Hodgkin's disease patients who were cured with radiotherapy and/or chemotherapy have an increased risk of secondary solid tumors (most commonly, lung, breast, and stomach cancers, as well as melanoma) and NHL 10 or more years after treatment. Unlike MOPP and similar chemotherapy combinations, radiotherapy for Hodgkin's disease is not leukemogenic.

Lung cancer Patients who are smokers should be strongly encouraged to quit the habit because the increase in lung cancer that occurs after irradiation or chemotherapy has been detected mostly in smokers.

Breast cancer The increase in breast cancer risk is inversely related to the patient's age at Hodgkin's disease treatment; no increased risk has been found in women irradiated after 30 years of age. Breast cancer is curable in its early stages, and early detection has a significant impact on survival. Breast examination should be part of the routine follow-up for women cured of Hodgkin's disease, and routine mammography should begin about 8 years after treatment.

TABLE 3: Chemotherapeutic regimens used for the treatment of Hodgkin's disease

Regimen	Dosage and schedule	Frequency
MOPP		
Mechlorethamine	6 mg/m^2 IV on day 1	
Oncovin	1.4 mg/m^2 IV on day 1 (maximum dose, 2.0 mg)	
Procarbazine	100 mg/m^2 PO on days 1-7	*Repeat cycle*
Prednisone[a]	40 mg/m^2 PO on days 1-14	*every 28 days*
ABVD		
Adriamycin	25 mg/m^2 IV on days 1 and 15	
Bleomycin	10 mg/m^2 IV on days 1 and 15	
Vinblastine	6 mg/m^2 IV on days 1 and 15	*Repeat cycle*
Dacarbazine	375 mg/m^2 IV on days 1 and 15	*every 28 days*
MOPP alternating with ABVD		
Therapy as above, with MOPP given on odd-numbered cycles and ABVD given on even-numbered cycles every 28 days		
MOPP/ABV hybrid		
Mechlorethamine	6 mg/m^2 IV on day 1	
Oncovin	1.4 mg/m^2 IV on day 1 (maximum dose, 2.0 mg)	
Procarbazine	100 mg/m^2 PO on days 1-7	
Prednisone	40 mg/m^2 PO on days 1-14	
Adriamycin	35 mg/m^2 IV on day 8	
Bleomycin	10 mg/m^2 IV on day 8	*Repeat cycle*
Vinblastine	6 mg/m^2 IV on day 8	*every 28 days*
Stanford V		
Doxorubicin	25 mg/m^2 IV on days 1 and 15	*Repeat cycle*
Vinblastine[b]	6 mg/m^2 IV on days 1 and 15	*every 28 days*
Mechlorethamine	6 mg/m^2 IV on day 1	*for a total of 3 cycles*
Vincristine[b]	1.4 mg/m^2 IV[c] on days 8 and 22	*Radiotherapy to*
Bleomycin	5 U/m^2 IV on days 8 and 22	*initial sites ≥ 5 cm*
Etoposide	60 mg/m^2 IV on days 15 and 16	*(dose: 36 cGy)*
Prednisone	40 mg/m^2 PO every other day (maximum dose, 2.0 mg)	

[a] In the original report, prednisone was given only in cycles 1 and 4.

[b] Vinblastine dose decreased to 4 mg/m^2 and vincristine dose to 1 mg/m^2 during cycle 3 for patients ≥ 50 years of age.

[c] Tapered by 10 mg every other day starting at week 10.

Coronary artery disease An increased risk of coronary artery disease has recently been reported among patients who have received mediastinal irradiation. To reduce this hazard, patients should be monitored and advised about other established coronary disease risk factors, such as smoking, hyperlipidemia, hypertension, and poor dietary and exercise habits.

Effects on bone and muscle growth In children, high-dose irradiation will affect bone and muscle growth and may result in deformities. Current treatment programs for pediatric Hodgkin's disease are chemotherapy-based; radiotherapy is limited to low doses.

In a case-controlled study performed at The Netherlands Cancer Institute, 48 women with breast cancer after Hodgkin's disease were matched with 175 women with Hodgkin's disease and no breast cancer. The study demonstrated that women who received chemotherapy followed by radiation therapy had a significantly decreased relative risk (RR) of developing breast cancer as compared with patients treated with irradiation alone (RR = .03; *P* = .005). For patients treated with irradiation alone, the risk of breast cancer increased significantly with increasing radiation dose to the breast (*P* trend = .01). Reaching menopause before the age of 35 years after treatment with chemotherapy and irradiation was associated with a markedly reduced risk of breast cancer (RR = .08; *P* = .001). The risk reduction with combined modality treatment indicates the importance of ovarian function in the tumorigenesis process of radiation-induced breast cancer *(Van Leeuwen FE, Klokman WJ, van't Veer MB, et al: Ann Oncol 13[suppl 2]:25, 2002).*

TREATMENT OF STAGES III-IV DISEASE

Chemotherapy has become curative for many patients with advanced stages of Hodgkin's disease. MOPP has been the primary effective combination chemotherapy regimen for advanced-stage disease since the 1960s. Over the past several years, ABVD has been shown to be more effective and less toxic than MOPP, particularly with respect to sterility and secondary leukemia.

Combination chemotherapy regimens

Doxorubicin-containing regimens A doxorubicin-containing regimen, such as ABVD or ABVD alternating with MOPP (Table 3), is the treatment of choice for patients presenting with stage III or IV disease, as demonstrated by a randomized phase III trial undertaken by the Cancer and Leukemia Group B (CALGB). This trial showed higher complete response rates with ABVD and ABVD/MOPP (82% and 83%, respectively) than with MOPP alone (65%).

One reason for the improved response rate in the groups treated with doxorubicin-containing regimens was the higher percentage of patients who were able to receive ≥ 85% of the expected chemotherapy dose, particularly in the ABVD group. In addition, rates of significant and life-threatening neutropenia were higher in patients treated with the MOPP-containing regimens than in those treated with other regimens.

Subsequent trials compared ABVD, alternating MOPP/ABVD, and an MOPP/ABV hybrid. Alternating MOPP/ABVD and the MOPP/ABV hybrid were found to be equally effective in treating advanced-stage Hodgkin's disease. However, a recent intergroup study that compared ABVD with MOPP/ABV hybrid (without irradiation) was closed early because of concerns of excess

TABLE 4: Toxicities associated with combination chemotherapy and radiation therapy

Acute toxicities

Alopecia
Nausea and vomiting
Diarrhea
Mucositis
Paresthesias and neuropathies
CNS confusion
Anemia, leukopenia, and thrombocytopenia
Disulfiram-like reaction following alcohol while taking procarbazine

Delayed toxicities

Secondary malignancies
- Acute myelogenous leukemia
- Acute lymphocytic leukemia
- Non-Hodgkin's lymphoma
- Melanoma
- Sarcoma
- Breast, gastric, lung, and thyroid cancers

Endocrine complications
- Infertility
- Hypothyroidism

Pulmonary complications
- Bleomycin-related lung toxicity
- Pulmonary fibrosis

Cardiac complications
- Cardiomyopathy
- Accelerated atherosclerotic heart disease
- Pericardial fibrosis

treatment-related deaths and second malignancies (mostly acute myelogenous leukemia and lung cancer) in the MOPP/ABV hybrid arm.

The German Hodgkin's study Group updated the results of a randomized study comparing COPP/ABVD (arm A) with standard dose BEACOPP (arm B) and to escalated-dose BEACOPP (arm C) for advanced-stage Hodgkin's disease. At a median follow-up of 40 months, failure-free survival was 70%, 79%, and 89% in arms A, B, and C, respectively ($P < .05$). Survival in arm A was inferior to that in arms B and C. There were more secondary cases of myelodysplastic syndrome/acute myelogenous leukemia (MDS/AML) in the escalated BEACOPP arm (A = 0, B = 2, C = 8 patients). Although escalated BEACOPP improves control of Hodgkin's disease, the associated MDS/AML is of concern, and thus modifications of the BEACOPP regimen are being tested in current trials *(Diehl V, Franklin J, Sieber M, et al: Blood 98: 576a, 2001).*

Shortened dose-intense regimens Recently, shortened dose-intense regimens have shown promise. For example, the 12-week Stanford V regimen (see Table 3) combined with IFRT produced a 5-year overall survival rate of 96% and a freedom-from-disease-progression rate of 89%. Freedom-from-disease-progression was significantly superior among patients with a prognostic score of 0-2, compared with those with a score of 3 and higher (94% vs 75%; $P = .0001$). Of interest, in 142 patients from Stanford, no secondary leukemia was observed, and 42 pregnancies were reported.

Another new regimen called BEACOPP (bleomycin, etoposide, Adriamycin [doxorubicin], cyclophosphamide, Oncovin [vincristine], procarbazine, and prednisone) combined with IFRT (in most patients) showed better results than did COPP/ABVD in studies by the German Hodgkin's Lymphoma Study Group.

Combined-modality therapy

Although the role of consolidation radiotherapy after induction chemotherapy remains controversial, irradiation is routinely added in patients with advanced-stage disease who present with bulky disease or who remain in uncertain complete remission after chemotherapy. Retrospective studies have demonstrated that adding low-dose radiotherapy to all initial disease sites after chemotherapy-induced complete response decreases the relapse rate by ~25% and significantly improves overall survival.

Interpretation of the impact of radiation in prospective studies has been controversial. However, a Southwest Oncology Group (SWOG) randomized study of 278 patients with stage III or IV Hodgkin's disease suggested that the addition of low-dose irradiation to all sites of initial disease after a complete response to MOP-BAP (mechlorethamine, Oncovin [vincristine], prednisone, bleomycin, Adriamycin [doxorubicin], and procarbazine) chemotherapy improves remission duration in patients with advanced-stage disease. An intention-to-treat analysis showed that the advantage of combined-modality therapy was limited to patients with nodular sclerosis. No survival differences were observed.

A recent meta-analysis demonstrated that the addition of radiotherapy to chemotherapy reduces the rate of relapse but did not show a survival benefit for the combined-modality approach.

The EORTC reported the results of a randomized study that evaluated the role of IFRT in patients with stage III/IV Hodgkin's disease who obtained a CR after MOPP/ABV. Patients received six or eight cycles of MOPP/ABV chemotherapy (number of cycles depended upon the response). Patients who did not receive a CR (40% of patients) were not randomized to receive chemotherapy and received IFRT. Of the 418 patients who reached a CR, 85 patients were not randomized to receive treatment for various reasons. A total of 161 patients were randomized to receive no RT and 172 patients were randomized to receive IFRT. The authors concluded that IFRT does not improve the treatment results in patients with stage III/IV Hodgkin's disease who reached a CR after six to eight courses of MOPP/ABV chemotherapy. Yet, in partial responders after six cycles of MOPP/ABV, the addition of IFRT yielded overall survival and event-free survival rates that were similar to those obtained in CR to chemotherapy patients *(Aleman BN, Raemaekers JM, Henry-Amar N, et al: Int J Radiat Oncol Biol Phys 51[suppl 1]:2, 2001; Blood [abstract] 98:768a, 2001).*

LONG-TERM TOXICITIES OF COMBINATION CHEMOTHERAPY

The CALGB trial and the intergroup trials mentioned earlier (see "Combination chemotherapy regimens") noted differences in the long-term toxicities of different combination chemotherapeutic regimens (Table 4).

Myelodysplasia and acute leukemia MOPP therapy is known to be related to the development of the myelodysplastic syndrome (MDS) and acute leukemia. These secondary hematologic malignancies began 2 years following therapy and declined by 10 years, with the maximum risk between 5 and 9 years. Patients with these malignancies have a poor prognosis.

The incidence of secondary leukemia appears to increase with cumulative doses of chemotherapy, age > 40 years when receiving chemotherapy for Hodgkin's

disease, and splenectomy. It is controversial whether combined-modality therapy increases the risk of leukemia compared with chemotherapy alone.

Cytogenetic studies of secondary leukemias reveal a loss of the long arm of chromosome 5 and/or 7. Less frequently, there is a loss of chromosome 18 or rearrangement of the short arm of chromosome 17. A balanced rearrangement of 11q23 and 2lq22 also has been described with etoposide therapy.

Other malignancies also are being observed with increasing frequency after chemotherapy, particularly lung cancer and NHL. These malignancies have a longer latency period and usually are not observed until 15 years after therapy.

Infertility is another long-term complication seen with combination chemotherapy. At least 80% of males are found to have permanent azoospermia or oligospermia following more than three cycles of MOPP chemotherapy; < 10% of men will have recovery of spermatogenesis within 1-7 years following the end of chemotherapy. The risk of infertility with ABVD chemotherapy is significantly lower than that with MOPP chemotherapy, approximately 15%-25%. All men who desire childbearing potential following therapy should be counseled regarding sperm banking.

In females, there is a 50% rate of primary ovarian failure overall. The risk is 25%-30% in patients treated at age 25 or younger but increases to 80%-100% in women older than age 25. Many women who do maintain ovarian function during chemotherapy will have premature menopause following therapy.

Pulmonary complications have been reported with ABVD chemotherapy and are related to bleomycin-induced lung toxicity. In a Memorial Sloan-Kettering Cancer Center study of 60 early-stage Hodgkin's disease patients receiving ABVD chemotherapy with or without mediastinal irradiation, 53% reported dyspnea on exertion or cough during ABVD chemotherapy and 37% had a significant decline in pulmonary function. Bleomycin was discontinued in 23% of patients. Following ABVD therapy, there was a significant decline in median forced vital capacity (FVC) and diffusing capacity of carbon monoxide (DLCO). Radiotherapy following ABVD chemotherapy resulted in a further decrease in FVC but did not significantly affect functional status. At longer follow-up, only 1 of 60 patients reported persistent dyspnea on minimal exertion.

A nested case-control study was conducted within a cohort of 5,519 patients with Hodgkin's disease treated in Britain during 1963 through 1993. For 88 cases of lung cancer and 176 matched control subjects, information on treatment and other risk factors were extracted from hospital case notes, and odds ratios for lung cancer in relation to these factors were calculated. The risk of lung cancer was borderline significantly higher in patients treated with MOPP chemotherapy than those who did not receive this treatment and increased with the number of cycles of MOPP ($P = .07$). Exclusion of lung cancer for which histologic confirmation was not available strengthened these associations. The results suggest that MOPP chemotherapy may lead to an elevated risk of lung cancer, at least in certain subgroups of patients. The role of chemotherapy in the etiology of lung cancer secondary to Hodgkin's disease merits further investigation *(Swerdlow AJ, Schoemaker MJ, Allerton R, et al: J Clin Oncol 19:1610-1618, 2001).*

In the CALGB trial, there were 3 fatal pulmonary complications in 238 patients; all 3 patients were older than age 40.

Pulmonary fibrosis has also been described after combined-modality therapy. Pulmonary function testing usually reveals a decreased diffusion capacity and restrictive changes prior to the onset of symptoms.

Cardiomyopathy is a recognized complication of doxorubicin therapy but is not commonly seen in patients receiving ABVD chemotherapy. Patients who are treated with six cycles of ABVD chemotherapy receive a total doxorubicin dose of 300 mg/m^2; cardiac toxicity is rarely seen in patients who receive a total dose ≤ 400 mg/m^2.

MANAGEMENT OF RELAPSED DISEASE

Relapse after radiation therapy

Patients with early-stage Hodgkin's disease who relapse after initial therapy with irradiation alone have excellent complete remission rates and 50%-80% long-term survival rates when treated with MOPP or ABVD. The dose regimens used for salvage therapy are the same as those outlined in Table 3.

Relapse after combination chemotherapy

Among patients with advanced-stage Hodgkin's disease, 70%-90% will have complete responses to treatment; however, up to one-third of patients with stage III or IV disease will relapse, usually within the first 3 years after therapy.

Various studies have identified the following as poor prognostic factors for response to first-line chemotherapy: B symptoms, age > 45 years, bulky mediastinal disease, extranodal involvement, low hematocrit, high ESR, high levels of CD30, and high levels of serum interleukin-10 (IL-10) and soluble IL-2 receptor.

The prognostic importance of CD20 expression on the R-S cells of classic Hodgkin's disease is controversial. The series from Memorial Sloan-Kettering Cancer Center demonstrated a worse outcome for patients with CD20-positive R-S cells with classic Hodgkin's disease, whereas no prognostic difference between CD20-positive and -negative cases was found in the experience at M. D. Anderson Cancer Center.

An International Prognostic Index has been devised for advanced Hodgkin's disease based on a retrospective analysis of 1,618 patients from

A comparison was recently made of 7 well-known prognostic models for Hodgkin's disease that were retrospectively applied to 516 patients with advanced disease. Three models were found to be the most predictive of outcome: the International Prognostic Factors Project Index (employing albumin, hemoglobin, gender, stage, age, WBC, and lymphocyte count), the Memorial Sloan-Kettering model (employing age, LDH, hematocrit, inguinal nodal involvement, and mediastinal mass bulk), and the International Database on Hodgkin's Disease model (employing stage, age, B symptoms, albumin, and gender). Integration of the three models in a linear model improved their predictive power —identifying patients with 10% and 50% risks of treatment failure, respectively, in 19% and 25% of the test population (*Gobbi PG, Zinzani PL, Broglia C, et al: Cancer 91:1467-1478, 2001*).

25 centers. In the final model, seven factors were used: albumin < 4 g/dL, hemoglobin < 10.5 g/dL, male gender, stage IV disease, age ≥ 45 years, WBCs ≥ 15,000/μL, and lymphocytes < 600/μL (or 8% of the WBC count). The worst prognostic group (7%) had a 5-year overall survival rate of 56% and a failure-free survival rate of 42%.

Once patients have relapsed, they are classified into three groups: those who achieve a complete response lasting > 12 months, those who relapse within 12 months, and those who never obtain a complete response to first-line chemotherapy.

A review of patients with relapsed Hodgkin's disease treated with salvage combination chemotherapy at the National Cancer Institute (NCI) found that patients with a longer disease-free survival have a greater likelihood of obtaining a durable remission than those with a short or no response to initial therapy.

Patients with durable responses to initial therapy Patients who relapse after a long disease-free interval have a 79% complete response rate to standard salvage chemotherapeutic regimens, half of which are durable remissions. These patients may benefit from high-dose chemotherapy salvage programs, although standard-dose salvage therapy is also a reasonable approach.

Patients with no or short response to initial therapy The choice of chemotherapeutic regimens for patients who never achieve a response or who relapse within 1 year is more difficult. It is unlikely that these patients will attain a lasting response to standard-dose chemotherapy. They should be offered high-dose chemotherapy, with or without radiotherapy, followed by hematopoietic cell support.

Results of high-dose chemoradiotherapy with autologous stem cell transplantation in 65 patients with relapsed or refractory Hodgkin's disease have been recently reported. At a median follow-up of 43 months, overall survival (OS) was estimated to be 73% and event-free survival (EFS) was estimated to be 58% by intent-to-treat analysis. In a multivariable logistic regression model, there were three adverse prognostic factors: extranodal sites of relapse or refractory disease, complete remission duration of less than 1 year or refractory disease, and B symptoms. Patients with 0 or 1 adverse factor had an OS of 90% and an EFS of 83%. Patients with two adverse factors had an OS of 57% and an EFS of 27%; those with three adverse factors had an OS of 25% and an EFS of 10% *(Moskowitz CH, Nimer SD, Zelenetz AD, et al: Blood 97:616-623, 2001).*

Two randomized studies (from Great Britain and Germany) demonstrated an event-free survival advantage with the high-dose therapy approach. Although a significant survival advantage was not observed due to the crossover design of the studies, most patients with refractory disease or postchemotherapy relapse are currently managed with high-dose chemoradiation and peripheral blood progenitor cell transplantation (PBPCT).

Salvage radiotherapy Relapse usually occurs in previous sites of disease, and selected patients initially treated with chemotherapy can also be treated with salvage radiotherapy.

High-dose chemotherapy with hematopoietic support The most effective treatment for patients who do not respond to standard-dose chemotherapy is high-dose chemotherapy, with or without radiation therapy, followed by hematopoietic reconstitution with bone

marrow transplantation (BMT) or PBPCT. No standard conditioning regimen has been used in this setting, as patients have had prior treatment with a variety of combinations of chemotherapy and radiation therapy. Although most patients who have received bone marrow have been treated with several regimens or have had poorly responsive disease from initial diagnosis, the complete response rate has ranged from 50% to 80%, with approximately 40%-80% of responding patients achieving durable remissions.

Recent analysis of prognostic factors in patients receiving high-dose salvage therapy indicated that B symptoms at relapse, extranodal disease, and more than minimal disease at transplantation are factors associated with a poor outcome. Patients with these poor-prognosis factors may require more than one intensive course of therapy, but only scanty information is available on this strategy.

Allogeneic BMT does not offer a survival advantage over autologous stem-cell transplantation in Hodgkin's disease. The safety of high-dose therapy programs for Hodgkin's disease has improved over the past decade; most major transplant centers report $< 5\%$ mortality in recent series.

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CHAPTER 32

Non-Hodgkin's lymphoma

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Between 1950 and 1999, the incidence of non-Hodgkin's lymphoma (NHL) rose by 90% in the United States, representing one of the largest increases of any cancer. Some of this increase may be artifactual, resulting from improved diagnostic techniques and access to medical care, or directly related to the development of NHL in 20- to 40-year-old men with human immunodeficiency virus (HIV) infection. However, additional factors must be responsible for this unexpected increase in frequency of NHL that has been observed throughout the United States.

The incidence of NHL per 100,000 persons has risen from 8.8 in 1972-74 to 19.1 in 1995-1999. The increases have been relatively higher in whites, males, and the elderly, and rates have risen more rapidly in rural than urban areas. Similar findings have been reported in other developed countries.

Currently, NHL represents approximately 4% of all cancer diagnoses (4% in males and 4% in females). Estimates from the American Cancer Society indicate that in the year 2003, some 53,400 new cases of NHL will be diagnosed in the United States and approximately 23,400 people will die of this disease.

Epidemiology

Gender The overall incidence of lymphoma is slightly higher in men than women. The incidence rate (per 100,000 population) between 1995-1999 was 50% higher in males (23.9) than females (15.8).

Age Except for high-grade lymphoblastic and small noncleaved cell lymphomas (the most common types of NHL seen in children and young adults), the median age at presentation for all subtypes of NHL exceeds 50+ years. Low-grade lymphomas account for 37% of NHLs in patients between the ages of 35 and 64 years at diagnosis but for only 16% of cases in those below the age of 35.

Race Incidence varies by race, with whites at higher risk than blacks and Asian-Americans. Most histologies, particularly low-grade small lymphocytic and follicular lymphomas, are more common in whites than blacks. The incidence of mycosis fungoides and other peripheral T-cell lymphomas is higher in black males and lowest in white females.

Geography Certain endemic geographical factors appear to influence the development of NHL in specific areas:

HTLV-1-associated NHL Human T-cell lymphotrophic virus-1 (HTLV-1)–associated T-cell lymphoma/leukemia occurs more frequently in Japan (Kyushu) and the Caribbean.

Burkitt's lymphoma in Africa The incidence (per 100,000 population) of Burkitt's NHL in Africa (Nigeria and Tanzania) is 5.7–7.6, as compared with 0.1 in the United States. The clinical features of Burkitt's lymphoma in Africa differ from those of cases reported to the American Burkitt's Lymphoma Registry. Etiologic endemic factors include malaria as a source of chronic B-cell antigenic stimulation and Epstein-Barr virus (EBV)–induced immortalization of B-lymphocytes.

Middle East lymphoma or α–chain disease α Heavy-chain disease is a disorder of B-lymphoid cells characterized by diffuse thickening of the small intestine due to a lymphoplasmacytic infiltrate with secretion of incomplete IgA heavy chains. This clinicopathologic entity is rarely encountered in individuals other than those of Mediterranean ethnic origin.

Follicular lymphomas are more common in North America and Europe but are rare in the Caribbean, Africa, China, Japan, and the Middle East.

Peripheral T-cell lymphomas are more common in Europe and China than in North America.

Disease site Malignant lymphomas are a heterogeneous group of neoplasms that usually arise or present in lymphoid tissues, such as lymph nodes, spleen, and bone marrow, but that may arise in almost any tissue. The most frequent sites for extranodal lymphomas, which constitute about 26% of all lymphomas, are the stomach, skin, oral cavity and pharynx, small intestine, and CNS. Although primary CNS lymphoma is rare, there has been a 3-fold increase in incidence, even if patients with HIV infection and other types of immunosuppression are excluded.

Survival The 5-year relative survival rate of patients with NHL increased from 28% between 1950 and 1954 to 55% between 1992 and 1998. These improvements in survival occurred mainly in young adults and children. The potential for cure varies among the different histologic subtypes and is directly related to stage at presentation and response to initial therapy.

Etiology and risk factors

Chromosomal translocations and molecular rearrangements Nonrandom chromosomal and molecular rearrangements play an important role in the pathogenesis of many lymphomas and correlate with histology and immunophenotype (Table 1). The most commonly associated chromosomal abnormality in NHL is the t(14;18)(q32;q21) translocation, which is found in 85% of follicular lymphomas and 28% of higher-grade NHLs. This translocation results in the juxtaposition of the *bcl-2* apoptotic inhibitor "oncogene" at chromosome band 18q21 to the heavy-chain region of the immunoglobulin locus within chromosome band 14q32.

TABLE 1: Correlation of chromosomal abnormalities in NHL with histology, antigen rearrangements, and oncogene expression

Cytogenetic abnormality	Histology	Antigen rearrangement	Oncogene expression
B-cell lymphoma			
t(14;18)(q32;q21)	Follicular (small cleaved, mixed, large cell), diffuse large cell	IgH	*bcl-2*
t(11;14)(q13;q32)	Mantle cell	IgH	*bcl-1*
t(1;14)(p22;q32)	MALT lymphoma	IgH	*bcl-10*
t(11;18)(q21;q21)	MALT lymphoma		API-2 on chromosome II MALT-1 on chromosome 18
t(9;14)(p13;q32)	Lymphoplasmacytic lymphoma	IgH	*PAX-5*
t(14;19)(q32;q13)	B-CLL	IgH	*bcl-3*
8q24 translocations	Small noncleaved		c-*myc*
t(8;14)(q24;q32)	(Burkitt's and	IgH	
t(2;8)(p11-12;q24)	non-Burkitt's	Ig-λ	
t(8;22)(q24;q11)	types)	Ig-κ	
(3;22)(q27;q11)	Diffuse (large cell, small cleaved cell)	Ig-κ	*bcl-6 (LAZ-3)*
Trisomy 12	Small lymphocytic, B-CLL		
T-cell lymphoma			
14q11 abnormalities			
inv 14(q11;q32)	Variable	TCR-δ	*tcl-1*
t(11;14)(p13;q11)	T-ALL	TCR-δ	*tcl-2*
t(10;14)(q24;q11)	Variable	TCR-δ	*hox-11* (*tcl-3*)
t(1;14)(p32;q11)	T-ALL	TCR-δ	*tcl* (*tal1*, *tcl-5*)
7q35 abnormalities			
t(7;9)(q34-36;q32)	T-ALL or lymphoblastic lymphoma	TCR-β	*tcl-4*
t(7;14)(q34-36;q11)	Variable	TCR-β	
t(7;19)(q34-36;q13)	T-ALL	TCR-β	*lyl-1*
t(2;5)(p23;q35)	Anaplastic large cell (Ki-1 positive)		*npm*, *alk*

alk = anaplastic lymphoma kinase gene; B-CLL = B-cell chronic lymphocytic leukemia; IgH = immunoglobulin heavy chain; Ig-κ = immunoglobulin kappa light chain; Ig-λ = immunoglobulin lambda light chain; *LAZ-3* = *LAZ-3* transcription factor gene; MALT = mucosa-associated lymphoid tissue; *npm* = nucleophosmin gene; T-ALL = T-cell acute lymphocytic leukemia; TCR = T-cell antigen receptor; API-2 = apoptosis inhibitor 2; MALT-1 = MALT lymphoma gene 1

The t(11;14)(q13;q32) translocation results in overexpression of *bcl-1* (cyclin D1/PRAD 1), a cell-cycle–control gene on chromosome 11q13, and has a diagnostic, nonrandom association with mantle cell lymphoma. The t(3;16)(q27;p11) translocation makes the gene for the IL-21 receptor a partner of BCL6, which is expressed in diffuse large cell lymphoma.

Chromosomal translocations involving 8q24 lead to c-*myc* deregulation and are frequently seen in high-grade small noncleaved lymphomas (Burkitt's and non-Burkitt's types), including those associated with HIV infection.

Environmental factors also may play a role in the development of NHL.

Occupations Certain workers have a slightly increased risk of developing NHL, including farmers, pesticide applicators, grain (flour) millers, meat workers, wood and forestry workers, chemists, painters, mechanics, machinists, printers, and workers in the petroleum, rubber, plastics, and synthetics industries.

Chemicals that have been linked to the development of NHL include a variety of pesticides and herbicides (2,4-D-organophosphates, chlorophenols), solvents and organic chemicals (benzene, carbon tetrachloride), wood preservatives, dusts (wood, cotton), and some components in hair dye.

Chemotherapy and radiotherapy Patients who receive cancer chemotherapy and/or radiation therapy are also at increased risk of developing NHL.

Viruses Several viruses have been implicated in the pathogenesis of NHL, including EBV, HTLV-1, Kaposi's sarcoma–associated herpesvirus (KSHV; also known as human herpesvirus 8, or HHV-8), and hepatitis C virus (HCV).

EBV is a DNA virus that has been associated with Burkitt's lymphoma, particularly in endemic areas of Africa; Hodgkin's disease; lymphomas in immunocompromised patients (ie, organ transplantation and HIV infection); sinonasal lymphoma (Asia and South America); and sporadically in other B- and T-cell lymphomas. EBV can transform lymphocytes in culture. B-lymphocytes from normal EBV-positive subjects grow as tumors in mice with severe combined immunodeficiency.

HTLV-1 is a human retrovirus that is endemic in certain areas of Japan and the Caribbean. HTLV-1 establishes a latent infection via reverse transcription in activated T-helper cells. A minority (5%) of carriers develop adult T-cell leukemia/lymphoma. A HTLV-1–like provirus has been detected in some patients with mycosis fungoides, although conflicting findings have been reported.

KSHV KSHV-like DNA sequences are frequently detected in body cavity–based lymphomas in patients with HIV infection and in those with multicentric (plasma cell variant) Castleman's disease.

HCV infection is associated with the development of clonal B-cell expansions and certain subtypes of NHL, particularly in the setting of essential (type II) mixed cryoglobulinemia. HCV may predispose B-cells to malignant transformation by enhancing signal transduction upon binding to the CD81 (TAPA-1) molecule.

Infection with *Borrelia burgdorferi*, the etiologic agent in Lyme disease, has been detected in about 35% of patients with primary cutaneous B-cell lymphoma in Scotland. A near-complete clinical and histological remission of a primary marginal zone B-cell lymphoma was observed after eradication of *B burgdorferi* with antibiotic treatment.

Immunodeficiency Patients with congenital and acquired states of immunosuppression are at increased risk of NHL.

Congenital immunodeficiency states that are associated with an increased risk include ataxia-telangiectasia, Wiskott-Aldrich syndrome, common variable hypogammaglobulinemia, X-linked lymphoproliferative syndrome, and severe combined immunodeficiency.

Acquired immunodeficiency states, such as HIV infection, iatrogenic immunosuppression (ie, organ or blood stem-cell transplantation recipients, long-term survivors of Hodgkin's disease), and a variety of collagen vascular and autoimmune diseases (eg, Sjögren's syndrome, rheumatoid vasculitis and Felty's syndrome, systemic lupus erythematosus, chronic lymphocytic thyroiditis, and angioimmunoblastic lymphadenopathy) also pose an increased risk of NHL.

GI lymphomas An increased incidence of GI lymphomas is seen in patients with celiac (nontropical) sprue and inflammatory bowel disease, particularly Crohn's disease. An aberrant clonal intraepithelial T-cell population can be found in up to 75% of patients with refractory celiac sprue prior to the development of overt T-cell lymphoma using immunophenotyping and T-cell receptor gamma gene rearrangement PCR techniques. Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is seen most frequently, but not exclusively, in association with *Helicobacter pylori* infection. In contrast to studies performed in European patients, Mexican patients with intestinal lymphomas show a very high frequency of EBV-positivity; this finding is not limited to T-cell NHLs, but rather, includes a significant portion of B-cell NHLs.

Signs and symptoms

Fever, weight loss, and night sweats, referred to as systemic B symptoms, as well as fatigue and weakness, are more common in advanced or aggressive NHL but may be present in all stages and histologic subtypes.

Low-grade lymphomas Painless, slowly progressive peripheral adenopathy is the most common clinical presentation in patients with low-grade lymphomas. Patients sometimes report a history of waxing and waning adenopathy before seeking medical attention. Spontaneous regression of enlarged lymph nodes can occur and can cause a low-grade lymphoma to be confused with an infectious condition.

Primary extranodal involvement and B symptoms are uncommon at presentation; however, both are common in advanced or end-stage disease. Bone marrow is frequently involved, sometimes in association with cytopenias. Splenomegaly is seen in about 40% of patients, but the spleen is rarely the only involved site at presentation.

Intermediate- and high-grade lymphomas The clinical presentation of intermediate- and high-grade lymphomas is more varied. Although the majority of patients present with adenopathy, more than one-third present with extranodal involvement, the most common sites being the GI tract (including Waldeyer's ring), skin, bone marrow, sinuses, GU tract, thyroid, and CNS. B symptoms are more common, occurring in about 30%-40% of patients.

Lymphoblastic lymphoma often presents with an anterior superior mediastinal mass, superior vena cava syndrome, and leptomeningeal disease with cranial nerve palsies.

US patients with Burkitt's lymphoma often present with a large abdominal mass and symptoms of bowel obstruction.

Screening and diagnosis

No effective methods are available for screening or identifying populations at high risk of developing NHL. A definitive diagnosis can be made only by biopsy of pathologic lymph nodes or tumor tissue. A formal review by an expert hematopathologist is mandatory. Additional studies, such as immunophenotyping and genotyping, are often necessary.

Initial diagnostic evaluation of patients with lymphoproliferative malignancy should include:

- Careful history (night sweats, weight loss, fever; neurologic, musculoskeletal, or GI symptoms)
- Physical examination (lymph nodes, including submental, infraclavicular, epitrochlear, iliac, femoral, and popliteal nodes; pericardial rub, pleural effusion, distended neck and/or upper extremity veins in superior vena cava syndrome; breast masses; hepatosplenomegaly, bowel obstruction, renal mass, and testicular or ovarian mass; focal neurologic signs, such as plexopathy, spinal cord compression, nerve root infiltration, and meningeal involvement; skin lesions)
- Biopsy of peripheral lymphadenopathy (excisional)
- Chest x-ray (mediastinal or hilar adenopathy, pleural effusions, parenchymal lesions)
- CT scan of the chest (mediastinal, hilar, or parenchymal pulmonary disease)
- CT scan of the abdomen and pelvis (enlarged lymph nodes, splenomegaly, filling defects in liver and spleen)
- Bilateral bone marrow biopsy
- Gallium scan (optional/selected cases); use of PET scans is increasing
- Bone scan (selected cases) if musculoskeletal symptoms are present or alkaline phosphatase is elevated; this modality is also being replaced by PET scan

- CBC with differential and platelet count (peripheral blood lymphocytosis with circulating malignant cells is common in low-grade and mantle cell lymphomas). Bone marrow and peripheral blood involvement may be present, and the distinction between leukemia and lymphoma is difficult to make in some cases.
- General chemistry panel (LDH level determination) is mandatory; β_2-microglobulin (β2M) is recommended
- HIV serology in at-risk patients with diffuse large cell, and other aggressive and small noncleaved histologies; HTLV-1 serology in select patients with cutaneous T-cell lymphoma, especially if they have hypercalcemia
- Cytogenetic and molecular analyses of lymph node, bone marrow, and peripheral blood (selected cases)
- Perform examination of CSF and strongly consider CNS prophylaxis in patients with (1) diffuse aggressive NHL with bone marrow, epidural, testicular, paranasal sinus, or nasopharyngeal involvement; (2) high-grade lymphoblastic lymphoma and small noncleaved cell lymphomas (Burkitt's and non-Burkitt's types); (3) HIV-related lymphoma; and (4) primary CNS lymphoma if no evidence of increased intracranial pressure
- Upper GI endoscopy and/or GI series with small bowel follow-through in patients with head and neck involvement (tonsil, base of tongue, nasopharynx) and those with a GI primary; mantle-cell lymphoma is associated with a high incidence of occult GI involvement
- Ultrasound of opposite testis in patients with a testicular primary
- Spinal MRI scan for epidural disease when clinically indicated (useful in the evaluation of suspected spinal cord compression)
- PET (FDG-glucose) scanning is gaining wider acceptance as a potential diagnostic approach for staging at diagnosis, response assessment, and relapse.

Lymphomas and other malignancies have increased levels of glucose metabolism, which can be detected by positron-emission tomography (PET) using fluorine-18 fluorodeoxyglucose (FDG). Emerging data increasingly support a role for the use of PET scans for staging and monitoring of treatment response in NHL. However, there are limited comparative data among gallium scanning, CT scanning, and PET. Differentiation between tumor and fibroses after first-line treatment may be a difficult problem, especially when a large mass at diagnosis does not disappear completely after therapy. Conventional radiographic techniques cannot differentiate between active tumor and fibroses, since 30%-60% of patients have a residual mass after completion of therapy, and only about 20% of those will relapse. In a retrospective study by Speapen et al, the prognostic significance of PET scan after the initial chemotherapy of NHL patients was evaluated. All patients with an abnormal PET scan relapsed after a short progression-free survival, compared with 15% of patients with normal PET scan. No false-positive results were noticed. These results are preliminary and need to be confirmed in larger studies, since reports of false-positive PET scans are noted in the literature.

TABLE 2: Working Formulation and Rappaport classification equivalents for NHL

Working Formulation	Rappaport equivalent
Low-grade	
A. Small lymphocytic	Diffuse, well-differentiated, lymphocytic
B. Follicular, small cleaved cell	Nodular, poorly differentiated, lymphocytic
C. Follicular, mixed, small cleaved and large cell	Nodular, mixed
Intermediate-grade	
D. Follicular, large cell	Nodular, histiocytic
E. Diffuse, small cleaved cell	Diffuse, poorly differentiated, lymphocytic
F. Diffuse, mixed small and large cell	Diffuse, mixed
G. Diffuse, large cell	Diffuse, histiocytic
High-grade	
H. Immunoblastic	Diffuse, histiocytic
I. Lymphoblastic	Lymphoblastic
J. Diffuse, small noncleaved cell	Diffuse, undifferentiated (Burkitt's and non-Burkitt's types)

PCR and Southern blot studies Circulating monoclonal lymphoid cells can be detected by polymerase chain reaction (PCR) or Southern blot techniques, but the clinical utility of these studies is not well defined.

Several studies have demonstrated the presence of circulating t(14;18)–positive cells in patients with durable remissions of follicular lymphoma, but whether this is a harbinger of relapse remains controversial. In one study, a higher failure-free survival rate was seen in follicular lymphoma patients achieving a molecular remission after chemotherapy; however, this difference did not impact the overall survival rate.

The t(14;18) translocation has been found in B cells from blood of normal individuals, indicating that additional oncogenic events are necessary to establish the neoplastic phenotype.

Pathology

Despite an improvement in immunologic, cytogenetic, and molecular techniques used by hematopathologists for diagnosing and classifying lymphoma, many problems and areas of confusion remain.

Working Formulation

Proposed in 1982 as a modification of the Rappaport classification of NHL, the Working Formulation established a uniform language that is clinically relevant and useful in predicting survival and curability (Table 2). This classification is based on two criteria: (1) morphology (growth pattern in lymph

TABLE 3: Lymphomas and atypical lymphoproliferative disorders not recognized by the Working Formulation

Mantle cell lymphoma[a]
Resembles follicular small cleaved cell NHL but derived from a different type of B cell found in mantle zone surrounding B-cell follicles; frequent detection of a t(11;14) translocation involving *bcl*-1 rearrangement; comprises ~ 5% of NHLs in Europe and the US; propensity for extranodal involvement and aggressive behavior; low potential for cure with standard therapies; bone marrow involved in > 75% of cases, peripheral blood involved in ~30%

Monocytoid B-cell lymphoma/marginal zone lymphoma of nodal type
Low-grade NHL; extremely indolent course; predominant by lymph node involvement

Lymphoma of mucosa-associated lymphoid tissue (MALT)
Tends to have an indolent natural history; primarily affects organs containing epithelial cells, such as the GI tract, lungs, breasts, thyroid, and salivary glands; 80% 5-year survival

Anaplastic large cell lymphoma[b]
Commonly infiltrates the sinusoids of lymph nodes; frequently misdiagnosed as HD, malignant histiocytosis, or metastatic carcinoma; skin often involved; most cases are of T-cell origin and some are characterized by the detection of a t(2;5) translocation

Mycosis fungoides
Indolent cutaneous T-cell lymphomas with a CD4+ phenotype; initially involves the skin but disseminates into lymph nodes and visceral organs in many patients; more advanced form (leukemic peripheral blood involvement and generalized erythroderma) known as Sézary syndrome; ulcerated lesion commonly infected; involvement of viscera (usually the lungs and liver) associated with very poor prognosis

Angiocentric lymphoma
T-cell neoplasm with propensity to invade and destroy blood vessels

T-cell–rich B-cell lymphoma
Previously classified as subset of diffuse lymphocyte-predominant HD; usually aggressive; response to multiagent chemotherapy and outcome similar to other large B-cell NHLs

Angiotropic (intravascular) large cell lymphoma
Usually of B-cell lineage; characterized by diffuse intravascular proliferation of neoplastic cells within capillaries, arterioles, and venules

Angioimmunoblastic lymphadenopathy (AILD)

Lymphoproliferative disorder characterized by diffuse lymphadenopathy, hepatosplenomegaly, skin rash, systemic symptoms, cytopenias, and polyclonal hypergammaglobulinemia; often evolves into T-cell lymphoma, but EBV-related B-cell NHLs can also develop

Divergent or discordant lymphoma

Large-cell histology in a lymph node with low-grade small cleaved cell lymphoma in bone marrow; histologic transformation of low-grade NHL into a more aggressive lymphoma occurs at annual rate of 3%-4% and is associated with increased morbidity and mortality

Composite lymphoma

Two histologic subtypes in the same lymph node, sometimes with coexistent HD

Castleman's disease
Lymphoproliferative disorder associated with both immunodeficiency (HIV infection) and increased rate of malignancy (lymphoma, HD, and KS); the hyalin vascular form is usually localized and the multicentric plasma cell variant is associated with HHV-8 infection

Adult T-cell leukemia/lymphoma
Aggressive T-cell malignancy with unique clinical features, including skin infiltration, lytic bone lesions, and hypercalcemia; associated with HTLV-1 infection

[a] Also known as mantle zone or lymphocytic lymphoma of intermediate differentiation. [b] Also known as Ki-1 lymphoma. EBV = Epstein-Barr virus; HIV = human immunodeficiency virus; HD = Hodgkin's disease; KS = Kaposi's sarcoma; HHV = human herpesvirus; HTLV-1 = human T-cell lymphotrophic virus-1

nodes and cytologic features of neoplastic cells) and (2) biological aggressiveness (low, intermediate, and high grade).

The terminology is based primarily on the Lukes-Collins and Kiel (Lennert) systems, which recognize the immunologic origin of NHL. Thus, the nodular (follicular) growth pattern represents lymphomas arising from follicular center cells (B-cells) of normal lymphoid follicles, whereas large cell lymphomas are derived from transformed B- or T-cells. The advantages of this classification system include a good correlation between histologic subtype and clinical course, and the potential for widespread application among different institutions because determination of immune surface markers is not required.

Unfortunately, the Working Formulation does not distinguish between neoplasms of B- and T-cell lineage or recognize other subtypes of lymphoma that are defined by immunophenotypic and genetic techniques and/or characterized by unique clinical and biological features (Table 3). In addition, the Working Formulation classifies immunoblastic lymphoma, a morphologic variant of diffuse large cell lymphoma, as a high-grade NHL, and yet its clinical course and survival do not differ from those of intermediate-grade diffuse large cell lymphoma.

REAL classification A revised European-American classification of lymphoid neoplasms (REAL classification) was developed by the International Lymphoma Study Group (ILSG). This approach to lymphoma categorization attempts to define the diseases recognized with currently available morphologic, immunologic, and genetic techniques. This system incorporates new lymphoproliferative disorders that were not recognized by the Working Formulation (Table 3) and omits the general grading of lymphomas into low-, intermediate-, and high-grade categories.

The list of lymphoid neoplasms recognized by the ILSG includes 12 different types of B-cell neoplasms and 11 types of T-cell malignancies, including precursor B-cell and T-cell acute leukemia. The subtypes of Hodgkin's disease are also included. The clinical relevance of the REAL classification is under study.

The most frequently occurring clinical entities that are recognized by the REAL classification are diffuse large B-cell lymphoma (31%), follicular lymphoma (22%), small lymphocytic lymphoma (6%), mantle cell lymphoma (6%), peripheral T-cell lymphoma (6%), lymphoma of mucosa-associated lymphoid tissue (MALT) type (5%), primary mediastinal large B-cell lymphoma (2%), anaplastic large (T-/null-cell lymphoma (2%), lymphoblastic lymphoma of T- or B-cell lineage, Burkitt's-like lymphoma (2%), marginal zone (monocytoid) B-cell lymphoma (< 1%), lymphoplasmacytic lymphoma (1%), and Burkitt's lymphoma (< 1%). When immunophenotyping is used, the diagnostic accuracy of the REAL classification exceeds 85% for most subtypes, with the exception of Burkitt's-like and lymphoplasmacytic lymphomas, for which the classification has diagnostic accuracy rates of 53% and 56%, respectively.

World Health Organization (WHO) classification The proposed WHO classification for lymphomas will use the principles of the REAL classification and will define each entity according to morphologic features, immunophenotype,

TABLE 4: REAL/WHO classification of lymphoid neoplasms

- B-cell neoplasms
  - Precursor B-cell neoplasm
    - *Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)*
  - Mature (peripheral) B-cell neoplasms
    - *B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma*
    - B-cell prolymphocytic leukemia
    - Lymphoplasmacytic lymphoma
    - Splenic marginal zone B-cell lymphoma (± villous lymphocytes)
    - Hairy cell leukemia
    - *Plasma cell myeloma*/plasmacytoma
    - Extranodal marginal zone B-cell lymphoma of MALT type
    - Nodal marginal zone B-cell lymphoma (± monocytoid B cells)
    - *Follicular lymphoma*
    - *Mantle cell lymphoma*
    - *Diffuse large B-cell lymphoma*
      - Mediastinal large B-cell lymphoma
      - Primary effusion lymphoma
    - *Burkitt's lymphoma/Burkitt cell leukemia*
- T-cell and NK-cell neoplasms
  - Precursor T-cell neoplasm
    - *Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)*
  - Mature (peripheral) T-cell neoplasms
    - T-cell prolymphocytic leukemia
    - T-cell granular lymphocytic leukemia
    - Aggressive NK-cell leukemia
    - Adult T-cell lymphoma/leukemia (HTLV-1+)
    - Extranodal NK/T-cell lymphoma, nasal type
    - Enteropathy-type T-cell lymphoma
    - Hepatosplenic γδ T-cell lymphoma
    - Subcutaneous panniculitislike T-cell lymphoma
    - *Mycosis fungoides*/Sézary syndrome
    - Anaplastic large cell lymphoma, T/null cell, primary cutaneous type
    - Peripheral T-cell lymphoma, not otherwise characterized
    - *Angioimmunoblastic T-cell lymphoma*
    - *Anaplastic large cell lymphoma, T/null cell, primary systemic type*
- Hodgkin's lymphoma (Hodgkin's disease)
  - Nodular lymphocyte-predominant Hodgkin's lymphoma
  - Classic Hodgkin's lymphoma
    - *Nodular sclerosis Hodgkin's lymphoma (grades 1 and 2)*
      - Lymphocyte-rich classic Hodgkin's lymphoma
    - *Mixed cellularity Hodgkin's lymphoma*
      - Lymphocyte depletion Hodgkin's lymphoma

Italic type denotes common clinical entities. MALT = mucosa-associated lymphoid tissue; HTLV = human T-cell lymphotrophic virus-1

genetic features, postulated normal counterpart, and clinical features. The WHO classification is similar to the REAL classification, with some modifications and reassessments based on more current data (Table 4).

The WHO modificiation of the REAL classification includes three types of follicular lymphoma (grades 1-3). Grades 1 and 2 correspond to follicular small-

cleaved cell and follicular mixed small-cleaved and large cell lymphoma, which are considered to be low-grade lymphomas by the Working Formulation (Table 3). Grade 3 corresponds to follicular large cell lymphoma, which is considered an intermediate-grade NHL in the Working Formulation, and is generally treated as a large cell lymphoma. The WHO/REAL classification considers B-cell small lymphocytic lymphoma to be synonymous with chronic lymphocytic leukemia.

Other indolent lymphomas recognized by the WHO/REAL classification, but not by the Working Formulation, include lymphoplasmacytic lymphoma, splenic marginal zone B-cell lymphoma, extranodal marginal zone lymphoma of MALT type, and nodal marginal zone B-cell lymphoma.

The REAL and WHO classifications have recognized marginal zone lymphomas (MZLs) as unique clinical and pathological entities, ie, extranodal (MALT), nodal, and splenic NHL subtypes. MALT NHL is extremely indolent and presents as localized stage I-II disease, rarely disseminating. The stomach is the most frequent site, but low-grade NHL (and former pseudolymphomas) of the lungs, thyroid, salivary gland, and orbit are of this type.

REAL/WHO classification vs Working Formulation Several studies have compared the REAL classification with the Working Formulation. In one study, the presence of a T-cell phenotype was associated with a worse prognosis in 68 out of 560 patients with Working Formulation intermediate-grade, immunoblastic NHL. The poor prognoses of these peripheral T-cell lymphomas were independent of the International Prognostic Index (IPI), suggesting that the immunophenotypic basis of the REAL classification is clinically relevant.

However, in a European study of 670 cases of NHL, only 3.8% of cases had a T-cell phenotype, and a statistically significant survival difference could not be demonstrated. In this analysis, mantle cell lymphoma and marginal zone B-cell lymphoma were seen in 11% and 5% of patients, respectively. These histologic subtypes, which are not recognized by the Working Formulation, were characterized by a shorter median survival, suggesting that the REAL classification may be of value in identifying NHL entities with distinct clinical behaviors and prognoses.

Staging and prognosis

Determining the extent of disease in patients with NHL provides prognostic information and is useful in treatment planning. However, histologic subclassification (Working Formulation or REAL/WHO classification) is the primary determinant of survival and potential for cure. Compared to patients with limited disease, those with extensive disease usually require different therapy, and certain extranodal sites of involvement, such as the CNS and testes, require specific treatment modalities.

Ann Arbor system Although initially devised for Hodgkin's disease, the Ann Arbor system has been routinely applied to NHL (Table 5). Because Hodgkin's disease commonly spreads via contiguous lymph node groups, this system is

TABLE 5: Ann Arbor staging classification for NHL[a]

Stage	Area of involvement
I	One lymph node region
I_E	One extralymphatic organ or site
II	Two or more lymph node regions on the same side of the diaphragm
II_E	One extralymphatic organ or site (localized) in addition to criteria for stage II
III	Lymph node regions on both sides of the diaphragm
III_E	One extralymphatic organ or site (localized) in addition to criteria for stage III
III_S	Spleen in addition to criteria for stage III
III_{SE}	Spleen and one extralymphatic organ or site (localized) in addition to criteria for stage III
IV	One or more extralymphatic organs with or without associated lymph node involvement (diffuse or disseminated); involved organs should be designated by subscript letters (P, lung; H, liver; M, bone marrow)

[a] Class A patients experience no symptoms; class B patients experience unexplained fever of ≥ 101.5°F; unexplained, drenching night sweats; or loss of >10% body weight within the previous 6 months.

based primarily on the distribution of lymphatic involvement with respect to the diaphragm and the presence of extralymphatic organ involvement. The Ann Arbor system does not reflect the noncontiguous nature of disease spread in NHL, does not discriminate well between stage III and IV intermediate-grade disease, and fails to account for tumor bulk or number of extranodal sites.

Prognostic factors Histology and morphology are the major determinants of treatment outcome and prognosis. Some patients with slow-growing low-grade lymphoma may remain well for many years with minimal or no initial therapy, whereas survival of patients with some types of high-grade lymphoma is measured only in weeks, unless aggressive treatment is initiated promptly. The biological and clinical behavior of these disorders varies among the different histologic subtypes.

The International Prognostic Index (IPI) was developed by 16 institutions and cooperative groups in the United States, Europe, and Canada as a prognostic factor model for aggressive NHL treated with doxorubicin-containing regimens. Clinical features that were independently predictive of survival (Table 6) included age (≤ 60 vs > 60 years), LDH (≤ 1 vs > 1 times normal), performance status (Eastern Cooperative Oncology Group [ECOG] 0-1 vs 2-4), Ann Arbor stage (I-II vs III-IV), and number of extranodal sites (≤ 1 vs > 1 site).

This index appears to be a very useful guide for selecting treatment for patients with aggressive diffuse large cell NHL by identifying subsets of patients in whom intensified primary therapy may be warranted. Because younger and older patients have markedly different prognoses and because younger patients are more likely to be considered for more intensive investigational regimens, an age-adjusted model for patients ≤ 60 years old has been proposed. In

TABLE 6: International Prognostic Index

Factor	Adverse prognosis
Age	≥ 60 years
Ann Arbor stage	III or IV
Serum LDH level	Above normal
Number of extranodal sites of involvement	≥ 2
Performance status	≥ ECOG 2 or equivalent

From: International non-Hodgkin's Lymphoma Prognostic Factors Project: N Engl J Med 329:987–994, 1993. LDH = lactate dehydrogenase; ECOG = Eastern Cooperative Oncology Group

younger patients, stage (III or IV), high LDH, and nonambulatory performance status are independently associated with decreased survival. A multivariate analysis of diffuse large cell and high-grade NHL suggests performance status best predicts an individual's ability to tolerate induction chemotherapy, and tumor stage is most predictive of long-term survival.

The IPI also appears to be useful in predicting outcome in patients with low-grade lymphoma and mantle cell lymphoma.

A new prognostic factor model has been devised based on a retrospective study of 987 cases of follicular lymphoma. Multivariate analysis showed that gender, age, number of extranodal sites, LDH, systemic symptoms, and erythrocyte sedimentation rate (ESR) were predictors of overall survival. The IPI was also useful in stratifying the same patients into different prognostic groups. In the group of patients ≤ 60 years old, gender, systemic symptoms, and ESR correlated with survival.

Treatment-related factors Time to complete remission has been identified as an important treatment-related prognostic factor in aggressive NHL. Patients who require > 5 cycles of standard chemotherapy to achieve remission have a high risk of relapse. Similarly, patients with gallium-avid tumors who have persistent gallium uptake at the midpoint of treatment are less likely to have durable remissions. Sequential PET scanning has demonstrated similar results.

Using DNA microarrays for gene expression profiling, three molecularly distinct forms of diffuse large B-cell lymphoma (DLBCL) corresponding to different states of B-cell differentiation have been characterized: "germinal center B-like DLBCL," "activated B-like DLBCL," and a heterogeneous subgroup termed "type 3 DLBCL." Patients with germinal center B-like DLBCL had a significantly better overall survival than those with the other DLBCL molecular profiles. The DLBCL gene expression profile appears to provide prognostic information independent of the IPI *(Rosenwald A, Wright G, Chan WC, et al: N Engl J Med 346:1937-1947, 2002)*. Using a similar microarray technology to analyze the expression of 6,817 genes (related to cell adhesion, apoptosis, Ras signaling, serine/threonine phosphorylation, and tumor immunity) in diagnostic tumor specimens of patients with DLBCL who received CHOP-based chemotherapy, two categories of patients with dramatically different 5-year survival (72% vs 9%, $P = .0004$) were identified. This model effectively delineated patients in IPI intermediate-risk categories (low-intermediate/high-intermediate) who are likely to be cured or die of their disease *(Shipp MA, Ross KN, Tamayo P, et al: Nat Med 8:68-74, 2002)*.

Dose intensity and schedule The doses of cyclophosphamide and doxorubicin administered during the first 12 weeks of therapy have been closely associated with survival in aggressive NHL, suggesting that a minimal dose is required to achieve optimal results in diffuse large cell lymphoma and that certain patients may benefit from dose escalation of the most active agents commonly used to treat aggressive NHL. These concepts are currently being tested in randomized clinical trials.

Immunobiological factors Various immunobiological factors have been suggested as predictors of outcome in NHL.

Immunophenotype Several studies have suggested that patients with aggressive nonanaplastic T-cell NHL have a higher relapse rate and decreased overall survival compared with patients with B-cell disease. These observations have been confirmed in updated REAL/WHO studies involving large numbers of patients.

Tumor cell proliferation Studies using the Ki-67 antibody, a marker of nuclear proliferation, have shown that increased tumor cell proliferation is a poor prognostic factor in diffuse large cell lymphoma and diffuse small cell lymphoma.

Antigen expression Because tumor antigens may be recognized in association with major histocompatibility complex (MHC) molecules, it has been postulated that the absence of MHC-encoded recognition structures could limit host tumor immunosurveillance. In a small series of patients with large cell lymphoma, the absence of human leukocyte antigens D-related (HLA-DR) in the tumor was associated with significantly shorter median survival. Similar investigations have correlated decreased HLA antigen expression with deficient numbers of CD8+ tumor-infiltrating lymphocytes (TILs), prompting speculation that loss of tumor MHC molecules results in low TILs.

Adhesion molecule expression Lymphomas expressing lymphocyte-homing receptor (CD44), which facilitates lymphocyte migration, are more likely to disseminate than are CD44-negative lymphomas. Several studies have shown that higher levels of CD44 expression in lymphoma are associated with more advanced stage at presentation and decreased survival.

Cytogenetic abnormalities and oncogene expression Lymphomas with abnormalities involving chromosomes 1, 7, and 17 have a worse prognosis than other lymphomas of similar stage and bulk that do not exhibit these changes. Mutations of p53 are associated with histologic transformation in follicular NHL—a phenomenon frequently associated with a poor prognosis. Expression of BCL-2 or CD5 in diffuse large cell lymphoma has also been associated with inferior survival.

Treatment

The most important therapeutic modality is chemotherapy (Table 7), especially for intermediate- and high-grade NHL. Surgery is useful in selected situations, such as GI lymphoma, particularly if the disease is localized or if there is a risk

TABLE 7: Chemotherapeutic regimens for NHL

Regimen	Dose	Route and frequency
CVP		
Cyclophosphamide	400 mg/m^2	PO on days 1-5 (or 1,000 mg/m^2 on day 1)
Vincristine	1.4 mg/m^2	IV on day 1 (maximum, 2 mg)
Prednisone	100 mg or 100 mg/m^2	PO on days 1-5
Repeat treatment every 21 days		
CHOP ± Rituximab		
Cyclophosphamide	750 mg/m^2	IV on day 1
Doxorubicin HCl	50 mg/m^2	IV on day 1
Oncovin	1.4 mg/m^2	IV on day 1 (maximum, 2 mg)
Prednisone	100 mg or 100 mg/m^2	PO on days 1-5
Rituximab	375 mg/m^2	IV on day 1
Repeat treatment every 21 days		
CHOEP ± Rituximab		
Cytoxan	750 mg/m^2	IV on day 1
Doxorubicin	50 mg/m^2	IV on day 1
Etoposide	100 mg/m^2	IV on days 1-3
Oncovin	1.4 mg/mL	IV on day 1 (maximum, 2 mg)
Prednisone	100 mg	PO on days 1-5
Rituximab	375 mg/m^2	IV on day 1
Repeat treatment every 21 days		
C-MOPP		
Cyclophosphamide	650 mg/m^2	IV on days 1, 8
Oncovin	1.4 mg/m^2	IV on days 1, 8
Procarbazine	100 mg/m^2	PO on days 1-14
Prednisone	40 mg	PO on days 1-14
Repeat treatment every 28 days		
MACOP-B		
Methotrexate[a]	400 mg/m^2	IV on weeks 2, 6, 10
Adriamycin	50 mg/m^2	IV on weeks 1, 3, 5, 7, 9, 11
Cyclophosphamide	350 mg/m^2	IV on weeks 1, 3, 5, 7, 9, 11
Oncovin	1.4 mg/m^2	IV on weeks 2, 4, 6, 8, 10, 12 (maximum, 2 mg)
Prednisone	75 mg	PO daily for 12 weeks; dose tapered over the last 15 days
Bleomycin	10 U/m^2	IV on weeks 4, 8, 12
Cotrimoxazole	2 tablets	PO twice daily throughout

Regimen	Dose	Route and frequency
FND		
Fludarabine	25 mg/m^2	IV on days 1-3
Mitoxantrone	10 mg/m^2	IV on day 1
Dexamethasone	20 mg	PO/IV on days 1-5
Repeat treatment every 21-28 days depending on hematologic recovery		
ProMACE-CytaBOM		
Cyclophosphamide	650 mg/m^2	IV on day 1
Etoposide	120 mg/m^2	IV on day 1
Adriamycin	25 mg/m^2	IV on day 1
Cytarabine	300 mg/m^2	IV on day 8
Bleomycin	5 U/m^2	IV on day 8
Oncovin	1.4 mg/m^2	IV on day 8 (maximum, 2 mg)
Methotrexate	120 mg/m^2	IV on day 8
Leucovorin	25 mg/m^2	PO q6h for 4 doses; start 24 hours after methotrexate
Prednisone	60 mg	PO on days 1-14
Cotrimoxazole	2 tablets	PO twice daily throughout
Repeat treatment every 28 days		
ProMACE-MOPP		
Cyclophosphamide	650 mg/m^2	IV on day 1
Etoposide	120 mg/m^2	IV on day 1
Adriamycin	25 mg/m^2	IV on day 1
Procarbazine	100 mg/m^2	PO on days 8-14
Mechlorethamine	6 mg/m^2	IV on day 8
Oncovin	1.4 mg/m^2	IV on day 8 (maximum, 2 mg)
Prednisone	60 mg	PO on days 1-14
Methotrexate	500 mg/m^2	IV on day 15
Leucovorin	50 mg/m^2	PO q6h for 5 doses; start 24 hours after methotrexate
Repeat treatment every 28 days		
m-BACOD		
Methotrexate	200 mg/m^2	IV on days 8, 15
Leucovorin	10 mg/m^2	PO q6h for 8 doses; start 24 hours after methotrexate
Bleomycin	4 U/m^2	IV on day 1
Adriamycin	45 mg/m^2	IV on day 1
Cyclophosphamide	600 mg/m^2	IV on day 1
Oncovin	1 mg/m^2	IV on day 1 (maximum, 2 mg)
Dexamethasone	6 mg/m^2	PO on days 1-5
Repeat treatment every 21 days		

[a] Methotrexate given as a 100-mg/m^2 IV bolus, then 300 mg/m^2 IV over 4 hours, followed 24 hours later by leucovorin, 15 mg PO, q6h for 6 doses.

of perforation. Orchiectomy is part of the initial management of testicular lymphoma. Radiation therapy plays a more limited role in the treatment of NHL but is particularly useful in localized disease and for palliation. A careful general evaluation of the patient is necessary to assess any contraindications to the planned treatment.

The introduction of radiolabeled antibodies into clinical practice will increase the role of radiotherapy in the future.

TREATMENT OF LOW-GRADE LYMPHOMAS

As a group, low-grade lymphomas (groups A, B, and C in Table 2) are characterized by indolent clinical behavior and comparatively prolonged survival (median survival, 6-10 years). Most patients have advanced-stage disease at diagnosis, and only about 10%-20% have stage I or II disease. Laparotomy is no longer used for staging because most stage I or II patients have disseminated disease below the diaphragm. There is little potential for cure (outside of the setting of allogeneic stem-cell transplantation) when the disease presents in more advanced stages, and, therefore, treatment is usually palliative.

The standard management of low-grade NHL is controversial and ranges from the "watch and wait" approach pioneered at Stanford University to the use of combination regimens containing doxorubicin (Adriamycin and others), such as CHOP (cyclophosphamide, doxorubicin HCl, Oncovin, and prednisone). A substantial proportion of patients are asymptomatic at presentation. However, the majority of patients require treatment within a few years because tumor growth produces symptoms, compromises vital organs, creates anxiety, or is cosmetically unacceptable. Many low-grade lymphomas present in elderly patients, who often have coexistent medical illnesses. Whereas a watch and wait approach is appropriate for older patients, newer treatment approaches are being tested in younger patients whose longevity is likely to be reduced by their disease.

Stage IA-IIA disease

Radiation therapy Patients with stage IA-IIA low-grade NHL (LGNHL) with disease that appears to be confined to the clinically involved lymph nodes and can be adequately encompassed by an irradiation field with acceptable toxicity, should be offered definitive irradiation as the present standard of care. Most clinical reports are composed of patients with follicular small cleaved cell and follicular mixed lymphoma, because the other low-grade histologies are rarely localized at presentation. Relapse-free rates at 10-15 years of 50% and cause-specific survivals of 60%-70% have been reported, usually in pathologically staged patients (results in clinically staged patients may be inferior).

The treatment of choice is irradiation alone to the entire involved lymphoid region, as defined by the Rai and Ann Arbor staging classifications, or the involved region plus one additional uninvolved region on each side of the involved nodes. The recommended dose is 30 Gy for nonbulky disease showing prompt regression, with 36 Gy delivered for bulky or slowly regressive

disease. Progression-free survival at 15 years of up to 66% and cause-specific survival of up to 87% have been reported for patients with stage IA disease, vs 26% and 54%, respectively, for patients with stage IIA disease.

As the majority of relapses occur outside the radiation fields, often in adjacent or distal lymph nodes, extended-field or total lymphoid irradiation has been used to try to improve cure rates. Clinical series have shown improvement in freedom from relapse only, with no significant difference in long-term survival.

Adjuvant chemotherapy The issue of whether adjuvant chemotherapy improves the prognosis of patients with early-stage low-grade NHL remains unresolved. Some have advocated adjuvant chemotherapy to selected stage II patients with unfavorable prognostic factors, such as systemic symptoms or more than two (or discontiguous) nodal sites, and to those with follicular mixed histology.

MALT marginal zone lymphoma MALT lymphomas are usually indolent and present as localized stage I/II disease, rarely disseminating. Tumors with t(11;18) are karyotypically stable and do not typically evolve into large B-cell lymphoma. The stomach is the most frequent site, but most low-grade NHL (and former pseudolymphomas) of the lung, thyroid, salivary gland, and orbit are of this type. Clinically, extranodal marginal zone lymphomas appear to be similar to other low-grade, node-based B-cell lymphomas.

MALT marginal zone lymphoma may be curable with local radiation, as it is usually clinically limited to the involved primary site or organ. Proliferation of lymphoma cells in gastric MALT marginal zone lymphoma depends on antigen-driven T cells, with the antigen frequently identified as *H pylori.* Combination therapy (eg, omeprazole [Prilosec], metronidazole, and amoxicillin) directed at the antigen results in the regression of most early lesions. However, tumors invading beyond the submucosa and lesions with t(11;18) or BCL10 overexpression are associated with a failure to respond to *H pylori* eradication.

Localized MALT marginal zone lymphoma that does not respond to antibiotics may be cured with local irradiation, consisting of 30 Gy in 1.5-Gy daily fractions directed to the stomach and perigastric lymph nodes. This treatment is safe, extremely effective, and allows gastric preservation. A single-institution experience reported a 96% CR and 90% freedom-from-treatment failure at a median follow-up of 4 years (Yahalom J, Portlock C, Gonzales M, et al: ASH [abstract], 2002). If local irradiation fails, then chemotherapy can be used and, finally, surgery.

Stage III/IV disease

Younger patients The management of younger patients with advanced low-grade lymphoma is probably the most controversial area in the treatment of NHL. Some of these patients will enjoy prolonged survival without initial therapy. Median disease-free survival is almost always between 1.5 and 3 years, and median overall survival ranges from 5 to 7 years. Patients with stage III disease have a better prognosis than patients with stage IV disease. Overall, 75% of patients with stage III disease can be expected to survive 5 years.

Chemotherapeutic options in younger patients with low-grade advanced disease include single-agent chemotherapy (chlorambucil [Leukeran] or cyclophosphamide with or without prednisone), CVP (cyclophosphamide, vincristine, and prednisone), or CHOP. A recent report suggested no advantage to the initial use of a relatively intensive combination, CHOP-B, vs single-agent cyclophosphamide. Newer agents, such as fludarabine (Fludara) and cladribine (2-CdA [Leustatin]), have significant antitumor activity in low-grade NHL and are being studied in combination regimens. Rituximab, either alone or combined with these agents, is being investigated.

Four weekly doses of rituximab (Rituxan) produced a 47% response rate in 60 patients with previously untreated low-grade lymphoma. Patients with responsive or stable disease received repeat 4-week courses of therapy at 6-month intervals for 2 years. Following the subsequent courses of rituximab, additional patients responded, producing an overall response of 73% and a complete response of 37%. A similar response was seen in follicular and small lymphocytic lymphoma, with a medium progression-free survival of 34 months.

Interferon The use of interferon-alfa (Intron A, Roferon-A) concomitantly with or as an adjuvant to conventional chemotherapy in follicular lymphoma appears to prolong disease-free survival, but its impact on overall survival and curability is controversial.

Recently, a meta-analysis of randomized trials concluded that IFN-α prolonged overall survival in follicular lymphoma patients receiving more intensive initial therapy with doxorubicin/mitoxantrone (Novantrone)-containing regimens, as compared with patients receiving less intensive initial therapy with single-agent alkylator therapy or CVP. However, the Southwest Oncology Group (SWOG) reported that the use of IFN-α after intensive induction chemotherapy with ProMACE-MOPP did not prolong relapse-free survival or overall survival in patients with advanced follicular NHL.

The National Cancer Institute (NCI) is sponsoring a phase III randomized multi-institution trial to assess the effects of patient-specific vaccines with lymphoma-derived idiotypes in patients with newly diagnosed, previously untreated, low-grade stage III or IV follicular lymphoma. Patients who achieve a complete remission after prednisone, doxorubicin, cyclophosphamide, and etoposide (PACE) will be randomized to receive a carrier-conjugated autologous idiotype vaccine in combination with GM-CSF (complete vaccine) or vaccine consisting of carrier plus GM-CSF only. Two-thirds of randomized patients will receive the complete vaccine. Accrual is ongoing.

These conflicting results make it difficult to specify recommendations regarding the role of IFN-α in the management of follicular lymphoma. Moreover, this agent is associated with substantial side effects, as compared with some of the newer agents, such as the monoclonal antibody (MoAb) rituximab (Rituxan; see "Targeted therapy of NHL" section).

Antigen-pulsed dendritic cells Investigators at Stanford University have used autologous antigen-pulsed dendritic cells to stimulate host antitumor immunity when infused as a vaccine in patients with previously untreated low-grade follicular lymphoma. All four patients treated in this pilot study developed measurable antitumor cellular responses. Two patients experienced clinical responses (one

complete response and one partial response). A molecular response (as measured by PCR analysis) was seen in a third patient.

Patients with poor prognostic factors The IPI also applies to low-grade lymphomas. Unfavorable prognostic factors include extent of bone marrow involvement (> 20%), bulky disease (≥ 5-7 cm), more than one extranodal site, LDH > 1 times normal values, elevated β2M, and nonambulatory performance status. Patients with these unfavorable clinical features have reduced longevity and are incurable with standard chemotherapy or combined-modality approaches, and should therefore be considered candidates for investigational clinical trials aimed at improving disease-free and overall survival.

Based on data from patients with relapsed disease, cytoreduction to a minimal residual disease state followed by autologous stem-cell transplantation or bone marrow transplantation (BMT) has been tested as a therapeutic intervention. Prolonged remissions have been witnessed; however, continuing relapses are seen. Whether this approach improves overall survival or is potentially curative will require longer follow-up and additional testing in randomized trials. Myelodysplasia and secondary leukemias remain a significant concern. For select patients, allogeneic stem-cell transplantation should be considered as a potentially curative approach.

Older patients Because of concomitant medical problems, older patients with asymptomatic, indolent NHL are often observed closely without any initial therapy. The decision to use any of the standard or newer modalities should be individualized, based on the presence of poor prognostic features and the patient's tolerance of planned therapy. Palliative treatment options include chlorambucil (daily dose, 0.1-0.2 mg/kg) or cyclophosphamide (1.5-2.5 mg/kg) with or without prednisone. Oral pulse chlorambucil (16 mg/m^2 for 5 days at 3-week intervals) usually results in a faster antitumor response compared with daily single-agent alkylator therapy.

bcl-2 antisense therapy is feasible and shows potential for antitumor activity in bcl-2–positive relapsed lymphoma. In this study, bcl-2 protein was reduced in 7 of 16 assessable patients *(Waters JS, Webb A, Cunningham D, et al: J Clin Oncol 18:1812-1823, 2000).* PS-341 (Ca proteosome inhibitor) has also demonstrated activity in low-grade NHL *(Orlowski RZ, Stinchcombe TE, Mitchell BS, et al: J Clin Oncol 20:4420-4427, 2002).*

Role of irradiation in stage III/IV, low-grade NHL (extensive stage) These patients can be observed and treated as necessary or enrolled on available clinical trials. Irradiation therapy here is used locally for palliation of symptomatic sites of disease and is extremely effective. Total-body irradiation is used as part of preparative regimens for BMT.

TRANSFORMED LYMPHOMAS

Histologic transformation of low-grade NHL to a more aggressive histology is well recognized, occurring in 30%-70% of patients during the course of their disease. This transformation is associated with an increased proportion of large cells and a rapidly progressive clinical course. A repeat biopsy usually shows diffuse large cell lymphoma, although other histologies such as Burkitt's or Burkitt's-like and anaplastic NHL can be seen. In the majority of cases, trans-

formed lymphoma represents evolution of the original malignant clone rather than development of a de novo malignancy. The transformation process may be associated with a variety of molecular changes, including dysregulation of *bcl*-6, c-*myc*, and P16INK4 (a cell-cycle inhibitor), and p53 mutations.

In a French study by Bastion and colleagues, predictive factors for histologic transformation included failure to achieve complete remission after initial therapy, low serum albumin level, and $\beta 2M > 3$ mg/L. In this study, the occurrence of histologic transformation was found to be an early event in the course of the disease, with a decreased risk at 6 or more years after diagnosis. However, other investigators have observed that the risk of histologic transformation is cumulative and not influenced by whether treatment is initiated at diagnosis or deferred until disease progression.

Histologic transformation is usually associated with poor prognosis and a median survival of 1 year with conventional therapy. However, a subgroup of patients with limited disease and no previous exposure to chemotherapy who attain a complete remission after histologic transformation may have a relatively long survival. Several retrospective studies have reported that patients with chemosensitive transformation can achieve a 5-year survival rate of about 37%-58% using high-dose chemotherapy and autologous stem-cell transplantation. These patients are still at risk for relapse of their low-grade NHL and need to be monitored for this possibility. More recently, radioimmunotherapy with tositumomab/iodine-131 (Bexxar) and ibritumomab tiuxetan (Zevalin) has been shown to be an effective palliative treatment for patients with transformed NHL.

TREATMENT OF INTERMEDIATE-GRADE LYMPHOMAS

The treatment of aggressive NHL has evolved from the use of radiotherapy alone in most patients, which is curative in patients with truly localized disease, to the current practice of using combination chemotherapy, which cures up to 90% of patients with stage I disease. High-grade immunoblastic lymphoma is essentially the same as diffuse large cell lymphoma with regard to biological behavior, treatment, and prognosis and thus is included in this section. The most widely used chemotherapy regimen in aggressive NHL is CHOP administered every 3 weeks.

Recent studies suggest that the combination of rituximab and CHOP is superior to the use of CHOP alone in older patients. Long-term follow-up of these studies will be required to determine if CHOP plus rituximab will be the new standard treatment for diffuse aggressive lymphomas for all patients (confirmation trials and studies in younger patients are in progress).

TREATMENT OF LARGE CELL NHL

Stage I/IIA nonbulky (limited stage)

Prior to the 1970s, most patients with stage I/II large cell lymphoma (intermediate grade in the Working Formulation) were treated with radiation alone, with overall cure rates of 40%-50%. Pathologically favorable stage I/II pa-

tients had even better outcomes, but relapse rates, even in these patients, were still 20%-30%. Pathologic staging, therefore, selected a group suitable for radiation alone.

This approach is no longer appropriate, in view of the success of chemotherapy and radiation in clinically staged patients. Excellent local and systemic control is obtained with combined-modality therapy. Horning et al (ASH 2001) showed in an ECOG phase III trial that 8 cycles of CHOP and radiation produced a 10-year disease-free survival of 57% compared to 46% with CHOP alone ($P = .04$). Overall survival was 64% vs 60%, respectively ($P = .23$) and time to disease progression of 73% vs 63%, respectively ($P = .07$).

Miller et al showed that CHOP (3 cycles of CHOP and irradiation) produced a progression-free survival at 5 years of 77% vs 64% for 8 cycles of CHOP alone ($P = .03$). Overall survival at 5 years was 82% vs 72%, respec-

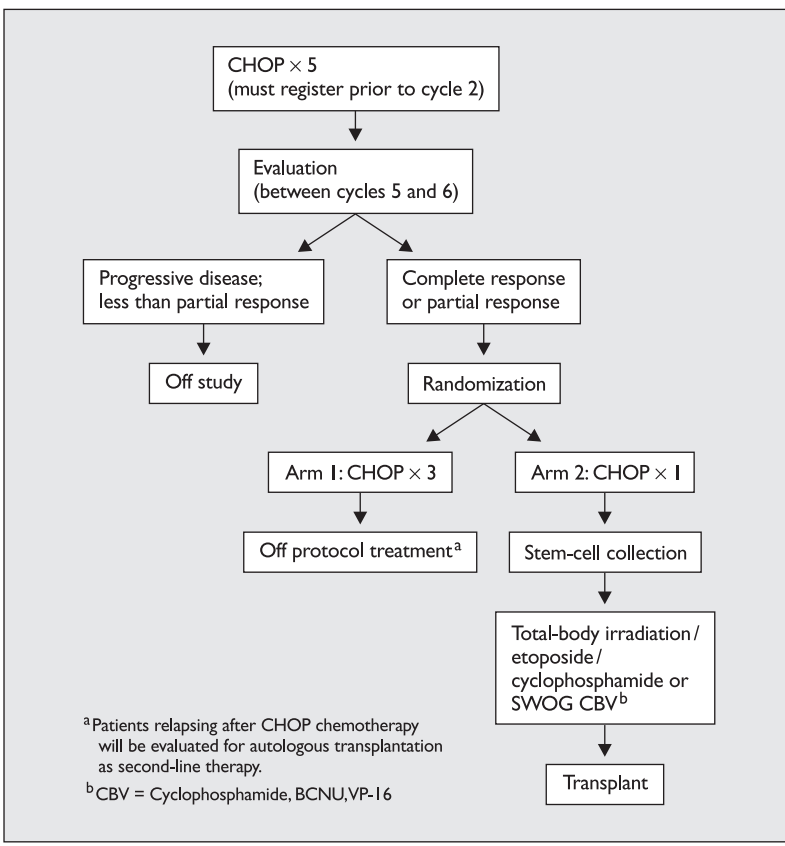

FIGURE 1: Intergroup study of diffuse aggressive lymphoma high-intermediate and high-risk prognostic groups

tively ($P = .02$). Recent update of this SWOG study was reported by Miller et al at ASH 2001, with 8.2 years median follow-up. The 5-year estimates for CHOP (× 3 plus radiation) vs CHOP (× 8) remained unchanged. Kaplain-Meier estimates now showed overlapping curves at 7 years for failure-free survival and 9 years for overall survival (OS). The treatment advantage for CHOP (× 3 plus irradiation) for the first 7-9 years was diminished because of excess late relapses and NHL deaths occurring between 5-10 years. Patients with IPI good risk factors (stage 1 disease, age < 60 years, normal serum LDH, and performance status 0-1) had 5-year OS of 94%; patients with one adverse risk factor (nonbulky stage II disease, age > 60, elevated LDH, or performance status of 2), had OS of 70%; those with 3 adverse risk factors had 5-year survival of 50%. These results were confirmed by a single arm (doxorubicin-containing chemotherapy) followed by involved-field irradiation conducted by the British Columbia Cancer Agency (Shenkier T, Voss N, Fairey R, et al: J Clin Oncol 20:197-204, 2002).

However, two recent reports from European investigators question the value of consolidation irradiation in early-stage disease (Fillet G, Bonnet C, Mounier N, et al: ASH [abstract], 2002; Reyes F, LePage E, Munch J, et al: ASH [abstract] 2002). Miller et al believed that three cycles of CHOP and irradiation remain the standard of treatment, based on survival advantages and decreased toxicity through the first 9 years, until further studies better define optimal treatment, ie, longer or different chemotherapy.

The lymphoma and transplant committees of SWOG, ECOG, and the Cancer and Leukemia Group B (CALGB) are conducting a randomized clinical trial of early vs delayed high-dose therapy for patients with high- and high-intermediate-risk diffuse aggressive lymphoma. Patients < 65 years old will receive 5 cycles of CHOP. Patients with chemosensitive disease will then be randomized to receive either 3 more cycles of CHOP or 1 additional cycle of CHOP followed by high-dose therapy and autologous stem-cell transplantation. Patients receiving standard CHOP will be offered transplantation at the time of relapse (see Figure 1). If this trial confirms the benefit of early stem-cell transplantation in poor-risk patients with chemosensitive diffuse aggressive NHL, subsequent studies will focus on increasing the number of patients who become eligible for transplant consolidation *(Fisher R: Ann Oncol 10[suppl 3]: [abstract 35] 12, 1999).*

Coiffier et al (N Engl J Med 346:235-242, 2002) treated patients with diffuse large B-cell NHL (DLBCL), 60-80 years old, with either eight cycles of CHOP or eight cycles of CHOP plus rituximab. Complete response (76% vs 63%, $P = .005$), event-free survival ($P < .001$), and overall survival ($P = .007$) were significantly higher with CHOP plus rituximab vs CHOP alone. Clinically relevant toxicity was not significantly greater with CHOP plus rituximab. Consequently, by extrapolation and evidence from other studies, the addition of rituximab to CHOP has become routine in the United States and is also being employed with combined modality therapy.

Until further studies define the optimal therapy for stage IA-IIA DLBCL, non-bulky lymphoma, many consider three cycles of CHOP with rituximab and involved-field/region irradiation the initial treatment of choice. For patients with bulky disease, a minimum of six cycles of CHOP is typically administered. Irradia-

tion doses of 30-35 Gy, delivered in 1.75-3.0 Gy over 3-4 weeks after completion of systemic therapy, appear to be adequate. Radiation fields usually include involved lymph node sites or an involved extranodal site and its immediate lymph node drainage areas. Furthermore, the disease should be easily encompassed in a radiation field with acceptable toxicity. Immunoblastic lymphoma (high grade in the Working Formulation) is now classified as large cell NHL in the REAL/WHO classification and is treated using the same strategy.

Disease site or potential toxicities may influence the treatment plan:

- Lymphomas of the head and neck may be managed with chemotherapy alone to avoid the acute mucositis and long-term xerostomia associated with radiation therapy fields that are large and include both parotid glands.
- Fully resected gastric or small intestinal lymphoma may be treated with chemotherapy alone. Patients at high risk of perforation or life-threatening hemorrhage may require surgical resection. Alternatively, chemotherapy followed by local radiation may allow gastric preservation in some patients.
- In younger patients, a brief period of chemotherapy (3-4 cycles of CHOP) followed by local irradiation may be used to prevent sterility in men and early menopause in women.
- Primary brain lymphomas continue to be problematic. At present, the recommended approach is chemotherapy, such as CHOP and/or high-dose methotrexate along with intrathecal chemotherapy, in conjunction with radiation therapy. Optimal dose and scheduling of radiation therapy remains to be determined (long-term neurotoxicity may be excessive in older populations).
- Combination chemotherapy with an anthracycline-containing regimen following orchiectomy has improved the results of therapy for primary testicular lymphoma. Because of the increased risk of recurrence in the CNS and opposite testis, intrathecal chemotherapy and radiation to the contralateral testis are recommended.

Stage III/IV disease

Early SWOG studies with CHOP reported complete response rates of 50%-55%, with 30%-35% long-term disease-free survival. Single-institution pilot studies of newer regimens, such as m-BACOD (methotrexate, bleomycin, Adriamycin, cyclophosphamide, Oncovin, and dexamethasone; Dana-Farber Cancer Center), ProMACE-CytaBOM (prednisone, methotrexate, Adriamycin, cyclophosphamide, etoposide, cytarabine, bleomycin, and Oncovin; National Cancer Institute [NCI]), and MACOP-B (methotrexate, Adriamycin, cyclophosphamide, Oncovin, bleomycin, and prednisone; Vancouver) resulted in 68%-86% complete response rates with 58%-69% survival rates.

To verify these results, the SWOG conducted a consecutive series of phase II trials with the newer regimens. Complete response rates varied from 49% to

TABLE 8: M. D. Anderson regimen (Hyper-CVAD/MTX-Ara-C) for mantle cell lymphoma, lymphoblastic lymphoma, and acute lymphoblastic leukemia

Cyclophosphamide	300 mg/m^2 infused over 3 h q12h × 6 doses (days 1-3) with mesna
Doxorubicin	50 mg/m^2/d on day 4
Vincristine	1.4 mg/m^2 (max 2 mg) IV on days 4 and 11
Dexamethasone	40 mg/d days 1-4 and 11-14
Alternate every 21 days with	
Methotrexate (MTX)	1 g/m^2 continuous infusion over 24 h (day 1)
Ara-C	3 g/m^2 over 2 h q12h × 4 doses (days 2 and 3)
Leucovorin rescue	50 mg PO at end of MTX infusion and then 25 mg PO q6h × 48 h

Aggressive supportive care including administration of cytokines, fluconazole (Diflucan), acyclovir (Zovirax), and trimethoprim-sulfamethoxazole is strongly recommended.

65% and survival rates ranged from 50% to 61%, which were very similar to results obtained with first-generation regimens (ie, CHOP) in a cooperative group setting, emphasizing the need for randomized, comparative trials.

Between 1986 and 1991, 1,138 previously untreated patients with stage II (bulky), III, or IV intermediate- or high-grade NHL were randomized to receive either standard therapy (CHOP) or one of the third-generation regimens (m-BACOD, ProMACE-CytaBOM, or MACOP-B). There was no difference in response rate, time to treatment failure, or overall survival between CHOP and the third-generation regimens. Moreover, the newer regimens were more toxic and expensive. Other randomized comparisons have failed to show an advantage of the third-generation regimens over CHOP.

Treatment recommendations Although CHOP remains the best available standard therapy, it is curative in < 50% of patients, indicating a need for new treatment approaches. The following recommended treatment strategies should be adjusted according to the level of risk, as defined by the prognostic factors validated by the IPI:

Age ≤ 60 years at low or intermediate risk Younger patients at low or intermediate risk (ie, normal LDH and ambulatory performance status) have 5-year survival rates > 50%. They should be treated with 6-8 cycles of a standard doxorubicin-containing regimen, such as CHOP. However, a recently reported investigation suggests an advantage with the addition of etoposide to the CHOP regimen (CHOEP) given every 2 or 3 weeks.

Age ≤ 60 years at high-intermediate or high risk The 5-year survival rate in younger patients deemed at high-intermediate or high risk (high LDH and/or nonambulatory performance status) is < 50%. Since the clinical features that correlate with relapse are also associated with a decreased likelihood of achieving an initial remission, these patients should be offered participation in clinical trials of dose-intensive treatment strategies aimed at improving the

The Groupe d'Etude des Lymphomes de l'Adulte that (GELA) has recently reported the addition of rituximab to the CHOP regimen (8 cycles) increases the complete response rate and prolongs event-free and overall survival in elderly patients (60-80 years) with diffuse large cell lymphoma (Coiffier B, Lepage E, Briere J, et al: N Engl J Med 346:235-242, 2002). In addition, a randomized trial conducted by the German Lymphoma Study Group suggests a benefit to administering CHOP q2 weeks with growth factor support in patients ≥ 65 years *(Trumper L, Kloess M: International Conference on Malignant Lymphoma [abstract], 2002).*

rates and durability of complete responses (see Figure 1).

Age > 60 years All patients over the age of 60 years should undergo evaluation of cardiac, pulmonary, and renal function and coexistent illness, which may complicate therapy.

Most older patients with advanced-stage aggressive NHL have 5-year survival rates < 50% as a result of decreased initial response, poor tolerance to therapy, and the need for dose reduction because of age. Approaches to elderly patients should include interventions aimed at preserving or increasing dose intensity and improving tolerance of therapy with the use of cytokines and infusional chemotherapy. Selected physiologically "younger" patients may be eligible for consolidation with high-dose therapy and hematopoietic stem-cell support.

Compromised cardiac or pulmonary function Patients with compromised cardiac function require individualized approaches, such as the use of a regimen that does not contain an anthracycline (eg, CVP [cyclophosphamide, vincristine, and prednisone], C-MOPP [cyclophosphamide, Oncovin, prednisone, and

TABLE 9: Protocol for lymphoblastic lymphomas[a]

Drug	Dose	Route and frequency
Cyclophosphamide	400 mg/m^2	PO on days 1-3, on weeks 1, 4, 9, 12, 15, 18
Doxorubicin	50 mg/m^2	IV on weeks 1, 4, 9, 12, 15, 18
Vincristine	1.4 mg/m^2	IV on weeks 1-6, 9, 12, 15, 18
Prednisone	40 mg	PO daily for 1 month, taper on weeks 5 and 6, then daily for 5 days on weeks 9, 12, 15, and 18
Cotrimoxazole	2 tablets	PO daily on weeks 1-21
Asparaginase	6,000 U/m^2	IM for 5 doses on weeks 3 and 4
Methotrexate[b]	12 mg	Intrathecally on week 3, then doses twice weekly on weeks 5 and 6; one dose on week 7
Mercaptopurine	75 mg/m^2	PO daily on weeks 21-52
Methotrexate	30 mg/m^2	PO weekly on weeks 21-52

[a] Whole-brain radiotherapy is given on weeks 6, 7, and 8 in 12 fractions, 200 cGy each, to a total dose of 2,400 cGy.

[b] If absolute granulocyte count is < 1,000/μL at the time of any intrathecal methotrexate dose, leucovorin should be given as a single 12-mg dose at 36-42 hours.

From Picozzi VJ, Coleman CN: Semin Oncol 17:96–103, 1990.

TABLE 10: Stanford University protocol for small noncleaved lymphoma

Drug	Dose	Route and frequency
Cyclophosphamide	1,200 mg/m^2	IV on day 1
Vincristine	1.4 mg/m^2	IV on day 1
Doxorubicin	40 mg/m^2	IV on day 1
Prednisone	40 mg/m^2	PO on days 1-5
Allopurinol	300 mg	PO on days 1-10 (first cycle only)
Methotrexate[a]	3 g/m^2	IV on day 10, q21d
Leucovorin	25 mg/m^2	PO q6h for 12 doses; start 24 h after methotrexate
Methotrexate	12 mg	Intrathecally on days 1 and 10 of cycles 2-4; give at onset of methotrexate infusion
Repeat treatment every 21 days		

From Bernstein JI, Coleman CN, Strickler JG, et al: J Clin Oncol 4:847–858, 1986.

[a] Methotrexate is given IV over 6 hours in 1 L of dextrose 5-in-water and 2 amp of sodium bicarbonate. Follow with 500 mL of dextrose 5-in-water and 2 amp of sodium bicarbonate.

procarbazine], or CEPP [cyclophosphamide, etoposide, procarbazine, and prednisone]); a reduction in total anthracycline dose (eg, by alternating CHOP with C-MOPP or CEPP); or the administration of doxorubicin by continuous infusion. Similarly, bleomycin should not be used in patients with compromised pulmonary function.

Role of irradiation in stage III/IV (advanced/extensive) and symptomatic or DLBCL
This is a disease that cannot be encompassed by an irradiation field with acceptable toxicity, or where there are associated unfavorable features indicating occult disseminated disease requiring a full curative course of combined chemotherapy. In such cases, irradiation may be added if there is localized residual disease after chemotherapy completion to improve local control. Irradiation can also be delivered to prechemotherapy areas of bulky disease, again to enhance local control. The above recommendations are based on the observation that when DLBCL relapses after definitive chemotherapy, it usually does so in initially involved or bulky areas of disease. The benefits of palliative irradiation should be weighed against the use of alternative chemotherapy salvage regimens.

Irradiation is also extremely effective in palliative situations and is a component of stem-cell transplant preparative regimens that incorporate total-body irradiation.

TREATMENT OF MANTLE CELL LYMPHOMAS

A recent retrospective multivariate analysis performed in 590 patients with mantle cell lymphoma identified disease stage, extranodal involvement, B-symp-

toms, LDH, performance status, and age as independent prognostic factors. Thus, the IPI also identified different patient risk groups. In contrast to previous studies, neither cytologic features nor architecture had an impact on survival, although there was a trend toward worse clinical outcome in patients with blastoid histology and diffuse tumor growth pattern. However, a high proliferation index, as determined by Ki-67 staining or number of mitoses per high-power field, was associated with an inferior outcome. The median survival was 3 years, with virtually no long-term survivors, and clinical outcome was not influenced by conventional chemotherapy.

Investigators at M. D. Anderson Cancer Center have used 4 courses of fractionated cyclophosphamide (1,800 mg/m^2) administered with doxorubicin, vincristine, and dexamethasone (hyper-CVAD) alternating with high-dose Ara-C and methotrexate (A-M) to treat 45 patients with mantle cell lymphoma, including 25 who were previously untreated. Originally designed for the treatment of acute lymphoblastic leukemia, hyper-CVAD/A-M (Table 8) induced a

TABLE 11: Vanderbilt regimen for small noncleaved cell lymphoma

Drug	Day	1	2	3	8	15	22
Cycle 1							
Cyclophosphamide		X	X				
Etoposide		X	X	X			
Vincristine					X		X
Bleomycin					X		X
Methotrexate						X	
Leucovorin					X		
Prednisone		X—					—I
Cycle 2							
Cyclophosphamide		X					
Etoposide		X	X	X			
Doxorubicin		X	X				
Vincristine					X		X
Bleomycin					X		X
Methotrexate						X	
Leucovorin						X	
Prednisone		X—					—I

From Waits TM, Greco FA, Greer JP, et al: J Clin Oncol 11:943–949, 1993.

Chemotherapy regimen: Second course begins on day 29. Drug doses (per day) are: cyclophosphamide, 1,500 mg/m^2; etoposide, 400 mg/m^2 during cycle 1 and 100 mg/m^2 during cycle 2; vincristine, 1.4 mg/m^2; bleomycin, 10 U/m^2; methotrexate, 200 mg/m^2; leucovorin, 15 mg/m^2 q6h for a total of 6 doses to begin 24 hours after methotrexate administration; and doxorubicin, 45 mg/m^2.

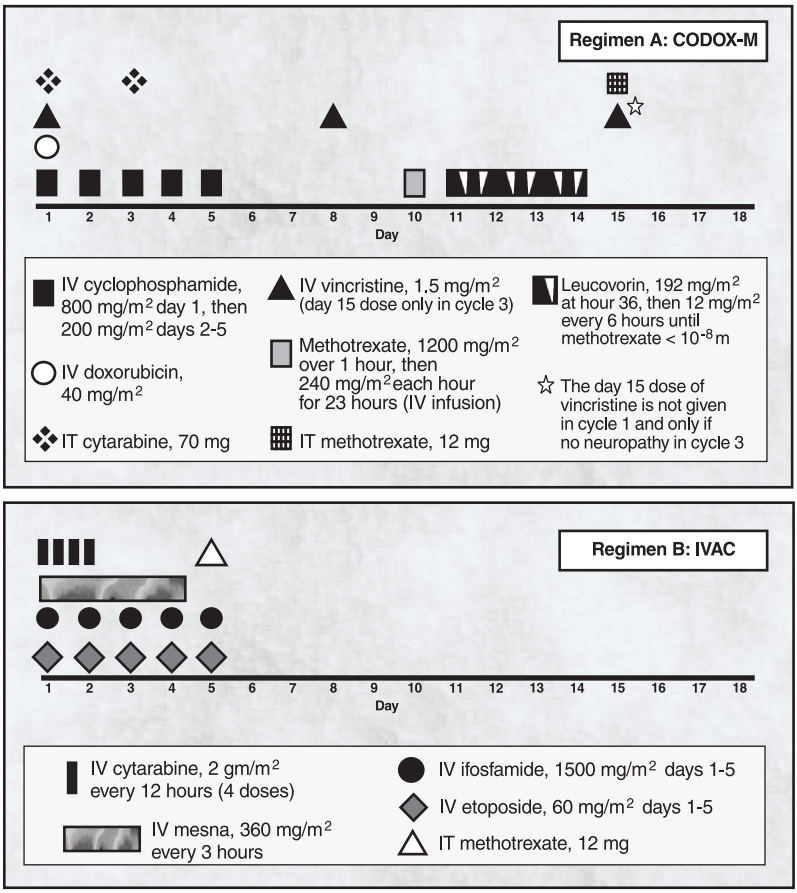

FIGURE 2: National Cancer Institute (NCI) Protocol for small noncleaved cell lymphoma

Adapted from Magrath I, Adde M, Shad A, et al: J Clin Oncol 14:925-934, 1996.

response rate of 94% (complete response, 38%; partial response, 56%) in the mantle cell lymphoma patients. After 4 cycles of this regimen, patients ≤ 65 years old were consolidated with either an autologous or allogeneic transplant. The hyper-CVAD/A-M (Table 8) regimen has also been used successfully in the treatment of high-grade lymphoblastic and small noncleaved cell lymphomas.

The overall survival and event-free survival rates at 3 years were 92% and 72%, respectively, in the 25 previously untreated patients (95% confidence interval, 45% to 98%), as compared with 25% and 17%, respectively, in the previously treated patients. Untreated patients had a better 3-year event-free survival rate than a historical control group who received a CHOP-like regimen (72% vs 28%), as well as a superior overall survival rate (92% vs 56%).

Though several series suggest that high-dose therapy improves outcome for patients with mantle cell lymphoma, randomized trials will be required to confirm these findings. Long-term follow-up of a City of Hope and Stamford trial incorporating autologous stem-cell transplantation has failed to demonstrate a plateau in the disease-free survival curve. Preliminary data from a randomized investigation conducted by the German Lymphoma Study Group suggests that the addition of rituximab provides added benefit (Hiddemann W, Unterhalt M, Dreyling M, et al: ASH [abstract], 2002).

Treatment recommendations

Autologous or allogeneic BMT in first complete or partial remission is recommended for patients with advanced-stage disease and poor-risk features only as part of a clinical trial. Patients with advanced mantle cell lymphoma should not receive CHOP chemotherapy alone. More aggressive regimens are recommended, such as the hyper-CVAD/A-M or CHOP in combination with rituximab. Novel approaches incorporating radiolabeled antibodies (tositumomab and ibritumomab), anti-idiotype vaccines, and nonmyeloablative allogeneic stem-cell transplants are being explored.

TREATMENT OF HIGH-GRADE LYMPHOMAS

Long-term survival among adults with these rapidly growing lymphomas was uncommon prior to the use of intensive combination chemotherapy and CNS prophylaxis. Although relatively infrequent in adults, high-grade lymphomas constitute the majority of NHLs in children. In general, patients can be divided into good- or poor-risk groups based on the extent of disease, as defined by the presence or absence of bone marrow or CNS involvement, tumor mass ≥ 10 cm, and LDH ≥ 1.5 times normal. The Ann Arbor staging system is suboptimal but, unfortunately, is still used in this patient population.

Lymphoblastic lymphomas

Lymphoblastic lymphomas were previously included in the diffuse, poorly differentiated category of the Rappaport classification and are sometimes misdiagnosed. These malignancies are histologically and cytologically indistinguishable from the lymphoblasts of acute lymphoblastic leukemia (ALL). Most lymphoblastic lymphomas are of T-cell phenotype.

Patients sometimes exhibit clinical features of both leukemia and lymphoma at presentation or during the course of their disease. Bone marrow involvement is common. Criteria to distinguish between these diseases are arbitrary, such as the presence or absence of > 25% marrow involvement, which is used by some pediatric oncologists. Mediastinal masses are seen in 50%-70% of patients at presentation, sometimes together with the superior vena cava syndrome.

Treatment recommendations Because of the propensity for CNS relapse during the course of lymphoblastic lymphomas, CNS prophylaxis using intrathecal chemotherapy with or without cranial irradiation is part of all successful treatment regimens. Currently, ALL-like regimens utilizing multiple drug combinations in alternating fashion with intrathecal chemotherapy and

TABLE 12: Comparison of EORTC and WHO classifications of primary cutaneous lymphomas

EORTC	WHO
B-cell lymphomas	
Indolent	
Follicle center cell lymphoma	Follicular lymphoma and diffuse large B-cell lymphoma
Immunocytoma (marginal zone B-cell lymphoma)	Extranodal marginal zone B-cell lymphoma
Large B-cell lymphoma of the leg	Diffuse large B-cell lymphoma and follicular lymphoma
Provisional	
Intravascular large B-cell lymphoma	Intravascular large B-cell lymphoma
Plasmacytoma	Plasmacytoma
T-cell lymphomas	
Indolent	
Mycosis fungoides	Mycosis fungoides
Mycosis fungoides-associated follicular mucinosis	Mycosis fungoides-associated follicular mucinosis
Pagetoid reticulosis CTCL, large cell, CD30+	Pagetoid reticulosis Primary cutaneous anaplastic large-cell lymphoma
Lymphomatoid papulosis	Lymphomatoid papulosis
Aggressive	
Sézary syndrome	Sézary syndrome
CTCL, large-cell, CD30-	Peripheral T-cell lymphoma, unspecified
Provisional	
Granulomatous slack skin	Granulomatous slack skin
Pleomorphic small/medium-sized CTCL	Peripheral T-cell lymphoma, unspecified
Subcutaneous panniculitislike T-cell lymphoma	Subcutaneous panniculitislike T-cell lymphoma

EORTC = European Organization for Research on the Treatment of Cancer; WHO = World Health Organization; CTCL = cutaneous T-cell lymphoma

maintenance therapy for 2-3 years (Tables 8 and 9) have demonstrated complete response rates of up to 80% with long-term survival rates of 45%. In addition, the German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia has reported a 51% overall survival rate at 1 year with an ALL-type regimen and mediastinal irradiation (Hoelzer D, Goklouget N, Digel W, et al: Blood 99:4379-4395, 2002).

Specific treatment strategies should be guided by risk factors that are predictive of outcome: standard risk (stage I-III and normal LDH) vs high risk (stage IV; high LDH; bone marrow, CNS, or other extranodal site of involvement). Additonal high-risk features include older age and B symptoms. Patients with adverse prognostic features are candidates for consolidation with autologous or allogeneic stem-cell transplantation after the completion of induction therapy. A trend toward improved relapse and overall survival has been reported by the European Group for Blood and Marrow Transplantation and the United Kingdom Lymphoma Group (Sweetenham J, Santini, Qian W, et al: J Clin Oncol 11:2927-2936, 2001).

Small noncleaved cell lymphomas

Small noncleaved cell lymphomas (Burkitt's and non-Burkitt's types) are the fastest growing and most aggressive of all the lymphomas. Prolonged staging procedures should be avoided because these neoplasms can double in size in a matter of days. High-risk features include elevated LDH, bone marrow involvement, and unresectable tumor masses > 10 cm.

Treatment recommendations A CHOP-like regimen with mid-cycle high-dose methotrexate for CNS prophylaxis developed at Stanford University (Table 10) resulted in durable complete remissions in 70%-80% patients without high-risk features but in only 20%-30% of patients with adverse prognos-

TABLE 13: Initial treatment options for cutaneous T-cell lymphoma by stage

Stage	Clinical features	Treatment options
IA	Limited patch, plaque (< 10% BSA)	Topical steroids, nitrogen mustard, or BiCNU, Targretin gel[a], spot electron-beam irradiation, PUVA
IB-IIA	Extensive patch, plaque (> 10% BSA)	Topical nitrogen mustard or BiCNU, PUVA, Targretin gel[a], total skin electron-beam irradiation, methotrexate, IFN, PUVA + IFN, Targretin capsules, PUVA + Targretin capsules
IIB	Tumors	Spot electron-beam irradiation, PUVA ± IFN, methorexate, Targretin capsules, ONTAK
III	Erythroderma without Sézary cells	PUVA, total skin electron-beam irradiation, topical Sézary cells nitrogen mustard, or BiCNU, Targretin capsules, IFN, PUVA + IFN, methotrexate, purine analogs, photopheresis
III	Erythroderma with Sézary cells	Extracorporeal photopheresis, PUVA + IFN, Targretin capsules ± PUVA, methotrexate, purine analogs, ONTAK
IV	Lymph node or visceral involvement	Skin-directed therapies plus Targretin capsules, IFN, ONTAK, purine analogs, cytotoxic chemotherapy

[a] Topical Targretin may cause irritation if applied to a large body surface area

BSA = body surface area; BiCNU = carmustine; PUVA = phototherapy with ultraviolet A (UVA with psoralen); IFN = interferon; ONTAK = denileukin diftitox

tic features. A brief, high-intensity, cyclophosphamide-based regimen devised at Vanderbilt University (Table 11) achieved durable responses in about 50% of high-risk patients.

Magrath and colleagues at the National Cancer Institute (NCI) have used four alternating cycles of CODOX-M (cyclophosphamide, doxorubicin, vincristine, prednisone, methotrexate) and IVAC (ifosfamide, etoposide, arabinoside, and mesna) plus intrathecal prophylaxis in 66 patients with high-risk small noncleaved cell lymphoma (Figure 2).

Event-free survival at 1 year and beyond was 92%, and no differences in outcome were seen between children and adults. The median potential follow-up period was 48 months (Adde M, Shad A, Venzon D, et al: Semin Oncol 25:33-39, 1998). This regimen is associated, however, with substantial hematologic toxicity and infectious complications. Several cases of peripheral neuropathy were seen almost exclusively in patients receiving concomitant vincristine and granulocyte-macrophage colony stimulating factor, suggesting that hematopoietic growth factors and cytotoxic chemotherapy should not be administered within 24 hours of each other.

Selected patients with high-risk features are candidates for autologous or allogeneic BMT during first complete or partial remission.

TABLE 14: Systemic therapies for cutaneous T-cell lymphoma (phase II studies)

Treatment	Response duration, months (median)
PEG-DOXO	15
TSEB + CAPO	13.7
VICOP-B	8.7
EPOCH	8
IFN 3-18 mU	5.4
IFN high dose	8
Fludarabine	3
2-CDA	4.3
Pentostatin (2-5 mg/m2 × 3)	1.3-8.3
ONTAK (9-18 μg/kg × 5 days)	7.3
Pentostatin and IFN	13.1
Fludarabine and IFN	6.5
Bexarotene (300 mg/m^2 daily)	7.5

PEG-DOXO = pegylated liposomal doxorubicin; TSEB = total skin electron-beam; CAPO = cyclophosphamide, Adriamycin, etoposide, vincristine, prednisone; VICOP-B = idarubicin, etoposide, cyclophosphamide, vincristine, bleomycin, prednisone; EPOCH = etoposide, vincristine, doxorubicin, bolus cyclophosphamide, oral prednisone; IFN = interferon; 2-CDA = cladribine; ONTAK = denileukin diftitox

Table 15: Investigational treatments for refractory cutaneous T-cell lymphoma

Alemtuzumab (Campath 1-H)
FK228 (depsipeptide)
Temozolomide
Intermediate-dose IL-2
IL-12 ± low-dose IL-2
^{90}Y anti-CD25 antibody
Anti–Tac-pseudomonas immunoconjugates
Autologous/allogeneic bone marrow transplantation

EPOCH = etoposide, vincristine, doxorubicin, bolus cyclophosphamide, and oral prednisone; IL = interleukin

CNS prophylaxis

Risk factors for CNS disease include histology (high-grade small noncleaved and lymphoblastic NHL) and special sites of involvement (bone marrow, testis, paranasal sinus, nasopharyngeal, and epidural) by diffuse aggressive NHL. Methotrexate (12-15 mg), cytarabine (Ara-C; 25-35 mg/m^2), or lipsomal Ara-C (50 mg) can be used for intrathecal therapy.

STEM-CELL TRANSPLANTATION IN POOR-RISK AGGRESSIVE NHL IN FIRST REMISSION

Phase II studies of high-dose therapy and stem-cell transplantation in poor-risk NHL in first complete remission have had encouraging results, particularly in patients with high-intermediate and high-risk diffuse aggressive NHL (as defined by the IPI). These results suggest that further study is warranted.

Single-institution studies have produced excellent overall and event-free survival rates ranging from 60% to 90% in patients with poor-risk features. The predicted results of conventional anthracycline-containing regimens in patients with these features are < 50%. The comparative results of high-dose therapy/stem-cell transplantation vs conventional induction or salvage regimens in slowly or partially responding patients are less straightforward, in part, because of limitations in the design of these studies, which failed to enroll enough patients to make meaningful conclusions.

All of the randomized studies comparing standard therapy vs stem-cell transplantation in first complete or partial remission have been performed in Europe and to date have not shown a benefit from the high-dose therapy arm. However, subset analyses have suggested a potential benefit for poor-risk patients (Haioun C, LePage E, Gisselbrecht C, et al: J Clin Oncol 18:3025-3030, 2000). Participation in these trials is essential to help define the optimal timing of stem-cell transplantation in poor-risk NHL. It is hoped that the current intergroup trial will resolve this issue.

TABLE 16: Monoclonal antibodies for lymphoid malignancies

Antigen	Antibody	Type	Investigational status
CD20	Rituximab (Rituxan)	Chimeric	FDA approved
	Tositumomab (Bexxar)	I-131-murine	Application submitted
	Ibritumomab (Zevalin)	Y-90-murine	FDA approved
CD52	Alemtuzumab (Campath)	Humanized	FDA approved
CD22	Epratuzumab	Humanized	Phase II/III
HLA-DR	Hu1D10 (Remitogen)	Humanized	Phase II

FDA = Food and Drug Administration

PRIMARY CUTANEOUS NHLS

Primary cutaneous NHLs (PCNHLs) represent the second most common site of extranodal NHLs, with an annual incidence of 0.3/100,000 population in western Europe and North America. They may be unifocal, regionally localized, or widespread. Changing nomenclature has made classification challenging. Table 12 shows the major entities of the European Organization for Research on the Treatment of Cancer (EORTC) classification proposal and its corresponding entities in the World Health Organization (WHO) classification. The EORTC divided subtypes by clinical behavior and histopathologic findings identifying indolent, intermediate, and aggressive T-cell and B-cell types. Most of skin T-cell NHLs exist in both classifications with similar designations. In contrast, there is significant disagreement between the two classifications regarding B-cell PCNHLs.

Primary cutaneous T-cell lymphoma

Primary cutaneous T-cell lymphoma (PCTCL) is characterized by localization of neoplastic T lymphocytes to the skin at presentation. Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common forms. MF presents with limited erythematous patch and plaque lesions, with usual progression to generalized involvement of the skin. There is subsequent tumor formation and nodal involvement. The TNMB staging system is used commonly in deciding therapy (see Table 13). Skin stage is the most important prognostic factor. CD30+ primary cutaneous large cell lymphoma (CD30 + PCTCL) is the next most common variant and has a favorable prognosis. It is usually limited to the skin and is considered indolent on the EORTC classification. It corresponds to primary cutaneous anaplastic large cell lymphoma (ALCL) in the EORTC entity of CD30– CTCL and CTCL, pleomorphic small/medium cell type. EORTC

identifies the former as aggressive and the latter as relatively aggressive. Both of them are considered as PCTCL unspecified in the WHO classification.

Treatment

Therapy for PCTCL is skin directed (topical chemotherapy, irradiation, and PUVA [psoralen with ultraviolet A activation]) or systemic (chemotherapy, photopheresis, IFN, retinoids).

Radiation therapy is very effective in controlling locally PCTCL. External-beam irradiation (photons) is used for resistant MF and for palliation of bulky tumor lesions. Superficial electron-beam therapy is tolerated better and is also effective. Only the skin is treated, with low-energy electrons, and the target volume usually does not exceed a depth of 5 mm. Significant myelotoxicity is therefore unusual. Standard dose for total skin electron-beam therapy is 36 Gy delivered by dual fixed-angle, six-field methods 4 days a week. Total skin electron-beam therapy results in 56%-96% CR rate in patients with stage IA-IIA disease.

There is a high relapse rate after total skin electron-beam therapy without adjuvant therapy, such as topical chemotherapy and PUVA. Relapse-free survival for stage IA disease is 33%-52% at 10 years. Local irradiation is the treatment of choice also for CD30+ CTCL, with a 90% 4-year survival rate. Photopheresis is most effective in generalized erythroderma and the SS.

Topical chemotherapy for MF includes mechlorethamine (nitrogen mustard) and carmustine (BiCNU). Topical nitrogen mustard is applied daily to the entire body surface with a solution of 10 mg in 50 mL of water.

PUVA consists of the ingestion of 8-methoxypsoralen (8-MOP), a member of photoactivated compounds that can inhibit both DNA and RNA synthesis through the formation of mono- or bifunctional thymine adducts, gene mutations, or sister chromatid exchanges. It is used in patients with stage I-II disease. The drug becomes activated when exposed to ultraviolet light, particularly in the 330- 340-nm range. Treatment is given 3 times a week during the clearing phase, followed by a tapering maintenance phase.

Systemic therapies are usually used for palliation of relapsed or refractory disease after skin-directed therapies or advanced disease at presentation of all variants (see Table 14). New treatments for refractory CTCL are shown in Table 15.

Primary cutaneous B-cell lymphoma

Primary cutaneous B-cell lymphoma (PCBCL) has been recently recognized as a distinct clinical entity arising in the skin. There is no evidence of extracutaneous disease at presentation, and 5-year survival is 89%-96%. Local recurrences are seen in 25%-68% of cases, but dissemination is rare.

Reactive lymphoid hyperplasia (RLH) is considered a reactive lymphocytic proliferation caused by various antigenic stimuli and is benign. RLH should be treated, as it may represent a precursor lesion of PCBCL. An association for PCBCL with *B burgdorferi* has been suggested but not verified. Etiology is otherwise largely unknown.

The most common types are follicular lymphoma, marginal zone lymphoma (MZL) of the MALT type, and DLBCL. Some refer to MZL of the skin as SALT lymphoma. There are several areas of disagreement between the EORTC and the WHO classifications regarding the features of specific PCBCLs and whether they are distinct entities (see Table 12). The EORTC system has tried to identify and define primary cutaneous lymphomas based upon clinical, pathologic, phenotypic, and genetic features. Though the EORTC system currently provides some clinical advantages for decision making, a future goal should be to improve the WHO classification so that one system would be applicable for all NHLs.

Dose-adjusted EPOCH (etoposide, prednisone, Oncovin, cyclophosphamide, and doxorubicin HCl) has been used by NCI investigators to treat patients with HIV-associated NHL. The complete response rate was 70%, and 2-year progression-free survival and overall survival rates were 83% and 72%, respectively. The use of antiretroviral therapy was suspended during EPOCH chemotherapy, without causing irreversible HIV progression *(Little R, Pearson D, Steinberg S, et al: Proc Am Soc Clin Oncol [abstract] 18:10a, 1999).*

Treatment

For the purposes of clinical treatment, PCBCL can be divided into two stages adapted from the Ann Arbor system: IE (limited extent or radio-encompassible with acceptable toxicity) and IV (widespread or extensive). PCBCL is highly responsive to irradiation and systemic chemotherapy. Stage IE follicular and MZLs should be treated with local irradiation. Even when surgical excision is used as local therapy, irradiation is often added postoperatively, due to a high risk of subsequent local failure. The inclusion of a 2-3 cm margin of resection and a radiation dose of 30 Gy give the lowest rate of local recurrence. Local recurrences after irradiation can be reirradiated with good results.

There is disagreement over the treatment of stage IE DLBCL. Some believe that brief chemotherapy with CHOP and rituximab followed by involved-field irradiation should be standard, whereas others consider this approach overtreatment and think local irradiation alone is sufficient.

Stage IV follicular and MZLs are treated with expectant observation, systemic chemotherapy with or without monoclonal antibodies (rituximab), or local irradiation depending on symptoms, cosmetic appearance, and patient preference. Stage IV DLBCL should be treated with an extended course of CHOP chemotherapy and rituximab. Irradiation can be added to local areas as necessary for improved local control.

TREATMENT OF HIV-RELATED LYMPHOMAS

Most lymphomas seen in patients who have HIV infection are of high-grade histology (immunoblastic and small noncleaved cell) and advanced stage at presentation. Extranodal disease is common, with unusual sites of presentation, including the rectum, CNS, and multiple soft-tissue masses. Some patients present with primary CNS lymphoma. Poor-risk factors include high LDH, large tumor bulk, extranodal disease, and low CD4 counts (< 100 cells/μL).

Chemotherapy

Because of their increased risk of opportunistic infections and impaired hematologic reserve, many patients are unable to tolerate aggressive chemotherapy regimens. Attenuated-dose regimens (such as CHOP or m-BACOD, with 50% reduction of the doxorubicin and cyclophosphamide doses plus growth factor support) are well tolerated, although hematologic toxicity remains a problem in some patients.

Novel oral or infusional combination chemotherapy regimens designed to produce responses and preserve an optimal quality of life are currently being tested. A subgroup of patients without adverse prognostic factors achieve durable remis-

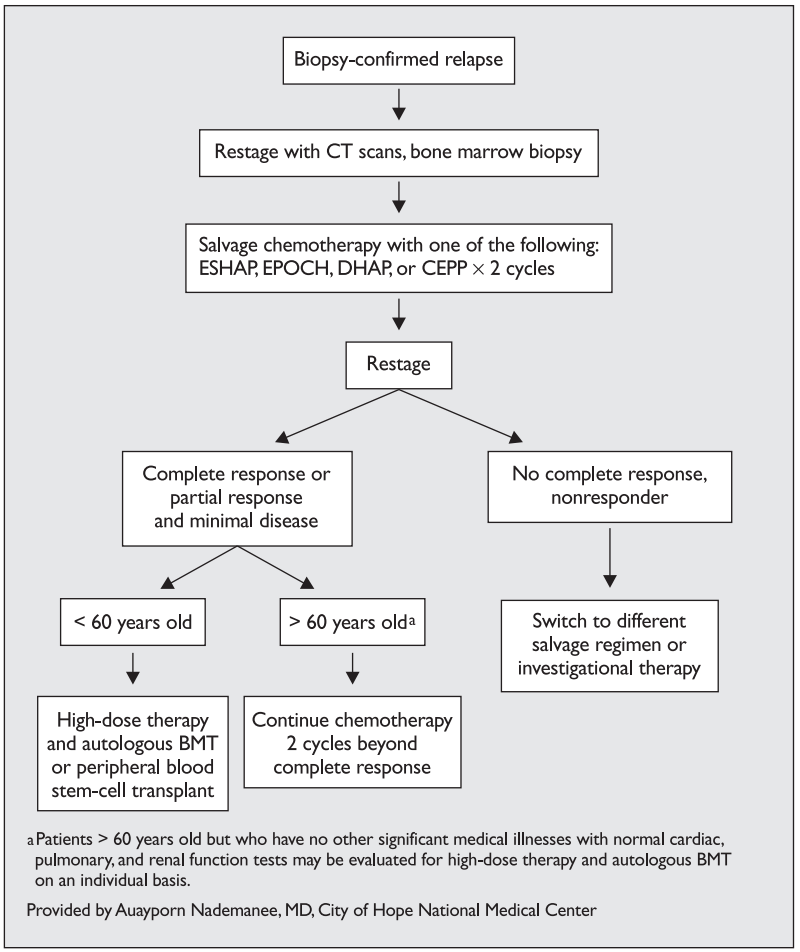

FIGURE 3: Treatment plan for patients with relapsed intermediate- or high-grade lymphoma. For chemotherapy regimens, see Table 17.

TABLE 17: Commonly used salvage regimens for NHL

Regimen	Dose	Route and frequency
EPOCH		
Etoposide	50 mg/m^2/d	Continuous 96-h IV infusion on days 1-5
Oncovin	0.4 mg/m^2/d	Continuous 96-h IV infusion on days 1-5
Doxorubicin HCl	10 mg/m^2/d	Continuous 96-h IV infusion on days 1-5
Cyclophosphamide	750 mg/m^2	IV on day 6
Prednisone	60 mg	PO on days 1-6
New cycle begins on day 21		
DHAP		
Platinol	100 mg/m^2	Continuous 24-h IV infusion on day 1
Ara-C	2 g/m^2	3-h IV infusion q12h for 2 doses on day 2
Dexamethasone	40 mg	IV on days 1-4
CEPP		
Cyclophosphamide[a]	600 mg/m^2	IV on days 1, 8
Etoposide[b]	70 mg/m^2	IV on days 1-3
Procarbazine	60 mg/m^2	IV on days 1-10
Prednisone	60 mg	PO on days 1-10
ESHAP		
Etoposide	40 mg/m^2	1-h IV infusion on days 1-4
Solu-Medrol	250-500 mg	15-min IV infusion on days 1-5
Ara-C	2 g/m^2	2-h IV infusion on day 5
Platinol	25 mg/m^2 (total dose, 100 mg/m^2)	Continuous 96-h IV infusion on days 1-4
MINE		
Mesna	1,333 mg/m^2	IV on days 1-3
Mesna	500 mg	PO 4 hr post ifosfamide
Ifosfamide	1,333 mg/m^2	IV (over 1 hr) on days 1-3
Mitoxantrone	8 mg/m^2	IV (over 15 min) on day 1
Etoposide	65 mg/m^2	IV (over 1 hr) on days 1-3
ICE		
Ifosfamide	5,000 mg/m^2	CIV × 24 hr on day 2
Mesna	5,000 mg/m^2	CIV × 24 hr on day 2
Carboplatin	AUC 5	IV on day 2
Etoposide	100 mg/m^2	IV on days 1-3

[a] Escalate 50 mg/m^2 as allowed [b] Escalate 15 mg/m^2 as allowed AUC = area under the curve

sions when treated aggressively. CNS prophylaxis with intrathecal chemotherapy is necessary to prevent meningeal dissemination. (For a more detailed discussion of HIV-related NHL, see chapter 29.)

Post-transplantation NHL

Post-transplantation lymphoproliferative disorders (PTLDs) comprise a histologic spectrum, ranging from hyperplastic appearing lesions to frank NHL or

multiple myeloma histology. The incidence varies from 1% in renal transplant recipients to 8% in lung transplant recipients, who require more potent immunosuppressive therapy. The use of anti-T-cell therapies or T-cell depletion in stem-cell transplantation recipients will increase the risk of PTLD. More than 90% of tumors are associated with Epstein-Barr virus (EBV). Reduction of immunosuppression can lead to disease regression. In anatomically limited PTLD, resection or targeted radiation treatment can be effective. Traditional chemotherapy has been associated with significant toxicity but can result in long-term disease-free remissions or cure. Biologic agents including interferon and more recently rituximab have shown significant promise. In vitro expanded EBV-specific cytotoxic T cells have been used for treatment and prophylaxis for PTLD following allogeneic stem-cell transplantation.

Primary CNS lymphoma

Primary CNS lymphoma is a rare form of NHL, arising within and confined to the CNS. Histologically, primary CNS lymphomas are indistinguishable from systemic NHL. More than 40% of patients have evidence of leptomeningeal dissemination, and 15% have ocular disease at presentation. A stereotactic needle biopsy is the procedure of choice for histopathologic diagnosis. Resection does not appear to improve survival. Modern management includes high-dose methotrexate alone or combined with agents that penetrate the CNS (high-dose Ara-C, vincristine, and procarbazine). Whole-brain radiotherapy has been considered a standard component of treatment; however, long-term neurotoxicity remains a concern, and, therefore, alternative approaches are being explored.

TARGETED THERAPY OF NHL

The biotechnology revolution has led to the development of targeted therapies for NHL, including unconjugated antibodies, radioimmunotherapy, and immunotoxins. Table 16 lists some of the commercially available and investigational monoclonal antibodies with clinical activity against lymphoid malignancies.

Rituximab

Rituximab is a genetically engineered, unconjugated, chimeric murine/human monoclonal antibody (MoAb) that targets the CD20 antigen found on the surface of most (> 90%) B-cell lymphomas. The FDA has approved this product for use as a single agent in the treatment of relapsed low-grade follicular NHL, and it is also under investigation for use in combination regimens for follicular, mantle cell, and diffuse aggressive NHL. When administered weekly for 4-8 weeks, rituximab produces a 48%-57% overall response rate in patients with relapsed low-grade lymphoma.

The new NHL standardized response criteria for the determination of complete response were used to reanalyze the results of the rituximab pivotal clinical trial. The new criteria rely on unidimensional measurements (short axis of a node). Both the complete response and overall response rates were signifi-

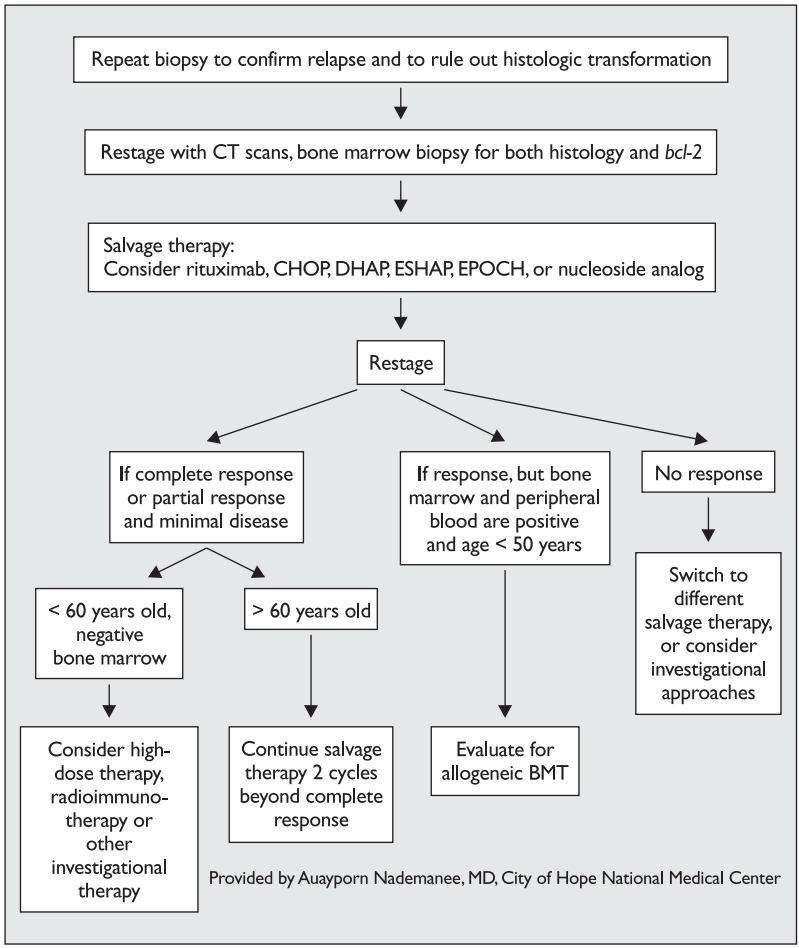

FIGURE 4: Treatment plan for patients with relapsed low-grade lymphoma

cantly higher (45% and 62%, respectively) when the new and less stringent criteria are applied. An update of the rituximab pivotal trial indicates that the median response duration is 11.6 months.

Retreatment with rituximab is efficacious in about 40% of initially responding patients. In a multicenter study involving 60 patients with indolent lymphoma who had previously responded to rituximab, 7 patients achieved a complete response when retreated. Median duration of response had not been achieved at a follow-up of 7.7+ months.

A 48% response rate to rituximab was observed in low-grade lymphoma patients with bulky tumor masses measuring ≥ 10 cm. The median duration of response in these patients was 5.9 months.

A study of rituximab therapy in seven patients with diffuse aggressive B-cell lymphoma who relapsed after autologous transplantation was recently reported. Six patients responded (one complete and five partial responses), and all five who were symptomatic had complete or partial resolution of symptoms.

Interestingly, the highest response rate in the pivotal trial of rituximab was seen in the subgroup who had undergone prior autologous transplantation. These data suggest a possible role for rituximab as consolidation or maintenance therapy given after conventional or dose-intensive treatment. In addition, based on the costs of chemotherapy and the management of adverse events, rituximab compares favorably with combination chemotherapy and single-agent fludarabine.

Radioimmunotherapy

Phase II and III trials suggest that radioimmunoconjugated MoAbs result in high overall and complete response rates compared with unconjugated antibodies.

Ibritumomab tiuxetan (Zevalin) is a yttrium 90 [^{90}Y]–conjugated anti-CD20 murine IgG1 κ antibody. Y^{90} is a pure, high-energy β-emitter with a path length of 5-10 mm, which may be advantageous for the treatment of bulky or poorly vascularized tumors. Ibritumomab tiuxetan selectively targets CD20-positive B-cell NHL with a favorable therapeutic index. Ibritumomab tiuxetan was approved by the FDA in February 2002.

The dose-limiting feature of this approach is hematologic toxicity. The degree of bone marrow involvement, by lymphoma and baseline platelet counts, appears to be a better predictor of hematologic toxicity than radiation dose, which was escalated from 0.2-0.4 miC/kg in a phase I/II clinical trial of this agent. These results may allow clinical parameters to replace dosimetry for the safe administration of ibritumomab tiuxetan. In this phase I/II study, the overall response rates were 82% among patients with recurrent, low-grade lymphoma and 43% in patients with intermediate grade histology. In rituximab-refractory patients, overall response rate was 74%, with a median time to disease progression for responders of 8.7 months (Witzig T, Gordon L, Multani P, et al: J Clin Oncol 20:2453-2463, 2002). The use of ibritumomab tiuxetan does not preclude subsequent treatment with chemotherapy (Ansell S, Ristow K, Habermann T, et al: J Clin Oncol 20:3885-3890, 2002).

Theoretical concerns have been raised that an enlarged spleen will act as an "antibody sink," thus limiting antibody-specific targeting. Yet, four of eight patients with splenomegaly achieved a response to ibritumomab tiuxetan, six of whom had complete resolution of splenomegaly. In contrast, 74% of patients without splenomegaly responded.

In a randomized study, patients with refractory low-grade (follicular or small lymphocytic lymphoma) received either rituximab or ibritumomab tiuxetan. The response rate for ibritumomab tiuxetan was 80% and complete response was seen in 30% of patients, whereas for rituximab, it was 56% and 16% (Witzig TE, Gordon CI, Cabanillas F, et al: J Clin Oncol 20:2453-2463, 2002). In a

separate investigation, lower doses of ibritumomab tiuxetan was evaluated in patients with mild thrombocytopenia. The response rate was 83%, with 37% of patients achieving complete remission (Wiseman GA, Gordon LI, Multani PS, et al: Blood 99:4336-4342, 2002).

Tositumomab (Bexxar) In a multi-institution study, 60 patients, 58% with low-grade lymphoma and 40% with transformed lymphoma, were treated with tositumomab, an iodine-131 (^{131}I)–conjugated anti-B1 antibody. Patients had received two or more prior chemotherapy regimens and not responded to or progressed during the last regimen. The response rate to the radiolabeled antibody treatment was 67%, compared with a 28% response to the prior treatment ($P = .0001$). The median response durations were 6.5 months after the antibody vs 3.5 months with prior treatment.

The main toxicity of tositumomab was hematologic, with blood count nadirs occurring at week 5-6 and recovery by weeks 8-9. Nonhematologic toxicity consisted of mild to moderate fatigue, fever, and nausea. Three patients developed antimurine antibodies.

These results indicate that tositumomab is an effective agent for the treatment of relapsed low-grade and transformed lymphoma. Trials of myeloablative doses of tositumomab followed by autologous stem-cell support are currently being conducted.

Another trial of the ^{131}I anti-B1 antibody produced a 100% response rate in 21 patients with previously untreated stage III-IV follicular NHL, suggesting a role for this agent earlier in the course of the disease.

Immunotoxins

CD25 (IL-2) is present on T-cell lymphomas and a subset of patients with indolent B-cell lymphomas and Hodgkin's disease. Several immunotoxins targeting this marker have been developed.

Denileukin diftitox (Ontak) has been approved by the FDA for the treatment of CD25-positive mycosis fungoides (cutaneous T-cell lymphoma). This agent is a novel recombinant fusion protein composed of the receptor-binding domain of IL-2 plus the diptheria toxin.

Denileukin diftitox produced a complete or partial response in 30% of patients with relapsed cutaneous T-cell lymphoma. Common adverse events included fever, chills, nausea, a flu-like syndrome, and the capillary leak syndrome. The activity of this agent in CD25-positive low-grade lymphoma is under investigation.

Anti-Tac (Fv)-PE38 Responses to a recombinant immunotoxin, anti-Tac (Fv)-PE38 (LMB-2), composed of a single-chain Fv form of the anti-CD25 antibody (anti-Tac) fused to a truncated *Pseudomonas* exotoxin, have been reported in patients with cutaneous T-cell lymphoma, hairy cell leukemia, and chronic lymphocytic leukemia.

TREATMENT OF RELAPSED DISEASE

The City of Hope approach to the management of lymphoma is summarized in Figures 3 and 4. Commonly used salvage regimens are listed in Table 17.

Autologous BMT

High-dose therapy with autologous hematopoietic stem-cell transplantation has been widely used for the treatment of NHL. Recently, there has been a trend toward the use of primed peripheral blood stem cells instead of bone marrow for hematopoietic reconstitution. Results of pilot phase II studies indicate that high disease-free survival rates (20%-50%) can be obtained with such therapy.

The M. D. Anderson Cancer Center reported results on 49 patients with relapsed NHL—20 with indolent NHL, 15 with diffuse large cell NHL, and 14 with mantle cell lymphoma—who received nonmyeloablative stem-cell transplant. Fludarabine and cyclophosphamide were used in indolent and mantle cell histologies, and fludarabine, cisplatin, and cytarabine were used for the diffuse aggressive lymphomas. Median age was 55 years (range, 21-68). Median number of prior chemotherapy regimens was 4 (range, 1-8). A prior autologous transplant had failed in 8 patients. Day 100 mortality was only 4%. With a median follow-up of 19 months, disease-free survival and overall survival for each of the histologic subtypes, respectively, are 85% and 85% for indolent NHL, 61% and 71% for diffuse large cell NHL, and 92% and 100% for mantle cell lymphoma. These data demonstrate the feasibility of nonmyeloablative transplantation in older patients and/or patients in whom an autologous transplant failed *(Khouri I, Saliba R, Lee M-S, et al: Blood 98[suppl 1]:416a, 2001).*

In addition, updated results of the Parma trial have, for the first time, demonstrated improved disease-free and overall survival rates with the use of high-dose therapy compared with a conventional salvage regimen. The Parma trial enrolled 215 younger (≤ 60 years old) patients with intermediate- or high-grade NHL that had relapsed (except in the bone marrow or CNS) after initial response to a doxorubicin-containing regimen. The 109 patients who responded to 2 cycles of DHAP (dexamethasone, Ara-C, and Platinol) were randomized to receive either 4 more cycles of DHAP or high-dose therapy (BEAC [BCNU, etoposide, Ara-C, and cyclophosphamide]) plus unpurged bone marrow. Patients in both arms who had tumor masses > 5 cm at relapse received involved-field radiation. At a median follow-up of 63 months, disease-free and overall survival rates were significantly higher (46% and 53%, respectively) in the high-dose therapy group than in the DHAP group (12% and 32%, respectively).

Treatment complications

Tumor lysis syndrome is a common complication after treatment of high-grade, bulky NHLs (due to their exquisite sensitivity to therapy and high proliferative capacity). The syndrome is characterized by renal failure, hyperkalemia, hyperphosphatemia, and hypocalcemia.

Measures to prevent this complication include: aggressive hydration, allopurinol, alkalinization of the urine, and frequent monitoring of electrolytes, uric acid, and creatinine. Dialysis is sometimes required. Recombinant urate oxydase

(Rasburicase) is now available for the prevention and treatment of hyperuricemia. (For a more comprehensive discussion of the tumor lysis syndrome, see chapter 47.)

Follow-up of long-term survivors

Relapse The most important risk to patients with NHL is relapse. Among patients with diffuse aggressive lymphomas, most recurrences are seen within the first 2 years after the completion of therapy, although later relapses may occur. Early detection of recurrent disease is important because these patients may be candidates for potentially curative high-dose therapy and stem-cell transplantation. Patients with advanced low-grade NHL are at a constant risk of relapse, and late recurrence of disease may be seen, sometimes after the patient has been in remission for more than a decade.

A recent analysis of registry data from the National Marrow Donor Program reported the results of matched-unrelated donor marrow transplantation in 158 NHL patients. The majority had relapsed or persistent disease following conventional therapy and presumably were not candidates for autologous transplantation. At 2 years, the progression-free survival and overall survival rates for the entire group of patients were 30%. This approach is associated with a 45% actuarial mortality within 100 days after transplant. Improvement in molecular typing techniques, supportive care, and treatment of graft-vs-host disease and better patient selection may ultimately lead to an improved outcome in this setting *(Bierman P, Molina A, Nelson G, et al: Proc Am Soc Clin Oncol [abstract] 18:3a, 1999).*

Physical examination at 2- to 3-month intervals and follow-up CT scans at 4- to 12-month intervals are recommended.

Secondary malignancies Long-term survivors are at increased risk of second cancers. In a survey of 6,171 NHL patients who survived 2 or more years, nearly 1,000 patients lived 15 or more years after diagnosis. Second cancers were reported in 541 subjects, with significant excesses seen for all solid tumors, acute myelogenous leukemia, melanoma, Hodgkin's disease, and cancers of the lung, brain, kidney, and bladder. The actuarial risk of developing a second malignancy at 3-20 years after diagnosis of NHL was 21%, compared with a population-expected cumulative risk of 15%.

Treatment complications With the decline in the role of radiation as part of the initial therapy for NHL, the risk of certain radiation-induced complications has been reduced or eliminated in more recently diagnosed patients. Nevertheless, total-body irradiation is often used as a component of myeloablative conditioning regimens. Also, transplant recipients are at increased risk of secondary myelodysplasia and acute myeloid leukemia, regardless of whether or not they received a radiation-containing conditioning regimen.

Long-term survivors need continued follow-up for possible treatment-related complications. Some of these toxicities may still be unknown. Careful documentation of late complications will be important in the design of future treatment strategies aimed at preserving or improving response rates and duration of remission while at the same time reducing toxicity.

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CHAPTER 33

Multiple myeloma and other plasma cell dyscrasias

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MULTIPLE MYELOMA

Multiple myeloma is a disseminated malignancy of monoclonal plasma cells that accounts for 8% of all hematologic cancers. In the year 2003, an estimated 14,600 new cases will be diagnosed in the United States, and 10,900 Americans will die of this disease. Incidence rates for myeloma (5.3 in men and 3.5 in women) and mortality rates (3.7 in men and 2.5 in women) per 100,000 population have remained stable for the past decade.

Epidemiology

Gender Males are affected more frequently than females (1.4:1.0 ratio).

Age The median age at presentation is 65 years, according to most tumor registries, although the median age reported in studies is approximately 60 years.

Race The annual incidence per 100,000 population is 6.4 among white men and 4.1 among white women. Among black men and women, the frequency doubles to 12.7 and 10.0, respectively, per 100,000 population. This racial difference is not explained by socioeconomic factors and is presumably due to unknown genetic factors.

Geography There is no clear geographic distribution of multiple myeloma. In Europe, the highest rates are noted in the Nordic countries, the United Kingdom, Switzerland, and Israel. France, Germany, Austria, and Slovenia have a lower incidence, and developing countries have the lowest incidence. This higher relative incidence in more developed countries probably results from the combination of a longer life expectancy and more frequent medical surveillance.

Survival The 5-year survival rate for all patients treated with conventional therapy is approximately 25%-30%. The 5-year survival rate is lower among patients ≥ age 65 (20%-25%) than in those < age 65 (30%-35%).

Etiology and risk factors

No predisposing factors for the development of multiple myeloma have been confirmed.

Environment Some causative factors that have been suggested include radiation exposure (radiologists and radium dial workers), occupational exposure (agricultural, chemical, metallurgical, rubber plant, pulp and paper workers and leather tanners), and chemical exposure to benzene, formaldehyde, epichlorohydrin, hair dyes, paint sprays, and asbestos. None of these associations has proven to be statistically significant, and all have been contradicted by negative correlations. The initial report that survivors of the atomic bombings in Japan had an increased risk of developing myeloma has been refuted by longer follow-up.

Viruses A preliminary report in a limited number of patients noted the presence of herpesvirus 8 in the dendritic cells in patients with multiple myeloma. However, further evaluation by a number of investigators has failed to confirm this result. Myeloma patients also do not have immune response against this virus.

Cytogenetics Metaphase cytogenetic abnormalities, especially 13q deletions or monosomy 13, are observed in 15%-20% of patients and have been shown to have prognostic significance in myeloma. Interphase fluorescent in situ hybridization (FISH) with specific probes to identify monoallelic deletions of retinoblastoma gene (*Rb-1*) have doubled the frequency of this powerful prognostic factor (30%-50%). 13q deletions thus identified are predictors of short survival. Other regions studied by FISH and found to indicate adverse prognosis include 17p13 (*p53*) deletions and 11q abnormalities.

Interactions between myeloma (MM) cells and their microenvironment, the extracellular matrix and the bone marrow stromal cells (BMSCs), allow MM cells to survive, grow, migrate, and resist apoptosis induced by traditional chemotherapies. These effects are partially mediated through various cytokines, including IL-6, VEFG, IGF-1, and IL-21. The molecular signals mediating the proliferative effects include the *ras*/*raf* MAPK cascade, whereas the P13-K/Akt pathway provides cell survival and drug resistance signals. Improved understanding of these interactions and the molecular mechanisms mediating them has now allowed us to evaluate novel therapies that directly target MM cells as well as act on the bone marrow microenvironment.

Genetic factors Although multiple myeloma is not an inherited disease, there have been numerous case reports of multiple incidence in the same family. However, a case-control study revealed no significant increase in the incidence among relatives of patients who had multiple myeloma, other hematologic malignancies, or other cancers.

Monoclonal gammopathy of unknown significance (MGUS) Patients with MGUS develop myeloma, macroglobulinemic lymphoma, or amyloidosis at a rate of 1% per year.

Signs and symptoms

The clinical features of multiple myeloma are quite variable. Findings that suggest the diagnosis include lytic bone lesions, anemia, azotemia, hypercalcemia, and recurrent infections. Approximately 30% of patients are free of symptoms and are diagnosed by chance.

Bone disease Bone pain, especially from compression fractures of the vertebrae or ribs, is the most common symptom. At diagnosis, 70% of patients have lytic lesions, which are due to accelerated osteoclast formation. These changes are induced by osteoclast-activating factors produced by the bone marrow microenvironment and, to a lesser extent, myeloma cells. These factors include interleukin (IL)-1B, tumor necrosis factor-α (TNF-α), and IL-6 as well as newly identified factors such as osteoprotogerin, TNF-related activation-induced cytokine (TRANCE), and receptor-activator of nuclear factor kappaB (RANK) ligand.

Anemia A normocytic, normochromic anemia is present in 60% of patients at diagnosis. This is due primarily to the decreased production of RBCs by marrow infiltrated with plasma cells. Patients with or without renal failure may also have decreased levels of erythropoietin, which may worsen the degree of anemia.

Hypercalcemia Among newly diagnosed patients, 20% have hypercalcemia (corrected serum calcium level, $>$ 11.5 mg/dL) secondary to progressive bone destruction, which may be exacerbated by prolonged immobility. Hypercalcemia should be suspected in patients with myeloma who have nausea, fatigue, confusion, polyuria, or constipation. It may suggest high tumor burden. It should be considered an oncologic emergency and promptly treated.

Renal failure Approximately 20% of patients present with renal insufficiency and another 20% develop this complication in later phases of the disease. Casts of Bence Jones protein in the distal tubule are the most common cause of renal failure, but hypercalcemia, dehydration, and hyperuricemia are contributing factors. Uncommonly, amyloidosis, light-chain deposition disease, nonsteroidal anti-inflammatory agents taken for pain control, and calcium stones may contribute to renal failure. More recently, bisphonate therapy has been associated with renal failure.

Infections Many patients with myeloma develop bacterial infections that may be serious. In the past, gram-positive organisms (eg, *Streptococcus pneumoniae, Staphylococcus aureus*) and *Haemophilus influenzae* were the most common pathogens. More recently, however, gram-negative organisms have become frequent. The increased susceptibility of myeloma patients to bacterial infections has been attributed to impairments of host-defense mechanisms, such as hypogammaglobulinemia, granulocytopenia, and low cell-mediated immunity.

TABLE 1: Common laboratory features of plasma cell dyscrasias

Multiple myeloma
Marrow plasmacytosis > 15%
Monoclonal immunoglobulin peak (usually > 3.0 g/dL)
Decreased levels of uninvolved immunoglobulins
Presence of Bence Jones protein
Lytic bone lesions or diffuse osteopenia
Smoldering myeloma
Same as multiple myeloma but without symptoms and;
Hemoglobin > 10.5 g/dL
Monoclonal immunoglobulin peak (< 4.5 g/dL)
Normal serum calcium and creatinine levels
No lytic bone lesions
Solitary plasmacytoma of bone (SPB)
Solitary bone lesion due to plasma cell tumor
Normal skeletal survey and MRI of skull, spine, and pelvis
Normal bone marrow plasmacytosis
No anemia, hypercalcemia, or renal disease
Preserved levels of uninvolved immunoglobulins
Monoclonal gammopathy of unknown significance (MGUS)
Monoclonal immunoglobulin level < 3.0 g/dL
Bone marrow plasma cells < 10%
No bone lesions
No symptoms due to plasma cell dyscrasia
Usually preserved levels of uninvolved immunoglobulins
Amyloidosis without myeloma
Same as MGUS plus evidence of amyloidosis on biopsy

Screening and diagnosis

No screening measures for multiple myeloma have proved to provide any benefit.

The diagnosis usually requires the presence of bone marrow plasmacytosis and a monoclonal protein in the urine and/or serum (Table 1). One immunoglobulin class is produced in excess, whereas the other immunoglobulin classes are usually depressed.

Initial work-up The initial work-up for patients suspected of having a plasma cell dyscrasia should include:

- CBC with differential count and platelet count
- routine serum chemistry panel (eg, calcium, BUN, creatinine)
- bone marrow aspirate to assess plasmacytosis

- serum protein electropheresis and immunofixation to define protein type
- 24-hour urine protein, electropheresis, and immunofixation
- quantitative immunoglobulin levels
- skeletal survey (bone scans contribute little since isotope uptake is often low in purely lytic bone disease)
- cytogenetics

MRI is an excellent tool for evaluation of spinal cord compression/impingement. In addition, MRI identifies generalized signal abnormalities and focal lesions that can be monitored after therapy. MRI is especially useful in staging nonsecretory disease presenting as macrofocal lesions.

In addition, prognostic factors, such as β_2-microglobulin (β2M), C-reactive protein, lactate dehydrogenase levels (LDH), plasma cell-labeling index, and ploidy, may provide useful data.

Laboratory and pathologic features

Peripheral blood The peripheral blood smear may reveal a normocytic, normochromic anemia with rouleaux formation.

Bone marrow Bone marrow examination usually reveals an increased number of plasma cells ($> 15\%$). These cells are strongly positive for CD38, CD138, and cytoplasmic immunoglobulin (cIg) and are negative for CD5, CD20, and surface immunoglobulin (sIg) expression. Whereas normal plasma cells express CD19, malignant plasma cells lose its expression, and this may be related to loss of *Pax-5* gene expression. CD10 expression is generally negative but has sometimes been noted in advanced disease. Monoclonality may be demonstrated by immunoperoxidase staining with κ and λ antibodies.

The pattern of bone marrow involvement in plasma cell myeloma may be macrofocal. As a result, plasma cell count may be normal when an aspirate misses the focal aggregates of plasma cells that are better visualized radiographically or on direct needle biopsy.

Monoclonal proteins The types of monoclonal protein produced are IgG (60%), IgA (20%), IgD (2%), IgE ($< 0.1\%$), or light-chain κ or λ only (18%). Biclonal elevations of myeloma proteins occur in $< 1\%$ of patients, and $< 5\%$ of patients are considered to have nonsecretory disease because their plasma cells do not secrete detectable levels of monoclonal immunoglobulin.

Staging and prognosis

Various criteria have been used to stage myeloma at different institutions, primarily due to the lack of standard definitions and consistency among investigators. However, the Durie-Salmon staging system is employed most frequently (Table 2). The variability in interpretation of staging criteria has resulted, in part, from imprecise quantification of the extent of bone lesions

TABLE 2: Durie-Salmon staging system for multiple myeloma

Stage	Criteria	Myeloma cell mass ($\times 10^{12}$ cells/m^2)
I	Hemoglobin > 10 g/dL	< 0.6 (low)
	Serum calcium level ≤12 mg/dL (normal)	
	Normal bone or solitary plasmacytoma on x-ray	
	Low M-component production rate:	
	IgG < 5 g/dL	
	IgA < 3 g/dL	
	Bence Jones protein < 4 g/24 h	
II	Not fitting stage I or III	0.6-1.2 (intermediate)
III	Hemoglobin < 8.5 g/dL	> 1.2 (high)
	Serum calcium level > 12 mg/dL	
	Multiple lytic bone lesions on x-ray	
	High M-component production rate:	
	IgG > 7 g/dL	
	IgA > 5 g/dL	
	Bence Jones protein > 12 g/24 h	

Subclassification	Criterion
A	Normal renal function (serum creatinine level < 2.0 mg/dL)
B	Abnormal renal function (serum creatinine level ≥ 2.0 mg/dL)

and from factors other than myeloma that contribute to hypercalcemia (eg, immobility) or anemia (eg, renal failure).

Prognosis

Cytogenetic abnormalities Chromosomal abnormalities, especially loss of whole chromosome 13 (monosomy) or deletions of parts of chromosome 13 (13q), have been associated with inferior survival after both standard chemotherapy and high-dose therapy. Multivariate analysis has shown these chromosomal changes to be the most important predictors of survival.

β2M level Serum β2M level is an important and convenient prognostic indicator. When cytogenetic changes are not studied, β2M is consistently the most important prognostic indicator on multivariate analysis. As β2M is excreted by the kidneys, high levels are observed in patients with renal failure; in this setting, the interpretation of an elevated value is unclear.

LDH level High LDH levels also have been associated with plasmablastic disease, extraosseous tumor, plasma cell leukemia, plasma cell hypodiploidy, drug resistance, and shortened survival.

Other indicators of shortened survival include elevated C-reactive protein, DNA hypodiploidy, high plasma cell-labeling indices, plasmablastic histology, and expression of the common acute lymphoblastic leukemia antigen (cALLA). Patients with DNA hypodiploidy are also less likely to respond to chemotherapy.

Treatment response criteria

Since the criteria for treatment response among patients with multiple myeloma have varied among institutions, response rates have been difficult to compare. Bence Jones protein is reduced more rapidly in responders than is serum myeloma protein because of the rapid renal catabolism of light chains.

The criteria for partial response are:

- $>$ 50% reduction in serum myeloma protein
- $>$ 90% reduction in Bence Jones protein

Criteria for complete response include:

- disappearance of serum myeloma protein and Bence Jones protein by immunofixation
- no monoclonal plasma cells in bone marrow

Treatment

Exciting advances in the understanding of tumor biology and microenvironment–and their potential interaction–should identify unique targets for rational therapeutic intervention. The rational design of therapy hopefully will improve its outcome, which has not improved with conventional chemotherapy over the past 3 decades. Only 5%-10% of myeloma patients live longer than 10 years, and there is no hint of a cured subgroup.

PREVIOUSLY UNTREATED PATIENTS

Chemotherapy

MP The combination of melphalan (Alkeran) and prednisone (MP) remains the standard regimen. The combination of multiple alkylating agents is not convincingly superior to MP. A meta-analysis of 18 published randomized trials comparing MP with other combination regimens arrived at the same conclusion. Combination chemotherapy is probably not superior to MP even in poor-risk patients (Table 3). Approximately 40% of patients have responded to the MP regimen, with a median remission duration of 18 months and an overall median survival of 3 years.

Melphalan and other alkylating agents should be used sparingly or completely avoided in patients who are candidates for high-dose therapy, as prior therapy affects stem-cell procurement. Extensive use of alkylating agents may also predispose patients to the subsequent development of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

TABLE 3: Proposed standard treatment of multiple myeloma

Disease or patient status	Treatment approach
Initial therapy	
Candidates for high-dose therapy	
VAD	Vincristine (0.5 mg/d IV) + Adriamycin (10 mg/m^2/d IV) both drugs given as continuous infusion on days 1-4 along with dexamethasone (40 mg) on days 1-4, 9-12, and 17-20 every 35 days
Dexamethasone	40 mg on days 1-4, 9-12, and 17-20 every 35 days
Dexamethasone/thalidomide	Dexamethasone as above with thalidomide (200 mg/d)
Noncandidates for high-dose therapy	
MP	Melphalan (8 mg/m^2/d PO) + prednisone (100 mg/d PO) on days 1-4 every 4-5 weeks
Resistant myeloma	
Resistant to MP	Dexamethasone or VAD or Thalidomide alone (200-800 mg)
Resistant to VAD or dexamethasone	Dexamethasone/thalidomide Intensive alkylating agent combinations (with G-CSF support and prophylactic antibiotic) Cyclophosphamide/etoposide DCEP or EDAP
	Newer agents: Bortezomib (Velcade) and Revimid (in clinical trials) and arsenic trioxide (Trisenox)

DCEP = dexamethasone, cyclophosphamide, etoposide, and cisplatin; EDAP = etoposide, dexamethasone, Ara-C, and cisplatin; G-CSF = granulocyte colony-stimulating factor

To standardize dosage for differences in melphalan absorption, evidence of adequate myelosuppression should be confirmed after 2-3 weeks. The dose should be increased by 20% increments every 4-5 weeks until adequate myelosuppression occurs.

VAD (vincristine, Adriamycin [doxorubicin], and dexamethasone)-based regimens spare stem cells and do not impair stem-cell collection; these regimens are preferably employed for induction prior to high-dose therapy (Table 3). Such regimens produced a response rate of 55% in untreated patients, without improvement in overall survival over MP. Responses occurred more rapidly with VAD-based regimens than with MP; these rapid responses provide an advantage in patients with hypercalcemia, renal failure, or severe bone pain. No dosage adjustment is necessary for renal failure.

Pulse dexamethasone alone has also been useful in patients who need vertebral radiotherapy for spinal cord compression or for painful vertebral compressions that require immediate irradiation, as this approach avoids severe myelosuppression (Table 3).

Dexamethasone/thalidomide Thalidomide (Thalomid) has been employed alone and in combination with dexamethasone as initial therapy in small cohorts of patients. When employed alone, response (50% reduction in paraprotein) was observed in 36% of patients; when it was used along with dexamethasone, the response rate was higher (72% and 64% in two studies). The results are slightly superior to those with dexamethasone alone and comparable to VAD. A definite increase in thrombotic episodes has been observed with this combination, prompting prophylactic administration of coumadin.

High-dose therapy following induction

High-dose therapy employed after induction therapy improves the response rate as well as event-free and overall survival. The impressive improvement in event-free survival (median, 28 vs 18 months) and overall survival (57 vs 42 months) reported in a randomized trial (IFM 90) has been confirmed by another large randomized trial (median overall survival, 54.8 vs 42.3 months) (MRC VII). Most of these studies enrolled patients < 65 years old. Older individuals (< 70 yrs) tolerate high-dose therapy with peripheral stem-cell support well, without excess mortality. Moreover, outcome, in terms of event-free and overall survival, is comparable to that in matched cohorts < 65 years old, making older individuals (≥ 65 years old) also candidates for high-dose therapy. More recently, older patients (age > 70) receiving intermediate-dose melphalan (100 mg/m^2) with stem-cell support have been shown to have a better outcome than matched controls receiving conventional therapy.

High-dose alkylating agents, most commonly melphalan at 200 mg/m^2 with peripheral blood stem-cell support, is now considered to be standard consolidation therapy (after initial induction therapy) in all symptomatic myeloma patients without significant comorbidity. Addition of total body irradiation (TBI) does not improve the outcome but increases morbidity and results in occasional mortality.

Tandem transplants Improved outcome reported after tandem transplants in large cohorts of patients in single-institution studies has been confirmed in a mature randomized study. Seven years postinitiation of therapy, the event-free survival (42% vs 21%) and overall survival (20% vs 10%) were superior for patients receiving tandem transplants (IFM 94). Another randomized trial with a shorter follow-up has confirmed the superior event-free survival (median, 34 vs 25 months) for patients receiving tandem transplants.

Radiotherapy

Higher doses of radiotherapy (40-50 Gy) are employed in local control and cure of solitary plasmacytoma of bone and extramedullary plasmacytoma. Lower doses (20-30 Gy) may be employed for palliation of local bone pain from tumor infiltration, pathologic fractures, and spinal cord compression. It should be emphasized that excellent pain relief may be obtained by prompt institution of high-dose corticosteroid therapy, especially in newly diagnosed patients.

Radiotherapy should be employed sparingly, as irradiation of multiple sites may impair stem-cell mobilization in patients who are candidates for high-

dose therapy. Employment of high doses of radiation to the spine may preclude the subsequent use of TBI as a conditioning regimen for high-dose therapy.

REMISSION MAINTENANCE

Alkylating agents

Maintenance therapy with alkylating agents has not prolonged survival times, compared with no maintenance therapy followed by the resumption of MP upon disease relapse. Continued alkylating agent treatment also exposes approximately 2% of patients to the risk of myelodysplasia or acute leukemia.

α-Interferon has been investigated as maintenance after conventional chemotherapy. A large overview of 24 randomized trials revealed a marginal improvement in median progression-free survival and overall survival durations of 6 months and 4 months, respectively. This minimal benefit is attained at significant cost and toxicity. High-dose therapy with improved response may be an optimal setting for maintenance. A small randomized study initially showed an improved progression-free survival (median 46 weeks vs 27 months); with a longer follow-up, progression-free survival and overall survival were not different. No conclusive evidence for a role of interferon as a maintenance therapy is yet available. A large, randomized, ongoing intergroup trial is addressing the issue of interferon maintenance therapy (postconventional therapy and auto-transplantation).

Steroids for maintenance Southwest Oncology group conducted a randomized study evaluating low-dose (10 mg) vs high-dose (50 mg) oral prednisone given every other day as maintenance after remission induction with a VAD-based regimen. Median progression-free survival (14 vs 5 months) and overall survival (37 vs 26 months) were improved with the higher dose of prednisone.

REFRACTORY OR RELAPSING DISEASE

Approximately 50% of patients with newly diagnosed multiple myeloma are unresponsive to chemotherapy. Moreover, in virtually all patients who respond initially (with the exception of those few who die of unrelated diseases), the myeloma will relapse. Of patients who relapse after an unmaintained remission, approximately 60% achieve a second, shorter remission or maintain a stable tumor load with resumption of the original therapy.

VAD

VAD is the treatment of choice for disease relapsing after MP therapy. VAD produced responses in 40% of patients with relapsing disease, compared with 25% of patients with primary unresponsive disease.

Pulse dexamethasone alone induced results similar to VAD in patients with primary resistant disease (response rate, 25% vs 25%-30%) but was inferior to VAD in relapsing patients (response rate, 25% vs 40%).

VAD-RESISTANT DISEASE

Combination chemotherapy

High doses of alkylating agents, alone or in combination, have been effective in approximately one-third of patients with VAD-refractory disease. IV melphalan (70-100 mg/m^2) and the combination of high-dose cyclophosphamide (Cytoxan, Neosar) and etoposide are two examples of such regimens (Table 3).

Thalidomide has established a role in therapy for refractory/relapsed multiple myeloma, with 30% of patients achieving at least 50% reduction in paraprotein levels. Remissions obtained are durable: In a large cohort of multiple myeloma patients receiving thalidomide, 2-year event-free survival rates of ~25% have been observed. Initially, thalidomide was employed in a dose-escalating schedule, starting at 200 mg and achieving a maximal dose of 800 mg. Recently, smaller doses have been employed in an effort to improve the tolerability and extend the use of this agent. Observations of synergy in clinical and experimental settings have encouraged use of thalidomide in combination with other agents, such as glucocorticoids and chemotherapy. Higher response rates have been reported with these combinations (Table 3).

Novel agents

IMiD Revimid (also known as CC-5013) is a small molecule, thalidomide analog with immunomodulatory effects. It has greater potency than thalidomide in preclinical studies of antitumor effect in myeloma cell lines. In a recently completed phase I study, the drug was administered orally at doses of 5, 10, 25, and 50 mg daily in 25 patients with relapsed or refractory myeloma. Responses were seen in over half the patients treated, with best paraprotein responses seen mainly between 25 and 50 mg daily. Significant somnolence, constipation, and neuropathy were not reported, but cytopenias were prominent after the first 4 weeks of treatment. Drug-dose modification, schedule changes, and G-CSF (granulocyte colony-stimulating factor, filgrastim, Neupogen) use may overcome this problem and are being studied in ongoing phase II trials.

Proteasome inhibition Bortezomib (Velcade, PS-341) is a first-in-class, potent, selective, and reversible small molecule inhibitor of the proteasome. The proteasome plays a key role in the degradation of ubiquinated proteins, which in turn have important functions in controlling tumor cell growth and survival both in vitro and in vivo. A recently completed, large multi-institution phase II trial of bortezomib (given IV at a dose of 1.3 mg/m^2 on days 1, 4, 8, and 11 every 21 days) demonstrated remarkable activity in a heavily treated, relapsed and refractory patient population, including post-transplantation failures and conditions not responding to thalidomide, with durable responses in about 35% receiving bortezomib alone (with a number of complete responses). Side effects related to the drug were predominantly gastrointestinal in nature, with neuropathy, fatigue, and reversible cytopenias also noted. Toxicities were generally manageable with supportive care and dose reduction. Phase III evaluation of this drug is under way, and studies combining bortezomib with other

TABLE 4: Supportive therapies for multiple myeloma

Problem	Therapy
Chronic anemia (especially with renal impairment)	Erythropoietin
Prolonged neutropenia with infection	G-CSF
Recurrent infections with IgG < 400 mg/dL	Gamma globulin
Osteoporosis	Bisphosphonates

G-CSF = granulocyte colony-stimulating factor

agents such as liposomal doxorubicin (Doxil) and thalidomide have begun.

Arsenic trioxide (Trisenox) has been evaluated in small phase II studies based on in vitro activity in cell lines and animal tumor models. Arsenic also has antiangiogenic activity. Arsenic trioxide, administered as daily IV infusion dosed at 0.15 mg/kg in a phase II study, has shown response in 3 of 14 relapsed refractory patients. Adverse effects included cytopenia requiring G-CSF support. Based on impressive preclinical data suggesting synergism among arsenic trioxide, dexamethasone, and ascorbic acid, a phase II evaluation of this combination is in progress.

Allogeneic transplantation Myeloablative therapy with autologous stem-cell support does not appear to be of clear benefit in patients with disease in resistant relapse. For younger patients with disease in resistant relapse or with poor prognosis (ie, deletion of chromosome 13), allogeneic transplantation may be an important option.

However, high treatment-related mortality (30%-50%) with myeloablative allogeneic transplantation has discouraged the use of allografts in early-phase myeloma. New nonmyeloablative procedures that reduce mortality and exploit a graft-vs-tumor effect are being studied. In one study, 34 patients, including patients with relapsed or refractory disease, received melphalan at 200 mg/m^2 with autografting and then (40-120 days later) received allograft after nonmyeloablative conditioning. Treatment-related mortality at day 100 was 6%, with 53% of the patients achieving complete response. With a median follow-up of 328 days after allografting, the overall survival rate was 81%.

Supportive therapies

Various supportive therapies may be beneficial in patients with multiple myeloma (Table 4).

Chronic anemia Patients with chronic symptomatic anemia and inappropriately low erythropoietin levels (often with renal failure) may benefit from a trial of erythropoietin (epoetin alfa [Epogen, Procrit]), 40,000 units given by SC injection once weekly.

Infection Infectious complications secondary to prolonged neutropenia after intensive chemotherapy may be reduced with G-CSF. Recurrent bacterial infections associated with a marked reduction in normal IgG (sometimes esti-

mated from the depression of IgM or IgA) may be reduced with monthly gamma globulin.

Results of one study suggest that trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis during induction therapy may decrease bacterial infections. This study also noted a higher incidence of nausea and skin rash in patients taking TMP-SMX compared with controls. Further study of antibiotic prophylaxis is necessary to determine its role in patients with myeloma.

Bone pain or imminent fracture Therapy with bisphosphonates, such as pamidronate (Aredia), alendronate (Fosamax), or zoledronic acid (Zometa), may prevent or delay bone pain or recurrent or imminent pathologic fractures in patients with stage III disease and at least one bone lesion. Pamidronate administered over the long term (21 monthly treatments) to stage III multiple myeloma patients with at least one lytic lesion has been shown to reduce skeletal events and decrease the need for irradiation. Moreover, patients without lytic lesions also show a decrease in bone mineral density, and this decrease persists despite therapy. These patients may also benefit from therapy with pamidronate. Several clinical and preclinical studies suggest that pamidronate may have an antimyeloma effect.

Zoledronic acid, a more potent bisphosphonate, has comparable efficacy and safety vs pamidronate in treatment of skeletal lesions. The ease of administration of a 4-mg dose, which reduces the infusion time to 15 minutes compared with 2 hours for pamidronate, has been recently approved by the FDA for prevention of bone-related complications in myeloma.

Percutaneous verebroplasty provides pain relief that is not only rapid, but sustained, and it also strengthens the vertebral bodies. This procedure consists of injection of polymethyl methacrylate, the principal component of bone cement, in the vertebral body. It is performed with the patient under general or local anesthesia. Transient worsening of pain and fever may occur and is responsive to nonsteroidal anti-inflammatory agents.

Absolute contraindications for percutaneous verebroplasty include coagulation disorders and lack of availability of emergency decompressive surgery. Decompressive surgery is essential, as the most significant complication of the procedure is epidural or foraminal leakages that cause spinal cord and root compressions.

A relative contraindication is vertebral compressions, which result in loss of more than 30% of original vertebral height. This makes the procedure technically complicated; however, experienced invasive radiologists have performed this procedure more readily in the past few years.

Smoldering myeloma

In 20% of patients with multiple myeloma, the disease is asymptomatic and is diagnosed by the chance finding of an elevated serum protein concentration during a screening examination.

Laboratory features Features of low tumor mass are usually present, without renal disease, hypercalcemia, or lytic bone lesions (Table 1).

Treatment Chemotherapy should be withheld until there is a risk of a complication, except in those few patients with features of a more aggressive nature of the disease, who should receive chemotherapy promptly.

Prognostic factors Recent studies have helped define prognostic criteria for groups at high risk of early disease progression (eg, cytogenetic changes [especially chromosome 13], labeling index of plasma cells [> 0.4%], β2M levels [4 mg/L], and diffuse disease activity or multiple focal lesions on MRI evaluation). Such criteria, along with the presence of lytic lesions, serum myeloma protein > 5 g/dL, and Bence Jones protein > 500 mg/24 h, identify patients at high risk of disease progression, in whom the early commencement of chemotherapy may be beneficial.

OTHER PLASMA CELL DYSCRASIAS

Other plasma cell dyscrasias include MGUS, solitary plasmacytoma of bone (SPB), solitary extramedullary plasmacytoma, Waldenström's macroglobulinemia, amyloidosis, the POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, and heavy-chain diseases.

Monoclonal gammopathy of unknown significance

MGUS occurs in 1% of normal individuals > 40 years old and rises progressively in frequency with age.

Laboratory features Common laboratory features of MGUS are listed in Table 1.

Treatment Approximately 25% of patients with this disorder develop multiple myeloma, macroglobulinemia, or non-Hodgkin's lymphoma over 20 years. The initial concentration of serum monoclonal protein is a significant predictor of disease progression at 20 years. The long period of stability supports the value of annual monitoring with serum electrophoresis and blood counts and suggests that chemotherapy may be withheld until there is evidence of a serious disorder.

Solitary plasmacytoma of bone

Approximately 3% of patients with myeloma have SPB.

Laboratory features All patients have either no myeloma protein or very low levels in serum or urine (Table 1). MRI may reveal abnormalities not detected by bone survey and may upstage patients to multiple myeloma. Persistence of monoclonal protein for more than 1 year after irradiation predicts early progression to multiple myeloma.

Treatment for SPB consists of radiation therapy (at least 45 Gy). Multiple myeloma becomes evident in most patients over time, so that only 20% of patients remain free of disease for more than 10 years. The median time for disease progression is 2 years.

Solitary extramedullary plasmacytoma

In contrast to SPB, solitary extramedullary plasmacytomas is often truly localized and can be cured in most patients with localized radiation therapy (45-50 Gy).

Waldenström's macroglobulinemia

This uncommon disease is characterized by lymphoplasmacytic bone marrow and tissue infiltrate in addition to elevated IgM production. The mutation pattern analysis suggests that final transformation occurs in the postgerminal center IgM memory B cell. Corresponding with variation in cell morphology, there is variation in immunophenotype. Mature plasma cells exhibit CD38 antigen; however, lymphoid cells are typically CD19, CD20, CD22, and fmc7 positive.

Waldenström's macroglobulinemia usually affects people in the fifth to seventh decades of life and can cause symptoms due to tumor infiltration (marrow, lymph nodes, and/or spleen), circulating IgM (hyperviscosity, cryoglobulinemia, and/or cold agglutinin hemolytic anemia), and tissue deposition of IgM (neuropathy, glomerular disease, and/or amyloidosis).

Hyperviscosity syndrome With hyperviscosity syndrome, patients may have visual symptoms, dizziness, cardiopulmonary symptoms, decreased consciousness, and a bleeding diathesis. Neuropathy is usually due to an IgM antibody reacting with a myelin-associated glycoprotein (MAG).

Therapy for hyperviscosity consists of plasmapheresis followed by chemotherapy to control the malignant proliferation. Patients with poor performance status and elderly patients unable to tolerate chemotherapy may be maintained with periodic plasmapheresis.

Treatment Alkylating agents in combination with steroids or purine analogs remain the mainstay of therapy. Alkylating agents alone or in combination with steroids effect a 50% reduction in paraprotein in about half the patients, and the median survival is around 5 years. The purine analogs fludarabine (Fludara) and 2-CdA (cladribine [Leustatin]) elicit a more rapid response than other agents, with a response rate of more than 75% observed in small series of patients. Preliminary results of a large, American multi-institution evaluation of fludarabine reported partial responses in only 33% of patients.

Purine analog therapy may result in significant myelosuppression in later cycles of therapy and prolonged immunosuppression with increased opportunistic infections. Purine analogs are effective salvage options in patients refractory to or relapsing following alkylator therapy. Patients refractory to one purine analog are rarely salvaged by a different purine analog. Patients with resistant re-

lapse are less likely to benefit (response rate, 18%) and should be considered for more intensive intervention, including high-dose therapy.

Other treatment options Rituximab (Rituxan), an anti-CD20 monoclonal antibody, is effective in Waldenström's macroglobulinemia because the CD20 antigen is usually present on the lymphoid cell component of macroglobulinemia. Preliminary results indicate that about 30% of previously treated patients (refractory or relapsing off therapy) may benefit from rituximab.

Striking activity of thalidomide in multiple myeloma has prompted its use in Waldenström's macroglobulinemia. In a series of 20 patients receiving thalidomide, 25% achieved a 50% reduction in paraprotein. Higher doses of thalidomide were not well tolerated in an elderly cohort of patients.

High-dose therapy with autologous bone marrow or blood stem-cell rescue has been effective in achieving 50% reduction in paraprotein in almost all patients in small pilot trials.

Amyloidosis

Amyloidosis occurs in 10% of patients with multiple myeloma. This infiltrative process results from organ deposition of amyloid fibrils, which consist of the NH_2 terminal amino acid residues of the variable portion of the light-chain immunoglobulin molecule. The abnormal protein is produced by clonal plasma cells.

Clinical features include the nephrotic syndrome, cardiomyopathy, hepatomegaly, neuropathy, macroglossia, carpal tunnel syndrome, and periorbital purpura.

Laboratory features Serum and urine immunofixation studies show a monoclonal immunoglobulin in approximately 80% of patients. The light chain is more frequently of λ than κ type. Diagnosis can be made by the presence of apple-green birefringence on polarized light examination of subcutaneous fat aspirates stained with Congo red.

Treatment of AL (monoclonal problem associated) amyloid Survival of patients with amyloidosis is variable. Patients with congestive heart failure have a median survival of only 4 months. Melphalan and prednisone (given orally) extend the median survival to 17 months, compared with 13 months in untreated patients. Complete hematologic response is rare; similarly, reversal of organ damage is uncommon. In a large cohort of patients receiving high-dose melphalan with stem-cell support, a complete hematologic response was observed in 47% of patients with at least 1 year of follow-up. However, the transplant-related mortality is very high with high-dose therapy (14%-37%). Complete hematologic response was associated with improved clinical response (improved organ function) and survival. Complete hematologic response in the absence of cardiac involvement predicted excellent outcome (1-year survival, 91%).

Patients with the overlap syndrome of myeloma and AL amyloid should be treated aggressively for myeloma; response can be seen both in terms of myeloma and resolution of amyloid symptoms.

POEMS syndrome

Clinical features and course The POEMS syndrome is a rare plasma cell dyscrasia that presents with peripheral, usually sensorimotor, neuropathy. An IgA λ monoclonal gammopathy is most common, and bone lesions, noted in nearly all patients, are usually osteosclerotic.

Other features include hyperpigmentation, hypertrichosis, thickened skin, papilledema, lymphadenopathy, peripheral edema, hepatomegaly, splenomegaly, and hypothyroidism. Diabetes mellitus is not part of this syndrome.

Compared with patients with symptomatic myeloma, individuals with the POEMS syndrome are younger (median age, 51 years) and live longer (median, 8 years). The clinical course is commonly characterized by progressive neuropathy.

Treatment Plasmapheresis does not appear to be of benefit, and patients are often treated similarly to those with myeloma. Patients presenting with isolated sclerotic lesions can have substantial resolution of neuropathic symptoms after local therapy for plasmacytoma with surgery and/or radiotherapy.

Heavy-chain diseases

Heavy-chain diseases are plasma cell dyscrasias characterized by the production of heavy-chain immunoglobulin molecules (IgG, IgA, IgM) that lack light chains.

α Heavy-chain disease results from lymphocyte and plasma cell infiltration of the mesenteric nodes and small bowel and has features of malabsorption, such as diarrhea, weight loss, abdominal pain, edema, and nail clubbing. The heavy-chain molecule may be detected in serum, jejunal secretions, and urine.

γ Heavy-chain disease Patients with γ heavy-chain disease may present with fever, weakness, lymphadenopathy, hepatosplenomegaly, and involvement of Waldeyer's ring. Eosinophilia, leukopenia, and thrombocytopenia are common. Treatment with regimens similar to those used for non-Hodgkin's lymphoma may be effective.

μ Heavy-chain disease is seen exclusively in patients with chronic lymphocytic leukemia (CLL). Vacuolated plasma cells are common in the marrow, and many patients have κ light chains in the urine. Therapy is similar to that used for CLL (see chapter 36).

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CHAPTER 34

Acute leukemias

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Hematopoietic malignancies account for 6%-8% of new cancers diagnosed annually. In the year 2003, an estimated 30,600 new cases of leukemia will be diagnosed, and 21,900 deaths will be attributable to leukemias of all types. The total age-adjusted incidence of leukemia, including both acute and chronic forms, is 9.6 per 100,000 population; the incidence of acute lymphoblastic leukemia (ALL) is 1.5 per 100,000 and of acute myelogenous leukemia (AML) is 2.7 per 100,000 population.

Epidemiology

Gender The incidence of both ALL and AML is slightly higher in males than in females.

Age Age-specific incidences of AML are similar to those of other solid tumors of adults, with an exponential rise after age 40 years. With regard to ALL, 60% of cases are seen in children, with a peak incidence in the first 5 years of life and a subsequent drop in incidence until age 60, when a second peak emerges.

Race and ethnicity The incidence of acute leukemia is slightly higher in populations of European descent. Also, a recent report from the University of Southern California indicates that acute promyelocytic leukemia (APL) is more common in Hispanic populations than in other ethnic groups.

Etiology and risk factors

There is wide diversity in the behavior of the various subsets of acute leukemias. Thus, it is unlikely that there is one common etiology for these aberrant cellular proliferations. There are, however, some accepted risk factors for leukemogenesis.

Chemical exposure Increased incidence of AML and myelodysplasia (preleukemia) has been reported in persons with prolonged exposure to benzene and petroleum products. The interval between exposure and onset of leukemia is long (10-30 years). Chromosomal damage is common.

Pesticide exposure also has been linked to some forms of AML. The incidence of AML is beginning to rise in developing countries, as industrialization and pollution increase.

Other environmental exposures Exposure to hair dyes, smoking, and nonionic radiation may also increase the risk of leukemia.

Prior chemotherapy or radiation Use of alkylating agents, such as cyclophosphamide (Cytoxan, Neosar) and melphalan (Alkeran), in the treatment of lymphomas, myeloma, and breast and ovarian cancers has been associated with the development of AML, usually within 3-5 years of exposure and often preceded by a myelodysplastic phase. Cytogenetic abnormalities, particularly monosomy 5, 7, 11, and 17, are common. Concurrent radiation exposure slightly increases the risk of leukemogenesis posed by alkylating agents.

Topoisomerase II inhibitors (etoposide, [VePesid] teniposide [Vumon], doxorubicin and its derivatives, and mitoxantrone [Novantrone]), used to treat ALL, myeloma, testicular cancer, and sarcomas, have also been implicated in leukemogenesis. These agents, in contrast to alkylators, are associated with a short latency period without antecedent myelodysplasia and with cytogenetic abnormalities involving chromosome 11q23 or 21q22 in the malignant clone.

Genetic disorders An increased incidence of AML is seen in patients with Down syndrome, Bloom syndrome, or Fanconi's anemia, as well as in individuals with ataxia-telangiectasia or Wiskott-Aldrich syndrome. In identical twins younger than age of 10, if one child develops leukemia (usually ALL), there is a 20% chance that the other twin will develop leukemia within a year; subsequently, the risk falls off rapidly and joins that of nonidentical siblings, which is three to five times that of the general population.

Signs and symptoms

Effects on hematopoiesis Leukemia manifests symptomatically by its impact on normal hematopoiesis. Thus, easy fatigability, bruising or bleeding from mucosal surfaces, fever, and persistent infection are all reflections of the anemia, thrombocytopenia, and decrease in functional neutrophils associated with marrow replacement by malignant cells. Bone pain is common in children with ALL (occurring in 40%-50%) but is less common in adults with acute leukemias (5%-10%).

WBC count elevation and pancytopenia Whereas a marked elevation in WBC count is the classic hallmark of leukemia, pancytopenia is more common, particularly in patients of all ages with ALL or in elderly patients with AML, who may have had preexisting marrow dysfunction (myelodysplasia). Only 10% of newly diagnosed patients with either AML or ALL present with leukocyte counts $> 100{,}000/\mu L$. These patients, however, constitute a poor prognostic group and are at increased risk of CNS disease, tumor lysis syndrome, and leukostasis due to impedance of blood flow from intravascular clumping of blasts, which are "stickier" than mature myeloid or lymphoid cells.

Leukostasis may manifest as an alteration in mental status; intermittent or persistent cranial nerve palsies, particularly those involving extraocular muscles; priapism; dyspnea; or pleuritic chest pain, due to small leukemic emboli in the pulmonary vasculature.

Physical findings in AML are usually minimal. Pallor, increased ecchymoses or petechiae, retinal hemorrhage, gingival hypertrophy, and cutaneous involvement are more common with monocytic (M4 or M5) variants of AML than with other variants of AML.

Hepatosplenomegaly and lymphadenopathy Mild hepatosplenomegaly and lymphadenopathy are seen in many cases, particularly in childhood ALL. Massive hepatosplenomegaly occurs infrequently and should raise the suspicion of a leukemia evolving from a prior hematologic disorder, such as chronic myelogenous leukemia (CML) or myelodysplasia. Mediastinal adenopathy is seen in 80% of cases of T-cell ALL, is less common in other ALLs, and is rare in AML.

Visceral involvement is also rare, occurring as an initial manifestation of AML in $< 5\%$ of cases, but it may be more frequent during subsequent relapses. These focal collections of blasts, called chloromas or granulocytic sarcomas, can present as soft-tissue masses, infiltrative lesions of the small bowel and mesentery, or obstructing lesions of the hepatobiliary or genitourinary system.

CNS involvement is uncommon at presentation in adult AML ($< 1\%$) and adult ALL (3%-5%). In most instances, CNS involvement is detected by screening lumbar puncture in high-risk patients who are asymptomatic at the time of the puncture. Symptoms, when they do occur, include headache, diplopia, cranial nerve palsies, radicular pain, and/or weakness in a particular nerve root distribution. CNS involvement usually is restricted to leptomeninges; parenchymal mass lesions are uncommon.

Testicular involvement Like the CNS, the testes appear to be a "sanctuary" for isolated relapses in pediatric but not adult ALL. Signs of testicular involvement include painless, asymmetrical enlargement.

Metabolic effects of acute leukemia relate primarily to the rate of cell death.

Hyperuricemia with possible interstitial or ureteral obstruction is seen predominantly in AML with moderate leukocytosis; this condition may be exacerbated by a rapid response to chemotherapy and the "tumor lysis syndrome" (hyperuricemia with renal insufficiency, acidosis, hyperphosphatemia, and hypocalcemia), which may occur within the first 24-48 hours after initiating chemotherapy. To prevent this complication, all patients should receive allopurinol (Zyloprim) and urine alkalinization before marrow-ablative chemotherapy is initiated. (For a more detailed discussion of hyperuricemia and tumor lysis syndrome, see chapter 47.)

Coagulopathies can also complicate the hemostatic defects associated with thrombocytopenia. Disseminated intravascular coagulation (DIC) is most often seen in APL (French-American British Cooperative group [FAB] subtype M3) due to release of procoagulants from the abnormal primary granules, which activate the coagulation cascade, leading to decreased factors II, V, VIII, and X, and fibrinogen, as well as rapid platelet consumption. Lysozyme released from monoblasts in M4 and M5 subtypes of AML can also trigger the clotting cascade. Finally, DIC can occur following asparaginase (Elspar) chemotherapy for ALL.

Diagnosis

Abnormalities on the CBC raise the possibility of leukemia. The diagnosis is substantiated pathologically by a bone marrow examination.

All patients should have cytochemistry, immunophenotyping by fluorescent-activated cell sorter (FACS) using monoclonal antibodies directed at leukemia-specific antigens and cytogenetic analysis of the marrow or peripheral blood blasts at diagnosis. Other tests used to evaluate metabolic abnormalities (electrolytes, creatinine, and liver function tests) and coagulopathies are also needed at diagnosis. A lumbar puncture should be performed at diagnosis in all pediatric patients with ALL and in all patients with neurologic symptoms regardless of age and pathology.

Pathology and cytogenetics

Acute leukemias comprise a group of clonal disorders of maturation at an early phase of hematopoietic differentiation. Morphology and cytochemical stains designed to detect intracellular myeloperoxidase or esterases have been the traditional methods used to classify acute leukemias into either myeloid or lymphoid derivations.

Coupling these traditional methods with cytogenetic analysis and highly specific monoclonal antibodies directed against cell-surface antigens has led to the detection of new prognostic factors and has provided an approach to detect minimal residual disease.

In 1997, a panel of hematopathologists met to update the FAB classification of hematologic malignancies, which had been based on morphology. They proposed a new classification, incorporating immunophenotyping, cytogenetics, and clinical disease features, which has been adopted by the World Health Organization (WHO) (Table 1). The cytogenetic and immunophenotypic groupings of the proposed WHO classification are seen in Tables 2 and 3.

Myeloid leukemias

The new WHO classification retains the morphologic subgroups of the FAB system but has created new categories that recognize the importance of certain cytogenetic translocations as predictors of response to therapy. In this category are AML with t(8;21) (q22,q22), AML with abnormal eosinophils and inv(16)(p13;q22) or t(16;16)(p13;q11), AML with 11q23 mixed-lineage leukemia (MLL) abnormalities and APL t(15;17)(q22;q11-12) (Tables 1 and 2).

The WHO classification also attempts to deal with the evidence that in many older patients, marrow dysfunction antedates the onset of acute leukemia. These myelodysplastic syndromes (MDSs) are characterized by ineffective hematopoietic production and disrupted maturation of one or more cell lines. These abnormalities are often accompanied by loss of chromosomal material, particularly loss of chromosomes –5 or 5q–, –7 or 7q–, and –3 or –20. As the bone marrow becomes more dysfunctional, increasing numbers of blasts are seen in the marrow.

TABLE 1: WHO classification for AML

AML with recurrent cytogenetic translocations
AML with t(8;21), (q22;q22)
AML with t(15;17), (q22;q11-12) + variants = APL
AML with abnormal bone marrow eosinophils inv(16)(p13;q22) or t(16;16)
AML with 11q23 (MLL) abnormalities
AML with multilineage dysplasia
With prior myelodysplastic syndrome (MDS)
Without prior MDS
AML and MDS, therapy-related
Alkylating agent-related
Epipodophyllotoxin-related (some may be lymphoid)
Other
Acute biphenotypic leukemias

In the FAB classification, the demarcation line between myelodysplasia and AML was 30% marrow blasts. However, patients with 20%-29% blasts (previously classified as refractory anemia with excess blasts in transition [RAEB-T]) have a biologic behavior and poor survival similar to those of patients with AML. The WHO has proposed changing the demarcation between MDS and AML to 20% marrow blasts and deleting the category of RAEB-T.

The WHO system further subdivides the AML patients with dysplastic maturation into those with or without antecedent cytopenias (usually 3 months prior to diagnosis had been the arbitrary cutoff point) and those with a history of prior exposure to chemotherapy agents (alkylating agents, epipodophyllotoxins, or others).

Lymphoblastic leukemias

Lymphoblastic leukemias can arise from either B-cell or T-cell progenitors that arrest at an early stage of maturation and then proliferate. Marrow involvement of $>25\%$ lymphoblasts is used as the demarcation line between lymphoblastic lymphoma, in which the preponderance of tumor bulk is in nodal structures, and ALL. Approximately 75% of adult ALLs are B cell in derivation and 25% are T cell.

Precursor B-cell ALL Most B-cell leukemias are early or "pre-B" cell, expressing CD19 and CD10 (the common acute leukemia antigen [cALLa]) but lacking surface or cytoplasmic immunoglobulin; this group of early B-cell leukemias has a more favorable prognosis than that of B-cell leukemias in which the cells have a more mature phenotype. Chromosomal rearrangements juxtaposing an oncogene with a promoter region are often seen in this disease category. The new WHO classification identifies these cytogenetic subgroups (Table 3).

Mature B-cell ALL The more mature B-cell ALL, or Burkitt-cell leukemia, is associated with translocations of the c-*myc* gene on chromosome 8 and the

TABLE 2: Correlation of FAB subtypes with monoclonal antibodies and cytogenetic abnormalities of AML

	Cytochemistry			Monoclonals for precursor cells			Myeloid markers			Monocyte markers			
FAB class	**MPO**	**PAS**	**Esterase**	**Tdt**	**HLA-DR**	**CD34 (My10)**	**CD13 (My7)**	**CD33 (My9)**	**CD15 (Leu Mi)**	**$CD11_b$ (M01)**	**Cd14 (My4)**	**Other**	**Common cytogenetic abnormalities**
M0 (undifferentiated)	< 3% +	–	–	±	+	+	+	±	±	–	–		11q13
M1 (myeloid)	< 3% +	–	–	±	+	+	+	+	–	±	–		–5, –7, –17 del 3p +21, +8
M2 (myeloid with differentiation)	> 10% +	–	–	–	+	–	+	+	+	±	–		t(8;21) del 3p or inv3 –5, –7 t(6;9), +8
M3 (promyelocytic APL)	++	–	–	–	–	–	+	+	±	–	–		t (15;17)
M4 (myelomonocytic)	+	–	+	–	+	–	+	+	+	+	+		inv(16) or –16q t(16;16) occ t(8;21),–5,–7 t(6;9)
M5 (monocytic)	–	+ block	++	–	+	–	±	+	+	+	+		t(9;11) (p21;p23) +8
M6 (erythroid)	–	++	–	–	±	–	±	±	–	±	–	Glycophorin A	–5q, –5, –7, –3, +8
M7 (megakaryocytic)	–	±	–	–	+	+	–	±	–	–	–	Platelet glycoprotein	inv or del 3 +8, +21

CD = cluster of differentiation; HLA-DR = human leukocyte antigen D-related; MPO = myeloperoxidase; PAS = periodic acid-Schiff; Tdt = terminal deoxynucleotidyl transferase

TABLE 3: Morphologic, immunologic, and cytogenetic classification of ALL

Category	Karyotype	Cell markers								
		Tdt	Ia	CD19	CD10	CyIg	SIg	CD7	CD2	CD33
Precursor B-cell ALL (cytogenetic subgroups)	t(9;22) = *BCR/ABL*	+	+	+	–	–	–	–	–	+
	t(v;11q23); MLL rearrangements including t(4;11)	+	+	+	+	–	–	–	–	–
	t(1;9) E2A/PBXI	+	+	+	+	–	–	–	–	–
	t(12;21) ETV/CBF	+	+	+	+	–	–	–	–	–
Burkitt -cell leukemia	t(8;14), t(8;22), t(2;8),6q–	–	+	+	±	±	+	–	–	–
Precursor T-cell ALL	t or del 9p	+	–	–	–	–	–	+	–	–
T-cell ALL	t(11;14), 6q–	+	–	–	–	–	–	+	+	–

CD = cluster of differentiation; CyIg = cytoplasmic immunoglobulin; Ia = I antigen; SIg = surface immunoglobulin; Tdt = terminal deoxynucleotidyl transferase

immunoglobulin heavy-chain gene on chromosome 14q32 in 80% of cases or with the light-chain genes of chromosome 2p11 or 22q11 in the other 20%. Burkitt-cell leukemia has increased in frequency recently, as it is one of the lymphoproliferative disorders that occur in individuals infected with the human immunodeficiency virus (HIV); leukemia may appear early in the course of the HIV infection before the onset of opportunistic infections or severe T-cell deficiency (see chapter 29).

T-cell ALL is frequently associated with translocations of T-cell receptor genes on chromosome 14q11 or 7q34 with other gene partners. T-cell ALL had been associated with a poor prognosis when treated with conventional ALL regimens but has now assumed a good risk status with more aggressive antimetabolite therapy. Precursor T-cell ALL has a poorer outcome.

Infection with human T-cell leukemia virus-1 (HTLV-1) should be looked for in T-cell ALL patients presenting with hypercalcemia and lytic bone lesions. HTLV-1 infection is endemic in southern Japan, the southern Pacific basin, the Caribbean basin, and sub-Saharan Africa. High infection rates are also seen in parts of Iran, India, and Hawaii. Recent immigrants from endemic areas retain a risk of infection similar to that of their point of origin. However, fewer than 0.1% of persons carrying HTLV-1 will develop T-cell leukemia.

ALL with myeloid antigen expression vs undifferentiated leukemia

A subset of patients with leukemia exhibit features of both myeloid and lymphoid differentiation. These patients were originally classified as having MLL. Patients with a leukemic clone that expresses two or more ALL antigens and one myeloid antigen comprise 20% of adult ALL cases. Although expression of myeloid antigen is considered to be a poor-risk feature in children, it does not constitute a distinct poor-risk feature in adults (Table 2).

Immunophenotyping has also helped define a group of patients with undifferentiated myeloid leukemia (M0) who previously were likely to be treated as if they had ALL. These leukemias have a primitive morphology and lack myeloperoxidase. On immunophenotyping, they express at least one early myeloid antigen, usually CD13 or CD 33, and no T- or B-cell markers. Based on immunophenotyping, undifferentiated leukemias are treated in the same manner as myeloid malignancies.

ALL prognostic factors

Cytogenetic abnormalities have a significant impact on the prognosis of patients with ALL. Approximately half of ALL patients have cytogenetic abnormalities; they usually take the form of translocations of genetic information, rather than deletions of genetic material, which are seen more commonly in AML.

Philadelphia chromosome The most ominous cytogenetic abnormality in ALL is the translocation of the *abl* gene from chromosome 9 to the breakpoint cluster region (BCR) on chromosome 22, forming a new gene product (Bcr-Abl) with tyrosine kinase activity. This translocation, referred to as the Philadelphia chro-

mosome (Ph), is found in 95% of cases of CML and in 20%-30% of newly diagnosed adult ALL patients.

The fusion protein produced by the *bcr/abl* translocation in Ph+ ALL (p190) differs from the product seen in CML (p210); the p190 product is a smaller protein than the p210 product and has higher tyrosine kinase activity. Use of polymerase chain reaction (PCR) techniques that target only the p210 product will underestimate the incidence of Ph+ ALL by 50% or more.

Although patients with Ph+ ALL may attain a morphologic remission with conventional chemotherapy (82%), almost all such patients will have persistent molecular evidence of disease. Patients who do achieve a molecular remission have a longer remission duration than those who continue to express p190 or p210 activity (30 vs 12 months).

Other translocations Translocations involving the *MLL* gene at chromosome 11q23 are partnered with several other chromosomes, including 4q21, 9q22, and 19q13. Translocations involving chromosome 11q23 are frequently seen in secondary leukemias, particularly those arising after chemotherapy with etoposide or teniposide. Although most of these translocations are associated with AML, ALL has also arisen in this setting. All the 11q23 translocations, as well as the more common (1;19) translocation, are associated with poorer outcomes when compared with similar immunophenotypes coupled with normal cytogenetics.

Treatment

Treatment for both ALL and AML patients can be subdivided into two or three phases. Induction chemotherapy is the initial treatment designed to clear the marrow of overt leukemia. This phase usually involves multiple drugs that cause pancytopenia for 2-3 weeks.

Consolidation therapy is the treatment given to clear residual leukemia involvement when patients are in morphologic remission. Molecular markers of residual disease can often be detected after induction chemotherapy, which indicates the need for further treatment. The intensity of consolidation therapy varies, depending on the risk of relapse (often based on cytogenetic risk groups and patient age).

Maintenance chemotherapy is used primarily in ALL and APL patients, since low-dose antileukemic agents administered over 18-24 months can prevent relapse.

TREATMENT OF ALL

Although 70%-80% of pediatric patients with ALL can anticipate a long-term remission or cure of disease with combination chemotherapy, the overall long-term disease-free survival rate for adults with ALL is 35%-50%. Poorer outcomes in adults are attributed to a higher incidence of unfavorable cytogenetic abnormalities [t(9;22), t(8;14), or t(4;11)] or coexpression of myeloid antigens, as well as to higher WBC counts at diagnosis.

TABLE 4: ALL induction and consolidation therapy

BFM REGIMEN (*Blood* 85:123-131, 1988)

Induction		Consolidation		CNS prophylaxis		Maintenance	
Phase I		**Phase I**[a]		**Weeks 5-8**		6-MP	60 mg/m^2 PO on weeks 10-18 and 29-130
VCR	2 mg IV on days 1, 8, 15, 22	VCR	2 mg IV on days 1, 8, 15, 22	MTX	10 mg IT on days 31, 38, 45, 52		
DNR	25 mg/m^2 IV on days 1, 8, 15, 22	Adria	25 mg/m^2 IV on days 1, 8, 15, 22	Cranial RT[c]	2,400 cGy (given along with phase II induction)	MTX	20 mg PO or IV weekly on weeks 10-18 and 29-130
PSE	60 mg/m^2 PO on days 1-28	Dex	10 mg/m^2 PO on days 1-28				
L-Asp	5,000 U/m^2 IV on days 1-14						
Phase II		**Phase II**					
CTX	650 mg/m^2 IV on days 29, 43, 57 (maximum, 1,000 mg)	CTX	650 mg/m^2 IV on day 29				
Ara-C	75 mg/m^2 IV on days 31-34, 38-41, 45-48, 52-55	Ara-C	75 mg/m^2 IV on days 31-34, 38-41				
6-MP	60 mg/m^2 IV on days 29-57	6-TG	60 mg/m^2 PO on days 29-42				

Adria = Adriamycin; Ara-C = cytarabine; BFM = Berlin-Frankfurt-Munster; CTX = cyclophosphamide; Dex = dexamethasone; DNR = daunorubicin; Dox = doxorubicin; L-Asp = L-asparaginase; 6-MP = 6-mercaptopurine; MTX = methotrexate; PSE = prednisone; RT = radiation therapy; 6-TG = 6-thioguanine; VCR = vincristine

[a] Begin week 20 [b] For patients > 60 years old, modify doses as follows: CTX, 800 mg/m^2 on day 21; DNR, 30 mg/m^2 on days 1-3; PSE, 60 mg/m^2 on days 1-7

[c] Cranial RT dose for prophylaxis is reduced to 1,800 Gy if patient is being considered for allogeneic BMT while in first CR

[d] Weeks 5-12 [e] Weeks 13-25 [f] Begin week 26 [g] Until 24 months from diagnosis

Induction and early intensification	CNS prophylaxis and interim maintenance	Late intensification	Prolonged maintenance
CALGB REGIMEN (*Blood* 85:2025-2037, 1995)			
Course I: Induction (4 wk)	**Course III: CNS prophylaxis and interim maintenance[e] (12 wk)**	**Course IV: Late intensification[f] (8 wk)**	**Course V: Prolonged maintenance[g]**
CTX 1,200 mg/m^2 IV on day 1[b]	Cranial RT 2,400 cGy on days 1-12	Dox 30 mg/m^2 IV on days 1, 8, 15	VCR 2 mg IV on day 1 of q4wk
DNR 45 mg/m^2 IV on days 1-3[b]			PSE 60 mg/m^2/d on days 1-5 of q4wk
VCR 2 mg IV on days 1, 8, 15, 22	MTX 15 mg IT on days 1, 8, 15, 22, 29	VCR 2 mg IV on days 1, 8, 15	MTX 20 mg/m^2 PO on days 1, 8, 15, 22
PSE 60 mg/m^2/d PO/IV on days 1-21[b]		Dex 10 mg/m^2/d PO on days 1-14	
L-Asp 6,000 IU/m^2 SC on days 5, 8, 11, 15, 18, 22	6-MP 60 mg/m^2/d PO on days 1-70		6-MP 80 mg/m^2/d PO on days 1-28
	MTX 20 mg/m^2 PO on days 36, 43, 50, 57, 64	CTX 1,000 mg/m^2 IV on day 29	
Course II: Early intensification[d] (4 wk; repeat once)		6-TG 60 mg/m^2/d PO on days 29-42	
MTX 15 mg IT on day 1		Ara-C 75 mg/m^2/d SC on days 29, 32, 36-39	
CTX 1,000 mg/m^2 IV on day 1			
6-MP 60 mg/m^2/d PO on days 1-14			
Ara-C 75 mg/m^2/d SC on days 1-4, 8-11			
VCR 2 mg IV on days 15, 22			
L-Asp 6,000 IU/m^2 SC on days 15, 18, 22, 25			

continued on following page

TABLE 4: ALL induction and consolidation therapy *(continued)*

LINKER REGIMEN	Dosage
Induction 1A (DVPAsp)	
Daunorubicin	60 mg/m^2 IV on days 1-3 (and day 15 if day 14 bone marrow had residual leukemia)
Vincristine	1.4 mg/m^2 IV on days 1, 8, 15, and 22 (capped at 2.0 mg if age > 40 years)
Prednisone	60 mg/m^2 PO on days 1-28
Asparaginase	6,000 U/m^2 SC on days 17-28
Consolidation 1B, 2B (HDAC/etoposide)	
Cytarabine	2,000 mg/m^2 IV over 2 hr on days 1-4
Etoposide	500 mg/m^2 IV over 3 hr on days 1-4
Consolidation 2A (DVPAsp)	
Daunorubicin	60 mg/m^2 IV on days 1-3
Vincristine	1.4 mg/m^2 IV on days 1, 8, and 15 (capped at 2.0 mg if age > 40 years)
Prednisone	60 mg/m^2 PO on days 1.21
Asparaginase	12,000 IU/m^2 SC 6 doses over 2 wk
Consolidation 1C, 2C, 3C (HDMTX/6-MP)	
Methotrexate	220 mg/m^2 IV bolus, then 60 mg/m^2/h x 36 hr on days 1-2, 15-16
Leucovorin	50 mg/m^2 IV every 6 hr for 3 doses, then oral leucovorin until methotrexate < 0.05 µmol/L
6-Mercaptopurine	75 mg/m^2 PO on days 1-28

DVPAsp = daunorubicin, vincristine, prednisone, and asparaginase; HDMTX = high-dose methrotrexate; 6-MP = 6-mercaptopurine

Adults also have poor tolerance for some of the chemotherapeutic agents used in treatment, such as asparaginase, as well as high rates of infection and comorbid disease, all of which result in a high incidence of end-organ toxicity and treatment delays.

Induction therapy

The initial goal of therapy is to rapidly reduce the leukemic burden to a level undetectable by conventional methods of light microscopy and flow cytometry, a state that is deemed a complete remission (CR). Two standard induction regimens used in ALL—the morphologic Hoelzer regimen, developed by the Berlin-Frankfurt-Munster (BFM) multicenter group, and the Larson regimen, developed by the Cancer and Leukemia Group B (CALGB)—as well as the newly reported Linker regimen are detailed in Table 4.

The addition of an anthracycline to the standard pediatric leukemia induction regimen of vincristine, prednisone, and asparaginase increased the CR rate in adults from 50%-60% to 70%-80% in several series. The addition of Ara-C or cyclophosphamide to these agents produced additional toxicity without any substantive increase in CR rates in unselected patients. In a recent CALGB study, the use of cytokines, ie, granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]), during induction in patients older than 60 years of age reduced treatment-related mortality from 31% to 5% when compared with placebo-treated controls.

T-cell ALL There is some evidence that patients with T-cell ALL may benefit from early treatment with Ara-C and cyclophosphamide. Pharmacologic studies show high levels of Ara-C triphosphate accumulation in T lymphoblasts and synergy between cyclophosphamide and Ara-C in cell lines of T-cell malignancies.

Mature B-cell ALL Patients with the more mature B-cell ALL (Burkitt-cell leukemia) experienced an improvement in survival when high doses of cyclophosphamide, methotrexate, and Ara-C were incorporated early in the treatment course. The probability of leukemia-free survival improved from 35% with standard ALL induction to 60%-70% with these newer regimens.

Consolidation therapy

The BFM, CALGB, and the new Linker consolidation regimens for ALL are outlined in Table 4. As yet, no randomized trials have compared these regimens. However, in sequential studies from Memorial Sloan-Kettering Cancer Center and the BFM group, as well as the Linker study, use of multiple cycles of non–cross-resistant drugs for three to eight cycles after remission followed by maintenance with methotrexate and mercaptopurine (Purinethol) resulted in overall long-term disease-free survival rates of 33%-38%.

In the new Linker trial, which intensifies the consolidation with alternating cycles of high-dose Ara-C and etoposide with high-dose methotrexate, the 5-year relapse-free survival rate was 60% for patients with standard-risk features. Prognostic features that were associated with a poor outcome in this study

included pre-B ALL with > 100,000 WBC count at diagnosis, cytogenetic abnormalities involving chromosome 11q23 or t(9;22), and time to remission > 30 days. Without either allogeneic or autologous transplantation, all high-risk patients relapsed within a short (1-9 month) time.

Prognostic factors for relapse The BFM trials have found the following factors to be associated with a poor outcome in ALL patients: time to CR > 4 weeks, age > 35 years, WBC count > 30,000/μL, and null-cell ALL (non-T, non-cALLa). Burkitt-cell leukemia patients were not included in this analysis. Patients with no risk factors had a 62% 5-year disease-free survival, whereas disease-free survival for those with one, two, and three risk factors fell to 33%, 22%, and 11%, respectively. Only 27% of patients older than age 15 years fell into the good-risk group.

Prognostic factors in a recent CALGB report included WBC count > 30,000 /μL, age > 60 years, absence of a mediastinal mass (ie, a non–T-cell ALL), and poor-risk cytogenetics, such as Ph + or t(4;11). Rates of survival at 3 years were 64%, 49%, 21%, and 0% for patients with one, two, three, and four risk factors, respectively.

Molecular techniques, such as PCR amplification of leukemia-specific sequences of RNA or DNA, have been used in research settings to reveal residual leukemia cells. These sensitive techniques can detect the persistence of cells with the leukemic phenotype at a sensitivity of 1 cell in 10^4 normal cells in patients who are deemed to be in CR by conventional techniques. In two pediatric studies, detection of leukemia-specific gene rearrangements ($\geq$ 1 cell in 10^4 normal cells) 5-6 months after initiation of treatment was associated with a high relapse rate.

High-risk patients Although the BFM regimen is now standard therapy for good-prognosis patients, high-risk patients are being selected for dose-intensive therapies, including high-dose Ara-C (HDAC) and methotrexate or etoposide, high-dose methotrexate, and asparaginase.

TABLE 5: M. D. Anderson regimen (Hyper-CVAD)

Cyclophosphamide	300 mg/m^2 infused over 3 hr q12h × 6 doses (days 1-3)
Doxorubicin	25 mg/m^2/d continuous infusion over 24 hr × 2 days to begin 12 hr after last cyclophosphamide (days 4 and 5)
Vincristine	1.4 mg/m^2 (max 2 mg) IV on days 4 and 11
Dexamethasone	40 mg/d days 1-4 and 11-14
Alternate q21d with	
Methotrexate (MTX)	1 g/m^2 continuous infusion over 24 hr (day 1)
Ara-C	3 g/m^2 over 2 hr q12h × 4 doses (days 2 and 3)
Leucovorin rescue	50 mg PO at end of MTX infusion and then 25 mg PO q6hr × 48 hr

Investigators at M. D. Anderson Cancer Center have reported on a regimen that alternates four cycles of fractionated high-dose cyclophosphamide, vincristine, doxorubicin, and dexamethasone with four cycles of HDAC and high-dose methotrexate (Table 5). When the regimen was used as salvage therapy for relapsed ALL, it produced a CR rate of 44%. When this regimen was used as initial therapy, the CR rate was 91% (with a median remission duration of 34 months), and the 5-year disease-free survival rate was 38%.

Transplantation Recent series have reported a disease-free survival rate of 55%-60% for "high-risk" ALL patients undergoing transplantation during first CR. When treated with conventional-dose chemotherapy, patients with Ph+ ALL have a disease-free survival rate of < 10% regardless of other risk factors and a median time to relapse of 12 months. These patients should be referred for allogeneic or matched-unrelated donor (MUD) transplantation expeditiously upon attaining a CR. Allogeneic transplantation has produced a 68% long-term disease-free survival rate in patients with Ph+ ALL who received a transplant during first CR. (Strategies for the most effective use of the various transplant options are discussed in chapter 38.)

CNS prophylaxis

The incidence of CNS relapse is much higher in patients with ALL than in those with AML; among pediatric ALL patients who did not receive adequate CNS therapy, the rate of CNS relapse was 20% in the first year.

Patients with ALL require preemptive therapy for occult CNS disease with either (1) intrathecal methotrexate and Ara-C combined with cranial irradiation or (2) high-dose systemic Ara-C or methotrexate combined with intrathecal therapy.

Maintenance therapy

Adult patients In adults, the benefit of maintenance therapy is unknown. In low-risk adults, who have an outcome more similar to that in the pediatric population, maintenance therapy would appear to be justified (see Table 4 for maintenance regimens). In individuals who have mature B-cell ALL, it is unlikely that maintenance therapy has any effect. In other high-risk adult populations, more than half of patients relapse while on maintenance therapy, indicating the need for other strategies to eradicate minimal residual disease.

For patients with Ph+ ALL, a nationwide trial is being developed that will use the tyrosine kinase inhibitor STI-571 (imatinib mesylate, Gleevec) during maintenance therapy to obtain a molecular remission. Patients who attain this PCR-negative state and who do not have a potential stem-cell donor would then have stem cells collected for autologous hematopoietic reconstitution following high-dose chemotherapy.

Treatment of relapse

Treatment of relapsed adult ALL is a major challenge. Since most protocols for initial treatment incorporate 6-11 agents with different cytotoxic mechanisms,

a selection process for drug resistance has occurred. The overall remission rates are 30%-40%, with a median remission duration of 6 months.

Salvage strategies include reinduction with the initial regimen in patients with late relapse or high-dose antimetabolites (cytarabine [Ara-C] or methotrexate [see hyper-CVAD regimen, Table 5]) in those who relapse early. Recent experimental approaches include monoclonal antibodies directed against leukemia-specific antigens conjugated to either radionuclides or toxins, tyrosine kinase inhibitors, allogeneic or autologous transplantation, or new agents.

In individuals with Ph+ ALL or CML in lymphoid blast crisis, imatinib-mesylate (Gleevec) can induce remissions in 40% of patients. These remissions are short-lived, but imatinib-mesylate may provide a bridge therapy to control the leukemia before patients proceed to allogeneic transplantation.

TREATMENT OF AML

Induction therapy

Ara-C and the anthracyclines have been the mainstays of initial therapy for AML since the 1970s. Idarubicin (Idamycin) is beginning to replace the older daunorubicin (Cerubidine) as the anthracycline of choice to pair with Ara-C.

Idarubicin, which attains higher intracellular drug concentration and longer retention, has shown superior response rates and response durations, as well as better overall survival, when compared with daunorubicin in younger (≤ 60 years old) patients.

Both mitoxantrone (Novantrone) and etoposide have significant antileukemic activity in relapsed or refractory leukemia, achieving remission rates of 30%-40%. However, a recent phase III trial compared daunorubicin plus standard Ara-C (D+A) with mitoxantrone plus etoposide (M+E) in newly diagnosed AML patients ≥ 56 years. The CR rates were 44% for D+A and 33% for M+E, with a median survival of 8 months and 6 months, respectively. There does not appear to be a clinical advantage to early use of M+E in older patients.

Increased dose intensity Two large cooperative trials showed no difference in the rate of CR when HDAC was compared with standard doses.

In the Australian Leukemia Study Group (ALSG) trial (Table 6), which randomized 301 patients younger than age 60 to receive either HDAC or standard 7-day infusional Ara-C combined with daunorubicin and etoposide, the CR rates were 71% and 74%, respectively. For patients who achieved a CR, remission duration was 45 months with HDAC vs 12 months with standard Ara-C. The 5-year disease-free survival rate was also significantly better in patients given HDAC than in those treated with standard-dose Ara-C (48% vs 25%), but overall survival was not statistically different, due to the higher number of deaths during induction in patients in the HDAC arm and the lack of effective salvage therapy for these patients.

In a Southwest Oncology Group (SWOG) protocol comparing HDAC (2 g/m^2

TABLE 6: AML induction and consolidation therapy

Induction		Consolidation	
AML induction and consolidation			
Ara-C	200 mg/m² IV as continuous infusion × 7 d	Ara-C[b]	3 g/m² q12h IV as 2- to 3-h infusion on days 1, 3, 5; repeat q28d × 4 cycles
IDA[a]	12 mg/m² IV on days 1-3		
ALSG regimen			
Ara-C[b]	3 g/m² IV q12h as 2- to 3-h infusion on days 1, 3, 5, 7 (8 doses)	Ara-C	100 mg/m² IV as continuous infusion × 5 d
Daun	50 mg/m² IV on days 1-3	Daun	50 mg/m² IV × 2 d
VP-16	75 mg/m² IV × 7 d	VP-16	75 mg/m² IV × 5 d

ALSG = Australian Leukemia Study Group; Ara-C = cytarabine; Daun = daunorubicin; IDA = idarubicin; VP-16 = etoposide

[a] Idarubicin has been substituted for Daun, 45 mg/m², which had been the prevalent anthracycline used in clinical trials prior to 1993. Mitoxantrone, 10 mg/m² × 5 days, has also been used as an alternative.

[b] For patients < 60 years of age

q12h × 12 doses) plus daunorubicin with the standard 7-day Ara-C infusion plus daunorubicin, the CR rates for patients younger than age 50 were 55% and 58%, respectively. For patients who achieved a CR and who received one cycle of consolidation with the same Ara-C dose schedule as they received for induction, the relapse-free survival rate was 32% vs 22% in favor of HDAC ($P = .05$). However, many patients who achieved a CR with HDAC did not receive consolidation therapy.

Dose intensity may be more important to achieving or maintaining remission in different subcategories of leukemia. In the SWOG trial, patients treated with standard-dose Ara-C who expressed the CD34 antigen had a lower CR rate than CD34-negative patients (36% vs 62%). HDAC, in contrast, produced a higher CR rate in CD34-positive patients. There was a strong correlation between CD34 expression and expression of the multidrug resistance (MDR1) gene product, suggesting that higher dose intensity may help overcome drug resistance.

Prognostic factors Cytogenetics and immunophenotyping for leukemia-associated antigens have helped define risk groups. In a large CALGB trial, patients with translocations 15,17 [t(15;17)] or 8,21 [t(8;21)] or inversion 16 [inv(16)] had a higher CR rate and longer median remission duration, whereas patients with monosomy 5 or 7 (–5, –5q, or –7) or trisomy 8 (+8) had a significantly lower CR rate and short remission duration. Patients with normal karyotypes or other cytogenetic abnormalities had an intermediate prognosis.

Poor-prognosis cytogenetic abnormalities, antecedent myelodysplasia, and MDR1 expression are found more frequently in older (> 60 years old) patients, which may account for the lower CR rates seen in this age group (40%-

60%) compared with their younger counterparts (60%-80%). Cytogenetic abnormalities, age, myelodysplasia, and high tumor burden (as evidenced by WBC count > 50,000/μL) are adverse factors both for attaining and maintaining remission. Remission rates are also lower in patients whose blasts express CD34+ or have high expression of the MDR1 gene. Recent studies have shown that an internal duplication of FLT_3 gene occurred in one-quarter of patients with AML; it was seen most commonly in patients with normal karyotypes or APL (34%-36%) and rarely in patients with known good- or poor-risk karyotypes. The abnormality was predictive for relapse (64% for FLT_3 -positive 44% for FLT_3-negative patients). The abnormality was most useful in predicting risk of recurrence in the group of patients with normal karyotypes (74% for FLT_3-positive and 46% for FLT_3-negative patients.

Immunophenotyping of AML blasts at diagnosis can identify aberrant antigen expression in up to 75% of patients. Spanish investigators used a quantitative assessment of persistence of abnormal phenotypes to look for minimal residual disease (MRD) in 126 patients with de novo AML in first clinical remission. Similar to the experience in pediatric ALL, relapse rates declined as the log depletion of tumor burden decreased. Relapse occurred in 89% of patients with 1% residual disease, 50% of patients with 10^{-2} - 10^{-3} cells, 14% of patients with 10^{-3}-10^{-4}, and 0% of patients with < 10^{-4} leukemic cells detected. This was the most sensitive predictor of relapse in this trial, followed by cytogenetic data and time to CR. Both immunophenotyping and FLT_3 mutations are still not commonly used as predictive indicators but may be used in the future to identify subgroups of patients requiring more intensive treatment strategies *(San Miguel JF, Vidrales MB, Lopez-Berges C, et al: Blood 98:1746-1751, 2001).*

Therapy-related AML has a particularly poor prognosis. At best, only 50% of patients will achieve a remission, usually of brief duration (median, 5 months), despite the use of aggressive drug combinations. Allogeneic or unrelated-donor transplants appear to offer the only curative option in these patients, achieving a 3-year disease-free survival rate of 25% in two recent studies of allogeneic transplantation.

GM-CSF A recent Eastern Cooperative Oncology Group (ECOG) study showed that granulocyte-macrophage colony-stimulating factor (GM-CSF, [Leukine]), used following completion of induction chemotherapy in older patients (55-70 years old), shortened the duration of neutropenia by 6 days and, thus, decreased treatment-related mortality, leading to both an improved CR rate and longer survival. The FDA approved GM-CSF for use in this setting. However, other trials using different cytokines in younger patients have not shown a survival benefit.

Consolidation therapy

Once remission of AML is attained, consolidation chemotherapy is required to achieve a durable remission or cure. Standard consolidation regimens are listed in Table 6.

Increased dose intensity In a CALGB study, 596 patients in CR were assigned to receive four courses of postremission Ara-C in one of three dosages: 100 mg/m^2 as a continuous infusion for 5 days, 400 mg/m^2 as a continuous

TABLE 7: AML relapse therapy

Ara-C	2-3 g/m² IV q12h as 3-h infusion × 8 doses	*plus*	Mitox	12 mg/m² IV on days 1-3[a] *or*
			Daun	60 mg/m² IV on days 5, 6 *or*
			VP-16	100 mg/m² IV daily × 5 d[a]
Topo	1.25 mg/m² q24h continuous infusion × 5 d	*plus*	Ara-C	1 g/m² over 2 h on days 1-5 *and*
			Amif	200 mg/m² qod starts day 6 until ANC > 1,500/μL
Ara-C	2 g/m²/d IV × 5 d	*plus*	FdURD	300 mg/m²/d × 5 d + G-CSF[a] +/– Ida 10 mg/m²/d on days 1-3
Mitox	10 mg/m² IV	*plus*	VP-16	100 mg/m² IV as 2-h infusion daily × 5 d
Gemtuz	4-9 mg/m² on days	1 and 14		

Amif = amifostine; ANC = absolute neutrophil count; Ara-C = cytarabine; Gemtuz = gemtuzumab ozogamicin (Mylotarg); Daun = daunorubicin; FdURD = fludarabine: G-CSF = granulocyte colony-stimulating factor; Ida = idarubicin; Mito = mitoxantrone; Topo = topotecan; VP-16 = etoposide

[a] Also used for relapsed ALL

infusion for 5 days, or 3 g/m² as a 3-hour infusion every 12 hours on days 1, 3, and 5. For patients ≤ 60 years old, the percentage of patients in CR at 4 years was significantly higher in the HDAC group (44%) than in either the 400-mg/m² or 100-mg/m² group (29% and 24%, respectively). For patients > 60 years old, consolidation dose intensity had no impact on disease-free survival, with all groups plateauing at a rate of 16% by 2 years.

Other approaches to consolidation include one to three cycles of consolidation followed by autologous or allogeneic bone marrow transplantation (BMT). Both of these approaches also tend to be limited to patients < 60 years old and have produced long-term disease-free survival rates of 45%-60% in several studies. (See chapter 38 for a more detailed discussion of transplantation approaches.) Long-term disease-free survival is strongly influenced by cytogenetic abnormalities present at diagnosis.

CNS prophylaxis

Routine CNS prophylaxis is recommended only for adult AML patients at high risk of CNS recurrences, ie, patients with WBC count > 50,000/μL at presentation or those with myelomonocytic or monocytic AML (FAB M4 or M5). Patients receiving HDAC (≥ 7.2 g/m²) for induction or consolidation therapy achieve therapeutic drug levels in the CSF, obviating the need for intrathecal therapy. Patients given conventional Ara-C doses may be treated with intrathecal methotrexate (12 mg IT) or Ara-C (30 mg IT). Both agents are combined with hydrocortisone (30 mg IT) for patients with active CNS disease.

TREATMENT OF REFRACTORY OR RELAPSED AML

Patients who do not respond to initial therapy or who relapse within 6 months of attaining a CR, as well as those with antecedent myelodysplasia or therapy-related AML, are considered to have relatively resistant disease.

Efforts to overcome drug resistance have focused on: (1) HDAC-containing regimens, (2) new agents, (3) targeted therapy using leukemia-specific monoclonal antibodies conjugated with radionuclides or toxins, and (4) nonchemotherapeutic agents to block the drug efflux pump associated with MDR1 gene expression.

HDAC High doses of Ara-C (2-3 g/m^2 for 8-12 doses) paired with mitoxantrone, etoposide, methotrexate, or fludarabine (Fludara) have produced short-lived CRs in 40%-60% of relapsed AML patients (see Table 7 for dosage regimens). Response rates were higher in patients who had received standard-dose Ara-C for induction and patients with relapsed leukemia than in those in whom induction therapy had failed. Median remission durations were 4-6 months.

Combinations of mitoxantrone and etoposide have been reported to produce a 40%-50% CR rate in populations at high risk of relapse, again with a median remission duration of 4-6 months. Combinations of intermediate-dose Ara-C (1 g/m^2/d for 6 days) with mitoxantrone and etoposide produced CR rates of 79% in relapsed patients and 46% in those who did not respond to induction or had AML evolving from myelodysplastic syndrome, with a median CR duration of 8 months.

New agents Topotecan (Hycamtin) in combination with Ara-C has been reported to produce a CR in 35%-70% of patients with high-grade myelodysplasia (RAEB or RAEB-T and AML).

Nucleoside analogs, such as cladribine (2-CdA [Leustatin]) and fludarabine, showed activity in pediatric AML. A recent British trial reported a 61% CR rate for a combination of fludarabine, Ara-C, G-CSF, and idarubicin, with a median CR duration of 7 months. Gemcitabine (Gemzar) (10 mg/m^2/min) in escalating duration of infusion (6-12 hours) paired with mitoxantrone (12 mg/m^2/d × 3 days) was used to treat 26 patients with relapsed or refractory AML and 8 patients with MDS or CML blast crisis. Five CRs and six partial remissions (PRs) were seen in the AML patients and four CRs and one PR was seen in the MDS/CML group. The maximum tolerated duration of gemcitabine infusion was 12 hours, with stomatitis and esophagitis being the nonhematologic toxicities in 50% of patients.

Troxacitabine, a new L nucleoside analog, was found to induce marrow aplasia in 75% of patients with refractory or relapsed AML and to produce a CR or PR in 3/16 (18%) of patients with a CR duration of +12 and +18 months. In patients with CML blast crisis, 6/17 (37%) of patients achieved a second chronic phase. Dose limiting toxicities were mucositis (12%) and skin rash (30%). Further studies with this drug in combination are under investigation *(Giles FJ, Garcia-Manero G, Cortes JE, et al: J Clin Oncol 20:656-664, 2002).*

Targeted therapy Gemtuzumab ozogamicin (CMA-676, Mylotarg), an anti-CD33 antibody conjugated with calicheamicin, has recently been approved by the FDA for the treatment of relapsed AML in older patients (Table 7). In

TABLE 8: APL induction and consolidation therapy

Induction		Consolidation	
European APL Study			
ATRA	45 mg/m² PO daily in 2 divided doses for a minimum of 45 d and a maximum of 90 d	**Cycle 1** Repeat induction doses of Ara-C and Daun	
Ara-C	100-mg/m² IV as a continuous infusion × 7 d	**Cycle 2** Ara-C	2 g/m² IV infused over 1 h q12h × 8 doses (days 1-4)
		6MP	90 mg/m²/d PO + MTX 15 mg/m²/wk PO × 2 years
		+/- ATRA	45 mg/m²/d for 15 d every 3 months
Daun	60 mg/m² IV × 3 d	Daun	45 mg/m² IV on days 1-3
or			
AIDA Protocol		**Cycle 1**	
ATRA	45 mg/m² PO daily	Ara-C	1 g/m² IV infused over 6 h daily × 4 d
IDA	12 mg/m² IV on days 2, 4, 6, 8	*plus* IDA	5 mg/m²/d IV × 4 d (3 h after end of Ara-C infusion)
		Cycle 2 Mitox	10 mg/m²/d IV on days 1-5
		plus VP-16	100 mg/m² × 5 d by 1-h infusion 12 h after Mitox
		Cycle 3 IDA	12 mg/m² IV on day 1
		plus Ara-C	150 mg/m² SC q8h × 5 d
		plus 6-TG	70 mg/m² PO q8h × 5 d

Ara-C = cytarabine; ATRA = all-*trans*-retinoic acid; Daun = daunorubicin; IDA = idarubicin; Mitox = mitoxantone; MTX = methotrexate; 6-TG = 6-thioguanine; 6MP = 6 mercaptopurine; VP-16 = etoposide

the preliminary phase II trials, 43% of AML patients who relapsed after a CR duration of more than 6 months achieved clearance of marrow and peripheral blood blasts when treated with gemtuzumab ozogamicin.

Treatment-related toxicity was low; the only infusional side effects were fever/chills and slow platelet plus granulocyte recovery (≥ 5 weeks). No cardiac or cerebellar toxicities were reported. Liver function abnormalities were reported in 25%-30% of patients. The median CR duration for responding patients was 9 months. Trials of gemtuzumab ozogamicin combined with Ara-C alone or with daunorubicin are in progress.

Multidrug resistance modification Cyclosporine (Neoral, Sandimmune) is a potent inhibitor of *p*-glycoprotein–mediated drug efflux. A SWOG trial compared HDAC, 3 g/m^2/d × 5 d, followed by daunorubicin, 45 mg/m^2/d as a continuous infusion on days 6-8, either alone (arm 1) or together with cyclosporine, 16 mg/m^2/d as a continuous infusion on days 6-8 (arm 2) in 226 patients with relapsed or refractory AML. Although the CR rates were similar for arms 1 and 2 (33% vs 40%), the relapse-free survival rates favored patients treated with the MDR modifier (9% for arm 1 vs 34% for arm 2 at 2 years; $P = .03$). The overall survival rate was also superior (12% for arm 1 vs 22% for arm 2 at 2 years; $P = .04$). Survival and induction response improved with increasing concentrations of daunorubicin intracellularly in cyclosporine-treated patients, suggesting that cyclosporine enhanced anthracycline cytotoxicity. Trials substituting the cyclosporine analog PSC-833 (Amdray) have not demonstrated a significant improvement in CR rate or survival.

Transplantation Although none of the above options currently offers more than a 10%-15% chance of long-term disease-free survival, they do provide temporary cytoreduction sufficient to permit further high-dose treatment strategies, such as BMT using sibling, unrelated donor or purged autologous marrow. Allogeneic BMT achieves a 30%-40% disease-free survival rate at 5 years in patients transplanted during first relapse or second remission. Autologous BMT also has curative potential for patients beyond first CR, with most large series reporting disease-free survival rates of 30%-35% in selected patients (usually those with good risk cytogenetics or initial CR duration over 1 year).

Reduced-intensity conditioning regimens are being explored as treatment options in older patients and in those with comorbidity that would otherwise preclude full-dose allogeneic transplantation.

New methods of marrow purging and post-transplant immune stimulation also are being explored to decrease relapse-related mortality.

TREATMENT OF APL

APL represents a uniquely homogeneous subset of AML defined by its cytogenetic abnormality, t(15;17), which results in fusion of the retinoic acid receptor (RAR) α-gene on chromosome 17 with the promyelocytic leukemia (PML) gene on chromosome 15. This abnormality yields the PML/RAR-α fusion protein, detectable by PCR techniques, which is useful for both diagnosis and evaluation of minimal residual disease. Most (80%) patients with APL have characteristic hypergranular blasts, and laboratory evidence of DIC is present in 70%-90% of patients at diagnosis or shortly after.

Because of the unique biology and specific clinical features of APL, coupled with a molecular abnormality that suggested a new therapeutic approach, induction and consolidation regimens for APL differ from strategies used for other FAB types. Treatments of APL are shown in Table 8.

Although low-dose heparin (5-15 U/kg/h) and factor replacement are used as supportive adjuncts during chemotherapy, hemorrhagic events contribute 10%-

15% excess mortality during induction chemotherapy of APL compared with other AML subtypes. The use of all-*trans*-retinoic acid (ATRA [Vesanoid]) as part of the initial therapy has substantially shortened the duration of DIC in comparison with chemotherapy-only regimens.

Standard-dose Ara-C and daunorubicin produce CR rates of 70%-80% and disease-free survival rates of 40%-50%.

Initial treatment options

Three large studies have shown that ATRA in combination with anthracycline-based chemotherapy results in an improved long-term disease-free survival. The recent European APL trial compared sequential ATRA followed by chemotherapy with concomitant ATRA plus chemotherapy (see Table 8, Regimen 1). Patients achieving CR received two cycles of consolidation therapy and then were randomized to receive 1) intermittent ATRA (2 weeks every 3 months for 2 years), 2) low-dose oral chemotherapy (6 mercaptopurine + methotrexate for 2 years), 3) both, or 4) observation. The CR rate in both induction arms was 92%. However, relapse rates were 6% for the ATRA plus chemotherapy arm vs 16% for ATRA followed by chemotherapy ($P = .04$).

A total of 289 patients were randomized to receive maintenance treatment. Relapse rates at 2 years were 30% for patients who received no maintenance treatment, 18% for patients receiving ATRA maintenance therapy alone, 14% for chemotherapy without ATRA, and 7% for patients receiving chemotherapy plus ATRA. Overall survival was significantly better in patients receiving maintenance chemotherapy with or without ATRA for 2 years.

All-trans-retinoic acid

Involvement of the RAR-α gene in the pathogenesis of APL suggested the use of retinoids as therapy. The HL60 (APL) cell line can be induced to differentiate in culture with ATRA, and a 1988 study from Shanghai showed CR rates of 85% with this retinoid. ATRA offers the advantages of a shorter neutropenic period (2 weeks) and slightly faster resolution of DIC (4 vs 7 days), as compared with standard chemotherapy with Ara-C and daunorubicin. Normalization of marrow morphology and cytogenetics requires 30-60 days with ATRA.

APL syndrome Approximately 25% of patients with APL develop "differentiation syndrome" (formerly known as ATRA syndrome). Symptoms of this syndrome are fever, respiratory distress with pulmonary infiltrates or pleural effusions, and cardiovascular collapse. Although these symptoms most often correlate with leukocytosis (WBC count > 10,000/μL), many patients develop symptoms with WBC counts between 5,000 and 10,000/μL. The syndrome is seen both in patients treated with ATRA and in those treated with arsenic trioxide (Trisenox).

Treatment of this syndrome involves prompt use of high-dose steroids, initiation of either hydroxyurea or conventional Ara-C/daunorubicin chemotherapy, and temporary discontinuation of ATRA or arsenic trioxide to control leukocytosis.

Temporary pseudotumor cerebri is another fairly common (10%) side effect of ATRA.

ATRA vs standard induction chemotherapy The Italian AIDA study combined ATRA with idarubicin for induction. The CR rate was 95%, with only 5% mortality during induction, suggesting that Ara-C is not required to achieve remission (Table 8).

New agents Arsenic trioxide recently received FDA approval for induction of remission and consolidation in patients with APL who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy and whose individual disease is characterized by the t(15;17) translocation or PML/RAR-α gene expression.

As a single agent, arsenic trioxide has produced complete responses in 34 of 40 (85%) patients with relapsed APL, with 86% of patients achieving molecular remission. Relapsed patients who received arsenic alone had a median relapse-free survival of 18 months; those who received arsenic trioxide followed by autologous or allogeneic transplantation have relapse-free survivals in excess of 70% at 2 years.

Although liver toxicity was reported in the original Chinese studies, the most significant toxicities in the US multicenter trial were the "APL syndrome," prolongation of the AT/QTc interval on echocardiography leading to ventricular arrhythmia, and peripheral neuropathy in 40% of patients. It is very important to monitor closely potassium, magnesium, and calcium levels almost daily during arsenic trioxide therapy and to maintain levels near the upper range of normal to prevent QT prolongation.

The US intergroup APL trial is incorporating arsenic trioxide consolidation therapy for APL in first CR. Patients are randomized to receive either two cycles of daunorubicin plus ATRA or two cycles of arsenic trioxide followed by two cycles of daunorubicin plus ATRA.

Monitoring response to therapy Reverse-transcriptase (RT) PCR for the PML/RAR-α fusion protein can be used to follow response to therapy. The marker clears slowly, with many patients still testing positive following induction therapy. However, patients with persistence of PML/RAR-α at the end of consolidation therapy are at high risk of relapse, as are those with reemergence of the marker following a period without detectable protein.

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CHAPTER 35

Chronic myelogenous leukemia

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Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder resulting from the neoplastic transformation of the primitive hematopoietic stem cell. The disease is monoclonal in origin, affecting myeloid, monocytic, erythroid, megakaryocytic, B-cell, and, sometimes, T-cell lineages. Bone marrow stromal cells are not involved.

CML accounts for 15% of all leukemias in adults. Approximately 4,300 new cases of CML will be diagnosed in 2003, and it is estimated that 1,700 patients will die of CML this year.

Epidemiology

Gender The male-to-female ratio is 1.4-2.2:1.

Age According to SEER (Surveillance, Epidemiology, and End Results) and MRC (Medical Research Council, UK) data, the median age of patients with CML is 67 years. However, most patients who are admitted to chemotherapy studies are 50-60 years old, with a median of ~53 years. Patients in bone marrow transplantion (BMT) studies are even younger, with a median age of ~40 years. Age differences must be considered in all studies because this variable may affect results.

Etiology and risk factors

The etiology of CML is unclear. Some associations with genetic and environmental factors have been reported, but in most cases, no such factors can be identified.

Genetic factors There is little evidence linking genetic factors to CML. Offspring of parents with CML do not have a higher incidence of CML than does the general population. There is also no correlation in monozygotic twins. There may be some correlation with HLA antigens CW3 and CW4. HLA-DR might be associated with a decreased risk of CML.

Environmental factors Nuclear and radiation exposures, including therapeutic radiation, have been linked to the development of CML. Exposure to chemicals has not been associated with greater risk.

Signs and symptoms

CML usually runs a biphasic or triphasic course. This process includes an initial chronic phase and a terminal blastic phase, which is preceded by an accelerated phase in 60%-80% of patients.

Chronic phase If untreated, chronic phase CML is associated with a median interval of 3.5-5.0 years before transforming to the more aggressive phases. During the chronic phase, CML is asymptomatic in 15%-40% of all cases, and in these cases, it is discovered on a routine blood examination.

In symptomatic patients, the most common presenting signs and symptoms are fatigue, left upper quadrant pain or mass, weight loss, and palpable hepatosplenomegaly. Occasionally, patients with very high WBC counts may have manifestations of hyperviscosity, including priapism, tinnitus, stupor, visual changes from retinal hemorrhages, and cerebrovascular accidents.

Patients in chronic phase CML do not have an increased risk for infections. Splenomegaly is documented in 30%-70% of patients. The liver is enlarged in 10%-40% of cases.

Accelerated phase This is an ill-defined transitional phase. One set of criteria that often predict a median survival of < 18 months includes the presence of $\geq$ 15% blasts, $\geq$ 30% blasts and promyelocytes, or $\geq$ 20% basophils in the peripheral blood; or a platelet count $< 100 \times 10^9$/L unrelated to therapy. Cytogenetic clonal evolution is also frequently considered a criterion for acceleration.

The accelerated phase is usually symptomatic, including the development of fever, night sweats, weight loss, and progressive splenomegaly.

Blastic phase The blastic phase morphologically resembles acute leukemia. Its diagnosis requires the presence of at least 30% of blasts in the bone marrow or peripheral blood. In some patients, the blastic phase is characterized by extramedullary deposits of leukemic cells, most frequently in the CNS, lymph nodes, skin, or bones.

Patients in blastic phase usually die within 3-6 months. Approximately 70% of patients in blastic phase have a myeloid phenotype; 25%, lymphoid; and 5%, undifferentiated. Prognosis is slightly better for patients with a lymphoid blastic phase than for myeloid or undifferentiated cases (median survival 9 vs 3 months).

Patients in blastic phase are more likely to experience symptoms, including weight loss, fever, night sweats, and bone pain. Symptoms of anemia, infectious complications, and bleeding are common. Subcutaneous nodules or hemorrhagic tender skin lesions, lymphadenopathy, and signs of CNS leukemia may also occur.

Laboratory features

Peripheral blood The most common feature of CML is an elevated WBC count, usually $> 25 \times 10^9$/L and frequently $> 100 \times 10^9$/L, occasionally with cyclic variations. The finding of unexplained, persistent leukocytosis (eg, $> 12\text{-}15 \times 10^9$/L) in the absence of infections or other causes of WBC count elevation should prompt a work-up for CML.

The WBC differential usually shows granulocytes in all stages of maturation, from blasts to mature, morphologically normal granulocytes. Basophils are elevated, but only 10%-15% of patients have ≥ 7% basophils in peripheral blood. Frequently, eosinophils are also mildly increased. The absolute lymphocyte count is elevated at the expense of T lymphocytes.

The platelet count is elevated in 30%-50% of patients and is higher than 1,000 $\times 10^9$/L in a small percentage of patients with CML. When thrombocytopenia occurs, it usually signals disease acceleration.

Some patients have mild anemia at diagnosis.

Neutrophil function is usually normal or only mildly impaired, but natural killer (NK) cell activity is impaired. As in the other myeloproliferative diseases, platelet function is frequently abnormal and nonspecific; it may have no clinical significance.

Bone marrow The bone marrow is hypercellular, with cellularity of 75%-90%. The myeloid-to-erythroid ratio is usually 10-30:1. All stages of maturation of the WBC series are usually seen, but the myelocyte predominates.

Megakaryocytes are increased early in the disease and may show dysplastic features. They are usually smaller than the typical normal megakaryocytes. Fibrosis may be evident at diagnosis but increases with disease progression and is usually an adverse prognostic finding.

Other laboratory findings Leukocyte alkaline phosphatase activity is reduced at diagnosis. Serum levels of vitamin B_{12} and transcobalamin are increased, sometimes up to 10 times normal values. Serum levels of uric acid and lactate dehydrogenase (LDH) are also frequently elevated.

There is increasing evidence of the role of angiogenic factors in CML. Patients with CML have elevated plasma levels of vascular endothelial growth factor (VEGF) and other angiogenic factors and increased microvascular density in bone marrow. In addition, patients with CML have elevated intracellular cellular VEGF levels, and high levels correlate with shorter survival *(Verstovsek S, Kantarjian HK, Manshouri T, et al: Blood 99:2265,2002)*. Furthermore, VEGF receptors 1 and 2 are expressed in CML cells, and expression of VEGF-R2 correlates with an adverse outcome *(Verstovsek S, Lunin SD, Kantarjian HM, et al: Leuk Res [in press], 2003)*. These findings suggest that therapeutic strategies that target VEGF and/or its receptor may have a role in treating CML.

Cytogenetic and molecular findings

Philadelphia chromosome The vast majority (90%-95%) of patients with CML have the Philadelphia (Ph) chromosome, which represents a balanced translocation between the long arms of chromo-

somes 9 and 22, t(9;22)(q34;q11). The c-*abl* proto-oncogene located in chromosome 9q34 encodes for a nonreceptor protein-tyrosine kinase expressed in most mammalian cells. In chromosome 22, the breakpoint occurs within the BCR gene and usually involves an area known as the breakpoint cluster region *(bcr),* located either between exons b3 and b4 or between exons b2 and b3. Therefore, two different fusion genes can be formed, both of them joining exon 2 of *abl* with either exon 2 (b2a2) or exon 3 of *bcr* (b3a2).

Upon translation, a new protein with a molecular weight of 210 kd ($p210^{BCR\text{-}ABL}$) is synthesized, which, compared to the normal c-*abl*, has markedly increased kinase activity and can transform transfected cells and induce leukemia in transgenic mice. Occasionally, the breakpoint can occur in other areas, leading to different transcripts (eg, $p190^{BCR\text{-}ABL}$ and rarely $p230^{BCR\text{-}ABL}$). The mechanism of oncogenesis of $p210^{BCR\text{-}ABL}$ is unclear, but, upon phosphorylation, it binds to proteins that link to *ras* signaling, suggesting that this oncogene is important in oncogenesis by BCR-ABL. The expression of several other genes is also regulated by the kinase activity of BCR-ABL.

External regulatory factors Cells from CML patients have a defect in cellular adhesion to stromal cells that affects the regulation of cell growth. Therefore, the normal regulatory function of stromal cells on hematopoietic cells is impaired. This faulty adhesion is due to deficient expression and/or malfunction of adhesion molecules, such as lymphocyte function-associated antigen-3 (LFA-3) and integrin-β. Also, levels of interleukin-1β (IL-1β) are elevated in patients with CML, and inhibitors of IL-1 can suppress CML clonogenic growth.

Staging and prognosis

Staging systems Several characteristics of CML, including age, spleen size, WBC and platelet counts, and percentage of blasts, eosinophils, and basophils in the peripheral blood, have been used to classify patients with CML. These factors have been incorporated into several staging systems.

Sokal's classification A frequently used risk classification is Sokal's prognostic risk system. In this system, the hazard ratio function is derived from the following formula: $\lambda_i(+)/\lambda_o(t) = \text{Exp}\ 0.0116\ (\text{age} - 43.4) + 0.0345\ (\text{spleen} - 7.51) + 0.188\ [(\text{platelets}/700)^2 - 0.563] + 0.0887\ (\text{blasts} - 2.10)$.

This risk classification defines three prognostic groups with hazard ratios of < 0.8, 0.8.-1.2, and > 1.2.

The synthesis staging system incorporates prognostic factors into a simple model for staging (Table 1).

The Hasford classification has been suggested to separate more clearly and without overlap risk groups who might be candidates for interferon therapy. In an analogous fashion, patients who might be candidates for transplantation can be assessed using the Gratwohl score.

TABLE 1: Synthesis staging system for CML

Characteristic	Stage	Definition
For chronic phase:		
Age ≥ 60 years	1	0 or 1 characteristic
Spleen ≥ 10 cm below costal margin	2	2 characteristics
Blasts ≥ 3% in blood or ≥ 5% in marrow	3	≥ 3 characteristics
Basophils ≥ 7% in blood or ≥ 3% in marrow		
Platelets ≥ 700×10^9/L		
For accelerated phase:		
Cytogenetic clonal evolution	4	≥ 1 characteristic (regardless of characteristics of chronic phase)
Blasts ≥ 15% in blood or bone marrow		
Blasts + promyelocytes ≥ 30% in blood or bone marrow		
Basophils ≥ 20% in blood or bone marrow		
Platelets $<100 \times 10^9$/L		

Treatment

CHRONIC PHASE

Conventional chemotherapy

Busulfan (Myleran) and hydroxyurea (Hydrea) are the chemotherapeutic agents used most frequently in CML. Busulfan is usually given at a dose of 0.1 mg/kg/d until the WBC count decreases by 50%, at which point the dose is reduced by 50%. Therapy is discontinued when the WBC count drops below 20×10^9/L and is restarted when it rises above 50×10^9/L.

Busulfan is associated with lung, marrow, and heart fibrosis and can cause an Addison-like disease. In 10% of patients, prolonged myelosuppression may be observed.

Hydroxyurea has a lower toxicity profile than does busulfan. The usual dose of hydroxyurea is 40 mg/kg/d; this dose is reduced by 50% when the WBC count drops below 20×10^9/L. The dose is then adjusted individually to keep the WBC count between 2 and 8×10^9/L.

Both busulfan and hydroxyurea can control the hematologic manifestations of CML in more than 70% of all patients, although hydroxyurea results in a longer duration of chronic phase and overall survival than does busulfan. Neither drug significantly reduces the percentage of cells bearing the Ph chromosome, and, therefore, transformation to the blastic phase is unchanged.

Homoharringtonine (HHT) is a plant alkaloid with potent myelosuppressive activity but little other toxicity when given as a continuous infusion.

Major cytogenetic responses (including complete and partial cytogenetic responses; see Table 2) have been achieved in 12% of patients in whom prior interferon (IFN) therapy has failed.

HHT in combination with cytarabine (Ara-C) produced a major cytogenetic

TABLE 2: Response definitions in CML

Response	Category	Criteria
Hematologic remission	Complete	Normalization of WBC counts to $< 9 \times 10^9$/L with normal differential; normalization of platelet counts to $< 450 \times 10^9$/L; disappearance of all signs and symptoms of disease
Cytogenetic response[b]	Complete[a]	No evidence of Ph chromosome-positive cells
	Partial[a]	5%-34% of metaphases Ph chromosome-positive cells
	Minor	35%-95% of metaphases Ph chromosome-positive cells
	None	Persistence of Ph chromosome in all analyzable cells

[a] Major cytogenetic response includes complete and partial cytogenetic responses.

[b] Response assessed on routine cytogenetic analysis with at least 20 metaphases counted.

response in 18% of patients refractory to IFN-α and in 84% of previously untreated patients.

Interferon

Recombinant IFN-α can induce a complete hematologic response (Table 2) in 70%-80% of patients with CML, with some degree of suppression of Ph-positive cells (referred to as a cytogenetic response) in 40%-60% of patients and a major cytogenetic response in 30%-40% of patients at M. D. Anderson Cancer Center. A complete cytogenetic response can be achieved in up to 20%-25% of patients. Randomized studies have documented a survival advantage for patients treated with IFN-α vs those treated with chemotherapy.

In patients who achieve complete cytogenetic responses, they are durable in ≥ 80% of cases. Patients who achieve a major cytogenetic response have a 5-year survival rate of 85% or more. Therefore, the goal of therapy in CML should be to achieve a major cytogenetic response in the majority of patients.

Predictors of response The response to IFN-α is dose-dependent, and the recommended dose is 5×10^6 U/m^2/d. Patients treated within 1 year from diagnosis (ie, early chronic phase) have the best response.

Interferon and Ara-C The combination of IFN-α and low-dose Ara-C given in several different ways has induced major cytogenetic responses in 40%-50% of patients in at least five single-arm phase II studies. A significant survival advantage was shown in one randomized trial comparing patients treated with IFN-α alone (French study), but this result has not been confirmed in another trial (Italian study).

Recent modifications may make molecular techniques for evaluation of residual disease more valuable, although they have been available for some years. Interphase fluorescent in situ hybridization in peripheral blood correlates well with bone marrow results and with cytogenetic analysis *(Le Gouill S, Talmant P, Milpied N, et al: J Clin Oncol 18:1533-1538, 2000)*. Sequential measurement of residual disease using a quantitative assay may help identify patients at higher risk of relapse and may aid in making decisions regarding duration of treatment *(Hochhaus A, Reiter A, Saubele S, et al: Blood 95:62-66, 2000)*.

Toxicity Most patients treated with recombinant IFN-α experience a transient flulike syndrome. Starting with 25%-50% of the recombinant IFN-α dose for the first week, giving the recombinant IFN-α at night, reducing the initial WBC count to 10-20 $\times$ 10^9/L with hydroxyurea prior to the start of recombinant IFN-α therapy, premedicating the patient with acetaminophen and using acetaminophen or cyclo-oxygenase-2 (COX-2) inhibitors as needed can help control these symptoms.

With chronic administration of IFN-α, late side effects occur, including chronic fatigue and weight loss. Less frequent side effects include diarrhea, alopecia, stomatitis, and neurotoxicity, usually in the form of recent memory loss or depression.

Dose adjustments for toxicity The IFN-α dose may be adjusted for toxicity as follows:

- For grade 3 or 4 toxicity, withhold therapy until recovery and restart at 50% of the initial dose.
- For persistent grade 2 toxicity, reduce the dose by 25%.
- For WBC counts $< 2 \times 10^9$/L or platelet counts $< 60 \times 10^9$/L, reduce the dose by 25%. However, it is important to maintain a WBC count of 2-4 $\times$ 10^9/L.

New formulations of INF-α attached to polyethylene glycol (PEG-IFN) have a longer half-life that allows for weekly administration. It may also be associated with decreased toxicity, allowing for increased dose intensity.

Imatinib mesylate (Gleevec) is a potent inhibitor of the tyrosine kinase activity of BCR-ABL and a few other tryosine kinases, such as PDGF-R and c-Kit. A phase I study in patients with CML in whom prior therapy with IFN-α had failed investigated imatinib at doses of 25-100 mg/d. Among the 54 patients treated at a dose of ≥ 300 mg/d, 53 patients (98%) had a complete hematologic response. Twenty-nine patients (54%) achieved a cytogenetic response, including 17 (31% of those treated at ≥ 300 mg/d) who

Activation of *ras* is one of the downstream pathways of *bcr/abl*. To be active, *ras* requires a prenylation process carried out prominently by farnesyl transferase (FT). FT inhibitors (FTIs) were developed as *ras* inhibitors, although they affect other important proteins (eg, RhoB, CNEP). FTIs have significant preclinical activity against CML cells, and two agents have been investigated in the clinic. R11577 was used in 22 patients with CML, most of whom were resistant to imatinib. Of 10 patients treated in the chronic phase, 6 had a hematologic response, including 3 with a minor cytogenetic response *(Cortes JE, Albitar M, Thomas D, et al: Blood 101:1692-1697, 2003, 2002)*. SCH66336 (lonafarnib) was administered to 13 patients in chronic or accelerated phase in whom imatinib had failed. Two patients achieved a hematologic response *(Cortes JE, Daley G, Talpaz M, et al: Blood [abstract] 100:164a, 2002)*. These drugs are now being investigated in combination with imatinib.

achieved a major cytogenetic response. Among patients in blast phase, 55% of those with a myeloid phenotype and 70% with a lymphoid phenotype responded. No significant grade ≥ 3 toxicity was observed.

This drug has recently been approved for patients with CML in chronic phase who did not respond to, or were intolerant to, IFN-α therapy, for patients with accelerated or blastic phase CML, regardless of prior therapy, and more recently for first-line therapy of chronic phase CML. Patients with chronic phase disease receive 400 mg/d orally, and patients in accelerated or blast phase receive 600 mg/d. More than 60% of patients in chronic phase in whom prior IFN-α therapy had failed or was not tolerated achieved a major cytogenetic response, including 41% with a complete cytogenetic response. The estimated progression-free survival (PFS) was 89% at 18 months. In a randomized trial comparing imatinib vs IFN-α + Ara-C in patients with newly diagnosed, previously untreated CML in early chronic phase, the rate of major cytogenetic response was 85% vs 22% with the IFN-α–based combination. The complete cytogenetic response was 74% vs 8%, respectively. The PFS at 18 months was 92% vs 74%, respectively. Although the follow-up is still short, it is clear that imatinib is the treatment of choice for patients with CML. Dosages can be adjusted for myelosuppression or nonhematologic toxicity, but at this time, it is not recommended to use doses lower than 300 mg/d.

The standard dose of imatinib in patients with chronic phase CML is 400 mg/d. However, the phase I study did not identify a maximum tolerated dose at doses up to 1,000 mg/d, and there is some suggestion that higher doses are superior. Two studies have investigated the use of high-dose imatinib (ie, 800 mg/d) in patients with chronic phase CML. The first, in patients in whom interferon therapy had failed, reported a complete cytogenetic response rate of 89%. The second study, in patients with previously untreated chronic phase CML, reported a complete cytogenetic response rate of 81%. More important, the rate of molecular remission was 41% in the first study and 19% in the second study despite a follow-up of only 11 months (vs 7% of patients treated with a standard dose, with a median follow-up of 20 months). These results suggest that high-dose imatinib may be more effective than standard dose *(Cortes JE, Talpaz M, Giles FJ, et al: Blood [abstract] 100:164a and 95a, 2002).*

In vitro studies have demonstrated additive or synergistic results with IFN-α and Ara-C. Several studies are evaluating combinations of imatinib with these agents. Some of these trials are still in early, dose-finding stages. Studies using combinations with IFN-α are frequently using the pegylated formulations of IFN-α-2a and IFN-α-2b. Data with these combinations are still preliminary.

Allogeneic BMT

Allogeneic BMT is potentially curative in CML, although late relapses have been reported. Results are better for patients in the chronic phase than in either the accelerated or blastic phase. Long-term survival rates of 50%-80% and disease-free survival rates of 30%-70% can be achieved in the chronic phase. The role of BMT is now changing in view of the results obtained with imatinib.

Predictors of response Early BMT within the first 1-3 years after diagnosis may be associated with a better outcome than BMT later in the course of disease. Younger patients also have a better outcome than older patients, with those

under 20 years of age having the best prognosis. The use of the Gratwohl score helps to separate those patients who may have a better outcome from those who will not.

Conditioning regimens, including total-body irradiation (TBI), have been traditionally used, but non-TBI–containing regimens (eg, with busulfan and cyclophosphamide [Cytoxan, Neosar]) have produced similar results.

Also, nonmyeloablative conditioning regimens frequently containing purine analogs ("mini"-BMT) have been tested recently in an attempt to expand the use of transplants to older patients or to patients with medical conditions that preclude conventional BMT.

Graft-vs-host disease The major morbidity from BMT is graft-vs-host disease (GVHD). T-cell depletion of the graft can reduce the incidence of this complication but at the expense of higher relapse and graft failure rates. (For a full discussion of GVHD, see chapter 38.)

Several mechanisms of resistance to imatinib have been described. Hochhaus et al has reported on 66 patients with CML (myeloid blast phase, n = 33; lymphoid blast phase, n = 2; accelerated phase, n = 16; or chronic phase, n = 13) or Ph chromosome-positive acute lymphoblastic leukemia (n = 2). Seven of 55 patients showed a > 10-fold increase in *bcr-abl* levels, 2 of 32 patients had genomic amplification, 19 of 36 patients had additional chromosomal abnormalities, and 23 of 66 patients had point mutations of of *abl* at the tyrosine kinase domain. These results demonstrate the heterogeneity of mechanisms present in the clinic, some of which (ie, clonal evolution) may be independent, at least in part, of *bcr-abl (Hochhaus A, Kreil S, Corbin AS, et al: Leukemia 16:2190-2196, 2002).*

Alternatives to matched-related donors For patients who do not have a matched-related donor, matched unrelated donor (MUD) transplants are reasonable alternatives. The 9-year experience from the National Marrow Donor Program in 1,432 patients reported a 3-year survival rate of 37.5%. Early transplantation results in better outcome, with patients transplanted in chronic phase having a 3-year disease-free survival of 63%. The outcome of patients transplanted in accelerated, blastic, or second chronic phase is inferior.

Relapse after BMT Donor leukocyte reinfusions are the most effective strategy to treat patients who relapse after BMT. With this strategy, 70%-80% of patients can achieve a cytogenetic complete response; the best results are achieved when patients are treated during cytogenetic relapse. Other alternatives for earlier relapses include IFN-α therapy, which can result in remission induction and a short-term survival advantage.

Autologous BMT

Although 40%-70% of patients can achieve some degree of suppression of Ph-positive cells upon engraftment of the autologous transplant, this result is usually short-lived, and most patients relapse within 1 year. Some patients previously refractory to IFN-α may regain sensitivity after autologous BMT.

Treatment recommendations

No compatible related donor Most patients (> 70%) do not have a related HLA-compatible donor. With the recent approval of imatinib for first-line therapy in CML, this should be considered standard for these patients.

Matched-related or one-antigen-mismatched donor When allogeneic bone marrow from a matched-related (or one-antigen-mismatched) donor is available, it could be considered as the initial option when transplant-related mortality is expected to be < 20%. The impressive results with imatinib are changing this algorithm, and it is probably appropriate to use imatinib as first-line therapy for all patients. If no cytogenetic response is achieved after 6 months of therapy or no major cytogenetic response is seen after 12 months, transplantation can be considered.

MUD Transplant-related mortality is > 20% in most centers. Therefore, it is recommended that imatinib be used for patients who have only an unrelated donor available and whose expected transplant-related mortality is > 20%. MUD BMT should be considered for patients who do not respond to imatinib therapy if they have a full match and their expected mortality is < 40%.

Imatinib failure When to consider failure to imatinib is still a matter of debate. However, most patients will achieve a hematologic response to imatinib within 3 months and some cytogenetic response by 6 months. Patients not achieving any cytogenetic response after 6 months of therapy have a very low probability (1%-15%) of later achieving a complete response. In contrast, patients having at least a minor cytogenetic response at 6 or 12 months still have a 20%-50% probability of achieving a complete cytogenetic response with continuation therapy. Increasing the dose of imatinib (eg, from 400 mg/d to 800 mg/d) may result in a major cytogenetic response in ~40% of patients. Patients in whom imatinib is failing to induce a response and who are not candidates for BMT should be offered investigational options. Agents currently being investigated alone or in combination with imatinib include decitabine, HHT, farnesyl transferase inhibitors, proteasome inhibitors, arsenic trioxide, antiangiogenic factors, and others.

ACCELERATED AND BLASTIC PHASES

Interferon

Patients with clonal evolution as their only criterion of accelerated disease may respond to interferon, especially when < 16% of metaphases bear the additional abnormality and the transformation occurs within the first 24 months from diagnosis.

Chemotherapy

Intensive chemotherapy regimens, including high-dose Ara-C and daunorubicin (Cerubidine), induce remissions in only 25%-35% of patients in accelerated or blastic phase (median survival durations of 8-18 months and 3 months, respectively). However, patients with a lymphoid blastic phase treated with therapy similar to that given for acute lymphocytic leukemia (ie, vincristine, doxorubicin, and dexamethasone, with or without cyclophosphamide) have a complete response rate of 60%.

Imatinib is also effective for patients with CML in transformation. Seventy-one percent of patients in accelerated phase treated with 600 mg/d of imatinib

Troxacitabine (formerly BCH4556) is a nucleoside analog with significant antileukemic activity. In a study of blast phase CML, 17 patients were treated with this agent at 8 mg/m^2/d for 5 days. Prior therapy for blast phase disease failed in nine of these patients (imatinib: six, allogeneic BMT: three). Four of 13 patients evaluable for response achieved a second chronic phase; the duration of the second chronic phase was 3-18 months. These results suggest that troxacitabine may be an active drug in this disease *(Giles FJ, Cortes JE, Andreeff M, et al: Proc Am Soc Clin Oncol [abstract] 287a, 2001).*

had a hematologic response. The major cytogenetic response rate was 24%, with a time to disease progression of 12 months at 67%. These results are significantly superior to those with 400 mg/d, making 600 mg/d the recommended dose in accelerated phase. In blast phase, 52% of patients achieve a hematologic remission and 31% a sustained remission lasting at least 4 weeks with imatinib. However, the median response duration is only 10 months, even when considering only patients with sustained remission (ie, lasting at least 4 weeks).

New agents and combination regimens (eg, cyclophosphamide, Ara-C, farnesyl transferase inhibitors, and topotecan [Hycamtin]) are currently being evaluated.

Decitabine is a hypomethylating agent with promising activity in patients in accelerated or blastic phase. Decitabine achieved an objective response in 33% of patients in blast phase and 66% of those in accelerated phase. Lower doses of decitabine achieve optimal demethylation with reduced toxicity and are currently being evaluated.

BMT

Compared with those results in patients in chronic phase, results with allogeneic BMT are worse in patients in accelerated or blastic phase, with 4-year survival rates of only 10%-30%. Patients in accelerated phase (determined on the basis of clonal evolution only) who undergo BMT < 1 year after diagnosis have a 4-year probability of survival of 74%.

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CHAPTER 36

Chronic lymphocytic leukemia

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Chronic lymphocytic leukemia (CLL) is a clonal malignancy that results from expansion of the mature lymphocyte compartment. This expansion is a consequence of prolonged cell survival, despite a low proliferative index. The affected lymphocytes are of B-cell lineage in 95% of cases, and the remaining cases involve T lymphocytes.

CLL is the most common leukemia in adults in western countries, and it accounts for approximately 25% of all leukemias. The proportion of cases diagnosed in the early stages of the disease (Rai stage 0) has risen from 10% to 50%, probably because of improved diagnosis (routine automated blood counts).

Epidemiology

Gender The male-to-female ratio is 2:1. This trend appears to be lost with age; the male-to-female ratio is 2.3:1.0 for patients < 50 years old, compared with 1.1:1.0 for those ≥ 75 years old. Despite this finding, the relative risk based on gender does not change substantially with age, because as the population ages, the proportion that is female rises. In the United States, for the age group 75-87 years, there are 1.67 more females than males. Therefore, relative risk of CLL for men is relatively constant, at 2.8 times that of women.

Age The median age at diagnosis is 70 years, and CLL is rarely seen before the age of 35 years.

Race In the American population, the incidence of CLL is similar in different races. However, the incidence is much lower in Asia (Japan, Korea, and China), Latin America, and Africa than in the United States.

Etiology and risk factors

The etiology of CLL is unclear. However, some factors associated with CLL have been identified.

Genetic factors There is a high familial risk for CLL, with family members of CLL patients having a twofold to sevenfold higher risk of developing the disease. CLL with a familial association tends to occur in younger age groups with subsequent generations, perhaps because of increased screening. Association with certain HLA patterns has not been consistent.

Environmental factors There is no documented association of CLL with exposure to radiation, alkylating agents, or known leukemogenic chemicals. However, exposure to some chemicals used in agriculture may increase the risk of developing CLL.

Viral infections Associations between CLL and several viruses, including human T-cell lymphotrophic viruses I and II (HTLV-I and HTLV-II) and Epstein-Barr virus (EBV), have been suggested. However, no conclusive evidence of a causal relationship exists. Adult T-cell leukemia/lymphoma, a T-cell disorder that can resemble CLL, is caused by HTLV-I.

Signs and symptoms

In approximately 20% of patients, CLL is asymptomatic at diagnosis and is discovered on a routine blood examination. When symptoms are present, they are nonspecific and include fatigue, weakness, and malaise.

Constitutional B symptoms (ie, fever, weight loss, and night sweats) are not common at diagnosis but may signal disease transformation. Patients frequently notice enlarged lymph nodes or abdominal discomfort and early satiety related to splenomegaly.

Patients with CLL have an increased susceptibility to infections, which may be the presenting complaint.

Lymphadenopathy is common at diagnosis. Lymph nodes are usually symmetrical, mobile, and nontender.

Splenomegaly and hepatomegaly The spleen and, less frequently, the liver may be enlarged. Splenomegaly may be massive in advanced cases. Only occasionally is splenomegaly found in the absence of lymphadenopathy, but recognition of such patients may identify a group who can significantly benefit from splenectomy.

Other organs In advanced disease, other organs may be involved, including the GI mucosa, prostate, lungs, pleura, and bones. Rarely is such involvement clinically important unless (Richter's) transformation has occurred.

Laboratory features

Peripheral blood The most constant feature of CLL is marked lymphocytosis, with median values of 30-50 $\times$ 10^9/L. The lymphocytes are small and mature appearing with little cytoplasm and clumped chromatin. A few larger nucleolated cells, which represent prolymphocytes, usually constitute $<$ 10% of the total lymphocytes. Diagnostic criteria for CLL defined by the National Cancer Institute (NCI) and International Workshop on CLL (IWCLL) are presented in Table 1.

A positive Coombs' test is seen in as many as 30% of patients at some time during the disease course, although it is uncommon ($<$ 5%) during early stages. Autoimmune phenomena are frequent, with hemolytic anemia and thromb-

TABLE 1: Diagnostic criteria for CLL according to the National Cancer Institute (NCI) and International Workshop on CLL (IWCLL)

Cells	NCI	IWCLL
Lymphocytes	≥ 5 x 10^9/L + ≥1 B-cell marker (CD19, CD20, CD23) + CD5	≥ 10 x 10^9/L + B-cell phenotype or bone marrow involvement
Atypical cells (eg, prolymphocytes)	< 55%	Not stated
Bone marrow lymphocytes	≥ 30%	> 30%

ocytopenia occurring most commonly. Autoimmune neutropenia and other autoimmune sequelae are infrequent.

Bone marrow The bone marrow can be hypercellular or normocellular, but the most characteristic feature is the presence of at least 30% mature lymphocytes. The lymphocyte infiltration can be interstitial, nodular, mixed interstitial and nodular, or diffuse. Diffuse lymphocyte infiltration is associated with a poor prognosis.

Other laboratory findings Hypogammaglobulinemia is seen in > 50% of patients with CLL, usually affecting IgA first, followed by IgM and IgG. However, 5%-10% of patients may have a small monoclonal peak. Paraproteinemia is more common at disease transformation.

Elevated serum levels of B_2-microglobulin (β2M)have been associated with a poor prognosis. Elevation of serum LDH levels is found in < 10% of patients at diagnosis and may indicate autoimmune hemolytic anemia or (Richter's) transformation to large-cell lymphoma.

Immunophenotyping More than 95% of all cases have a B-cell phenotype. In these patients, CD19 and/or CD20 are always coexpressed with CD5, which is expressed on T cells and a subset of normal B cells. Other markers, such as CD21 and CD22, may also be expressed. Expression of CD23 helps to differentiate CLL from mantle cell lymphoma, in which cells coexpress CD19 and CD5 but lack CD23.

Expression of surface immunoglobulins is usually weak and is lower than in normal B lymphocytes or most other B-cell lymphomas.

Cytogenetic and molecular findings

Chromosomal abnormalities

Chromosomal abnormalities occur in 50%-65% of CLL patients with analyzable metaphases. Because of the low mitotic rate in CLL, traditional karyotypic methods frequently fail. Fluorescent in situ hybridization (FISH) has improved

the detection of clonal genetic abnormalities in CLL patients. In a landmark study, Dohner et al evaluated 325 patients with CLL. Using a variety of fluorescent probes, they identified chromosomal aberrations in 82%. Among these findings was the recognition that some subtypes (17p and 11q) had more pronounced lymphadenopathy as well as markedly shorter time to initiate chemotherapy and shorter overall survival than did other types**.** In this study, the most frequent change was a deletion in 13q14 (55% of patients). Other typical abnormalities included deletion 11q22-23 (18%), trisomy 12q13 (16%), and deletion 17p13 (7%).

These genetic abnormalities help explain some of the clinical variations seen in CLL. For example, patients with 13q deletions tend to have modest or absent lymphadenopathy, whereas patients with deletion 17p or 11q frequently have bulky adenopathy.

Disease progression also is heavily influenced by the underlying genetic abnormality. Time from diagnosis to treatment averaged only 9 months for patients with 17p abnormalities, compared with 92 months for patients with 13q deletions.

Prognostic importance These chromosomal abnormalities were potent predictors of outcome with the following median survivals: deletion 17p = 32 months; deletion 11q = 79 months; trisomy 12 = 114 months; and deletion 13q = 133 months.

Molecular abnormalities

No single gene has been implicated in the pathogenesis of CLL. However, several genes are involved to some extent.

Retinoblastoma gene The retinoblastoma 1 (*rb1*) gene is located in the long arm of chromosome 13, but despite the frequent abnormalities in this region, the retained *RB1* allele is usually unaffected. A more telomeric region to the *rb1* gene (D13S25) is frequently affected, and in at least some cases, the abnormality is homozygous, suggesting the presence of a tumor-suppressor gene in this region.

Mutations of *ras* Despite the frequent involvement of chromosome 12, *ras* mutations are uncommon in CLL.

Overexpression of *bcl*-2 Abnormalities of the long arm of chromosome 14 frequently involve region 14q32, the site encoding for the immunoglobulin heavy-chain gene. However, gene translocations, such as t(11;14)(q13;q32) and t(14;18)(q32;q21) (which juxtapose genes *bcl*-1 and *bcl*-2 to the heavy-chain immunoglobulin gene), are relatively uncommon and should prompt consideration of alternative diagnoses (mantle cell or follicular lymphoma). Nevertheless, increased expression of *bcl*-2 mRNA and protein are very common in CLL. Since overexpression of *bcl*-2 inhibits apoptosis, it is possible that this gene participates in the pathogenesis of CLL.

Mutations in *p53* Mutations in the *p53* tumor-suppressor gene are seen in 15% of all patients with CLL (17p abnormality detected by FISH), but these mutations are more common in patients with advanced-stage disease or transformation.

Multidrug resistance gene Approximately 40% of patients with CLL have overexpression of the multidrug resistance gene (*MDR1*).

Staging and prognosis

Staging systems Two staging systems of CLL are commonly used: one proposed and later modified by Rai and the other proposed by Binet (Table 2). Both systems include three categories of low, intermediate, and high risk, with median survival durations of approximately 10, 6, and 2 years, respectively.

Other prognostic factors Stage of disease has been considered the main prognostic indicator for CLL. However, other factors have prognostic implications, such as chromosomal aberrations, serum levels of β2M, pattern of bone marrow infiltration, the lymphocyte doubling time, and serum levels of soluble CD23.

Mutational status of Ig V_H and expression of CD38 also have been identified as prognostic characteristics in CLL. Patients with unmutated V genes showed a significantly shorter survival irrespective of stage than those with a mutated gene. Patients with stage A disease and an unmutated V gene had a median survival of 95 months, compared with 293 months for patients with a mutated gene. Mutation of V gene is somewhat associated with expression of CD38. Patients with mutated V genes frequently have low expression of CD38. These patients appear to require minimal therapy and have prolonged survival.

Treatment

EARLY-STAGE DISEASE

Since patients with early-stage CLL have a good long-term prognosis, and early therapy has not changed the outcome of the disease, patients in the early stages should not be treated unless specific indications exist (Table 3). Recent randomized trials comparing chlorambucil (Leukeran) vs no therapy have documented no advantage for patients with early-stage CLL who received inmmediate therapy with chlorambucil. New alternatives for treatment of high-risk early-stage CLL (eg, high plasma levels of β2M) are being investigated (eg, monoclonal antibodies).

CONVENTIONAL CHEMOTHERAPY

Single-agent chemotherapy

Chlorambucil The most frequently used single agent for CLL is chlorambucil, given as either 0.1 mg/kg daily or 20-40 mg/m^2 every 4 weeks. Therapy is continued until the signs or symptoms requiring therapy are controlled.

TABLE 2: Staging systems for CLL

RAI SYSTEM

Rai stage	Modified Rai stage (risk)	Clinical characteristics	Median survival (yr)
0	Low	Lymphocytosis in peripheral blood and bone marrow only	> 10
I	Intermediate	Lymphocytosis and enlarged lymph nodes	6
II		Lymphocytosis and enlarged spleen and/or liver	
III	High	Lymphocytosis and anemia (hemoglobin < 11 g/dL)	2
IV		Lymphocytosis and thrombocytopenia (platelets < 100×10^9/L)	

BINET SYSTEM

Binet stage	Clinical characteristics	Median survival (yr)
A	Hemoglobin ≥10 g/dL, platelets ≥100×10^9/L, and < 3 areas involved	> 10
B	Hemoglobin ≥10 g/dL, platelets ≥100×10^9/L, and ≥ 3 areas involved	6
C	Hemoglobin < 10 g/dL, platelets < 100 x 10^9/L, or both (independent of areas involved)	2

Chlorambucil is frequently combined with oral prednisone (30-100 mg/m^2/d), although there is no clear evidence that the combination improves responses or overall survival over chlorambucil alone. Prednisone is of value, however, in the management of autoimmune cytopenias.

Cyclophosphamide (Cytoxan, Neosar) is an alternative to chlorambucil. The usual dose is 0.5-1 g/m^2 every 3-4 weeks together with vincristine and steroids (eg, COP [cyclophosphamide, vincristine (Oncovin), and prednisone] regimen; see below).

Combination chemotherapy

COP and CHOP Various drug combinations have been used in CLL, mostly in patients with advanced-stage disease. The most frequently employed combinations have been COP and these three drugs plus doxorubicin (CHOP). The dose of doxorubicin used is usually low (25 mg/m^2). A higher dose of doxorubicin (50 mg/m^2) has been employed in some regimens, such as CAP (cyclophosphamide, doxorubicin [Adriamycin], and prednisone).

Response rates have been 40%-85% with these combinations. In randomized studies, COP was no better than chlorambucil plus prednisone. Although CHOP initially achieved better survival than COP (in Binet stage C) or

TABLE 3: Suggested indications for therapy for early-stage CLL

Progressive disease-related symptoms (eg, fever, night sweats, weight loss)
Bone marrow involvement with progressive anemia and thrombocytopenia
Progressive or painful splenomegaly
Progressive or bulky lymphadenopathy
Rapidly increasing lymphocytosis
Autoimmune hemolytic anemia or thrombocytopenia

chlorambucil plus prednisone, longer follow-up has not confirmed this survival advantage.

NEW APPROACHES

Nucleoside analogs

Fludarabine (Fludara), now perhaps the drug of choice for treating CLL, has been demonstrated in a randomized trial to be more active than chlorambucil for the treatment of CLL. When given to previously treated patients at a dose of 25-30 mg/m^2/d for 5 days every 3-4 weeks, this nucleoside analog produced responses in 20%-50% of patients, with 5%-15% of patients achieving a complete response (CR) and an additional 5%-20%, a "nodular partial response (PR)," ie, a CR but with the presence of lymphoid nodules in the bone marrow (Table 4). In previously untreated patients, the response rate was 67%-80%, with 8%-35% of patients achieving a CR.

The addition of prednisone or chlorambucil to fludarabine therapy did not improve the response rate and is associated with an increased incidence of opportunistic infections and other toxicities. A large randomized study comparing fludarabine, CAP, and CHOP demonstrated an increased response rate with fludarabine but no difference in survival (Table 5). Randomized trials of fludarabine vs chlorambucil in previously untreated patients showed improvements in response rate (overall and CR), duration of response, and progression-free survival with fludarabine but no survival advantage.

Other nucleoside analogs Cladribine (2-chlorodeoxyadenosine, 2-CdA [Leustatin]) is also active in CLL when given at doses of 0.1 mg/kg/d (or 4 mg/m^2/d) for 7 days. At therapeutic doses, this agent appears to be associated with more myelosuppression, particularly thrombocytopenia, than fludarabine. This finding limits its utility in treating CLL, but a direct comparison with fludarabine has not been reported.

The third purine analog active against CLL is pentostatin (Nipent). Previously, toxicity limited its use as an antineoplastic agent. More recently, recognition that use of this drug requires close attention to hydration and renal function (it is both toxic to and cleared by the kidneys) has renewed interest in clinical

TABLE 4: Response criteria in CLL according to the IWCLL

Complete response
Resolution of lymphadenopathy, splenomegaly, hepatomegaly, and constitutional symptoms
Normalization of blood counts:
Neutrophils > 1.5×10^9/L
Platelets > 100×10^9/L
Lymphocytes < 4×10^9/L
Normalization of bone marrow
< 30% lymphocytes[a]
Nodular or focal infiltrates[b]
Partial response
Downstaging (from Binet stages C to A or B and from B to A)[b]
or
> 50% decrease in absolute lymphocyte count, splenomegaly, lymphadenopathy, hepatomegaly
neutrophils ≥ 1.5×10^9/L
platelets ≥ 100×10^9/L
hemoglobin > 11 g/dL
> 50% improvement in peripheral blood counts[a]

[a] NCI criteria; [b] IWCLL criteria

evaluation with this agent. Preliminary studies of pentostatin combined with cyclophosphamide demonstrate responses in > 70% of previously treated patients with acceptable toxicity.

Combination chemotherapy The combination of fludarabine (30 mg/m^2/d for 3 days) and cyclophosphamide (300 mg/m^2/d for 3 days) has resulted in an improved response (overall and CR) rate vs fludarabine alone. Longer follow-up is needed to assess the effect of this combination on survival.

Recent data suggest that the addition of a monoclonal antibody to fludarabine-based therapy may markedly improve CR rates in this disease. A study conducted by the Cancer and Leukemia Group B (CALGB) randomized patients with previously untreated CLL to receive fludarabine or a combination of fludarabine and the anti-CD20 antibody rituximab (Rituxan) at standard doses. Patients in both arms subsequently received a consolidation course of rituximab for 4 weeks.

Overall response rates were high in both arms, but there was a significantly higher CR rate (33%) in the concurrent arm than in the arm with fludarabine alone (15%). The CR rate increased in both groups after consolidation therapy with rituximab. The group at M. D. Anderson Cancer Center has developed a regimen combining 3 days of fludarabine and cyclophosphamide with 1 dose of rituximab given monthly. The overall response rate in previously untreated

TABLE 5: Comparison of fludarabine, CAP, and CHOP treatment for CLL

Patient characteristic	Response rate		
	Fludarabine	CAP	CHOP
Response	71%	58%	72%
Complete response	8%	2%	9%
Median survival	69 months	70 months	67 months

CAP = Cyclophosphamide, Adriamycin, and prednisone; CHOP = Cyclophosphamide, low-dose doxorubicin, vincristine (Oncovin), and prednisone

patients was 95%, and two-thirds of the patients achieved CR. More important, molecular remission, or polymerase chain reaction (PCR) negativity, in the bone marrow was detected in half of the patients in CR. Kennedy et al combined alemtuzumab (Campath 1H), a chimeric monoclonal antibody targeting the pan-lymphocyte antigen CD52, with fludarabine in six patients whose disease was refractory to each agent used singly. There were five responses, including one CR. The authors noted that the observed responses were better than the prior response after each agent used singly.

Bone marrow transplantation

Both allogeneic and autologous bone marrow transplantation (BMT) have produced some encouraging results in patients with CLL.

Allogeneic BMT is a viable option for younger patients with CLL, particularly if they have not responded to alkylating-agent and/or nucleoside-analog therapy and are in advanced disease stages. The series reported to date, including a majority of patients with advanced, refractory disease, has documented a CR rate in excess of 70%. The response is sustained in most patients, although follow-up is still short. BMT using nonablative conditioning regimens has produced encouraging results and should be considered in the setting of a clinical trial, particularly for patients > 60 years.

Autologous BMT Since the median age of CLL patients is usually higher than the age considered acceptable for allogeneic BMT, autologous transplants using purged marrow have also been investigated. In general, results have been disappointing, but some CRs have been obtained and maintained for at least 10 months.

Monoclonal antibody-targeted therapy Monoclonal antibodies (MoAbs) have been

Standard-dose rituximab (375 mg/m^2 weekly × 4) has moderate activity against CLL, with 25% responses *(Huhn, Schilling, Wilhelm, et al: Blood 98:1326-1331, 2001)*. Two trials using escalated dosing, however, reported higher response rates. In one trial, the antibody was given for 4 weeks but escalated on weeks 2-4 to 500-2,250 mg/m^2. A response rate of 36% was noted in 40 previously treated CLL patients, with a dose response noted *(O'Brien S, Kantarjian H, Thomas DA, et al: J Clin Oncol 19:2165-2170, 2001)*. Another trial administered the standard dose of rituximab thrice weekly for 4 weeks. A 45% response rate was observed in 33 patients with small lymphocytic lymphoma/CLL (*Byrd JC, Murphy T, Howard RS, et al: J Clin Oncol 19:2153-2163, 2001)*.

used in CLL patients in an attempt to exploit antibody-mediated cytotoxicity. Alemtuzumab was recently approved by the FDA for the treatment of refractory CLL. Alemtuzumab has produced a response rate of 44% in patients with heavily pretreated CLL. In a recent pivotal trial in fludarabine-refractory patients, alemtuzumab resulted in an overall response rate of 33%.

Rituximab also has been investigated (see box on previous page) and is active both as a single agent and in combination with chemotherapy. Because of rituximab's efficacy without significant toxicity, it is assuming a greater role in the treatment of patients with CLL. Other antibodies, including an anti-CD23 antibody and HuD10, are currently in early-phase testing.

Splenectomy may be beneficial for patients in whom hypersplenism is believed to be the cause of cytopenias (particularly in patients without significant lymphadenopathy) or for palliation when splenomegaly is symptomatic and refractory to chemotherapy. Cytopenias frequently respond to splenectomy, which is associated with minimal mortality in experienced hands.

Treatment recommendations

Traditionally, the initial therapy for CLL has been chlorambucil with or without prednisone. However, accumulating data suggest that fludarabine has significantly greater activity. This agent produces higher overall and CR rates and provides a longer remission duration than chlorambucil. Newer data suggest that combination chemotherapy, particularly a nucleoside analog combined with an alkylating agent, may provide higher response rates, and the addition of MoABs to such regimens appears to increase the CR rates.

The development of nonmyeloablative transplants has provided the possibility of allogeneic transplantation for CLL, where the median age of patients is in the 60s, but this new technique should only be performed in the context of a clinical trial. An effort should be made to enroll patients in clinical trials that offer them the possibility of receiving some of the new alternatives that may eventually achieve the goal of curing CLL.

Complications

Infections Patients with CLL are prone to multiple infections. Hypogammaglobulinemia plays a central role in the predisposition of patients to this problem, and prophylactic IV administration of immunoglobulin preparations may reduce the incidence of infections.

Autoimmune cytopenias frequently complicate CLL and may be precipitated/aggravated by therapy (eg, fludarabine) for CLL. Autoimmune hemolytic anemia can be treated successfully with prednisone in the majority of patients. Combinations of cyclophosphamide with rituximab are beneficial in cases refractory to prednisone, splenectomy, or cyclosporine (Neoral, Sandimmune). Similar approaches may be useful for autoimmune thrombocytopenia. In a study from M. D. Anderson Cancer Center, 31 patients with CLL and autoimmune anemia or thrombocytopenia received cyclosporine (300 mg/day). Sixty-

three percent of patients responded, with a median duration of response of 10 months. No grade 3-4 toxicity was seen.

Pure red cell aplasia is a relatively uncommon complication of CLL, which is mediated by immune mechanisms. Therapy with cyclosporine (3-6 mg/kg/d) may be effective.

TRANSFORMATION

Large-cell lymphoma CLL transforms into a large-cell lymphoma (LCL) in 3%-10% of patients. This phenomenon, known as Richter's transformation, has an aggressive presentation with fever and other B symptoms and progressive lymphadenopathy. Extranodal involvement occurs in approximately 40% of patients. Paraproteinemia and a sharp rise in serum lactic dehydrogenase (LDH) levels can be frequently seen.

The prognosis of patients who progress to LCL is variable and depends in part on the degree of prior treatment used for the underlying CLL. In treatment-naive patients, standard therapy for LCL with CHOP (or CHOP and rituximab) may offer long-term control of the transformed component. In patients who have had significant prior therapy, the disease is often refractory, and combination chemotherapy including BMT is frequently ineffective.

Prolymphocytic leukemia More rarely, CLL can transform into prolymphocytic leukemia, characterized by a $>55\%$ increase in prolymphocytes. The transformation is frequently accompanied by progression of splenomegaly, cytopenias, and refractoriness to therapy.

Other diseases Anecdotal cases of CLL evolving into acute lymphocytic leukemia, myeloma, low-grade and Hodgkin's lymphomas have been reported.

HAIRY-CELL LEUKEMIA

Hairy-cell leukemia (HCL) is an infrequent B-cell malignancy usually associated with pancytopenia and splenomegaly. About 600 cases are reported yearly in the United States. Despite its relative rarity, there are a disproportionate number of highly effective therapies available.

Epidemiology and etiology

The male-to-female ratio of HCL is 4:1. The median age at presentation is 50 years. The etiology is unknown.

Differential diagnosis

HCL can be confused with malignant lymphomas, splenic lymphoma with villous lymphocytes (SLVLs), CLL, other non-Hodgkin's lymphomas in leukemic phase, and occasionally even myelodysplastic syndromes.

Treatment

The indications for treatment of HCL are an absolute neutrophil count (ANC) < 1,000/μL, platelet count < 100×10^3/μL, or hemoglobin < 10 g/dL; leukemic phase of HCL; symptomatic splenomegaly; recurrent infections; or autoimmune complications.

Response criteria The criteria for a CR are normalization of the CBC, with ANC > 1,500/μL, platelet count > 100,000/μL, and hemoglobin > 12 g/dL; regression of organomegaly to normal; and bone marrow and peripheral blood free of hairy cells. PRs require reduction of the hairy cells in the bone marrow to < 50%, < 5% hairy cells in peripheral blood, > 50% reduction in organomegaly, and normalization of the CBC.

Splenectomy is reserved for patients with splenic rupture, infarcts, a massively enlarged spleen, severe hypersplenism, or failure to respond to systemic chemotherapy.

Interferon-α (IFN-α) at a dose of 3 mU/d administered by IM or SC injection for 6 months followed by 3 mU/d three times weekly for 12 or 24 months, induces a CR in 8%-10% of patients and a PR in 74%. The median time to response was 6 months in patients achieving a PR and 14 months in those achieving a CR. Patients frequently relapse between 12 and 24 months after discontinuation of therapy.

Purine analogs Pentostatin is a purine analog that binds to adenosine deaminase (ADA). The recommended dose is 4 mg/m^2 by IV bolus every other week until a CR is obtained. Usually, patients require a median of 8 courses (range, 4-15). The CR rate varies between 59%-89% in different studies, and the PR rate varies between 4%-37%. Responses can last for many years, and patients who relapse often respond to retreatment with pentostatin. In a recent update of a large randomized trial comparing pentostatin and IFN-α, Flinn et al reported that in 241 patients with HCL treated with pentostatin, the 10-year overall survival was 81%, with only 2 deaths (1%) attributable to HCL. Similarly, Catovasky et al published follow-up data on 159 patients, which showed a 4-year event-free survival of 84%.

Cladribine shows activity in treating HCL similar to that of pentostatin. Due to this finding and the fact that cladribine is given as 1 cycle of a 7-day continuous infusion or 5-day bolus, this agent usually is the preferred treatment of this disorder. Piro et al treated 144 HCL patients with cladribine, 0.1 mg/kg/d by continuous IV infusion for 7 days. A total response rate of 97% was obtained, with 85% CRs and 12% PRs. Response was independent of previous treatment with IFN or splenectomy, and three patients whose disease was refractory to pentostatin responded to cladribine. Recovery of blood cell counts occurred by day 61 (range, 11-268 days).

At M. D. Anderson Cancer Center, Estey et al treated HCL patients and noted an 89% response rate, with 78% achieving a CR.

Four HCL patients who relapsed after responding to cladribine were retreated again with the same drug, resulting in two CRs and one PR.

The largest series reporting long-term follow-up results on patients with HCL treated with cladribine was from the Scripps group. A total of 349 patients, with a median duration of response follow-up of 59 months, were evaluated. Twenty-six percent had relapsed at a median of 29 months, but most of them were patients who had only achieved a PR. The time-to-treatment-failure rate at 48 months was only 16% in complete responders.

For patients who relapse after therapy with cladribine or pentostatin, Kreitman et al reported on an exciting new treatment with an anti-CD22 antibody fused to a truncated Pseudomonas exotoxin. In 16 patients refractory to cladribine, there were 11 CRs and 2 PRs with only 3 relapses at a median follow-up of 16 months *(Kreitman RJ, Wyndham HW, Bergeron K, et al: N Engl J Med 345:241-247, 2001).*

Immunotoxin Recently, the NCI evaluated a recombinant immunotoxin containing an anti-CD22 variable domain fused to a truncated Pseudomonas exotoxin; it was given by IV infusion every other day for a total of three doses. Sixteen patients whose disease was resistant to cladribine were treated; two achieved PR and 11 achieved CR. Three of the 11 patients who had CR relapsed and were retreated; all of these patients achieved a second CR.

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CHAPTER 37

Myelodysplastic syndromes

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Myelodysplastic syndromes (MDS) are a group of hematologic disorders of the pluripotent hematopoietic stem cells. These disorders are characterized by ineffective hematopoiesis, including abnormalities in proliferation, differentiation, and apoptosis. The overall clinical result is peripheral cytopenias in the setting of a normocellular or hypercellular bone marrow and a high incidence of transformation to acute leukemia.

The incidence of MDS is about 2 cases per 100,000 population per year, with 30 cases per 100,000 population per year in patients > 70 years old. At least 10,000 new cases are diagnosed annually in the United States.

Epidemiology

Gender The overall incidence of MDS is slightly higher in males than in females (1.5-2.0:1).

Age MDS is a disease associated with age, with a median age at diagnosis of about 70 years. MDS is rare in children; childhood cases are usually associated with monosomy of chromosome 7.

Etiology and risk factors

MDS is a clonal disorder of bone marrow stem cells. The vast majority of cases (80%-90%) occur de novo, whereas 10%-20% of cases are secondary. The etiology of de novo MDS is unclear. Exposure to radiation and/or cytotoxic agents is a recognized etiologic factor in secondary disease forms. Cumulative exposure to environmental toxins, genetic differences in leukemogen susceptibility and metabolism, and genomic senescence may contribute to disease pathogenesis in de novo cases.

Genetic factors It has been suggested that a genetic change causes an irreversible alteration in the structure and function of the stem cell, with disruption of a multistep process involving control of cell proliferation, maturation, and interactions with growth factors; mutations of tumor-suppressor genes and proto-oncogenes; and deregulation of apoptosis.

Constitutional childhood disorders, such as Fanconi's anemia, Shwachman-Diamond syndrome, Down's syndrome, neurofibromatosis, and mitochondrial cytopathies, have been associated with MDS and monosomy 7.

Environmental factors Exposure to benzene and its derivatives results in karyotypic abnormalities often seen in MDS and acute myelogenous leukemia (AML). Persons chronically exposed to insecticides and pesticides may have a higher incidence of MDS than the general population.

An increased incidence of MDS has been reported among smokers and ex-smokers, possibly linked to associated exposures to polycyclic hydrocarbons and radioactive palladium present in tobacco smoke.

An association of MDS with magnetic fields, alcohol, or occupational exposure to other chemicals has not been confirmed.

Antineoplastic drugs Therapy-related myelodysplasia and therapy-related AML are recognized long-term complications of cancer chemotherapy and radiotherapy. Therapy-related MDS usually develops 3-7 years after exposure to chemotherapy and is most frequently related to complete or partial loss of chromosome 7. Approximately 80% of cases of AML occurring after exposure to antineoplastic drugs are preceded by MDS.

More than 85% of patients who develop chemotherapy-related leukemia or MDS have been exposed to alkylating agents. Patients exposed to nitrosoureas have a relative risk of developing MDS or AML of 14.4 and a 6-year actuarial risk of 4%. The mean cumulative risk of leukemia in patients exposed to epipodophyllotoxins (eg, etoposide and teniposide [Vumon]) is about 5% at 5 years. Most of these therapy-related leukemias are not preceded by a dysplastic phase.

Autologous bone marrow transplantation (BMT) has also been associated with a 5-year actuarial risk of MDS of 15% (95% confidence interval, 3.4%-16.6%). Fluorescent in situ hybridization (FISH) analyses of pretreatment bone marrow specimens for informative cytogenetic markers indicate that these secondary myeloid malignancies derive from clones demonstrable before the transplant procedure. A recent study suggested that prior therapy with fludarabine (Fludara) and older age were associated with the development of MDS or AML in patients with lymphoid malignancies after autologous stem-cell transplantation (SCT).

Classification

The French-American-British (FAB) group proposed a classification system for MDS that consists of five subgroups, based on the percentage of blast cells in the peripheral blood and bone marrow, presence of ringed sideroblasts in the bone marrow, and monocyte count in the peripheral blood (Table 1). The five subgroups are:

- refractory anemia (RA)
- refractory anemia with ringed sideroblasts (RARS)
- refractory anemia with excess of blasts (RAEB)

TABLE 1: Main features of MDS according to the FAB classification

FAB subgroup	BM blasts (%)	Ringed sideroblasts (%)	PB monocytes ($\times 10^9$/L)	Chromosomal abnormalities (%)	Associated karyotype	Rate of leukemic progression (%)	Median survival (mo)
RA	< 5	< 15	< 1	30	5q-, -7, +8, 20q-	12	32
RARS	< 5	≥ 15	< 1	20	+8, 5q-, 20q-	8	42
RAEB	5-20	Variable	< 1	45	-7, 7q-, -5, 5q-, +8	44	12
RAEB-t	21-30	Variable	Variable	60	-7, 7q-, -5, 5q-, +8	66	5
CMML	1-20	Variable	≥ 1	30	-7, +8, t(5;12), 7q-, 12q-	14	20

BM = bone marrow; CMML = chronic myelomonocytic leukemia; FAB = French-American-British; PB = peripheral blood; RA = refractory anemia; RAEB = refractory anemia with excess of blasts; RAEB-t = refractory anemia with excess of blasts in transformation; RARS = refractory anemia with ringed sideroblasts

- refractory anemia with excess of blasts in transformation (RAEB-t)
- chronic myelomonocytic leukemia (CMML)

The presence of Auer rods in granulocyte precursors classifies a patient as having RAEB-t, even if blasts comprise < 20% of bone marrow cells. The presence of ≥ 30% blast cells in the bone marrow establishes the diagnosis of AML rather than MDS.

More recently, the World Health Organization (WHO) has proposed a modified classification of hematologic malignancies. The following changes have been proposed, based on the effect of cytogenetics, molecular genetics, history of prior therapy, and history of prior myelodysplasia on clinical behavior:

- The FAB classification of refractory anemia with excess blasts in transformation (RAEB-t) is eliminated.
- The blast percentage that defines AML is > 20%.
- The presence of dysplasia in two or more cell lines (multilineage dysplasia) and 5q- syndrome are regarded as separate entities of MDS within the categories of RA or RARS.
- RAEB is divided into two categories distinguished by marrow blast percentage (ie, RAEB-1: 5%-9%; RAEB-2: 10%-19%) or the presence of Auer rods (RAEB-2).
- A category is added to include unclassifiable myelodysplastic syndrome defined by nonerythroid, single-lineage dysplasia.
- CMML is included in a separate category of myelodysplastic/myeloproliferative diseases that also includes atypical chronic myelogenous leukemia and juvenile myelomonocytic leukemia.

This proposal has raised controversy because biologic features like spontaneous apoptosis and measures of angiogenesis are similar between RAEB-t and other MDS but different from those of AML.

Signs and symptoms

Nearly 50% of patients with MDS are asymptomatic at the time of initial diagnosis. Signs and symptoms relate to hematopoietic failure, leading to anemia, thrombocytopenia, or leukopenia.

Symptoms related to anemia may range from fatigue to exertional dyspnea that may exacerbate angina or develop congestive heart failure.

Infection Approximately one-third of patients report recurrent localized or systemic infections as a result of granulocytopenia or dysfunctional granulocytes and monocytes.

Bleeding manifestations, such as petechiae or gross hemorrhage, can occur with thrombocytopenia. However, < 10% of patients present with serious bleeding.

Organomegaly and lymphadenopathy Splenomegaly and/or hepatomegaly

may be found in 5%-25% of patients. When a large spleen is seen, the possibility of CMML is raised.

Acute neutrophilic dermatosis (Sweet's syndrome) and pyoderma gangrenosum may be observed in patients with CMML or AML.

Paraneoplastic syndromes Diabetes insipidus vasculitis and other rare paraneoplastic syndromes have been described in patients with MDS associated with monosomy 7.

Laboratory features

Peripheral blood

Anemia is the most frequent abnormality in MDS, with > 80% of patients presenting with hemoglobin concentrations < 10 g/dL. The anemia is usually normocytic or macrocytic, but the mean corpuscular volume rarely exceeds 120 μm^3.

Other RBC abnormalities Hypochromic changes and red shape abnormalities are frequent, including poikilocytosis, anisocytosis, elliptocytosis, macro-ovalocytosis, and sometimes stomatocytes. Stippled and nucleated RBCs can be observed in 10% of cases. Reticulocyte counts are usually reduced.

WBC abnormalities The peripheral WBC count may be normal or low. The proportion of monocytes may be increased, and a circulating monocyte count of $\geq 1 \times 10^9$ defines CMML.

Neutropenia is seen in about 50% of MDS patients at diagnosis, often associated with pseudo–Pelger-Huët anomaly (neutrophils have a condensed chromatin and unilobed or bilobed nuclei with a pince-nez shape), ring-shaped nuclei, hypogranulation, and hypolobulation or other signs of dysgranulopoiesis.

Granulocytes frequently disclose reduced myeloperoxidase activity, increased α-naphthyl acetate esterase activity, and other functional abnormalities.

Abnormalities in the surface marker expression of leukocytes have also been observed.

Chemotactic and bactericidal capability is impaired, which can potentiate the risk of infection, even in the presence of normal WBC counts.

Patients frequently have a decreased number of natural killer cells and helper T lymphocytes.

Platelet abnormalities Thrombocytopenia is present at diagnosis in approximately 30% of patients; isolated thrombocytopenia may precede the development of overt MDS by 2-10 years.

Platelets may be abnormally large, have poor granulation, or have large, fused central granules.

Decreased platelet aggregation is observed when patients with MDS are challenged with collagen or epinephrine.

Thrombocytosis may be seen in association with the 5q- syndrome.

Bone marrow

Bone marrow aspiration and biopsy should be performed in every patient suspected of having MDS. The bone marrow is normocellular or hypercellular in 85%-90% of patients with MDS but may be hypocellular in as many as 10%-15%.

Trilineage dyspoiesis The main feature of MDS is trilineage dyspoiesis, although myelodysplastic features do not always involve all three lineages.

Dyserythropoiesis Erythroblasts usually have a megaloblastoid appearance, although most frequently this is less pronounced than in vitamin B_{12} or folic acid deficiency. Iron may be abnormally deposited in mitochondria and is easily stained with Prussian blue, producing a ring-shaped stain around the nucleus. Pathologic sideroblasts have five or more granules/cell.

Dysgranulopoiesis The characteristic findings in dysgranulopoiesis are hypogranulation and hyposegmentation with nuclear morphology abnormalities.

Excess bone marrow blasts Bone marrow blasts $>$ 5% but $<$ 30% are seen in approximately 50% of patients with MDS; in the context of myelodysplasia, this finding is specific for MDS.

The FAB group distinguishes three types of blasts on the basis of maturation morphology. Type I blasts have an uncondensed nuclear chromatin, one to three nucleoli, and basophilic cytoplasm without a Golgi zone. Cytoplasmic granules and Auer rods are absent. In type II blasts, the nuclear/cytoplasm ratio is lower than in type I blasts, and few primary granules are seen. Type III blasts have 20 or more azurophilic granules without a Golgi zone.

Dysmegakaryocytopoiesis At least 10 megakaryocytes should be evaluated. Micromegakaryo-cytes are small cells with a diameter two times smaller than the normal megakaryocyte ($<$ 80 μm). Multiple dispersed small nuclei or mononucleated forms, as well as hypogranulated megakaryocytes, also can be found.

Identification of genes specific to MDS is an active area of research. Such genes could not only aid in the molecular diagnosis of this disease but could potentially provide a target for specific therapy. Using DNA microarrays, Miyazato et al identified a number of genes with differential expression in MDS and AML. Among them, one encoding a delta-like protein was considered particularly interesting. This gene was overexpressed in 12 of 22 (55%) of patients with MDS and 3 of 31 (10%) with AML. Additional studies investigating these potential genes are ongoing (*Miyazato A, Ueno S, Ohmine K, et al: Blood 98:422-427, 2001*).

Other abnormalities An increase in reticulin and collagen fibers in the bone marrow may be seen in some patients.

Angiogenesis Recently, increased marrow vascularity and increased levels of angiogenic mitogens vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) have been described in patients with MDS.

Other laboratory findings

Serum iron, transferrin, and ferritin levels may be elevated. As a result of ineffective hematopoiesis, lactic dehydrogenase (LDH) and uric acid concentrations are frequently increased.

Monoclonal gammopathy, polyclonal hypergammaglobulinemia, or hypogamma-globulinemia are found occasionally.

Cytogenetic and molecular findings

Chromosomal abnormalities

Clonal cytogenetic abnormalities are found at diagnosis in 50%-60% of patients with de novo MDS and 75%-85% of those with secondary MDS or AML. An interesting feature that distinguishes MDS from AML is the high incidence of complete or partial chromosomal loss or, less frequently, chromosomal gain and the relative rarity of translocations. Among the translocations, unbalanced translocations leading to a loss of chromosomal material are most frequent.

Common cytogenetic abnormalities are listed in Table 1. None of them is characteristic of MDS, since all can be found in other myeloid disorders.

Some of the most frequent abnormalities are interstitial deletion of the long arm of chromosome 5 (5q-), monosomy of chromosome 7, trisomy of chromosome 8, 20q-, and loss of the Y chromosome. "Complex" cytogenetic abnormalities involving three or more chromosomes occur in approximately 15% of de novo MDS cases and 50% of secondary MDS cases.

Therapy-related MDS Loss of chromosome 7 and/or 7q- has been reported in as many as 50% of patients previously exposed to chemotherapy for other malignancies, most frequently in association with prolonged use of alkylating agents. Other abnormalities commonly associated with prior exposure to alkylating agents include -5 and/or del(5q) in 25% of cases and involvement of chromosomes 17p and 21 in 10%-15%. Complex chromosomal abnormalities may be found in nearly 50% of patients.

Previous exposure to the epipodophyllotoxins etoposide and teniposide has been associated with abnormalities of the long arm of chromosome 11 (11q23) or, less often, chromosome 21 (21q22). However, patients with these abnormalities most frequently develop a secondary leukemia in the absence of an antecedent myelodysplastic phase.

The role of VEGF and its receptor in CMML and MDS has been investigated by Bellamy et al. Coexpression of VEGF and at least one of its receptors was identified in neoplastic cells from patients with MDS or CMML. Furthermore, VEGF stimulated leukemia colony formation in 12 patients and neutralization with an anti-VEGF antibody inhibited colony-forming unit (CFU)-leukemia formation in 9 of 15 CMML or RAEB-t patient specimens. These results suggest that VEGF may have an autocrine function in CMML and MDS promoting self-renewal of leukemic progenitors. Thus, therapeutic approaches targeting VEGF are of interest in MDS and are currently being pursued *(Bellamy W, Richter L, Sirjani D, et al: Blood 97:1427-1434, 2001).*

Cytogenetics and FAB classification

RA and RARS Approximately 15%-30% of patients with RA and RARS have abnormal karyotypes. The most frequent abnormality in patients with RA is 5q, present in 70% of patients, whereas the most common abnormalities in patients with RARS are 5q-, +8, and 20q- (each occurring in 20% of patients).

RAEB and RAEB-t Nearly 60% of patients with RAEB and RAEB-t have cytogenetic abnormalities, with 5q-, -7, 7q-, and +8 being the most frequent.

CMML Chromosomal abnormalities are found in 25%-30% of patients with CMML; the predominant abnormalities include -7, 7q-, +8, 12q-, and t(5;12). Interestingly, 5q- is seen in < 1% of cases of CMML.

Monosomy 7 is found in up to 25% of children with MDS, most frequently as an isolated abnormality. In contrast, older patients most often have monosomy 7 associated with other chromosomal abnormalities.

5q- Syndrome

The interstitial deletion characteristic of the 5q- syndrome involves bands 5q13 to 5q33, regions known to contain genes coding for granulocyte-macrophage colony-stimulating factor (GM-CSF [Leukine]), macrophage colony-stimulating factor (M-CSF), interleukin (IL)-3 , IL-4, IL-5, IL-9, IL-12, M-CSF receptor, platelet-derived growth factor receptor, interferon-regulatory factor-1 (IRF-1) endothelial cell growth factor, glucocorticoid receptor, and early growth response gene-1 (EGR-1).

Clinical features This syndrome has characteristic clinical features, including older age, female predominance, diagnosis of RA without excess (< 5%) of blasts in 75% of cases, macrocytosis with severe anemia, erythroblastopenia, normal leukocyte counts, normal or increased platelet counts, and hypolobulated megakaryocytes in the bone marrow.

Progression to AML is rare, and prognosis is usually good. However, not every patient with a del(5q) has this syndrome and its associated good prognosis.

Molecular findings

The *ras* family of genes is most frequently associated with MDS, although other abnormalities involving NF1, FMS, p53, TEL, EVI, AXL, TEC, HCK, c-*mpl*, and other genes have also been described.

Mutations in *ras* Mutations in the *ras* family occur in approximately 20%-40% of patients with MDS but are most frequently found in those with CMML. Mutations in *ras* are more common in codons 12, 13, and 61. Mutations in N-*ras* are more common than those in K-*ras* or H-*ras*.

A difference in the surface expression of phosphatidylserine (a marker of apoptosis) on cell membranes among de novo AML, MDS, and secondary AML and normal bone marrow cells has been found (increased in MDS and secondary AML). Epigenetic silencing of the *p15* tumor-suppressor gene by promoter hypermethylation antedates AML transformation in > 70% of patients.

Staging and prognosis

Prognostic factors

FAB and WHO classifications The FAB classification has been used most frequently to evaluate survival and risk for AML transformation (Table 1). The WHO classification has similar prognostic implications.

Cytogenetics Patients with complex karyotypes and abnormalities in chromosome 7 have a poor prognosis, whereas those with a normal karyotype, -Y, 5q-, or 20q- have a better prognosis.

Peripheral cytopenias (hemoglobin $<$ 10 g/dL, absolute neutrophil count (ANC) $<$ 1.5×10^9/L, and platelet count $<$ 100×10^9/L) are associated with a poor prognosis.

Other prognostic factors Other parameters associated with a poor outcome include CD34 cell expression, high serum LDH levels, expression of the c-*mpl* gene, *ras* mutations, *p*-glycoprotein expression, p15 inactivation, and p53 mutations. However it is unclear whether these factors have independent prognostic value.

International Prognostic Scoring System (IPSS)

An International MDS Risk Analysis Workshop has proposed a system that combines clinical, morphologic, and cytogenetic data to generate a "consensus" prognostic system.

TABLE 2: International Prognostic Scoring System (IPSS) for MDS

Characteristic	Value	Score
Bone marrow blasts (%)	< 5	0
	5-10	0.5
	11-20	1.5
	21-30	2.0
Karyotype[a]	Good	0
	Intermediate	0.5
	Poor	1.0
Cytopenias	0-1	0
	2-3	0.5
Risk group	**Sum of score**	
Low	0	
Intermediate 1	0.5-1.0	
Intermediate 2	1.5-2.0	
High	≥ 2.5	

[a] Good = diploid, -y, del(5q), del(20 q); Poor = chromosome 7 abnormalities or complex (≥ 3) abnormalities; Intermediate = all others.

By multivariate analysis, the most significant independent variables were percentage of bone marrow blasts, number of cytopenias, and cytogenetics (Table 2). It is important to keep in mind, however, that other variables (eg, age and prior therapy) not included in this system may alter prognosis and influence the results of therapy among patients in similar IPSS groups.

Treatment

The treatment of MDS is sometimes controversial. Suggested guidelines are outlined in Table 3 and discussed below.

Supportive care

The use of transfusions affords temporary benefits and is an alternative that can be considered in patients with lower-risk MDS or that otherwise can be used in conjunction with more definitive therapy.

Differentiation therapy

Differentiation therapy includes the use of such agents as retinoids and hexamethylene bisacetamide (HMBA).

TABLE 3: Suggested approach to the treatment of MDS

Diagnosis	Characteristics	Treatment
RA, RARS	IPSS score low or intermediate 1	Observation Supportive care (transfusions, growth factors?) New approaches (amifostine, ATG, AZA, DAC, antiapoptotic therapy, thalidomide)
RA, RARS	IPSS score intermediate 2 or high	Therapy with curative intent, eg, chemotherapy (topotecan or anthracycline + Ara-C), AZA, low-dose DAC, SCT(< 60 years old, HLA-identical sibling)
RAEB, RAEB-t CMML	All "Chronic phase"	Therapy with curative intent, eg, topotecan-based combinations, anthracyclines + Pgp-antagonist, oral camptothecins (topotecan, 9-NC), SCT
	Transformed	AML-like chemotherapy, (anthracyclines + Pgp-antagonist), SCT

AML = acute myelogenous leukemia; Ara-C = cytarabine; ATG = antithymocyte globulin; AZA = azacytidine; CMML = chronic myelomonocytic leukemia; DAC = decitabine; IPSS = International Prognostic Scoring System; 9-NC = 9-nitrocamptothecin; Pgp = *p*-glycoprotein; RA = refractory anemia; RAEB = refractory anemia with excess of blasts; RAEB-t = refractory anemia with excess of blasts in transformation; RARS = refractory anemia with ringed sideroblasts; SCT = stem-cell transplantation

In view of the evidence of increased angiogenesis in MDS patients, thalidomide (Thalomid) has been investigated in clinical trials. Eighty-three patients with MDS (36 with RA, 24: RAEB, 6: RAEB-t, 13: RARS, and 4: CMML) were treated with thalidomide, starting with 100 mg daily and increasing to 400 mg daily. Thirty-two (39%) of patients stopped therapy before 12 weeks. Although no complete or cytogenetic response was observed, 16 patients (19%) showed hematologic improvement (15: erythroid, 1: platelet), with 10 patients becoming transfusion independent. Responders had lower blast counts, shorter duration of pretreatment platelet transfusion requirements, and higher pretreatment platelet counts than nonresponders *(Raza A, Meyer P, Dutt D, et al: Blood 98:958-965, 2001)*.

Retinoids The use of oral 13-*cis*-retinoic acid (CRA, isotretinoin [Accutane]) has produced some responses among low-risk patients. However, it has been associated with significant toxicity when used at a high dose (100 mg/m^2/d) and has failed to show an improvement in survival. The addition of tocopherol has been reported to improve response and survival.

Cytokines

Recombinant human erythropoietin (rHuEPO [Epogen, Procrit]) has been reported to decrease transfusion requirements in 15%-25% of patients with MDS, usually those with low plasma levels of EPO (< 100 mU/mL). The addition of granulocyte colony-stimulating factor (G-CSF [Neupogen]) or GM-CSF to rHuEPO may increase the response rate, mostly in patients with low transfusion requirements. The benefit is frequently transient. IL-11 (at low doses of 10 µg/kg/d) has been used in patients with bone marrow failure disorders, including MDS. Among 11 patients with MDS, 4 (45%) had a platelet response and 1 had a multilineage response. The median platelet increase was 95×10^9/L. Thus, this approach may be beneficial for some patients.

IL-11 is a cytokine involved in thrombopoiesis currently used for management of postchemotherapy thrombocytopenia. Kurzrock et al treated 16 patients with MDS or other marrow failure disorders with low-dose IL-11 (10 µg/kg/d). Six patients (38%) had a platelet response, and two had a multilineage response; among MDS patients, five responded (one multilineage). Among responders, the median peak increase in platelet counts was 95×10^9/L (range 55 to 130×10^9/L). The responses lasted 12, 13, 14+, 25, 30, and 30+ weeks. There were no grade 3 side effects. This study suggests that low-dose IL-11 may be beneficial for some patients with MDS.

G-CSF and GM-CSF may improve neutropenia and decrease infections in up to 70% of MDS patients, but the effect is usually transient. No increase in the probability of developing AML has been demonstrated with extended use of these cytokines.

Other alternatives

Antithymocyte globulin (ATG [Atgam]) has been associated with response (defined as independence from transfusions) in 34% of patients, which was sustained for a median of 36 months in 81% of them. Also, 48% had a sustained platelet improvement and 55% had an increase in neutrophils. Younger

Thalidomide has modest activity in MDS. New thalidomide analogs are being investigated. They include selective cytokine inhibitory drugs (SelCIDs) and immunomodulatory drugs (IMiDs). The clinical activity of CC5013, an IMiD, has recently been reported. Fifteen patients with MDS who were transfusion dependent or had symptomatic anemia were treated. Six of 9 evaluable patients had an erythroid response, including 4 who became transfusion independent. Three of 5 evaluable patients had a cytogenetic response. The treatment had minimal nonhematologic toxicity *(List A, Kurtin S, Glinsmann-Gibson BJ, et al: Blood [abstract] 100:96a, 2002).*

patients and those with low platelet counts are more likely to respond than older patients and those with higher platelet counts.

Cyclosporine (Neoral, Sandimmune) significantly increases cell colony growth in laboratory studies of hypoplastic RA. Responses have been reported in a limited number of patients.

Amifostine (Ethyol) is a phosphorylated thiol amine first used as a cytoprotective agent for cisplatin (Platinol)-based chemotherapy. In vitro and clinical studies showed that amifostine stimulates normal hematopoiesis, with an increase in reticulocytes, hemoglobin levels, and platelet and WBC counts. Used as a single agent, it has been associated with a single- or multi-lineage hematologic improvement in 42% of patients with MDS.

Azacytidine and 5-Aza-2´-deoxycytidine (DAC, decitabine) are hypomethylating agents that have shown activity in MDS. In a randomized trial, 191 patients with MDS (63% RAEB or RAEB-t) were treated with azacytidine or supportive care. Responses were observed in 60% of those treated with azacytidine (CR: 6%; PR: 10%; improvement: 47%) compared with 5% with supportive care. There was a significant improvement in probability of transformation to AML and overall survival when the confounding effect of early crossover to azacytidine was eliminated. In a multicenter phase II study, 66 patients (73% RAEB or RAEB-t) were treated with decitabine. The overall response rate was 49% (CR: 20%; PR: 4%; improvement: 24%). The actuarial median response duration was 31 weeks and median survival was 22 months. In addition, 31% of patients with cytogenetic abnormalities presented before treatment achieved a cytogenetic response. Cytogenetic response conferred a survival advantage to these patients. These agents continue to be evaluated in clinical trials. Further evaluation of these drugs, alone or in combination, is needed.

Arsenic trioxide (ATO) has significant activity against acute promyelocytic leukemia. In vitro, it induces apoptosis in MDS. A phase II trial is currently evaluating the clinical activity of ATO in MDS. Thirty-two patients received ATO (0.25 mg/kg IV 5 d/wk for 2 weeks every 4 weeks). Six of 25 (24%) patients responded, including 1 patient (CMML) who achieved a PR, 3 patients with major erythroid hematologic improvement (HI) (2 with a decrease in blast count to < 5%), 1 with a major platelet HI, and 1 with a minor HI in neutrophils *(List A, Schiller G, Mason J, etal: Blood [abstract] 100:790a, 2002).*

Steroids, androgens, and pyridoxine are rarely effective, although they are often used clinically.

Chemotherapy

The rationale for this strategy stems from the concepts that MDS is a clonal disorder and that MDS and AML are overlapping illnesses with an arbitrary delineation resulting from the FAB classification (ie, a 30% blast threshold).

The Cancer and Leukemia Group B (CALGB) treated 874 AML and 33 MDS patients with AML-like chemotherapy. The CR rate was 79% for MDS patients vs 68% for AML patients ($P = .37$, median CR duration was 11 vs 15 months ($P = .28$), and median survival was 13 vs 16 months. The authors concluded that the FAB distinction between MDS (RAEB and RAEB-t) and AML has minimal therapeutic implications.

Estey et al treated 372 patients with AML, 52 with RAEB, and 106 with RAEB-t with AML-type chemotherapy. CR rates were 62% for patients with RAEB, 66% for those with RAEB-t, and 66% for those with AML ($P = .79$). Event-free survival was significantly better for patients with AML/RAEB-t than for patients with RAEB. However, when cytogenetics and other prognostic variables were considered in a multivariate analysis, no difference in outcome could be identified among FAB subgroups.

These findings suggest that the prognosis is determined more by cytogenetics and other prognostic features than by the percentage of blasts or FAB classification. However, this finding does not necessarily mean that MDS and AML are biologically equivalent entities.

Combination regimens Different combination chemotherapy regimens have been investigated. The combination of Ara-C and anthracycline is the cornerstone of intensive chemotherapy, leading to CRs in 40%-60% of patients. However, despite the fact that cytogenetic remissions generally accompany CRs, median remission duration and survival times are brief, rarely exceeding 1 year. The death rate during induction therapy is 5%-20%.

Myeloblasts in RAEB-t and secondary AML commonly express the multidrug exporter *p*-glycoprotein (Pgp), which extrudes anthracyclines and limits their activity. A recent randomized, controlled trial performed by the Southwest Oncology Group (SWOG) reported a twofold improvement in survival for patients treated with an anthracycline- and Ara-C-containing induction and consolidation regimens with the Pgp antagonist cyclosporine added.

It is possible that certain drugs can be more specific for use in MDS.

Topotecan (Hycamtin), a topoisomerase I inhibitor, has shown significant activity as a single agent in the treatment of MDS, with a CR rate of 37% in previously treated patients

Farnesyl transferase inhibitors (FTIs) have been investigated in MDS with promising results. R115777 was used in a phase I study to treat 18 patients with MDS with a starting dose of 300 mg twice daily for 21 days every 28 days. Six patients (33%) had an objective response *(Kurzrock R, Sebti S, Kantarjian H, et al: Blood [abstract] 98:623a, 2001)*. In a phase II study, 23 patients with high-risk MDS were treated with R11577 (600 mg twice daily for 28 days every 42 days). Two of 16 (13%) evaluable patients responded *(Kurzrock R, Cortes J, Ryback ME, et al: Blood [abstract] 98:848a, 2001)*. SCH66336 (lonafarnib), another FTI, was investigated in a phase I study; its starting dose was 200 mg twice daily. Six of 16 (38%) evaluable patients had clinical activity *(List A, DeAngelo D, O'Brien S, et al: Blood [abstract] 100:789a, 2002)*. In a phase II study, 3 of 15 patients with MDS treated with SCH66336 (200 mg twice daily) had a hematologic improvement, and 6 of 12 patients with CMML had normalization of monocytes *(Cortes J, Holyoake T, Silver R, et al: Blood [abstract] 100:793a, 2002)*.

with RAEB/RAEB-t and 27% in patients with CMML. Median CR duration was 7.5 months and survival was 10.5 months. Topotecan is well tolerated, with a death rate during induction therapy of < 5%.

Combinations of topotecan with Ara-C resulted in a 56% CR rate (66% in previously untreated patients). Similar CR rates were observed despite the risk category. This regimen is well tolerated, with an induction mortality of 7%. A randomized trial of topotecan and Ara-C vs idarubicin (Idamycin) and Ara-C showed that the topotecan combination was an equivalent regimen, possibly with lower toxicity.

A small fraction of patients with CMML have rearrangements involving the platelet-derived growth factor receptor β (PDGFβR). Several PDGFβR fusion genes have been identified, involving at least four known genes: TEL(ETV6), HIP1, H4(D10S170), and Rabaptin-5; they have been identified by translocations involving chromosome 5q33. These fusion genes lead to intrinsic activation of the tyrosine kinase activity PDGFβR. This process can be inhibited by imatinib, and clinical activity has been reported in patients with these abnormalities. Three patients with a t(5;12)(q33;p13) and the TEL(ETV6)/PDGFβR fusion gene and one with t(5;12)(q33;q13) with an unknown partner for PDGFβR were treated with imatinib. All achieved rapid hematologic and cytogenetic responses, and in all cases, the levels of the transcript decreased significantly *(Apperley JF, Gardembas M, Melo JV, et al: N Engl J Med 347:481-487, 2002)*. One patient with CMML and a t(5;17)(q33;p13.3) and the RAB5EP/PDGFβR fusion gene also responded dramatically to imatinib *(Magnusson MK, Meade KE, Nakamura R, et al: Blood 100:1088-1091, 2002)*. In contrast, patients with CMML or MDS without these fusion genes did not respond to imatinib *(Cortes J, Giles F, O'Brien S, et al: Blood [abstract] 100:800a, 2002)*.

SCT

Allogeneic SCT can be of benefit in a subset of MDS patients. However, most series have concentrated on younger patients, who constitute a minority of patients with MDS and frequently have favorable cytogenetics and therefore a better prognosis. The best results to date have been reported in patients with a better prognosis (ie, those with RA/RARS). In most series, allogeneic SCT is associated with a long-term remission rate of approximately 40%, a 30% relapse rate, and a 30% rate of transplant-related deaths.

The timing of transplantation remains controversial. Runde et al reported on a group of 131 patients (median age, 33 years; range, 2-55 years) who underwent allogeneic SCT as front-line therapy without prior induction chemotherapy. The 5-year disease-free survival rate was 34%, overall survival rate was 41%, and transplant-related mortality was 38%. The actuarial probability of relapse at 5 years was 39%, with better results observed in the RA/RARS subgroup.

Patients with adverse cytogenetics have a poor outcome with other treatment modalities, and SCT can be considered for such patients during first CR. However, the long-term outcome for these patients after SCT has not proved to be superior to that after any other approach, although the procedure appears curative in a small percentage of patients. Therefore, SCT should be considered in the setting of a research program.

New applications for allogeneic SCT (eg, nonmyeloablative) to make this option available to the typical MDS patient (who is frequently older and has

other associated medical problems), as well as matched-unrelated donor SCT, should be investigated further.

Autologous SCT In the majority of MDS patients, lymphocytes do not appear to be part of the clone, suggesting the presence of normal nonclonal stem cells. De Witte et al described 79 patients with MDS or secondary AML who underwent autologous SCT during first CR. The 2-year survival, disease-free survival, and relapse rates were 39%, 34%, and 64%, respectively. The 2-year survival rate for the MDS group was 40% and treatment-related mortality was 9%. The best outcome was seen among patients with RA/RARS.

BMT is an option for patients with CMML. A recent report on 50 adult patients with CMML included patients receiving graft from identical sibling (n = 38), related-matched (n = 1), related-mismatched (n = 5), or unrelated (n = 7) donors. The estimated 5-year probability of relapse was 49%, and disease-free survival was 18%. Patients who received T-cell–depleted grafts (n = 11) tended to have an increased probability of relapse (62%) compared with those who had no T-cell depletion (45%); patients who developed graft-versus-host disease (GVHD) had a 29% probability of relapse compared with 51% among those without GVHD *(Kroger N, Zabelina T, Guardiola P, et al: Br J Haematol 118:67-73, 2002).*

Treatment recommendations

Treatment of patients with MDS is an evolving and controversial issue, and enrollment in a clinical trial should be encouraged. Treatment can probably be designed according to the IPSS.

Patients with RA and RARS, particularly those with low- or intermediate-risk scores, can be treated with supportive measures, although the use of hematopoietic-promoting agents such as erythropoietin, amifostine, ATG, and thalidomide alone or in combination should be explored. Demethylating agents (azacytidine and decitabine) are promising alternatives. Patients with RA or RARS who have intermediate-2 or high-risk disease should probably be treated in the same manner as patients with RAEB and RAEB-t.

Patients with RAEB or RAEB-t are usually in the intermediate-2 and high-risk groups, with significant risk of mortality from cytopenias or AML evolution. They should be considered for treatment options with the intention to cure. Chemotherapy should be considered.

SCT is an alternative for younger patients in complete remission with an HLA-identical sibling, particularly patients with adverse cytogenetic abnormalities. However, the best results to date have been reported in patients with a better prognosis (ie, those with RA/RARS). Therefore, allogeneic transplantation and other transplant alternatives should be considered in a research setting (eg, mixed-unrelated donor, minitransplants, etc.).

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CHAPTER 38

Hematopoietic cell transplantation

Stephen J. Forman, MD

Hematopoietic cell transplantation (HCT) is the IV infusion of hematopoietic progenitor cells designed to establish marrow and immune function in patients with a variety of acquired and inherited malignant and nonmalignant disorders. They include hematologic malignancies (eg, leukemia, lymphoma, and myeloma), nonmalignant acquired bone marrow disorders (aplastic anemia), and genetic diseases associated with abnormal hematopoiesis and function (thalassemia, sickle cell anemia, and severe combined immunodeficiency). HCT also is used in the support of patients undergoing high-dose chemotherapy for the treatment of malignant diseases for which hematologic toxicity would otherwise limit drug administration (eg, breast, germ-cell, and ovarian cancers).

Types of transplantation

Since the advent of HCT in the 1960s, several different methods of transplantation have evolved. At present, the hematopoietic cells used for HCT are obtained from either bone marrow or peripheral blood. The decision to use a certain type of HCT is dictated by the patient's disease and condition and the availability of a donor. In some cases, more than one approach is possible. Table 1 summarizes the advantages and disadvantages of each stem-cell source.

Allogeneic BMT, matched related This method involves procurement of bone marrow from an HLA-identical sibling of the patient. In some cases, a partially matched sibling or family donor (one antigen mismatch) can be used for bone marrow transplantation (BMT).

Allogeneic BMT, matched unrelated Given that there are a limited number of alleles of the HLA system, typing of large numbers of individuals has led to the observation that full matches for patients exist in the general population. Tissue typing is performed on the patient's blood, and a search of the computer files of various international registries is made to determine whether a patient has a match with an unrelated individual.

Haploidentical transplantation involves the transplantation of large numbers of T cell-depleted stem cells from a donor, usually a sibling or a parent, who are half matched to the patient. Although these are the most difficult transplantations to perform successfully, there is great interest in this approach because most patients will have a donor in their family who is at least a 50% HLA

match. Although most transplants will engraft and few patients will have significant graft-vs-host disease (GVHD), the relapse rate is high and the process of immune reconstitution is quite slow, with patients often having troublesome infections for a long time after transplantation.

Autologous BMT This form of transplantation entails the use of the patient's own bone marrow, which is harvested and then cryopreserved prior to administration of chemotherapy and/or high-dose radiation therapy. Following completion of therapy, the marrow cells are then thawed and reinfused into the patient to reestablish hematopoiesis.

Autologous peripheral blood stem-cell transplantation With the recognition that the marrow stem cells circulate in the peripheral blood, methods have been devised to augment the number of these cells in the patient's circulation. The blood is then collected on a cell separator and frozen, similar to autologous marrow, to be utilized after high-dose chemotherapy and/or radiation therapy. This is now the most common source of stem cells used in the autologous setting.

Syngeneic transplantation In this form of transplantation, marrow or peripheral blood stem cells are procured from an individual who is a genetic identical twin to the patient.

Donor leukocyte infusion This method involves the infusion of mononuclear cells from the marrow donor into the recipient to treat relapse after transplantation. The cells can mediate an antitumor effect, known as a graft-vs-tumor effect (often in association with concomitant GVHD), and can achieve remission of the malignancy.

Nonmyeloablative or reduced-intensity transplantation This approach uses lower doses of chemotherapy, with or without total-body irradiation and immunosuppression, to facilitate engraftment of donor stem cells. Donor stem cells obtained from either the peripheral blood or marrow are then infused into the patient, leading to hematopoietic engraftment. The major therapeutic effect that results from this type of transplantation is a graft-vs-tumor effect, as the nonmyeloablative regimen has little antitumor efficacy. Some disorders such as chronic myelogenous leukemia (CML), low-grade lymphoma, and multiple myeloma are particularly sensitive to this approach.

Cord blood transplantation The blood in the umbilical cord of newborn babies contains large numbers of stem cells, which have been shown to be capable of long-term engraftment in children and some adults after transplantation. Similar to unrelated-donor registries, cord blood banks are now being developed to store cord blood cells that can be utilized for unrelated-donor transplantation. Given the immunologic immaturity of cord blood cells, these transplants can be accomplished even when there are disparities (mismatching) in the HLA typing between the donor and recipient. Cord blood transplants are generally used in situations where an adult unrelated donor cannot be identified through the international registries.

TABLE 1: Stem-cell sources for allogeneic BMT

Type	Advantages	Disadvantages
Allogeneic		
Sibling donor 6/6 HLA match or 5/6	Match able to be identified rapidly (2 weeks)	GVHD (25%-40%) for non–T-cell-depleted marrow grafts
(2%-5%)	Low rate of graft rejection	Only 30% of patients will have sibling donor
Matched-unrelated donor	Extends donor availability (60%-70% of patients will have potential match)	Takes time to find donor (6 weeks to > 6 months)
	Higher graft-vs-tumor effect	Higher graft failure rates (5%-10%)
		Higher GVHD rates (50%-60%)
Umbilical cord donor	Lesser degrees of match can be used	Limited number of cells (reduced applicability to large recipient)
		Slower engraftment
	Much lower rate of GVHD (10%-20%) despite one and two antigen mismatches	Higher rate of graft failure (10%)
		No chance for second infusion for graft failure or DLI for relapse
Haploidentical family donor	Almost all patients have a sibling, parent, or child who is haploidentical. These donors can be used if patient has relapsed or refractory disease and no better donor has been identified	Needs much more profound immunosuppression (T-cell depletion of donor product included) to achieve engraftment
		High risk of infectious complications
		Graft failure rate of 10%-15%
Syngeneic Identical twin	No need for immunosuppression	No graft-vs-tumor effect
	No GVHD	

DLI = donor lymphocyte infusion; GVHD = graft-vs-host disease

Allogeneic transplantation

HLA typing

Finding a related donor As noted above, matched-related allogeneic BMT involves a donor who is an HLA-matched sibling of the recipient. The formula for calculating the chances of a particular person having an HLA-matched sibling is $1 - (0.75)^N$, where N denotes the number of potential sibling donors. In general, a patient with one sibling has a 25% chance of having a match. The average American family size usually limits the success of finding a family donor to approximately 30% of patients.

HLA typing is performed on blood samples obtained from the patient and potential donor. Serologic methods have been used to detect the identity of the class I and II antigens; molecular methods are now utilized for more refined matching of both classes. A match is noted when the major class I antigens (A and B loci), as well as class II antigens (DR), are the same as those of the donor. Each sibling receives one set of antigens (A, B, DR) from each parent (chromosome 6). Genotypic identity can be confirmed by testing the parents and determining the inheritance of each set of antigens.

Finding an unrelated donor In cases in which the patient needs an allogeneic transplant and a donor cannot be found within the family, the identification of a matched-unrelated donor is accomplished by searching the computer files of the National Marrow Donor Program, as well as other international registries. As there are multiple alleles of any given HLA locus, serologic identity does not necessarily imply genotypic identity, such as is the case among sibling donor-recipient pairs. The development of oligonucleotide probes has greatly increased the precision of HLA typing and has allowed for more specific selection of bone marrow donors by matching molecular alleles of the class I and II antigens.

Advantages and disadvantages

The major advantages of an allogeneic graft include the absence of malignant cells contaminating the graft; the potential for an immunologic anticancer graft-vs-tumor effect; and the ability to treat malignant and nonmalignant disorders of the bone marrow, including genetic and immunologic diseases.

The disadvantages of an allogeneic transplant include the difficulty in finding an appropriate HLA-matched donor and the development after BMT of GVHD, which contributes to the morbidity and mortality of the procedure.

Autologous transplantation

Advantages and disadvantages

In autologous transplantation, the reinfused stem cells come from either the patient's own bone marrow or peripheral blood. These cells do not cause GVHD, and, thus, autologous transplantation is associated with less morbidity and mortality than allogeneic BMT and increases the number of patients who can undergo the procedure, as well as the upper age limit.

The disadvantages of autologous BMT include the likelihood of tumor cell contamination within the graft in many diseases, which can cause relapse; the lack of a significant therapeutic graft-vs-tumor effect; and the limited ability to use autologous stem cells in the treatment of patients not in remission or with inherited nonmalignant lymphohematopoietic diseases. Table 2 summarizes the advantages and disadvantages of these two approaches.

TABLE 2: Comparison of allogeneic vs autologous stem-cell transplantation

Allogeneic
Advantages
No tumor contamination of the graft and no prior marrow injury from chemotherapy (less risk of later myelodysplasia)
Graft-vs-tumor effect
Can be used for patients with marrow involvement by tumor or with bone marrow dysfunction, such as aplastic anemia, hemoglobinopathies, or prior pelvic irradiation
Disadvantages
Dose-intensive regimen limited by toxicity (usually limited to patients < age 55)
Takes time to identify donor if no sibling donor available/limited availability of donor for some ethnic groups
Higher early treatment-related mortality from graft-vs-host disease and infectious complications (20%-40% depending on age and donor source)
Autologous
Advantages
No need to identify donor if peripheral blood marrow uninvolved by tumor at time of collection
No immunosuppression = less risk of infections
No graft-vs-host disease
Dose-intensive therapy can be used for older patients (usually up to age 70)
Low early treatment-related mortality (2%-5%)
Disadvantages
Not feasible if peripheral blood stem cells/marrow involved
Possible marrow injury leading to late myelodysplasia (either from prior chemotherapy or transplant regimen)
No graft-vs-tumor effect
Not all patients can be mobilized to give adequate cell doses for reconstitution

Modifications of the stem-cell graft

The disadvantages of both allogeneic and autologous transplantation have led to the development of modifications of the stem-cell graft.

Removing T cells from donor marrow With regard to allogeneic BMT, it is known that contaminating T cells from the donor mediate the onset and persistence of GVHD. T cells have been removed from the donor marrow in an attempt to prevent the development of severe GVHD. However, this approach has increased the incidence of both graft rejection and relapse of malignancy. Some investigators are exploring planned add-back of donor T cells after hematopoietic recovery to help prevent relapse.

Primed peripheral blood stem cells from marrow donors are currently undergoing exploration to determine their effect on transplant-related complications and GVHD. Thus far, the data show that this approach induces more rapid engraftment without increasing acute GVHD. However, some studies have reported an increase in chronic GVHD.

Eliminating tumor cells from autologous grafts Although autologous peripheral blood stem-cell transplantation has led to more rapid restoration of hematopoiesis, it is associated with a higher relapse rate than allogeneic BMT. Attempts to deplete the autologous graft of tumor cells have included in vitro purging with monoclonal antibodies and/or chemotherapeutic agents and the enrichment of stem cells over various separation columns.

Post-transplantation immunomodulation For patients undergoing autologous transplantation, several post-transplantation immunomodulating strategies—eg, cyclosporine (Neoral, Sandimmune) and interleukin-2 (IL-2, aldesleukin [Proleukin])—are being tested to determine whether they will decrease relapse by augmenting immunologic antitumor responses following transplantation.

Collection of the graft

Although busulfan-based regimens are the most commonly used worldwide for allogeneic transplantation, the oral administration of the drug leads to unpredictable absorption, which has been correlated with relapse (low absorption) and increased toxicity (increased absorption). Recent studies with an intravenous formulation of the drug have shown much more predictable pharmacokinetics, less toxicity, and good survival when utilized in the transplantation regimen.

Allogeneic bone marrow cells Current techniques for harvesting bone marrow involve repeated aspirations from the posterior iliac crests, designed to obtain adequate numbers of cells that can lead to hematopoiesis. While the donor is under general or spinal anesthesia, between 1 to 3×10^8 cells/kg of the recipient's body weight are procured. The procedure has no long-term side effects and poses little risk if care is taken to ensure that the donor has no confounding medical conditions. In most cases of ABO incompatibility, the marrow can be treated to remove RBCs in order to prevent lysis after infusion.

Autologous peripheral stem cells Collection of circulating peripheral blood progenitor cells is performed via an apheresis technique. Although this procedure can be accomplished in an individual with baseline blood count, the number of cells and the efficiency of collection are increased if the cells are procured during WBC recovery following chemotherapy or after the administration of hematopoietic growth factors.

The most effective strategy appears to be the collection of cells after both chemotherapy and administration of growth factors. In most circumstances, adequate numbers of cells can be collected utilizing granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) or granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine]) to prime the patient prior to one to three apheresis procedures.

Currently, the adequacy of the number of hematopoietic stem cells is assessed by determining the number of cells that have the CD34 antigen (stem-cell) marker. Usually, a minimum of 2×10^6 CD34 cells/kg of body weight is required to ensure engraftment.

The use of autologous stem cells continues to undergo refinement. Approaches under study include ex vivo expansion to augment the number of progenitor cells, as well as techniques that separate hematopoietic cells from any potential contaminating tumor cells. In addition, hematopoietic stem cells are the usual targets of marrow-based gene therapy utilizing viral vectors for transduction of cells prior to cryopreservation.

Indications for transplantation

The expanded methods of stem-cell transplantation have complicated the choice for patients and their physicians among the different types of transplantation in some instances. Therefore, the decision requires evaluation of the patient and the disease involved. In general, for disorders that require replacement of an abnormally functioning hematopoietic system, such as thalassemia and aplastic anemia, an allogeneic transplantation is performed. However, as genetic therapy for hematopoietic stem cells becomes more of a reality, even patients with these diseases may be candidates for autologous transplantation after gene modification (adenosine deaminase deficiency, chronic granulomatous disease).

Hematologic malignancies The most common use of allogeneic BMT has been for the eradication of hematologic malignancies, such as leukemia and non-Hodgkin's lymphoma. For some disorders (aplastic anemia, myelodysplasia, leukemia in relapse, CML, allogeneic transplantation is the only significant therapeutic option, whereas for other diseases (acute myelogenous

TABLE 3: Disease sensitivity to a graft-vs-malignancy effect

Most sensitive
Chronic myelogenous leukemia
Low-grade lymphoma
Mantle cell lymphoma
Chronic lymphocytic leukemia
Intermediate
Acute myelogenous leukemia
Intermediate-grade lymphoma
Multiple myeloma
Renal cell carcinoma
Least sensitive
Acute lymphoblastic leukemia
High-grade lymphoma
Hodgkin's disease(?)

TABLE 4: Acute and long-term toxicities of common preparative agents used for BMT

Agent	Acute toxicity	Long-term toxicity
Total-body irradiation	Nausea, vomiting, enteritis, mucositis	Cataracts, sterility, pneumonitis
Cyclophosphamide	Nausea, vomiting, hemorrhagic cystitis, cardiac toxicity	Sterility, leukemia
Etoposide	Skin rash, hypotension, acidosis, mucositis	Leukemia
Carmustine (BiCNU)	Seizures, nausea, vomiting, headaches	Interstitial pneumonitis
Busulfan	Seizures, nausea, vomiting, veno-occlusive disease	Alopecia, pulmonary fibrosis
Cisplatin	Renal impairment, hearing loss, tinnitus	Hearing loss, tinnitus, neuropathy
Thiotepa	Nausea, vomiting, CNS changes, veno-occlusive disease	—
Paclitaxel	Allergic reactions	Neuropathy
Fludarabine	Hemolytic anemia	Prolonged immune suppression, EBV-related lympho-proliferative disorder
Melphalan	Nausea	Peripheral neuropathy

EBV = Epstein-Barr virus

leukemia in remission, lymphoma, Hodgkin's disease, multiple myeloma), either autologous or allogeneic marrow grafting may be possible.

Nonmyeloablative or reduced-intensity transplantation approaches are being studied worldwide, which has facilitated transplantations for many people who otherwise would not have been candidates due to concomitant medical problems or older age. The results indicate that malignancies that are not rapidly progressive are the most responsive. Thus, patients with low-grade lymphoma, myeloma, myelodysplasia, and CML are probably good candidates for this type of allogeneic transplantation, whereas those with advanced disease such as leukemia in relapse or high-grade lymphoma benefit less, as the allogeneic antitumor effect requires time to develop and achieve remission of the disease. Table 3 shows the relative sensitivity of different hematologic malignancies to a graft-vs-malignancy tumor effect that could be mediated by a nonmyeloablative transplant.

Solid tumors In general, only autologous transplantation is utilized for some solid tumors, such as breast, germ-cell, and ovarian cancers. Studies and longer follow-up of recently completed trials are continuing to determine whether there is a benefit in the use of transplant-based approaches in the treatment of high-risk (stages II, IIIA, IIIB) and metastatic (stage IV) breast cancer. Re-

markably, recent studies have shown that renal cell carcinoma can be treated successfully utilizing nonmyeloablative allogeneic transplantation.

Timing of transplantation

The Goldie-Coldman model proposes that the probability that a tumor contains treatment-resistant cells is a function of its size and inherent mutation rate. This finding suggests that the likelihood of cure is greatest when marrow transplantation is performed early in the natural history of an inherently chemosensitive tumor. Studies to date indicate that patients undergoing transplantation late in their disease course have inferior disease-free survival, compared with those who undergo transplantation early.

Phases of transplantation

PREPARATIVE PHASE

In the first phase of marrow transplantation, the preparative phase, patients receive high-dose chemotherapy and/or radiation therapy (sometimes referred to as a conditioning regimen).

Allogeneic transplantation The conditioning regimen used in the allogeneic setting has both a therapeutic component designed to eliminate tumor cells and an immunosuppressive component to prevent host immune responses from rejecting the transplanted donor graft. The doses of radiation and chemotherapy employed take advantage of the steep dose-response curve that exists for many malignancies. The doses have been established based on the limitations of other nonhematopoietic organs, such as the liver and lungs.

Typically, preparative regimens for allogeneic BMT consist of total-body irradiation (TBI) and/or chemotherapeutic agents (cyclophosphamide [Cytoxan, Neosar], busulfan [Myleran], and etoposide). The most commonly used regimens are (1) TBI (1,200-1,400 cGy administered in multiple fractions over a period of days) and cyclophosphamide (60 mg/kg for 2 days); (2) fractionated TBI and etoposide (60 mg/kg); or (3) busulfan (16 mg/kg over 4 days) and cyclophosphamide (60 mg/kg for 2 days).

Autologous transplantation For patients undergoing autologous transplantation, stem cells are reinfused following high-dose therapy to reestablish hematopoiesis as rapidly as possible. The regimens used for autologous BMT depend on the disease being treated.

Toxicities of preparative regimens The acute toxicities of irradiation and chemotherapy include nausea and vomiting, which can be managed by prophylactic use of antiemetics, particularly serotonin antagonists. Busulfan can cause seizures; prophylactic phenytoin (Dilantin) is effective in preventing this complication. Both cyclophosphamide and etoposide require forced hydration to reduce toxicities. Table 4 lists the acute and long-term toxicities of the major agents used in BMT preparative regimens.

TABLE 5: Clinical classification of acute GVHD according to organ injury

Level of injury	Organ injury		
	Skin	**Liver (bilirubin)**	**GI tract**
1	Maculopapular rash on < 25% of body surface	2-3 mg/dL	500-1,000 mL of liquid stool per day
2	Maculopapular rash on 25%-50% of body surface	> 3-6 mg/dL	1,000-1,500 mL of liquid stool per day
3	Generalized erythroderma	> 6-15 mg/dL	>1,500 mL of liquid stool per day
4	Generalized erythroderma with formation of bullae and desquamation	> 15 mg/dL	Severe abdominal pain with or without ileus

Clinical grade[a]	Organ injury		
	Skin	**Liver (bilirubin)**	**GI tract**
I	1 or 2	0	0
II	1-3	1	1
III	2 or 3	2 or 3	2 or 3
IV	2-4	2-4	2-4

[a] Grade II or higher requires skin injury plus liver and/or GI tract injury. Grade IV requires an extreme decrease in performance status.

TRANSPLANT PHASE

After completion of the preparative regimen, there is a day or more wait before reinfusion of marrow or peripheral blood stem cells. This delay allows for elimination of any active drug metabolites so that the reinfused cells are not injured by any remaining drug.

Minimal toxicities are associated with the infusion. They include headache, nausea, and dizziness. Dizziness is related more to the cryoprotectant dimethyl sulfoxide (DMSO) used to store cells from most patients undergoing autologous transplantation.

SUPPORTIVE CARE PHASE

Following administration of the preparative regimen and during and after marrow transplantation, all patients require strict attention to infectious disease-related complications secondary to neutropenia. The duration of neutropenia following transplantation increases the risk of complicating infections. Patients undergoing full allogeneic transplantation usually require more stringent isolation, whereas patients undergoing autologous transplantation need less rigorous protection. With the availability of more effective antiemetics (eg, ondansetron [Zofran] and granisetron [Kytril]), portions of the transplantation can now be performed in the outpatient setting.

Following allogeneic transplantation, various complications may develop that require treatment. For some complications, prophylactic measures can be instituted to prevent their occurrence.

Neutropenic sepsis

Nearly all patients undergoing transplantation will develop fever, often with positive blood cultures, within 7 days of becoming neutropenic. Sepsis usually is caused by enteric bacteria or those found on the skin, and antibiotic choices are based on initial assessment and the results of blood cultures. The antibiotics chosen are continued until the WBC count begins to rise (> 500 k/μL neutrophils). Most patients undergoing allogeneic transplantation usually receive bowel decontamination (eg, with a fluoroquinolone, such as levofloxacin [Levaquin], 500 mg/d PO) in the post-transplantation phase to reduce the risk of serious infection during neutropenia.

Prevention of fungal infections For patients who are expected to have prolonged neutropenia, various methods of antifungal prophylaxis are used, including low-dose IV amphotericin B (Fungizone; 5-10 mg/d), IV or PO fluconazole (Diflucan; 200 mg bid), or voriconazole (Vfend; 200 mg IV or PO bid). For patients who continue to have a high fever despite systemic antibiotics, the dose of IV amphotericin B is usually increased to 25-30 mg/d, depending on renal tolerance, and is continued until the neutrophil count recovers. The use of liposomal amphotericin B (AmBisome or Abelcet) formulations has improved safety and toxicity of antifungal therapy and is particularly worthwhile in patients with renal compromise.

Mucositis, nausea, and anorexia

Regimen-related toxicity often results in severe oral mucositis, nausea, and anorexia. Patients often require supplemental parenteral nutrition to maintain adequate caloric intake during this period. Because of the mucositis, enteral feedings are usually not employed, and total parenteral nutrition is maintained until the patient is able to eat. Studies are exploring novel agents that could prevent severe mucositis or accelerate healing with keratinocyte growth factor (KGF).

Oral HSV reactivation

Nearly all patients who are seropositive for herpes simplex virus (HSV) will have a reactivation of the virus, which can accentuate the pain and oral discomfort following BMT. To prevent this problem, most transplant programs utilize acyclovir (Zovirax) at a dose of 250 mg/m^2 tid during the neutropenic phase.

The ideal therapy for preventing reactivation of the virus after transplant is the infusion of cytomegalovirus (CMV)-specific T cells during the early post-transplantation risk period. Studies have shown that the infusion of donor-derived CMV-specific T cells can alter the natural history of infection and protect many patients from CMV disease, eliminating the need for antiviral drugs. Numerous studies are ongoing to develop this approach to treating viral disease after transplantation, including immunization of the donor so that an augmented immune system is transplanted into the patient.

TABLE 6: Prophylaxis of acute graft-versus-host disease

Day	Cyclosporine	Methotrexate
-2	5 mg/kg IV daily	
+1	5 mg/kg IV daily	15 mg/m^2 IV single dose
+3	5 mg/kg IV daily	10 mg/m^2 IV single dose
+4	3 mg/kg IV daily	
+6	3 mg/kg IV daily	10 mg/m^2 IV single dose
+11	3 mg/kg IV daily	10 mg/m^2 IV single dose
+15	2.75 mg/kg IV daily	
+36	10 mg/kg PO daily	
+84	8 mg/kg PO daily	
+98	6 mg/kg PO daily	
+120	4 mg/kg PO daily	
+180	off	

Transfusion

All patients will require both RBCs and platelets in proportion to the duration of the pancytopenia. Platelets are kept over 10,000-20,000/μL because of complicating bleeding from mucositis, although, in some instances, a lower threshold is feasible. Patients no longer receive granulocyte transfusions unless they have uncontrolled sepsis with positive blood cultures. For patients who are negative for cytomegalovirus (CMV) and who have a CMV-negative donor, CMV-negative cell support is generally provided (see "CMV infection" section).

All blood products are irradiated to prevent engraftment of lymphoid cells and are often filtered to reduce CMV or alloimmunization and febrile reactions. Most patients receive single-donor platelet pheresis products, which may need to be HLA-matched if the patient shows evidence of refractoriness to the transfusion (ie, if platelets fail to rise after transfusion).

Veno-occlusive disease

In the first few weeks after BMT, a syndrome of veno-occlusive disease (now called sinusoidal obstruction syndrome), characterized by hepatomegaly, jaundice, and fluid retention, develops in 5%-20% of patients. It is caused by damaged endothelial cells, sinusoids, and hepatocytes and is related to the intensity of the cytoreductive therapeutic regimen.

The diagnosis of veno-occlusive disease is usually made on clinical grounds, based on the occurrence (usually within 8-10 days after starting the cytoreductive regimen) of the triad of hepatomegaly, weight gain, and jaundice. Patients also exhibit renal sodium retention, and prognosis is related to the degree of liver and kidney dysfunction and the level of bilirubin. The use of regimens that contain busulfan has been associated with the highest incidence of veno-occlusive disease.

Treatment Once veno-occlusive disease has occurred, treatment is primarily supportive, consisting of careful management of fluid overload, kidney dysfunction, and other attendant complications. In few cases, the early use of thrombolytic agents can reverse established veno-occlusive disease. Defibrotide is now being tested as an agent that can help reverse the syndrome.

Acute GVHD

GVHD is a clinical syndrome that results from the infusion of immunocompetent lymphocytes accompanying the marrow graft that are capable of recognizing minor HLA-related antigens in the host and initiating an immunologic reaction. This syndrome may arise after allogeneic transplantation or rarely after transfusion of cellular blood products in patients who are immunodeficient and share HLA loci that allow engraftment of transfused cells. For unknown reasons, the primary organs affected by acute GVHD are the skin, liver, and GI tract.

The syndrome usually occurs within 20-60 days after transplantation and can vary in severity. Table 5 shows a commonly used grading system for GVHD. This system has both therapeutic and prognostic importance.

Prophylaxis All patients undergoing non–T-cell-depleted transplantation require some form of GVHD prophylaxis. The most common regimens involve a combination of methotrexate and cyclosporine or FK506 (tacrolimus [Prograf]), or cyclosporine and prednisone. Cyclosporine, in the absence of GVHD, is tapered over 6-12 months after BMT. Table 6 shows a common regimen used to prevent GVHD after an allogeneic sibling transplantation.

Treatment Despite prophylaxis, many allogeneic transplant recipients still develop some degree of GVHD and require increasing doses of prednisone (1-2 mg/kg/d). For patients who do not respond to steroids, antithymocyte globulin (10 mg/kg/d for 5-10 days) has been used. Daclizumab (Zenapax; 1 mg/kg on days 1, 4, 8, 15, and 22) is likely a more effective agent than antithymocyte globulin.

Chronic GVHD

Chronic GVHD may occur within 3-6 months in patients who have undergone allogeneic marrow transplantation. It is often preceded by acute GVHD, which may or may not have resolved. Although chronic GVHD is also related to infusion of T cells with the marrow graft, it resembles other autoimmune connective tissue diseases, such as scleroderma, Sjögren's syndrome, biliary cirrhosis, and bronchiolitis obliterans. Patients with chronic GVHD often have accompanying cytopenias and immune deficiency.

Treatment Chronic GVHD is generally treated with prolonged courses of steroids, cyclosporine, FK506, and, occasionally, azathioprine (Imuran) and other modalities, such as psoralen-ultraviolet A light (PUVA) for skin and mouth GVHD. Thalidomide (Thalomid), mycophenolate (CellCept), rapamycin, and photopheresis have also been employed, with varying response rates. Like that for acute GVHD, the prognosis for chronic GVHD is related to the extent of organ compromise and response to treatment.

GVHD and relapse Although, in general, GVHD has contributed to significant morbidity and mortality in patients undergoing allogeneic marrow transplantation, it is also associated with reduced relapse rates, primarily in patients with hematologic malignancies.

Late infections

Late infections after BMT are caused by impaired cellular and humoral immunity. The most common late pathogens include *Pneumocystis carinii*, varicella zoster, and encapsulated bacteria.

***Pneumocystis* prophylaxis** All patients undergoing allogeneic transplantation require prophylaxis against *P carinii*. This can be accomplished with 1 double-strength trimethoprim-sulfamethoxazole tablet bid twice a week once hematopoiesis has been restored. Alternatively, inhaled pentamidine (NebuPent, Pentam 300) has been utilized, but due to failures with this approach, it is not preferred.

Treatment of herpes zoster Approximately 40% of patients will develop herpes zoster (either dermatomal or disseminated), which is often treated with oral or IV acyclovir. A patient may complain of severe localized pain for several days before the rash develops. The use of valacyclovir (Valtrex) for 1 year after BMT can reduce the risk of reactivation of herpes zoster after allogeneic BMT.

Bacterial prophylaxis Many patients with chronic GVHD develop an accompanying severe immunodeficiency syndrome that leaves them susceptible to infection with encapsulated bacteria, primarily in the sinuses and lungs. In some cases, prolonged prophylaxis with trimethoprim-sulfamethoxazole or penicillin is necessary, as well as immunoglobulin replacement.

CMV infection

Historically, CMV interstitial pneumonia has been responsible for approximately 15%-20% of patient deaths following allogeneic marrow transplantation. CMV pneumonia occurs 7-10 weeks after BMT and is due to reactivation of latent CMV in the patient or is acquired from donor marrow or transfusions. Active CMV infection, GVHD, and the inability to develop a virus-specific immune response that limits viral infection are risk factors for CMV pneumonia.

Diagnosis Infection is detected by the combination of an abnormal chest x-ray, hypoxemia, and the detection of CMV in bronchoalveolar lavage or lung biopsy specimens, as well as the absence of other pathogens.

Treatment The only consistent treatment has been the combination of ganciclovir (Cytovene), 5 mg/kg bid for 3 weeks, and IV immunoglobulin, given every other day. Although the reason for the synergy between these agents is unclear, neither one alone is effective in reversing pneumonia once it has developed.

Prevention in CMV-seronegative patients The most successful means of preventing CMV infection in CMV-seronegative patients who have a seronegative donor is to limit their exposure to the virus by providing CMV-negative blood and platelet support. As most patients who undergo marrow transplan-

tation are seropositive, this strategy has limited application. However, the presence of leukocytes in blood products increases the transmission of CMV. Thus, the use of CMV-seronegative blood products in CMV-seronegative recipients decreases the incidence of primary CMV infection. Also, CMV status should be determined in all patients prior to BMT in order to plan for post-transplantation transfusion strategies.

Prevention in CMV-seropositive patients The most effective strategy for preventing reactivation of CMV infection in patients who are seropositive is the preemptive use of ganciclovir, either prophylactically in all seropositive patients or at the first sign of CMV after transplantation (as indicated by blood culture, shell viral culture, or antigen or polymerase chain reaction [PCR] detection of the virus). The timing and duration of prophylaxis are somewhat controversial.

Ganciclovir has been the most effective agent for both strategies, as it significantly reduces both virus reactivation and associated disease. However, if one waits until after virus reactivation to initiate ganciclovir therapy, there are some patients who will not benefit from a prophylactic strategy, namely those in whom reactivation occurs simultaneously with disease. Ganciclovir has many side effects, including neutropenia and elevated creatinine levels, and thus exposes a large number of patients to potential toxicity.

The required duration of ganciclovir treatment is also unclear, but it would appear that at least 6 weeks is necessary to protect the patient from reactivation and the development of pneumonitis within the first 3 months after BMT. Some patients have developed a late CMV pneumonia after drug discontinuation that is probably related to ganciclovir inhibition of the development of CMV-specific cytolytic T cells. Nevertheless, the use of ganciclovir has reduced the problems related to CMV pneumonia and should be a part of every management strategy for preventing complications following allogeneic transplantation.

Other post-transplantation therapies

Growth factors have found their most significant use in the acceleration of hematopoietic recovery after autologous reinfusion of stem cells. Clinical trials in allogeneic transplantation have not yet shown an advantage to their use, probably due to the immunosuppressive medications used to prevent GVHD. Studies do support the use of G-CSF or GM-CSF after autologous marrow transplantation, although the impact of these growth factors on acceleration of hematopoietic recovery, beyond that achieved with the use of primed autologous stem cells, is still under investigation.

IL-2 also is being explored as a post-transplantation immunomodulating agent to increase immune tumor surveillance and possibly decrease relapse due to either surviving tumor cells in the patient or cells that were infused with the marrow graft.

Erythropoietin (Epogen, Procrit) is sometimes used in patients who have persistent anemia after transplantation.

Management of relapse

Despite the intensity of the preparative regimen, some patients relapse after allogeneic BMT. For patients with CML, withdrawal of immunosuppression to allow for an augmented graft-vs-tumor effect sometimes leads to remission. Other CML patients may respond to post-transplantation interferon, which appears to be a very useful approach. Intriguingly, infusion of donor lymphoid cells in CML patients is an effective means of inducing hematologic and cytogenetic responses in those who have relapsed after transplantation; this approach has led to complete and durable remissions.

Some patients with acute myelogenous leukemia have responded to either infusion of donor stem cells or the combination of chemotherapy and donor stem cells. Patients with acute lymphoblastic leukemia have had the lowest response rate to this strategy. Patients who develop myelodysplasia after autologous transplant can sometimes be treated with an allogeneic transplantation to restore normal hematopoiesis.

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CHAPTER 39

Pain management

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Most patients with advanced cancer and up to 60% of patients with any stage of the disease experience significant pain. The World Health Organization (WHO) estimates that 25% of all cancer patients die with unrelieved pain.

The cause of cancer pain should be treated whenever possible. By doing so, one can frequently achieve rapid, lasting pain relief and may prevent the problems associated with untreated progressive disease, such as spinal cord compression and pathologic fracture. Also, the need for pain medications may be diminished, thus reducing side effects and drug interactions.

In most cancer patients, pain can be relieved adequately, and yet it is undertreated for a multitude of reasons. The problem is not trivial, as unrelieved pain is known to be a risk factor for suicide in cancer patients. Current efforts are being directed toward standardizing pain treatment and separating issues of pain treatment from those of substance abuse.

The effective management of cancer patients with pain is best accomplished with coordination of the services of multidisciplinary professionals, community volunteers, and the family.

Pathophysiology

Pathophysiologic classification of pain forms the basis for therapeutic choices. Pain states may be broadly divided into those associated with ongoing tissue damage (nociceptive) and those resulting from nervous system dysfunction in the absence of ongoing tissue damage (non-nociceptive or neuropathic).

Damage to the nervous system may result in pain in an area of altered sensation. Such pain is typically described as burning or lancinating. Patients may report bizarre complaints, such as painful numbness, itching, or crawling sensations. The postamputation phenomenon of phantom pain (pain referred to the lost body part) may be disabling.

Psychological factors Psychological factors may affect the reporting of pain. Chronic unrelieved pain has psychological consequences, but this does not support a psychiatric basis for the pain complaint. "Psychogenic pain" or somatoform pain disorder is rare in cancer patients.

Pain syndromes

Cancer pain syndromes vary by tumor type and are related to patterns of tumor growth and metastasis. Pain may also be related to antineoplastic therapy or may be unrelated to either the neoplasm or its treatment.

Elements of management

Elements of cancer pain management include a proper medical evaluation, psychosocial assessment, formulation of the pain "diagnosis," and consideration of pharmacologic and nonpharmacologic treatments. Ongoing care is needed to monitor the efficacy of analgesics and the evolution of different symptoms during treatment or disease progression.

The steps in medical decision-making are to:

- determine whether primary antineoplastic therapy is indicated for palliation
- tailor pharmacologic analgesic therapy to individual needs
- consider concurrent nonpharmacologic analgesic methods
- monitor response and modify treatment accordingly (Figure 1)

The patient is the focus of care, although family members and others often participate in treatment decisions and require emotional support.

Medical evaluation

Pain history Begin with a thorough history. As there are no objective means with which to verify the presence of pain, one must believe a patient's complaint. The physiologic signs of acute pain—elevated blood pressure and pulse rate—are unreliable in subacute or chronic pain.

Most cancer patients report more than one site of pain. A detailed history of each type of pain should be elicited (Table 1). As the chief complaint resolves, what was initially a secondary problem may require attention.

Pain-rating scales should be used to establish a baseline against which the success of treatment may be judged (Figure 2). Behavioral observations may be used to assess patients who are unable to communicate. Although there are standardized tools for preverbal children, they are not available for impaired adults. Thus, it is sometimes necessary to treat pain presumptively.

The physical examination includes careful neurologic testing, especially if neuropathic pain is suspected. Pain in an area of reduced sensation, allodynia (ie, when normal stimuli are reported as painful), and hyperpathia or summation of painful stimuli indicate a neuropathic process. The assessment should evaluate the putative mechanisms that may underlie the pain.

Review of disease extent and current conditions The extent of disease and current medical conditions must be determined.

FIGURE 1: Algorithm for the integration of management approaches to cancer pain

[a] For a discussion of the WHO analgesic ladder, see pages 772-773.

Adapted from Foley KM, Arbit E, in DeVita VT, Hellman S, Rosenberg SA (eds): Cancer: Principles & Practice of Oncology, 3rd ed, vol 2, pp 2064-2087. Philadelphia, JB Lippincott, 1989.

TABLE 1: Features of the pain history—"PQRST"

P	Provocative factors, palliative factors
Q	Quality (characteristics)
R	Region, pattern of radiation, referral
S	Severity, intensity (use pain-rating scales [Figure 2])
T	Temporal factors: onset, duration, time to maximum intensity, frequency, daily variation

Diagnostic tests should be reviewed and supplemented as necessary.

Treatment and drug history Cancer treatment and prior analgesic interventions, along with their outcomes, should be recorded. Psychological dependency on licit or illicit drugs, including alcohol, must be identified.

Psychosocial assessment

To establish trust, the evaluating clinician should explore with the patient the significance of the pain complaint. The impact of pain and other symptoms on functional status must be understood to establish treatment goals. Suffering may be attributable to many factors besides physical complaints. The clinician should ask about such psychological factors as financial worries, loss of independence, family problems, social isolation, and fear of death. Often, cancer patients meet diagnostic criteria for the psychiatric diagnosis of adjustment disorder with anxiety and/or depressed mood.

Patient subgroups

To help define therapeutic goals, the patient's age and prognosis may be considered. Adjustments in drug doses are usually needed for elderly patients, who are more sensitive to analgesics and their side effects. Adolescents may require relatively larger doses of opioids. Pain in children is underreported and should be specifically elicited using age-appropriate assessment tools.

Pharmacologic treatment

The WHO has devised a three-step analgesic ladder outlining the use of nonopioid analgesics, opioid analgesics, and adjuvant medications for progressively severe pain. According to this schema, a nonopioid analgesic, with or without an adjuvant agent, should be tried first (step 1). If pain persists or increases on this regimen, the patient should be switched to an opioid plus a nonopioid agent, with or without an adjuvant medication (step 2). If pain continues or intensifies despite this change in therapy, a strong opioid analgesic should be prescribed, with or without a nonopioid and/or an adjuvant agent (step 3).

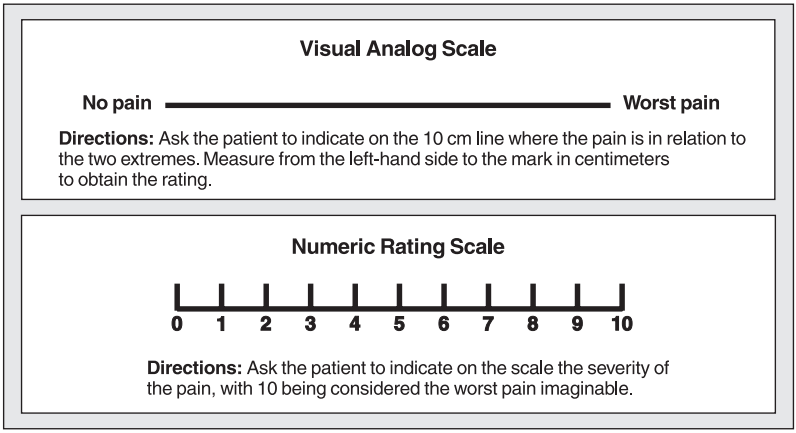

FIGURE 2: Pain-rating scales used to establish a baseline against which treatment results are judged

Nonopioid analgesics

Nonopioid analgesics are associated with ceiling effects, and exceeding the maximum dose ranges can result in organ toxicity. Potential side effects, such as hematologic, renal, and GI reactions, may be of clinical concern in cancer patients (Table 2). Cyclooxygenase type 2 (COX-2) inhibitors are many times more potent against COX-2 than COX-1. Their safety profile may be better than that of other nonsteroidal anti-inflammatory drugs (NSAIDs).

Opioid analgesics

General guidelines for the use of opioid therapy are outlined in Table 3.

Dosage Opioid agonists do not exhibit ceiling effects. Dosing is guided by efficacy and limited by side effects (Table 4). Dosages of tablets combining a NSAID or acetaminophen and an opioid are limited according to the nonopioid component.

Routes of administration The oral route should be used when possible, though some patients may express a preference for an alternative route. If so, or if the oral route is infeasible or systemic side effects are uncontrollable, alternative routes are indicated, such as transdermal, transmucosal, rectal, and neuraxial infusion. Such alternative routes of administration of certain opioid agonists (see Table 5) may improve patients' quality of life and may be particularly useful for treating certain types of cancer pain.

Side effects of opioids can usually be anticipated and treated. In particular, with regular opioid dosing, laxatives should be prescribed for constipation.

TABLE 2: Nonopioid analgesics and NSAIDs useful for treating cancer pain

Generic name (usual dosage range)	Maximum dose/day	Adverse effects/ comments
Acetaminophen (325-975 mg q4-6h)	4,000 mg	Hepatic and renal impairment
Acetylsalicylic acid (aspirin, ASA) (325-975 mg q4-6h)	4,000 mg	Dyspepsia and GI ulceration, antiplatelet effect, bleeding
Celecoxib	400 mg	[a]
Choline magnesium trisalicylate (500-1,500 mg q8-12h)	4,500 mg	Dyspepsia, reduced antiplatelet effect, hypermagnesemia in renal failure
Choline salicylate (435-870 mg q3-4h)	5,220 mg	Dyspepsia, reduced antiplatelet effect
Magnesium salicylate (300-600 mg q4h)	4,800 mg	Same as choline salicylate
Salsalate (1,000-1,500 mg q8-12h)	4,000 mg	Same as choline salicylate
Sodium salicylate (325-650 mg q3-4h)	5,200 mg	Same as choline salicylate
Ibuprofen (200-800 mg q4-6h)	2,400 mg	[b]Dermatitis +
Ketoprofen (25-75 mg q6-8h)	300 mg	[b]Headache +++
Ketorolac tromethamine (Oral: 10 mg q4-6h; parenteral: 60 mg, then 15-30 mg q6h)	Oral: 40 mg Parenteral: 120 mg	[b]Limit duration of therapy; headache +++, GI bleeding [b]Limit therapy to 5 days; headache +++, GI bleeding
Meclofenamate sodium (50-100 mg q4-6h)	400 mg	[b]Headache +, dermatitis +
Mefenamic acid (250 mg q6h)	1,000 mg	[b]Limit therapy to 7 days
Naproxen sodium (220-550 mg q8-12h)	1,375 mg	[b]Headache +
Naproxen (250-500 mg q8-12h)	1,500 mg	[b]Headache +
Rofecoxib	50 mg	[a]
Valdecoxib	10 mg	[b]

[a] Safety profile may confer advantage in treating cancer patients.

[b] Minor adverse reactions include dyspepsia, heartburn, nausea, vomiting, anorexia, diarrhea, constipation, flatulence, bloating, epigastric pain, abdominal pain, dizziness, and drowsiness. Major adverse reactions that may appear at any time include renal failure, hepatic dysfunction, bleeding, and gastric ulceration.

+ Each plus sign represents a 5% incidence of the reported adverse effect.

Adapted with permission, from American Pain Society: Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 4th ed. Skokie, Illinois, American Pain Society, 1998.

NSAIDs = nonsteroidal anti-inflammatory drugs

TABLE 3: Guidelines for the use of opioid analgesics

Start with an analgesic with the potential to provide relief

Know the essential pharmacology of the analgesic:

- Analgesic type
- Pharmacokinetics
- Influences of coadministered drugs, disease, or age on analgesic disposition and response
- Equianalgesic starting dose for the drug and route to be used
- Route of administration and a dosage form to fit the patient's needs

Individualize/titrate the dosage

Administer analgesics regularly after the initial dose titration

Provide for breakthrough pain

Use drug combinations that enhance analgesia

Recognize and treat side effects

Make conversions from one route to another or from one agent to another using known equianalgesic doses

Manage physical dependence (ie, prevent withdrawal)

Adapted, with permission, from Inturrisi C: Cancer 63(suppl):2308–2320, 1989.

TABLE 4: Opioid agonist analgesics for mild to moderate pain

Drug	Equianalgesic dose to 650 mg of aspirin[a]	Dose interval	Half-life (h)	Comments
Codeine	32-65 mg	q4-6h	2-3	b,c
Hydrocodone	—	q3-4h	4	b
Oxycodone	2.5 mg	q3-6h	—	b

[a] The equianalgesic dose should not be interpreted as the starting, standard, or maximum dose but rather a guide for switching drugs or changing routes of administration.

[b] Doses of products containing aspirin or acetaminophen should be monitored for safety.

[c] Doses above 65 mg provide diminished incremental analgesia with increasing doses, but side effects may worsen.

Adapted with permission from American Pain Society: Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 3rd ed. Skokie, Illinois, American Pain Society, 1992.

Physical dependence and tolerance to some effects develop with chronic opioid use. Tolerance to respiratory depression, sedation, and nausea is likely to develop. Tolerance to analgesia is not a major clinical problem and can usually be managed by changing the dose or substituting another agent.

TABLE 5: Opioid agonist analgesics for severe pain

Drug	Equianalgesic dose (mg) to 10 mg of IV morphine		Half-life	
	Oral	Parenteral	(h)	Comments
Fentanyl, oral transmucosal	[a]	NA	[a]	For breakthrough cancer pain
Fentanyl, transdermal	NA	100 µg/h	—	[b, c] Patch sizes of 25, 50, 75, 100 µg/h; slow onset to effect, necessitating "breakthrough" analgesics
Hydromorphone	4 mg	1.5 mg	2-3	[b]
Levorphanol	4 mg	2 mg	12-16	[b]
Methadone	20 mg	10 mg	15-36	[b] Risk of delayed toxicity due to accumulation; reduce dose or lengthen dose interval if over-sedation occurs after 4-5 days; may schedule as prn initially
Morphine sulfate, controlled release	30 mg	NA	3	[b] Mg-for-mg conversion from immediate-release form; do not crush or chew tablets
Morphine sulfate, immediate release	30 mg	10 mg	3	[b]

Most current definitions of addiction imply a behavioral syndrome of compulsive, harmful use but do not require the existence of physical dependence or tolerance. Aberrant drug-taking is not likely to occur in patients without a history of substance abuse.

Precautions during chronic therapy During chronic opioid therapy, certain precautions should be observed:

- Normeperidine is a toxic metabolite of meperidine that accumulates with repetitive dosing; thus, use of meperidine for chronic pain should be limited. Propoxyphene is also relatively contraindicated due to accumulation of norpropoxyphene.
- Placebo use is discouraged, as it does not help distinguish the pathophysiology of pain.

Drug	Equianalgesic dose (mg) to 10 mg of IV morphine		Half-life	
	Oral	Parenteral	(h)	Comments
Oxycodone, controlled release	15 mg	NA	—	b, d
Oxycodone, immediate release	15 mg	NA	2-3	b
Oxymorphone	NA	1 mg	2-3	b

Adapted with permission from American Pain Society: Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 4th ed. Skokie, Illinois, American Pain Society, 1998.

NA = not applicable

[a] See package insert for dosing instructions.

[b] Common side effects include constipation, nausea, and sedation. Uncommon side effects include itching, dry mouth, and urinary retention. Rare side effects are hypotension and inappropriate antidiuretic hormone secretion.

[c] Patch duration = 72 hours but may be 48 hours for some patients.

Equianalgesic conversion for fentanyl:

Parenteral morphine dose (mg/24 h)	Transdermal fentanyl (μg/h)
8-22	25
23-37	50
38-52	75
53-67	100
68-82	125
83-97	150

[d] Available alone and in combination with aspirin or acetaminophen; at higher doses, use as a single agent.

- Physical withdrawal symptoms can be avoided by tapering doses.
- A change in mental status should not be attributed to opioid therapy until medical and neurologic factors have been fully evaluated.
- Mixed agonist-antagonist drugs and partial agonist drugs are not recommended for cancer pain.

Adjuvant medications Neuropathic pain may be less responsive to standard analgesics alone. Adjuvants, such as antidepressants, anticonvulsants, benzodiazepines, local anesthetics, neuroleptics, psychostimulants, antihistamines, corticosteroids, levodopa, calcitonin, and bisphosphonates, are useful for particular indications (Table 6). These agents may be administered via oral and other routes.

TABLE 6: Adjuvant drug therapy for cancer pain

Antidepressants
Anticonvulsants
Anxiolytics
Muscle relaxants
Topical local anesthetics
Amphetamines
Phenothiazines
Corticosteroids

Anesthetic and neurosurgical approaches

Anesthetic/neurosurgical approaches to managing cancer pain are fundamentally of two types: stimulating and ablative (neurodestructive; Table 7).

Local anesthetic blocks

Local anesthetic neural blockade may be performed for diagnostic, prognostic, or therapeutic purposes. Diagnostic and prognostic nerve blocks help characterize the underlying mechanism of pain and may be predictive of whether a subsequent neurolytic block will relieve pain or produce side effects. The pain-relieving effect may outlast the drug effect.

Another common approach to managing cancer pain is epidural or subarachnoid infusion of opioids, local anesthetics, and other nonopioid analgesics.

Neuroablative procedures

Neuroablation (neurolysis) involves intentionally destroying the nervous structures implicated in the transmission of pain. Needles are usually inserted percutaneously under radiologic guidance to inject alcohol or phenol or to heat or freeze needle tips to induce localized nerve injury. Neurosurgical procedures can be performed on any part of the nervous system.

Neurolytic blocks (see Table 8) have a limited but important role in the management of refractory cancer pain. They are usually reserved for pain that is severe and expected to persist in patients with a limited life expectancy. Although complications may be quite serious, they are infrequent when blocks are administered by experienced personnel with access to radiologic guidance.

The most important factors limiting the more widespread application of neurolytic blocks are (1) the potential for the development of new neuropathic pain that may arise due to the intended nerve injury and (2) the risk of neurologic deficits (eg, paralysis, loss of bladder and bowel control).

Well-controlled studies of neurolysis are lacking, but large clinical series report significant pain relief in 50%-80% of patients, with the best results obtained in patients who have received multiple blocks. Effects tend to average 6 months in duration.

Specific nerve block procedures

Peripheral neurolysis Technically, a nerve block can be performed at almost any site. Neurolysis of peripheral nerves subserving limb function (eg, brachial plexus) is usually avoided except in imminently terminal patients or when the limb is already rendered useless.

Subarachnoid neurolysis Subarachnoid injections of alcohol and phenol can usually be performed on an outpatient basis without radiologic guidance or special equipment and are suitable for aged or debilitated patients. Subarachnoid neurolysis may need to be repeated to obtain durable analgesia.

Sympathetic nerve blocks are often considered relatively early. Since sympathetic fibers innervate vasculature and viscera and do not subserve somatic motor or sensory function, a neurologic deficit is unlikely.

Celiac plexus block is one of the most efficacious and common nerve blocks used to provide prolonged relief of cancer pain. It is indicated for upper abdominal and back pain secondary to malignant neoplasms of the pancreas, stomach, liver, and other abdominal viscera. Complication rates are uniformly low, and favorable results are reported in 70%-90% of patients in large series.

TABLE 7: Anesthetic/neurosurgical approaches for controlling cancer pain

Procedure	Usual indication(s)	Examples
Local anesthetic blocks with or without steroids	Diagnostic blocks Prognostic blocks Acute pain, muscle spasm Premorbid chronic pain Postsurgical syndromes Herpes zoster	Trigger point injection Intercostal block Epidural steroids
Neurolytic/neuroablative blocks and ablative neurosurgery	Localized refractory pain that is expected to persist, usually in the presence of short life expectancy; pain localized to a region that is associated with a low risk of neurologic complications	Alcohol celiac plexus block Phenol intercostal block Percutaneous cordotomy Midline myelotomy
Spinal analgesics	Refractory pain, usually in lower body sbut may be widespread or diffuse	Externalized epidural catheter Intrathecal catheter with fully implanted pump

TABLE 8: Neurolytic procedures[a] that may be considered early in certain pain situations

Procedure	Indication
Celiac plexus neurolysis	Abdominal pain, back pain
Superior hypogastric plexus neurolysis	Pelvic pain
Phenol saddle block	Perineal pain with urinary diversion
Thoracic subarachnoid neurolysis	Focal chest wall pain
Intercostal neurolysis	Focal chest wall pain
Lumbar subarachnoid neurolysis	Unilateral leg pain

[a] The risk-benefit ratio of these procedures in the specified settings is sufficiently favorable and well established to warrant early consideration.

Superior hypogastric plexus block is likewise very effective for pelvic pain and is associated with minimal risks of bladder or limb paresis.

Intraspinal analgesia

Spinal administration of opioids produces pain relief in the absence of changes in motor, sympathetic, and sensory function. Dilute local anesthetics may need to be added in patients with refractory pain. Other nonopioid agents may be added to enhance analgesia.

Intraspinal analgesia is nondestructive and reversible and can be titrated to effect. Although most commonly considered for lower extremity and truncal pain, this approach can often be used for more widespread pain. Despite a high upfront cost, implanted intrathecal systems become more cost-effective over time, can be programmed with a laptop or hand-held computer, and may be less likely than externalized systems to become infected or migrate. Emerging information suggests that implantable drug delivery systems may offer advantages in terms of pain relief, side effects, and perhaps even extended survival, though further study is needed.

Neuroablative surgery

Although ready access to neurosurgical opinion and intervention is an important component of a comprehensive cancer pain control program, only a few procedures are performed today with any frequency.

Percutaneous cordotomy The procedure in main use is percutaneous cordotomy, which is especially well suited for unilateral pain confined to the contralateral trunk or lower limb. It involves ablation of the lateral spinothalamic tract of the spinal cord. Cordotomy is ideally suited to the treatment of intractable unilateral lower extremity pain because proprioception, tactile sensation, and motor strength are usually preserved.

Surgery for bone metastasis

Surgical intervention is warranted for bone metastases to stabilize a pathologic fracture or preempt an impending fracture. The objectives of surgery are to palliate pain, reduce patient anxiety, improve patient mobility and function, facilitate nursing care, and control local tumor when nonsurgical therapies fail. In general, surgery involves excision of all gross tumor followed by stabilization of the bone, prior to or after fracture, by means of an internal fixation or prosthetic device.

Indications

No strict criteria have been established for surgical treatment. Clinical parameters, such as the patient's general medical condition, performance status, nature of the primary tumor, effectiveness of other therapies, extent of extraskeletal disease, and degree of osseous involvement, as well as the patient's life expectancy, must be considered before surgery.

Fracture and long bone pain In general, the presence of a pathologic fracture, an impending fracture, or a painful lesion in a long bone despite radiotherapy should be considered indications for surgery. A pathologic fracture can result from structural insufficiency and can develop in the absence of viable tumor following treatment with irradiation and/or systemic therapy.

Other considerations Patients deemed to be candidates for surgery should have an expected longevity of >1 month. All patients should be medically able to withstand the planned surgical procedure. The surgical goals should be achievable with reasonable certainty, and the potential benefits should outweigh the operative risks. All surgical interventions should be performed with the intent to provide benefit that will outlast the patient's anticipated survival.

Lesion site Major long bones (femur, tibia, and humerus), the vertebrae, and periacetabular regions demand specific attention, as optimal patient function and mobility are predicated on a stable, painless extremity. Osseous destruction sufficient to compromise the mechanical integrity of these bones should be addressed surgically. Lesions in the weight-bearing bones of the lower extremity (femur and tibia) are particularly vulnerable to fracture.

Lesions in the humerus should be treated surgically when the upper extremities serve a weight-bearing function (eg, assisted ambulation using a walker, crutches, or cane). Early surgical intervention, aggressive rehabilitation, and vigilant postoperative surveillance may optimize patient outcome.

Surgical procedures

Tumor excision For most patients, tumor removal is performed as part of the surgical procedure. Usually, this is accomplished by curettage of the metastatic deposit. For highly vascular lesions (renal cell carcinoma, multiple myeloma, and thyroid carcinoma), intraoperative blood loss can be minimized by preoperative transcatheter arterial embolization on the day of or the day before surgery.

Bone stabilization Following tumor excision, restoration of the osseous integrity of the tumor-bearing bone usually is achieved by insertion of an internal fixation device, either an intramedullary nail or plates/screws secured with bone cement. Joint replacement may be performed when the tumor involves the end of the bone or when no reasonable fixation into native bone can be accomplished. Progression of local tumor just distal or proximal to the end of a fixation device may lead to a fracture about the fixation, which could preclude subsequent salvage attempts. Therefore, an attempt is made to stabilize the entire bone.

There are no clearly defined criteria for the presence of an impending fracture of a long bone. Current guidelines, derived from retrospective clinical studies, include lytic lesions > 2.5 cm in diameter, cortical destruction > 50%, and pain despite local irradiation. In the proximal femur, an avulsion fracture of the lesser trochanter places the hip at high risk for fracture and should be treated operatively.

Resection As a rule, few metastatic deposits arising in the extremities should be removed by wide resection. In selected patients who have a reasonable likelihood of an extended life expectancy, such as patients with a solitary plasmacytoma or a solitary metastasis from renal cell or thyroid carcinoma, resection of a solitary metastasis should be considered.

Deposits in expendable bones, such as the fibula and clavicle, may be resected. Resection may be indicated in selected cases of rapidly aggressive tumors in bone or when extensive bone destruction secondary to metastasis precludes stabilization. Highly vascular tumors for which preoperative embolization has been unsuccessful and the risk of massive hemorrhage is high also should be considered for resection.

Amputation for extremity metastases is indicated rarely but may have a role in patients with intractable pain, those with a fungating tumor or a tumor that has invaded major blood vessels, and those whose poor medical condition precludes a lengthy reconstruction procedure.

Treatment of spinal metastases

The spine is the most frequently involved site of metastatic disease to bone. Progressive neurologic loss; fracture, with or without neurologic compromise; spine instability; and refractory pain are all indications for surgery. The goals of intervention are to relieve neurologic compression, restore spinal stability, alleviate pain, and reestablish patient mobility.

An aggressive approach with early detection and intervention can reduce patient morbidity. All surgical interventions should be performed with the intent to outlast anticipated patient longevity. The intended benefits should be weighed carefully against potential operative risks.

Surgical approach The surgical approach is dictated by the location of tumor compression, regardless of the level of vertebral involvement. In general, the results of surgical decompression and stabilization are satisfactory if surgical principles are applied appropriately.

For patients with a projected life span of < 1 year, a nonbiologic reconstruction with polymethyl methacrylate (PMMA) bone cement with pins and/or plate fixation is usually sufficient to provide stability. For patients in whom survival is anticipated to exceed 1 year, a biological reconstruction (bone graft) should be used. Posteriorly, rods fixed with wires and/or screws are used to provide stability.

Role of radiation therapy

Cancer pain can often be relieved by radiation therapy delivered by localized external-beam irradiation (also known as involved-field irradiation), wide-field external-beam irradiation (eg, hemibody irradiation [HBI]), or systemic treatment with radioactive isotopes (eg, strontium-89 chloride [Metastron], samarium SM-153 lexidronam (Quadramet), phosphorus-32, and iridium-131). Since the most common cause of cancer pain is bone metastasis, this discussion will focus on the use of irradiation in its treatment. Other examples of cancer pain due to primary or metastatic cancer that are amenable to irradiation include headache from CNS involvement, pain due to localized neural involvement (eg, brachial plexus or sciatic nerve), visceral pain (eg, liver or adrenal), pain due to effusions (eg, pericardial or pleural), and pain due to obstruction (eg, urethral, esophageal).

TREATMENT OF BONE METASTASES

Irradiation is an extremely effective means of palliating painful bone metastases. Total dose and fractionation of radiation therapy are designed to use the fewest fractions possible consistent with the goals of maximizing the therapeutic effect and minimizing the side effects, inconvenience, and expense of treatment. In some situations, short treatment schedules of 1-5 fractions are appropriate, whereas in others, longer schedules of 10 or more fractions may be required.

Localized irradiation

Approximately 80% of patients report significant pain relief from localized irradiation, the most common approach. Local fields should encompass areas of painful bone metastases with a margin (eg, several centimeters or one to two vertebral bodies), but field size may be limited by normal tissue tolerance, administration of chemotherapy, or prior irradiation.

The American Patterns of Care Study has identified the most commonly used treatment regimen for irradiation of bone metastases to be 30 Gy in 10 fractions over 2 weeks; however, 20 Gy in 5 fractions may be just as effective. Many clinicians still believe that nerve pain and impending fracture may benefit from a higher dose fractionation schedule, and use of such a schedule is not uncommon.

Hemibody irradiation

An alternative approach in patients with several symptomatic sites is wide-field HBI.

Upper HBI Patients with multiple sites of metastases whose dominant sites of painful bone metastases include the ribs, shoulder girdle, cervicothoracic spine, and skull may be treated with large anterior and posterior fields encompassing the upper hemibody, using the superior aspect of the iliac crest as the lower margin of the field. Because of the inclusion of the upper abdomen and lungs within the treatment fields, it is customary to hydrate patients prior to treatment and also to premedicate them with corticosteroids and antiemetics to prevent nausea and hypotension.

The parotid gland should be blocked from the treatment field to prevent xerostomia. If there is no skull involvement, the head may be excluded to avoid alopecia. In general, corrections for lung density are not made, and the dose is limited to 6 Gy.

Lower HBI can be utilized when there are extensive symptomatic bone metastases involving the lumbar spine, pelvis, and lower extremities. The hypotension associated with upper HBI has not been observed when the lower body is irradiated. However, it is common practice to premedicate patients with corticosteroids, antidiarrheal agents, and antiemetics to prevent nausea and diarrhea associated with irradiating the small bowel with lower HBI.

HBI vs involved-field irradiation Although there are similar overall response rates with involved-field irradiation and HBI, the complete relief rate is higher for involved-field irradiation. In addition, involved-field irradiation suppresses bone marrow function to a lesser extent than HBI, which can cause significant leukopenia and thrombocytopenia for 2-4 weeks after irradiation. However, recurrence of pain in or around the initial painful site is seen more often with involved-field irradiation than with HBI (54% vs 13%).

HBI plus involved-field irradiation In RTOG (Radiation Therapy Oncology Group) study 82-06, the addition of HBI to involved-field irradiation produced significantly better palliation than involved-field irradiation alone, as shown by a delay in disease progression, a decrease and delay in new disease within the hemibody, and a decrease in the retreatment rate.

Systemic radiotherapy

Strontium-89 is a systemic radionuclide that has clinical efficacy in the palliation of pain from bone metastases. Reduction of pain due to bone metastases has been observed most frequently in patients with metastases from prostate cancer.

The primary toxicity of strontium-89 is myelosuppression, particularly thrombocytopenia. Therefore, it should not be administered to patients with thrombocytopenia or significant bone marrow suppression. Strontium-89 levels in bone are regulated much like calcium, and strontium-89 has less hematologic toxicity than phosphorus-32.

Samarium-153 is a β-emitting radioisotope that is bound to a phosphonate that preferentially localizes in active bone, specifically in sites of metastatic disease. Mild-to-moderate myelosuppression was noted in the samarium-153 group, yet a potential advantage of samarium-153 over strontium-89 is the decreased incidence and severity of hematologic toxicity noted with samarium-153.

Physical treatments

Cancer patients may benefit from formal rehabilitation evaluation and treatment. Physical modalities, such as massage, ultrasonography, hydrotherapy, transcutaneous electrical nerve stimulation (TENS), electroacupuncture, and trigger-point manipulation, are indicated for musculoskeletal pain. Also, any of these techniques may enhance exercise tolerance in a patient undergoing rehabilitation. Skillful soft-tissue manipulation is probably underutilized. Electrical stimulation may also be applied to the peripheral nerves, spinal cord, and even deep brain structures.

Management of psychological, sociocultural, and spiritual factors

The appropriate treatment of cancer pain must extend beyond the physical complaint. Psychological, sociocultural, and spiritual factors significantly affect the patient's quality of life. Plato reminds us that physicians err when we separate the soul from the body. Thus, the clinician must always care for the whole person. A multifactorial approach to pain management recognizes the complexity of the human being, especially in one with a terminal illness.

Although the physician's initial therapeutic goal is to cure the disease, cancer is often incurable. Caring entails recognizing the whole person as a physical, intellectual, social, emotional, and spiritual being. Empathic caring helps the patient perceive the value in life despite the gravity of the situation.

Psychological factors, such as anxiety and depression, must be thoroughly addressed, as revealed by emerging evidence from the disciplines of psychooncology and psychoneuroimmunology. Attitude and state of mind affect the individual's perception of pain and response to it in myriad ways and may affect the duration of survival.

A detailed discussion of pharmacologic and nonpharmacologic approaches to anxiety and depression in cancer patients may be found in chapter 42. In addition, patients may regain a much needed sense of control by using psychological techniques, such as imagery, hypnosis, relaxation, biofeedback, and other cognitive or behavioral methods.

Sociocultural influences affect the patient's experience and expression of pain. This is especially true for the patient whose cancer does not respond to therapy and progresses to end-stage disease.

Pain may be an unwelcome reminder of the presence and progression of cancer. Concomitant fear, anger, frustration, disappointment, and other negative emotions may hold the patient hostage to physical pain.

Existential distress may bridge an undesirable transition from hopeful coping with pain to hopeless suffering from it. As patients are confronted with personal mortality, the limits of their life span move from an abstract concept to a real issue. Self-image changes, and patients may develop emotional and psychic turmoil, which may compromise their medical condition and treatment.

Achieving relief of psychic suffering may enable the patient to transcend physical pain, enhancing the effects of pain medications and other treatments. Prayer, meditation, counseling, clergy visits, and support groups may all be beneficial. Relieving suffering means allowing the patient and family to realize some satisfaction in life and even find contentment or peace in the face of failing health and imminent death. Palliative care of the family includes bereavement counseling in anticipation of and after the loss of a loved one.

Ongoing care

The goals of pain management must be frequently reviewed and integrated into the overall management plan. Communication among the professional staff, patient, and family is essential. A sensitive, frank discussion with the patient regarding his or her wishes should guide medical decision-making during all phases of the illness.

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CHAPTER 40

Management of nausea and vomiting

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Marked progress in controlling chemotherapy-induced emesis has occurred over the past 10 to 20 years. Nonetheless, nausea and vomiting remain among the most distressing side effects of anticancer chemotherapy. With the increased use of chemotherapy in primary and adjuvant treatment settings, the need for improved control of emesis remains an important consideration in both medical oncology and supportive care.

Recently, several major oncology groups have published consensus reports or guidelines on the prevention of chemotherapy-induced emesis. In addition, an understanding of the neuropharmacology of this problem is useful in planning patient care.

Pathophysiology of emesis

Although the mechanism by which anticancer chemotherapy induces emesis is still not completely understood, studies have established the basis for our current understanding of this complex problem.

Stimulation of chemotherapy receptors

Reflex-induced emesis is caused by stimulation of receptors in the CNS and/or GI tract. These receptor areas relay information to the vomiting center in the medulla, which then coordinates the act of vomiting. The chemotherapy receptor trigger zone (CTZ), also located in the medulla, serves as a "chemosensor" and is exposed to blood and CSF. These areas are rich in a variety of neurotransmitter receptors.

Dopamine For many years, the dopamine receptors were the main focus of interest in antiemetic research. Available antiemetics, such as phenothiazines (chlorpromazine and prochlorperazine) and substituted benzamides (metoclopramide) were known to affect these receptors, as were butyrophenones (haloperidol and droperidol).

Serotonin In recent years, the role of the neurotransmitter serotonin (5-hydroxytryptamine [5-HT]) has been elucidated. The improved antiemetic activity of higher doses of metoclopramide was explained not by its dopamine-binding properties, but by the fact that it also affects serotonin receptors.

This led to the development of several highly specific compounds that interact solely with serotonin receptors, specifically the type 3, or 5-HT_3, receptor subtype. The 5-HT_3 receptor, which is found in both the GI tract and CNS, is an important mediator of the emetic reflex.

Substance P New research indicates that tachykinins, such as substance P, may play an important role in emesis, as well as in pain and a variety of inflammatory conditions. These neurotransmitters are 11–amino acid molecules that bind to specific receptors. Substance P binds to the neurokinin type 1, or NK_1, receptor.

Several NK_1 receptor antagonists have been synthesized and used both preclinically and in clinical trials in patients receiving cancer chemotherapy. Results indicate that these agents may be effective against a broad range of causes of emesis, and that they appear to have promising activity in early randomized trials.

Emetic problems

Emesis related to chemotherapy

Both nausea and vomiting are seen in patients receiving cancer chemotherapy. Nausea occurs at a slightly higher frequency than vomiting and is modestly more difficult to control. The control of vomiting is strongly correlated with the control of nausea, although occasional patients experience nausea without vomiting.

In patients receiving chemotherapy, several emetic problems have been identified. The three most common problems are outlined below:

Acute chemotherapy-induced emesis is defined as nausea or vomiting that occurs within the initial 24 hours of chemotherapy administration. The time of greatest risk is from 1 to 4 hours after chemotherapy with most agents.

Delayed emesis is emesis that begins ≥ 24 hours after chemotherapy. Delayed emesis is particularly likely to occur in patients who have received cisplatin (Platinol), carboplatin (Paraplatin), or cyclophosphamide (Cytoxan, Neosar). Recent data indicate that this problem may begin somewhat earlier than 24 hours in some patients.

Anticipatory emesis is defined as a conditioned vomiting response following inadequate antiemetic protection with earlier courses of chemotherapy.

Emesis unrelated to chemotherapy

Patients receiving anticancer drugs may also develop emesis for other reasons. These include emesis induced by concomitant medications (such as analgesics, anti-infectives, or bronchodilators) or by tumor-related complications (such as intestinal obstruction or brain metastases). In these instances, adjustment of medication or treatment of tumor-related complications are more important than selecting an antiemetic agent.

Patient characteristics and emesis

History of poor emetic control Poor control of emesis with past courses of chemotherapy predisposes a patient to unsatisfactory antiemetic results with any subsequent treatment, regardless of the emetic stimulus or antiemetic employed. Both delayed and conditioned anticipatory emesis are more likely to occur in these patients, and there is likely to be greater difficulty in controlling acute emesis.

Prior alcohol intake history Emesis is easier to control in patients with a history of chronic, high alcohol intake (> 100 g/d of alcohol [approximately five alcohol units or drinks]). In a prospective evaluation of 52 patients receiving high-dose cisplatin and an effective combination antiemetic regimen, 93% of those with a history of high alcohol intake had no emesis, as opposed to 61% of those without such a history. This difference in emesis control is independent of the patient's current alcohol intake.

Age Most trials have found that it is easier to control emesis in older patients. Also, younger patients have a predilection for developing acute dystonic reactions when dopamine-blocking antiemetics are administered (see "Antiemetic agents for high-emetic-risk chemotherapy" section).

Gender It is more difficult to control emesis in women than in men given the same chemotherapy and antiemetic regimen.

Motion sickness Patients with a history of motion sickness are more likely to develop chemotherapy-induced nausea and vomiting.

The above predisposing factors appear to be additive. One can identify patients at particularly high risk of emesis, such as younger women without a prior history of high alcohol intake. Awareness of these factors is helpful in monitoring individual patients and in interpreting the results of clinical trials.

Chemotherapeutic agents and emesis

Emetic potential The most accurate predictor of the risk of emesis is the chemotherapeutic agent that a patient is receiving. Several different classifications of commonly used chemotherapy agents have been devised. Table 1 is based on the consensus reports of the American Society of Clinical Oncology (ASCO) and of the Multinational Association for Supportive Care in Cancer (MASCC). Both have produced similar, although not identical lists; the nomenclature used in this report reflects that of the ASCO publication (September 1999).

The emetic potential of a chemotherapeutic combination is determined by identifying the most emetic agent in the combination. Other agents in a combination may also increase the risk.

In general, agents that have the highest *incidence* of emesis also induce the most *severe* emesis. Differences occur among patients and even between identical treatment courses in the same patient. Both the dose and route of administra-

TABLE 1: Emetic potential of chemotherapy agents

Level	Frequency of emesis (%)[a]	Agent
High	> 99	Cisplatin Dacarbazine Hexamethylmelamine Mechlorethamine
Moderate	30-90	Carboplatin Carmustine Cyclophosphamide Cytarabine Doxorubicin Epirubicin Idarubicin Ifosfamide Mitoxantrone Procarbazine Streptozocin
Low	10-30	Docetaxel Etoposide Fluorouracil Irinotecan Gemcitabine Methotrexate (> 50 mg/m^2) Mitomycin Paclitaxel Topotecan
Minimal	< 10	Bleomycin Busulfan Chlorambucil Fludarabine Hydroxyurea Methotrexate (≤ 50 mg/m^2) Melphalan Thioguanine Vinblastine Vincristine Vinorelbine

[a] Proportion of patients experiencing emesis in the absence of effective antiemetic prophylaxis

tion of the chemotherapeutic agent can affect the incidence of nausea and vomiting.

Time of onset of emesis In patients receiving initial chemotherapy of high emetic risk, nausea or vomiting typically begins between 1-2 hours after chemotherapy. Two agents, cyclophosphamide and carboplatin, may be associ-

ated with a late onset of emesis; ie, 8-18 hours following chemotherapy administration.

Antiemetic agents for high-emetic-risk chemotherapy

Careful antiemetic research has shown that several agents are safe and effective. Doses and administration schedules of many of these agents are given in Table 2. Antiemetic therapy can be administered either orally or intravenously.

Among the best studied agents are: ondansetron (Zofran), granisetron (Kytril), dolasetron (Anzemet), metoclopramide (Reglan), haloperidol, dexamethasone, lorazepam, dronabinol (Marinol), prochlorperazine, and chlorpromazine.

The combination of a single prechemotherapy dose of a 5-HT_3 antagonist and dexamethasone is the current best therapy to prevent emesis in patients receiving chemotherapy of high emetic risk (both cisplatin and noncisplatin) as listed in Table 1.

Serotonin antagonists: Ondansetron, granisetron, and dolasetron

Ondansetron, granisetron, and dolasetron are highly selective 5-HT_3 receptor antagonists. All are equally effective in controlling emesis induced by a variety of chemotherapeutic agents. Oral and IV routes of administration are equally effective, as demonstrated in large randomized trials. In addition, single-dose regimens given before chemotherapy are as effective as more cumbersome multiple- or continuous-dose regimens. These findings are valid for cisplatin and for chemotherapeutic agents of lesser emetic potential.

All three serotonin receptor antagonist agents are similar with regard to efficacy and side effects, and the choice of one agent over another may reflect economic factors rather than therapeutic index. Doses of these agents are given in Table 2.

Side effects Ondansetron, granisetron, and dolasetron have all demonstrated excellent safety characteristics over a large dosing range. Toxicities have been minor, and have included headache, mild, transient elevation of hepatic enzyme levels, constipation, and, with some agents, minor prolongation of cardiac conduction intervals.

Dystonic reactions and akathisia (restlessness), which may be treatment-limiting with antiemetic agents known to block dopamine receptors, are not seen with serotonin antagonists, even when given on consecutive days. This is of particular importance for younger patients, in that several regimens used to treat malignancies in this age group utilize a daily schedule of chemotherapy.

Efficacy The serotonin antagonists have been reported to achieve complete control of emesis in 30%-50% of patients receiving cisplatin. These agents have also proved to be at least as effective against all other chemotherapeutic agents, with complete control rates of about 70%.

TABLE 2: Dosage and administration schedules of antiemetic agents for acute emesis for chemotherapy of high emetic risk

Antiemetic agent	Dosage[a]	
	Oral	Intravenous
Dolasetron	100 mg once	100 mg (1.8 mg/kg) once
Granisetron	1 mg or 2 mg once	1 mg (0.01 mg/kg) once
Ondansetron	16-24 mg once or 8 mg bid	8 mg (0.15 mg/kg) once
Dexamethasone	20 mg once	20 mg once over 5 min
Metoclopramide	2-3 mg/kg q2-3h	2-3 mg/kg q2h
Haloperidol	1-2 mg q4-6h	1-3 mg q4-6h
Dronabinol	5 mg/m^2 q4h	
Prochlorperazine	Not recommended	10-20 mg q3-4h
Lorazepam[b]	0.5-2.0 mg	0.5-2.0 mg q4-6h

[a] All agents are to be administered prior to chemotherapy, usually 30 minutes beforehand, although the serotonin antagonists can be effective if administered as late as immediately before the start of chemotherapy. Recommended dosages have been found to be effective in clinical trials and may vary from those given in package inserts.

[b] Lorazepam is indicated only as an adjunct to antiemetics in this setting.

Many trials have examined the benefit of adding corticosteroids to a serotonin antagonist. Typically, the complete control of emesis is improved by 10%-20% in patients receiving highly emetic chemotherapy. Both the ASCO and MASCC guidelines recommend that a corticosteroid *always* be added whenever a serotonin antagonist is indicated (ie, in all patients receiving chemotherapy of high emetic risk).

Dexamethasone

The antiemetic mechanism of action of dexamethasone remains unclear. Several open studies and randomized trials, and a recent meta-analysis have all confirmed its effectiveness in controlling emesis and its safety. Other corticosteroids are also effective; however, dexamethasone is the most widely studied steroid and is available in oral and parenteral dosage forms as an inexpensive generic product.

Dexamethasone is an ideal agent for use in combination antiemetic regimens and as a single agent for patients receiving chemotherapy of intermediate emetic risk ($<$ 30% incidence).

Dose Dexamethasone doses have generally ranged from 4 to 20 mg/d. In a recent randomized trial in patients receiving chemotherapy of high emetic risk, a single 20-mg dose was superior in completely controlling both nausea and vomiting. Thus, the 20-mg dose is recommended in this setting.

Side effects Toxicities associated with short courses of dexamethasone used for antiemetic therapy have been mild and generally consist of insomnia and mild epigastric burning. Care using this agent in patients with diabetes is particularly warranted.

Metoclopramide

Metoclopramide has proven to be safe and most effective when given in high IV doses. Until recently, metoclopramide was thought to function as an antiemetic through blockade of dopamine receptors. However, research has now shown that high concentrations of this agent effectively block 5-HT_3 receptors as well.

Efficacy In patients receiving cisplatin, metoclopramide is superior or at least equivalent to most classes of antiemetic agents. However, randomized trials comparing metoclopramide with serotonin antagonists in high-risk settings have shown advantages for the latter agents. Metoclopramide is a second-choice agent, after the serotonin antagonists, in these settings.

Side effects Commonly observed side effects with metoclopramide include mild sedation, dystonic reactions, and akathisia. As mentioned above, dystonic reactions are age-related. In a report summarizing the experience of nearly 500 patients receiving metoclopramide, the incidence of trismus or torticollis was only 2% in those over 30 years old; in contrast, a 27% occurrence was reported in younger patients. Also, dystonic reactions are more common when dopamine-blocking agents are given on consecutive days.

Acute dystonic reactions are not allergic in nature. In general, dystonic reactions and akathisia can be prevented or easily controlled by administering diphenhydramine, benztropine, or a benzodiazepine. These reactions should not be viewed as a contraindication to further use of dopamine-blocking drugs if satisfactory antiemetic control is obtained.

Haloperidol and droperidol

Both haloperidol and droperidol exert their antiemetic action through dopaminergic blockade. A formal study comparing haloperidol with metoclopramide in patients receiving cisplatin found both agents to be effective, although metoclopramide afforded better emetic control.

Dose Haloperidol doses of 1-3 mg given IV q4-6h have been used. Droperidol doses of 0.5-2.5 mg IV q4h have been studied.

Side effects Toxicities of haloperidol and droperidol include sedation, dystonic reactions, akathisia, and occasional hypotension.

Lorazepam

Although lorazepam and other benzodiazepines are potent antianxiety agents that can be useful additions to antiemetic therapy, they should not be used as single agents for chemotherapy-induced emesis. Lorazepam has been shown to achieve a high degree of patient acceptance and subjective benefit but only a minor objective antiemetic activity.

Dose Lorazepam is usually given at doses of 0.5-1.5 mg/m^2 IV, or 1-2 mg PO. These doses, especially the higher IV administrations, can be associated with marked sedation lasting for several hours.

Dronabinol and cannabinoids

Many trials have tested the antiemetic effects of dronabinol (delta-9-tetrahydrocannabinol [THC]), a component of marijuana. Dronabinol has modest antiemetic activity, similar to that seen with oral prochlorperazine. One double-blind, randomized trial in patients receiving highly emetic chemotherapy compared inhalant marijuana with dronabinol. The control of emesis was poor with both agents, and there was a slight preference of patients for oral dronabinol over smoked marijuana.

Semisynthetic cannabinoids (such as nabilone) have been tested but appear to have no clear advantage over dronabinol. The modest antiemetic activity of cannabinoids makes them distant choices for the control of any chemotherapy-related emetic situation.

Dose Dronabinol has been tried in many doses and schedules. The most useful doses have ranged from 5 to 10 mg/m^2 PO q3-4h.

Side effects are more frequently associated with cannabinoids than with other agents and are particularly bothersome in older adults. They include dry mouth, sedation, orthostatic hypotension, ataxia, dizziness, euphoria, and dysphoria.

Phenothiazines

The results of antiemetic trials with this class of agents have been poor. Randomized trials have found prochlorperazine, given orally or intramuscularly, to be less effective than metoclopramide or dexamethasone, and equivalent to or less effective than dronabinol. IV phenothiazines are more effective than oral administration, but can cause profound hypotension on occasion (unlike serotonin antagonists or metoclopramide). The relatively poor therapeutic index of these agents make them third- or fourth-line drugs for this indication.

Side effects of phenothiazines include sedation, akathisia, hypotension, and dystonic reactions.

Investigational agents

As mentioned previously, small randomized trials have reported encouraging antiemetic activity of the NK_1 receptor antagonists. These agents appear to have antiemetic activity similar to that reported with serotonin antagonists.

In acute emesis settings, NK_1 receptor antagonists appear to enhance the activity of the combination corticosteroids plus serotonin antagonists. When used for delayed emesis, NK_1 receptor antagonists have been reported to be very active.

TABLE 3: Antiemetic regimens for acute emesis, by emetic risk

Risk Level	Recommended antiemetic regimen[a]
High (cisplatin)	Serotonin antagonist *plus* Dexamethasone (20 mg)
High (noncisplatin)	Serotonin antagonist *plus* Dexamethasone (20 mg)
Intermediate	Single agent, such as dexamethasone (4-20 mg)
Low	No preventive agent is recommended for general use

[a] See Table 2 for doses.

Combination antiemetic regimens

Table 3 summarizes recommended antiemetic regimens, according to the emetic potential of the chemotherapy regimen.

Serotonin antagonist plus dexamethasone Combinations of a 5-HT_3 antagonist and dexamethasone are the most effective regimens for controlling acute chemotherapy-induced emesis. Use of these two agents combined has proven to be more effective than either agent alone.

Treatment of acute emesis

A management strategy to prevent acute chemotherapy-induced emesis is outlined in Table 3. All patients should receive education and reassurance, as well as antiemetics tailored to the chemotherapy regimen. For regimens that commonly cause emesis (> 30% or high risk), antiemetic combinations are recommended; for regimens of intermediate risk (10%-30% incidence), a single agent, such as dexamethasone, will usually suffice. As stated in Table 3, chemotherapy of low risk typically does not require preventive treatment.

The rationale for treating high-risk patients receiving either cisplatin or other chemotherapy with the same antiemetic combination at the same doses is based on our current understanding of the neuropharmacology of emesis. Once all of the relevant receptors (5-HT_3) are saturated by the antiemetic, dose escalation will not be helpful. However, to achieve maximal benefit, it is necessary to give a dose that achieves this saturation. Thus, the lowest fully effective dose is the proper one for any chemotherapy-associated emetic setting in which a serotonin antagonist is to be given.

DELAYED EMESIS

Delayed emesis is defined as nausea or vomiting beginning or persisting ≥ 24 hours after chemotherapy administration. The pathophysiology of this problem is unclear, but it is particularly common after high-dose cisplatin (≥ 50 mg/m^2), carboplatin (≥ 300 mg/m^2), cyclophosphamide (≥ 600-1,000 mg/m^2), or doxorubicin (50 mg/m^2).

In one natural history study, 89% of patients experienced some delayed emesis from 24 to 120 hours after high-dose cisplatin, with a peak incidence occurring between 48 and 72 hours. With anthracyclines or cyclophosphamide, the rate of delayed emesis without preventive antiemetics is about 30%.

Investigations have indicated that delayed emesis may begin earlier. When combinations of a serotonin antagonist plus dexamethasone fail, the initial emetic episode is often at 17- to 23-hours following chemotherapy. In some trials, antiemetics to prevent delayed emesis have been initiated at 16 to 17 hours.

Treatment options The combination of oral dexamethasone and metoclopramide has been found to be superior to dexamethasone alone or placebo in a double-blind, randomized trial. The recommended dose and schedule of these antiemetic agents for the prevention of delayed emesis is given in Table 4.

TABLE 4: Treatment regimens for delayed emesis

Risk level	Recommended antiemetic regimen	Dose and schedule
High (cisplatin)	Metoclopramide	30–40 mg PO bid for 3 days
	plus	
	Dexamethasone	8 mg PO bid for 3 days
	Alternative regimen:	
	Serotonin antagonist such as	
	Ondansetron	8 mg PO bid for 3 days
	or	
	Dolasetron	100 mg PO bid
	or	
	Granisetron	1 mg PO bid
	plus	
	Dexamethasone	Same as above
Moderate	Same regimens as for cisplatin, except that the regimen may be given for just 2 days. In some patients with lower risk characteristics, dexamethasone alone may be sufficient.	
Low	No preventive regimen is recommended for general use	
Minimal	No preventive regimen is recommended for general use	

The majority of trials examining the role of 5-HT_3 antagonists as single agents in the control of delayed emesis have been disappointing. The 5-HT_3 receptor may be less involved in the pathophysiology of delayed emesis. Regimens combining a serotonin antagonist with dexamethasone can lessen delayed emesis (see Table 4 for dosages) and are comparable to metoclopramide and dexamethasone in activity but are markedly more costly. In moderate risk setings, dexamethasone alone may be sufficient for many patients.

Perhaps the greatest single problem in antiemetic prescribing is the omission of dexamethasone in acute and (especially) in delayed emesis prevention.

ANTICIPATORY EMESIS

This problem is defined as nausea or vomiting beginning before the administration of chemotherapy in patients with poor emetic control during previous chemotherapy. As this is a conditioned response, the hospital environment or other treatment-related associations may trigger the onset of emesis unrelated to chemotherapy. Strong emetic stimuli combined with poor emetic control increases the likelihood that anticipatory emesis will occur.

Treatment approach Behavioral therapy involving systematic desensitization can be helpful in managing anticipatory emesis. Also, benzodiazepines appear to be useful.

Perhaps the best approach to anticipatory emesis is prevention. This underscores the need to provide the most effective and appropriate antiemetic regimens with the initial course of emesis-producing chemotherapy. A recent study reported that, although patients still experience anticipatory symptoms, they generally are not severe or clinically significant. This may reflect an overall improvement in antiemetic therapy.

SUGGESTED READING

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CHAPTER 41

Hematopoietic growth factors

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For years, chemotherapy-associated myelosuppression has represented a major limitation to a patient's tolerance of anticancer therapy. In addition, the clinical consequences of chemotherapy-induced myelosuppression (such as febrile neutropenia, dose reductions, or lengthy dose delays) may have had significant negative effects on patient quality of life or even response to treatment.

Before the widespread availability of agents to stimulate host hematopoiesis, administration of antibiotics, transfusion of blood products, and reductions or delays in chemotherapy dose have been the major means of combating the myelotoxicity of chemotherapy. It is now possible to stimulate clinically relevant production of several formed elements of the blood: neutrophils, erythrocytes, and platelets.

This chapter summarizes data supporting the clinical activity of several hematopoietic growth factors. A thorough knowledge of these data will help clinicians to make judicious, informed decisions about how to use these agents most responsibly.

Hematopoietic growth factors

Over the past several years, a great deal of progress has been made in understanding the process of hematopoiesis by which mature cellular elements of blood are formed. Hematopoietic growth factors are a family of regulatory molecules that play important roles in the growth, survival, and differentiation of blood progenitor cells, as well as in the functional activation of mature cells.

Table 1 lists the recombinant human hematopoietic growth factors (also known as hematopoietic cytokines) that have been approved by the Food and Drug Administration (FDA) for clinical use: (1) granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]), pegfilgrastim [Neulasta], (2) yeast-derived granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine]), (3) recombinant human erythropoietin (epoetin alfa, EPO [Epogen, Procrit]), (4) darbepoetin alfa (Aranesp), and (5) interleukin-11 (IL-11, oprelvekin [Neumega]). In addition, several other hematopoietic cytokines are under clinical development.

The commercial availability of these recombinant human hematopoietic growth factors has led to their wide clinical application in oncology practice. How-

TABLE 1: FDA-approved indications for hematopoietic growth factors/cytokines

Growth factor/ cytokine	Generic name	Trade name(s)	Distributor(s)/ manufacturer(s)	Indication(s)
G-CSF	Filgrastim	Neupogen	Amgen	Cancer patients receiving myelosuppressive chemotherapy
	Pegfilgrastim	Neulasta	Amgen	Patients with nonmyeloid malignancy following BMT
				For mobilization of PBPCs
				Patients with severe chronic neutropenia
				Following induction chemotherapy in AML
GM-CSF	Sargramostim	Leukine	Immunex	Following autologous BMT
				BMT engraftment delay or failure
				Following induction chemotherapy in older patients with AML
				Allogeneic BMT For mobilization of PBPCs and for use after PBPC transplantation
EPO	Epoetin alfa	Epogen	Amgen	Anemia in chronic renal failure patients (predialysis or dialysis)
		Procrit	Ortho Biotech	Anemia in zidovudine-treated HIV-infected patients
				Anemia in patients with nonmyeloid malignancy receiving chemotherapy
				Anemia in patients scheduled for elective, noncardiac, nonvascular surgery
	Darbepoetin alfa	Aranesp	Amgen	Anemia in chronic renal failure patients
				Anemia in patients with nonmyeloid malignancy receiving chemotherapy
IL-11	Oprelvekin	Neumega	Genetics Institute	Following myelosuppressive chemotherapy in patients with nonmyeloid malignancy who are at high risk for severe thrombocytopenia

AML = acute myelogenous leukemia; BMT = bone marrow transplantation; PBPC = peripheral blood progenitor cell

ever, the substantial costs of colony-stimulating factor (CSF) utilization as supportive care for patients receiving myelosuppressive chemotherapy makes it imperative to identify the optimal settings in which their use can make a significant difference in patient outcomes.

This chapter discusses the appropriate uses of only the FDA-approved hematopoietic growth factors/cytokines: G-CSF, GM-CSF, EPO, darbepoetin alfa, and IL-11. For a more detailed review of recommendations for the use of myeloid CSFs, readers are referred to the evidence-based, clinical practice guidelines developed in 1994 (and subsequently updated biennially) by the American Society of Clinical Oncology (ASCO). The ASCO guidelines were formulated to encourage reasonable use of CSFs when their efficacy has been well documented but to discourage excess use when marginal benefit is anticipated. These clinical practice guidelines have been published and are most easily accessed at the official web site of ASCO (www.asco.org). Similar clinical practice guidelines have been developed for the use of EPO (and, by extension, for darbepoetin) by the American Society of Hematology (ASH) in conjunction with ASCO (see Rizzo et al: http://www.asheducationbook.org/cgi/content/full/2001/1/10).

Myeloid growth factors

Two myeloid growth factors are currently licensed for clinical use in the United States: G-CSF and GM-CSF.

G-CSF is lineage-specific for the production of functionally active neutrophils. G-CSF has been extensively evaluated in several clinical scenarios. G-CSF was first approved in 1991 for clinical use to reduce the incidence of febrile neutropenia in cancer patients receiving myelosuppressive chemotherapy.

This broad initial indication has since been expanded even further, to include many other areas of oncologic practice, such as stimulation of neutrophil recovery following high-dose chemotherapy with stem-cell support. In addition, G-CSF is indicated to increase neutrophil production in endogenous myeloid disorders, such as congenital neutropenic states.

GM-CSF, primarily a myeloid-lineage–specific growth factor, stimulates the production of neutrophils, monocytes, and eosinophils. It has been extensively evaluated and received a more narrow FDA approval in 1991 for clinical use in patients with nonmyeloid malignancies undergoing autologous bone marrow transplantation (BMT). Since that initial indication, GM-CSF has also been approved for an expanded range of conditions, such as mitigation of myelotoxicity in patients with leukemia who are undergoing induction chemotherapy.

To date, no large-scale randomized trials have directly compared the efficacy of these two CSFs in the same clinical setting. Future comparative trials may help determine the optimal clinical utility of these CSFs in different clinical situations.

INDICATIONS

Uses to support chemotherapy

CSFs have been used to support both conventional and intensified doses of chemotherapy. The use of CSFs in this setting can be defined as prophylactic or therapeutic.

Prophylactic use is defined as the administration of a growth factor to prevent febrile neutropenia. "Primary prophylaxis" denotes the use of CSF following the first cycle of multicourse chemotherapy *prior to* any occurrence of febrile neutropenia. The term "secondary prophylaxis" is reserved for the use of CSFs to prevent a subsequent episode of febrile neutropenia in a patient who has already experienced infectious complications in a previous chemotherapy cycle.

Primary prophylaxis G-CSF has been evaluated in at least three major randomized clinical trials in cancer patients receiving chemotherapy. The use of G-CSF as primary prophylaxis reduced the incidence of febrile neutropenia by approximately 50% in these trials, in which the incidence of febrile neutropenia in the control group was high ($\geq 40\%$). The value of CSF in patients receiving less myelosuppressive regimens has not been clearly established. Pharmacoeconomic sensitivity analyses have suggested that CSF use is less likely to be cost-effective if the anticipated risk of febrile neutropenia is $< 20\%$.

Since most standard chemotherapy regimens are designed to induce a risk of neutropenic fever far less than 40%, the ASCO guidelines suggest that CSFs should not be used routinely with the initial cycles of chemotherapy. Primary prophylaxis with any CSF in the setting of conventional-dose chemotherapy should be reserved for patients who are judged to be at an unacceptably high risk of significant morbidity or mortality from chemotherapy-related infectious complications.

Secondary prophylaxis Available data indicate that the use of CSFs as secondary prophylaxis in patients who have had a prior episode of febrile neutropenia can decrease the likelihood of febrile neutropenia in subsequent cycles of chemotherapy. It is important to recognize that this conclusion has never been specifically proven in any randomized clinical trial. Rather, it has been derived from analyses of subsets of patients who crossed over from the placebo arms of the initial randomized clinical trials.

Thus, in clinical settings where maintenance of chemotherapy dose appears to be important, secondary prophylaxis with CSF to prevent new episodes of neutropenic fever is appropriate. However, in situations where clinical data supporting the value of maintaining dose intensity are lacking, chemotherapy dose reduction should be considered as an alternative to CSF use.

Therapeutic use is defined as the administration of a growth factor at the time when neutropenia or neutropenic fever is documented in a patient who had not been receiving CSF previously.

Clinical trials do not support the routine use of CSFs as an adjunct to antibiotics in the treatment of all patients with uncomplicated febrile neutropenia. Given the efficacy of most antibiotic regimens, the favorable outcomes usually attained with conventional approaches (including broad-spectrum antibiotics), and the potential "extra" cost associated with CSF therapy in patients who may exhibit rapid neutrophil recovery even without such therapy, it is unlikely that routine use of CSFs would have any significant impact on the clinical course of unselected patients with febrile neutropenia.

However, in certain high-risk patients who have features predictive of poor outcome (eg, sepsis syndrome, pneumonia, fungal infection), use of a CSF with antibiotics may be justified. In order to conduct appropriate clinical trials to test the hypothesis that CSF support may improve the outcomes of subsets of patients, selection of patients based on risk-stratification criteria that have been validated to predict poor outcomes or delayed recovery from neutropenia will be critical. Certain trials performed with more selective entry criteria have, in fact, shown statistically significant benefits from the use of CSFs as an adjunct to antibiotics in patients with febrile neutropenia. Further analyses of these data and the performance of larger-scale, confirmatory studies are needed to further assess the therapeutic use of CSFs.

There are no indications for CSF use to treat uncomplicated neutropenia without fever. A large-scale randomized clinical trial noted no difference in patients who had CSF support in whom afebrile neutropenia was detected vs those patients whose hematologic status was allowed to recover spontaneously without CSF support. Thus, low neutrophil counts alone do not represent a reason to prescribe CSF support.

Use to increase dose intensity of chemotherapy

The available evidence indicates that CSF use can permit chemotherapy dose maintenance or allow modest increases in dose intensity in clinical scenarios where the main toxicity is neutropenia. However, there has been no evidence of improved clinical outcomes from any level of increased dose intensification made possible with CSF-supported chemotherapy; specifically, the addition of CSF support to allow higher-than-standard levels of chemotherapy has not been shown to result in meaningful improvements in response rate, duration of response, or survival. The importance of dose continues to be a controversial topic in oncology. Nonetheless, available current data indicate that dose intensification for most common solid tumors does not significantly improve outcomes in general. Most importantly, increasing chemotherapy doses with stem-cell support does not change short-term clinical outcomes in women undergoing chemotherapy for breast cancer in either the adjuvant or metastatic therapy setting.

Nonetheless, in patients with potentially curable disease for which chemotherapy dose delivery may be critical, the use of CSF support to maintain dose intensity may be appropriate. Outside of clinical trials, and in the absence of strong evidence that dose is truly a critical determinant of outcomes, modification of

chemotherapy dose and implementation of reasonable supportive care measures remain sound alternatives.

Use following stem-cell transplantation

Autologous stem-cell and/or marrow transplantation High-dose chemotherapy with autologous hematopoietic stem-cell support has been used in the treatment of several malignancies, based on the notion that dose intensity may be an important determinant of response in chemosensitive malignancies. The prolonged period of myelosuppression following such cell-supported high-dose therapy, with its attendant increased risk of infectious and bleeding complications, has been deemed justifiable in such diseases as Hodgkin's disease, lymphomas, multiple myeloma, high-risk or relapsed germ-cell cancers, and sarcomas, for which other, less toxic therapeutic options yield suboptimal outcomes.

Several randomized trials have documented that CSFs can effectively reduce the duration of neutropenia, infectious complications, and hospitalization in patients who are receiving high-dose cytotoxic treatment with autologous bone marrow transplantation (BMT). GM-CSF was the first hematopoietic growth factor evaluated and approved for clinical use in this setting. G-CSF has subsequently been approved for this indication as well.

Allogeneic BMT Similar beneficial effects of CSFs have been seen following allogeneic BMT, and the routine use of hematopoietic growth factors is appropriate in this setting. There has been no evidence of any increase in graft-vs-host disease, graft rejection, or relapse with the use of CSFs.

Delayed or inadequate neutrophil engraftment CSFs can also be useful in patients who have delayed or inadequate neutrophil engraftment following progenitor cell transplantation.

Mobilization of PBPCs

CSFs have been used successfully to enhance mobilization of peripheral blood progenitor cells (PBPCs) into the peripheral blood. Available data suggest that mobilization of PBPCs may decrease the costs of harvesting cells and post-transplantation supportive care. Reinfusion of mobilized PBPCs following high-dose chemotherapy results in more rapid hematopoietic recovery than does autologous BMT. CSFs have also been utilized to mobilize donor PBPCs for allogeneic transplantation.

Administration of CSFs can enhance hematopoietic recovery following PBPC transplantation.

Use in myeloid malignancies

AML Since myeloid leukemia cells express receptors for CSFs, there has been a concern that leukemia cells might be stimulated after chemotherapy. However, given the high incidence of infectious complications following induction therapy for AML, especially in older patients, studies have evaluated CSFs in this setting. Data from several such studies demonstrate that CSFs, when given after the completion of induction chemotherapy, can shorten the duration of

neutropenia and may reduce infectious complications. There does not appear to be any overtly detrimental effect, on either response rate or regrowth of leukemia, of CSF administration following induction therapy.

GM-CSF has been approved for use in AML patients (≥ 55 years old) following induction therapy to shorten the time to neutrophil recovery and to reduce severe, life-threatening infections. Clinical data on the use of CSFs in younger patients (< 55 years old) are currently limited. G-CSF has also proven effective in mitigating myelotoxicity of leukemia therapy without increasing the risk of leukemic relapse or impairing response rates.

MDS Patients with myelodysplastic syndrome (MDS) are prone to infections related to neutropenia and functional abnormalities of mature neutrophils. While no data supporting the safety of long-term CSF use are available, short-term use of CSFs may be appropriate in severely neutropenic patients who experience recurrent infections. CSFs have not been shown to have a significant impact on clinical outcomes in patients with MDS or other marrow dysfunction states overall, perhaps reflecting abnormalities in the underlying stem-cell pool, which is unable to respond optimally to pharmacologic doses of CSFs.

Severe chronic neutropenia (ie, an absolute neutrophil count [ANC] < 500/μL) resulting from congenital, cyclic, or idiopathic neutropenia is often associated with recurrent infections. G-CSF is effective in normalizing neutrophil levels and significantly reducing the incidence of infections in > 90% of patients with these conditions.

TOXICITY

G-CSF

G-CSF has been a remarkably well-tolerated growth factor overall, based on extensive clinical experience with this cytokine over the past decade.

Bone pain The predominant side effect observed with the use of G-CSF is mild to moderate bone pain, which typically occurs in the lower back, pelvis, or sternum in about one-third of patients. Bone pain is usually seen at the initiation of G-CSF therapy or at the very beginning of neutrophil recovery. Occasionally, with vigorous marrow response to CSF stimulation, the pain can be severe and may require analgesics for control.

Uncommon side effects Other uncommon side effects include exacerbation of preexisting psoriasis, Sweet's syndrome (neutrophilic dermatitis), and cutaneous vasculitis. Chronic administration of G-CSF to patients with congenital or idiopathic neutropenia has been associated with splenomegaly.

Laboratory abnormalities observed with the rise in WBC count that occurs during G-CSF administration include elevations in serum lactate dehydrogenase (LDH), uric acid, and alkaline phosphatase levels. Finally, a modest decrease in platelet count without significant clinical sequelae has been reported occasionally with G-CSF use.

GM-CSF

Yeast-derived GM-CSF is generally well tolerated at recommended doses. In the transplant setting, no excessive toxicity is seen in patients treated with this form of GM-CSF, as compared with controls.

Constitutional symptoms In phase I-II trials in other settings, the most commonly reported side effects of GM-CSF have included constitutional symptoms, such as fever, bone pain, myalgia, headaches, and chills. These side effects have been dose- and schedule-dependent and are seen more frequently when GM-CSF is administered at higher doses and by continuous IV infusion than when given at recommended doses by the SC route.

Uncommon side effects Other less frequently observed side effects of GM-CSF include diarrhea, anorexia, facial flushing, dyspnea, and edema. Other side effects that have been reported with *Escherichia coli*–derived GM-CSF, such as the first-dose phenomenon and capillary leak syndrome, have rarely been observed with sargramostim.

Laboratory abnormalities, such as elevations of LDH, uric acid, and alkaline phosphatase, decreases in serum cholesterol and albumin, and occasional thrombocytopenia, have been reported with GM-CSF.

DOSE, ROUTE, AND SCHEDULE OF ADMINISTRATION

Recommended doses The recommended dose of the filgrastim version of recombinant human G-CSF is 5 μg/kg/d. This dose is clinically well tolerated and is effective in reducing the duration of neutropenia. Smaller trials have suggested that doses < 5 μg/kg/d may be effective in reducing the duration of neutropenia following chemotherapy. G-CSF also has been given in doses ≥ 100 μg/kg/d without dose-limiting toxicity. However, doses > 5 μg/kg/d have not been shown to have improved efficacy in supporting conventional chemotherapy, compared to lower doses.

G-CSF is used at a higher dose (10 μg/kg/d) for mobilization of progenitor cells and following BMT. Outside of the context of stem-cell mobilization and transplantation, however, there are no data indicating that doses in excess of 5 μg/kg/d are ever required.

The recommended dose of yeast-derived GM-CSF following autologous BMT is 250 $\mu g/m^2/d$ given by a 2-hour IV infusion. In phase I-II studies in the chemotherapy setting, activity has been observed at doses ranging from 250 to 750 $\mu g/m^2/d$. In patients with MDS, neutrophil responses have been seen at much lower doses (30 to ≥ 250 $\mu g/m^2/d$).

Although recommended doses in patients receiving chemotherapy are 5 μg/kg/d for G-CSF and 250 $\mu g/m^2/d$ for GM-CSF, rounding these doses to the nearest vial size is appropriate for cost-savings and convenience. In patients with MDS, the dose can be titrated to the smallest effective level to avoid untoward side effects.

Route of administration The SC route is the preferred route of administering both G-CSF and GM-CSF, for convenience. However, IV infusion is an acceptable route for both CSFs, if clinically indicated.

Timing of administration To obtain the greatest benefit from CSFs, the appropriate timing of administration is 24-48 hours following the completion of chemotherapy. CSF therapy should be continued until neutrophil recovery is adequate. The discontinuation of CSF therapy after neutrophil recovery is sometimes followed by a decline in ANC, especially in patients with compromised bone marrow reserve. This fall in neutrophil counts can be quite precipitous with G-CSF and appears to be somewhat less pronounced following discontinuation of GM-CSF. Therefore, blood counts should be checked before initiating the next cycle of chemotherapy.

Initiation of the next cycle of chemotherapy is not recommended for at least 24 hours after the completion of CSF therapy because of the potential concern that progenitor cells, which are rapidly dividing following CSF administration, may be sensitized to chemotherapy. Future trials should help determine the optimal interval that should be allowed between CSF discontinuation and initiation of the next chemotherapy cycle. There remains some theoretical concern that serial exposure of cycling progenitor cells to chemotherapy may accelerate cumulative marrow damage.

Because of the same concern, concurrent administration of CSFs with chemotherapy or radiotherapy is not recommended outside of the context of clinical trials. Trials using GM-CSF concurrently with radiotherapy to the chest area have shown excessive hematologic toxicity, especially thrombocytopenia. It has been speculated that CSF-mobilized progenitor cells in the great vessels may be sensitized to radiation delivered to the chest.

Next-generation versions of filgrastim: Implications for dosing There has already been a great deal of work done in testing an investigational new version of G-CSF in an effort to allow less frequent dosing. By attaching residues of polyethylene glycol to the protein backbone of G-CSF, a new molecule (pegfilgrastim) has been created with a longer half-life than the standard recombinant human G-CSF. This agent has recently been approved by the FDA under the trade name Neulasta. The efficacy and safety of treatment with pegfilgrastim have been reported at the annual meetings of ASCO and ASH. This molecule may allow dosing with a single injection per chemotherapy cycle (eg, 1 dose every 3 weeks).

Erythropoietin

Erythropoietin, an RBC lineage–specific glycoprotein hormone, was the first hematopoietic growth factor to become commercially available for clinical use in the United States. Recombinant human EPO has been approved for the treatment of anemia of chronic renal failure in predialysis or dialysis patients, anemia associated with zidovudine (Retrovir) therapy in patients infected with human immunodeficiency virus (HIV), anemia in cancer patients receiving

chemotherapy, and anemia in patients scheduled for elective, noncardiac, nonvascular surgery. In 2001, a new erythropoietic drug (darbepoetin alfa) was approved by the FDA to allow a new option of treatment of anemia associated with chronic renal failure. In 2002, darbepoetin alfa was aproved by the FDA for the treatment of chemotherapy-induced anemia in patients with nonmyeloid malignancies. Darbepoetin is a hyperglycosylated molecule based on the protein backbone structure of human erythropoietin. The increased level of glycosylation allows a longer duration of the drug in the circulation of humans after administration (up to 3 times longer half-life compared with EPO).

TREATMENT OF ANEMIA IN CANCER PATIENTS

Anemia is the most common hematologic problem in cancer patients and can be further exacerbated by administration of chemotherapy. Many of the symptoms of anemia, including fatigue, exercise intolerance, and depression, may contribute to a lack of well-being and diminished quality of life in cancer patients.

The etiology of anemia in patients with malignancy can be multifactorial, including anemia of chronic disease, diminished erythroid progenitor cells secondary to chemotherapy or radiotherapy, occult blood loss, nutritional deficiencies, and infiltration of the bone marrow by malignant cells. The mechanism for anemia of chronic disease appears to be related, in part, to elaboration of inflammatory cytokines, such as tumor necrosis factor (TNF), interferons, and interleukin-1 (IL-1). These inhibitory cytokines may contribute to diminished EPO production by the kidneys, decreased responsiveness of erythroid progenitors to EPO, and impaired iron utilization in the bone marrow.

Chemotherapy-induced anemia The anemia caused by chemotherapy is due mainly to drug effects on bone marrow precursor cells and is proportional to chemotherapy dose intensity. In addition, with platinum agents, anemia may be related to renal effects of these drugs on EPO production. Based on these observations, multicenter trials in the United States and Europe have examined the efficacy of recombinant human EPO in correcting the anemia of cancer and cancer therapies.

Several trials, both randomized and nonrandomized, support the hypothesis that recombinant erythropoietin can significantly reduce transfusion requirements and improve patient-reported quality of life. The functional and quality-of-life benefits noted with EPO supplementation appear to be independent of disease response to the concurrent anticancer chemotherapy, although patients with progressive disease derive less benefit than do patients with stable disease or an objective response to chemotherapy. In addition, the specific type of chemotherapy is irrelevant, as these effects have been noted with all types of chemotherapy.

Overall, about 60% of cancer patients receiving chemotherapy respond to EPO treatment. The cost-effectiveness of EPO therapy is very much related to the functional outcomes achieved with this treatment, and therapy should be monitored constantly to ensure that the results obtained are worthy of continuing the treatment with this agent.

There is no single, simple algorithm available to identify which patients may benefit most from erythropoietic therapy as an adjunct to chemotherapy. Available data suggest that patients with baseline anemia or a fall in hemoglobin value > 2 g/dL after the first cycle of chemotherapy are more likely to need blood transfusions. The best predictors of a clinical response to EPO therapy are an early rise in hemogloblin values and an increase in reticulocyte counts. A large (> 2,000-patient), community-based study found that 75% of patients who achieved at least a 1-g/dL rise in hemoglobin by week 4 of EPO therapy subsequently had even more robust evidence of response to EPO and clinical benefit.

DOSE AND SCHEDULE OF ADMINISTRATION

The current FDA-approved recommended initial dose of EPO in cancer patients is 150 U/kg SC 3 times a week. This dose can be increased to 300 U/kg 3 times weekly if an adequate response (ie, a decrease in transfusion requirements or rise in hemoglobin value [≥ 1 g/dL]) does not occur after 4 weeks of therapy. However, very few oncologists use the thrice-weekly regimen of EPO dosing anymore. A more common practice, based on data from several clinical trials, is to administer EPO at a dose of 40,000 units SC *once weekly*. This dose is well tolerated and appears to be equivalent in clinical effectiveness to three-times-weekly dosing while increasing patient convenience. EPO is approved by the FDA for once-weekly administration in the surgery population. A recent pharmacokinetic/pharmacodynamic study in healthy volunteers demonstrated that once-weekly EPO doses of 600 U/kg resulted in similar increases in hemoglobin level as did 150 U/kg 3 times weekly.

A patient who does not respond after 8 weeks of EPO therapy (despite a dose increase) is unlikely to respond to higher doses. The dose of EPO should be reduced appropriately if there is a rapid rise in hemoglobin or if hematocrit values exceed 40% and should be titrated to maintain the desired hemoglobin value. If response is suboptimal, the clinician should consider checking levels of nutritional cofactors (eg, iron). Patients (especially premenopausal women) may require supplemental iron to avoid depletion of marginal iron stores and to adequately support erythropoiesis stimulated by EPO.

Darbepoetin alfa has a longer half-life than EPO and requires less frequent dosing. The current FDA-approved recommended initial dose of darbepoetin alfa in cancer patients is 2.25 µg/kg SC once a week. This dose can be increased to 4.5 µg/kg once a week at 6 weeks if hemoglobin increases less than 1 g/dL. However, in the community oncology setting, the dose of darbepoetin alfa often used is 200 µg/kg every 2 weeks, with an increase to 300 µg/kg every 2 weeks at 6 weeks if hemoglobin increases less than 1 g/dL.

ADVERSE REACTIONS IN CANCER PATIENTS

When given at recommended doses, EPO has been well tolerated in cancer patients receiving chemotherapy.

In a randomized, placebo-controlled trial, 93 patients who had received platelet transfusions for thrombocytopenia (nadir platelet count, ≤ 20,000/μL during the preceding chemotherapy cycle) were randomized to receive placebo or IL-11 at 25-50 μg/kg SC once daily for 14-21 days following the same doses of chemotherapy. Of the 82 evaluable patients, 8 of 27 treated with 50 μg/kg of IL-11 ($P < .05$), 5 of 28 treated with 25 μg/kg ($P = .23$), and 1 of 27 given placebo avoided platelet transfusions. Side effects of IL-11 consisted of fatigue, fluid retention, and cardiovascular symptoms, including atrial arrhythmia (10% of patients) and syncope *(Tepler I, Elias S, Smith JW II, et al: Blood 87:3607, 1996).*

Hypertension associated with a significant rise in hemoglobin has been observed rarely in cancer patients receiving EPO therapy. Therefore, blood pressure should be monitored carefully, especially in patients with a history of hypertension or cardiac disease.

Seizures Occasionally, seizures have been observed in patients with underlying CNS disease and in the context of a significant rise in blood pressure.

Cytokines with thrombopoietic activity

Although G-CSF and GM-CSF have significantly reduced neutropenia in patients receiving chemotherapy, thrombocytopenia still remains a frequent dose-limiting toxicity of several chemotherapeutic regimens. Several hematopoietic cytokines with thrombopoietic activity have been evaluated in clinical trials. These include IL-1, IL-3, IL-6, IL-11, thrombopoietin (TPO), megakaryocyte growth and development factor (MGDF), and hybrid/synthetic cytokines, such as PIXY321 (a GM-CSF/IL-3 fusion protein) or SC71858 (promegapoietin, a synthetic cytokine comprising mutated versions of IL-3 and TPO).

Most of these cytokines have shown modest thrombopoietic activity and have the potential to induce nonspecific biological activities, including some undesirable effects. To date, IL-11 is the only thrombopoietic cytokine that has received FDA approval for clinical use.

Interleukin-11

IL-11 is a pleiotropic cytokine with thrombopoietic activity. In vitro, IL-11 acts synergistically with other hematopoietic growth factors, such as TPO, IL-3, and stem-cell factor (c-kit ligand), to promote the proliferation of hematopoietic progenitor cells and to induce maturation of megakaryocytes.

IL-11 was approved by the FDA to prevent severe thrombocytopenia and to reduce the need for platelet transfusions following myelosuppressive chemotherapy in patients with nonmyeloid malignancies who are at risk of severe thrombocytopenia based on the results of a randomized clinical trial of IL-11 in cancer patients who required at least one platelet transfusion after a chemotherapy cycle. In this trial, the use of IL-11 as secondary prophylaxis reduced the need for platelet transfusions in a subsequent cycle of chemotherapy.

However, it should be recognized that severe thrombocytopenia requiring platelet transfusions is an uncommon acute problem with initiation of standard-dose chemotherapy. Nonetheless, thrombocytopenia can represent a cumulative

problem with the many chemotherapeutic regimens often used to treat solid tumors, especially in patients with more heavily pretreated marrows.

Major bleeding is a rare complication related to chemotherapy-induced thrombocytopenia. Therefore, the appropriate use of thrombopoietic agents will require careful attention to several end points, including the need for platelet transfusions, ability to deliver chemotherapy without treatment-limiting thrombocytopenia, the safety profile of the thrombopoietic agent, and the associated health care costs.

Dose and schedule of administration The recommended dose of IL-11 in adults is 50 μg/kg SC once daily. Therapy is started from 6 to 24 hours after the completion of chemotherapy and is continued until the post-nadir platelet count is ≥ 50,000/μL. Dosing beyond 21 days per treatment cycle is not recommended.

Adverse reactions Patients treated with IL-11 commonly experience mild to moderate fluid retention, as manifested by peripheral edema and/or dyspnea. In some patients, preexisting pleural effusions have increased during IL-11 administration. Therefore, patients with a history of pleural or pericardial effusions or ascites should be carefully monitored during IL-11 therapy. In addition, fluids and electrolytes should be monitored carefully in patients requiring the use of a diuretic.

Moderate decreases in hemoglobin values (thought to be related to dilutional anemia) have also been observed in patients receiving IL-11. The fluid retention and anemia are reversible within several days after IL-11 is discontinued.

IL-11 should be used with caution in patients with a history of cardiac arrhythmias, since palpitations, tachycardia, and atrial arrhythmias (atrial fibrillation or flutter) have been reported in some patients receiving this agent.

The next generation of blood growth factors will take advantage of molecular engineering techniques with the aim of allowing more convenient dosing with equivalent or improved effectiveness. The paradigm of this approach has been the development of darbepoetin alfa, which was genetically engineered to exhibit an improved pharmacokinetic profile in humans. The result of this work has been the availability of an FDA-approved novel erythropoietic stimulatory agent with a safety profile similar to the currently available recombinant human erythropoietin. A different technique has been used to create a longer-lasting version of recombinant human G-CSF. Other molecules to target and stimulate hematopoietic growth factor receptors are also in clinical development, including orally available new drugs.

Thrombopoietin

TPO is a lineage-dominant hematopoietic cytokine that regulates proliferation and maturation of cells of the megakaryocyte/platelet lineage. Preclinical studies have clearly shown that TPO cells are the key regulators of megakaryocyte mass and platelet production. Mice with induced genetic defects in TPO or its receptor, c-*mpl*, have > 90% loss of platelet production capacity.

The results of initial clinical trials of TPO are encouraging and suggest an important role for this agent in the treatment of cancer patients undergoing myelo-

suppressive treatment. No recombinant version of TPO has yet been approved by the FDA, showing the difficulty in developing thrombopoietic growth factors.

Development of TPO and related molecules has been complicated by the development of antibodies directed against some—but not all—of the recombinant human versions of this molecule. Clinical development of MGDF, a highly truncated recombinant version of TPO, was halted due to the occurrence of neutralizing antibodies directed against TPO. These potentially dangerous antibodies could prolong thrombocytopenia. However, similar antibodies have not been detected with the full-length version of recombinant human TPO. For that reason, further clinical trials of TPO continue. This promising agent does not produce the edema or other nonspecific side effects that occur with IL-11, and, thus, further data from larger trials of TPO are awaited.

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CHAPTER 42

Depression, anxiety, and delirium

Alan Valentine, MD

Psychiatric disorders are common in the setting of malignant disease, occurring in almost 50% of patients. Many cancer patients cope well with their disease. For those who do not, untreated psychological and neuropsychiatric disorders can seriously compromise quality of life and treatment compliance. Although there are a wide variety of presentations, three behavioral syndromes that are often encountered in clinical practice will be discussed here: depression, anxiety, and delirium.

Depression

"Depression" exists on a continuum ranging from an emotion common in daily life (sadness) to a syndrome of severe physical and psychological symptoms consistent with a defined psychiatric disorder (major depressive disorder).

In cancer patients, identical symptoms may be caused or influenced by physical (eg, tumor site, pain), psychological (eg, stress, premorbid function, maturity), and social (eg, finances, interpersonal relationships) factors. Depression occurs more frequently in the setting of severe illness; several studies of cancer inpatients report a prevalence of 25%-42%.

SIGNS AND SYMPTOMS/DIAGNOSIS

Patients with depressive syndromes experience specific symptoms that vary in intensity and severity.

Psychological symptoms include dysphoria (sadness), anhedonia (pervasive loss of pleasure in activities), feelings of guilt or low self-esteem, and thoughts of death or suicide.

Somatic symptoms include sleep disturbance, change in appetite, loss of libido, fatigue, diminished concentration, and psychomotor agitation or withdrawal.

Focus of diagnostic evaluation Although the diagnosis of major depressive disorder requires that multiple symptoms (including dysphoria or anhedonia) must be present for at least 2 weeks, patients who do not meet these criteria may be in significant distress. The diagnosis of depression in medi-

cally ill patients is complicated by the fact that somatic symptoms of depression may also be caused by factors related to disease and treatment. For this reason, when evaluating the depressed cancer patient, special attention should be paid to psychological symptoms, which are less likely to be directly related to treatment.

ETIOLOGY

Psychological causes

Isolated symptoms Isolated depressive symptoms, if temporally related to an identifiable stressor, may be classified as adjustment disorders. In the setting of malignancy, obvious stressors include the initial diagnosis, treatment failure, or disease progression. Patients may also face potential psychosocial stressors, including changes in independence, body image, finances, and family function, as well as issues related to death and dying.

Persistent symptoms Persistent mood symptoms may indicate the presence of an evolving major depressive disorder. Major depressive disorder is common in the general population (point prevalence, ~6%) and is a recurrent disease. Patients with a history of mood disorder are at risk for relapse in the face of a cancer diagnosis.

Disease- and treatment-related causes

Presenting symptom of malignancy Depression may be a presenting symptom of some primary malignancies, including primary pancreatic and gastric carcinomas. Primary and metastatic brain tumors may cause frontal lobe syndromes or personality changes that mimic depression and other psychiatric disorders.

Drugs Many drugs used in general medical practice are associated with psychiatric syndromes. The most common of these are β-blockers, antihypertensives, barbiturates, opioids, and benzodiazepines.

In contrast, few drugs used as primary and supportive therapies for cancer are commonly associated with depression. The exceptions to this rule are corticosteroids, cytokines (especially interferon-alfa [IFN-α; Intron A, Roferon-A] and interleukin-2 [Proleukin]), and whole-brain radiation therapy. Depressive syndromes may also be seen with certain chemotherapeutic agents, including asparaginase (Elspar) and procarbazine (Matulane). Patients treated with tamoxifen may complain of depression or "chemobrain." The latter term usually refers to cognitive slowing. Day and colleagues, extending their earlier work, have recently shown a lack of association between tamoxifen treatment and depression, even in women at higher risk for mood disorders.

MANAGEMENT

Management of depressive syndromes involves accurate diagnosis, use of antidepressant medication, and psychotherapy. Patients should be assessed

for somatic and psychological symptoms of depression. The clinician should always ask about suicidal thoughts or intent. Metabolic and thyroid function should be evaluated, and medications should be reviewed.

The decision to treat depression is a matter of clinical judgment. *If mood disorder symptoms adversely affect quality of life, work or family relationships, or ability to participate in cancer therapy, intervention is indicated.* Because the diagnosis of depression can be difficult to make in patients with cancer, it is best to have a low threshold for the initation of treatment, in order to minimize the risk of missing a reversible disorder.

TABLE 1: Selected antidepressants used in cancer patients

Drug	Starting dose	Maintenance dose	Comments
Selective serotonin reuptake inhibitors			
Sertraline	25-50 mg qAM	50-150 mg/d	Usually well tolerated; possible nausea
Fluoxetine	10-20 mg qAM	20-60 mg/d	Long half-life; possible nausea, sexual dysfunction
Paroxetine	20 mg/d qAM	20-60 mg/d	Possible nausea, sedation
Citalopram	20-60 mg	20-60 mg/d	Usually well tolerated; possible nausea, sexual dysfunction, fatigue
Tricyclic antidepressants			
Nortriptyline	25-50 mg qhs	50-200 mg/d	Moderate sedation; useful for neuropathic pain
Amitriptyline	25-50 mg qhs	50-200 mg/d	Maximal sedation; anticholinergic effects; useful for neuropathic pain
Desipramine	25-50 mg qAM or hs	50-200 mg/d	Modest sedation; anticholinergic effects; useful for neuropathic pain
Other agents			
Venlafaxine	18.75-37.5 mg	75-225 mg/d	Possible nausea; may be useful for neuropathic pain, hot flashes
Bupropion	50-75 mg	150-450 mg/d	Activating; no reports of sexual dysfunction; risk of seizures in predisposed patients
Methylphenidate	5 mg (2.5 mg qAM, noon)	10-60 mg/d	Activating; rapid effect possible; monitor blood pressure
Mirtazapine	15 mg qhs	15-45 mg qhs	Sedating, variable appetite-stimulant, antiemetic effects

Antidepressants

Selected antidepressants used in cancer patients are listed in Table 1. No antidepressant has been shown to be more effective than any other in the cancer setting. Often, the choice of an antidepressant is based on side effect profile.

In the general population, antidepressants often take at least 2 weeks or longer to produce initial relief of symptoms. There is some anecdotal evidence that more rapid effect is seen in cancer patients. As a general rule, antidepressant therapy should continue for 4-6 months after symptoms stabilize.

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), and citalopram (Celexa), are often used in patients with cancer because of their benign side effect profile. In particular, their lack of anticholinergic and α-adrenergic–blocking properties makes them attractive options for patients with a serious medical illness.

Unlike the tricyclic agents (discussed below), the SSRIs are not lethal in overdose, making them a safe choice in the treatment of patients experiencing suicidal ideations.

Side effects Mild nausea and anxiety are common side effects of all SSRIs, which vary in severity from patient to patient. Sexual dysfunction may occur with fluoxetine and paroxetine. Sedation may occur with paroxetine.

Dosage In ambulatory patients with normal metabolic function, SSRIs can be started at the same doses used in general psychiatry (ie, 20 mg/d qAM for fluoxetine, 50 mg/d qAM for sertraline, 20 mg/d qAM for paroxetine). These doses can be increased if there is no response within 2-3 weeks.

Hospitalized or elderly patients, those with compromised renal or hepatic function, and those receiving highly emetogenic treatments should be started at one-half or even one-quarter of these starting doses, which can then be increased if tolerated.

Tricyclic antidepressants (TCAs) These older antidepressants (eg, amitriptyline, nortriptyline, and desipramine) remain effective options for the treatment of depression in cancer patients. The sedative properties of TCAs (amitriptyline > nortriptyline > desipramine) can be useful in the treatment of insomnia associated with depression. In addition, TCAs are useful adjuncts in the treatment of neuropathic pain.

TCAs have the advantage of established therapeutic blood levels, although the applicability of these levels to cancer patients is uncertain.

Side effects The common side effects of TCAs include sedation, dry mouth, orthostatic hypotension, constipation, and blurred vision. These side effects are related to anticholinergic, α-adrenergic–blocking, and antihistaminic properties of TCAs and are often the reason these drugs are not used as first line of treatment in depressed medically ill patients. TCAs must be used cautiously in patients with active suicidal ideations and in those with cardiac conduction abnormalities.

Dosage Initial dosing of TCAs should be conservative (25-50 mg PO qhs for nortriptyline, 25-50 mg qhs for amitriptyline, 25-50 mg qAM or hs for desipramine), with escalation if tolerated every 4-7 days. Therapeutic response is sometimes seen at doses lower than those used in the general population, that is lower than 75-150 mg/d for nortriptyline, 150-300 mg/d for amitriptyline, and 200-300 mg/d for desipramine.

Atypical and newer antidepressants Bupropion (Wellbutrin) is activating, which may be of potential benefit in patients with psychomotor slowing. Another advantage is that it is not associated with sexual dysfunction. However, bupropion has been associated with seizures and, therefore, should be used with caution (if at all) in patients with a current or past history of seizures.

Venlafaxine (Effexor), nefazodone (Serzone), and mirtazapine (Remeron) are newer agents with selective effects on serotonin and norepinephrine metabolism. They may exacerbate nausea and should be started at low doses to establish whether they can be tolerated. Venlafaxine may be effective against treatment-induced hot flashes. Mirtazapine has sedative, appetite-stimulant, and antiemetic effects, which can be very useful in selected cases.

Psychostimulants

Psychostimulants that have direct or indirect dopamine-agonistic properties, such as dextroamphetamine, methylphenidate, and pemoline (Cylert), have an established role in the treatment of depression in the medically ill. Psychostimulants are activating agents useful in patients with psychomotor retardation, deconditioning, or apathy states associated with depression, as well as in those with CNS disease or treatment side effects.

The antidepressant effects of psychostimulants may be seen more quickly than those of first-line antidepressants. Improvements in mood, physical activity, well-being, and appetite are sometimes observed within 24-48 hours of the initiation of psychostimulant treatment.

Side effects Like other activating agents, psychostimulants may cause insomnia, anxiety, palpitations, and GI upset. Hypertension or hypotension may also occur.

Dosage Initial dosing should be conservative (eg, 5 mg/d in 2 divided doses every morning and noon for methylphenidate, 5 mg/d qAM for dextroamphetamine). If tolerated, stimulant doses can be increased until a therapeutic effect is achieved or side effects develop.

Psychotherapy

Although antidepressants alone are effective in the treatment of depression, patients often require and benefit from psychotherapy.

In some cases, this can be limited to support while response to medication is monitored. Other patients may require cognitive-behavioral interventions to help them deal with misperceptions about disease status or to resolve preexisting issues.

For some patients, group therapy can be helpful, although others find it difficult to interact with patients who are equally or more severely ill.

Anxiety

Like depression, the term "anxiety" refers to both a subjective emotion and a constellation of signs and symptoms that can be of physical or psychological origin.

Especially in seriously ill patients, subjective anxiety may be the first sign of a serious or catastrophic medical event. It is also common at disease milestones, especially at initial diagnosis, time of recurrence, and progression to the terminal phase. In patients whose disease is stable or in remission, anxiety frequently occurs before or at the time of routine reevaluation.

SIGNS AND SYMPTOMS/DIAGNOSIS

Psychological symptoms Patients who experience anxiety typically complain of feeling worried, irritable, and frightened. They may appear depressed; there is considerable comorbidity between the two syndromes. Patients are often hyperalert and hypervigilant. The affective state is labile; individuals may cry suddenly or experience paroxysmal temper outbursts. Thought processes are ruminative; individuals cannot distract themselves from worry.

If anxiety proceeds to panic, patients may experience feelings of impending doom or annihilation. Occasionally, distress is so intense that patients experience suicidal thoughts. The hyperaroused state makes sleep difficult and impairs appetite. Physical and psychological fatigue and exhaustion may follow.

Physical symptoms Numerous physical symptoms may be experienced, especially as anxiety becomes more severe.

Cardiovascular signs and symptoms include palpitations and tachycardia, as well as subjective chest tightness or pain.

Respiratory symptoms include dyspnea; patients may hyperventilate and feel light-headed or dizzy.

GI symptoms are common and include difficulty in swallowing, abdominal cramping, nausea, diarrhea, and constipation.

Patients may become diaphoretic. Preexisting pain may be aggravated.

ETIOLOGY

Psychological causes

For many patients, the diagnosis of cancer is extremely stressful. Anxiety is often a function of fear. Patients anticipate the possibility of pain, suffering, or death. Concerns about loss of control and independence, finances, and family obligations also contribute.

Painful or unpleasant diagnostic or therapeutic procedures and medications may lead to anxiety, which can become conditioned. For example, conditioned anxiety states, such as anticipatory nausea, develop in some individuals after such treatments as chemotherapy and confinement for bone marrow transplantation.

Patients who achieve remission often worry about possible recurrence. Associated anxiety may become more pronounced shortly before clinic visits or tests.

Anxiety may also become more pronounced when active treatment ends. In some cases, the process of diagnosis and treatment is so psychologically difficult that a post-traumatic stress disorder develops.

Generalized anxiety disorder and panic disorder are relatively common in the general population. Affected individuals are at risk for exacerbation of the anxiety disorder in the face of a cancer diagnosis. Individuals who have specific phobias (eg, to blood, needles, or hospitals) will likely suffer intense anxiety at diagnosis or during treatment and may require referral to a mental health specialist.

Especially in the elderly, anxiety may mask an underlying mood disorder, usually depression.

Disease- and treatment-related causes

Toxic-metabolic states Hypoxia should be the initial metabolic consideration in anxious patients. Possible causes include anemia and pulmonary edema.

Anxiety may be the initial manifestation of pulmonary embolus.

Electrolyte disturbances may cause anxiety, especially if they are severe or occur in the setting of CNS impairment.

Endocrine disturbances (eg, hyperthyroidism, hypercalcemia, and hyperadrenalism) also can cause anxiety. These endocrine disturbances may be preexisting conditions, a function of disease, and/or a side effect of treatment.

Anxiety may be an early sign of sepsis.

Drugs Several medications commonly used in oncology may cause anxiety of variable severity. For example, corticosteroids can produce anxiety that varies from mild nervousness to frank agitation resembling mania.

Antiemetics, including promethazine, prochlorperazine, and metoclopramide, are associated with akathisia, a sense of internal restlessness and anxiety that compels patients to move in order to achieve relief. The anxiety can be quite severe; patients suffering from severe akathisia have attempted suicide. Antipsychotic medications (eg, haloperidol, chlorpromazine) also can cause akathisia.

Anticholinergic medications (eg, benztropine), opioids, and benzodiazepine anxiolytics can cause paradoxical reactions that include anxiety; this is especially true in geriatric patients and in those with CNS impairment.

Drug toxicity (eg, immunosuppressants, bronchodilators, psychostimulants) and drug withdrawal states (eg, opioids, benzodiazepines, alcohol) often produce anxiety, which may evolve into delirium.

Disease factors The most important of these factors is inadequate pain relief, which may cause or exacerbate anxiety and depression. Hormone-secreting tumors (eg, pheochromocytomas, small-cell lung tumors, some thyroid carcinomas) also may cause paroxysmal symptoms of anxiety or panic.

MANAGEMENT

The initial approach to anxious patients depends on the severity of anxiety and their medical status. In all cases, the multiple possible medical causes of anxiety should be considered and addressed or corrected. In some cases, it is not possible to remove offending medications (ie, corticosteroids), and symptomatic relief must be provided while these agents continue to be used.

Psychotherapy

Supportive therapy of anxious patients is universally appropriate. Anxious patients benefit from reassurance that they are not alone, that help is available, and that action will be taken to help them deal with the cause of their distress.

Patients suffering from phobic or conditioned anxiety states, as well as those with anxious depression, may benefit from specialized treatment, including cognitive therapy, guided imagery, self-relaxation training, and biofeedback. These techniques, which may require referral to a specialist, provide patients with a sense of control and teach skills that can be applied to minimize future threats.

Anxiolytics

Selected anxiolytic medications that are commonly used to treat anxiety in cancer patients are listed in Table 2.

Benzodiazepines are the mainstays of pharmacologic treatment of anxiety. These medications are generally safe and effective. Issues related to dependence or oversedation are usually not of major concern.

Benzodiazepines have variable hypnotic, antiemetic, and muscle-relaxant effects useful in other aspects of supportive care of cancer patients. Caution is required when these agents are used in the settings of serious illness (because of the risk of additive sedation with other medications), advanced age, or CNS impairment (because of the risk of disinhibition or delirium).

TABLE 2: Selected drugs used to treat anxiety in cancer patients

Drug	Dose range (prn or scheduled)	Comments
Benzodiazepines		
Lorazepam	0.5-2.0 mg PO/IM/IVP/IVPB q4-12h	Versatile; favorable metabolic profile useful in severely ill; can be administered via continuous infusion in rare cases
Alprazolam	0.25-1.0 mg PO q6-24h	Potent, rapid onset and cessation of effects; tolerance may develop quickly; antidepressant effects
Diazepam	2-10 mg PO/IM/IV q6-24h	Useful for general/persistent anxiety but problematic in elderly or seriously ill patients
Clonazepam	0.5-2.0 mg PO q6-24h	Useful for general/persistent anxiety, episodic anxiety, and aggressive behavior in some CNS-impaired patients

IVP = IV push; IVPB = IV piggyback

Short-acting benzodiazepines, such as lorazepam and alprazolam, have a rapid onset but relatively short duration of action, making them useful for treating intermittent paroxysmal anxiety or panic attacks. For the same reason, they are also useful in patients with severe medical illness.

Typical doses are 0.5-1.0 mg PO/IM/IVP/IVPB (lorazepam) every 4 to 12 hours or 0.25-0.5 mg PO (alprazolam) every 6 to 8 hours as needed. For patients with persistent anxiety, these medications can be given on a regular schedule.

In cases of extremely severe anxiety, lorazepam may be administered via continuous infusion. Its lack of active metabolites make it a good choice in patients with hepatic or renal compromise.

Tolerance develops more rapidly to short-acting benzodiazepines than to their longer-acting counterparts. Therefore, if short-acting agents are used for any length of time, they should be discontinued gradually.

Longer-acting benzodiazepines, such as diazepam and clonazepam, are useful for persistent anxiety. Their longer duration of action is such that they do not "wear off" quickly, leaving patients unprotected. Tolerance does not develop as quickly to these agents, and patients with generalized anxiety disorders may be maintained on them for years.

Clonazepam is typically given at a dose of 0.5-1.0 mg every 6 to 8 hours on a scheduled basis, whereas the diazepam dose typically starts at 2-10 mg every 6 to 24 hours. Higher doses are often required.

These drugs have multiple active metabolites that can adversely affect the elderly and patients with renal or hepatic impairment. In these patients, it is best to "start low and go slow."

Other medications At low doses, antipsychotic medications, such as thioridazine, haloperidol, and risperidone (Risperdal), may be used as anxiolytics. These agents are most appropriate for patients with a history of adverse reactions to benzodiazepines or for those at high risk for these reactions.

Opioid analgesics are effective anxiolytics in some terminally ill patients, especially those in whom compromised respiratory function is a cause of anxiety.

Delirium

Delirium (also known as encephalopathy, acute confusional state, and other names) is the most common mental disorder of purely organic origin in the cancer setting. This syndrome is characterized by diffuse brain dysfunction, caused by one or more pathologic factors related to disease or its treatment.

The prevalence of delirium is a function, in part, of the severity of medical illness. In some surveys, 15%-30% of cancer inpatients and up to 85% of those who are terminally ill experience delirium. The overall prevalence of delirium in the inpatient setting is expected to increase with the aging of the general population.

SIGNS AND SYMPTOMS/DIAGNOSIS

The onset of delirium is acute, within hours to days, and is characterized by alterations in arousal, perception, and cognition. There may be a prodromal phase of irritability or anxiety.

Alterations in arousal Delirious patients demonstrate a sensorium (or level of alertness) that varies from hyperalert and vigilant to obtunded or stuporous. Psychomotor activity varies in a similar way; a hyperactive or hypoactive delirium may be encountered.

Alterations in perception/cognition Delirious patients may have perceptual difficulties, with illusions and hallucinations, which they cannot distinguish from reality. Patients may also experience delusions, often of the paranoid type. Typically, patients have lucid intervals (minutes to hours), during which their mental status appears to be appropriate and intact.

Cognition is impaired because patients cannot attend to and register new information.

Other signs/symptoms Typically, delirious patients have a disordered sleep/wake cycle, which may be a function of the delirium or may be a preceding cause. Autonomic dysfunction may be encountered in patients with hyperaroused states.

Left untreated, delirium may resolve spontaneously or evolve into another neuropsychiatric disorder. Failure of delirium to resolve with aggressive management may signal a preterminal event.

ETIOLOGY

Disease- and treatment-related causes

As with anxiety states, delirium can have many possible causes in cancer patients. Often, etiology is multifactorial, and in up to 50% of cases, a definite etiology cannot be identified.

Direct and indirect disease effects Primary and metastatic brain tumors will occasionally present as delirium, as will leptomeningeal carcinomatosis and paraneoplastic syndromes. Most, but not all, patients with these diseases also have frank neurologic signs.

Toxic-metabolic abnormalities Hypoxia, which often causes anxiety, may also produce delirium, especially as a function of a rapidly evolving insult.

Severe electrolyte disturbances, especially sodium and potassium, may cause delirium, as may altered serum calcium and magnesium levels.

Other common toxic-metabolic causes of delirium include liver and renal failure, systemic or CNS infection, and severe nutritional deficiencies.

Cancer therapies Corticosteroids, which are ubiquitous in cancer treatment, produce a wide variety of psychiatric side effects, including an agitated psychotic state that resembles delirium.

Irradiation of the brain occasionally causes delirium, which typically begins during or immediately after the completion of treatment. This side effect is thought to be due to edema and raised intracranial pressure. It is usually controlled or prevented by corticosteroid therapy.

Chemotherapeutic and biotherapeutic agents Many chemotherapeutic and biotherapeutic agents have been associated with delirium or encephalopathic states, although some are more often responsible than others. They include ifosfamide (Ifex), methotrexate, and cytarabine (cerebellar syndrome). Interleukin-2, alone or in combination with IFN-α, may cause an agitated delirium. Toxic levels of immunosuppressants (eg, FK-506) and antiviral agents also have been associated with encephalopathies.

Other drugs Benzodiazepines, opioid analgesics, and anticholinergic medications (eg, benztropine) can induce delirium in certain situations. Usually, this occurs when high doses of these agents are used in seriously ill patients. However, the elderly and patients with CNS compromise are vulnerable to this adverse effect when given low doses, especially at night.

Severe alcohol withdrawal is a common cause of hyperactive delirium.

MANAGEMENT

Evaluation

Initial management of delirium involves a search for a reversible cause. In all cases, physical and neurologic examinations are indicated. An exhaustive work-up for all possible causes is usually not necessary. The patient's clinical situation and known history should provide guidance. Attention should be paid to the patient's metabolic and respiratory status. Evaluation of hepatic and renal function should be completed.

The role of prescribed and illicit medications, chemotherapeutic agents, and biotherapeutic agents should be considered.

Diagnostic tests Diagnostic imaging of the brain (eg, CT, MRI) may be indicated. In some cases, electroencephalography may help establish the presence of an encephalopathic state. Assessment of CSF is appropriate for patients with suspected CNS infection or leptomeningeal carcinomatosis.

TABLE 3: Selected medications used to treat delirium in cancer patients

Drug	Dose range	Comments
Antipsychotics		
Haloperidol	0.5-2.0 mg PO/IM/IVPB/SC q4-12h	IV route twice as potent as PO route and has fewer side effects; 2.0-5.0-mg bolus/continuous infusion for severe agitation
Chlorpromazine	25-100 mg PO/IM/IVP/IVPB q4-12h	Very sedating; may be administered as continuous infusion; monitor blood pressure
Risperidone	0.5-3.0 mg PO q12-24h	Useful in elderly patients; may pose lower risk of parkinsonian effects; not useful for severe agitation
Benzodiazepine		
Lorazepam	0.5-4.0 mg PO/IM/IVP/IVPB q4-12h	Most effective when used with an antipsychotic; when used alone can exacerbate delirium; may be administered as a continuous infusion
Anesthetic		
Propofol	10-50 mg IV qh	Rapid onset, short duration of action; not an antipsychotic; dose can be titrated to desired level of sedation

IVP = IV push; IVPB = IV piggyback

Behavioral management

The patient's safety must be secured. Depending on individual circumstances, this may require close observation, use of physical restraints, or neuroleptic medications. Unless there is a medical contraindication, restraints should not be used without medications to assist in calming the patient.

Ideally, patients should be managed in a setting of moderate environmental stimulation. Both sensory overstimulation and deprivation are disadvantageous. Because delirious patients are often anxious or frightened, the presence of family members can provide reassurance.

Antipsychotics

If more conservative measures are ineffective, pharmacotherapy is required to treat delirium. Antipsychotic medications treat sensory and cognitive misperceptions as well as provide anxiolysis and some degree of sedation. Table 3 lists selected drugs often used to treat delirium in cancer patients.

Haloperidol is a potent antipsychotic that may administered by PO, IM, IV, or SC routes (with the SC route often used for terminal delirium). The IV formulation is twice as potent as the PO preparation.

Side effects Haloperidol is usually well tolerated, although it does carry a risk of producing akathisia and parkinsonian side effects. These side effects can be treated with benztropine, benzodiazepines, and other medications. The risk of these adverse reactions can be minimized by IV administration.

Dosage Elderly or end-stage patients usually require very modest doses (0.5-1.0 mg PO or IV at night or twice daily) to control delirium. Especially in hyperactive delirium, higher and more frequent dosing is usually required (eg, 2-5 mg PO/IVPB every 6 hours). Total doses of ≥ 100 mg/d may be administered via a continuous infusion in unusual cases.

Chlorpromazine is a potent antipsychotic that is more sedating than haloperidol and may be administered by the same routes. *Typically*, chlorpromazine is given at a dose of 25-50 mg PO/IVPB every 6 to 12 hours. Rapid calming of an agitated patient may require IM or IV doses of 50-100 mg. Chlorpromazine can be given by IV infusion if necessary.

Chlorpromazine has significant anticholinergic and α-adrenergic–blocking effects, which can be problematic if used in seriously ill patients or elderly patients vulnerable to hypotensive episodes.

Risperidone is given orally. At doses of 0.5-3.0 mg once or twice daily, it is useful in treating low-intensity delirium or delusional symptoms, especially in elderly patients, in whom it may have fewer adverse effects than oral haloperidol. Risperidone is not useful for treating acute agitation.

Other agents

Benzodiazepines are used as adjuncts in the control of hyperactive delirium. They are the treatment of choice for alcohol withdrawal delirium. Lorazepam, 0.5-4.0 mg IV or IM may be given with haloperidol to rapidly control acute agitation. It is sometimes effective to alternate doses of lorazepam and haloperidol every 30 minutes until the patient falls asleep.

Benzodiazepines do not have antipsychotic properties and, if used by themselves, will exacerbate disinhibition and cognitive impairment of a delirious patient, unless a sufficiently large dose is given to cause sleep.

Propofol (Diprivan) is a short-acting anesthetic that is effective in achieving rapid sedation. It is often administered as a continuous IV infusion in the ICU setting. Propofol does not have antipsychotic properties.

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CHAPTER 43

Anorexia and cachexia

Charles Loprinzi, MD

Many patients with advanced cancer undergo a wasting syndrome associated with cancer anorexia/cachexia and asthenia. In a study that looked at symptoms in cancer patients being entered on a palliative care service, anorexia/cachexia and asthenia were more common problems than were pain or dyspnea. Patients who exhibit such symptoms generally have a short survival time, respond poorly to cytotoxic agents, and suffer from increased toxicity from these agents.

In addition, cancer anorexia/cachexia is oftentimes associated with weakness, fatigue, and a poor quality of life. This problem not only affects the patient but also frequently has an impact on family members, as the patient is no longer able to participate fully in eating as a social activity.

Diagnostic criteria

Although some authors have tried to define criteria for diagnosing cancer cachexia, in general, it is not difficult to identify affected patients. In North Central Cancer Treatment Group (NCCTG) research trials involving over 2,500 patients, very simple criteria for anorexia/cachexia have been used:

- a 5-lb weight loss in the preceding 2 months and/or an estimated daily caloric intake of < 20 calories/kg
- a desire by the patient to increase his or her appetite and gain weight
- the physician's opinion that weight gain would be beneficial for the patient

Management

Nutritional counseling

Nutritional counseling, as provided by written materials, dietitians, physicians, and nurses, has been recommended, although its value has not been well demonstrated. Recommendations typically include eating frequent, small meals (as opposed to large meals), consuming larger quantities of food in the morning than in the evening, and avoiding spicy foods. Patients may do better if they are not exposed to the aroma of cooking. Although the benefits of such nutritional counseling are clearly limited, it does appear reasonable to provide.

Appetite stimulants

Corticosteroids were the first agents to undergo placebo-controlled, double-blind evaluation for possible use in cancer cachexia. The first such trial, conducted in the 1970s by Moertel and colleagues at the Mayo Clinic, demonstrated that corticosteroids can stimulate appetite in patients with advanced, incurable cancer. Several subsequent placebo-controlled trials, using various steroid preparations and doses, have confirmed these results.

Dexamethasone (3-8 mg/d) is a reasonable option for clinical use. Known detriments to corticosteroid use include the well-known toxicities associated with chronic administration, including myopathy, peptic ulcer disease, infection, and adrenal suppression. Many patients with advanced cancer anorexia/cachexia, however, do not survive long enough to suffer from these toxicities.

A pilot evaluation of the androgen (Oxandrin), oxandrolone, was reported at the May 2002 ASCO meeting. Although the authors were encouraged by their preliminary findings, further evaluation is indicated before recommending this drug for the treatment of cancer anorexia/cachexia *(Von Roenn JH, Tchekmedyian S, Shen K-N, et al: Proc Am Soc Clin Oncol [abstract] 21:363a, 2002).*

Progestational agents Several placebo-controlled, double-blind clinical trials have demonstrated that progestational agents, such as megestrol acetate (Megace) and medroxyprogesterone acetate, can lead to appetite stimulation and weight gain in patients with anorexia/cachexia. These trials also demonstrated that the effect of these drugs is seen in a matter of days and that they are effective antiemetics.

Although high doses of progestational agents can cause adrenal suppression because of their mild corticosteroid-type activity (a phenomenon not well understood by many clinicians), they do not appear to cause many of the side effects attributable to classic corticosteroids (such as peptic ulcer disease, myopathy, and opportunistic infections). In lieu of this adrenal suppression, however, stress doses of corticosteroids may be necessary in patients with trauma or infection or in surgical patients while on progestational agents. On the other hand, progestational agents increase the risk of thromboembolic phenomena–a side effect that is not seen with classic corticosteroids.

A report of the randomized, double-blind clinical trial comparing megestrol acetate vs dronabinol vs both agents was recently published by the North Central Cancer Treatment Group (NCCTG). The results clearly indicated that megestrol acetate was a better appetite stimulant than was dronabinol at the dose studied. Furthermore, the addition of dronabinol to megestrol acetate did not confer any additional benefits *(Jatoi A, Windschilt HE, Loprinzi CL, et al: J Clin Oncol 20:567-573, 2002).*

A dose-response study with megestrol acetate demonstrated a positive correlation between appetite stimulation and increased megestrol acetate doses, as doses ranged from 160 to 800 mg/d. Nonetheless, given that appetite stimulation has been demonstrated with megestrol acetate doses as low as 240 mg/d, much lower doses are used by many physicians, based primarily on cost considerations.

In the United States, a liquid formulation of megestrol acetate is considerably less expensive than the tablet form, and, milligram for

milligram, the liquid preparation is more bioavailable. It is reasonable to start with 400 mg/d of liquid megestrol acetate, titrating this dose upward (maximum, 800 mg/d) or downward based on clinical response or the emergence of side effects.

Two reports of a single trial of adenosine triphosphate vs a control group were reported recently in prominent oncology journals (J Clin Oncol and J Natl Cancer Inst), each time with associated editorial. Despite promising preliminary data from this study, further evaluation is needed to better clarify benefits and toxicities from this approach.

A randomized, prospective clinical trial comparing the utility of megestrol acetate (800 mg/d) to dexamethasone (0.75 mg qid) demonstrated similar effects of these medications on patients' appetites but different toxicity profiles. Whereas megestrol acetate was associated with a higher incidence of thromboembolic phenomena, dexamethasone was associated with more myopathy, cushingoid body changes, and peptic ulcers.

Other agents Various other drugs have been evaluated definitively for the treatment of cancer anorexia/cachexia and have been demonstrated to provide little or no benefit. These drugs include fluoxymesterone (Halotestin) pentoxifylline (Trental), hydrazine sulfate, dronabinol (Marinol), and cyproheptadine (Periactin). Of note, however, the antiserotonergic drug cyproheptadine does appear to be a relatively strong appetite stimulant in patients with the carcinoid syndrome, presumably because it directly counteracts the large amounts of serotonin secreted in patients with this syndrome.

A number of other drugs have been evaluated in a pilot fashion for the treatment of cancer anorexia/cachexia. They include branched-chain amino acids, thalidomide (Thalomid), metoclopramide (Reglan) and eicosapentaenoic acid. It is hoped that new information will be available in the near future to shed light on the possible therapeutic roles of these agents.

Enteral or parenteral nutrition

Despite the demonstrated efficacy of corticosteroids and progestational agents in patients with cancer anorexia/cachexia, these drugs do not have a major long-term impact on the vast majority of such patients. Consequently, other treatment approaches, such as enteral or parenteral nutritional methods, have been studied extensively. Several randomized trials failed to demonstrate that these nutritional approaches improve either quantity or quality of life. As a result, experts generally agree that the routine use of parenteral or enteral nutrition cannot be justified in patients with advanced cancer anorexia/cachexia.

There is new interest in inhibitors of tumor necrosis factor (TNF), also known as cachectin, as targeted therapy for patients with anorexia/cachexia. Agents under study include thalidomide (Thalomid) and the monoclonal antibodies etanercept (Enbrel) and infliximab (Remicade). Results from studies of these agents should hopefully be available over the next few years.

There are, however, rare circumstances in which parenteral nutrition may play a role in patients with advanced cancer. For example, patients with GI insufficiency due to surgery, radiation therapy, or abdominal carcinomatosis (with-

out impending failure of other organs) may be appropriate candidates for parenteral nutrition.

Prophylactic therapy

Given the positive impact of corticosteroids and progestational agents on cancer anorexia/cachexia and the fact that many patients with advanced cancer die with, and/or of, inanition, the potential prophylactic use of these agents was evaluated. A double-blind trial randomized patients with newly diagnosed extensive-stage small-cell lung cancer to receive megestrol acetate or placebo along with standard chemoradiation. This trial was unable to demonstrate any beneficial effect of megestrol acetate on treatment response, quality of life, or survival.

Thus, patients should not be treated prophylactically for cancer anorexia/cachexia. Rather, such treatment should be reserved for patients in whom anorexia/cachexia is a patient-determined, symptomatic clinical problem.

Nutrition as it relates to end-of-life care

Anorexia and cachexia are major problems for many oncology patients as they approach the final stage of life. Family members are generally more distressed than the patients if/when appetite stimulants do not provide relief. Questions commonly arise about giving enteral or parenteral nutrition or about how patients can be "forced" to consume more calories in the belief that the patients would feel better, get stronger, and live longer. A small measure of appropriate education, noting that the intake of more calories does not appear to have a clinical benefit, provides substantial relief. It is worthwhile to note that patients randomized to receive total parenteral nutrition or appetite stimulants (such as megestrol acetate) do not live any longer than do control patients and that "force feeding" is not in the patients' best interests.

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CHAPTER 44

Fatigue and dyspnea

Eduardo Bruera, MD, and Catherine Sweeney, MD

Fatigue and dyspnea are two of the most common symptoms associated with advanced cancer. Fatigue is also very commonly associated with cancer treatment and occurs in up to 90% of patients undergoing chemotherapy. Both symptoms have many possible underlying causes. In most patients, the etiology of fatigue or dyspnea is multifactorial with many contributing interrelated abnormalities. In a recent study of advanced cancer patients, fatigue was found to be significantly correlated with the intensity of dyspnea. This chapter will discuss the mechanisms, clinical features, and management of both these troublesome and often undertreated symptoms in cancer patients.

Fatigue

Fatigue has been defined as easy tiring and decreased capacity to maintain performance. It results in physical or mental weariness following exertion and is transient in most of us. In cancer patients, fatigue is often severe; has a marked anticipatory component; and results in lack of energy, malaise, lethargy, and diminished mental functioning that profoundly impairs quality of life. It may be present early in the course of the illness, may be exacerbated by treatments, and is present in almost all patients with advanced cancer.

MECHANISM

The mechanism of cancer-related fatigue is not well understood. Substances produced by the tumor are postulated to induce fatigue. Blood from a fatigued subject when injected into a rested subject has produced manifestations of fatigue. The host production of cytokines in response to the tumor can also have a direct fatigue-inducing effect. Muscular or neuromuscular junction abnormalities are a possible cause of chemotherapy- or radiotherapy-induced fatigue. In summary, fatigue is the result of many syndromes–not just one. Multiple mechanisms are involved in causing fatigue in most patients with advanced cancer.

CLINICAL FEATURES

The causes of fatigue in an individual patient are often multiple with many interrelated factors. Figure 1 summarizes the main contributors to fatigue in cancer patients.

Cachexia Cancer cachexia results from a complex interaction of host and tumor products. Host cytokines such as tumor necrosis factor, interleukin-1, and

interleukin-6 are capable of causing decreased food intake, loss of body weight, a decrease in synthesis of both lipids and proteins, and increased lipolysis. Tumors are also capable of producing lipolytic factors (lipolytic factor, toxohormone L-2) and proteolytic by-products (proteolysis-inducing factor). The metabolic abnormalities involved in the production of cachexia and the loss of muscle mass resulting from progressive cachexia may cause profound weakness and fatigue. However, many abnormalities described in Figure 1 are capable of causing profound fatigue in the absence of significant weight loss.

Immobility has been shown to cause deconditioning and decreased endurance to both exercise and normal activities of daily living. On the other hand, overexertion is a frequent cause of fatigue in noncancer patients. It should also be considered in younger cancer patients who are under aggressive antineoplastic treatments such as radiation therapy and chemotherapy, and who are nevertheless trying to maintain their social and professional activities.

Psychological distress In patients without cancer who present with fatigue, the final diagnosis is psychological in almost 75% of patients (depression, anxiety, and other psychological disorders). The frequency of major psychiatric disorders in cancer patients is low. However, symptoms of psychological distress or adjustment disorders with depressive or anxious moods are much more frequent. Patients with an adjustment disorder or a major depressive disorder can have fatigue as their most prevalent symptom.

Anemia related to advanced cancer or chemotherapy has been associated with fatigue, and its treatment results in improvement of fatigue and quality of life in these patients.

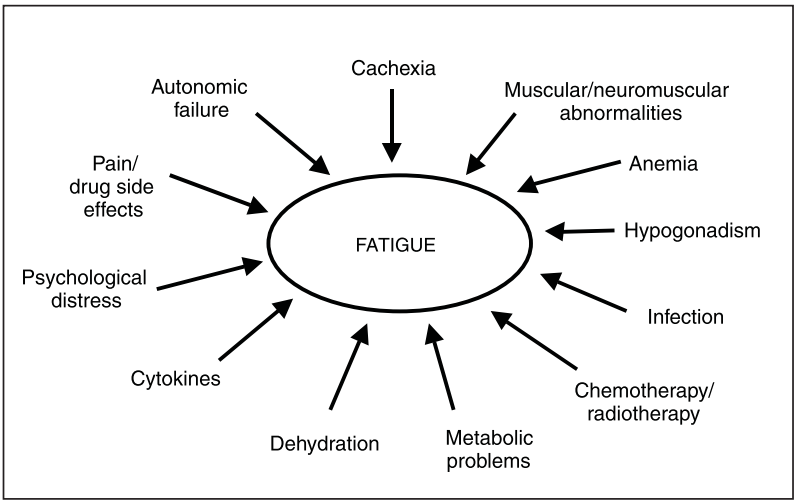

FIGURE 1: Contributors to fatigue in cancer patients

Autonomic failure Autonomic insufficiency is a frequent complication of advanced cancer. Autonomic failure has also been documented in patients with a subset of severe chronic fatigue syndrome. Although the association between fatigue and autonomic dysfunction has not been established in cancer patients, it should be suspected in patients with severe postural hypotension or other signs of autonomic failure.

Hypogonadism Research has shown that both intrathecal and systemic opioid therapy, as well as cachexia and some antineoplastic therapies, can result in hypogonadotropic hypogonadism. This can lead to fatigue, depression, and reduced libido.

Chemotherapy and radiotherapy These treatments are common causes of fatigue in cancer patients. Chemotherapy and radiotherapy for malignancy cause a specific fatigue syndrome. Combined therapy with the two modalities appears to cause worse fatigue than either modality given alone. The pattern of fatigue reported by patients with cancer who receive myelosuppressive chemotherapy is cyclical. It begins within the first few days after therapy is started, peaks around the time of the WBC nadir, and diminishes in the week thereafter, only to recur again with the next cycle of chemotherapy. Fatigue tends to worsen with subsequent cycles of chemotherapy, which suggests a cumulative dose-related toxic effect. Compared with women with no history of cancer, former patients with breast cancer who had received adjuvant chemotherapy reported more fatigue and worse quality of life due to this symptom. Similar results have been noted in breast cancer patients who have been treated with high-dose chemotherapy and autologous stem-cell support compared with control patients without a history of cancer.

Radiation therapy tends to cause a different pattern of fatigue. It is often described as a "wave" that starts abruptly within a few hours after treatment and subsides shortly thereafter. Fatigue has been noted to decrease in the first 2 weeks after localized treatment for breast cancer but then to increase as radiation therapy persists into week 4. It then decreases again 3 weeks after radiation therapy ceases. The mechanism for fatigue in these situations is not well understood.

Surgery is another common cause of fatigue in patients with cancer. In addition, commonly used medications such as opioids and hypnotics may cause sedation and fatigue.

Comorbid conditions not necessarily related to cancer such as renal failure or congestive cardiac failure may coexist and contribute to the problem.

Fatigue is sometimes referred to as asthenia, tiredness, lack of energy, weakness, and exhaustion. Not all these terms have the same meaning to all patient populations. Moreover, different studies of fatigue and asthenia have looked at different outcomes ranging from physical performance to the purely subjective sensation.

TABLE 1: Assessment of fatigue

Functional capacity	
	Treadmill performance (time, speed)
	Number of errors (eg, driving, pilots)
Task-related fatigue (eg, treadmill, driving)	
	VAS (visual analog scales), numerical scale
	Pearson and Byars Fatigue Feeling Checklist
Performance status	
	ECOG (Eastern Cooperative Oncology Group)
	Karnofsky performance status
	Edmonton Functional Assessment Tool (EFAT)
Subjective assessment of fatigue	
	VAS, numerical scale
	Brief Fatigue Inventory
	Piper Fatigue Self-Report Scale

ASSESSMENT

Since fatigue is essentially a subjective sensation, it is by nature difficult to assess. There is agreement that self-assessment should be the "gold standard."

Table 1 summarizes the four most common approaches to the assessment of fatigue. The first category in Table 1 looks at the objective function that the patient is capable of performing when subjected to a standard task. These functional tasks have limited value in cancer care, however, as they are very difficult for the advanced cancer patient to perform.

The second category in Table 1 attempts to assess the subjective effects of standard tasks.

The third category in Table 1 has been the most commonly used in oncology. The two most common scales (ECOG [Eastern Cooperative Oncology Group] and Karnofsky) consist of a physician's rating of the patient's functional capabilities after a regular medical consult. A physiotherapist performs the Edmonton Functional Assessment Tool and attempts to determine the functional status, as well as all the obstacles to clinical performance in these patients.

The fourth category in Table 1 is the most relevant for both clinical management and clinical trials in fatigue. Visual analog scales (VAS), numerical scales, the Brief Fatigue Inventory, and the Piper Fatigue Self-Report Scale have been validated. In addition, there are validated functional assessments in most QOL (quality of life) questionnaires.

In addition to the assessment of the intensity of fatigue, the clinical assessment of these patients requires clinicians to determine the impact of all factors on the presence of fatigue in a given patient.

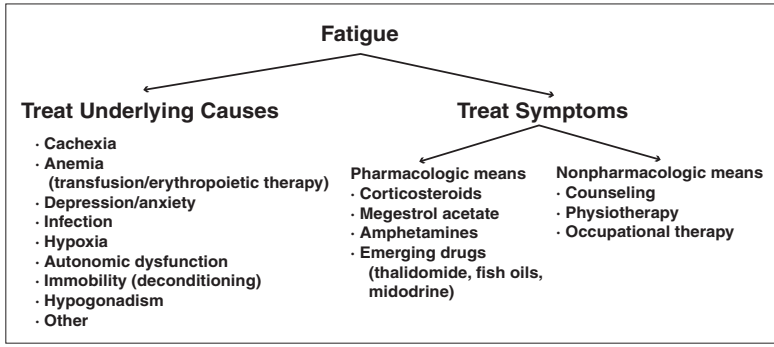

FIGURE 2: Therapeutic approach to managing fatigue

MANAGEMENT

In order to optimally treat fatigue, it is vital to identify and prioritize the different underlying factors in each individual patient. A thorough history, including recent treatment history, physical examination, and medication review, in addition to simple laboratory investigations will help identify possible underlying causes. Figure 2 outlines a therapeutic approach to fatigue management in cancer patients. Whenever possible, an attempt should be made to treat these contributing factors. It is impossible to determine at a given time, with certainty, if one of these identified problems is a major contributor to fatigue or is simply a coexisting problem in a given patient. Therefore, it is of great importance to measure the intensity of fatigue and the patient's performance before and after treating any contributing factor. If the level of fatigue does not improve after correction of these abnormalities, it is clear then that further treatment will not result in improvement in the future.

In patients with cancer treatment-related fatigue, it is very important to exclude specific causes, such as hypothyroidism, hypogonadism, and anemia, and to consider other potential adverse effects of treatment. If specific problems are identified they should be appropriately managed. For instance, patients with anemia may experience symptomatic improvement with the administration of erythropoietic therapy (epoetin alfa [Procrit] and darbepoetin alfa [Aranesp]) at the dose and frequency interval that best fits the patient's need. Epoetin alfa may be administered weekly by subcutaneous injection; darbepoetin alfa has a longer half-life, requiring less frequent dosing. Dosages and schedules of both agents may be increased if necessary. (See chapter 41 ["Dose and schedule of administration" section] for specific information about dosages and schedules.)

In many patients, there will be no identified reversible causes. A number of effective pharmacological and nonpharmacological symptomatic treatments are available for these patients.

TABLE 2: Management of specific causes of dyspnea in cancer patients

Cause	Treatment
Airway obstruction by tumor	Corticosteroids (eg, dexamethasone 6-8 mg qid), radiation therapy
Pleural or pericardial effusion	Drain if effusion is significant
Pneumonia	Antibiotics (oral route preferred)
Carcinomatous lymphangitis	Corticosteroids (eg, dexamethasone 6-8 mg qid)
Congestive heart failure	Diuretic therapy (eg, furosemide 10-20 mg IV/SC), ACE inhibitors, etc.
Underlying asthma, COPD	Optimize bronchodilators, corticosteroids if required
Anemia	Transfuse packed red blood cells, erythropoietic therapy

Pharmacological treatments

Corticosteroids There is substantial evidence that corticosteroids can reduce fatigue and other symptoms in cancer patients. They are probably best retained for short-term use. Their beneficial effects generally last between 2 and 4 weeks, and longer term use carries the risk of serious adverse effects. Most studies have used the equivalent of prednisone 40 mg/day.

Progestational agents Megestrol acetate (Megace 160-480 mg/day) has in recent studies of terminally ill patients been shown to have a rapid (less than 1 week) beneficial effect on appetite, fatigue, and general well-being.

Psychostimulants Psychostimulants (eg, methylphenidate 5-10 mg morning and noon) may be of use in treating fatigue related to concurrent opioid use or depression. There is insufficient evidence for their use in the management of other cancer patients.

In addition to these three agents, a number of other drugs have been tried in preliminary studies in patients with fatigue. Preliminary positive results have been observed with both thalidomide (Thalomid) and fish oil. In addition, there is recombinant erythropoietin for the treatment of anemia and midodrine (ProAmatine) in cases of autonomic failure.

Nonpharmacological treatment

Physiotherapy and occupational therapy Physiotherapy can encourage increased activity where appropriate and provide active range of motion to prevent painful tendon retraction. Recent evidence suggests that aerobic exercise can reduce fatigue during chemotherapy. Assessment of the home environment by an occupational therapist can be very useful. The provision of ramps, walkers, wheelchairs, elevated toilets, and hospital beds can allow the patient to remain at home in a safe environment.

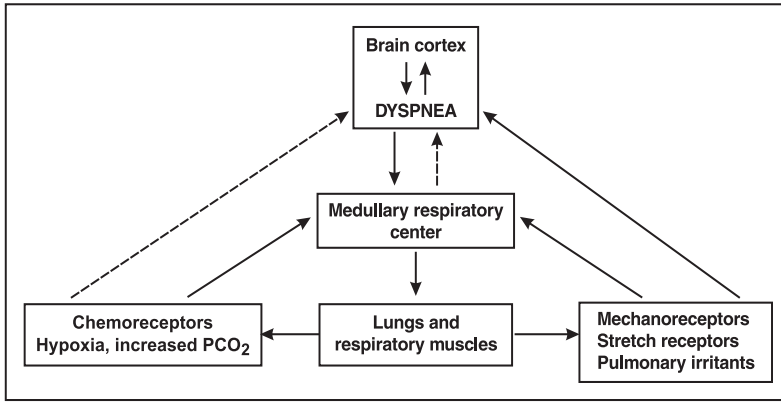

FIGURE 3: Mechanisms of dyspnea

Dyspnea

Dyspnea has been defined as an uncomfortable awareness of breathing. It is a subjective sensation and does not necessarily correlate with clinical findings in a given patient. It occurs in up to 75% of patients with advanced cancer, and good symptom control is less frequently achieved, even by experienced palliative care teams, than with other symptoms of terminal cancer such as pain or nausea.

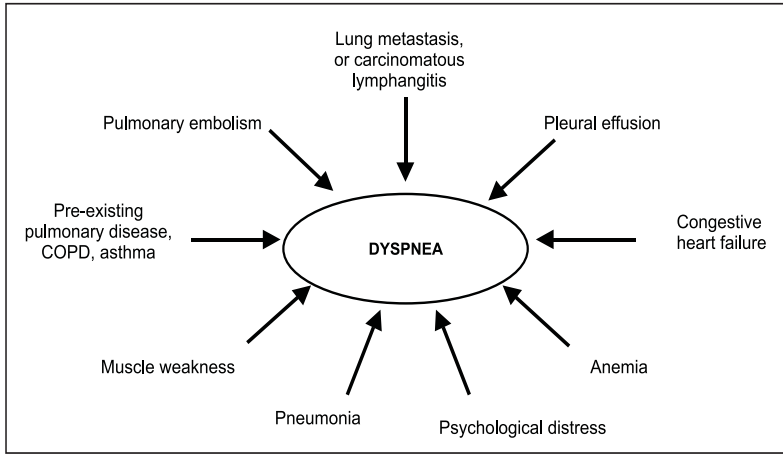

FIGURE 4: Main causes of dyspnea in patients with advanced cancer

MECHANISM

The pathophysiology of dyspnea is complex and has not been completely elucidated. The respiratory center in the medulla controls breathing, but dyspnea is the result of cortical stimulation. Abnormalities of blood gases detected by both lung and central chemoreceptors and stimulation of lung and respiratory muscle mechanoreceptors stimulate the respiratory center. Mechanoreceptors respond to stretch and irritants and also have a demonstrated effect on the brain cortex causing dyspnea. In addition, it is possible that both the chemoreceptors and the medullary respiratory center stimulate the cerebral cortex directly contributing to the sensation of dyspnea. Figure 3 summarizes the mechanisms of dyspnea.

CLINICAL FEATURES

There are many causes of dyspnea in patients with advanced cancer. The main factors are represented in Figure 4.

Direct tumor effects Dyspnea may be the result of direct primary or metastatic tumor effects such as airway obstruction, atelectasis, parenchymal lung involvement, phrenic nerve palsy, carcinomatous lymphangitis, or superior vena caval obstruction.

Indirect tumor effects Indirect cancer effects include pneumonia, anemia, pleural effusion, and pulmonary embolism. Cardiac complications of cancer such as congestive heart failure, pericarditis, or a pericardial effusion may contribute to the problem. Intra-abdominal disorders such as gross ascites or hepatomegaly may cause elevation of the diaphragm and may interfere with respiratory function. Generalized muscle weakness due to cachexia or fatigue may exacerbate breathlessness. Preexisting lung diseases including asthma or chronic obstructive pulmonary disease (COPD) may contribute to the problem.

Treatment side effects Contributing treatment side effects include pneumonitis or fibrosis following chemotherapy or radiotherapy.

Psychological conditions Anxiety, depression, or somatization will alter the patient's perception of dyspnea. Anxiety has been found to be an independent correlate with the intensity of dyspnea in cancer patients with moderate to severe dyspnea.

Any of these factors may occur in isolation or in combination, and care is needed during assessment as there are often many contributors in an individual patient.

ASSESSMENT

Dyspnea is a subjective sensation and researchers have found much variability in the expression of dyspnea in individuals with similar levels of functional abnormalities. In addition, the patient's perception of dyspnea can be influenced by their beliefs and intrapsychic and cultural factors. The presence or absence of physical signs such as tachypnea, wheezing, or use of accessory muscles is not a reliable indicator of the degree of distress felt by the patient. The intensity of dyspnea can be easily assessed using verbal, numeric, or visual

analogue scales similar to those used in pain or nausea. Recently, maximal inspiratory pressure has been found to be an independent correlate of the intensity of dyspnea. Physical examination, chest x-ray, and pulse oximetry should be performed. Other investigations such as CBC, echocardiogram, or pulmonary function tests may be indicated.

MANAGEMENT

Specific causes

Underlying specific causes will require treatment as indicated in Table 2

Symptomatic management

The three modalities of symptomatic treatment in cancer-related dyspnea are oxygen therapy, drug therapy, and counseling.

Oxygen therapy In hypoxemic cancer patients with dyspnea, oxygen has been shown to give significant symptomatic relief. Oxygen can be administered by nasal cannula at 2-6 L/minute or by mask and titrated to maintain O_2 saturation at $>$ 90%. Care must be taken in patients with COPD.

Drug therapy There is substantial evidence that systemic opioids have a beneficial effect on cancer-related dyspnea. This is possible without inducing respiratory depression. The optimal type, dose, and mode of administration have not been determined. If the patient is already on opioids, the breakthrough dose can be used to manage dyspnea as well as pain. If not, morphine can be started at 5-10 mg PO (or 2.5-5 mg SC) q4h with additional prn doses of 2.5-5 mg PO (or 2.5 mg SC) q1h for breakthrough dyspnea. Nebulized opiates are not recommended, as there is insufficient evidence to support their use.

Benzodiazepines have not been found to be effective in the general management of dyspnea, but they may be useful for treatment of episodes associated with anxiety attacks. Regular use should be avoided where possible to limit side effects such as confusion or falls.

A number of conditions that cause dyspnea in cancer patients respond to corticosteroid medication, including superior vena caval obstruction, carcinomatous lymphangitis, and COPD. However, corticosteroids may adversely affect muscle function, and the diaphragm may be more susceptible than other muscles. This may be of importance because of the frequency of muscle weakness and fatigue in patients with advanced cancer.

Counseling Dyspnea is a variable symptom and is exacerbated by physical activities. Patients and families should be educated so they can identify factors likely to worsen dyspnea. Devices such as bathroom aids and wheelchairs can help reduce physical activity, and the addition of portable oxygen can enable the patient to remain active and autonomous. Medication used for symptomatic relief such as opioids can be administered 30-45 minutes prior to dyspnea-causing maneuvers. The family should be educated that dyspnea is subjective and that tachypnea and use of accessory muscles do not necessarily indicate that the patient is suffering. The aim of treatment is to relieve the patient's subjec-

tive dyspnea and not abatement of physical signs of respiratory distress.

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CHAPTER 45

Long-term venous access

Stephen P. Povoski, MD

The use of multidrug chemotherapy and bone marrow transplantation in cancer treatment has made the utilization of reliable, long-term venous access (LTVA) an essential component of cancer therapy. The placement of LTVA devices not only permits the delivery of these complex therapeutic regimens but also drastically improves patients' quality of life.

Indications

No definitive guidelines are available for utilization of central venous access. There are several important factors to consider when deciding upon LTVA device placement:

- the frequency and duration of therapy
- the frequency of blood draws
- the nature of therapy (eg, delivering vesicating agents into a central vein decreases the risk of extravasation)
- the need for supportive therapies (eg, total parenteral nutrition or systemic antibiotics)
- the need for stem-cell collection, plasmapheresis, and bone marrow reinfusion
- patient preference

Patient selection

Long-term venous access should always be considered an elective procedure. Therefore, before an LTVA device is placed, the patient should have recovered from acute infections and the treatment of complications. If there is an absolute need for immediate central venous access before such times, a temporary percutaneous central venous access catheter can be placed. A history of vascular access catheter insertion, deep venous thrombosis of an upper extremity or central vein, thoracic surgery, neck surgery, irradiation, or mediastinal and thoracic disease should alert the surgeon to possible changes in normal venous drainage.

Physical examination, documenting the integrity of the skin, changes in the skin secondary to previous surgical treatment and reconstruction, sites of previous central venous access catheter insertions, evidence of venous obstruction (presence of venous collaterals in skin of the chest, unilateral arm swelling, or superior vena cava syndrome), and pulmonary reserve, should be evaluated in every patient. If there is any evidence of venous obstruction or a history of multiple previous central venous access catheters, the physical examination should be complemented with a formal venous imaging study.

Duplex Doppler ultrasound can visualize the patency and flow of the neck and arm veins. Intrathoracic veins and the right atrium are not well visualized by duplex Doppler ultrasound but are better visualized with transesophageal echocardiography. This can be utilized preoperatively or intraoperatively.

CT and MRI are very useful for documenting the presence of thrombosis and the patency of major intrathoracic veins.

Venography is still the gold standard for studying venous anatomy. Venography should be performed whenever the clinical situation warrants it and noninvasive venous imaging studies fail to provide a definitive diagnosis. This can be utilized preoperatively or intraoperatively.

Chest radiography can disclose important information (such as the presence of pleural effusions, lung metastases, mediastinal adenopathy, and mediastinal tumors) that can modify selection of a site for LTVA placement.

Contraindications and precautions

Neutropenia A neutrophil count $< 1{,}000/mm^3$ is a relative contraindication to the placement of an LTVA device since patients with neutropenia may have a higher incidence of septic episodes. The use of prophylactic antibiotics may reduce the incidence of infection in patients with a low absolute neutrophil count (ANC).

Thrombocytopenia and platelet dysfunction are frequently encountered in the cancer patient. Preoperative platelet transfusion to approximately 50,000/mL may allow the catheter to be safely placed with a reduction in the risk of bleeding complications. In those patients with thrombocytopenia refractory to platelet transfusions, venous cutdown may be a safer approach for catheter placement.

Clotting factor abnormalities Many cancer patients have abnormalities in their clotting factors secondary to malnutrition or chemotherapy. Correction of these abnormalities with vitamin K or fresh frozen plasma may be necessary.

Active infection The presence of an active infection represents an absolute contraindication to the placement of an LTVA device. In those patients with an active infection who require long-term antibiotic treatment, a temporary central venous access catheter or a peripherally inserted central venous catheter is preferable.

LTVA device selection

Two types of LTVA devices are available. There are tunneled external catheters that have skin surface access (Hickman, Broviac, Groshong, Quinton). Likewise, there are subcutaneous implanted ports (Port-A-Cath, Infusaport). Both types of central venous access devices are available with different lumen diameters and lumen numbers. Peripherally placed central venous access devices (P.A.S. Port System, PICC) have become popular because of their ease of placement. PICC devices can be placed by specially trained nursing personnel. Important differences between tunneled external catheters and subcutaneous implanted ports are outlined in Table 1.

General considerations An important general consideration in the selection of an appropriate LTVA device is that the infusion flow resistance depends on the catheter length and catheter lumen diameter. Likewise, catheters with a split valve at the tip (Groshong catheter) are less reliable for blood drawing.

Frequency of device access Subcutaneous implanted ports are preferred in patients who require intermittent device access for treatment or blood drawing. Tunneled external catheters are preferred in patients who require continuous or frequent device access for treatment, blood drawing, or delivery of supportive therapies (parenteral nutrition, blood product transfusion, pain medication) or who are receiving therapy that would be potentially toxic if extravasated into the subcutaneous tissue. Peripherally placed devices are used mainly in patients who require single, continuous, infusional therapy (systemic antibiotics, hydration, pain medication), as is seen frequently for palliation.

TABLE 1: Differences between tunneled catheters and implanted ports

Characteristic	Tunneled external catheters	Subcutaneous implanted ports
Lumen	Single, dual, and triple lumen	Single and dual lumen only
Maintenance	Usually daily; requires patient training	Monthly; no patient training required
Activity	Some restrictions (eg, swimming)	No restrictions
Blood draw	Very reliable	Moderately reliable
Cost	Higher maintenance cost	Higher initial cost
Access	External	Percutaneous Huber needle
Flow gauge	Determined by the lumen diameter	Determined by the Huber needle gauge
Complication rate	Higher	Lower
Removal	Can usually be done in the office or at the bedside	May require a second surgical procedure

Number of lumens The choice of the number of lumens should be based on the intensity and complexity of the therapy.

Specially designed catheters There are specially designed catheters for hemodialysis or apheresis treatment. These catheters are shorter in length and have a lumen that is larger in diameter and is staggered at the tip to prevent recirculation. These catheters have a higher incidence of kinking, and, thus, care should be taken to avoid sharp angles at the skin exit site. In patients who already have an LTVA device in place and require short-term access for apheresis or stem-cell collection, consideration should be given to placing a temporary percutaneous hemodialysis or apheresis catheter rather than replacing the existing LTVA device.

Insertion technique

Placement of LTVA devices is best performed in a surgical suite or an appropriate interventional radiology suite to minimize the incidence of infections. Most procedures are performed on an outpatient basis or immediately prior to a scheduled admission. Local anesthesia and short-acting barbiturates and sedatives are safe and provide excellent patient comfort and sedation. The use of intraoperative fluoroscopy is strongly recommended to document appropriate device placement and to prevent potential complications.

The most common technique used in LTVA device placement is the percutaneous method of Seldinger, using the subclavian or internal jugular vein. Alternatively, a venous cutdown of the cephalic, external jugular, internal jugular, or saphenous vein can provide appropriate access for central venous device placement.

Placement of tunneled external catheters

For the percutaneous approach, the patient is placed supine and in the Trendelenburg position. Patients who cannot tolerate the Trendelenburg position frequently can have their device placed through a venous cutdown approach. A rolled sheet placed vertically in the small of the back is preferred by some to rotate the tips of the shoulders posteriorly. The region of the anterior chest, neck, and shoulders is prepped and draped in a sterilized fashion. The skin overlying the anticipated venipuncture site is infiltrated with a local anesthetic.

Vein penetration The venipuncture needle is carefully and slowly advanced, bevel up, into the vein, while the attached syringe is aspirated (without Luer-lock). If the vein is unable to be accessed after multiple attempts with the venipuncture needle, the contralateral side should not be approached during the same session without documenting the absence of complications.

Guidewire placement Once easy flow of blood into the syringe confirms vein penetration, the bevel is rotated downward, the syringe is disconnected without allowing introduction of air through the venipuncture needle, and a flexible J guidewire is advanced through the venipuncture needle.

Fluoroscopy should be used to confirm the placement of the tip of the guidewire within the right atrium. Atrial arrhythmia may be seen when the guidewire is advanced into the right atrium. If pulsatile blood flow is noted upon introducing the venipuncture needle (indicating an arterial puncture), the venipuncture needle should be withdrawn and local pressure applied for 5-10 minutes (see "Complications"). Resistance to the advancement of the guidewire is usually due to misdirection of the guidewire into a secondary vein or migration of the guidewire outside the vein. Fluoroscopy will confirm the guidewire position. If the guidewire is suspected to be outside the vein, the venipuncture needle and the guidewire should be removed together, as a unit, to prevent shearing of the guidewire. If the guidewire is suspected to be in the wrong vein tributary, the venipuncture needle can be removed and a 16-gauge angiocatheter can be placed over the guidewire prior to readjusting the position of the guidewire.

Catheter placement The anticipated skin exit site and subcutaneous tunnel for the external catheter are infiltrated with a local anesthetic. The catheter is then advanced along the subcutaneous tunnel from the anticipated skin exit site to the venipuncture site. The catheter is then measured and custom cut to reach the junction between the superior vena cava and right atrium (approximately at the fourth anterior intercostal space). The catheter cuff is positioned midway in the subcutaneous tunnel.

The dilator and peel-away introducer sheath are slowly and carefully advanced over the guidewire under fluoroscopy. The guidewire is gently and slightly withdrawn and advanced while the dilator and peel-away introducer sheath are advanced over the guidewire to confirm that they are indeed threading over the guidewire and that the guidewire has not migrated outside the vessel. The dilator and guidewire are then withdrawn from the peel-away introducer sheath. The catheter is then advanced through the peel-away introducer sheath and the tip of the catheter is advanced to the junction of the superior vena cava and right atrium.

Difficulties in advancing the catheter through the peel-away introducer sheath usually imply that the peel-away introducer sheath is bent. This occurs most frequently during subclavian vein approach if the venipuncture is attempted too medially and through the costoclavicular ligament. If the catheter cannot be advanced through the peel-away introducer sheath, repeat venipuncture in a more lateral position may be necessary. The catheter should never be handled with sharp instruments. Only nontoothed forceps should be used, if needed.

Confirmation of catheter position Prior to removal of the peel-away introducer sheath, the catheter position should be confirmed by fluoroscopy. Failure to position the fluoroscopic beam perpendicular to the patient will give a false impression of the catheter position.

At the completion of catheter placement, the entire catheter should be examined with fluoroscopy to confirm position and to rule out any kinking that would prevent normal functioning. Catheter infusion (looking for impedance to inflow/infusion) and withdrawal (looking for interruption of flow on blood return) should be tested in the surgical suite prior to heparinization of the cath-

eter lumen. A chest x-ray should be obtained in the recovery room to rule out complications and as a permanent record of catheter position. Lastly, ultrasonography may be used during catheter placement to aid in vein localization for venous access and to determine the position of the catheter tip.

Placement of subcutaneous implanted ports

The procedure for placing a subcutaneous implanted port is similar to that for a tunneled external catheter, except for the creation of a subcutaneous port pocket. To prevent wound disruption, the subcutaneous port pocket should permit no tension in the placement of the port. The port is sutured to the muscular fascia to prevent port migration and is placed over the rib cage to provide easy access.

Device care

Subcutaneous implanted ports require flushing with a heparin solution (2-3 mL; 100 U/mL) after each use or monthly during periods of nonuse. During continuous infusion therapy, the noncoring (Huber) access needle should be replaced every third to fifth day.

Tunneled external catheters require more frequent care. The exit site is cleaned with an antiseptic agent and an occlusive dressing is applied. This is generally done daily; however, some now advocate only biweekly cleanings and dressing changes. Hickman catheters are generally flushed daily with a heparin solution (2-3 mL; 100 U/mL) or after each use, and protective caps are replaced biweekly. However, some now advocate only biweekly flushing with a heparin solution (2-3 mL; 100 U/mL). Groshong catheters generally only require weekly flushing with 5 mL of a saline solution.

Complications

During device insertion

Complications during device placement are generally related to the method of insertion and the experience of the operator.

Pneumothorax is the most common complication of the percutaneous insertion technique, especially via the subclavian vein approach. The incidence of pneumothorax has been reported in most series to be approximately 1% to 5%. It appears to be more frequently seen in nutritionally compromised and emaciated patients. Its incidence has also been thought to be related to the number of attempts required to access the vein and to the experience of the operator. Utilization of a venous cutdown approach eliminates the risk of pneumothorax.

Pneumothorax is usually recognized on a postoperative upright chest x-ray. The ability to detect a small pneumothorax on chest x-ray can be aided by performing an expiratory film. Delayed pneumothorax can develop several

hours to several days after attempted percutaneous device insertion. If the pneumothorax is small (< 5%), the patient can be followed with subsequent chest x-rays and the air occupying the pneumothorax can be left in place to be reabsorbed. 100% oxygen can aid in reabsorption of a pneumothorax. Patients with a larger pneumothorax are generally treated by placement of a chest tube that is connected to a closed suction system or a Heimlich valve (one-way valve).

Iatrogenic arterial puncture occurs most frequently with the percutaneous internal jugular approach and less frequently with the percutaneous subclavian vein approach. Pulsatile flow confirms an arterial puncture. In this instance, the venipuncture needle should be removed and the vessel compressed for 5-10 minutes. If an arterial puncture is initially unrecognized and the guidewire is passed into the vessel, a position of the guidewire to the left of the thoracic spine on fluoroscopy should alert the operator's suspicions for the occurrence of this complication. In a patient with a persistent left vena cava, the guidewire will also be seen to the left of the spine on fluoroscopy. An intraoperative venogram may help to confirm the diagnosis.

Hemothorax as a result of injury to major vessels is seen less than 1% of the time. It can be life threatening, however, when it does occur. During the percutaneous approach, injury to one of the major vessels with the venipuncture needle, guidewire, or dilator and peel-away introducer sheath may result in a hemothorax. Careful attention to insertion technique and use of fluoroscopy will help to prevent this complication. Utilization of a venous cutdown approach is much less likely to injure a major vessel.

Most patients who develop a hemothorax can be treated with a large-bore, laterally placed chest tube connected to a closed suction system. Many of these closed suction systems have a blood re-infusion collecting system. Thoracotomy may be indicated in certain circumstances [in patients with ongoing bleeding (> 500 mL/hr) or with a massive hemothorax (> 1,500 mL)].

Local hematomas can occur frequently in thrombocytopenic patients or coagulopathic patients. They are best treated by local compression. Adequate replacement of platelets and clotting factors prior to device placement can help prevent these complications.

Catheter tip malposition is usually recognized and corrected at the time of catheter placement with the use of intraoperative fluoroscopy. However, catheters situated in the azygos vein or the right internal mammary vein can look strikingly similar to catheters situated in the superior vena cava in an anterior-posterior projection under intraoperative fluoroscopy. Frequently, these catheters do not withdraw blood easily and the catheter tip does not move with the cardiac rhythm. Lateral rotation of the intraoperative fluoroscope and utilization of intraoperative venography can help to differentiate this sometimes subtle finding.

Other device-related complications

Catheter compression, fracture, and embolization can occur when a catheter placed by the percutaneous subclavian approach is inserted too medially along the clavicle at the medial costoclavicular ligament. In such cases, the catheter may become chronically compressed between the clavicle and the first rib. This can be recognized radiographically as a "pinch-off sign." Chronic compression of the catheter may result in structural fatigue of the catheter wall that may eventually cause fracturing and distal embolization of the catheter. This can be prevented by ensuring that the venipuncture site is situated more laterally on the clavicle as well as 1-2 cm below the clavicle. If this problem is recognized during catheter placement, the catheter should be removed and then placed through a different venipuncture site.

Device malfunction can be divided into two types: (1) inability to withdraw blood from a device and (2) inability to infuse into a device. Inability to withdraw blood from a device, despite retaining the ability to infuse into the device, is most frequently caused by a fibrin sheath at the tip of the catheter that produces a one-way valve effect. Less frequently, it is due to a catheter tip positioned against the side wall of the vein. In patients with this problem, a Valsalva maneuver or repositioning of the patient can sometimes result in a successful blood withdraw.

Inability to both withdraw blood from and infuse into a device can result from many mechanical causes such as catheter tip malposition, catheter kinking, catheter intraluminal thrombosis, intraluminal precipitation of medications, or venous thrombosis. A simple chest x-ray can identify some of these mechanical causes. Venography and venous duplex Doppler ultrasound imaging are also useful.

Thrombolytic therapy, using tissue plasminogen activator (TPA) or alteplase (recombinant TPA), can help to restore the ability to withdraw blood from a device or to clear a device from intraluminal thrombosis or intraluminal precipitation of medications. Usually 1-2 mg of TPA in 1-2 cc of sterile water is instilled into the device, left in place for 1-2 hours, and then aspirated. Alternatively, 2.5 cc aliquots (diluted to 1 mg/mL) of alteplase can be used in a similar fashion. This may be repeated daily for several days until total patency is restored. Likewise, chemical occlusion of a device resulting from precipitation of chemotherapeutic agents, poorly soluble salts (calcium, magnesium, or phosphates), or antibiotics (amikacin [Amikin], vancomycin) can be successfully treated with instillation of 0.2 to 1.0 mL of 0.1 N hydrochloric acid. The solution is irrigated in and out of the device for 2 minutes, left in place for 1 hour, and then aspirated. This may be repeated daily for several days until total patency is restored. No side effects or metabolic acidosis has been associated with hydrochloric acid at these doses.

External catheter damage External catheters can be damaged at the site of a catheter clamp or at a suture site. The use of needleless connections for infusions and irrigations should prevent needle damage to external portions of the catheter. Most external catheters have repair kits to replace any damaged external portion of the catheter.

Drug extravasation into the subcutaneous tissues can occur with subcutaneous implanted ports when there is inappropriate placement or accidental dislodgment of the Huber access needle from the implanted port. This may result in chemical cellulitis, tissue necrosis, and loss of soft tissues in the area of extravasation. Clinical signs of extravasation include pain, burning, soft-tissue swelling, skin erythema, and skin vesicle formation at the infusion site. If drug extravasation is suspected, the infusion should be stopped and the Huber access needle should be immediately withdrawn. Management depends on the type of drug infused and the amount of drug extravasated.

Venous thrombosis occurs more commonly than believed. The incidence of venous thrombosis varies in multiple studies, ranging from 0% to 65%. The incidence of venous thrombosis is higher in patients in whom the catheter tip is placed in the innominate vein or proximal superior vena cava as compared with the distal superior vena cava/right atrial junction. Ideally, the catheter tip should be positioned at the superior vena cava/right atrial junction and should be free floating. The incidence of venous thrombosis is higher in patients with multiple lumen catheters than in those with single lumen catheters. The incidence of venous thrombosis is higher in patients in whom the device was placed percutaneously than in those who underwent a venous cutdown approach. Preexisting hypercoagulable states predispose patients to the development of venous thrombosis.

Ipsilateral arm swelling, pain, and development of collateral veins in the skin overlying the chest wall should alert the clinician to the possibility of venous thrombosis. Venography, venous duplex Doppler ultrasound imaging, and CT/MRI scan can establish the diagnosis and the site of the obstruction.

Prophylaxis In one prospective randomized study, cancer patients without abnormal clotting parameters were randomized to receive either 1 mg/day of warfarin or placebo for 90 days following insertion of a central venous access device. Venous thrombosis documented by superior vena cava venograms was 37.5% in the placebo group (n = 40) as compared with 9.5% in the treatment group (n = 42). There was no prolongation of coagulation parameters in the treatment group. In another prospective randomized study, cancer patients were randomized to receive either 2,500 IU/day of subcutaneous low-molecular-weight heparin (Fragmin) or no antithrombotic prophylaxis for 90 days following insertion of a catheter. Venous thrombosis documented by superior vena cava venograms was 62% in the no antithrombotic prophylaxis group (n = 13) as compared with 6% in the anticoagulation group (n = 16).

Treatment should be directed toward prevention of pulmonary embolism, avoidance of clot propagation, prevention of the post-phlebitic syndrome, and preservation of the LTVA device, if possible. With these objectives in mind, the LTVA device should be removed only if it is no longer necessary or if initial therapy for venous thrombosis fails. The patient can be initially treated with systemic heparinization or subcutaneous low-molecular-weight heparin followed by conversion to oral anticoagulation with warfarin. The LTVA device may be kept in place as long as the patient is asymptomatic and there is no

contraindication to anticoagulation. Anticoagulant therapy should be continued for at least 3 months.

Device-related infections

Device-related infections can be divided into device-related bacteremia and site infections. Site infections consist of subcutaneous catheter tunnel infections and subcutaneous port pocket infections.

In general, device-related infections are thought to be greater for tunneled external catheters than subcutaneous implanted ports and greater for multiple lumen catheters than single lumen catheters. However, considerable controversy on this topic exists in the literature, since various studies examining device-related infection rates differ significantly with respect to patient characteristics, device maintenance schedules, and diagnostic criteria for defining a device-related infection. Differing device-use patterns and patient medical illness acuity are thought to explain the difference in device-related infection rates between tunneled external catheters and subcutaneous implanted ports and between multiple lumen catheters and single lumen catheters.

It is controversial whether utilization of perioperative antibiotics for LTVA device placement decreases the incidence of device-related infections. Some studies have evaluated the addition of antibiotics (such as vancomycin) to the standard heparin-flush solution administered through LTVA devices in an attempt to prevent device-related infections. Such results should be viewed with caution, however, in light of the increased incidence of vancomycin-resistant organisms in the hospital inpatient population.

Device-related bacteremia

Device-related bacteremia is a potentially life-threatening complication, especially in the immunocompromised patient. The infection generally is caused by gram-positive cocci (coagulase-negative staphylococci) or enteric gram-negative bacilli (*Enterobacteriaceae*, *Escherichia coli,* and *Pseudomonas* species). Less frequently, device-related bacteremia is caused by fungi (*Candida* species). The incidence of fungal infection is significantly higher in immunocompromised patients.

Criteria for diagnosis of device-related bacteremia vary among institutions. Some institutions utilize quantitative analysis of blood culture results, whereas others utilize qualitative analysis of blood culture results. Quantitative analysis involves comparing the number of colony-forming units seen in blood drawn through the device to blood drawn through the periphery. Usually, a 5- to 10-fold increase in the number of colony-forming units from blood drawn from the device as compared with concomitant peripheral cultures (or in the absence of positive peripheral cultures, $>$ 1,000 colony-forming units from blood drawn from the device) signifies device-related bacteremia.

Qualitative analysis involves comparing positivity and negativity of blood cultures drawn from both the device and the periphery. Usually, simultaneous

positive blood cultures drawn from both the device and the periphery, along with clinical relevance, signifies device-related bacteremia.

Management If device-related bacteremia is suspected, appropriate systemic antibiotic coverage should be instituted after device and peripheral blood cultures are obtained. Antibiotic selection should be reassessed after organism identification and antibiotic sensitivities are available. Up to 70% of cases of device-related bacteremia can be successfully treated with a course of appropriate systemic antibiotics. The indications for device removal are the persistence of positive blood cultures after an appropriate course of systemic antibiotics, hypotension or severe systemic compromise, infections caused by *Candida* species, or recurrent infections caused by the same organism after successful systemic antibiotic therapy.

Site infections

Site infections consist of subcutaneous catheter tunnel infections and subcutaneous port pocket infections. They can be superficial or deep. These infections are usually caused by gram-positive cocci (coagulase-negative staphylococci). Swelling, tenderness, and warmth over the site usually indicate a site infection. In the neutropenic patient, fever is often the only symptom. Swab culture of the skin exit site of the external catheter or the skin around the Huber access needle overlying the implanted port can sometimes identify the offending organism.

Management Local care at the skin exit site of the tunneled external catheter or removal of the Huber access needle from the subcutaneous implanted port and systemic antibiotics can be effective for most superficial site infections. Deep-seated subcutaneous catheter tunnel infections and subcutaneous port pocket infections may require device removal for successful eradication of the infection. Site infections caused by *Candida* species usually require device removal.

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CHAPTER 46

Prevention and management of radiation toxicity

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The aim of radiation oncology is the achievement of uncomplicated locoregional control of malignancy by the use of radiation therapy (RT). Accomplishing this goal requires precise knowledge of tumoricidal and tolerance doses of the various normal tissues at risk within the RT field.

Types of RT injury

Radiation injuries can be divided into functional impairment and oncogenesis. There are also different phases of RT injury.

Early effects are usually seen during treatment or within the first few weeks after its completion. These reactions are very common, can be significant and symptomatic, but eventually seem to heal completely. Nevertheless, despite what may appear to be total recovery, significant residual damage is often present.

Intermediate effects typically occur several weeks to months after the completion of RT.

Late effects are usually rare and are encountered many months to years after RT. Functional impairments may take a very long time to become apparent; an example is memory problems in children who have received cranial irradiation. Oncogenesis is usually a late effect of RT.

Tolerance doses of radiation

Numerous studies have attempted to specify RT tolerance doses for the various tissues and structures of the body. The minimal tolerance dose (TD 5/5) and maximal tolerance dose (TD 50/5) refer to a severe complication rate of 5% and 50%, respectively, within 5 years of RT completion (Table 1). These tolerance doses have been valuable but were drastically revised recently because of the advent of combined-modality therapy (see "Combined chemotherapy and irradiation") and altered RT fractionation regimens.

TABLE 1: Normal tissue tolerance to therapeutic irradiation

	TD 5/5 Volume[a]			TD 50/5 Volume[a]			
Organ	**1/3**	**2/3**	**3/3**	**1/3**	**2/3**	**3/3**	**Selected end point**
Kidneys	5,000	3,000[b]	2,300		4,000[b]	2,800	Clinical nephritis
Bladder		8,000	6,500		8,500	8,000	Symptomatic bladder contracture and volume loss
Bone							
Femoral head		5,200			6,500		Necrosis
TMJ	6,500	6,000	6,000	7,700	7,200	7,200	Marked limitation of joint function
Rib cage	5,000			6,500			Pathologic fracture
Skin			100 cm^2 / 5,000			100 cm^2 / 6,500	Telangiectasis
Skin	10 cm^2 / 7,000	30 cm^2 / 6,000	100 cm^2 / 5,500			100 cm^2 / 7,000	Necrosis/ulceration
Oral mucosa			50 cm^3 / 6,000			50 cm^3 / 7,500	Ulcer/fibrosis
Brain	6,000	5,000	4,500	7,500	6,500	6,000	Necrosis/infarction
Brainstem	6,000	5,300	5,000			6,500	Necrosis/infarction
Optic nerve			5,000			6,600	Blindness
Chiasma			5,000			6,500	Blindness
Spinal cord	5 cm / 5,000	10 cm / 5,000	20 cm / 4,700	5 cm / 7,000	10 cm / 7,000		Myelitis/necrosis
Cauda equina			6,000			7,500	Clinically apparent nerve damage
Brachial plexus	6,200	6,100	6,000	7,700	7,600	7,500	Clinically apparent nerve damage
Eyes (lens)			1,000			1,800	Cataract requiring intervention
Eyes (retina)			4,500			6,500	Blindness
Ears (middle/external)	3,000	3,000	3,000[b]	4,000	4,000	4,000[b]	Acute serous otitis
Ears (middle/external)	5,500	5,500	5,500[b]	6,500	6,500	6,500[b]	Chronic serous otitis

[a] There is insufficient information for recommendations where no values are provided. Clinical judgment and experience are used in these instances, and extrapolation from available information is made.

[b] < 50% of volume does not make a significant change.

Adapted from Emami B, et al: Int J Radiat Oncol Biol Phys 21:109-122, 1991; and Rubin P, Casarett GW: Clinical Radiation Pathology, 1968.

Organ	TD 5/5 Volume[a] 1/3	2/3	3/3	TD 50/5 Volume[a] 1/3	2/3	3/3	Selected end point
Parotid[b]		3,200[b]	3,200[b]		4,600[b]	4,600[b]	Xerostomia
Larynx	7,900[b]	7,000[b]	7,000[b]	9,000[b]	8,000[b]	8,000[b]	Cartilage necrosis
Larynx		4,500	4,500[b]			8,000[b]	Laryngeal edema
Lungs	4,500	3,000	1,750	6,500	4,000	2,450	Pneumonitis
Heart	6,000	4,500	4,000	7,000	5,500	5,000	Pericarditis
Esophagus	6,000	5,800	5,500	7,200	7,000	6,800	Clinical stricture/ perforation
Stomach	6,000	5,500	5,000	7,000	6,700	6,500	Ulceration/ perforation
Small intestine	5,000		4,000[b]	6,000		5,500	Obstruction/ perforation/fistula
Colon	5,500		4,500	6,500		5,500	Obstruction/ perforation/ ulceration/fistula
Rectum			6,000			8,000	Severe proctitis/ necrosis/fistula/ stenosis
Liver	5,000	3,500	3,000	5,500	4,500	4,000	Liver failure
Testes			± 500			2,000	Sterility
Ovaries			± 300			1,200	Sterility
Vagina			$\frac{5\ cm^3}{9,000}$			10,000	Ulcer/fistula
Pituitary			4,500				Hypopituitarism
Thyroid			4,500			7,000	Hypothyroidism
Muscle			5,000				Clinical myositis
Muscle			10,000				Atrophy
Cartilage (child)			1,000			3,000	Growth arrest
Bone (child)			$\frac{10\ cm^3}{2,000}$			$\frac{10\ cm^3}{2,000}$	Growth arrest

TMJ = temporomandibular joint

TD 5/5 (minimal tolerance dose) and TD 50/5 (maximal tolerance dose) refer to the RT doses required to produce a severe complication rate of 5% and 50%, respectively, within 5 years of RT completion. These RT dose values are used for guidance only and are not absolute. They are modified appropriately depending on the prevailing circumstances.

1/3, 2/3, and 3/3 refer to the approximate volume of organ that is irradiated.

Chemoradiosensitivity of normal tissues Cell-cycle kinetics, mitotic behavior, and differentiation determine the chemoradiosensitivity of normal tissues. The dividing cell is more vulnerable to RT than the quiescent cell, especially one that is functionally mature.

Dose-limiting organs and tissues have been divided into three classes according to their RT tolerance doses and importance to survival:

- Class I organs are those in which irreparable damage leads to death or severe morbidity.
- Class II organs are those in which damage is associated with moderate morbidity.
- Class III organs are those in which damage produces minimal morbidity.

Combined chemotherapy and irradiation

In combined-modality therapy, several temporal strategies with different rationales are utilized: concurrent RT and chemotherapy, local RT followed by chemotherapy, chemotherapy followed by local RT, and alternating chemotherapy and RT cycles.

POTENTIAL INTERACTIONS

When used in combination, RT and chemotherapy can act independently, with each mode acting in isolation in different parts of the body. The combined use of the two modalities can also result in increased or decreased therapeutic activity, as well as various possible adverse interactions:

- Damaging effects of RT on the target organ can be increased by chemotherapy. Some chemotherapeutic agents are RT enhancers or reactivators, which, when used concurrently with RT, can produce reactions in various tissues at much lower RT doses than expected.
- Damaging effects of chemotherapy on the target organ can be increased by RT.
- Independent injuries can be caused by the individual treatment modality in the same organ, which can combine to increase the resulting dysfunction. Subclinical residual injury from one treatment modality may be uncovered by the subsequent use of a seemingly safe dose of another modality.
- An injury can be produced that is not commonly seen with either modality alone.

The inherent difficulty in understanding these consequences is further complicated by the number of chemotherapeutic agents generally combined in treatment protocols and the variety of conventional or altered RT delivery techniques.

Quantification of treatment toxicity

In addition to therapeutic efficacy, quantification of RT toxicity is crucial for evaluating new regimens and selecting therapy for individual patients. The optimal therapeutic ratio requires not only complete tumor clearance but also minimal residual injury to surrounding vital normal tissues.

Morbidity scoring schemes developed by the Radiation Therapy Oncology Group (RTOG), European Organization for Research on the Treatment of Cancer (EORTC), and the National Cancer Institute (NCI) are used most commonly. The late effects of normal tissues (LENT) scoring system was recently adopted by the RTOG and EORTC. It grades toxicity according to four parameters, denoted by the acronym "SOMA," which stands for subjective (symptoms reported), objective (signs on examination), management (instituted), and analytic (tissue function assessed by objective diagnostic tools). In 1997, the NCI with the American (eg, RTOG) and international cooperative groups, the pharmaceutical industry, and the World Health Organization (WHO) revised and expanded the Common Toxicity Criteria (CTC) by integrating systemic agent, radiation, and surgical criteria into a comprehensive and standardized system. The CTC v. 2.0 replaces the previous NCI, CTC, and the RTOG Acute Radiation Morbidity Scoring Criteria. It improves acute radiation toxicity criteria, thereby achieving better clarity and consistency among treatment modalities.

TOXIC EFFECTS AND THEIR MANAGEMENT

The incidence and severity of normal tissue toxicity from RT depend on a wide variety of factors, including total dose, fraction size, interval between fractions, quality and type of RT, dose rate, intrinsic radiosensitivity, and specific tissue irradiated. The most common toxic effects seen in different organ systems are outlined below and in Table 2, along with recommended treatments. Where appropriate, the specific effects of chemoradiation therapy are discussed separately.

Oral rinse of 15 mL of 2% morphine solution vs viscous lidocaine with Mylanta and diphenhydramine were administered to head and neck cancer patients receiving chemoradiation therapy. The morphine oral rinse decreased significantly pain duration and severity and duration of functional impairment *(Cerchietti LCA, Navigante AH, Bonomi MR, et al: Cancer 95:2230-2236, 2002).*

Head and neck

ORAL MUCOSA

Acute effects Oral mucositis results from radiation-induced mitotic death of the basal cells of the oral mucosal epithelium. It appears about 2 weeks after initiation of RT and can progress from patchy to confluent mucositis.

Regular lavage of the oral cavity with bicarbonate of soda or normal saline solutions (mix 1 tsp of baking soda or 1 tsp of salt with 1 qt of water) is soothing, promotes oral hygiene, and restores normal oral pH. Topical anesthetic

TABLE 2: Possible irradiation side effects and treatment

Organ	RT side effects	Treatment
Skin	Erythema and dry desquamation	Nonionic moisturizers (eg, Lotionsoft applied tid); topical 1% hydrocortisone cream or ointment applied tid prn, especially for pruritus; Aquaphor; TheraCare cream; vitamin A and E ointment or cream; Biafine, gentle washing; avoid skin irritants
	Moist desquamation	Normal saline compresses or modified Burow's solution soaks before applying creams; polymyxin B/neomycin cream applied tid; Nu-Gel protective wound dressings; antifungal agents for *Candida*, eg, ketoconazole cream; silver sulfadiazine, vitamin A and E ointment
	Ulceration/necrosis	Exclude and treat infections; normal saline compresses; modified Burow's solution soaks; polymyxin B/neomycin cream applied tid; debridement of necrotic tissue, vitamin E (1,000 IU/d), pentoxifylline (400 mg PO bid-tid); flexible hydroactive dressings (eg, DuoDerm); debriding with fibrinolysin and desoxyribonuclease (eg, Elase)
	Chronic skin changes (eg, skin dryness)	Moisturizers; sun blocks
Oral and oropharyngeal mucosa	Mucositis	Saline/bicarbonate solution oral lavage qid; equal parts of topical lidocaine viscous/diphenhydramine/simethicone mixture for analgesia to swish in mouth or for gargling (5-10 mL qid prn); RadiaCare oral wound rinse; systemic analgesics prn; antifungals (eg, nystatin, swish and swallow (100,000-200,000 U PO qid); ketoconazole (200 mg/d PO), itraconazole (100-200 mg /d PO), or fluconazole (100-200 mg/d PO) may be helpful; sucralfate suspension (1 g/10 mL), swish and swallow (10 mL PO qid), Gelclair
Esophagus	Esophagitis	Equal parts of topical lidocaine viscous/diphenhydramine /simethicone mixture for analgesia (5-10 mL PO qid); systemic analgesics prn; nasogastric, gastrostomy, or jejunostomy feeding tube; sucralfate, omeprazole, metoclopramide, or ranitidine sometimes useful especially in the presence of GE reflux
Salivary glands	Sialadenitis/parotitis	Aspirin/NSAIDs
	Xerostomia	Sialogogues; pilocarpine (5 mg PO tid-qid), during and post-RT; fluoride gel applications to prevent dental caries; artificial saliva (eg, Salivart Moi-Stir); amifostine (200 mg/m^2 infused IV over 3 min before daily RT), to protect salivary glands (only in head and neck cancer patients receiving postresection adjuvant RT)

Organ	RT side effects	Treatment
Salivary glands	Thick saliva	Papain enzyme
Ears	Otitis externa	Hydrocortisone/neomycin/polymyxin B ear drops tid
	Serous otitis media phenylephrine otic solution	Decongestants; myringotomy;
Mandible	Temporomandibular joint fibrosis	Daily stretching exercises
	Osteoradionecrosis	Complete any necessary dental work (especially extractions) pre-RT; hyperbaric oxygen; eliminate infection with antibiotics; pentoxifylline; perform sequestrectomy only if all else fails
Lungs	Radiation pneumonitis	Prednisone (30-60 mg/d PO for 2-3 weeks), with appropriate tapering
	Pulmonary fibrosis	Supportive measures (eg, oxygen/bronchodilators), pentoxifylline
Bladder	Acute cystitis	Phenazopyridine (100-200 mg PO tid prn), for dysuria; flavoxate (200 mg PO tid prn), for urinary frequency/urgency; oxybutynin (5 mg PO tid prn), for frequency/urgency
Prostate	Obstructive urinary	Terazosin or doxazosin (1-2 mg/d PO); symptoms tamsulosin (0.4 mg/d PO); finasteride (5 mg/d PO)
Bowel	Diarrhea	Low-residue diet; loperamide or diphenoxylate (1-2 tabs PO qid prn); exclude *Clostridium difficile* infection; psyllium PO sometimes helpful; cholestyramine (4-8 g PO qid); octreotid (0.1 mg SC tid)
	Proctitis	Anusol-HC cream and Nupercainal ointment perianally or Anusol suppositories per rectum tid prn; psyllium PO sometimes helpful; glucocorticoid retention enemas (eg, Cortenema); mesalamine suppositories (eg, Rowasa); sulfasalazine
Breasts	Erythema and dry desquamation	Nonionic moisturizers (eg, Lotionsoft, TheraCare, Aquaphor applied tid); topical 1% hydrocortisone cream applied tid prn; Biafine, gentle washing; avoid skin irritants
	Moist desquamation	Normal saline compresses or modified Burow's solution soaks before application of creams; polymyxin B/neomycin cream applied tid; Nu-Gel or Telfa protective, nonadherent wound dressings; antifungal agents for *Candida*; silver sulfadiazine to prevent infections; vitamin A and E ointment to promote healing

Gelclair is a bioadherent oral gel that forms a protective coating over the oral mucosa, shielding exposed nerve endings while providing rapid and durable pain relief *(Innocenti et al: Pain Symp Manage 24:456-457, 2002)*.

mixtures, such as viscous lidocaine, diphenhydramine, and simethicone (in equal parts) and RadiaCare oral wound rinse, may relieve oral discomfort.

Sucralfate suspension (Carafate, 1 g/10 mL) protects the oral mucosa by a coating action; a 10-mL oral dose should be swished and swallowed four times daily. This agent may have a prophylactic benefit and may also aid in the healing process. Fentanyl (Duragesic) patches or Actiq may be necessary for pain control to promote oral intake.

Candida species can colonize the damaged mucosa and exacerbate the mucositis. Oral candidiasis is treated with topical or systemic antifungal agents, such as nystatin (100,000-200,000 U PO qid); ketoconazole (Nizoral; 200 mg/d PO); fluconazole (Diflucan; 100-200 mg/d PO); clotrimazole troches dissolved orally bid-qid; and itraconazole (Sporanox; 100 mg PO bid).

Antibiotics are necessary when superimposed bacterial infection may be present; these may include clindamycin (Cleocin), penicillin V, ciprofloxacin (Cipro), or clarithromycin (Biaxin). Mucosal healing is complete within 2-3 weeks after completion of RT.

Late effects can be characterized by pallor and thinning of the oral mucosa with loss of pliability, submucosal ulceration, and necrosis with exposure of underlying bone and soft tissue. Few interventions are of value once chronic damage has occurred.

Soft-tissue necrosis may be very painful and require systemic or topical anesthetics, eg, viscous lidocaine mixed with equal parts of simethicone and diphenhydramine. Scrupulous hygiene is essential, and antibiotics are used when infection is present. Surgical intervention involves grafting of tissue. Hyperbaric oxygen may promote healing of soft-tissue necrosis.

Effects of chemoradiation therapy The acute ulceration of mucosal epithelium that results from chemoradiation therapy of the head and neck is most severe when both modalities are given simultaneously. Drugs that tend not to produce mucositis, such as cisplatin (Platinol), are preferable. Percutaneous endoscopic gastrostomy (PEG) tubes are essential to administer nutrition, hydration, and medications during definitive chemoradiation therapy for head and neck malignancies.

Recombinant human keratinocyte growth factor (rHuKGF) effectively reduced the duration of severe oral mucositis in patients undergoing a preparative regimen of total body irradiation + etoposide + cyclophosphamide (Cytoxan, Neosar) before autologous peripheral stem-cell transplantation (SCT) from 7.7 days to 4.0 days ($P = .001$).

In recent trials, amifostine decreased the incidence and severity of RT toxicity in head and neck cancer patients while preserving antitumor activity. Mucositis, xerostomia, and hematologic toxicity were all decreased by amifostine, allowing for the intensification of chemoradiation therapy, with better results *(ASTRO [abstract] 51:19, 2001)*.

SALIVARY GLANDS

Acute effects Tenderness and marked swelling of the salivary glands (sialadenitis/parotitis) may occur within a few hours after they are first irradiated and usually subside within a few days. These effects can be treated with aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).

Xerostomia Saliva becomes thickened and output decreases during RT, eventually leading to xerostomia. Commencing treatment with a salivary gland stimulant, such as pilocarpine tablets (Salagen, 5 mg PO tid-qid), maintains salivary output during irradiation and lessens morbidity. After completion of RT, pilocarpine stimulates the remaining salivary glands to increase saliva output.

Significant preservation of salivary gland function was found when oral pilocarpine was used concomitantly with curative RT in a phase III randomized study (RTOG 9709), compared with patients for whom pilocarpine was omitted during RT. This finding indicates a prophylactic effect on irradiated salivary glands by pilocarpine.

Amifostine (Ethyol) is now approved by the FDA as a salivary gland radioprotector in head and neck cancer patients who have undergone a complete resection of their cancer and will be receiving adjuvant RT that includes the parotid salivary glands. Amifostine (200 mg/m^2), is administered daily as a 3-minute IV infusion 15-30 minutes before standard RT (1.8-2.0 Gy) to reduce the incidence of moderate to severe xerostomia in patients in whom the radiation field includes the parotid glands.

In recent studies, amifostine was well tolerated before irradiation when delivered via the simpler subcutaneous route, which appeared safer and just as effective as the intravenous route *(Koukourakis M, Kyrias G, Kakolyris S, et al: Proc Am Soc Clin Oncol [abstract] 21:286a, 2002).*

Glyceride, baking soda, guaifenesin, and carbonated drinks may improve the acute problems caused by thickened saliva. Always ensure that patients being treated with RT are adequately hydrated. Dehydration makes saliva thicker and reduces output. Papain, the proteolytic enzyme found in papayas, helps dissolve thick saliva.

Chronic effects Xerostomia may persist for months to years, with recovery depending on the volume irradiated, the total RT dose, and individual patient variation. Xerostomia is treated with saliva substitutes and sialogogues, including water and glycerin preparations, commercially prepared "artificial saliva," eg, Salivart, Xero-Lube, Moi-Stir, and salivary gland stimulants, eg, bromhexine and pilocarpine tablets.

Cevimeline (Evoxac) is being assessed for efficacy and safety in the treatment of radiation therapy-induced xerostomia. It is presently FDA approved for Sjögren's syndrome.

Daily pilocarpine (15-30 mg in divided doses) may be administered following RT to increase salivary output. Early improvement may be observed, but up to 12 weeks of uninterrupted therapy may be necessary to assess whether a beneficial response will be achieved.

TASTE BUDS

Some patients experience loss of food flavor during the acute mucosal reaction to RT, due to damage of the taste bud cells. These cells are capable of repopulating within 4 months after treatment, but some degree of permanent impairment may remain. Sour and bitter tastes are suppressed to a greater extent than are sweet and salty tastes. Xerostomia and mucositis also contribute to the dysgeusia.

EXTERNAL AND MIDDLE EAR

Inflammatory changes in the external auditory meatus and middle ear occur during RT or soon thereafter and may be manifested by pain, infection, or decreased hearing. Hydrocortisone/neomycin/polymyxin B ear drops or benzocaine/antipyrine/phenylephrine otic solution (Tympagesic) may be used for otitis externa. Decongestants and/or antihistamines, eg, pseudoephedrine/triprolidine, pseudoephedrine/guaifenesin, astemizole (Hismanal), and fexofenadine HCl (Allegra), are useful for otitis media, but occasionally myringotomy is performed to relieve discomfort. Possible superimposed infections are treated also with oral antibiotics, eg, clarithromycin, and amoxicillin/potassium clavulanate (Augmentin).

PHARYNX AND ESOPHAGUS

Pharyngitis and esophagitis with resultant dysphagia develop 2-3 weeks after RT commencement. Dysphagia usually resolves 2-3 weeks after the completion of irradiation (see also section on the esophagus in "Gastrointestinal system" later in this chapter).

Oral topical analgesics (see previous section on "Oral mucosa") or systemic analgesics are used to provide relief and enable adequate nutrition. Sucralfate suspension is useful as a mucosal protective coating agent and may promote healing. A nasogastric, gastrostomy, or jejunostomy tube may be necessary for nutritional support.

SKELETON AND SOFT TISSUES

Mandible Irradiation can diminish the ability of bone to withstand trauma and avoid infection, with resultant osteoradionecrosis (a hypovascular, hypocellular dissolution of bone). Important risk factors include poor nutrition and oral hygiene, trauma (especially dental extractions), continued tobacco and alcohol consumption, RT quality, total dose, overall duration, and frequency (daily vs bid). To decrease the risk of these adverse effects, any necessary dental work (especially extractions) should be performed at least 10 days prior to the initiation of RT.

Dental extractions performed after RT must be done judiciously, since they may initiate osteoradionecrosis. Hyperbaric oxygen may be useful prior to teeth extractions from heavily irradiated bones. It is also used to aid healing in established cases of osteoradionecrosis. Pentoxifylline (Trental) improves blood flow.

Infection can expand the area of necrosis and cause severe pain. Antibiotics (eg, clarithromycin, ciprofloxacin, and amoxicillin/potassium clavulanate) are often necessary and require long-term administration. Sequestrectomy is performed only if all conservative measures have failed.

Teeth Loss of adequate saliva for food lubrication and buffering of acids can lead to multiple problems, including dental caries. Optimal oral and periodontal hygiene must be maintained indefinitely. Daily topical fluoride applications, preferably a fluoride gel held in contact with the teeth by a tray, are extremely effective. Attempts should be made to replace or increase salivary flow (see previous section on "Salivary glands").

Temporomandibular joint (TMJ) Masticatory muscle and TMJ fibrosis can result in trismus. Stretching exercises may alleviate this problem. The Therabite jaw motion rehabilitation system provides anatomically correct motion of the jaw to patients experiencing hypomobility of the mandible. It consists of a mouthpiece and lever that exerts appropriate force to increase the interdental gap.

Soft tissues Soft-tissue necrosis is rare but may occur after insertion of an ill-fitting prosthesis or treatment with a very high local dose of radiation, as is delivered by an interstitial implant. Conservative management includes oral hygiene, antibiotics, pentoxifylline, and hyperbaric oxygen.

Irradiation of the neck, by itself, produces little or no impairment of function but in the postoperative setting may exacerbate surgically induced limitations of head and neck motion by up to 20%. Physical therapy prevents contractures. Patients should stretch the affected area prophylactically several times a day. This practice is especially useful in preventing trismus.

LARYNX

Edema of the arytenoids may occur after a course of RT to the larynx. It may be managed conservatively by resting the voice and administering antibiotics and steroids. Pentoxifylline may also be tried. Edema persisting for more than 3 months following RT may be due to recurrent or persistent tumor.

Lungs

Radiation pneumonitis When doses of thoracic RT exceed tolerance levels, pulmonary reactions are expressed clinically as a pneumonitic process 1-3 months after the completion of therapy. This process can prove lethal if both lungs are involved or if threshold doses of chemotherapeutic drugs have been exceeded. Recovery from acute pneumonitis usually occurs, and the second phase of fibrosis follows almost immediately, with eventual progression to the late fibrotic phase.

Acute symptoms include low-grade fever, congestion, cough, dyspnea, pleuritic chest pain, and hemoptysis. Evidence of consolidation may be found in the region corresponding to the pneumonitis. The acute pneumonitic phase is relatively short-lived but can be severe. Chest x-ray and CT show a diffuse infiltrate corresponding to the RT field.

Management Optimal management is clearly prevention. Corticosteroids can foster recovery from acute RT pneumonitis; a dose of 30-60 mg of prednisone is administered daily for 2-3 weeks and then tapered. Antibiotics for proven infection and supplemental oxygen may be necessary.

In recent phase III randomized trials of lung cancer patients treated with chemoradiation therapy, amifostine significantly reduced acute pneumonitis from 23% to 3.7% ($P = .037$), without any reduction in tumoricidal activity.

Pulmonary fibrosis develops insidiously in the previously irradiated field and stabilizes after 1-2 years, with most patients being asymptomatic. Symptoms are proportional to the extent of lung parenchyma involved and the preexisting pulmonary reserve and are generally minimal if fibrosis is limited to $< 50\%$ of one lung. If fibrosis exceeds this limit, dyspnea associated with progressive chronic cor pulmonale may become clinically manifest.

Radiologic changes consistent with fibrosis are usually seen. Retraction of the involved lung with elevation of the hemidiaphragm are the two predominant findings. CT scanning is currently favored for imaging this region. Pulmonary function tests may show mild deterioration as fibrosis develops. Significant changes are not seen when small volumes of lung tissue are irradiated due to functional compensation from adjacent lung regions. Diffusion capacity studies provide the best assessment of whole lung function.

Management Radiation-induced fibrosis presently appears to be irreversible. Management consists of supportive measures, such as oxygen, bronchodilators (ie, albuterol), and ipratropium bromide (Atrovent). Counseling on the risks of smoking is imperative. Pentoxifylline with vitamin E has recently been shown to cause regression of RT-induced fibrosis.

Amifostine is effective in reducing acute and late toxicities of pneumonitis and lung fibrosis in patients with locally advanced non–small-cell lung cancer treated with irradiation and chemotherapy *(Throuvalas N, Antonabou D, Petridis A, et al: ASTRO [abstract] 54:106, 2002).*

Effects of chemoradiation therapy The pneumonitis and fibrosis associated with RT can also be seen with several chemotherapeutic drugs, including bleomycin (Blenoxane), methotrexate, mitomycin (Mutamycin), nitrosoureas, alkylating agents, and vinca alkaloids. Obviously, these agents can potentiate the damaging effects of RT on the lungs.

Cardiovascular system

PERICARDIAL DISEASE

Acute pericarditis is a rare complication of RT that usually follows irradiation of a radiosensitive mass contiguous to the heart. Signs and symptoms are similar to those of acute, nonspecific pericarditis and include chest pain, fever, and, often, electrocardiographic (ECG) abnormalities.

Pericardial effusion Chronic pericardial effusion may be asymptomatic or lead to cardiac tamponade, which must then be relieved by pericardiocentesis or pericardiectomy.

Pericardial constriction can occur as a final stage of either of the two pericardial syndromes or may develop insidiously without an obvious antecedent event.

MYOCARDIAL DISEASE

Pancarditis Patients treated with RT alone can develop cardiomyopathy and present with severe signs and symptoms of pericardial disease, along with constriction and severe heart failure. Pathologically, there are alterations in the pericardium and myocardium. This condition has been termed "pancarditis." Radiation myocardiofibrosis may occur to a minor degree in asymptomatic patients.

Radiation cardiomyopathy is uncommon with modern treatment techniques unless tolerance doses are exceeded. Simultaneous or sequential chemotherapy (especially with the anthracyclines) aggravates the condition. The interaction between the two modalities appears to be additive. Risk factors for anthracycline cardiotoxicity are other types of heart disease, such as valvular, coronary, or myocardial lesions and hypertension, as well as age > 70 years.

Management The best treatment is clearly prevention. In patients treated with RT and concomitant or sequential doxorubicin, downward adjustment of tolerance doses is appropriate. Dexrazoxane (Zinecard) is a cardioprotective agent used in the prevention and reduction of cardiotoxicity that can be associated with doxorubicin HCl. Dexrazoxane has been shown to reduce doxorubicin-induced cardiomyopathy and allows administration of higher doses of doxorubicin in randomized trials. No evidence has shown an adverse effect of dexrazoxane on the antitumor activity of doxorubicin.

CORONARY ARTERY DISEASE

Radiation-induced coronary artery disease has the same clinical manifestations as are observed in patients who have not received RT. Treatment, including coronary artery bypass surgery, is also the same.

VALVULAR DEFECTS AND CONDUCTION ABNORMALITIES

Other cardiac problems attributed to RT include valvular defects (due to myocardial fibrosis adjacent to valves) and conduction abnormalities (due to ischemic fibrosis of the conduction system).

Skin

Acute effects The acute skin reaction occurs during the first 7-10 days following RT and begins with erythema, progressive pigmentation, epilation, and desquamation as the dose increases. Dry desquamation may then progress to moist desquamation, which usually heals by 50 days following RT or may not heal completely and even progress to necrosis.

Management Symptomatic treatment that controls pain, keeps the radiation field clean, and removes the crust suffices until epithelial remodeling and reepitheliali-

zation restore the skin to normal. Daily normal saline compresses or modified Burow's solution soaks are useful. Topical hydrocortisone creams and nonionic moisturizers, such as Lotionsoft, TheraCare, Biafine, and Aquaphor, are used to alleviate pruritus and the acute inflammatory response to irradiation, whereas antibiotic agents and silver sulfadiazine are prescribed to prevent infection in areas of moist desquamation.

Patients should be advised to wash their skin gently and dry it by dabbing. Irritating skin products should be avoided. Nu-Gel protective wound dressings can also be used; they provide a soothing sensation when cooled. Telfa nonadhesive pads are used to protect the wound. Vitamin A and E ointment or cream promotes healing. Silvadene cream and antibiotic creams prevent infection.

Late effects occur many weeks following RT. A variable period during which the skin appears normal follows the acute reaction. Scaling, atrophy, telangiectasis, subcutaneous fibrosis, and necrosis can then develop and progress for long periods. Telangiectasis develops in an atrophic dermis under a thin epidermis as an area of reddish discoloration displaying multiple, prominent, thin-walled, dilated vessels. Fibrosis is characterized by progressive induration, edema, and thickening of the dermis and subcutaneous tissues and is most severe in areas where there was an earlier moist desquamation.

Management Permanent use of skin moisturizers may be necessary, and irradiated skin must always be protected from the sun. Medical management of chronic ulcers is directed at relieving symptoms and treating infections while attempting to promote healing. Surgical management consists of excision and grafting of the irradiated area. Laser treatment of telangiectasis improves cosmesis. Pentoxifylline (400 mg PO bid-tid) increases blood velocity and may promote healing. One clinical trial showed striking regression of chronic radiotherapy-induced fibrosis in patients after they were treated for at least 6 months with pentoxifylline (400 mg bid) and tocopherol (vitamin E), 1,000 IU/d.

Effects of chemoradiation therapy An additive response between chemotherapy and RT should be anticipated. An increased erythematous response is seen in breast cancer patients receiving combined therapy that includes methotrexate.

The most consistent aggravated skin responses occur in patients with anal, vulvar, or penile carcinoma who receive RT and fluorouracil (5-FU). The first reaction, which occurs following the initial infusion of 5-FU during the first week of RT, is quite mild. The acute moist reaction produced after the second infusion of 5-FU and the higher accumulated RT doses is more severe. It involves the entire field but heals after a few weeks. Similar reactions are noted in patients with head and neck cancer who receive chemoradiation therapy.

Central nervous system

BRAIN

Acute effects are quite rare during conventionally fractionated brain RT. Acute encephalopathic changes have been noted in conjunction with several cytotoxic agents, including cisplatin, asparaginase (Elspar), ifosfamide (Ifex), methotrexate, cytarabine (Ara-C), interferon, and interleukin-2 (IL-2, aldesleukin [Proleukin]). Clinical changes include alteration of mental status or level of consciousness, focal worsening of neurologic signs, and/or generalized seizures. These changes are commonly thought to be due to RT-induced edema and are usually adequately treated with concomitant corticosteroid administration.

Subacute or early delayed reactions Two types of subacute or early delayed reactions have been observed after RT.

Somnolence syndrome is noted 2-6 months after RT and is characterized by somnolence, anorexia, and irritability without accompanying focal neurologic abnormalities. The syndrome is usually transient (resolving within 2-5 weeks), associated with an uneventful recovery, and thought to be due to demyelination following a temporary inhibition of myelin synthesis. The somnolence syndrome is commonly seen after cranial RT for childhood acute lymphocytic leukemia (ALL). Similar transitory, self-limited changes of fatigue and/or exacerbation of focal neurologic signs are noted following full cranial or local RT for primary CNS tumors.

Focal neurologic signs seen after the treatment of CNS tumors may be related to intralesional reactions and are probably indicative of tumor response and/or perilesional reactions, such as edema or demyelination. These signs may be associated with imaging changes, such as focal enhancement, indicating areas of blood-brain barrier disruption and inhomogeneity in the white matter. New RT techniques appear to be quite frequently associated with subacute CNS reactions.

Clinical deterioration and MRI changes representing intralesional necrosis with diffuse pontine swelling have occurred in up to 40% of patients 1-6 months after hyperfractionated RT for brainstem gliomas. High-dose, volume-limited stereotactic radiosurgery is followed by transient white matter alterations, often apparent on MRI. These abnormalities generally begin ≥ 6 months after RT and are usually self-limited. Similar phenomena have been reported following interstitial brain implants.

Late effects Various late CNS effects have been described following RT.

Focal radiation necrosis Localized necrosis develops between 6 months and 2 years following irradiation. New anatomically related functional/irritative signs and symptoms are seen, associated with increasing intracranial pressure.

CT changes are usually confined to the high-dose volume and include low-density white matter changes with irregular enhancement, often associated with surrounding diffuse edema and a variable degree of mass effect. MRI shows similar local changes associated with more extensive areas of white matter alterations, including edema. Differentiating necrosis from tumor recurrence/

progression is usually difficult. Fluorine-1–labeled deoxyglucose (18-FDG) PET scans indicate hypometabolic findings.

Corticosteroids and surgical resection of focal areas of radiation necrosis can result in clinical improvement of neurologic deficits.

Post-irradiation diffuse white matter injury Low-density changes diffusely involving one or both cerebral hemispheres may be evident within several months following full-brain RT. It is common to see white matter alterations extending peripherally beyond the high-dose RT volume.

MRI is more sensitive than CT to white matter changes and shows injury initially limited to periventricular white matter and later extending to include most of the rest of the cerebral white matter. Ventricular dilatation and cortical atrophy are seen with more severe white matter injury.

Symptoms vary widely from mild lassitude or personality changes to marked, incapacitating dementia. Progressive memory loss precedes frank dementia in cases with pronounced ipsilateral or diffuse bilateral changes.

Combined-therapy diffuse white matter injury/leukoencephalopathy In its milder forms, this syndrome is characterized by transient lassitude, dysarthria, or seizures temporally related to the administration of prophylactic cranial RT and methotrexate in children with ALL. The syndrome appears to be continuous, with more severe CNS damage (including progressive degrees of ataxia, confusion, and memory loss) ultimately leading to dementia or death. More recently, similar clinical events of varying severity have been noted 12-18 months after treatment in adults surviving intensive chemotherapy and prophylactic cranial irradiation (PCI) for small-cell lung carcinoma (SCLC).

Imaging findings are similar to those noted above for post-irradiation diffuse white matter injury. Dystrophic calcifications (mineralizing microangiopathy) are noted as late changes in leukoencephalopathy and are most often limited to the basal ganglia and gray-white matter interface.

Neuropsychological effects Intellectual impairment has been reported increasingly among long-term cancer survivors. Cognitive changes in children are marked by memory deficits and learning disabilities. Memory deficits are apparent by 6 months, whereas a decline in global IQ is more often noted beyond 1-2 years after treatment. Neurocognitive impairment is most pronounced in children $<$ 4-7 years old. Deterioration in IQ is statistically significant primarily in children following full-brain or supratentorial RT for primary CNS tumors.

Retrospective studies have reported neurotoxicity in approximately 19% of long-term survivors of SCLC who received PCI and chemotherapy. Problems include memory loss, confusion, dementia, ataxia, psychomotor retardation, and optic atrophy. Discernible intellectual decline is first seen at 4-6 months after therapy and becomes more pronounced 2-3 years later. These studies did not assess neuropsychological function before RT was administered. Other studies that have assessed similar patients' neuropsychological function before and after PCI have not found any evidence of neurotoxicity.

Cerebrovascular effects Arterial cerebrovasculopathy is an infrequent effect that occurs almost exclusively following RT to the parasellar region. Single- or multiple-vessel narrowing/obliteration results in deficits typical of stroke. Vasculopathy is usually related to RT for optic chiasmatic/hypothalamic gliomas in children.

Radiation-induced neurologic tumors Most RT-induced gliomas occur in patients who were irradiated as children and young adults. The 30-year cumulative risk for these tumors is about 0.8%.

SPINAL CORD

Transient radiation myelopathy has an incidence of approximately 15%, with a latency period of 1-29 months after RT, and is seen especially in patients who received mantle-field RT for Hodgkin's disease. This syndrome is due to transient demyelination in the posterior columns and/or lateral spinothalamic tracts within the RT field.

Patients experience sudden electric-like shocks radiating down from the spine to the extremities on neck flexion (Lhermitte's sign); these shocks are usually symmetrical and unrelated to a specific dermatome. Neurologic examination is otherwise normal. The clinical picture reverses spontaneously after an average of about 5 months.

Delayed radiation myelopathy Patients present with a several month history of progressive neurologic signs and symptoms, such as paresthesias and decreased pain and temperature sensation. A bimodal frequency distribution of latency has been reported, with peaks at 13 and 26 months, possibly corresponding to white matter parenchymal and vascular damage, respectively. Symptoms usually progress over 6 months and involve all spinal cord systems but may develop acutely following infarction of the spinal cord.

Temporary remissions have been reported following treatment with steroids or hyperbaric oxygen, but about 50% of patients die of secondary complications. Larger daily RT fractions, decreased number of treatments, treatment of larger lengths of spinal cord, and high total doses increase the risk of RT-induced myelopathy.

Effects of chemoradiation therapy Although experimental data are sparse, simultaneous administration of RT and chemotherapeutic agents known to be neurotoxic (eg, methotrexate, cisplatin, vinblastine [Velban], and Ara-C) may further reduce spinal cord tolerance. Intrathecal chemotherapy can produce myelopathy; thus, its use in combination with RT clearly must be approached with caution. Studies of hyperfractionated RT regimens have shown the spinal cord to be the dose-limiting organ. The interval between RT fractions should be at least 6 hours and preferably longer.

Eyes and adnexa

OCULAR ADNEXA AND ANTERIOR SEGMENT

Acute effects include transient skin erythema, conjunctivitis, epilation of hair follicles in the irradiated field, conjunctivitis, and chemosis. The cornea develops epithelial edema, leading to punctate epithelial keratopathy. Perilimbal injection may be seen with mild keratouveitis. Treatment involves artificial tear drops and topical steroids. Antibiotic eyedrops may be added to prevent or treat infection.

Late effects result in chronic structural changes, such as trichiasis, closure of eyelid puncta, and ectropion or entropion. Skin changes can progress in some areas to pallor, atrophy, telangiectasis, and loss of the eyelashes. Keratitis sicca (dry eye syndrome) may be caused by damage to the lacrimal, goblet, meibomian, and accessory lacrimal glands, which are essential to adequate tear film production. Epiphora may be due to excessive tearing from reflex aqueous production in response to keratitis sicca but may also herald closure of the nasolacrimal drainage system.

Management of epiphora is directed toward determining the cause of the chronic tearing and treating the underlying pathology. Keratitis is managed with aggressive lubrication (Celluvisc, Lacrilube, Lacinsent), eye patching, and antibiotic drops to prevent recurrent corneal erosions.

LENS

Radiation induces cataracts by damaging the germinal zone of the lens epithelium; this damage usually presents as subcapsular opacifications. The frequency, latency, and progression of lens opacities are a function of RT dose and fractionation. Prevention of damage with customized lens shields during RT is clearly the best management.

RETINA

Radiation-induced retinopathy is caused by an occlusive microangiopathy, which is manifested by cotton wool exudates, microaneurysms, telangiectasis, retinal hemorrhage, macular edema, proliferative neovascularization, vitreous hemorrhage, and pigmentary changes. Central retinal artery and vein occlusion have been described. Incomplete perfusion of the capillary bed, as shown by fluorescein angiography, is the most consistent finding. Visual symptoms depend on the retinal area that has been damaged. Radiation-induced and diabetic retinopathies are similar pathologically.

Argon panretinal photocoagulation has resulted in regression of fibrovascular neovascularization. Focal and grid macular treatment can stabilize the progression of visual loss in some patients with macular edema.

OPTIC NERVE

Radiation optic neuropathy (RON) presents as sudden, painless, monocular loss of vision. Visual-field abnormalities usually associated with RON include optic nerve fiber bundle defects and central scotomas.

Effective treatment for RON has not been identified. Prevention is most important and is accomplished by avoiding large single fractions in stereotactic radiosurgery and short intense schedules comprising large fractions.

SECONDARY NEOPLASMS

Children with heritable retinoblastoma have a cancer diathesis, and RT further increases this risk. The most common tumor occurring within the RT field is osteosarcoma of the facial bones. Other secondary neoplasms reported include soft-tissue sarcomas, brain tumors, leukemia, and melanoma.

Bladder, urethra, and ureter

Bladder injury may be either global or focal. Symptoms of global injury include urinary frequency, urgency, decrease in bladder capacity, and cystitis. Symptoms of focal injury include bleeding, ulceration, stone formation, and fistulas.

Acute RT cystitis presents with symptoms of dysuria and urinary frequency and urgency. The incidence varies widely, depending on factors related to radiation timing, dose, and volume. Acute symptoms subside within several weeks following RT.

Management is generally symptomatic. Phenazopyridine hydrochloride (Pyridium) is used as a topical analgesic for dysuria. Oxybutynin chloride (Ditropan), an antispasmodic that relaxes bladder smooth muscle by inhibiting the muscarinic effects of acetylcholine, is useful in relieving symptoms of urinary frequency and urgency. Flavoxate hydrochloride (Urispas) and hyoscyamine sulfate (Levsin) counteract bladder muscle spasm.

Terazosin hydrochloride (Hytrin) and doxazosin mesylate (Cardura), both at 1-2 mg PO daily, may be used in prostate cancer patients who develop obstructive urinary symptoms during pelvic RT. Tamsulosin (Flomax) and finasteride (Proscar) are also used in these patients.

Late effects The interval between RT and the onset of late complications is several months to years, with a median of approximately 13-20 months. Most bladder complications occur within 2-3 years of therapy and include decreased bladder capacity, hematuria from telangiectasis, chronic irritative or obstructive urinary symptoms, and fistulas.

Urethral strictures occur more frequently when there is a history of a prior transurethral resection of the prostate. Defects in urethral resistance are less common than strictures. Severe sphincteric insufficiency may be managed with periurethral injection of polytetrafluoroethylene collagen. Patient-controlled low pressure sphincters may be placed surgically. Urethral strictures are most often managed with simple endoscopic incision or open surgical repair.

Ureteral injury is rarely seen and is reported primarily following pelvic RT and chemotherapy. The length of the ureter irradiated, the presence of tumor, and surgical manipulation all affect tolerance of the ureter to RT.

Management The assessment and management of bladder dysfunction after RT, with or without chemotherapy, require adequate evaluation, including radiography and urodynamics to determine the precise cause of the dysfunction. Drugs to increase bladder storage include propantheline bromide, (Pro-Banthine) oxybutynin chloride, and imipramine hydrochloride (Tofranil). Drugs to increase outlet resistance include ephedrine hydrochloride, pseudoephedrine hydrochloride, and phenylpropanolamine. Severe reductions in bladder capacity that do not respond to pharmacotherapy may be managed with bladder augmentation using a segment of intestine.

Severe hemorrhage caused by RT complications should be treated with cystoscopy and selective cauterization of bleeding sites, followed by irrigation with various agents, such as alum, silver nitrate, or dilute formalin.

Female reproductive system

VULVA

Acute effects Acutely, the vulva demonstrates erythema, which progresses to confluent moist desquamation that is radiation volume- and dose-dependent. The reaction is greatest in the intertriginous areas. Acute effects resolve 2-6 weeks after completion of RT. Skin edema of the vulva and mons pubis may develop 1-3 months after treatment. It is usually painless but can be severe and become chronic. Streptococcal lymphangitis may also develop.

Late effects develop 6-12 months following RT and include vulvar skin thinning, atrophy, dryness, pain, pruritus, and telangiectasis. Epilation is usually complete, and increased skin pigmentation may also develop. Fibrosis of the underlying subcutaneous tissues can result in dyspareunia if it involves the clitoris or vaginal introitus. Painful late ulceration with chronic serous drainage 1-2 years after RT may also occur.

Management The key to management of vulvar skin reactions is aggressive, individualized personal hygiene. Twice-daily sitz baths and gentle skin cleansing should be followed by complete drying of the vulvar region. The best method for drying the skin is a small fan or hair dryer (cool setting). This regimen should be closely followed until the skin is completely healed.

Topical steroid and antibiotic creams are applied for symptomatic relief and to prevent infection, respectively (see previous section on "Skin"). Whirlpool baths may be beneficial. Ulceration or necrosis requires debridement, which should continue until granulation tissue has formed. Myocutaneous flaps may be necessary.

Atrophic vulvar skin, once healed, may benefit from topical estrogen or testosterone creams. Daily dilatation to prevent fibrotic stenosis of the introitus may be necessary.

VAGINA

Acute effects Erythema, moist desquamation, confluent mucositis, severe congestion, and submucosal hemorrhage can be seen acutely and may resolve within 2-3 months after irradiation. Some patients demonstrate progressive vascular damage and ischemia, which result in epithelial sloughing, ulcer formation, and necrosis. These changes may require 4-8 months to heal.

Late effects include thinning and atrophy of the vaginal epithelium with development of telangiectasis. Reduced vaginal capacity due to fibrosis and decreased lubrication results in dyspareunia. Thin, filmy adhesions or synechiae develop and can become permanent, with fusion of the vaginal walls (agglutination) if not managed appropriately. Vaginal ulceration or necrosis may develop several months following RT.

Management Acute RT vaginitis is managed with vaginal douching (using a mixture of 1 part hydrogen peroxide to 10 parts water 2-3 times daily until resolution). Daily vaginal dilatation is required once the acute reaction has resolved to prevent vaginal stenosis. Intravaginal estrogen cream appears to stimulate epithelial regeneration and may be used twice weekly to promote healing, prevent vaginal mucosal atrophy, and improve lubrication and elasticity.

Fistula formation may be treated with periodic debridement and antibiotics. Urinary and fecal diversion is sometimes required, with delayed reanastomosis and myocutaneous grafting for repair.

CERVIX AND UTERUS

Superficial ulceration of the cervix is an inevitable consequence of RT for carcinoma of the cervix that may persist for months, resulting in a thin, clear vaginal discharge.

Cervical os stenosis occurs 3-6 months following high-dose brachytherapy for cervical and endometrial carcinoma.

Rare complications Rarely, hematometra can develop due to residual functioning endometrium, which responds to hormonal stimulation. There is consequent retention of hemorrhagic debris because of obliteration of the endocervical canal or cervical os stenosis. True necrosis of the endometrial cavity also occurs rarely following RT for endometrial carcinoma. An uncommon complication of pelvic RT is development of high-grade endometrial carcinoma or uterine sarcoma many years after therapy.

Management Cervicitis, ulceration, and necrosis of the cervix are managed with douching (1 part hydrogen peroxide to 10 parts water 2-3 times daily until resolution) and debridement as necessary. Dilatation of the stenotic cervical os may be necessary to prevent hematometra or, in the case of uterine necrosis, to allow drainage of necrotic material.

OVARIES AND REPRODUCTIVE/ENDOCRINE FUNCTION

Hormonal changes Premenopausal women with intact ovaries exposed to sufficiently high RT doses experience premature menopause. In a North Cen-

tral Cancer Treatment Group (NCCTG) randomized trial, venlafaxine (Effexor) has been found to substantially reduce hot flashes in women with breast cancer experiencing menopausal symptoms and in whom estrogen and progesterone preparations are contraindicated.

Ovarian carcinoma following pelvic RT for carcinoma of the cervix is extremely uncommon.

Sexual dysfunction is a frequent occurrence following surgery, RT, and chemotherapy for pelvic malignancies and results in psychosexual problems.

Management The ovaries can be protected by moving them away from areas that are to be irradiated. A sexual function history should be obtained from all patients at 3 months after RT using one of the several available psychological instruments. Interventions include improving personal hygiene, hormones, vaginal lubrication, and routine use of a vaginal dilator. Hormonal replacement is accomplished with oral conjugated estrogens or estradiol patches (Estraderm) and progesterone as necessary.

Male reproductive system

Testicular dysfunction following RT includes azoospermia, oligospermia, and hormonal changes. Recovery of sperm count may take months to years. Oligospermia occurs after very low doses of RT. It may therefore be precipitated by exposure to scattered RT from other treatment sites, as well as by total-body RT used as a conditioning regimen for bone marrow transplantation (BMT). Sterility develops at higher RT doses. Erectile dysfunction is seen in patients receiving high RT doses to the pelvis, as for prostate cancer.

Management The best management is prevention by appropriate RT field tailoring and shielding. Sperm-banking should always be carried out if there are fertility concerns. Sildenafil citrate (Viagra) is now available for impotent patients.

Gastrointestinal system

LIVER

Radiation- and chemotherapy-induced liver disease The chief hepatic toxicity of chemotherapy and RT is subacute, beginning 7-90 days after completion of therapy. There are many similarities between radiation-induced liver disease (RILD) and combined modality-induced liver disease (CMILD). Pathologically, the common lesion for both is veno-occlusive disease (VOD).

RILD occurs approximately 4-8 weeks after the completion of RT. Symptoms include fatigue, rapid weight gain, increased abdominal girth, and right upper quadrant discomfort. Patients are rarely jaundiced and may develop ascites and hepatomegaly with elevated alkaline phosphatase levels out of proportion to the other hepatic enzymes. CT scan shows low density in the irradiated region of the liver.

CMILD differs from RILD in some respects, with the most distinctive differences being the faster onset of the former and the early expression of jaundice. Liver enzymes are mildly increased, and bilirubin levels are significantly elevated. As CMILD produces no distinctive changes on imaging studies, the diagnosis is one of exclusion.

CMILD is most commonly seen in the setting of allogeneic BMT, which requires aggressive preparative techniques involving administration of both high-dose chemotherapy and total-body RT. Patients present 1-4 weeks post-transplantation with at least two of the following conditions: jaundice, weight gain, right upper quadrant pain, hepatomegaly, ascites, and encephalopathy.

Chronic RILD The liver usually heals after the subacute RT injury, but chronic fibrosis may develop depending on the degree of RT and chemotherapy injury. When fully expressed, the damage resembles finely nodular cirrhosis both pathologically and clinically. Irradiation to parts of the liver can cause localized fibrosis with no clinical sequelae of hepatic insufficiency if the consequent hypertrophy/hyperplasia of the untreated organ provides sufficient functional compensation.

Management No established therapies exist for RILD, although the use of anticoagulants and steroids has been suggested. The majority of patients with this syndrome also respond to conservative diuresis. There are also no established therapies for CMILD.

ESOPHAGUS

Acute effects Symptoms of gastroesophageal reflux with dysphagia develop approximately 2 weeks following initiation of RT. Early RT esophagitis is generally the dose-limiting reaction in aggressive multimodality therapy, as is used for esophageal and lung cancers. Decreased mucosal thickness may progress to frank ulceration, which may heal with fibrosis and cause benign strictures. Amifostine significantly decreased severe esophagitis in lung cancer patients treated with chemoradiation therapy in recent phase III randomized trials from 26%.-6.5% ($P = .038$).

Analgesics, topical anesthetics (see previous section on "Oral mucosa"), sucralfate, H_2-receptor blockers (ranitidine [Zantac], cimetidine [Tagamet], famotidine [Pepcid]), omeprazole (Prilosec), antacids, or metoclopramide [Reglan] are used for symptomatic relief. Sucralfate slurry may also be used prophylactically, pre- and post- RT daily to reduce the severity of esophagitis, and may promote healing (see also the pharynx and esophagus section under "Head and neck ").

Late effects Formation of benign strictures and changes in motility secondary to muscle and/or nerve damage cause chronic dysphagia. Strictures develop a median of 6 months after RT and generally are not seen before 3 months. Strictures are dilated with Maloney or Savory dilators. Prokinetic drugs, such as metoclopramide, can lessen gastroesophageal reflux by increasing lower esophageal sphincter pressure and the rate of gastric emptying. Cisapride (Propulsid) also increases GI motility.

Effects of chemoradiation therapy Such drugs as cisplatin, 5-FU, dactinomycin (Cosmegen), doxorubicin, bleomycin, and methotrexate can augment the acute effects of RT on the esophagus, but the effect of these agents on late complications is not yet well established.

STOMACH

Acute effects Acute nausea and vomiting can occur shortly after the daily delivery of RT. Gastric secretions are suppressed acutely but recover later. Erosive and ulcerative gastritis can develop 2-3 weeks after RT begins but is generally transient and abates rapidly after the completion of RT.

Use of antiemetics (eg, ondansetron [Zofran], metoclopramide, prochlorperazine [Compazine], granisetron [Kytril], dronabinol [Marinol], lorazepam [Ativan], and chlorpromazine [Thorazine]), and a decrease in the RT daily dose per fraction may ameliorate acute nausea and vomiting. Antiemetics begun within an hour before RT delivery may prevent the nausea and vomiting that may occur shortly after such therapy.

Late effects of irradiation on the stomach include the following conditions:

Dyspepsia arises at 6 months after RT (range, 2-20 months) as vague gastric symptoms.

Gastritis develops at 12 months after RT (range, 1-48 months) and is accompanied by radiologic evidence of spasm or stenosis of the antrum. The pathologic basis is fibrosis of the submucosal tissue, leading to mucosal fold smoothening and atrophy.

Ulceration typically arises at 5 months after RT (range, 1-72 months). Radiation-induced ulcers are indistinguishable from peptic ulcers. Spontaneous healing may occur but can be accompanied by submucosal fibrosis, which can produce antral fibrosis. Progressive stomach contracture results in early satiety, anorexia, and weight loss.

Ulcer with perforation may develop at 2 months after RT (range, 1-30 months).

Late RT toxicities have been treated with H_2-receptor antagonists and sucralfate. Surgery (eg, partial gastrectomy) is utilized for perforation, bleeding, or gastric outlet obstruction.

SMALL AND LARGE INTESTINES

The tolerance of the small and large bowels is a major dose-limiting factor in the treatment of many cancers of the abdomen and pelvis.

Acute effects Nausea, vomiting, early satiety, anorexia, and fatigue are frequent acute effects. Nausea and vomiting may develop shortly after RT delivery, necessitating the use of prophylactic antiemetics. Acute proctocolitis in patients undergoing pelvic RT is extremely common, manifesting clinically as watery bowel movements with rectal urgency and tenesmus. Patients receiving RT following low anterior resection experience frequent small stools since the rectal vault capacity is markedly diminished. Hematochezia occurs infrequently and is often due to hemorrhoidal irritation.

Radiation enteritis develops if significant volumes of small bowel are irradiated. Symptoms appear 2-3 weeks after the initiation of RT, and the enteritis increases in severity until several days after treatment is discontinued. Loose to watery diarrhea with voluminous frequent stools and cramping abdominal pain are characteristic of fully developed enteritis.

Management Diarrhea is treated with a low-residue diet and loperamide or diphenoxylate (Lomotil), 1-2 tabs PO qid prn. Psyllium is sometimes helpful, as is cholestyramine (Prevalite, Questran). *Clostridium difficile* infection should be ruled out. Octreotide (Sandostatin) 0.1 mg SC tid (long-acting analog of somatostatin) was compared with diphenoxylate in a randomized trial and was found to be more effective in controlling diarrhea induced by pelvic irradiation.

Similarly, proctitis may be treated according to the prevailing problem. Anusol-HC cream or Anusol suppositories are effective for alleviation of local symptoms of proctitis, such as tenesmus. Oral sucralfate may promote healing of proctitis. Mesalamine suppositories and glucocorticoid retention enemas may be used for unresponsive proctitis and sulfasalazine for associated bleeding. (For management of nausea and vomiting, see previous section on "Stomach.")

Late small bowel effects The median onset of late small bowel RT effects is 1-5 years following the completion of RT and may be hastened by concomitant chemotherapy. Obstruction, the most common late effect, is preceded by sporadic or gradually increasing episodes of acute colicky abdominal discomfort. Perforation presents with an acute abdomen. Occasionally, late bowel damage is manifested by massive bleeding. Radiographic findings include fibrosis and ischemia. Spasm is seen, with altered bowel transit times, ulceration, thickened folds, narrowed bowel segments, and marked mesenteric adhesions.

Malabsorption is a common sequela of the late changes of RT and can include bile salt wasting from extensive ileal involvement. Stasis predisposes to bacterial overgrowth. Enterocolonic fistulas can also cause massive intraluminal bacterial overgrowth with severe steatorrhea and vitamin B_{12} deficiency.

Late large bowel injury becomes manifest earlier than late injury to the small bowel (within 2 years of treatment; median, 6-18 months). Fistulas occur more often in the rectum than elsewhere in the gut and are confined almost exclusively to cases in which brachytherapy was used for gynecologic cancer. They usually occur along the anterior rectal wall posterior to the vaginal fornix.

Other chronic symptoms include strictures, tenesmus, bleeding, cramps, obstipation, diarrhea, and rectal urgency; surgical intervention is sometimes necessary if these symptoms become severe enough. Radiographically, the most frequent appearance of large bowel injury is a smooth, elongated narrowing. Alternatively, submucosal changes can give the appearance of a nodular or thumbprinting effect on the large bowel wall. Mesenteric shortening can produce retraction of the transverse colon.

Ulceration is frequent and sometimes simulates diverticulitis. Bleeding can occur from sites of ulceration and telangiectasis.

Management Mild cases of chronic RT injury to the small and large intestines can be managed by a low-residue diet, stool softeners, psyllium, loperamide, or diphenoxylate. Fiber laxatives give a firmer consistency to the stool and soften it. Cholestyramine can improve diarrhea due to small bowel injury by binding bile salts that are irritative to irradiated bowel. Bleeding from sites of ulceration and telangiectasis can be treated by endoscopic laser therapy. Patients with malabsorption may benefit from pancreatic enzymes (eg, Pancrease) or lactase enzymes (eg, LactAid). Flatulence may be treated with simethicone. Pentoxifylline increases blood velocity and may promote healing. Again, mesalamine suppositories and glucocorticoid enemas may be helpful, as may sulfasalazine.

Surgical management for late bowel complications is controversial. Some favor an aggressive approach, with lysis of all adhesions to free up the full length of the small bowel and resection of all severely involved segments. Others advocate a much more conservative approach of bypassing injured bowel by the simplest procedure possible.

Effects of chemoradiation therapy Dactinomycin or concurrent doxorubicin enhances the risk of late intestinal complications. Bolus infusion of 5-FU, which is included in most chemoradiation therapy regimens, has not been shown to increase the risk of late intestinal complications. High-dose infusional 5-FU, however, may enhance the risk of late intestinal complications.

Thyroid

HYPOTHYROIDISM

Primary hypothyroidism may be seen in patients who have received therapeutic RT doses to the cervical area. Subclinical hypothyroidism is the most common finding, with clinical hypothyroidism seen less frequently. The cumulative risk of developing overt or subclinical hypothyroidism is approximately 50%, and half of this risk manifests within 5 years of therapy. The use of iodinated radiographic contrast agents prior to RT, especially the ethiodized oil emulsion used in lymphangiography in Hodgkin's disease and other lymphomas, has been proposed as a contributing factor.

Hypothyroidism has been documented after irradiation to the craniospinal axis for CNS tumors, after total-body RT for BMT, and after RT for Hodgkin's disease or head and neck malignancies.

Hypothyroidism may develop as the result of thyrotropin (thyroid-stimulating hormone [TSH]) deficiency or hypothalamic injury following RT for pituitary adenomas, brain tumors, or head and neck cancers. Thyrotropin deficiency may be the sole manifestation of pituitary injury or may be accompanied by loss of corticotropin, gonadotropins, and growth hormone.

HYPERTHYROIDISM

Thyrotoxicosis (Graves' disease) may also develop after external irradiation of the thyroid, as seen in Hodgkin's disease patients. These patients develop hypothyroidism after several months.

THYROID ENLARGEMENT, NODULARITY, AND DEVELOPMENT OF NEOPLASMS

Hashimoto's thyroiditis has been observed after RT of the thyroid in patients with Hodgkin's disease. Persistently elevated TSH results in hyperstimulation of the thyroid gland with development of nodules (adenomas or carcinomas). The actuarial risk of developing thyroid cancer after RT has been reported to be 1.7%, as compared with an expected risk of 0.07% in the normal population matched for age and sex. The relative risk of developing thyroid cancer after RT for Hodgkin's disease is approximately 15.6 (95% confidence interval [CI], 6.3-32.5), and the absolute risk is 33.9 cases per 100,000 person-years.

Management Serum TSH and free thyroxine (FT_4) should be determined annually, and levothyroxine sodium should be prescribed for subclinical hypothyroidism. Cancer risk may also be reduced by limiting the effects of TSH on RT-damaged thyroid follicles. (For further discussion of the evaluation of thyroid nodules and management of thyroid carcinomas, see chapter 5.)

Hematopoietic stem-cell compartment

Acute effects Lymphopenia occurs almost immediately after RT because lymphocytes are exquisitely sensitive and die in interphase. Neutropenia occurs in the first week after irradiation of large volumes of bone marrow, followed by thrombocytopenia in 2-3 weeks and anemia in 2-3 months.

A rapid depletion of vital stem cells occurs within 1 week following appropriate total-body doses. The microvasculature usually survives the conventional doses used for total-body RT and allows the implantation and proliferation of transferred stem cells, resulting in recovery. Acute effects are not usually seen unless a substantial portion of bone marrow is treated. RT is usually not commenced if the absolute neutrophil count is $< 1.5 \times 10^3/\mu L$, with platelets $< 75 \times 10^3/\mu L$. A hemoglobin of 10 g/dL (100 g/L) is desirable during RT. Adequate oxygenation increases tumor radiosensitivity.

Permanent ablation or hypoplasia The capacity of the unexposed bone marrow to compensate by accelerating its rate of hematopoiesis is sufficient when the RT field involves < 10%-15% of the bone marrow. When 25%-50% of bone marrow is irradiated, permanent ablation or hypoplasia also occurs at similar dose levels as for small fields. The unirradiated marrow becomes hyperactive to meet the demands for hematopoiesis.

When 50%-75% of the bone marrow is irradiated, hematopoietic activity increases in the unexposed marrow segments, followed by extension of functioning marrow into previously quiescent areas. Although hematopoietic stem cells are exquisitely radiosensitive, it is damage to the bone marrow stroma that primarily accounts for chronic RT injury. Ir-

The American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) now recommend epoetin for anemia, with hemoglobin levels < 10 g/dL, related to cancer treatment. The use of epoetin for anemia (10-12 g/dL) should be determined by clinical circumstances *(Rizzo JD, Lichtin AE, Woolf SH, et al: J Clin Oncol 19:4083-4107, 2002).*

reversible injury after RT is a consequence of irreparable damage to the microvasculature, manifested by irrevocable bone marrow fibrosis.

Management Treatments for bone marrow injury include transfusions of erythrocytes, platelets, and possibly granulocytes in patients who have severe neutropenia ($< 200/\mu L$) and documented infections that have not responded to appropriate antibiotics. Administration of growth factors is a common supportive measure in patients with RBC or WBC deficiencies. Erythropoietin (Epogen, Procrit) has been used for anemia, granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) for neutropenia, and oprelvekin (Neumega) for thrombocytopenia. Peripheral blood stem-cell transfusions are effectively used as an alternative to autologous BMT. Allogeneic BMT is an obvious approach to restoring marrow function in patients with chronic marrow failure.

Effects of chemoradiation therapy When RT and chemotherapy are administered concurrently and sufficient time is allowed for recovery of peripheral blood cell counts (1-2 months), the increased marrow toxicity of the second modality reflects the irreparable damage caused by the first modality. The potential effects of chemoradiation therapy are much more complicated when both modalities are used simultaneously.

Bone

Inhibition or impairment of skeletal growth is an important dose-limiting toxicity of ionizing radiation, especially in children. Few attempts have been made to quantify RT-related growth arrest or to develop consistent methods for assessing its impact on function and cosmesis. Consequently, the impact of various treatments and the influence of clinical interventions once complications have developed have been difficult to evaluate.

Axial skeletal growth arrest may be terminated by irradiation, resulting in disproportionate sitting and standing heights.

Scoliosis can be caused by partial RT of vertebral bodies, soft-tissue asymmetry caused by surgery, and RT-induced hypoplasia of the rib cage and pelvis. Failure to correct leg-length discrepancies can also cause back problems, including scoliosis.

Slipped capital femoral epiphysis has also been reported as a complication of hip RT in children.

Abnormalities of craniofacial growth can cause significant cosmetic and functional deformities.

Management Careful RT technique to exclude the epiphyseal growth plates can minimize the risk of serious late effects. Early intervention can prevent secondary progressive injury and improve the functional result of treatment in the fully grown individual.

Mild asymptomatic scoliosis may be treated conservatively. Physical therapy and exercise programs can be helpful. In cases of severe back pain and spinal

curvatures > 20°, braces may improve support. Surgical intervention with placement of a Harrington rod is recommended only for severe cases.

Appropriate shoe lifts can correct leg-length discrepancies. Prompt recognition of capital femoral epiphysis slippage is extremely important. Surgical treatment typically consists of pinning, but severe cases may require osteotomy and osteoplasty.

Nerves and muscles

PERIPHERAL NERVES

Peripheral nerve damage from RT is rare, but latency is important in its evaluation. Peripheral nerve damage has been seen following intraoperative RT and appears to be the dose-limiting toxicity in many cases. Cranial nerve injury is not usually seen.

Brachial plexopathy increases in incidence when large daily RT doses are used and is sometimes reported after axillary RT (eg, for breast cancer). Breast cancer patients who have received chemotherapy have a higher incidence of brachial plexopathy than those receiving RT only.

Sacral plexus injuries after RT for carcinoma of the cervix have also been reported occasionally.

MUSCLES

Late complications include limb contracture, edema, decreased range of motion, pain, and decreased muscle strength. They may be of minor or severe functional importance. Latency is very important in the evaluation of muscle injury since progression may continue for as long as 10 years after RT. Chemotherapy does not seem to have a major impact on the incidence of late soft-tissue injury but does increase the rate of acute reactions.

Management is aimed at decreasing the size of the RT field, thereby sparing more functional healthy tissue, as long as cure is not compromised. Vigorous physical therapy and rehabilitation during and especially after RT are important. Muscle relaxants, eg, cyclobenzaprine (Flexeril), and anxiolytics, such as lorazepam, are useful for muscle spasms. Pentoxifylline may be tried to improve blood flow velocity and promote healing.

Neuroendocrinologic system

Growth hormone deficiency, the most common RT-induced endocrine disturbance, is most evident in the growing child as a reduction in growth velocity. In the postpubertal individual, growth hormone deficiency is associated with a relative decrease in muscle mass and an increase in adipose tissue.

Gonadotropin deficiency Young children may fail to enter puberty and females may experience primary amenorrhea. Adult deficiency may be associated with infertility, sexual dysfunction, and decreased libido.

Early sexual maturation Precocious puberty may be seen in patients who have received cranial RT.

TSH deficiency Excessive weight gain and lethargy can be seen with complete TSH deficiency of long duration. Children may have poor linear growth and delayed puberty.

Adrenocorticotrophic deficiency and hyperprolactinemia may also be seen.

Kidneys

A number of overlapping clinical syndromes are recognized, depending on the renal volume irradiated and the RT dose delivered.

Radiation nephropathy Acute radiation nephropathy (up to 6 months) following RT is rarely symptomatic; the glomerular filtration rate may be decreased. Signs and symptoms in the subacute period (6-12 months) include dyspnea on exertion, headaches, ankle edema, lassitude, anemia, hypertension, elevated blood urea, and urinary abnormalities. Benign or malignant hypertension is seen in the chronic period (generally after 18 months), depending on the severity of the renal damage.

Chronic radiation nephropathy, in its mildest forms, may not be diagnosed for many years after RT. The only abnormalities may be proteinuria and azotemia with urinary casts or mild hypertension. A contracted kidney is seen on IV pyelography. Death may occur from chronic uremia or left-ventricular failure, pulmonary edema, pleural effusion, and hepatic congestion.

Other syndromes More recently, hyperreninemic hypertension has been described following unilateral renal RT, as has the nephrotic syndrome.

Management Hypertension and peripheral and pulmonary edema should be treated actively with appropriate medications, and anemia should be corrected. Renal tubular function may show some recovery. Dialysis and transplantation are sometimes necessary.

Effects of chemoradiation therapy Combined-modality treatment appears to intensify RT-induced renal changes.

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CHAPTER 47

Oncologic emergencies and paraneoplastic syndromes

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SUPERIOR VENA CAVA SYNDROME

Superior vena cava syndrome (SVCS) is a common occurrence in cancer patients and can lead to life-threatening complications such as cerebral or laryngeal edema. Although most commonly resulting from external compression of the vena cava by a tumor, SVCS can also stem from nonmalignant causes in cancer patients.

Etiology

Malignant causes

Primary intrathoracic malignancies are the cause of SVCS in approximately 87%-97% of cases. The most frequent malignancy associated with the syndrome is lung cancer, followed by lymphomas and solid tumors that metastasize to the mediastinum.

Lung cancer SVCS develops in approximately 3%-15% of patients with bronchogenic carcinoma, and it is four times more likely to occur in patients with right- vs left-sided lesions.

Metastatic disease Breast and testicular cancers are the most common metastatic malignancies causing SVCS, accounting for > 7% of cases. Metastatic disease to the thorax is responsible for SVCS in ~3%-20% of patients.

Nonmalignant causes

Thrombosis The most common nonmalignant cause of SVCS in cancer patients is thrombosis secondary to venous access devices (see chapter 45).

Other nonmalignant causes include cystic hygroma, substernal thyroid goiter, benign teratoma, dermoid cyst, thymoma, tuberculosis, histoplasmosis, actinomycosis, syphilis, pyogenic infections, radiation therapy, silicosis, and sarcoidosis. Some cases are idiopathic.

Signs and symptoms

Classic symptoms Patients with SVCS most often present with complaints of facial edema or erythema, dyspnea, cough, orthopnea, or arm and neck edema. These classic symptoms are seen most commonly in patients with complete obstruction, as opposed to those with mildly obstructive disease.

Other associated symptoms may include hoarseness, dysphagia, headaches, dizziness, syncope, lethargy, and chest pain. The symptoms may be worsened by positional changes, particularly bending forward, stooping, or lying down.

Common physical findings The most common physical findings include edema of the face, neck, or arms; dilatation of the veins of the upper body; and plethora or cyanosis of the face. Periorbital edema may be prominent.

Other physical findings include laryngeal or glossal edema, mental status changes, and pleural effusion (more commonly on the right side).

Diagnosis

It is important to establish the diagnosis and underlying etiology of SVCS, since some malignancies may be more amenable than others to specific treatment regimens. In the majority of cases, the diagnosis of SVCS is evident based on clinical examination alone.

The following diagnostic procedures may aid in establishing the diagnosis and etiology of SVCS: chest x-ray, bronchoscopy, limited thoracotomy or thoracoscopy, contrast and radionuclide venography, Doppler ultrasonography, and CT (especially contrast-enhanced spiral CT), and MRI.

Prognosis

The prognosis of SVCS depends on the etiology of the underlying obstruction. A review by Schraufnagel showed the average overall survival after the onset of SVCS to be 10 months, but there was wide variation (± 25 months) depending on the underlying disease, with an average survival of 7.6 months. This duration was not significantly different from the survival duration of 12.2 months in patients presenting with SVCS as the primary manifestation of the disease. Thoracic malignancy, the most common cause of SVCS, had a poor prognosis of < 5 months.

Treatment

Treatment includes radiotherapy, chemotherapy, thrombolytic therapy and anticoagulation, expandable wire stents, balloon angioplasty, and surgical bypass.

Most patients derive sufficient relief from obstructive symptoms when treated with medical adjuncts, such as diuretics and steroids (see "Adjunctive medical therapy"), so they can tolerate a work-up to determine the etiology of the SVCS.

In some instances, it is appropriate to delay treatment for 1-2 days if necessary to establish a firm tissue diagnosis.

Radiotherapy and chemotherapy

Both radiotherapy and chemotherapy are treatment options, depending on the tumor type. The specific drugs and doses used are those active against the underlying malignancy.

Life-threatening symptoms, such as respiratory distress, are indications for urgent radiotherapy. A preliminary determination of the treatment goal (potentially curative or palliative only) is necessary prior to the initiation of treatment, even in the emergent setting.

Radiation therapy is the standard treatment of non–small-cell lung cancer (NSCLC) with SVCS. Recent studies suggest that chemotherapy may be as effective as radiotherapy in rapidly shrinking SCLC. Chemoradiation therapy may result in improved ultimate local control over chemotherapy alone in SCLC and non-Hodgkin's lymphoma. Retrospective reviews of patients with SCLC have reported equivalent survival in patients with or without SVCS treated definitively with chemoradiation therapy.

Reasonable palliative courses can range from 2,000 cGy in 1 week to 4,000 cGy in 4 weeks. Curative regimens can range from 3,500 to 6,600 cGy based on histology. If indicated, more rapid palliation may be achieved by delivering daily doses of 400 cGy up to a dose of 800-1,200 cGy, after which the remainder of the appropriate total dose can be given in more standard daily fractions of 180 to 200 cGy. Some European investigators have used doses as high as 600 cGy 1 week apart in elderly patients.

Anticoagulation and thrombolysis

Anticoagulation for SVCS has become increasingly important due to thrombosis related to intravascular devices. In certain situations, the device remains in place. Both streptokinase and urokinase have been used for thrombolysis, although urokinase has been more effective in lysing clots in this setting. Urokinase is given as a 4,400-U/kg bolus followed by 4,400 U/kg/h, whereas streptokinase is administered as a 250,000-U bolus followed by 100,000 U/h. The use of thrombolytic therapy is controversial for catheter-related thrombosis, however.

Stenting

Placement of an expandable wire stent across the stenotic portion of the vena cava is an appropriate therapy for palliation of symptoms of SVCS when other therapeutic modalities cannot be used or are ineffective. Use of stents is limited when intraluminal thrombosis is present.

Other interventional treatments

Balloon angioplasty and surgical bypass also have been used in appropriate patients but are rarely indicated. Balloon angioplasty may be considered in

patients with SVCS, significant clinical symptoms, and critical superior vena cava obstruction demonstrated by angiography. Surgical bypass usually is limited to patients with benign disease; however, for a select group of patients with SVCS, bypass may be an important aspect of palliative treatment. Other palliative efforts may be considered prior to bypass in this patient population.

Adjunctive medical therapy

Medications that may be used as adjuncts to the treatments described above include diuretics and steroids.

Diuretics may provide symptomatic relief of edema that is often immediate, although transient. The use of diuretics is not a definitive treatment, and resulting complications may ensue, such as dehydration and decreased blood flow. Loop diuretics, such as furosemide (Lasix), are often used. Dosage depends on the patient's volume status and renal function.

Steroids may be useful in the presence of respiratory compromise. They are also thought to be helpful in blocking the inflammatory reaction associated with irradiation.

Dosage depends on the severity of clinical symptoms. For severe and significant respiratory symptoms, hydrocortisone, 100-500 mg IV, may be administered initially. Lower doses every 6-8 hours may be continued. Tapering of the steroid dosage should begin as soon as the patient's condition has stabilized. Prophylactic gastric protection is advised during steroid administration.

SPINAL CORD COMPRESSION

Spinal cord compression develops in 1%-5% of patients with systemic cancer. It should be considered an emergency, as treatment delays may result in irreversible paralysis and loss of bowel and bladder function.

Etiology

Compression of the spinal cord is due predominantly to extradural metastases (95%) and usually results from tumor involvement of the vertebral column. A tumor may occasionally metastasize to the epidural space without bony involvement.

Site of involvement The segment most often involved is the thoracic spine (70%), followed by the lumbosacral (20%) and cervical spine (10%).

Most common malignancies Spinal cord compression occurs in a variety of malignancies; the most common are lung, breast, unknown primary, prostate, and renal cancers.

Signs and symptoms

Early signs Over 90% of patients present with pain localized to the spine or radicular in nature (ie, not due to bony involvement but rather due to neural

compression). Pain, which is usually secondary to bony involvement, is often exacerbated with movement, recumbency, coughing, sneezing, or straining. The majority of patients experience pain for weeks to months before neurologic symptoms appear.

Intermediate signs If cord compression goes untreated, weakness often develops next. It may be preceded or accompanied by sensory loss.

Late signs Symptoms of autonomic dysfunction, urinary retention, and constipation are late findings. Once autonomic, motor, or sensory findings appear, spinal cord compression usually progresses rapidly and may result in irreversible paralysis in hours to days if untreated.

Physical findings may include tenderness to palpation or percussion over the involved spine, pain in the distribution of the involved nerve root, muscle weakness, spasticity, abnormal muscle stretch reflexes and extensor plantar responses, and sensory loss. Sensory loss occurs below the involved cord segment and indicates the site of compression. In patients with autonomic dysfunction, physical findings include a palpable bladder or diminished rectal tone.

Diagnosis

The first step in the diagnosis of spinal cord compression is an accurate neurologic history and examination.

X-rays More than 66% of patients with spinal cord compression have bony abnormalities on plain radiographs of the spine. Findings include erosion and loss of pedicles, partial or complete collapse of vertebral bodies, and paraspinous soft-tissue masses. Normal spine films are not helpful for excluding epidural metastases.

MRI The standard for diagnosing and localizing epidural cord compression is the MR scan. Gadolinium-enhanced MRI has been especially helpful in assessing cord compression secondary to spinal epidural abscesses, as gadolinium enhances actively inflamed tissues and defines anatomic boundaries. An abnormal signal within the disk space suggests the possibility of infection.

Primary or secondary neoplasms involving the vertebral bodies generally demonstrate a long T1, resulting in decreased signal intensity on a T1-weighted image, and a long T2, with increased signal intensity on the T2-weighted image.

CT and myelography If MRI is unavailable, a CT scan and/or myelogram may be used to diagnose and localize epidural cord compression.

Prognosis

Treatment outcome correlates with the degree and duration of neurologic impairment prior to therapy. In a prospective analysis of 209 patients treated for spinal cord compression with radiotherapy and steroids, Maranzano and Latini reported that of patients who were ambulatory, nonambulatory, or paraplegic prior to treatment, 98%, 60%, and 11%, respectively, were able to ambulate

following therapy. Treatment outcome was superior in the most radiosensitive malignancies (eg, lymphoma) than in the less sensitive cancers (renal cell carcinoma). Almost all ambulatory patients treated with either radiation alone or laminectomy followed by postoperative radiation remained ambulatory after treatment, whereas ~10% of patients whose lower extremities were paralyzed could walk after treatment.

Treatment

The goals of treatment of spinal cord compression are recovery and maintenance of normal neurologic function, local tumor control, stabilization of the spine, and pain control. The choice of treatment depends on the clinical presentation, availability of histologic diagnosis, rapidity of the clinical course, type of malignancy, site of spinal involvement, stability of the spine, and previous treatment.

For example, Maranzano and Latini treated 53 consecutive patients, from 1993 to 1995, with 800 cGy × 2 (to 1,600 cGy) given over 2 weeks. At a median follow-up of 25 months (range, 6-34 months), 67% of the patients experienced pain relief, and 63% showed improvement in motor function. No late toxicities were reported. This regimen was suggested for patients with less "radioresponsive" tumors (eg, NSCLC, renal cell carcinoma, melanoma, and sarcoma) and for those with paralysis or a short life expectancy. The regimen was similar to 300 cGy × 10 in terms of symptom relief, survival, and duration of response, regardless of tumor histology.

Steroids

Dexamethasone should be administered if the patient's history and neurologic examination suggest spinal cord compression. There is controversy as to whether an initial high-dose of IV dexamethasone (100 mg) followed by 10 mg of dexamethasone every 6 hours is necessary. Some studies have suggested lower doses are just as effective.

Radiation therapy

Radiation therapy alone is now the standard initial treatment for most patients with spinal cord compression due to a radiosensitive malignancy. Treatment outcome is contingent upon both the relative radiosensitivity of the malignancy and the neurologic status of the patient at the time radiotherapy is initiated.

Radiation portal In general, the treatment volume should include the area of epidural compression (as determined by MRI or myelography) plus two vertebral bodies above and below. Consideration should be given to including adjacent areas of abnormalities if feasible. Careful matching techniques should be employed in patients treated to adjacent vertebral levels, a situation that is not uncommon.

Radiation dose and fractionation The chosen regimen should take into account such factors as field size and normal tissue tolerance. Smaller fields are appropriately treated to 2,000-3,000 cGy over 1 or 2 weeks, respectively.

Larger fields may occasionally necessitate longer courses, such as 4,000 cGy over 4 weeks, to minimize side effects.

Retreatment may be entertained, particularly when no effective alternative exists. Usually, doses of 2,000 cGy over 2 weeks can be used for retreatment. It is important, however, to counsel the patient regarding the risk of radiation neuropathy. Furthermore, only those patients who had a lasting response to the initial treatment should be reirradiated, as tumors that were refractory to the first course or that recur within 3 months are unlikely to respond to subsequent courses.

Surgery

Vertebral body resection for a tumor anterior to the cord and posterior laminectomy for a tumor posterior to the cord may be appropriate treatment options for relieving spinal cord compression in patients who require spinal stability, have undergone previous radiotherapy in the area of the compression, require a tissue diagnosis of malignancy, or experience progression of the cord compression despite optimal treatment with steroids and radiation.

In general, surgical decompression should be strongly considered in patients whose cord compression is caused by a relatively radioresistant cancer and who have a severe neurologic deficit (such as bowel or bladder dysfunction). Unfortunately, many patients in this situation are not candidates for aggressive surgery. In these cases, radiotherapy is offered, albeit with limited expectations for neurologic recovery.

Chemotherapy

Chemotherapy may be an effective treatment of spinal cord compression in select patients with a chemosensitive metastatic tumor. It also may be considered in combination with other treatment modalities, such as radiotherapy, or as an alternative if those modalities are not suitable options for relieving cord compression.

HYPERCALCEMIA

Hypercalcemia is the most common metabolic emergency seen in individuals with cancer, occurring in an estimated 10%-20% of patients.

Etiology

The malignancies most commonly associated with hypercalcemia include myeloma, lung cancer (epidermoid tumors more often than small-cell tumors), and renal cancer. In some cases, the pathogenesis of hypercalcemia may relate to the release of parathyroidlike hormones, prostaglandins, and osteoclast-activating factor.

TABLE 1: Symptoms associated with hypercalcemia by organ system

General	CNS	Cardiac	GI	Renal
Dehydration	Weakness	Bradycardia	Nausea and vomiting	Polyuria
Anorexia	Hypotonia	Short QT interval	Constipation	Nephrocalcinosis
Pruritus	Proximal myopathy	Prolonged PR interval	Ileus	
Weight loss	Mental status changes	Wide T wave	Pancreatitis	
Fatigue	Seizure Coma	Atrial or ventricular arrhythmia	Dyspepsia	

Signs and symptoms

Symptoms of hypercalcemia may involve various organ systems, including the central nervous, cardiac, GI, and renal systems (Table 1).

Bony metastasis vs paraneoplastic syndrome The signs and symptoms of hypercalcemia secondary to bony metastases are often indistinguishable from those of hypercalcemia as a paraneoplastic syndrome. The laboratory findings may vary. A tumor secreting an immunoreactive parathyroid hormone (iPTH)-like substance will have increased levels of cyclic adenosine monophosphate (cAMP), low levels of serum phosphorus, and variable levels of iPTH, depending on the specificity of the assay. Many patients with bony metastases also exhibit features consistent with "ectopic" hyperparathyroidism.

Diagnosis

An accurate history and physical examination are often the most helpful diagnostic tools to exclude correctable nonmalignant causes of hypercalcemia. Hypercalcemia in association with occult malignancies is rare. The presence of weight loss, fatigue, or muscle weakness should increase clinical suspicion of malignancy as the cause of hypercalcemia.

Laboratory findings In patients with hypercalcemia of malignancy, serum iPTH levels, determined by a double-antibody method, are extremely low or undetectable; levels of inorganic phosphorus are low or normal; and levels of 1,25-dihydroxyvitamin D are low or normal.

Use of additional tests to identify the underlying malignancy responsible for the hypercalcemia often depends on the history and physical findings.

Treatment

Asymptomatic patients with minimally elevated calcium levels (< 12.0 mg/dL) may be treated as outpatients with close monitoring of calcium levels and symptoms. Encouragement of oral hydration, mobilization, and elimination of drugs that contribute to hypercalcemia are essential. Patients who are symptomatic or have calcium levels ≥ 12.0 mg/dL should be considered for inpatient management if medically appropriate. An algorithm for the acute and chronic treatment of hypercalcemia of malignancy is shown in Figure 1.

Volume expansion (eg, lactated Ringer's solution, 0.9% NaCl) Volume expansion and natriuresis increase renal blood flow and enhance calcium excretion secondary to the ionic exchange of calcium for sodium in the distal tubule. The volume required depends on the extent of hypovolemia, as well as the patient's cardiac and renal function. Often, infusion rates of 250-500 mL/h are needed. Typically, the onset of action is 12-24 hours.

Loop diuretics There is much controversy over the effectiveness of loop diuretics in the treatment of hypercalcemia. In theory, furosemide-induced natriuresis should enhance urinary calcium excretion. However, in most cases of significant hypercalcemia, hypovolemia is present. Thus, once euvolemia has been achieved with saline infusion, diuretics may be useful in preventing hypervolemia. Diuretic dosages depend on the patient's underlying renal function, and the dosing frequency should be based on hourly urine output. In patients with normal renal function, furosemide, 20-40 mg IV, may be initiated after volume expansion is achieved, with subsequent doses given when urine output is < 150-200 mL/h.

Bisphosphonates (etidronate [Didronel], clodronate, pamidronate [Aredia], and zoledronic acid [Zometa]) bind avidly to hydroxyapatite crystals and inhibit bone resorption. Their antiresorptive effects may be mediated by inhibition of osteoclasts and activation by cytokines. Bisphosphonates also inhibit recruitment and differentiation of osteoclast precursors. They are poorly absorbed from the GI tract, have a very long half-life in bone, and appear to accumulate at sites of active bone turnover.

Pamidronate is the most commonly used bisphosphonate. It has been shown to be effective in restoring normocalcemia in 60%-100% of patients with hypercalcemia secondary to malignancy. The recommended dose is 90 mg IV over 4 hours. The single IV dose over 4 hours, lack of renal toxicity, and superiority over etidronate make pamidronate a logical choice for bisphosphonate therapy for hypercalcemia of malignancy. Side effects include low-grade fever and mild hypocalcemia and hyomagnesemia. *Clodronate*, another bisphosphonate indicated for cancer-associated hypercalcemia, is dosed at 300 mg IV daily for 5 consecutive days (infused over at least 2 hours) or 800-3,200 mg/d orally. *Zoledronic acid* (4 mg IV) is a new bisphosphonate that can be infused faster and has fewer systemic side effects than other bisphosphonates.

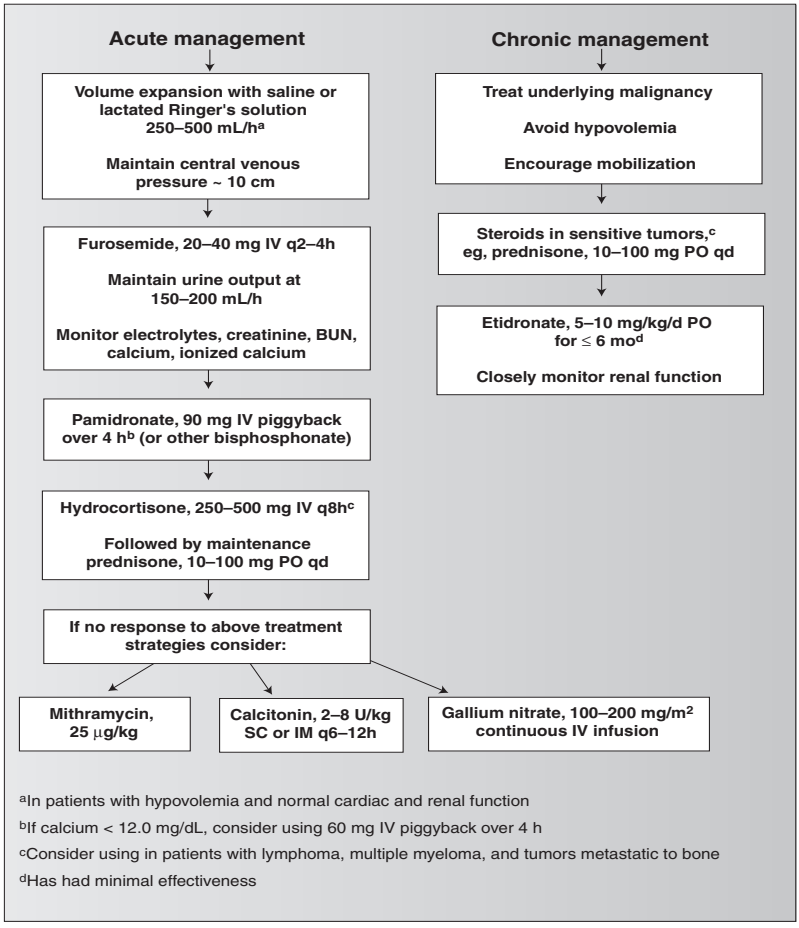

FIGURE 1: Algorithm for the treatment of hypercalcemia of malignancy

Corticosteroids In certain malignancies, such as lymphomas and hormone-sensitive breast cancers, corticosteroids may be of some value in producing a direct antitumor effect. In the majority of solid tumors, however, steroids are of limited or no value.

The onset of action is 3-5 days. Doses of prednisone (or its equivalent) may range from 10 to 100 mg/d.

Calcitonin inhibits bone degradation by binding directly to receptors on the osteoclast. It has few serious side effects (rare hypersensitivity) and can be given to patients with organ failure.

Calcitonin's onset of action is 2-4 hours, but its hypocalcemic effect is of short duration and peaks at 48 hours. There is little response to continued treatment. Doses range from 2 to 8 U/kg SC or IM every 6-12 hours.

Plicamycin (Mithracin) has direct osteoclast inhibitory effects and may also block the effects of vitamin D or parathyroid hormone. It reportedly is effective in ~80% of patients with hypercalcemia secondary to malignancy.

The onset of action of plicamycin is 24-48 hours. The duration of normocalcemia varies, but retreatment is required in 72-96 hours in most patients. The usual dose is 25 μg/kg (range, 10-50 μg/kg).

Significant toxicity increases with multiple injections and includes renal and liver toxicity. Thrombocytopenia is a common side effect.

Gallium nitrate (Ganite) directly inhibits osteoclasts and increases bone calcium without producing cytotoxic effects on bone cells. It successfully restores normocalcemia in 75%-85% of patients.

Gallium's onset of action is 24-48 hours. The dose range is 100-200 mg/m^2 given by continuous IV infusion for 5 days.

A study by Bertheault-Cvitkovic et al suggested that gallium may be superior to pamidronate for the acute normalization of cancer-related hypercalcemia. In other comparative trials, gallium proved to be more effective than both calcitonin and etidronate in patients with hypercalcemia that is secondary to malignancy.

Gallium therapy has some disadvantages, including the need for inpatient care and daily IV infusions and potential nephrotoxicity. It has been recommended that the drug not be used in patients with creatinine levels > 2.5 mg/dL.

In the first randomized, double-blind, placebo-controlled study to assess ibandronate (third-generation amino-bisphosphonate) for prevention of skeletal-related events (SREs) in patients with multiple myeloma stage II or III, patients received either ibandronate (2 mg) or placebo as a monthly IV bolus injection for 12-24 months along with conventional chemotherapy. The occurrence of SREs per patient's year and time to first SRE were not significantly different between the two treatment groups. The trial concluded that monthly injections of ibandronate (2 mg IV) in patients with multiple myeloma neither reduced bone morbidity nor prolonged survival *(Menssen HD, Sakalová A, Fontana A, et al: J Clin Oncol 20:2353-2359, 2002)*.

HYPERURICEMIA

Compared with hypercalcemia, hyperuricemia is a less common metabolic emergency in cancer patients.

Etiology and risk factors

Hyperuricemia occurs most often in patients with hematologic disorders, particularly leukemias, high-grade lymphomas, and myeloproliferative diseases (polycythemia vera). It may occur secondary to treatment of the malignancy.

Drugs Hyperuricemia is also associated with certain cytotoxic agents (eg, tiazofurin, and aminothiadiazoles). Various other drugs can contribute to hyperuricemia by increasing uric acid production or decreasing its excretion. Diuretics (thiazides, furosemide, and ethacrynic acid [Edecrin]) cause an acute uricosuria, and hyperuricemia may occur secondary to volume contraction. Antituberculous drugs, such as pyrazinamide (Rifater) and ethambutol (Myambutol), as well as nicotinic acid (niacin) are also associated with hyperuricemia.

Extensive or aggressive tumors Patients with extensive, anaplastic, or rapidly proliferating tumors are at greatest risk for hyperuricemia. These patients include patients with bulky lymphomas and sarcomas, those with chronic myelocytic leukemia or chronic lymphocytic leukemia and extreme leukocytosis, and those undergoing remission-induction chemotherapy for acute leukemia.

Renal impairment Individuals with preexisting renal impairment are also at risk of becoming hyperuricemic.

Signs and symptoms

Patients with clinical syndromes caused by hyperuricemia present with significant elevations of serum uric acid. Gouty arthritis may be seen occasionally, but the most significant complication is renal dysfunction, particularly acute renal failure. Clinical symptoms associated with renal dysfunction vary depending on the degree of dysfunction and the timing of its development. In patients with acute renal failure, clinical symptoms may include abnormal mental status, nausea and vomiting, fluid overload, pericarditis, and seizures.

Diagnosis

The diagnosis of hyperuricemia is based on laboratory findings of high serum uric acid levels, hyperuricosuria, and increased serum creatinine and urea nitrogen levels.

Prognosis

Prognosis often depends on the etiology of the hyperuricemia.

Treatment

Prophylactic measures against the development of hyperuricemia should be undertaken prior to the initiation of chemotherapy. Drugs that increase serum urate levels or produce acidic urine (eg, thiazides and salicylates) should be discontinued if possible. Alkalinization of the urine should be initiated to maintain a urine pH $>$ 7.0. Usually, sodium bicarbonate solution (50-100 mmol/L) is added to IV fluids and then adjusted so that an alkaline urinary pH is maintained. The carbonic anhydrase inhibitor acetazolamide (Diamox) may be used

to increase the effects of alkalinization. It is important to remember that alkalinization is secondary to the overall goal of decreasing urinary uric acid concentration by increasing urinary volume.

Allopurinol (Zyloprim), a xanthine oxidase inhibitor, is the mainstay of drug treatment and may be started 1-2 days prior to cytotoxic treatment. Doses range from 300-600 mg/d, and therapy is usually continued for 1-2 weeks or until the danger of hyperuricemia has passed.

Acute oliguria In patients who develop acute oliguria, ureteral obstruction by urate calculi should be considered. This condition should be evaluated by ultrasonography or CT. Administration of IV contrast agents for pyelography should be avoided, as they may increase the risk of acute tubular necrosis.

Dialysis Patients with advancing renal insufficiency and subsequent renal failure may benefit from peritoneal dialysis or hemodialysis. Dialysis has been shown to be effective in reversing renal failure caused by urate deposition.

TUMOR LYSIS SYNDROME

The tumor lysis syndrome occurs due to the rapid release of intracellular contents into the bloodstream, leading to life-threatening concentrations. If the resulting metabolic abnormalities remain uncorrected, patients may develop renal failure and sudden death.

Etiology and risk factors

Tumor lysis syndrome most commonly develops during the rapid growth phase of high-grade lymphomas and in leukemia patients with high leukocyte counts; it is less common in patients with solid tumors. The syndrome is often iatrogenic, caused by cytotoxic chemotherapy. Because of clinicians' increased awareness of the tumor lysis syndrome during the past decade and the use of adequate prophylaxis prior to the initiation of chemotherapy, there are fewer cases currently. Occasionally, the syndrome occurs following treatment with radiation, glucocorticosteroids, tamoxifen, or interferon.

Patients at risk The typical patient at risk for tumor lysis syndrome tends to be young (< 25 years of age) and male and has an advanced disease stage (often with abdominal disease) and a markedly elevated lactate dehydrogenase level.

Other predisposing factors include volume depletion, concentrated acidic urine pH, and excessive urinary uric acid excretion rates.

Signs and symptoms

The syndrome is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and, often, oliguric renal failure.

Diagnosis

The diagnosis of the tumor lysis syndrome is based on the development of increased levels of serum uric acid, phosphorus, and potassium, decreased levels of serum calcium, and renal dysfunction following chemotherapy.

Prognosis

Prognosis varies depending on the adequate correction of metabolic abnormalities and the underlying etiology of tumor lysis.

Treatment

Prophylactic measures Patients at risk for tumor lysis syndrome should be identified before the initiation of chemotherapy and should be adequately hydrated and given agents to alkalinize the urine. Treatment with allopurinol (IV or PO) may be instituted to minimize hyperuricemia. The recommended dose of IV allopurinol ranges from 200 to 400 mg/m^2/d. This regimen should be started 24-48 hours before the initiation of cytotoxic treatment. The dose may be equally divided into 6-, 8-, or 12-hour increments, but the final concentration should not exceed 6 mg/mL. (For oral dosages of allopurinol, see "Hyperuricemia, treatment" earlier in this chapter.)

Serum electrolytes, uric acid, phosphorus, calcium, and creatinine levels should be checked repeatedly for 3-4 days after chemotherapy is initiated, with the frequency of monitoring dependent upon the clinical condition and risk profile of the patient.

Established tumor lysis Once tumor lysis is established, treatment is directed at vigorous correction of electrolyte abnormalities, hydration, and hemodialysis (as appropriate in patients with renal failure).

HYPOGLYCEMIA

Hypoglycemia (glucose level $<$ 50 mg/dL) develops most frequently in patients with insulin-secreting islet-cell tumors. More than 80% of these patients have intermittent, transient CNS dysfunction secondary to hypoglycemia. Mesenchymal tumors (fibrosarcomas, leiomyomas, rhabdomyosarcomas, liposarcomas, and mesotheliomas) account for approximately 50% of non–islet-cell malignancies associated with hypoglycemia. In hepatomas, hypoglycemia is a frequent paraneoplastic complication in 21% of cases.

Etiology

Mechanisms proposed for malignancy-induced hypoglycemia include secretion of insulinlike substances, excessive glucose metabolism by the tumor, and failure of counterregulatory mechanisms that usually prevent hypoglycemia.

Signs and symptoms

Symptoms of hypoglycemia may include weakness, dizziness, diaphoresis, nausea, tachycardia, pallor, headache, visual disturbances, lethargy, agitation, confusion, and inappropriate behavior.

Pattern of symptoms Symptoms may be worse in the morning prior to food intake and may improve during the day after food ingestion.

Serious complications More serious complications from hypoglycemia include seizures and coma.

Diagnosis

The diagnosis of hypoglycemia associated with malignancy may often be suspected from the history and physical examination.

Classic triad (Whipple's triad) The diagnosis is firmly established when the following triad occurs: symptoms consistent with hypoglycemia, low plasma glucose concentration, and relief of symptoms when the plasma glucose concentration is increased to the normal range.

Insulinoma An increase in serum levels of both insulin and C peptide is diagnostic of insulinoma.

Prognosis

The prognosis of hypoglycemia often depends on the response of the underlying malignancy to antitumor therapy.

Treatment

The aggressiveness of treatment depends on the clinical presentation and degree of hypoglycemia.

Acute treatment of symptomatic hypoglycemia consists of the IV administration of 50% dextrose solution.

Mild hypoglycemia Patients with mild hypoglycemia may respond to increased feedings. Their serum glucose level should be monitored frequently following feedings.

Significant hypoglycemia In patients who have more significant hypoglycemia, corticosteroids and glucagon may provide symptomatic relief. Glucagon, 1 mg IM (or SC), may be administered to treat severe hypoglycemia. It is especially useful in outpatients with or without problems with IV access. Injection of glucagon may cause vomiting, and care should be taken to prevent aspiration. Continuous infusions of glucagon with portable pumps may be considered; however, the most effective long-term management is treatment of the underlying tumor.

TABLE 2: Criteria for the diagnosis of SIADH

Criterion	Definition
Hyponatremia	Serum sodium < 135 mEq/L
Hypo-osmotic plasma	Plasma osmolality < 280 mOsm/kg
Hyper-osmotic urine	Urinary osmolality > 500 mOsm/kg
Hypernatremic urine	Urinary sodium > 20 mEq/L (without diuretic therapy)

SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a paraneoplastic condition that is associated with malignant tumors (particularly small-cell lung cancer [SCLC]), CNS disease (eg, infection, intracerebral lesions, head trauma, and subarachnoid hemorrhage), and pulmonary disorders (eg, tuberculosis, pneumonia, and abscess).

Signs and symptoms

Hyponatremia is the most common presenting sign of SIADH. Patients who experience a rapid fall in plasma sodium levels are usually the most symptomatic.

Other presentations Patients with SIADH can also experience malaise, altered mental status, seizures, coma, and, occasionally, death. Focal neurologic findings can occur in the absence of brain metastases.

Diagnosis

To make a diagnosis of SIADH, certain criteria must be met (Table 2). In addition to those criteria, patients should have normal renal, adrenal, and thyroid function, along with normal extracellular fluid status.

Drug history It is important to obtain a full list of the medications that the patient is taking, since certain drugs can impair free water excretion either by acting on the renal tubule or by inducing pituitary arginine vasopressin (AVP). These drugs include morphine, cyclophosphamide (Cytoxan, Neosar), vincristine, chlorpropamide (Diabinese), amitriptyline, and clofibrate (Atromid-S).

Treatment

The major focus of treatment for SIADH related to malignancy is successful treatment of the underlying cancer.

Acute treatment is indicated in patients who are symptomatic and who have severe hyponatremia (eg, serum sodium level < 125 mEq/L). The goals of therapy in these patients are to initiate and maintain rapid diuresis with IV furosemide (1 mg/kg body weight) and to replace the sodium and potassium lost in the urine. Usually, the latter goal can be achieved by administering 0.9% saline with added potassium.

This rapid correction should not exceed a 20-mEq/L rise in serum sodium concentration during the first 48 hours. Patients who experience too rapid a rise in serum sodium concentration may suffer neurologic damage and central pontine myelinolysis.

Chronic treatment The mainstay of chronic therapy is water restriction to 500-1,000 mL/d. When this measure alone is unsuccessful, demeclocycline (Declomycin), 300-600 mg PO bid, may be used in patients without liver disease. The onset of action may be > 1 week.

NONBACTERIAL THROMBOTIC ENDOCARDITIS

Nonbacterial thrombotic endocarditis is characterized by the presence of sterile, verrucous, bland, fibrin-platelet lesions associated predominantly with left-sided heart valves. This paraneoplastic syndrome can occur with or without disseminated intravascular coagulation (DIC).

Nonbacterial thrombotic endocarditis has been seen in patients with a variety of malignancies, especially adenocarcinomas. In addition, it can occur in both early and late stages of malignancy.

Signs and symptoms

Patients with nonbacterial thrombotic endocarditis are usually afebrile, and one-third or fewer have systolic heart murmurs.

Signs/symptoms of emboli Typically, patients with this entity present with signs and symptoms consistent with emboli to the brain, as well as other organs. Patients with emboli to the brain may experience the acute or gradual onset of neurologic symptoms associated with focal neurologic deficits or more diffuse abnormalities, such as seizures or confusion.

Diagnosis

Echocardiography may be useful in diagnosing nonbacterial thrombotic endocarditis in patients who have vegetations > 2 mm. However, most patients have smaller vegetations.

Cerebral angiography Patients who present with neurologic symptoms due to this entity will have multiple arterial occlusions on cerebral angiography.

Treatment

The major focus of treatment is directed toward the underlying malignancy. In addition, heparin has been used with limited success.

LAMBERT-EATON SYNDROME

The Lambert-Eaton syndrome is strongly associated with SCLC. It is caused by antibodies that interfere with the release of presynaptic acetylcholine at the neuromuscular junction.

Signs and symptoms

Fatigue/muscle weakness This syndrome is characterized by fatigue and proximal muscle weakness, particularly of the pelvic girdle and thighs.

Autonomic symptoms Many patients with this disorder have autonomic symptoms, one of the most common of which is dry mouth.

Other symptoms Other possible symptoms include diplopia or blurred vision, ptosis, dysarthria, dysphagia, and paresthesias.

Diagnosis

Patients with the Lambert-Eaton syndrome show an improvement in muscle strength with exercise.

Electromyographic (EMG) studies are helpful in making the diagnosis. These studies reveal an increase in the muscle action potential with repeated nerve stimulation at rates faster than 10 per second.

Edrophonium test In addition, in contrast to individuals with myasthenia gravis, patients with the Lambert-Eaton syndrome have a poor response to the edrophonium test.

Treatment

Chemotherapy is the first line of treatment since 90% of patients with SCLC will respond to this measure. In fact, recovery from the Lambert-Eaton syndrome has been noted in some patients treated with chemotherapy.

Other therapies For patients in whom chemotherapy fails to improve symptoms or control the tumor, guanidine has been reported to be useful, as has 3,4-diaminopyridine.

Guanidine is taken orally beginning with a dose of 5-10 mg/kg/d divided throughout the waking hours. The dose may be increased to a maximum of 30 mg/kg/d on the basis of the patient's clinical response. However, side effects may be severe at doses $>$ 1 g/d. Also, the dose of guanidine should not be increased more often than every 3 days since the maximum response to a dose may not be seen for 2-3 days. At dosages of 5-25 mg 3-4 times per day, 3,4-

diaminopyridine can significantly improve symptoms. Side effects of this drug include perioral and acral paresthesias, insomnia, and epigastric distress.

In addition, treatment with plasmapheresis, steroids, immunosuppression, and IV gamma globulin are all of potential benefit.

POLYMYOSITIS/DERMATOMYOSITIS

The relationship between polymyositis/dermatomyositis and malignancy was established long ago. The most commonly associated malignancies are breast, lung, and ovarian cancers. An increased incidence of cancer patients with dermatomyositis (10%) has been observed, but the association of cancer with polymyositis is less clear.

Signs and symptoms

Muscle weakness Patients with this syndrome typically experience proximal muscle weakness that progresses over weeks to months. Weakness in the hips, thighs, and shoulder girdle may cause patients to have difficulties in getting out of a chair, climbing stairs, or combing their hair. Patients also may experience dysphagia, as well as weakness of the flexor muscles of the neck.

In the majority of cases, the distal muscles of the extremities are not involved. Also, most patients do not have involvement of the extraocular muscles.

Rashes Patients with dermatomyositis can have involvement of the eyelids, forehead, cheeks, chest, elbows, knees, and knuckles with the classic heliotrope rash. A more diffuse rash may also occur.

Diagnosis

Muscle enzymes and erythrocyte sedimentation rate Patients with polymyositis/dermatomyositis usually have an elevation in their serum muscle enzyme levels and erythrocyte sedimentation rate (ESR).

EMG studies and muscle biopsies In addition, EMG tracings are abnormal, and muscle biopsies reveal minimal inflammatory changes, along with muscle fiber necrosis in patients with polymyositis/dermatomyositis.

Treatment

Steroids In addition to treatment of the underlying malignancy, patients with polymyositis or dermatomyositis are treated with high-dose oral steroids (eg, prednisone, 60-80 mg/d). Other supportive measures, such as range-of-motion exercises, are also prescribed.

Immunosuppressives In patients who do not respond to steroid therapy, immunosuppressive therapy is often added. This type of therapy needs to be tailored to the individual patient, and consultation with a rheumatologist should be considered.

Therapy for skin disease The skin disease of dermatomyositis can be treated with a variety of measures, such as topical corticosteroids, antimalarials, photoprotection, and, at times, low-dose methotrexate.

VENOUS THROMBOEMBOLIC COMPLICATIONS OF CANCER

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are common and potentially serious clinical challenges. In the United States, the estimated incidence of DVT and PE is approximately 450,000 and 355,00 cases per year, respectively. The actual incidence is likely much higher than presently documented due to often vague complaints and symptoms. PE may be associated with increased mortality and contributes to approximately 240,000 deaths annually in the United States.

Armand Trousseau noted the association between thrombosis and cancer more than 125 years ago. The risk of venous thromboembolism (VTE) in cancer patients depends upon the type and extent of the malignancy, the type of cancer treatment, the existence and nature of comorbidities, and changes in hemostasis of the blood, which have been noted in over 90% of cancer patients. The prevalence of clinically noted venous thrombosis in cancer patients is 15%; patients undergoing surgery, hormonal therapy, and chemotherapy have the highest risk. Venous thrombosis is the second leading cause of death in cancer patients.

Etiology of VTE in cancer patients

The etiology of VTE in cancer patients may be attributed to several factors, including hypercoagulable states, surgical interventions, chemotherapy, indwelling central venous catheters, and prolonged immobilization.

The mechanisms by which tumors cause a hypercoagulable state are not completely understood, but they may be attributed to abnormalities of blood composition (increased plasma levels of clotting factors, cancer procoagulant A, tissue factor, and cytokines) and increased release of plasminogen activator. Postoperative VTE was more common in patients with malignant disease (36%) than in those patients with benign disease (20%), according to recent analyses of several clinical trials in surgical patients.

Patients undergoing chemotherapy are at increased risk of venous thrombosis secondary to endothelial cell damage from drug toxicity. Also, women with breast cancer treated with tamoxifen experience a small, but significantly increased, incidence of venous thrombosis, and the combination of tamoxifen plus chemotherapy increases the thrombotic rate over that of single agents.

Data from one trial demonstrated a statistically significant increase in PE in participants without a history of PE who were receiving tamoxifen. Three patients in the tamoxifen arm had pulmonary emboli. The events occurred between 2 and 60 months from initiation of tamoxifen.

Indwelling central venous catheters predispose patients to upper extremity thrombosis and thrombosis of the axillary/subclavian vein. The catheters are also prone to occlusion. Increased venous stasis owing to immobility also promotes blood pooling into the intramuscular venous sinuses of the calf and may lead to thrombosis formation.

TUMOR TYPE ASSOCIATED WITH VTE

Several tumor types have been associated with higher rates of VTE, including those arising from the pancreas, lungs, and other mucin-secreting tumors. In general, tumor types associated with an increased incidence of thromboembolic events reflect the frequency of the tumors in the general population: in women, the most common tumors are breast, lung, gynecologic, and gastrointestinal tumors; in men, prostate, lung, and gastrointestinal tumors are most common.

Treatment

Several classes of agents have been used for prevention and treatment of VTE. Nonpharmacologic approaches to prophylaxis may include intermittent pneumatic compression, elastic stockings, and inferior vena cava filters. Commonly used pharmacologic agents for thromboprophylaxis and treatment of VTE include unfractionated heparin (UFH) (standard, low-dose, or adjusted-dose), oral anticoagulants such as warfarin, and low molecular weight heparin (LMWH).

Initial treatment of DVT and PE includes inpatient UFH or LMWH and, more recently, outpatient LMWH for low-risk patients with DVT. (Although patients with PE have been treated with LMWH as outpatients, it is not the standard of care in the United States.)

UFH generally is administered as a bolus of 5,000 U followed by a continuous drip, usually initiated between 750-1,000 U/h. A baseline partial thromboplastin time (PTT) and prothrombin time (PT) are drawn prior to initiation of treatment. PTT is then rechecked approximately 4-6 hours after treatment is begun, and the UFH is titrated to approximately 1.5 to 2 times control in most patients.

Warfarin is usually begun on day 1 or 2 of treatment; therapy is monitored by PTT and dosages adjusted to maintain an international normalized ratio (INR) between 2.0 and 3.0. (Patients with prosthetic valves require a higher INR.) It is standard practice to maintain UFH for 4-5 days while the warfarin is titrated to therapeutic levels. Most patients are maintained on warfarin for 3-6 months depending upon underlying risk factors. There is controversy regarding the duration of anticoagulation, and some investigators maintain that patients with active cancer should continue anticoagulation for as long as the cancer remains active. Patients with recurrent VTE are usually maintained on anticoagulants for the rest of their lives.

Patient response to warfarin depends on numerous factors, such as age, diet, alcohol consumption, and liver and gastrointestinal function, as well as concomitant medications.

Recent studies have demonstrated the safety and efficacy of LMWH in the treatment and management of VTE. Several studies have demonstrated no appreciable differences in recurrent thromboembolism and in increased risk of bleeding with UFH and LMWHs. Because LMWHs do not require a continuous drip and frequent serum testing, some low-risk patients are now treated as outpatients. Studies are ongoing in the cancer patient population.

In the United States, enoxaparin (Lovenox) has FDA approval for prevention and treatment of DVT. Tinzaparin (Innohep) also has FDA approval for the treatment of DVT. Dalteparin (Fragmin), another LMWH agent approved for prophylaxis, has been approved by the FDA for cardiac use; approval of dalteparin for treatment of VTE is anticipated soon.

LMWH doses vary by product and are not equivalent. Enoxaparin is generally administered twice a day for treatment of VTE, whereas the indications for tinzaparin and dalteparin are for once-daily dosing. The commonly administered dose for treatment of DVT with enoxaparin is 1 mg/kg SC every 12 hours. Tinazaparin is given via SC injection at a dose of 175 IU/kg body weight once daily, and the dalteparin dose is 200 IU/kg SC once daily. Therapy with LMWH is continued for a minimum of 5 days. Generally, laboratory monitoring is unnecessary, although for individuals with renal insufficiency or those < 50 kg body weight or with obesity, plasma antifactor Xa concentrations may need to be monitored.

An international study comparing the long-term treatment benefits of dalteparin vs warfarin in cancer patients with VTE, long-term dalteparin substantially reduced the rate of recurrent VTE compared to warfarin therapy without an increase in bleeding.

DIFFICULTIES IN ANTICOAGULATION

Often therapeutic challenges arise in patients on anticoagulation therapy for VTE who require surgical interventions and, therefore, temporary discontinuation of their anticoagulation treatment.

When should anticoagulation be discontinued preoperatively? The timing of discontinuation of anticoagulation depends upon the type of treatment and the surgical intervention planned. For patients on continuous-drip heparin, the drip may be discontinued 4-6 hours prior to the procedure. A PTT should be drawn prior to the procedure to check for total reversal of the treatment. In cases where only partial reversal is noted or an emergency arises, fresh frozen plasma may be administered for rapid reversal.

Patients on warfarin may be advised to discontinue their medication 2-3 days prior to the planned procedure. This approach allows for a gradual reduction in the anticoagulation effect. An INR should be checked prior to the procedure. If partial reversal is noted or an emergency arises, vitamin K and/or fresh frozen plasma may be administered for acute reversal.

For high-risk patients (prosthetic valve, recurrent VTE), it may be reasonable to switch from warfarin to either UFH or LMWH, with appropriate discontinuation prior to the procedure. Both UFH and LMWH have shorter reversal

times than does warfarin although LMWHs are not fully reversible. Another option is to continue warfarin until shortly before the procedure, reversing treatment with vitamin K and/or fresh frozen plasma. The risk/benefit ratio should be considered when reviewing the options for the individual patient.

When should anticoagulation be restarted postoperatively? Timing of postoperative therapy depends on the type of procedure undertaken and its associated risk of bleeding. Direct communication between the surgeon and the physician managing the anticoagulation treatment is necessary. When the surgeon believes that the risk of bleeding is at an acceptable level, anticoagulation should be restarted. It may be prudent to utilize UFH or LMWH prior to the initiation of warfarin, especially if a substantial risk of bleeding remains.

Which surgical patients are at highest risk of VTE? Surgery has long been known to be a risk factor for VTE. The nature of surgery in part determines the relative risk: Patients undergoing orthopedic surgery are at a particularly high risk. The risk is modified by the presence of other factors such as underlying malignancy, age, obesity, and history of previous thromboembolism. Recent meta-analyses of clinical trials have shown that based on rates observed in control subjects, there is a high overall risk of DVT during general surgery; there is a confirmed incidence of DVT of 25% noted by the fibrinogen uptake test. The risk is even higher (29%) in surgical patients with malignancy. Risk is also increased in those individuals with multiple risk factors (eg, age $>$ 65 years, obesity, bed rest $>$ 5 days). A comparison of commonly used prophylaxis in 160 clinical trials indicates that overall, low-dose UFH and LMWH are the most effective agents in reducing the incidence of DVT after general surgery. A higher dosage of the prophylactic agent may be needed for adequate prevention in patients with malignant disease.

What treatment should be considered when patients have recurrent VTE on therapeutic doses of anticoagulation? There are several options for this difficult therapeutic challenge. Patients who develop recurrence of thrombosis while on therapeutic doses of anticoagulation should be considered for inferior vena cava filter placement. The filter will not prevent new clots from forming, but it does provide a physical barrier to prevent propagation of clots to the pulmonary bed. Alternatively, an inferior vena cava filter can be placed to avoid the need for long-term anticoagulant therapy if there are contraindications to anticoagulation. Or, another LMWH may be utilized prior to placement of an inferior vena cava filter since there may be other complications related to filter placement (ie, postphlebitis syndrome, clotting of filter).

Depending upon patient prognosis and tumor factors, other comorbidities, and propensity for bleeding, continued therapy with warfarin or LMWH may also be considered in addition to filter placement.

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CHAPTER 48

Infectious complications

James Ito, MD

Infections are among the most common, potentially serious complications of cancer and its treatment. This chapter will discuss infections during febrile neutropenia, pneumonias, catheter-associated infections, and two GI infections (*Clostridium difficile*-associated diarrhea and typhlitis). Special sections will focus on fungal and viral infections.

INFECTION DURING FEBRILE NEUTROPENIA

It has long been recognized that the incidence of infection is high in patients who develop a fever during neutropenia and that empiric antimicrobial therapy is warranted in such patients.

Definitions

Fever is usually defined as a temperature ≥ 38.3°C.

Neutropenia is defined as a neutrophil count of 500/μL, although patients with a neutrophil count between 500 and 1,000/μL in whom a decrease is anticipated are considered to be neutropenic. Patients with a neutrophil count < 100/μL are at greatest risk for infection, as are those with a rapid decrease in neutrophil count and those with protracted neutropenia.

Etiology

Bacteria Infections occurring during episodes of febrile neutropenia are caused predominantly by aerobic gram-negative bacilli (especially *Escherichia coli, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*) and gram-positive cocci (coagulase-negative staphylococci, β-hemolytic streptococci, viridans streptococci, enterococci, and *Staphylococcus aureus*). In recent years, gram-positive infections have become more prominent with the increasing use of indwelling IV catheters.

Fungi Fungal infections usually occur after a patient has received broad-spectrum antimicrobial therapy and/or steroids. The most common fungal pathogens are *Candida* species (predominantly *C albicans* and *C tropicalis*) and *Aspergillus* species. Less common are *Trichosporon, Fusarium,* and *Rhizopus* infections (see also "Fungal infections" section).

Viruses Viral infections occurring during neutropenia are caused predominantly by herpesviruses and respiratory viruses. The herpesviruses include herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV). The respiratory viruses include adenovirus, respiratory syncytial virus, parainfluenza virus, influenza A and B viruses, and rhinovirus (see also "Viral infections" section).

Activity continues in the development of new antifungal agents. Voriconazole has just been approved by the FDA and appears to have good activity against a wide variety of molds, including the often amphotericin B-resistant *Scedosporium* and *Fusarium* species. In a recent head-to-head study with amphotericin B *(Herbrecht R, Denning DW, Patterson FT, et al: N Engl J Med 347:408-415, 2002)*, voriconazole led to better responses, improved survival, and fewer side effects for primary therapy of invasive aspergillosis. This study is the first time that any antifungal agent has demonstrated superiority over the gold standard amphotericin B. Also, a new echinocandin antifungal agent, micafungin (which has not been approved by the FDA as of this writing), has demonstrated superiority over the current standard antifungal agent fluconazole in prophylaxis in BMT recipients *(Van Burik, et al: Forty-Second Interscience Conference on Antimicrobial Agents and Chemotherapy [abstract], 2002)*.

Signs and symptoms

The most remarkable aspect of the febrile, neutropenic patient is the lack of physical findings. This is due to the neutropenia and the absence of an inflammatory response at the infection site. The patient may have only a fever with or without chills or rigors. Even if the patient has pneumonia, there may be few respiratory symptoms. Likewise, a perirectal abscess may be relatively asymptomatic.

Diagnosis

An initial evaluation and diagnostic work-up of any fever in a neutropenic patient should begin immediately but should not delay the initiation of empiric therapy (see below). A complete history (exposures, past infections, rashes, cough, abdominal pain, diarrhea) should be taken and a physical examination (skin lesions, exit site and tunnel of right atrial catheter, oropharynx, abdomen, perineum) should be performed.

Diagnostic work-up should include:

- at least two sets of blood cultures, one from a peripheral vein and one from each port of a central venous catheter. If fever persists in the face of negative cultures, blood cultures for fungi and acid-fast bacilli should be considered.
- culture of any drainage from a catheter exit site
- stool examination for *C difficile* and other bacterial/protozoal agents
- urine culture and urinalysis
- chest radiograph
- aspiration or biopsy of any skin lesions

CT If indicated by signs or symptoms, CT scans of the brain (followed by lumbar puncture), chest, abdomen, and pelvis can be performed.

Laboratory tests Determination of serum transaminases, CBC, and serum creatinine is also recommended.

Treatment

INITIAL EMPIRIC ANTIBIOTIC THERAPY

Initial antibacterial therapy in the febrile, neutropenic patient should be broad-spectrum and should be based on the prevalence and susceptibility of bacterial isolates seen in the individual hospital setting (Figure 1). When choosing an antibiotic, the clinician also should take into consideration the patient's allergies, renal and hepatic function, and other drugs he or she is receiving that may interact with the empiric antimicrobial agent. Finally, any special circumstance, such as the suspicion of an indwelling IV catheter-associated infection, may influence the antibiotic choice.

Either single antibiotics or antibiotic combinations can be used for initial empiric therapy (see Table 1 for dosage regimens).

The choice of initial empiric antibiotic therapy for the febrile, neutropenic patient is dictated in part by the susceptibility pattern of blood isolates seen at a particular cancer center. If the prevalence of extended-spectrum beta-lactamase (ESBL) gram-negative bacteria is high, for example, one probably would not want to use a third-generation cephalosporin such as ceftazidime as initial empiric monotherapy. (Some data suggest that prolonged use of ceftazidime monotherapy in this setting promotes the emergence of ESBL bacteria.) City of Hope has been using ceftazidime as initial monotherapy for the past 15 years, however, without a significant rise in the incidence of resistant gram-negative infections, and this experience has been shared by other *centers (Collin BA, Leather HL, Wingard JR, et al: Clin Infect Dis 33:947-953, 2001).*

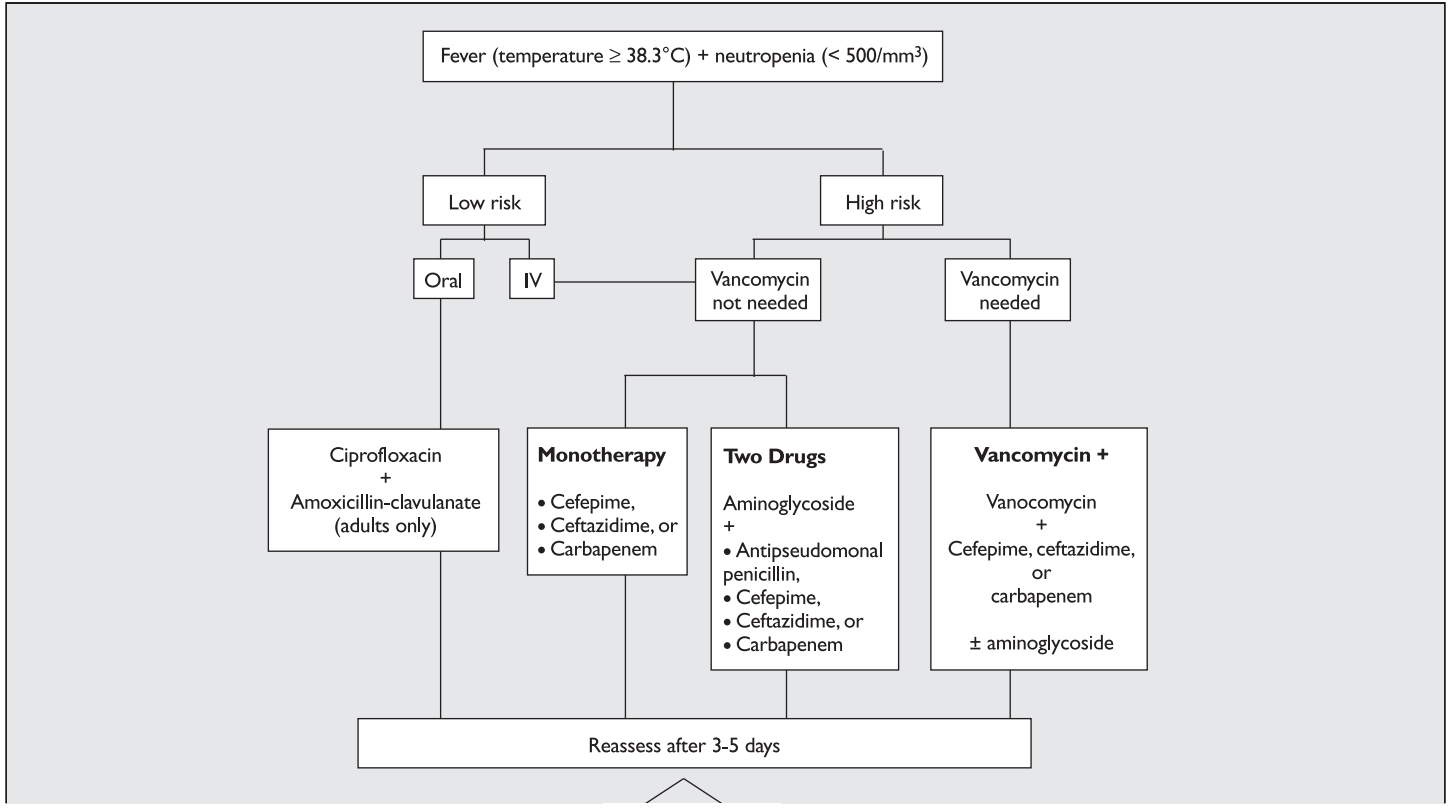
Monotherapy

Ceftazidime, cefepime (Maxipime), imipenem-cilastatin (Primaxin), or meropenem (Merrem), when used as monotherapy, avoids the potential for nephrotoxicity. However, none of these antibiotics covers for coagulase-negative staphylococci, methicillin-resistant *S aureus,* vancomycin-resistant or vancomycin-susceptible enterococci, some strains of penicillin-resistant *Streptococcus pneumoniae,* and viridans streptococci. Also, ceftazidime does not cover anaerobes well, and imipenem-cilastatin may have CNS toxicity at high doses.

Duotherapy

Aminoglycoside plus antipseudomonal β-lactam The aminoglycoside could be gentamicin, tobramycin, or amikacin (Amikin). The β-lactam could be ticarcillin (Ticar) or piperacillin (Pipracil), either alone or with a β-lactamase inhibitor; mezlocillin (Mezlin); ceftazidime; or cefoperazone (Cefobid).

Advantages of the combination of an aminoglycoside and an antipseudomonal β-lactam include possible synergistic effects against gram-negative bacilli and decreased emergence of resistant strains. The major disadvantages of the combination are potential nephrotoxicity, ototoxicity, hypokalemia, and the need to monitor drug levels of the aminoglycoside. Also, gram-positive coverage is not ideal.


Fever (temperature ≥ 38.3°C) + neutropenia (< 500/mm3)
Low risk
High risk
Oral
IV
Vancomycin not needed
Vancomycin needed
Ciprofloxacin + Amoxicillin-clavulanate (adults only)
Monotherapy
• Cefepime,
• Ceftazidime, or
• Carbapenem
Two Drugs
Aminoglycoside +
• Antipseudomonal penicillin,
• Cefepime,
• Ceftazidime, or
• Carbapenem
Vancomycin +
Vanocomycin + Cefepime, ceftazidime, or carbapenem
± aminoglycoside
Reassess after 3-5 days

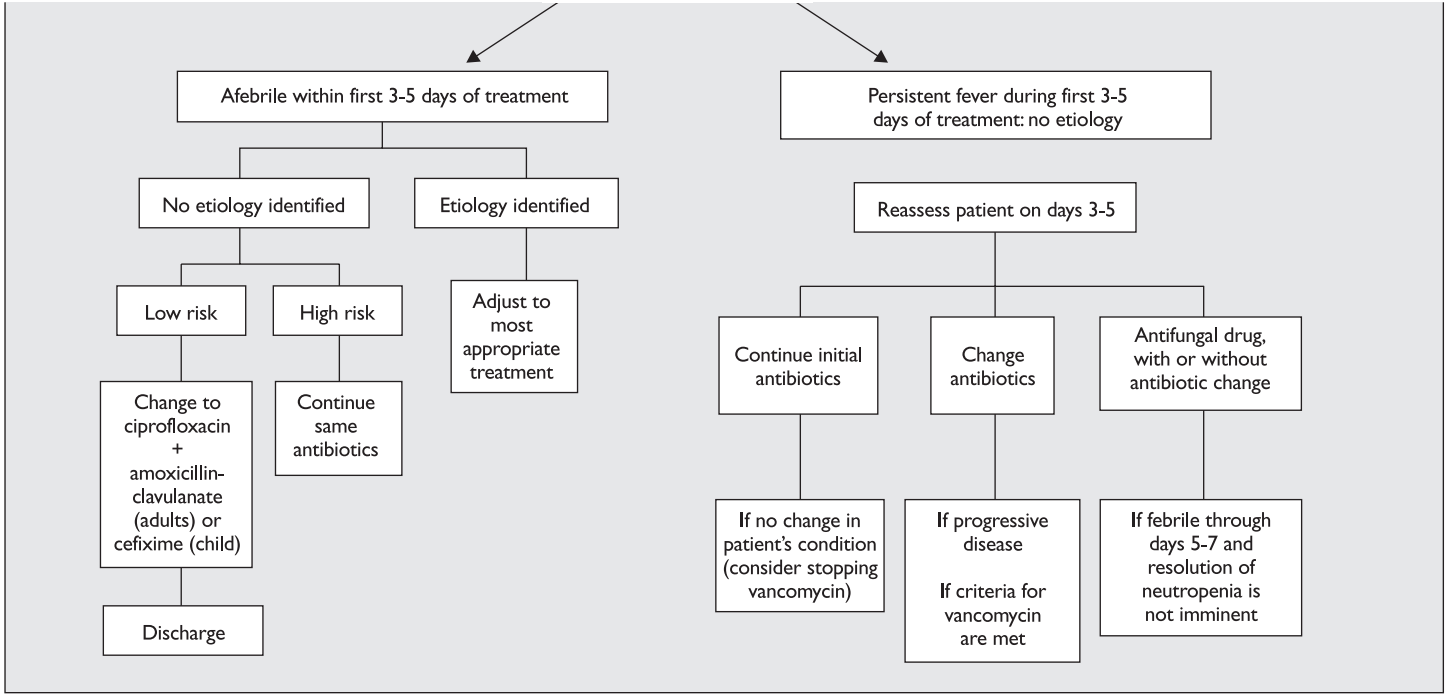


FIGURE 1: Guide to the initial management of the febrile neutropenic patient Clin Infect Dis 34:730-751, 2002.

Adapted, with permission, from Hughes WT et al: 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 34:730-751, 2002.

TABLE 1: Dosing schedules of selected antimicrobials

Drug	Dose	Frequency	Route
Antibiotics			
Ceftazidime	2 g	q8h	IV
Cefepime	2 g	q8h	IV
Imipenem-cilastatin	500 mg	q6h	IV
Meropenem	1 g	q8h	IV
Piperacillin	3 g	q4h	IV
Vancomycin	15 mg/kg	q12h	IV
	7.5 mg/kg	q6h	IV
	125 mg (for *C difficile*-associated diarrhea)	qid	PO
Quinupristin/dalfopristin	7.5 mg/kg	q8h	IV
Linezolid	600 mg	q12h	IV/PO
Gentamicin/tobramycin	2 mg/kg (loading dose)		IV
	1.5 mg/kg (maintenance)	q8h	IV
Amikacin	8 mg/kg (loading dose)		IV
	7.5 mg/kg (maintenance)	q8h	IV
Cefazolin	2 g	q6h	IV
Nafcillin	2 g	q4h	IV
Ciprofloxacin	400 mg	q12h	IV
	750 mg	bid	PO
Ofloxacin	400 mg	q12h	IV/PO
Levofloxacin	500 mg	q24h	IV/PO
Metronidazole	500 mg	q6h	IV
Clindamycin	900 mg	q8h	IV
TMP-SMZ	15 mg/kg/d	q6h	IV
Erythromycin	1 g	q6h	IV
Amoxicillin/clavulanate	500 mg	q8h	PO
Ampicillin/sulbactam	3 g	q6h	IV
Clarithromycin	500 mg	bid	PO

Vancomycin plus one or two drugs The use of vancomycin as part of the initial regimen is controversial. Certainly a majority of documented bacteremias in neutropenic febrile patients are caused by gram-positive organisms, and most of them are due to coagulase-negative staphylococci. Also, vancomycin is probably the preferred drug for viridans streptococcal sepsis and the drug of choice for methicillin-resistant *S aureus* and *Corynebacterium* infections. On the other hand, there is concern for the overuse of vancomycin and the emergence of vancomycin-resistant enterococci (and now *S aureus*). A study by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada did not support the use of vancomycin in initial empiric therapy.

It should be noted that the Centers for Disease Control and Prevention (CDC) advises against the use of vancomycin in initial empiric therapy for a febrile, neutropenic patient "unless initial evidence indicates that the patient has an infection caused by gram-positive microorganisms (eg, at an inflamed exit

Drug	Dose	Frequency	Route
Antifungal agents			
Amphotericin B			
Therapy	0.5-1.0 mg/kg	qd	IV
Prophylaxis	0.1-0.2 mg/kg	qd	IV
Fluconazole	400 mg	qd	IV or PO
Itraconazole capsules	200 mg (loading dose)	tid × 4 d	PO
	200 mg (maintenance)	bid	PO
Itraconazole oral solution	(see capsules above)		
Itraconazole injection	200 mg (loading dose)	bid × 4 doses	IV
	200 mg (maintenance)	qd	IV
Amphotericin B			
Lipid complex	5 mg/kg	qd	IV
Cholesteryl sulfate	3-6 mg/kg	qd	IV
Liposome	3-5 mg/kg	qd	IV
Caspofungin acetate	70 mg (loading dose)		IV
	50 mg (maintenance)	qd	IV
Voriconazole	6 mg/kg (loading dose) × 2	q12h	IV
	4 mg/kg (maintenance)	q12h	IV
	200 mg (maintenance) for > 40 kg	q12h	PO
	100 mg (maintenance) for ≤ 40 kg	q12h	PO
Antiviral agents			
Acyclovir			
For HSV	5 mg/kg	q8h	IV
For VZV	10 mg/kg	q8h	IV
For HSV encephalitis	15 mg/kg	q8h	IV
Ganciclovir	5 mg/kg (induction)	q12h	IV
	5 mg/kg (maintenance)	qd	IV
Foscarnet	60 mg/kg (induction)	q8h	IV for 14 d
	90 mg/kg (maintenance)	qd	IV
Amantadine, rimantadine	100 mg	bid	PO
Zanamivir	5 mg	bid	inhalation
Oseltamivir	75 mg	bid	PO

HSV = herpes simplex virus; TMP-SMZ = trimethoprim-sulfamethoxazole; VZV = varicella zoster virus

site of Hickman catheter) and the prevalence of infections caused by MRSA [methicillin-resistant *S aureus*] in the hospital is substantial."

Thus, it is recommended (in the 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever developed by the Infectious Diseases Society of America) that vancomycin be added to the initial regimen (eg, with ceftazidime) in selected patients, including:

- patients with clinically obvious, serious catheter-related infections
- patients undergoing intensive chemotherapy that produces substantial mucosal damage (ie, high-dose cytarabine [Ara-C], which increases the risk of penicillin-resistant streptococcal infections, particularly those due to viridans streptococci)
- patients receiving prophylaxis with quinolones before the onset of the febrile episode

- patients who have known colonization with pneumococci that are resistant to penicillin and cephalosporins or methicillin-resistant *S aureus*
- patients with a blood culture positive for gram-positive bacteria before final identification and susceptibility testing
- patients with hypotension or other evidence of cardiovascular impairment

Double β-lactam therapy usually consists of a third-generation cephalosporin (ceftazidime or cefoperazone) and a ureidopenicillin (piperacillin, ticarcillin, or mezlocillin). The advantages of this regimen are low toxicity (mainly renal) and theoretical synergism. However, it is more costly (compared with monotherapy) and has the possibility of antagonism.

CHANGES IN INITIAL THERAPY

Defervescence If the fever subsides after 3 days of empiric therapy and a specific organism is identified, antibiotic therapy can be modified to provide optimal treatment. Broad-spectrum coverage should continue. Antibiotics can be discontinued after 7 days if all evidence of infection has been eradicated.

If no organism is isolated, treatment with the initial regimen should be continued for a minimum of 7 days. If the patient is clinically well, the regimen can be switched to an oral antibiotic, such as cefixime (Suprax) or a quinolone.

Persistent, unresponsive fever If the fever persists after 4-7 days of antibiotic therapy, reassessment is recommended. If no infectious etiology is determined, a change in or addition to the antibiotic regimen is recommended.

If vancomycin was not part of the initial empiric regimen, many physicians would consider adding it. However, because of the recent recommendation by the CDC against empiric vancomycin use, it probably should not be added unless there is a strong clinical or microbiological reason to do so. Instead, cefazolin or nafcillin could be added for better gram-positive coverage. If the initial regimen did not provide anaerobic coverage, metronidazole could be added. Finally, if fever and neutropenia persist despite 3-5 days of antibiotic therapy, an antifungal agent (amphotericin B [Fungizone], liposomal amphotericin B [AmBisome], amphotericin B lipid complex [Abelcet], voriconazole [Vfend]), or even fluconazole [Diflucan] if the risk of mold infection is low) should be added.

Duration of antimicrobial therapy The most important determinant of the duration of therapy is the absolute neutrophil count (Figure 2).

Prevention

Attempts at preventing infection in the neutropenic host focus on two broad areas: preventing acquisition of pathogenic organisms and suppressing or eradicating endogenous microbial flora.

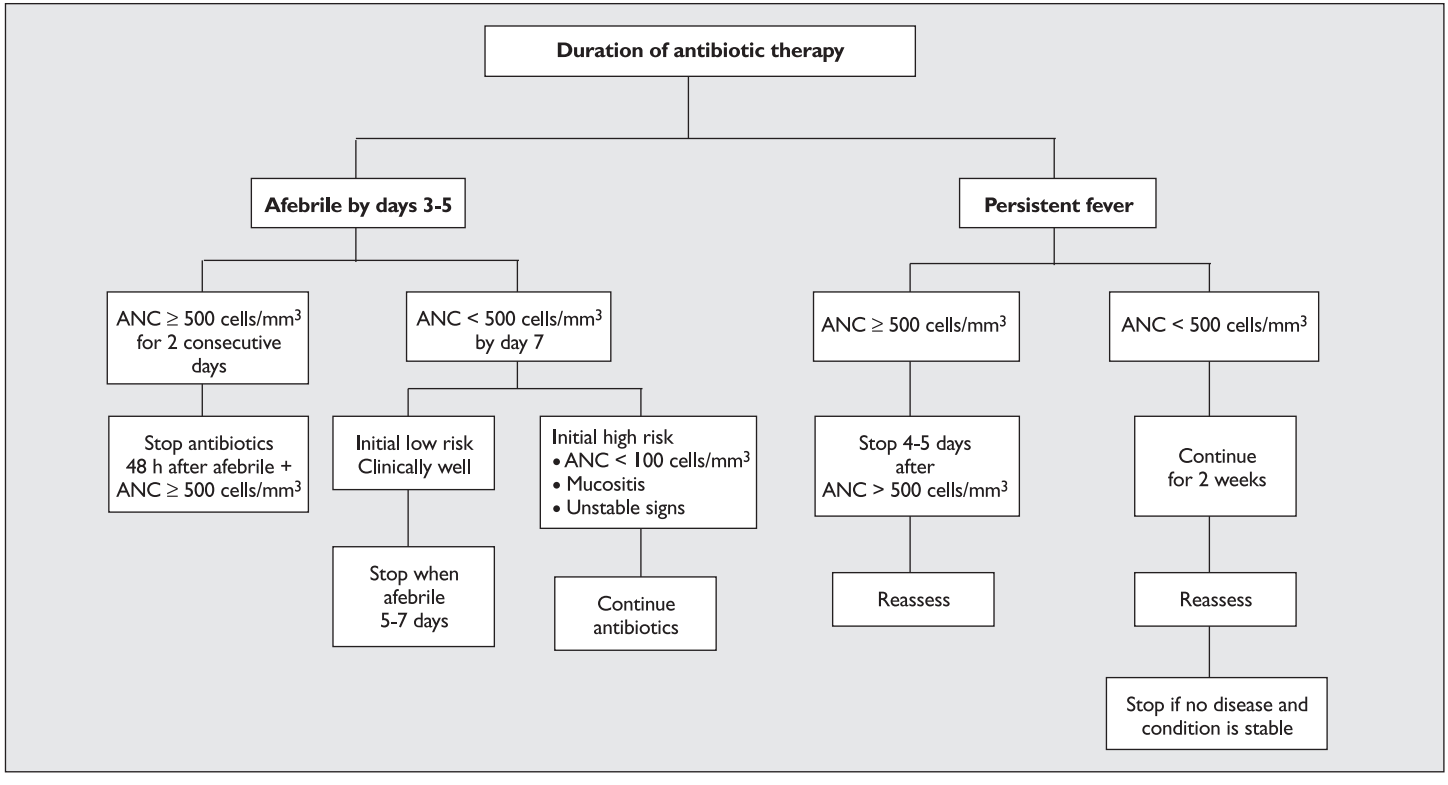


FIGURE 2: Duration of antibiotic therapy ANC = absolute neutrophil count

Adapted, with permission, from Hughes WT et al: 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 34:730-751, 2002.

Hygienic measures

Hand-washing The simplest, most effective, and least expensive way to prevent acquisition of potential pathogens is to institute strict hand-washing precautions.

Diet A cooked diet with elimination of fresh fruit and vegetables is also recommended.

Water and air Water purification systems (to eliminate *Legionella* organisms) and high-efficiency particulate air (HEPA) filtration systems (to eliminate fungal spores) can decrease rates of acquisition of these pathogens.

"Protective" environments The use of more "protective" environments for neutropenic patients is controversial. The total protective environment, which consists of a totally sterile environment and an aggressive antimicrobial regimen, can reduce the rate of infection but does not contribute to increased survival and is also costly.

Antibiotic prophylaxis

Prophylactic antimicrobial therapy generally falls into three categories: oral nonabsorbable antibiotics, selective decontamination regimens, and systemic prophylaxis.

Nonabsorbable antibiotics Although the use of oral nonabsorbable antibiotics has demonstrated some reduction in infection rates, this option has become less popular due to its cost, side effects, unpalatability, poor compliance, and selection of resistant organisms.

Selective decontamination with trimethoprim-sulfamethoxazole (TMP-SMZ), ie, establishment of "colonization resistance" by preserving anaerobic flora while reducing aerobic bacteria, has not resulted in clear-cut reductions in infection rates. Moreover, the disadvantages of prolonged neutropenia and emergence of resistant organisms make this regimen less desirable than others.

Fluoroquinolones More recently, fluoroquinolones (eg, ciprofloxacin [Cipro], ofloxacin [Floxin], and levofloxacin [Levaquin]) have been shown to be effective. However, breakthrough gram-positive infections and the emergence of resistant gram-negative bacilli are of concern with these agents.

***Pneumocystis carinii* pneumonia** In patients at risk for *P carinii* pneumonia (patients undergoing allogeneic bone marrow transplantation [BMT], those with lymphoma, or those receiving steroids), TMP-SMZ, administered for only 2 or 3 days per week, can reduce the incidence of infection.

Antifungal prophylaxis

Both fluconazole and low-dose amphotericin B can lower the incidence of fungal infection, especially *Candida* infection. (See Table 1 for doses of these antifungals.) However, fluconazole may select for resistant *Candida* species (eg, *C krusei*) and is not active against *Aspergillus* organisms. Both antifungal agents should be reserved for use in patients at highest risk for invasive fungal infection (see "Fungal infections" section).

Antiviral prophylaxis

Acyclovir (Zovirax) Patients at risk for mucositis (ie, those undergoing induction therapy for leukemia or lymphoma or BMT) who have evidence of prior HSV infection (positive serology) can receive prophylaxis with twice-daily IV acyclovir (see Table 1 for dose).

Ganciclovir (Cytovene) has been shown to be an effective "preemptive" and prophylactic antiviral in preventing CMV interstitial pneumonia in allogeneic BMT recipients who show evidence of CMV in bronchoalveolar lavage fluid or blood (see "Viral infections" section).

PNEUMONIA

A significant number of infections in cancer patients are due to pneumonia. For example, 25% of documented infections in patients with nonlymphocytic leukemia are caused by pneumonia. Also, 50% of allogeneic BMT recipients will develop pneumonia.

Etiology and risk factors

Some of the risk factors that predispose cancer patients to pneumonia are cellular and humoral immune deficiencies, neutropenia, impaired tracheobronchial clearance, use of antibiotics and steroids, and surgery.

Etiologic agents The etiologic agents responsible for pneumonia in the cancer patient run the gamut of most bacterial, fungal, and viral organisms.

Noninfectious processes mimicking pneumonia Numerous noninfectious processes can mimic pneumonia in cancer patients. They include congestive heart failure, aseptic emboli, metastatic disease, adult respiratory distress syndrome, hemorrhage, radiation injury, hypersensitivity disorders and reactions, and trauma.

Pinpointing the pathogen Certain characteristics of each cancer patient may help predict the specific etiologic agent.

Type of immunosuppression One characteristic that is particularly useful is the type of immunosuppression that the patient is experiencing. This depends on the type of neoplastic disease (eg, lymphoma, leukemia) and, more importantly, the type of therapy (eg, chemotherapy, radiation therapy, allogeneic BMT). For example, certain gram-negative and gram-positive bacteria are more prevalent during neutropenia, whereas other bacteria (*S pneumoniae*, *Haemophilus influenzae*) are more common with a humoral immune deficiency, such as occurs after splenectomy (see Table 2).

Timing of pneumonia Another important characteristic is the timing of the pneumonia; in other words, the phase of the immunosuppression can help predict the etiology. For example, an interstitial pneumonia occurring during the first 30 days after allogeneic BMT would not be expected to be due to CMV (Figure 3).

TABLE 2: Altered host defenses and associated respiratory pathogens in immunocompromised patients with cancer

Granulocytopenia
Gram-negative bacilli: *Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, Enterobacter* species
Gram-positive cocci: *Staphylococcus aureus*, *Staphylococcus epidermidis*, group D streptococci, α-hemolytic streptococci
Gram-positive bacilli: *Bacillus* species, *Clostridium* species
Fungi: *Aspergillus* species, *Zygomycetes*, *Fusarium* species, *Trichosporon beigelii*, *Candida* species, *Torulopsis glabrata*
Cellular (T-lymphocyte) immune defects
Bacteria: *Mycobacterium* species, *Nocardia asteroides*, *Legionella* species, *Listeria monocytogenes, Salmonella* species
Viruses: Cytomegalovirus, varicella zoster virus, herpes simplex virus, Epstein-Barr virus
Protozoa: *Pneumocystis carinii, Toxoplasma gondii*
Fungi: *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*
Helminths: *Strongyloides stercoralis*
Humoral (B-lymphocyte) immune deficiency
Bacteria: *Streptococcus pneumoniae*, *Haemophilus influenzae*
Impaired tracheobronchial clearance
Bacteria and fungi colonizing the lower respiratory tract
Invasive procedures: Mechanical disruption of epithelial barriers
Bacteria and fungi colonizing the respiratory tract and skin
Altered neurologic function
Bacteria and fungi colonizing the oropharynx and upper respiratory tract

Adapted, with permission, from Walsh TJ, Rubin R, Pizzo PA: Respiratory diseases in patients with malignant neoplasms, in Shelhamer J, Pizzo PA, Parillo JE, et al (eds): Respiratory Disease in the Immunosuppressed Host, p 640. Philadelphia, JB Lippincott, 1991.

Other factors Finally, other factors, such as the duration of neutropenia, prior antimicrobial therapy, other agents (such as steroids) used, and the specific local microbiota help in prediction. For example, if an allogeneic BMT patient receiving steroids for graft-vs-host disease (GVHD) develops nodular infiltrates after weeks of broad-spectrum antibacterial antibiotics, an *Aspergillus* species would be highly suspected.

Signs and symptoms

Cough Although a productive cough is almost always present in a normal host with pneumonia, often neither a cough nor sputum is seen in an immunocompromised cancer patient with such an infection.

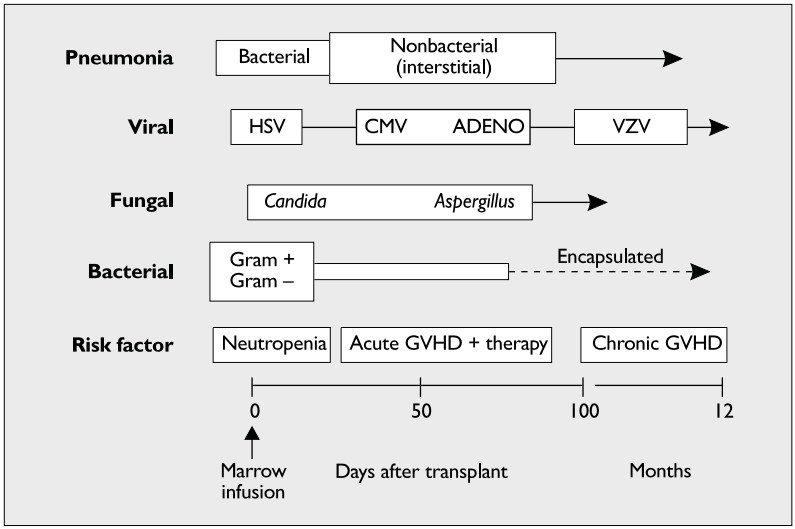


FIGURE 3: Timing of infectious syndromes after BMT

ADENO = adenovirus; CMV = cytomegalovirus; GVHD = graft-vs-host disease; HSV = herpes simplex virus; VZV = varicella zoster virus

Adapted, with permission, from Meyers JD: Infections in marrow recipients, in Mandell GL, Doublas RG, Bennett JE (eds): Principles and Practice of Infectious Diseases, 2nd ed, pp 1674-1676. New York, Wiley, 1985.

Fever, however, is almost invariably present in the cancer patient with pneumonia and, by itself, should prompt a work-up for pneumonia.

Other possible symptoms include shortness of breath, pleuritic chest pain, and hemoptysis.

Diagnosis

Because pneumonia can progress rapidly and result in high morbidity and mortality in the compromised host, and because the etiologic agent is often difficult to ascertain, the clinician needs to be aggressive in diagnosing and treating these infections.

The diagnosis of pneumonia is most commonly made by a simple chest radiograph. However, there are rare occasions when a pulmonary infiltrate or small nodular lesion is seen only on a CT scan.

Etiologic diagnosis

An etiologic diagnosis is made by the following: sputum (expectorated or induced), bronchoscopy with bronchoalveolar lavage and transbronchial biopsy, transthoracic needle biopsy/aspiration, and open lung biopsy.

Sputum An adequate sputum specimen is difficult to obtain from cancer patients, especially during neutropenia.

Bronchoscopy with bronchoalveolar lavage is a much more sensitive technique than sputum analysis but may miss the organism when the pulmonary disease is peripheral or nodular.

Transthoracic needle biopsy/aspiration may be helpful if the lesion is proximal but may be contraindicated in a severely thrombocytopenic patient. This procedure is indicated when there is a focal/nodular lesion in the periphery.

Open lung biopsy is the most definitive diagnostic procedure but also the most invasive. It is still not clear whether the information obtained by open biopsy improves overall survival. The less invasive thoracoscopic open lung biopsy is becoming more popular than open lung biopsy.

Smears and cultures Both fluid and tissue specimens should be sent for bacterial smears (including acid-fast bacilli and modified acid-fast bacilli) and cultures (including those for anaerobes, acid-fast bacilli, and *Legionella* organisms), fungal smears (potassium hydroxide) and cultures, cytology (for viral inclusions and silver stains for fungi and *P carinii*), and histopathology.

Treatment

The therapeutic approach to pneumonia in the cancer patient should take into consideration the category of immunosuppression (neoplastic disease and immunosuppressive therapy), as well as the timing of onset and pattern of the pneumonia.

EMPIRIC ANTIBIOTIC THERAPY

In neutropenic patients experiencing their first fever and localized pulmonary infiltrates, one can justify initiating empiric therapy similar to that used for febrile, neutropenic patients (see discussion above), since the majority of pneumonias in this setting are caused by gram-negative bacteria. However, in other situations, such as pneumonia that has a later onset, develops after empiric antibiotics have been initiated, is more aggressive or severe, occurs in a more severely compromised host (eg, a patient who has had allogeneic BMT), or is characterized by a diffuse or interstitial infiltrate, one should proceed to immediate bronchoscopy with bronchoalveolar lavage (and possibly transbronchial biopsy).

ADDITIONS TO EMPIRIC THERAPY

If no diagnosis is forthcoming after bronchoscopy and bronchoalveolar lavage, additions to empiric therapy should be made.

Anaerobic, gram-positive, and *Legionella* coverage Certainly, anaerobic coverage should be considered, as well as gram-positive coverage. *Legionella* coverage should be added, especially if warranted by the epidemiologic setting.

Antifungal and antituberculous therapy Finally, antifungal therapy should be initiated if there is no response to antibacterial therapy and especially if there are nodular or cavitary lesions. In addition, if such lesions are present and/or the epidemiologic setting is compatible, antituberculous therapy should be added.

Further diagnostic procedures If bronchoscopy with bronchoalveolar lavage does not reveal an etiology and the pneumonia is progressing despite empiric therapy, consideration should be given to transthoracic needle biopsy/aspiration and open lung biopsy. As mentioned above, if there is a peripheral, focal lesion, transthoracic needle biopsy/aspiration can be attempted.

The ultimate diagnostic procedure is open biopsy, but because its contribution to increased survival is unknown, the decision to proceed with this most invasive procedure must be undertaken carefully.

SPECIFIC ANTIMICROBIAL THERAPY

The specific antimicrobial therapy suggested for each etiology is listed in Table 3.

Prevention

Methods to prevent pulmonary infections fall into the following categories: colonization prevention, antibiotic prophylaxis (and preemptive treatment), vaccination, and immunomodulation.

Hand-washing The simplest method of colonization prevention is hand-washing.

Other colonization prevention methods, such as protective environments, are discussed in the previous section.

Air and water With regard to pulmonary pathogens, HEPA-filtered rooms can eliminate *Aspergillus* spores from the immediate environment. Water supplies can be checked for *Legionella* contamination and/or adequate disinfection maintained (eg, chlorination, copper/silver ionization, temperature [60°C]).

Antimicrobial prophylaxis is discussed in the previous section.

Active immunization The influenza and pneumococcal (killed) vaccines should be administered to cancer patients.

Immunomodulation Immunomodulators, such as granulocyte colony-stimulating factor (G-CSF [Neupogen]) and granulocyte-macrophage colony-stimulating factor (GM-CSF [Leukine]), may help reduce infection by decreasing the duration of neutropenia. (For more on growth factors, see chapter 41.)

CATHETER–ASSOCIATED INFECTIONS

Chronic indwelling right atrial catheters are commonly placed in cancer patients, as they permit frequent, long-term vascular access for drug and blood product administration, hyperalimentation, and blood drawing.

TABLE 3: Probable causes of and treatments for pulmonary infiltrates in granulocytopenic patients

Pattern of infiltrate	Probable organisms	Treatment
Localized		
Early[a]	*Klebsiella* species, other Enterobacteriaceae, *Pseudomonas aeruginosa*	Empiric antibacterial therapy
Refractory[b]	Resistant Enterobacteriaceae and resistant *P aeruginosa*	Modify according to susceptibility
	Pseudomonas maltophilia	
	Pneumocystis carinii[c]	TMP-SMZ
	Legionella species[c]	Erythromycin with or without rifampin
	Mycoplasma species	Erythromycin
	Mycobacterium tuberculosis[c]	Isoniazid, rifampin, and pyrazinamide
	Nocardia asteroides[c]	TMP-SMZ
	Cryptococcus neoformans[c]	Amphotericin B
	Histoplasma capsulatum[d]	Amphotericin B
	Aspergillus species[e]	High-dose amphotericin B with or without flucytosine
Late[a,b]	*Aspergillus* species	High-dose amphotericin B with or without flucytosine[f]
	P carinii[c]	TMP-SMZ
	Trichosporon beigelii	High-dose amphotericin B with or without flucytosine[f]
	Fusarium species	High-dose amphotericin B with or without flucytosine[f]
	Mucoraceae	High-dose amphotericin B
	Candida species	Amphotericin B with or without flucytosine
	Resistant Enterobacteriaceae and resistant *P aeruginosa*	Modify according to susceptibility
	Xanthomonas maltophilia	TMP-SMZ
	Legionella species[c]	Erythromycin with or without rifampin

Hickman and Broviac catheters have an exit site on the skin surface, are anchored with a subcutaneous Dacron felt cuff, and have a subcutaneous tunnel entering the venous system (via the subclavian, external jugular, internal jugular, cephalic, saphenous, or femoral veins), where they lead into the superior or inferior vena cava or right atrium. These catheters can have single, double, or triple lumens. Another type of catheter has a totally implanted port (Port-A-Cath) that is accessed percutaneously.

There are four types of catheter-associated infections: exit site infections, tunnel infections, catheter-associated bacteremia/fungemia, and septic thrombophlebitis.

Pattern of infiltrate	Probable organisms	Treatment
Late	*N asteroides*[c]	TMP-SMZ
	M tuberculosis[c]	Isoniazid, rifampin, and pyrazinamide
	H capsulatum[d]	Amphotericin B
	Coccidioides immitis[d]	Amphotericin B
Diffuse	*P carinii*[c]	TMP-SMZ
	Legionella species[c]	Erythromycin with or without rifampin
	Chlamydia pneumoniae	Erythromycin or tetracycline
	M tuberculosis[c]	Isoniazid plus rifampin
	H capsulatum[d]	Amphotericin B
	Strongyloides stercoralis[d]	Thiabendazole
	Cytomegalovirus	Ganciclovir plus IV immune globulin, foscarnet
	If diagnostic procedure is not possible	Empiric therapy with erythromycin and TMP-SMZ

TMP-SMZ = trimethoprim-sulfamethoxazole

Adapted, with permission, from Walsh TJ, Pizzo PA: Ann Intern Med 117:424-428, 1992.

[a] The terms "early" and "late" refer to the time of development of pulmonary infiltrates during the course of granulocytopenia.

[b] Serial chest radiographs and, where appropriate, a baseline and follow-up CT scan of refractory and late focal infiltrates are recommended.

[c] Granulocytopenic patients who have concomitant defective cell-mediated immunity or who are receiving corticosteroids are at particularly high risk for these infections.

[d] Granulocytopenic patients from endemic areas who have concomitant defective cell-mediated immunity or who are receiving corticosteroids are at particularly high risk for these infections.

[e] Granulocytopenic patients with a previous episode of pulmonary aspergillosis have a high risk of developing recurrent pulmonary aspergillosis early in the course of subsequent cytotoxic chemotherapy.

[f] These pulmonary fungal infections often develop in patients who are already receiving empiric amphotericin B (0.5 mg/kg/d). These pulmonary mycoses may be more responsive to higher doses of amphotericin B (1.0-1.5 mg/kg/d). Refractory infections may require investigational antifungal triazoles or lipid formulations of amphotericin B, depending on the organism.

There are approximately 0.4 infections per 100 catheter-days and 0.26 bacteremias per 100 catheter-days.

Etiology

It is assumed that catheter-associated infections are caused by tracking of organisms from the skin along the catheter, contamination of the lumen during manipulation, or direct seeding during bacteremia/fungemia.

Staphylococci By far the most common microorganisms associated with cath-

eter infections are coagulase-negative staphylococci. The next most common pathogen is coagulase-positive *S aureus*.

Less common pathogens include gram-negative bacilli, gram-positive bacilli (such as *Corynebacterium* JK and *Bacillus* species), fungi (especially *Candida* species), and rapidly growing mycobacteria.

Signs and symptoms

Exit site infections may be manifested by local erythema, warmth, and tenderness. Purulent drainage may be present.

Tunnel infections are characterized by tenderness along the subcutaneous track.

Catheter-associated bacteremia/fungemia usually displays no local findings. A fever may be the only sign, but other signs and symptoms of sepsis or even full-blown septic shock syndrome may be present.

Septic thrombophlebitis Likewise, septic thrombophlebitis may have no findings, except those associated with sepsis or venous thrombosis (edema).

Diagnosis

In any cancer patient with a right atrial catheter who becomes febrile or is shown to be bacteremic or fungemic, a catheter-associated infection should be suspected.

Cultures A catheter-associated infection is more likely when blood cultures from the catheter sampling are positive while those from the peripheral vein are negative. A catheter infection should be assumed when the organism isolated is a coagulase-negative *Staphylococcus, Corynebacterium*, *Bacillus,* or *Candida* species or a mycobacterium.

If signs are consistent with an exit site or tunnel infection, an attempt should be made to culture any exit site drainage.

Treatment

Catheter removal

Although it was once believed that all catheters had to be removed in order to eradicate infection, it is now clear that many catheters can be salvaged. An exception to this guideline would be if the organism isolated is *Corynebacterium* JK, a *Bacillus* species, a *Candida* organism, or a rapidly growing mycobacterium. Some physicians would add to this list *S aureus*, vancomycin-resistant enterococci, *P aeruginosa*, polymicrobial bacteremia, and *Fusarium* species. The catheter also should be removed in patients with septic thrombophlebitis or evidence of septic emboli. A tunnel infection or pocket-space abscess should prompt catheter removal as well. Finally, fever or bacteremia that

persists (> 72 hours) after therapy has been initiated necessitates removal of the catheter if there is no other source of infection.

Antibiotic therapy

Empiric therapy If a catheter-associated infection is suspected, vancomycin should be initiated empirically.

Specific therapy When a microorganism has been isolated and tested for sensitivity, specific antimicrobial therapy should be added. If the catheter is left in place, a minimum of 14 days of parenteral (not oral) therapy should be administered through the catheter (rotating through each part) and follow-up cultures should be obtained.

Search for infectious metastasis

Whether or not the catheter is removed, if the patient remains febrile, a search for metastatic infection sources (lungs, liver, spleen, brain, heart valves) should be initiated.

Fibrinolytics and anticoagulants

The use of fibrinolytics and anticoagulation is controversial. Anticoagulation is probably indicated in cases of septic thrombophlebitis.

C DIFFICILE–ASSOCIATED DIARRHEA

Although many infectious complications involve the GI tract and abdomen in cancer patients, *C difficile*-associated diarrhea and typhlitis are the most important clinically.

Diarrhea is common in the cancer patient during chemotherapy. One of the most common causes of diarrhea is antibiotic-associated colitis. By far the predominant etiology of antibiotic-associated colitis is *C difficile.*

Etiology and risk factors

Antibiotics The major risk factor for *C difficile*-associated diarrhea is treatment with antibiotics, especially broad-spectrum β-lactams with activity against enteric bacteria and clindamycin (Cleocin). Antibiotic therapy causes a disruption in the normal bacterial flora of the colon. This allows for colonization with *C difficile*, a spore-forming anaerobe present in the hospital environment, via the oral-fecal route. Pathogenic strains then produce toxins that cause diarrhea and pseudomembranous colitis.

Other risk factors include surgery (primarily colonic, gastric, and pelvic), colon carcinoma, leukemia, and uremia. Obviously, the hospitalized cancer patient undergoing chemotherapy and/or surgery and receiving broad-spectrum antibiotics is most vulnerable to this infection.

Signs and symptoms

Infection with *C difficile* can be asymptomatic. When signs and symptoms do occur, they may range from mild to moderate diarrhea with lower abdominal pain, to antibiotic-associated colitis without pseudomembrane formation, to pseudomembranous colitis, to fulminant colitis. Fulminant colitis may be associated with toxic megacolon and even viscus perforation and peritonitis. On occasion, a patient may present with just abdominal pain or fever and no diarrhea.

Pseudomembranes may be absent in mild disease but usually are present in severe disease and are easily recognized on sigmoidoscopic or colonoscopic examination as adherent yellow plaques that may coalesce over large areas.

Diagnosis

The development of diarrhea or even abdominal pain or fever in a cancer patient should prompt a work-up for *C difficile*-associated diarrhea.

Stool cytotoxin test The laboratory diagnosis of *C difficile* infection depends on the demonstration of *C difficile* toxins in the stool. The gold standard is the stool cytotoxin test, a tissue-culture assay that demonstrates cell rounding by *C difficile* toxin B.

Enzyme immunoassay Another test that can demonstrate *C difficile* toxins (A and/or B) in the stool is an enzyme immunoassay. It is less expensive and faster than the cytotoxin test and does not need to be performed by specially trained laboratory personnel.

Stool culture Although a stool culture for *C difficile* may also be obtained, it has less significance in making the diagnosis.

Treatment

INITIAL MANAGEMENT

The initial step in the management of *C difficile*-associated diarrhea is to discontinue antibiotic therapy. Patients may not require any other therapy. However, stopping antibiotics in a cancer patient may not be possible or the patient may be severely ill from the colitis. In these instances, specific anti-*C difficile* therapy is required.

Specific antibiotic therapy

Metronidazole and vancomycin Metronidazole (250 mg PO qid) or vancomycin (125 mg PO qid), both given for 10 days, are the drugs of choice. Metronidazole is preferred because it is less expensive and because use of vancomycin may promote the emergence of vancomycin-resistant enterococci.

For the patient who cannot tolerate oral medications, IV metronidazole (500 mg q6h) can be given. IV vancomycin should not be used, as high intraluminal levels cannot be attained.

Other agents that might be used for treatment include bacitracin ([Baciguent];25,000 U PO qid) and cholestyramine (Questran [Prevalite]; 4 g PO qid).

TREATMENT OF RELAPSE

Relapse occurs in 10%-20% of patients. Mild cases may not need to be treated. If treatment is indicated, a repeat 7- to 14-day course of either metronidazole or vancomycin may be administered. If the infection persists after repeat therapy, longer courses (4-6 weeks) followed by a gradual tapering of the dose may be helpful.

Prevention

Contact isolation Patients with *C difficile*-associated diarrhea and those who are known carriers should be placed in "contact isolation," ie, the use of gloves, gowns, and careful hand-washing should be instituted.

Disinfection During outbreaks, the use of sodium hypochlorite to disinfect contaminated surfaces has been recommended.

Antibiotic prophylaxis of high-risk patients or carriers is not recommended.

TYPHLITIS

Typhlitis (necrotizing enterocolitis) occurs in patients who are severely neutropenic, usually in the setting of chemotherapy. Pathologically, the areas of involvement include the cecum and terminal ileum. Typhlitis is characterized by bowel wall edema, diffuse or patchy necrosis involving the mucosa alone or the full thickness of the bowel wall, mucosal ulcerations, hemorrhage, inflammatory infiltrates, and infiltration of the bowel wall by bacteria or fungi. This is a broad-spectrum disease. Mild cases are self-limiting when treated with bowel rest/antibiotics. Death may occur in severe cases.

Signs and symptoms

Signs and symptoms of typhlitis can be nonspecific but usually include fever, abdominal pain (typically in the right lower quadrant), and abdominal distention. The patient may have diarrhea (sometimes bloody), nausea, and vomiting or may demonstrate signs and symptoms consistent with those of acute appendicitis.

Physical findings There may be abdominal guarding and rebound tenderness, diminished bowel sounds, or even a mass in the right lower quadrant of the abdomen.

Diagnosis

Radiographs or CT scans of the abdomen may demonstrate a thickened cecum, mass, or even gas within the colon wall.

Treatment

Mortality from typhlitis is high (> 50%) and therapy is controversial. However, broad-spectrum antibiotics covering both gut aerobes and anaerobes and resection of necrotic bowel are recommended.

FUNGAL INFECTIONS

Fungal infections are a leading cause of morbidity and mortality in cancer patients. These infections pose a formidable management challenge, in that diagnosis is often difficult to make at an early stage and, therefore, appropriate treatment may be delayed.

Etiology and risk factors

***Candida* species** The most common fungal infections in cancer patients are caused by *Candida* species. Of the candidal pathogens found in these patients, *C albicans* is the most common. However, more recently other *Candida* species, such as *C tropicalis, C glabrata, C parapsilosis, C krusei,* and *C lusitaniae*, have become more prevalent. This finding is significant, as many of these species (*C krusei, C glabrata, C lusitaniae*) can be resistant to fluconazole and less susceptible to amphotericin B.

Major risk factors for candidal infections include neutropenia, a breakdown in physical defense barriers (such as mucositis induced by chemotherapy and radiation therapy), broad-spectrum antibiotics, immune dysfunction (caused by chemotherapy and steroids), surgery (especially GI surgery), long-term indwelling vascular catheters, and poor nutritional status/total parenteral nutrition.

***Aspergillus* species** are less common causes of infection in cancer patients than candidal organisms but are more virulent. The most common of the *Aspergillus* species is *A fumigatus*, followed by *A flavus, A niger,* and *A terreus.*

Risk factors for *Aspergillus* infections include severe immunosuppression (primarily allogeneic BMT), steroid therapy, GVHD, and environmental exposure.

Other fungi Other emerging fungal pathogens in the cancer patient include *Fusarium*, *Trichosporon*, *Rhizopus,* and *Scedosporium* species; *Pseudallescheria boydii; Malassezia furfur;* and the dematiaceous/pigmented fungi (eg, *Bipolaris spicifera, Cladosporium bantianum).*

Finally, the endemic fungi, *Coccidioides immitis* and *Histoplasma capsulatum,* are often more virulent and aggressive than other fungi in the immunocompromised host.

Signs and symptoms

Candidiasis

Candidiasis can present as a wide spectrum of diseases, from mucosal infection to disseminated and invasive disease.

Local mucosal infection Oropharyngeal candidiasis can present as classic thrush with beige plaques. It may be painful, as there may be a concurrent mucositis due to the ablative chemotherapy. Oropharyngeal candidiasis may extend into the esophagus as esophagitis, which may manifest as odynophagia. Epiglottitis may present as odynophagia and laryngeal stridor.

Disseminated infection Candidemia may present simply as an asymptomatic fever or may result in a full-blown septic shock syndrome (acute disseminated candidiasis). In contrast, chronic disseminated candidiasis, which involves the chronic, indolent infection of different organs, such as the liver, spleen, and kidneys, may be manifested by fever alone.

Aspergillosis

Invasive aspergillosis most commonly involves the lungs and sinuses. However, it can also disseminate to the brain (and may be the most common cause of brain abscesses in BMT patients). Less commonly, aspergillosis can disseminate to other organs, including the skin.

Pulmonary aspergillosis Signs and symptoms of invasive pulmonary aspergillosis include pleuritic pain, pulmonary hemorrhage, hemoptysis, and cavitation. The chest radiograph or CT scan may demonstrate pulmonary nodular infiltration and/or cavitary lesions.

Sinusitis Patients with sinusitis may have few signs (swelling) or symptoms (pain), especially if they are neutropenic.

Brain abscess Patients with brain abscesses may have headaches and neurologic signs consistent with the specific site of the lesion.

Skin involvement may present as necrotizing skin nodules or ulcers.

Other infections

***Fusarium* infections** The signs and symptoms of *Fusarium* infections are similar to those of aspergillosis; ie, pulmonary infiltrates, sinusitis, and cutaneous lesions are prominent.

***Trichosporon* infections** are similar to *Candida* infections, in that they can cause disseminated disease in multiple organs.

***Rhizopus* species** cause sinopulmonary disease.

***P boydii* and *Scedosporium* species** are similar to *Aspergillus* species in their structure and predilection for the respiratory tract.

C immitis* and *H capsulatum also target the lungs but can disseminate to other organs.

Diagnosis

Diagnosis of fungal infection in the cancer patient requires documentation by culture or histologic examination. Unfortunately, no diagnostic tests that are sensitive, specific, or useful are available for most of these infections.

Candidiasis Although the diagnosis of oropharyngeal candidiasis often is made on clinical grounds, the lesions should be scraped for microscopic examination and culture. Biopsy of esophageal lesions via endoscopy should be performed to confirm *Candida* (as opposed to HSV or CMV) as the etiology of the infection.

A positive blood culture for *Candida* (especially a species other than *C albicans)* should never be considered a "contaminant" and often implies a right atrial catheter infection. Less likely to result in positive blood cultures are chronic, deep-seated infections, such as hepatosplenic candidiasis. Such infections require biopsy for confirmation.

***Aspergillus* species,** like other species, such as *Rhizopus, P boydii,* and dematiaceous fungi, are rarely found in the bloodstream and require tissue sampling for diagnosis. Occasionally, bronchoalveolar lavage fluid or sinus drainage will yield *Aspergillus*, but often a lung biopsy is required.

***Fusarium*, *Scedosporium*, and *Trichosporon* species,** in contrast to *Aspergillus* species, are often found in the bloodstream.

Skin lesions Any skin lesion should be suspected of being of fungal origin and should be biopsied, cultured, and examined histologically.

Antigen tests and polymerase chain reaction (PCR) Although antigen tests for both *Candida* and *Aspergillus* species have been developed, as well as PCR for *Aspergillus* organisms, they either have not shown promise or have yet to undergo clinical trials.

Search for sites of infection When a fungal infection is suspected or documented, a search for possible sites of infection should ensue. For a blood culture that grows a *Candida* species, the intravascular catheter should, in most cases, be removed for diagnostic as well as therapeutic reasons, and the catheter tip should be cultured. A CT scan of the abdomen should be obtained. In cases of suspected *Aspergillus* infection, in addition to a chest CT scan, a CT scan of the brain and sinuses should be performed.

Treatment

Candidiasis

Local mucosal candidiasis In patients with local mucosal candidiasis (including esophagitis), oral fluconazole or itraconazole (Sporanox) can be used. If the patient has difficulty in taking oral medication, IV fluconazole should be used. If the patient has been receiving prophylactic fluconazole when candidiasis develops, amphotericin B should be used.

Candidemia If candidemia is documented, the intravascular catheter should be removed. This step should be followed by a short 500-mg course of amphotericin B if no further cultures are positive and the patient defervesces and demonstrates no other site of infection.

Disseminated, deep-seated candidiasis (eg, hepatosplenic infection) is treated with amphotericin B. This infection is difficult to treat, however, and often requires high total doses of this nephrotoxic drug. Fluconazole has been used with occasional success in patients who do not respond to amphotericin B.

Three lipid formulations of amphotericin B are now available for the treatment of invasive fungal infections: amphotericin B lipid complex, amphotericin B cholesteryl sulfate (Amphotec), and liposomal amphotericin B. The major advantage of these preparations is that they are less nephrotoxic than conventional amphotericin B. However, they are much more expensive.

A randomized, double-blind, multicenter trial suggested that liposomal amphotericin B is less infusionally toxic and nephrotoxic (when measured during the first week) than amphotericin B lipid complex. There was also a trend (although statistically insignificant) toward a higher response rate and lower mortality rate in the liposomal amphotericin B group. However, it must be stressed that this was not a therapeutic study in patients with documented invasive fungal infections.

In addition to the indication for use in patients (with fungal infections) refractory to or intolerant of conventional amphotericin B therapy, the FDA granted liposomal amphotericin B an additional indication for use as empiric therapy for presumed fungal infections in patients with depressed immune function and fever of unknown origin. Thus, liposomal amphotericin B can be used as empiric fungal therapy in cancer patients, with efficacy equal to that of conventional amphotericin B but with less toxicity.

Antifungal combinations Except in the case of cryptococcal meningitis (for which fluconazole is synergistic with amphotericin B), there is no evidence that combinations of antifungals are more effective than single-agent therapy. However, it is recommended that fluconazole be added to amphotericin B in the more resistant non-*albicans Candida* infections. Since fluconazole is toxic to marrow, blood levels should be followed.

Aspergillosis

Antifungal therapy Amphotericin B deoxycholate (1.0-1.5 mg/kg/d) has been the standard therapy for invasive aspergillosis. However, a new triazole antifungal agent, voriconazole, led to better responses, improved survival, and fewer adverse events compared with amphotericin B when used as initial therapy in patients with invasive aspergillosis. In addition, new antifungals and new formulations of amphotericin B have recently been approved for use in invasive aspergillosis in patients who are intolerant of or refractory to conventional amphotericin B. They include amphotericin B lipid complex, amphotericin B cholesteryl sulfate, liposomal amphotericin B, itraconazole oral solution, intra-

venous itraconazole, and caspofungin acetate (Cancidas). All of these formulations are less nephrotoxic than amphotericin B deoxycholate.

Antifungal combinations There is no evidence that combination antifungal therapy is more effective for treating invasive aspergillosis than is single-agent therapy.

Surgical removal of infected sites In addition to antifungal therapy, it is important to attempt surgical removal of infected sites, if at all feasible. Sinus surgery should be performed. Resection of pulmonary lesions should be attempted if there are only one or two limited, discrete lesions.

Infections with other fungi

Although amphotericin B is the drug of choice for most invasive fungal infections, there are exceptions. *Scedosporium* and *Fusarium* species are often resistant to amphotericin B, and voriconazole may be the drug of choice in these infections. Voriconazole, however, is not active against *Zygomycetes* species, and amphotericin B should be used in such cases. The dematiaceous/pigmented fungi also may be better treated with itraconazole. For *Trichosporon* infections, voriconazole may be more effective than amphotericin B.

Prevention

Because invasive fungal infection occurs with high frequency in the setting of BMT, most prophylactic studies have been performed in marrow transplant recipients. Thus, the following recommendations apply mainly to this group, although prophylaxis can be justified when the incidence of these infections in any population is high enough.

Fluconazole Two randomized, placebo-controlled studies using prophylactic fluconazole (400 mg/d) have demonstrated a decrease in invasive and superficial *C albicans* infections. One study showed a reduction in mortality. As fluconazole is not active against *C krusei, C glabrata,* or *Aspergillus* species, there is concern that prophylactic use of fluconazole will increase the incidence of these resistant fungi. Some authors have reported such an occurrence.

Low-dose amphotericin B was observed, in a retrospective study, to decrease the incidence of *Candida* infection. However, this regimen only delayed the onset of *Aspergillus* infections.

Micafungin has recently been shown to be superior to fluconazole in patients undergoing BMT. It was more effective in preventing aspergillosis. However, micafungin has not yet been approved by the FDA in the United States.

Other prophylactic regimens have been used in small numbers of patients with varying degrees of success. They include aerosolized amphotericin B, intranasal amphotericin B, IV/oral itraconazole, and amphotericin B lipid complex.

HEPA filtration Other than using prophylactic antifungals, there is very little that can be done to prevent fungal infections in cancer patients. The

one possible exception is the use of HEPA filtration, which can eliminate *Aspergillus* spores from the environment. However, most patients emerge from this environment still possessing the same risk factors (steroids, GVHD) for aspergillosis.

VIRAL INFECTIONS

Opportunistic viral infections are a particular problem in cancer patients who undergo BMT and those with hematologic cancers. Accurate diagnosis of viral infections is important, as treatment is available for many of them.

Etiology

As mentioned above, viral infections in cancer patients are caused predominantly by herpesviruses (HSV, VZV, CMV, and EBV). The herpesvirus infections usually are reactivations of latent infections. Respiratory viruses that infect cancer patients include respiratory syncytial virus, influenza viruses A and B, parainfluenza virus, rhinovirus, and adenovirus.

Signs and symptoms

Although all of the herpesviruses can cause fever and a septic picture, HSV usually presents as mucositis or a vesicular rash, VZV as a vesicular rash in a dermatomal distribution, and CMV, in the BMT setting, as an interstitial pneumonia. When HSV or VZV disseminates, each virus can cause disseminated cutaneous lesions or visceral (liver, lung, brain) involvement. VZV infection can present with GI symptoms, such as epigastric or general abdominal pain.

Diagnosis

In order to make a specific viral etiologic diagnosis, tissue or fluid must be obtained from the infected site and processed for histologic/cytologic examination and culture.

Vesicular skin lesions When a cancer patient presents with a vesicular rash, it is invariably due to either HSV or VZV. If the distribution of lesions is in a dermatomal pattern, a clinical diagnosis of VZV can be made. However, if there is cutaneous dissemination, the vesicular lesions should be aspirated (and sent for viral culture) or scraped down to the base, smeared on a glass slide, and sent for direct fluorescent antibody staining (for HSV and VZV).

Visceral involvement When there is visceral involvement with either HSV, VZV, or CMV, biopsy material is examined for inclusions and is submitted for culture.

Respiratory infection For the respiratory viruses, diagnosis is usually made by examination of bronchoalveolar lavage fluid (obtained by bronchoscopy) or biopsy (obtained by transbronchial, percutaneous thoracic, thoracoscopic,

or open lung biopsy). In the special case of CMV interstitial pneumonitis in the BMT setting, diagnosis of infection (prior to disease onset) can be made by detection of antigens or virus in the bloodstream, in addition to evidence of the virus in bronchoalveolar lavage fluid.

Antibody testing is of little use in the diagnosis of viral infection in the cancer patient.

Treatment

HSV infection Localized HSV infection is usually treated with acyclovir, 5 mg/kg IV q8h. If there is dissemination, a dose of 10 mg/kg q8h can be used, and if there is CNS involvement, up to 15 mg/kg IV q8h can be utilized. If acyclovir-resistant HSV is suspected, foscarnet (Foscavir) can be used (see Table 1 for doses). However, this is a nephrotoxic drug.

VZV infection is usually treated with acyclovir, administered at a dose of 10 mg/kg IV q8h.

CMV infection is treated with ganciclovir or foscarnet. Ganciclovir is the drug of choice but is toxic to bone marrow.

In the BMT setting, "preemptive" treatment (treatment to prevent disease after evidence of infection is obtained) consists of ganciclovir, 5 mg/kg IV bid for 14 days. Actual treatment of CMV interstitial pneumonia consists of ganciclovir, 5 mg/kg IV q12h, along with immunoglobulin, 500 mg/kg IV every other day for 21 days (induction phase). Maintenance therapy (for as long as immunosuppression is present) consists of ganciclovir, 5 mg/kg/d IV for 5 days each week, and immunoglobulin, 500 mg/kg IV every week.

Foscarnet can be used instead of ganciclovir if there is marrow toxicity but poses a potential risk of nephrotoxicity.

Respiratory viral infection Among the respiratory viruses, there is specific antiviral therapy only for respiratory syncytial virus and influenza A. Ribavirin (Virazole), 1.1 g/d by aerosol (20 mg/mL), has been used for respiratory syncytial virus and rimantadine (Flumadine) or amantadine (Symmetrel), both 100 mg PO bid, for influenza A.

Prevention

Herpesvirus infections

Acyclovir HSV and VZV reactivate with great frequency in cancer patients undergoing chemotherapy and/or radiation therapy. This finding is especially true in the BMT population, in which 80% of HSV-seropositive patients and up to 40% of VZV-seropositive patients have a reactivation of HSV or VZV. Therefore, in HSV-seropositive BMT patients, prophylactic acyclovir is indicated. However, prophylaxis may only delay the onset of infection. Any HSV infection that occurs during acyclovir prophylaxis should be considered

acyclovir-resistant. Acyclovir has also been shown to reduce the incidence of CMV infection after BMT.

Ganciclovir is the drug of choice for prophylaxis against CMV in the BMT setting, however. It can be used as preemptive therapy, as described above, but can also be used universally as true prophylaxis to reduce the incidence of CMV infection. However, because of its marrow toxicity (ie, neutropenia) and high cost, ganciclovir cannot be strongly recommended as universal prophylaxis.

CMV-seronegative blood support In the small group of BMT recipients who are CMV-seronegative, the use of CMV-seronegative blood support has been shown to dramatically reduce CMV infection.

Varicella zoster immune globulin In any susceptible cancer patient exposed to VZV, varicella zoster immune globulin should be administered within 96 hours of exposure.

Varicella virus vaccine (Varivax) should not be given to those with hematologic malignancies, malignant neoplasms, or immunodeficiencies, with the exception of those with childhood leukemia in remission for 1 year when selected criteria are met.

Influenza

Influenza vaccine Although the efficacy of the influenza vaccine is unknown in the BMT setting, it should be administered to all cancer patients.

Rimantadine or amantadine can be given prophylactically during an outbreak of influenza.

SUGGESTED READING

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CHAPTER 49

Fluid complications

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MALIGNANT PLEURAL EFFUSION

Pleural effusion is usually caused by a disturbance of the normal Starling forces regulating reabsorption of fluid in the pleural space, secondary to obstruction of mediastinal lymph nodes draining the parietal pleura. Tumors that metastasize frequently to these nodes, eg, lung cancer, breast cancer, and lymphoma, cause most malignant effusions. It is, therefore, puzzling that small-cell lung cancer infrequently causes effusions.

Pleural effusion restricts ventilation and causes progressive shortness of breath by compression of lung tissue as well as paradoxical movement of the inverted diaphragm. Pleural deposits of tumor cause pleuritic pain.

Pleural effusions commonly occur in patients with advanced-stage tumors, who frequently have metastases at multiple sites (eg, brain, bone, and other organs), physiologic deficits, complications (eg, malnutrition, debilitation), and other comorbidities. Because of these numerous clinical and pathologic variables, it is difficult to perform meaningful trials in patients with pleural effusions. For the same reason, it is often difficult to predict a potential treatment outcome for the specific patient with multiple interrelated clinical problems.

Diagnosis

The new onset of a pleural effusion may herald the presence of a previously undiagnosed malignancy or, more typically, complicate the course of a known tumor.

Thoracentesis The first step in management in almost all cases is thoracentesis. An adequate specimen should be obtained and sent for cell count; determination of glucose, protein, lactate dehydrogenase (LDH), and pH; and appropriate cultures and cytology. A negative cytology result is not uncommon and does not rule out a malignant etiology.

The Light criteria (LDH $>$ 200 U/L; pleural-serum LDH ratio $>$ 0.6, and pleural-serum protein ratio $>$ 0.5) help categorize pleural effusions as exudates. The majority of undiagnosed exudates are eventually diagnosed as malignant, whereas $<$ 5% of transudates are shown to be caused by cancer.

Image-guided percutaneous cutting-needle biopsy of pleural thickening demonstrated by CT (24) or ultrasonography (9) in the presence of pleural effusion safely achieved a positive biopsy in 21 of 24 malignant effusions, for an overall diagnostic accuracy of 91% *(Adams RF, Gleeson FV: Radiology 219:510-514, 2001).*

Pleural biopsy If cytology of an exudative effusion is negative and malignant disease is still suspected (approximately 50% of cases), blind pleural biopsy has a low diagnostic yield that can be improved by image guidance.

Thoracoscopy Thoracoscopic examination is emerging as a reliable diagnostic technique with a low complication rate. It allows comprehensive visualization of one pleural cavity, coupled with the opportunity to biopsy areas of disease. This method provides a definitive diagnosis and allows the pathologist to suggest possible sites of primary disease based on the histopathology. Furthermore, this technique permits the diagnosis and staging of malignant mesothelioma if it is the cause of the effusion. Thoracoscopy also offers the opportunity for simultaneous treatment.

Bronchoscopy may be helpful when an underlying lung cancer is suspected, especially if there is associated hemoptysis, a lung mass, atelectasis, or a massive effusion. It may also be helpful when there is a cytologically positive effusion with no obvious primary tumor.

PROGNOSIS

Prognosis with malignant pleural effusion varies by primary tumor. For example, median survival for lung cancer is 3 months while it is 10 months for breast cancer. Median survival is also lower in patients with encasement atelectasis (3 months).

Treatment

INITIAL TREATMENT

Because the specific clinical circumstances may vary markedly in different patients, treatment must be individualized to provide the best palliation for each patient. In general, malignant pleural effusion should be treated aggressively as soon as it is diagnosed. In most cases, effusion will rapidly recur after treatment by thoracentesis or tube thoracostomy alone. If the clinician decides to administer systemic chemotherapy for the underlying primary malignancy, in tumors such as breast cancer, lymphoma, and small-cell lung cancer, it is important to monitor the patient carefully for recurrent effusion and treat such recurrences immediately.

If a malignant pleural effusion is left untreated, the underlying collapsed lung will become encased by tumor and fibrous tissue in as many as 10%-30% of cases. Once this encasement atelectasis has occurred, the underlying lung is "trapped" and will no longer reexpand after thoracentesis or tube thoracostomy. Characteristically, the chest x-ray in such cases shows resolution of the pleural effusion after thoracentesis, but the underlying lung remains partially collapsed. This finding is often misinterpreted by the inexperienced clinician as evidence of a pneumothorax, and a chest tube is placed. The air space per-

sists and the lung remains unexpanded, even with high suction and pulmonary physiotherapy. Allowing the chest tube to remain in place can worsen the situation by causing bronchopleural fistulization and empyema.

Physical techniques

To avoid encasement atelectasis, pleural effusion should be treated definitively at the time of initial diagnosis. Multiple physical techniques of producing adhesions between the parietal and visceral pleura, obliterating the space, and preventing recurrence have been used. They include open or thoracoscopic pleurectomy, gauze abrasion, or laser pleurodesis. Surgical methods have not been demonstrated to have any advantage over simpler chemical pleurodesis techniques in the treatment of malignant effusions but can easily be employed when unresectable tumor with associated effusion is found at the time of thoracotomy.

Chemical agents

Multiple chemical agents have been used.

Tetracycline Tetracycline pleurodesis results in a lower incidence of recurrence when compared with tube thoracostomy alone, but often causes severe pain.

Doxycycline and minocycline are probably equivalent in efficacy to tetracycline.

Bleomycin Intrapleural bleomycin (Blenoxane), in a dose of 60 U, has been shown to be more effective than tetracycline and is not painful, but it is costly. Absorption of the drug can result in systemic toxicity. Combined use of tetracycline and bleomycin has been demonstrated to be more efficacious than the use of either drug singly.

Talc pleurodesis was first introduced by Bethune in the 1930s. Talc powder (Sclerosol Intrapleural Aerosol) has demonstrated efficacy in numerous large studies, preventing recurrent effusion in 70%-92% of cases. Talc is less painful than tetracycline. Cost is minimal, but special sterilization techniques must be mastered by the hospital pharmacy.

Talc can be insufflated in a dry state at the time of thoracoscopy or instilled as a slurry through a chest tube. The dose should be restricted to no more than 5 g.

Our group and others have noted problems with residual multiloculated effusions following talc use. It is important to ensure that the talc does not solidify and form a concretion in the chest tube, thus preventing the drainage of pleural fluid and complete reexpansion of the lung following pleurodesis. Such an event is more likely with the use of small-bore chest tubes.

Distribution of 99mTC sestamibi-tagged talc was studied in 20 patients with and without patient rotation. Radioisotope distribution was unequal and limited and did not improve in patients who were turned from side to side. Regardless, 85% of patients experienced success in management of pleural effusion *(Mager HJ, Measen B, Verzijlbergen F, et al: Lung Cancer 36:77-81, 2002).*

Pleurodesis technique With any form of pleurodesis, a 24- to 32-French tube has cus-

tomarily been inserted through a lower intercostal space and placed on underwater seal suction drainage until all fluid is drained and the lung has completely reexpanded. Because severe lung damage can be produced by improper chest tube placement, it is imperative to prove the presence of free fluid by a preliminary needle tap and to enter the pleural space gently with a blunt clamp technique, rather than by blind trocar insertion. If there is any question about the presence of loculated effusion or underlying adhesions, the use of CT or sonography may enhance the safety of the procedure. In the case of large effusions, especially those that have been present for some time, the fluid should be drained slowly to avoid reexpansion pulmonary edema.

Significant complications can occur with both thoracentesis and chest tube thoracostomy. These procedures should not be performed by inexperienced practitioners without training and supervision.

Premedications If doxycycline or talc is to be used, the patient should be premedicated with narcotics. Intrapleural instillation of 20 mL of 1% lidocaine before administration of the chemical agent may help reduce pain.

Following instillation of the chemical agent, the chest tube should remain clamped for at least 2 hours. If high-volume drainage persists, the treatment can be repeated. The chest tube can be removed after 2 or 3 days if drainage is < 300 mL/day.

Cardillo reported long-term results after the use of thoracoscopic talc (5 g) pleurodesis under general anesthesia in 611 patients. Chest tube drainage continued for 3-5 days postoperatively. The operative mortality rate was 0.81%. Success was achieved in 92% *(Cardillo G, Facciolo R, Carbone L, et al: Eur J Cardiothorac Surg 21:302-305, 2002).*

Follow-up x-rays at monthly intervals assess the adequacy of treatment and allow early retreatment in case of recurrence.

Alternative approaches Use of small-bore tubes and outpatient pleurodesis has been advocated by some investigators and has the potential for reducing hospital stay and treatment cost. Patz performed a prospective, randomized trial of bleomycin vs doxycycline (72% bleomycin vs 79% doxycycline) pleurodesis via a 14-French catheter and found no difference in efficacy.

Other approaches that must be considered experimental at this time include silver nitrate pleurodesis and the use of various biological agents, including *Corynebacterium parvum,* OK-432, tumor necrosis factor, interleukin-2 (Proleukin), interferon-α (Intron A, Roferon-A), interferon-β (Betaseron), and interferon-γ (Actimmune).

TREATMENT OF ENCASEMENT ATELECTASIS

If encasement atelectasis is found at thoracentesis or thoracoscopy, tube thoracostomy and pleurodesis are futile and contraindicated.

Surgical decortication has been advocated for this problem. This potentially dangerous procedure may result in severe complications, however, such as bronchopleural fistula and empyema.

Pleuroperitoneal shunts The Royal Brompton Hospital, London group reported experience with pleuroperitoneal shunts in 160 patients with malignant pleural effusion and a trapped lung. Effective palliation was achieved in 95% of patients; 15% of patients required shunt revisions for complications.

Intermittent thoracentesis, as needed to relieve symptoms, may be the best option in patients with a short anticipated survival.

Catheter drainage Another new option is to insert a tunneled, small-bore, cuffed, silicone catheter (PleurX Pleural Catheter, Denver Biomaterials, Inc., Denver, Colorado) into the pleural cavity. The patient or family members may then drain fluid, using vacuum bottles, whenever recurrent effusion causes symptoms. Putnam prospectively compared PleurX catheter drainage with doxycycline pleurodesis and found the two to be equally effective. We have found this device to be useful and well tolerated by patients and caregivers. Pleuroperitoneal shunts and PleurX catheters can have problems with catheter plugging, infection, and local tumor implants along the catheter track.

Kakuda reported on placement of 61 PleurX catheters in 50 patients with malignant pleural effusions at City of Hope. Thirty-four percent had lung cancer and 24% had breast cancer. There were no operative deaths. In cases where the catheter was placed under thoracoscopic control, 27 of 38 patients (68%) had encasement atelectasis visualized. Eighty-one percent had a good result with control of effusion, with subsequent catheter removal (19%) or intermittent drainage for > 1 month or until death (62%). Five percent had major complications, including empyema and tumor implant *(Kakuda JR, Grannis FW: Chest [abstract 364] [suppl]6:1655, 2002).*

Chemotherapy options depend on the cell type of the tumor and the general condition of the patient. Although intrapleural chemotherapy offers the possibility of high-dose local therapy with minimal systemic effects, only a small number of studies have been performed.

Shoji et al from Kyoto University in Japan used intrapleural 5-FU (250 mg/body) and cisplatin (10 mg/body) through an implantable access system (Infuse-a-Port) in 22 patients in an outpatient setting, including 17 with non–small-cell lung cancer (NSCLC). Median survival time was 403 days. They suggest that intrapleural chemotherapy for malignant pleural effusion is safe and possibly effective *(Shoji T, Tanaka F, Yanagihara K, et al: Chest 121:821-824, 2002).*

Ang and colleagues from Singapore report longer mean survival (12 months vs 5 months) when systemic chemotherapy was given to 71 patients who initially presented with malignant pleural/pericardial effusions. New studies in this area are much needed.

Radiation therapy may be indicated in some patients with lymphoma but has limited effectiveness in other tumor types, particularly if mediastinal adenopathy is absent.

Chylothorax not due to trauma is usually secondary to cancer, most frequently lymphoma. An added element of morbidity is conferred by the loss of protein, calories, and lymphocytes in the draining fluid. Chylothorax secondary to lymphoma is usually of low volume and responds to talc pleurodesis in combination with radiotherapy or chemotherapy.

Injection of green dye into lymphatics in various areas of the pericardium in 12 human cadavers demonstrated lymphatic channels emptying into the tracheobronchial nodes (n = 35) and less often into the prepericardial nodes (n = 14) *(Riquet M, Le Pimpec-Barthes F, Hidden G: Surg Radiol Anat 23:317-319, 2001).*

PERICARDIAL EFFUSION

Pericardial effusion develops in 5%-15% of patients with cancer and is sometimes the initial manifestation of malignancy. Most pericardial effusions in cancer patients result from obstruction of the lymphatic drainage of the heart secondary to metastases. The typical presentation is that of a patient with known cancer who is found to have a large pericardial effusion without signs of inflammation. Bloody pericardial fluid is not a reliable sign of malignant effusion.

The most common malignant causes of pericardial effusions are lung and breast cancers, leukemias (specifically acute myelogenous, lymphoblastic, and chronic myelogenous leukemia [blast crisis]), and lymphomas (approximately 80% of cases). Pericardial effusions caused by sarcomas, melanomas, thymoma, as well as GI, ovarian, and cervical cancers are less common.

Not all pericardial effusions associated with cancer are malignant, and cases with negative cytology may represent as many as half of cancer-associated pericardial effusions. Such effusions are more common in patients with mediastinal lymphoma, Hodgkin's disease, or breast cancer. Other nonmalignant causes include drug-induced or postirradiation pericarditis, tuberculosis, collagen diseases, uremia, and congestive heart failure. Many effusions that initially have negative cytology will become positive over time.

Tamburro observed a decrease in the highest value of the upper plethysmographic peak of the pulse-oximetry waveform during inspiration in eight children with pericardial tamponade. This finding lessened in each child after pericardiocentesis. He concluded that analysis of pulse-oximetric waveforms may be a widely available, easily interpretable, and reliable method of detecting the pulsus paradoxus associated with large pericardial effusions *(Tamburro RF, Ring JC, Womback K: Pediatrics 109:673-677, 2002).*

Tamponade occurs when fluid accumulates faster than the pericardium can stretch. Compression of all four heart chambers ensues, with tachycardia and diminishing cardiac output. Fluid loading can counteract intrapericardial pressure temporarily; reciprocal filling of right- and left-sided chambers with inspiration and expiration, secondary to paradoxical movement of the ventricular septum, is a final mechanism to maintain blood flow before death.

Diagnosis

A high index of suspicion is required to make the diagnosis of pericardial effusion.

Signs and symptoms Dyspnea is the most common symptom. Patients may also complain of chest pain or discomfort, easy fatigability, cough, and orthopnea or may be completely asymptomatic. Signs include distant heart sounds and pericardial friction rub. With cardiac tamponade, progressive heart failure

occurs, with increased shortness of breath, cold sweats, confusion, pulsus paradoxus > 13 mm Hg, jugular venous distention, and hypotension.

Chest x-ray Chest radiographic evidence of pericardial effusion includes cardiomegaly with a "water bottle" heart, an irregular, nodular contour of the cardiac shadow, and mediastinal widening.

ECG The ECG shows nonspecific ST- and T-wave changes, tachycardia, low QRS voltage, electrical alternans, and atrial dysrhythmia.

Pericardiocentesis and echocardiography An echocardiogram not only can confirm a suspected pericardial effusion but also can document the size of the effusion and its effect on ventricular function. However, a pericardial tap with cytologic examination (positive in 50%-85% of cases with associated malignancy) may be necessary to confirm the diagnosis of malignant effusion or to differentiate it from other causes of pericardial effusion. Serious complications, including cardiac perforation and death, can occur during pericardiocentesis, even when performed by experienced clinicians.

Maggiolini reported on 53 pericardiocenteses in 48 patients using a new device with a needle carrier supported by a bracket with two fixed angulations mounted on the probe. There were no cardiac punctures *(Maggiolini S, Bozzano A, Russo P, et al: Am J Soc Echocardiogr 14:821-824, 2001).*

Tumor markers or special staining and cytogenetic techniques may improve the diagnostic yield, but ultimately an open pericardial biopsy may be necessary.

CT and MRI as diagnostic adjuncts may provide additional information about the presence and location of loculations or mass lesions within the pericardium and adjacent structures.

Cardiac catheterization may occasionally be of value to rule out superior vena caval obstruction, diagnose microvascular tumor spread in the lungs with secondary pulmonary hypertension, and document constrictive pericarditis before surgical intervention. Pericardial fluid has been aspirated in experimental animals by femoral vein catheterization and needle puncture of the right atrial appendage from within. This technique has not been used in humans.

Pericardioscopy allows visualization and biopsy at the time of subxiphoid or thoracoscopic pericardiotomy and can improve the diagnostic yield.

Prognosis

In general, cancer patients who develop a significant pericardial effusion have a high mortality, with a mean time to death of 2.2-4.7 months. However, about 25% of selected patients treated surgically for cardiac tamponade enjoy a 1-year survival.

Treatment

GENERAL CONCEPTS

As is the case with malignant pleural effusion, it is very difficult to evaluate treatments for pericardial effusion because of the many variables. Since malignant pericardial effusion is less common than malignant pleural effusion, it is more difficult to collect data in a prospective manner. Certain generalizations can, however, be derived from available data:

- All cancer patients with pericardial effusion require a systematic evaluation and should not be dismissed summarily as having an untreatable and/or terminal problem.
- Ultimately, both the management and natural course of the effusion depend on: (1) the underlying condition of the patient, (2) the extent of clinical symptoms associated with the cardiac compression, and (3) the type and extent of the underlying malignant disease.

GENERAL TREATMENT APPROACHES

Asymptomatic, small effusions may be managed with careful follow-up and treatment directed against the underlying malignancy. On the other hand, cardiac tamponade is a true oncologic emergency. Immediate pericardiocentesis, under echocardiographic guidance, may be performed to relieve the patient's symptoms. A high failure rate is anticipated because the effusion rapidly recurs unless steps are taken to prevent this. Therefore, a more definitive treatment plan should be made following the initial diagnostic/therapeutic tap.

In patients with symptomatic, moderate-to-large effusions who do not present as an emergency, therapy should be aimed at relieving symptoms and preventing recurrence of tamponade or constrictive pericardial disease. Patients with tumors responsive to chemotherapy or radiation therapy may attain longer remissions with appropriate therapy.

There are two theoretical mechanisms for control of pericardial effusion: creation of a persistent defect in the pericardium allowing fluid to drain out and be reabsorbed by surrounding tissues or injury to the mesothelium resulting in the formation of fibrous adhesions that obliterate the pericardial cavity.

Postmortem studies have demonstrated that both of these mechanisms are operative. The fact that effusions can recur implies that there is either insufficient damage to the mesothelial layer or that rapid recurrence of effusion prevents coaptation of visceral and parietal pericardium and prevents the formation of adhesions. This, in turn, would suggest that early closure of the pericardial defect can result in recurrence.

TREATMENT METHODS

Various methods can be used to treat malignant pericardial effusion.

Observation Observation alone may be reasonable in the presence of small *asymptomatic* effusions.

Pericardiocentesis is useful in relieving tamponade and obtaining a diagnosis. Echocardiographic guidance considerably enhances the safety of this procedure. Ninety percent of pericardial effusions will recur within 3 months after pericardiocentesis alone, with a very short median survival.

At the National Taiwan University, cardiologists performed percutaneous double-balloon pericardiotomy in 50 patients with cancer and pericardial effusion and followed their course using serial echocardiograms. Success without recurrence was achieved in 88%. Fifty percent of patients died within 4 months and 25% survived to 11 months *(Wang H-J, Hsu K-L, Chiang F-T, et al: Chest 122:893-899, 2002).*

Pericardiocentesis and percutaneous tube drainage can now be performed with low risk and are recommended by some clinical groups. Problems that may occur include occlusion or displacement of the small-bore tubes, dysrhythmia, recurrent effusion, and infections. The Mayo Clinic group recommends initial percutaneous peri-cardiocentesis with extended catheter drainage as its technique of choice.

Intrapericardial sclerotherapy and chemotherapy following percutaneous or open drainage have been reported to be effective treatments by some groups. Problems include pain during sclerosing agent treatments and recurrence of effusions. Good results have been reported with instillation of a number of agents. Agents are selected based on their antitumor or sclerosing effect.

Pericardiocentesis and balloon pericardial window After percutaneous placement of a guidewire following pericardiocentesis, a balloon dilating catheter can be placed across the pericardium under fluoroscopic guidance and a window created by balloon inflation.

At City of Hope, Cullinane et al reported on 62 patients with malignant disease who had surgical pericardial window for management of pericardial effusion. Windows were created either thoracoscopically (32) or by subxiphoid (12) or limited thoracotomy (18) approaches. Primary tumors included NSCLC, breast, hematologic, and other solid organ malignancies. Three recurrent effusions (4.8%) required reoperations. Eight patients (13%) died during the same admission as their surgical procedure. Median survival was much lower for patients with NSCLC (2.6 mo) than for patients with breast cancer (11 mo) or hematologic malignancy (10 mo). Surgical pericardial window is a safe and durable operative procedure that may provide extended survival in certain subgroups of cancer patients *(Cullinane CA, Paz, IB, Grannis FW: Proc Am Soc Clin Oncol [abstract] 21:388a, 2002).*

Subtotal pericardial resection is seldom performed today. Although it is the definitive treatment, in that there is almost no chance of recurrence or constriction, higher morbidity and longer recovery time render this operation undesirable in patients who have a short anticipated survival. Its use is restricted to cancer patients with recurrent effusions who are in good overall condition and are expected to survive for up to 1 year.

Limited pericardial resection (pericardial window) via anterior thoracotomy has a lower morbidity than less invasive techniques, but recovery is delayed. There is a small risk of recurrence. Cardiac herniation is possible if the size of the opening in the pericardium is not carefully controlled.

Subxiphoid pericardial resection can be performed with the patient under local anes-

thesia and may be combined with tube drainage and/or pericardial sclerosis. Our group and others have noted recurrences following this technique.

Subxiphoid pericardioperitoneal window through the fused portion of the diaphragm and pericardium has been developed to allow continued drainage of pericardial fluid into the peritoneum. Experience with the procedure is limited, but recurrences may be less frequent than those associated with subxiphoid drainage alone.

Thoracoscopic pericardial resection is our current treatment of choice and has been performed by our group, as well as by others, with low morbidity, mortality, and recurrence rates. General anesthesia with single-lung ventilation is required.

Technical factors Prior pleurodesis for malignant pleural effusion makes an ipsilateral transpleural operation difficult or impossible. In lung cancer patients, major airway obstruction may preclude single-lung anesthesia and, thus, thoracoscopic pericardiectomy. Prior median sternotomy may prohibit the use of a subxiphoid approach.

Complications A 30-day mortality rate of 10% or higher has been reported for all of these modalities but is related more to the gravity of the underlying tumor and its sequelae. A small percentage of patients will develop severe problems with pulmonary edema or cardiogenic shock following pericardial decompression. The mechanisms of these problems are poorly understood. Late neoplastic pericardial constriction can occur following initially successful partial pericardiectomy.

Radiotherapy

External-beam irradiation is utilized infrequently in this clinical setting but may be an important option in specialized circumstances, especially in patients with radiosensitive tumors who have not received prior radiation therapy. Responses ranging from 66% to 93% have been reported with this form of treatment, depending on the type of associated tumor.

Systemic therapy

Chemotherapy Systemic chemotherapy is effective in treating pericardial effusions in patients with lymphomas, hematologic malignancies, or breast cancer. Long-term survival can be attained in these patients. If the pericardial effusion is small and/or asymptomatic, invasive treatment may be omitted in some of these cases. Data regarding the effectiveness of systemic chemotherapy or chemotherapy delivered locally in prevention of recurrent pericardial and pleural effusion are quite limited. New studies in this area are badly needed.

Biological therapy with various agents is in the early stages of investigation.

MALIGNANT ASCITES

Malignant ascites results when there is an imbalance in the secretion of proteins and cells into the peritoneal cavity and absorption of fluids via the lym-

phatic system. Greater capillary permeability as a result of the release of cytokines by malignant cells increases the protein concentration in the peritoneal fluid. Recently, several studies have demonstrated higher levels of VEGF ([vascular endothelial growth factor], a cytokine known to cause capillary leak) in the sera and effusions of patients with malignancies.

Signs and symptoms

Patients with malignant ascites usually present with anorexia, nausea, respiratory compromise, and immobility. Complaints of abdominal bloating, heaviness, and ill-fitting clothes are common. Weight gain despite muscle wasting is a prominent sign.

Diagnosis

A malignant etiology accounts for only 10% of all cases of ascites. Nonmalignant diseases causing ascites include liver failure, congestive heart failure, and occlusion of the inferior vena cava or hepatic vein. About one-third of all patients with malignancies will develop ascites. Malignant ascites has been described with many tumor types but is most commonly seen with gynecologic neoplasms (~50%), GI malignancies (20%-25%), and breast cancer (10%-18%). In 15%-30% of patients, the ascites is associated with diffuse carcinomatosis of the peritoneal cavity.

Physical examination does not distinguish whether ascites is due to malignant or benign conditions. Patients may have abdominal fullness with fluid wave, anterior distribution of the normal abdominal tympany, and pedal edema. Occasionally, the hepatic metastases or tumor nodules studding the peritoneal surface can be palpated through the abdominal wall, which has been altered by ascitic distention.

RADIOLOGIC STUDIES

Radiographs Ascites can be inferred from plain radiographs of the abdomen. Signs include a ground-glass pattern and centralization of the intestines and abdominal contents.

Ultrasonography Abdominal ultrasonography has been shown to be the most sensitive, most specific method for detecting and quantifying ascites. It also permits delineation of areas of loculation.

CT Abdominal CT is effective in detecting ascites. In addition, CT scans may demonstrate masses, mesenteric stranding, omental studding, and diffuse carcinomatosis. Intravenous and oral contrasts are necessary, thus increasing the degree of invasiveness of this modality.

The mRNA expression level of four different tumor rejection genes (BAGE, GAGE, MAGE-1, and MAGE-3) was studied in 44 ascites specimens, 27 from patients with ovarian cancer and 17 from patients with non-neoplastic diseases. The sensitivity and specificity of detecting malignant ascites using this profile of gene expression are 94% and 94%, respectively. The positive predictive value was 96% and the negative predictive value was 89% *(Hofman M, Ruschenburg I: Cancer [Cancer Cytopathol] 96:187-193, 2002).*

Paracentesis After the diagnosis of peritoneal ascites has been made on the basis of the physical examination and imaging, paracentesis should be performed to characterize the fluid. The color and nature of the fluid often suggest the diagnosis. Malignant ascites can be bloody, opaque, chylous, or serous. Benign ascites is usually serous and clear.

Analysis of the fluid should include cell count, cytology, LDH, proteins, and appropriate evaluation for infectious etiologies. In addition, the fluid can be sent for the determination of tumor markers, such as CEA, CA-125, and P-53, and human chorionic gonadotropin-β (hCG-β). The hCG-β level is frequently elevated in malignancy-related ascites and has been combined with cytology to yield an 89.5% efficiency in diagnosis. The use of DNA ploidy indices allowed 98.5% sensitivity and 100% sensitivity in the identification of malignant cells within ascitic fluid.

Laparoscopy Several studies have utilized minimally invasive laparoscopy as the diagnostic tool of choice. The fluid can be drained under direct visualization, the peritoneal cavity can be evaluated carefully, and any suspicious masses can be biopsied at the time of the laparoscopy.

Prognosis

The presence of ascites in a patient with malignancy often portends end-stage disease. Median survival after the diagnosis of malignant ascites ranges from 7 to 13 weeks. Patients with gynecologic and breast malignancies have a better overall prognosis than patients with GI malignancies.

Treatment

The primary goal of treatment is the palliation of symptoms. Management can be divided into medical and surgical modalities.

Medical therapy

Traditionally, the first line of treatment is medical management. Medical therapies include repeated paracentesis, fluid restriction, diuretics, chemotherapy, and intraperitoneal sclerosis.

Repeated paracentesis, probably the most frequently employed treatment modality, provides significant symptomatic relief in the majority of cases. The procedure is minimally invasive and can be combined with abdominal ultrasonography to better localize fluid collections. High-volume paracentesis has been performed without inducing significant hemodynamic instability and with good patient tolerance.

Significant morbidity occurs with repeated taps and becomes more severe with each tap necessary to alleviate symptoms. Ascitic fluid contains a high concentration of proteins. Routine removal of ascites further depletes protein stores. The removal of large volumes of fluid also can result in electrolyte abnormalities and hypovolemia. In addition, complications can result from the proce-

dure itself. They include hemorrhage, injury to intra-abdominal structures, peritonitis, and bowel obstruction.

With the placement of an intraperitoneal port, used also for the instillation of intraperitoneal chemotherapy, removal of ascitic fluid is possible without the need for repeated paracentesis.

Contraindications to repeated paracentesis are viscous loculated fluid and hemorrhagic fluid.

Diuretics, fluid and salt restriction Unlike ascites from benign causes such as cirrhosis and congestive heart failure, malignant ascites responds poorly to fluid restriction, decreased salt intake, and diuretic therapy. The most commonly used diuretics (in patients who may have some response to diuretic treatment) are spironolactone (Aldactone) and amiloride (Midamor). Patients with massive hepatic metastases are most likely to benefit from spironolactone.

A novel approach was recently reported using the bispecific antibody HEA125xOKT3, which redirects T cells to carcinoma cells and also increases tumor cell lysis. The antibody was injected weekly into the peritoneum of 10 ovarian cancer patients with malignant ascites. All 10 responded to the treatment: 8 patients with complete resolution of ascites and 2 patients with decreased ascites. In addition, 8 of the 10 patients also had a decreased serum CA-125 level *(Marme A, Strauss G, Bastert G, et al: Int J Cancer 101:183-189, 2002).*

Starting doses are 100-150 mg tid for spironolactone and 5 mg qd for amiloride. The onset of action for spironolactone is delayed (3-4 days), whereas the effects of amiloride are seen after 24 hours. The most common complications associated with these diuretics are painful gynecomastia, renal tubular acidosis, and hyperkalemia.

Chemotherapy, both systemic and intraperitoneal, has had some success in the treatment of malignant ascites. The most commonly used agents are cisplatin (Platinol) and mitomycin (Mutamycin). Intraperitoneal hyperthermic chemotherapy has been used with some efficacy in GI malignancies to decrease recurrence of ascites, as well as to prevent the formation of ascites in patients with peritoneal carcinomatosis.

The safety and efficacy of systemic 5-FU followed by methotrexate were studied in a phase II trial in advanced gastric cancer patients with ascites. The authors report that in 37 patients, 35% had an objective response with decreased ascites and 11% had a complete response with resolution of ascites. The median survival was 155 days *(Muro K, Shirao K, Shimada Y, et al: Proc Am Soc Clin Oncol [abstract] 20:132b, 2001).*

Sclerotherapy Sclerosing agents include bleomycin (60 mg/50 mL of normal saline), tetracycline (500 mg/50 mL of normal saline), and talc (5 g/50 mL of normal saline). Responses are seen in ~30% of patients treated with these agents.

Theoretically, intraperitoneal chemotherapy and sclerosis obliterate the peritoneal space and prevent future fluid accumulation. If sclerosis is unsuccessful, it may produce loculations and make subsequent paracentesis difficult.

Other systemic therapies There are several reports of the use of gold-198 or phosphorus-32 in patients with peritoneal effusions, with response rates of 30%-

50%. Experimental models and early clinical trials have shown that an intraperitoneal bolus of tumor necrosis factor (45-350 $\mu g/m^2$) given weekly may be effective in resolving malignant ascites.

Surgery

Limited surgical options are available to treat patients who have refractory ascites after maximal medical management, demonstrate significant decrease in quality of life as a result of ascites, and have a life expectancy of >3 months.

Peritoneovenous shunts have been used since 1974 for the relief of ascites associated with benign conditions. In the 1980s, shunting was applied to the treatment of malignant ascites.

The LeVeen shunt contains a disc valve in a firm polypropylene casing, whereas the Denver shunt has a valve that lies within a fluid-filled, compressible silicone chamber. Both valves provide a connection between the peritoneal cavity and venous system that permits the free flow of fluid from the peritoneal cavity when a 2- to 4-cm water pressure gradient exists.

Success rates vary with shunting, depending on the nature of the ascites and the pathology of the primary tumor. Patients with ovarian cancer, for example, do very well, with palliation achieved in $\geq 50\%$ of cases. However, GI malignancies are associated with a poorer response rate of 10%-15%.

Patient selection Candidates for shunt placement should be carefully selected. Cardiac and respiratory evaluations should be performed prior to the procedure. Shunt placement is *contraindicated* in the presence of the following:

- a moribund patient whose death is anticipated within weeks
- peritonitis
- major organ failure
- adhesive loculation
- thick, tenacious fluid

Complications of shunting Initial concerns about the use of a shunt in the treatment of malignant ascites centered around intravascular propagation of tumor. In practice, there has been little difference in overall mortality in patients with and without shunts.

Disseminated intravascular coagulation During the early experience with shunting, particularly in cirrhotic patients, symptomatic clinical disseminated intravascular coagulation (DIC) developed rapidly and was a major source of morbidity and mortality. However, this complication occurs infrequently in the oncologic population.

The pathophysiology of DIC has been studied extensively and is thought to be multifactorial. The reinfusion of large volumes of ascitic fluid may cause a deficiency in endogenous circulating coagulation factors by dilution. Secondarily, a fibrinolytic state is initiated by the introduction of soluble collagen (contained within the ascitic fluid) into the bloodstream, leading to a DIC state. Infrequently, full-blown DIC results and requires ligation or shunt removal.

Discarding 50%-70% of the ascitic fluid before establishing the peritoneovenous connection may prevent this complication.

Commonly, coagulation parameters are abnormal without signs or symptoms. In some institutions, these laboratory values are so consistently abnormal that they are used to monitor shunt patency. Abnormalities most commonly seen include decreased platelets and fibrinogen and elevated prothrombin time, partial thromboplastin time, and fibrin split products.

Other common complications include shunt occlusion (10%-20%), heart failure (6%), ascitic leak from the insertion site (4%), infection (< 5%), and perioperative death (10%-20% when all operative candidates are included).

Shunt patency may be associated with the presence of malignant cells. One study found that patients with positive cytology had a 26-day shunt survival, as compared with 140 days in patients with negative cytology. Other studies have failed to demonstrate a correlation between ascites with malignant cells and decreased survival.

Clearly, shunting is not a benign procedure, but in carefully selected patients who have not responded to other treatment modalities and who are experiencing symptoms from ascites, it may provide needed palliation. Because of the limited effectiveness of peritoneovenous shunts, patients should be carefully selected prior to placement.

Radical peritonectomy Other surgical procedures used to treat malignant ascites have been proposed. They include radical peritonectomy combined with intraperitoneal chemotherapy. This is an extensive operation with significant morbidity, although initial results appear to demonstrate that it decreases ascites production. To date, no randomized trial has demonstrated that radical peritonectomy increases efficacy or survival.

SUGGESTED READING

ON MALIGNANT PLEURAL EFFUSION

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APPENDIX I

Performance scales

Karnofsky performance index

Definition		
Able to carry on normal activity and to work	100	Normal; no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home, care for most personal needs; a varying amount of assistance is needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance, but is able to care for most of his needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospitalization is indicated although death not imminent
	20	Very sick; hospitalization necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

From Karnofsky DA, Abelmann WH, Craver LF, et al: The use of the nitrogen mustards in the palliative treatment of carcinoma. Cancer 1:634–656, 1948.

The Karnofsky performance index and WHO (Zubrod) scale (on the following page) are included here because they are commonly used as proxy measures for quality of life. Because they measure only one dimension of the construct, they would not be considered quality-of-life measures by today's standards. However, given their historical relevance and current high frequency of usage as proxy measures, we have included them here.

WHO (Zubrod) scale

This scale is used to measure performance of which the patient is *capable.* For example, a patient in the hospital for metabolic studies may be fully capable of performing normal activities, but will remain in bed through his or her own choice. Such a patient should be coded 0, "normal."

0	Normal activity
1	Symptoms, but nearly fully ambulatory
2	Some bed time, but needs to be in bed < 50% of normal daytime
3	Needs to be in bed > 50% of normal daytime
4	Unable to get out of bed

From Zubrod CG, Schneiderman M, Frei E III, et al: Appraisal of methods for the study of chemotherapy of cancer in man: Comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. J Chron Dis 11:7–33, 1960.

APPENDIX 2

Internet resources for information on cancer

The World Wide Web has become an almost-indispensible electronic forum for finding the latest information on cancer diagnosis, treatment, and prevention. The following discussion highlights a few of those websites that cater to the needs of oncology professionals and researchers.

Cancer.gov, the National Cancer Institute's website

One of the most comprehensive websites for evidence-based cancer information is supported and maintained by the National Cancer Institute (NCI). The site provides a wide variety of resources to help meet the user's informational needs, including summaries on cancer treatment, prevention, and supportive care, as well as information on ongoing clinical trials, a bibliographic cancer database, funding opportunities, research programs, and cancer incidence and mortality data.

The NCI's vast website provides information suitable to clinical practitioners, researchers, patients, and the general public. Among the cancer resources available from the home page (http://cancer.gov) are:

- peer-reviewed, frequently updated summaries on cancer treatment, screening, prevention, genetics, and supportive care (http://cancer.gov/cancerinfo/pdq/);
- a registry of approximately 1,800 open and 12,000 closed international cancer clinical trials, plus resources and information for clinical investigators and patients (http://cancer.gov/clinicaltrials/);
- a comprehensive database of NCI-supported basic and clinical research programs (http://researchportfolio.cancer.gov/);
- a directory of NCI research tools and resources (human, animal, and genomic) for cancer researchers (http://resresources.nci.nih.gov/);
- statistical databases and resources, including cancer incidence by gender, race, ethnicity, and type of cancer; 5-year survival rates; frequencies of childhood cancers; and cancer mortality in the United States by gender and race (http://cancer.gov/statistics/); and
- CANCERLIT, a database of more than 1.8 million citations and abstracts from over 4,000 different sources, including biomedical journals, proceedings from scientific meetings, books, reports, and doctoral theses (www.nci.nih.gov/search/cancer_literature/).

PubMed

PubMed (http://pubmed.gov/), a service of the National Library of Medicine, provides access to over 12 million MEDLINE citations in abstract form dating back to the mid-1960s. New features at PubMed are icons that alert researchers to whether the full text of a MEDLINE citation is available and a growing list of biomedical books that can be read and searched online, including the fifth edition of Holland and Frei's *Cancer Medicine.*

Cancer Information Service (CIS)

CIS is a nationwide network of 14 regional offices supported by the NCI. Through its toll-free phone service, CIS provides accurate, up-to-date information on cancer to the public. The phone number is 1-800-4-CANCER. The service responds to calls in English and Spanish.

Reliable information on cancer causes and prevention and a collection of recently issued *NCI Cancer Facts* fact sheets and the new *What You Need To Know About*™ series of patient guides are also available online by following links from the CIS home page (http://cis.nci.nih.gov/).

Cancer.org, the American Cancer Society website

This large, complex website is most easily searched by specifying key words, such as "breast cancer" or "survival rates," in the search form on the home page (www.cancer.org). Most of the information available is intended for patients, especially those who have been newly diagnosed with cancer, and the general public, with several notable exceptions.

One of them is the American Cancer Society publication *Cancer Facts & Figures 2003,* available online in Adobe Acrobat format at http://www.cancer.org/docroot/STT/STT_0.asp. Estimates of the numbers of new cancer cases and deaths for the current year are presented according to gender, site, and stage. Also presented is information on cancer mortality, the probability of developing cancer at certain ages, and cancer survival in adults and children.

Surveillance, Epidemiology, and End Results (SEER)

The NCI's SEER program collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 14% of the US population. Trends in age-adjusted SEER cancer incidence and mortality, by race and gender, are presented, as well as 5-year survival rates, by race and gender, and much more. The home page is http://seer.cancer.gov/.

Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention (CDC) maintains several websites for both health professionals and researchers, as well as the public.

Links to CDC statistical reports and online databases are available in the "data warehouse" section of the National Center for Health Statistics website (www.cdc.gov/nchs/datawh.htm). Information on CDC cancer prevention pro-

grams may be accessed at the National Center for Chronic Disease Prevention and Health Promotion's website (www.cdc.gov/nccdphp/).

CancerNetwork.com

Another excellent source of reliable cancer information is CancerNetwork.com (www.cancernetwork.com). The site features:

- the full text of over 6,000 peer-reviewed medical journal articles from the pages of *ONCOLOGY* and *Oncology News International;*
- the full text of this handbook;
- the complete proceedings of over 80 cancer symposia, conferences, and workshops, held around the world and focusing on new treatments;
- free continuing medical education courses on a variety of cancers;
- MEDLINE access through an advanced search form that makes it easy to locate abstracts by date, author, and type of publication;
- a comprehensive drug-reference guide to more than 150 pharmaceuticals used to treat cancer and its complications; and
- a *Genetics of Cancer* resource center, offering both basic and clinical genetics information on a health-professional level.

Oncology Tools

Developed by the US Food and Drug Administration's Center for Drug Evaluation and Research (CDER), Oncology Tools provides direct access to such FDA documents as cancer drug labeling, approval summaries, and advisory committee transcripts. Specialized information is also available for health-care professionals and others, including cancer-related regulatory tools, references for performing clinical studies, and drug-dose calculators. The website, located at www.fda.gov/cder/cancer/, can be searched by specific types of cancer and by approved drug therapies.

CenterWatch

CenterWatch (www.centerwatch.com) offers a worldwide directory of clinical trials in all therapeutic areas. Each listing contains a brief summary of the study, the general inclusion/exclusion criteria, and contact information. The database is easily searched, even by a newcomer, and the website has become a major influence for patient recruitment into active clinical trials.

Coalition of National Cancer Cooperative Groups

The Coalition of National Cancer Cooperative Groups was founded in 1997 by the Cancer and Leukemia Group B (CALGB), Eastern Cooperative Oncology Group (ECOG), North Central Cancer Treatment Group (NCCTG), National Surgical Adjuvant Breast and Bowel Project (NSABP), Pediatric Oncology Group (POG), and Radiation Therapy Oncology Group (RTOG). The coalition's website (http://www.cancertrialshelp.org/medicalCommunity/

medicalCommunity.jsp) provides details on the coalition's initiatives in many areas and features a new software tool, TrialCheck℠, for locating ongoing clinical trials among the coalition's cooperative groups.

Other Web sources of cancer information

- OncoLink (www.oncolink.com) is a popular website maintained by the University of Pennsylvania, offering a broad variety of news articles, fact sheets, and annotated links to cancer-related information at other websites. The site includes multimedia slide shows, video films, and audio lectures on a wide range of topics.
- The American Society of Clinical Oncology's (ASCO) website, located at www.asco.org, contains cancer information for patients, including information on treatment, support groups, and other resources. Health professionals can access information on ASCO policies, clinical guidelines, publications, and a searchable database of abstracts from ASCO's annual scientific meetings dating back to 1995.
- An exhaustive collection of articles and reviews on hematologic malignancies, mostly in Adobe Acrobat format and all intended for a professional audience, may be found at the American Society of Hematology's (ASH) website (www.hematology.org). The site also offers a direct link to the Society's official journal, *Blood,* where the full text of all articles dating back to January 1996 can be downloaded and printed.
- The National Comprehensive Cancer Network's (NCCN) website, at www.nccn.org, provides access to the NCCN's current Clinical Practice Guidelines, links to ongoing clinical trials at member institutions, and a physician directory for referrals.
- Other cancer society and organization websites worth visiting include those of the American Association for Cancer Research (www.aacr.org), the Leukemia & Lymphoma Society (www.leukemia-lymphoma.org), the American College of Radiology (www.acr.org), the American Urological Association (www.auanet.org), and the Oncology Nursing Society (www.ons.org). Among European sites, the sites maintained by the International Union Against Cancer (www.uicc.org), CancerBACUP (www.cancerbacup.org.uk), and the European Organization for Research and Treatment of Cancer (http://www.eortc.be/) are extensive, information-rich resources designed primarily for health professionals.
- Links to the Web pages of state and other regional cancer registries may be found at www.askcnet.org/dataq/cancer.htm. This site also includes links to cancer registries around the world, but perhaps a better source for them is at www.ikr.nl/canregs.htm. Still another place to look for cancer registries and statistical data in the United States and Canada is the website maintained by the North American Association of Central Cancer Registries (www.naaccr.org).