

CHAPTER 15 ■ PRIMARY ANTICANCER TREATMENTS

There is no national cancer care program or system of care in the United States. Efforts to diagnose cancer and coordinate care are left to individual physicians, health plans, and cancer care centers. Health care concerns are magnified with a cancer diagnosis because of the nature of the disease, the complexity of management, the frequent reliance upon new and experimental interventions, and the high costs of care. The continuum of care spans prevention, early detection and screening, diagnosis and treatment of new cases, care of survivors, palliative care, and finally, support for terminally ill patients and their families.

Upon diagnosis of cancer, patients and their families have to cope not only with the diagnosis and an uncertain outcome but also with unfamiliar procedures and the presentation of treatment options. Patients are often asked to make choices between different therapeutic options, and many wish to be involved in the decision-making process of their care. Detailed information on treatment options has a number of beneficial effects, including the ability of the patient to gain control, to reduce anxiety, to improve compliance, to create realistic expectations, to promote self-care and participation, and to generate feelings of safety and security. Increasingly, patients are health consumers and want to be active participants in medical decision-making. As communities have become better educated and information about health care has become more accessible, a fundamental shift in society's expectations of clinicians has occurred. There is increased accountability of clinicians to standardize medical care according to best medical practices and to improve health care outcome. The quality of information available to patients on health care treatment options has improved, particularly with access to the internet, and with pressure from various consumer advocacy groups, patients now more frequently participate in treatment decisions. For example, the decision making regarding early-stage breast cancer is complex, and the decision-making process is problematic for many patients, especially minority patients.¹ Katz et al.² examined the relationship between patient involvement in decision making and type of surgical treatment for women with breast cancer. The authors surveyed a population-based sample of women diagnosed in 2002 with early-stage breast cancer from Detroit and Los Angeles, which are two areas that have previously demonstrated differing practice patterns with respect to breast-conserving surgery. Among these women, approximately 70% underwent breast conserving surgery, and 30% received mastectomy. Thirty-seven percent of the women perceived the surgeon to recommend neither surgical procedure over the other. However, when a specific recommendation was perceived by women, breast-conserving

surgery was reported as being recommended by the surgeon more often (49% of women) than mastectomy (15% of women). Almost 80% of the women reported making their own decision or sharing the decision with their surgeon. Greater patient involvement in decision-making was associated with greater use of mastectomy rather than greater use of breast-conserving surgery.

There are often many therapeutic options for treating different cancers. Traditionally, most cancers have been treated with surgery, radiation, chemotherapy, or some combination of the three. Surgery is the mainstay of treatment for solid tumors (ie, most cancers except lymphoma or leukemia). For most nonmetastatic cancers, and locally confined tumors, surgery can be curative. Radiation is the primary treatment for some cancers (notably Hodgkin disease and other lymphomas), but is most often used in conjunction with surgery. Chemotherapy (including hormone therapy) may be used alone to treat some cancers (lymphomas or leukemia) but it is used more often in combination with surgery and radiation. In many cases, patients begin a protracted course of chemotherapy after surgery. Surgery and radiation therapy generally attempt to cure localized malignancies, whereas chemotherapy treats disseminated neoplasms. Recently, the advantages of combined therapy have become evident, and an increasing number of patients receive combinations of these three therapeutic approaches.³ The rationale for such combination therapy comes from observations that surgery is most likely to fail locally at the edges of tumor resection (*positive surgical margins*), radiation therapy is most likely to fail in the center of tumors, and chemotherapy is most likely to fail in the presence of bulk disease.

Other types of treatments use the body's own immune system to resist disease. Biologic response modifiers modeled on the body's own natural products (eg, interferon, the interleukins, and tumor necrosis factor) are commonly used in conjunction with other treatments. Much of cancer treatment involves managing cancer symptoms such as pain or the effects of treatment. Some effects of treatment are short-lived (eg, nausea or hair loss) but others may be permanent (eg, infertility). Frequently, cancer patients also consider complementary or alternative options to conventional treatment. However, the majority of patients use complementary and alternative medicine to supplement their cancer treatment or help them cope with the treatment and/or its side effects. The more popular therapies appear to be dietary treatments, herbalism, homeopathy, hypnotherapy, and imagery/visualization.⁴ A European study indicated that 36% of cancer patients reported using some form of complementary therapy,⁴ and most U.S. studies report a higher use, often above 40%.⁵⁻⁶ This form of treatment is discussed further in "Complementary

and Alternative Treatment.” The more traditional primary treatments of radiation therapy, chemotherapy and biotherapy, and surgery are discussed further.

RADIATION THERAPY

Radiation therapy is the most widely and frequently used treatment for cancer⁷ and is primarily delivered utilizing three different modalities: external beam radiation therapy (EBRT), brachytherapy, or radioimmunotherapy. EBRT delivered via a linear accelerator is the most commonly used therapeutic radiation. Radiation is produced in the form of high-energy x-rays by a device that uses high-frequency electromagnetic waves to accelerate charged particles, such as photons and electrons, through a linear tube. Linear accelerators have the ability to treat with shallow depth penetration (electrons) or deep depth penetration (photons). Research suggests that DNA is the target of the cytotoxic effects of radiation.⁸ The unit of radiation is the Gray (Gy), which is equal to 100 rads. EBRT can be administered with high-energy photons or electrons. Dosage is specified by the number of Grays for a number of fractions, eg, 3 Gy for ten fractions. Radiation tolerance is inversely proportional to the daily radiation dose and volume irradiated. Conformal and intensity modulated radiation therapies (IMRTs) are newer external techniques that improve the ability to localize the radiation dose and minimize side effects in adjacent normal tissue. Conformal therapy localizes the radiation dose with multiple fields and can be adapted to targets with irregular contours. IMRT is a refinement of conformal therapy whereby different doses of radiation are delivered to different areas in the same radiation fraction. Intraoperative radiation therapy (IORT) is the delivery of irradiation at the time of surgery and is performed by different techniques, including intraoperative electron beam techniques and high-dose-rate brachytherapy. IORT is usually given in combination with EBRT with or without chemotherapy and surgical resection. The addition of IORT to conventional treatment methods has improved local control as well as survival in many disease sites in both the primary and locally recurrent disease settings.

Brachytherapy involves the temporary or permanent placement of selected radioactive sources directly into a body cavity (intracavitary), into tissue (interstitial), into a passageway (intraluminal), or onto a tissue surface (plaque) (Fig 15.1). Brachytherapy delivers a prescribed treatment dose to a specified tumor volume with a rapid fall-off in radiation dose to adjacent normal tissues. High- or low-dose-rate brachytherapy can be used to treat a number of malignancies, including gynecologic, breast, lung, esophageal, and head and neck cancers, brain and prostate tumors, choroidal melanoma, and others. Brachytherapy can be used as primary treatment or in combination with EBRT to cure or palliate malignancies. By irradiating a small volume of tissue, complications are minimized and organ function can be preserved. Brachytherapy is most often performed using reactor-produced radionuclides such as cesium-137, iridium-192, iodine-125, palladium-103, and gold-198.

With palliative radiation, shorter EBRT schedules that include administering a higher radiation dose with each radiation fraction are generally used. This is called

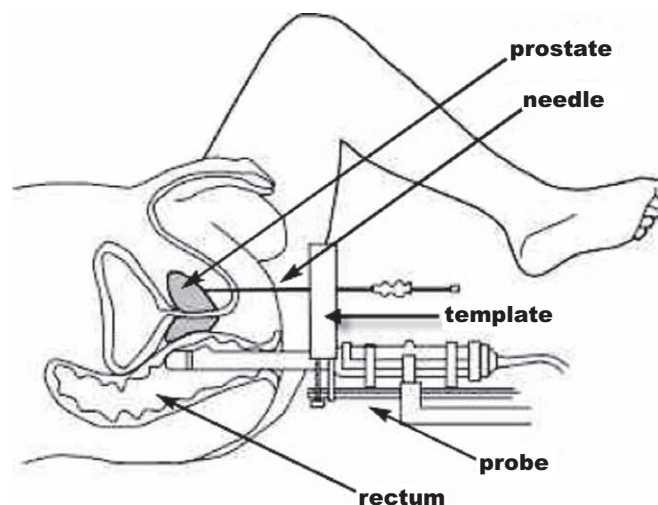


FIGURE 15.1 Prostate brachytherapy. An ultrasound probe is placed in the rectum for needle placement. The template is used to aid accurate placement of the needles delivering the seeds.

hypofractionation. It is believed that relief can occur more rapidly due to greater tumor cell kill per fraction. Furthermore, as patient survival is generally shorter, there is less concern about late-onset tissue toxicity. Longer courses with smaller fractions provide more durable pain relief due to larger absolute numbers of tumor cell kill without the increased risk of increased normal tissue toxicity. Table 15.1 lists cancers commonly treated by conventional radiation.

Radiosurgery is an EBRT technique that uses multiple convergent beams to deliver a high single dose of radiation to a small volume. In radiosurgery, multiple, highly collimated beams of radiation are stereotactically directed toward a radiographically discrete treatment site. The hallmark of all stereotactic radiation techniques is the rapid dose fall-off at the target edges. The most common use is for intracranial lesions, in which a stereotactic frame is applied to the head; high-resolution neurodiagnostic imaging is performed to define the target; image-integrated three-dimensional (3D) dose planning is performed by high-speed computers; and an accurate and

TABLE 15.1

DISEASES COMMONLY TREATED BY PRIMARY RADIATION THERAPY

Hodgkin disease
Non-Hodgkin lymphoma
Cervical carcinoma (stage dependent)
Prostate carcinoma (stage dependent)
Head and neck cancers
Breast cancer (stage dependent)
Multiple metastatic tumors of the central nervous system
Retinoblastoma
Choroidal melanoma
Unresectable lung carcinoma
Unresectable pancreatic carcinoma
Unresectable sarcoma

dependable technology is used to deliver photon energy to the target volume to achieve the desired clinical effect.

Radiosurgery is currently performed with one of two types of high-energy radiation technologies: x-rays, produced by linear accelerators, and the Gamma Knife, producing γ rays. Radiosurgery is used to treat malignant tumors, such as selected cases of brain metastases and malignant gliomas (for which stereotactic radiosurgical boosts are used in conjunction with fractionated radiation therapy), as well as benign tumors (eg, meningiomas, acoustic neuromas, and pituitary adenomas). It has become an important treatment alternative to surgery for a variety of intracranial lesions.

Linear accelerator-based stereotactic radiosurgery techniques have traditionally been used to treat central nervous system CNS tumors. The process combines stereotactic localization techniques, 3D planning imagery, and a sharply focused beam of radiation aimed at a specific, well-defined intracranial lesion. When treating intracranial CNS tumors, patients are positioned in a halo device used for immobilization or noninvasive system with image guidance, primarily to ensure accuracy and reproducibility of the treatment set-up. The CyberKnife is a compact 6-MV linear accelerator (LINAC) that is

mounted on a computer-controlled robotic arm and can deliver multiple, nonisocentric, noncoplanar radiation beams. It is essentially a robotic, frameless, image-guided stereotactic radiosurgery system (Fig 15.2). By using bone landmarks or implanted fiducial markers, stereotactic radiosurgery has been used to treat lesions of the spine, pancreas, prostate, and lung. Because this type of radiosurgery does not require the application of a head frame, staged radiosurgery (ie, fractionation) is feasible. Two standard diagnostic x-ray tubes are rigidly fixed to the CyberKnife treatment room and are set up so that two orthogonal (90-degree offset) images of the target can be obtained. The images are gathered using two amorphous silicon x-ray screens capable of generating high-resolution digital images. For initial coarse alignment, identical features from anatomy are visually identified by the operator, and the position of the patient is adjusted by use of a five-axis support table. When the patient's position is adjusted so that the offset is less than 10 mm, the CyberKnife tracking system automatically compensates for alignment offset and patient motion by adjusting the location of the treatment "isocenter." In addition, tracking of the position of either a radiopaque (skeletal) target directly or of radiopaque fiducials with known

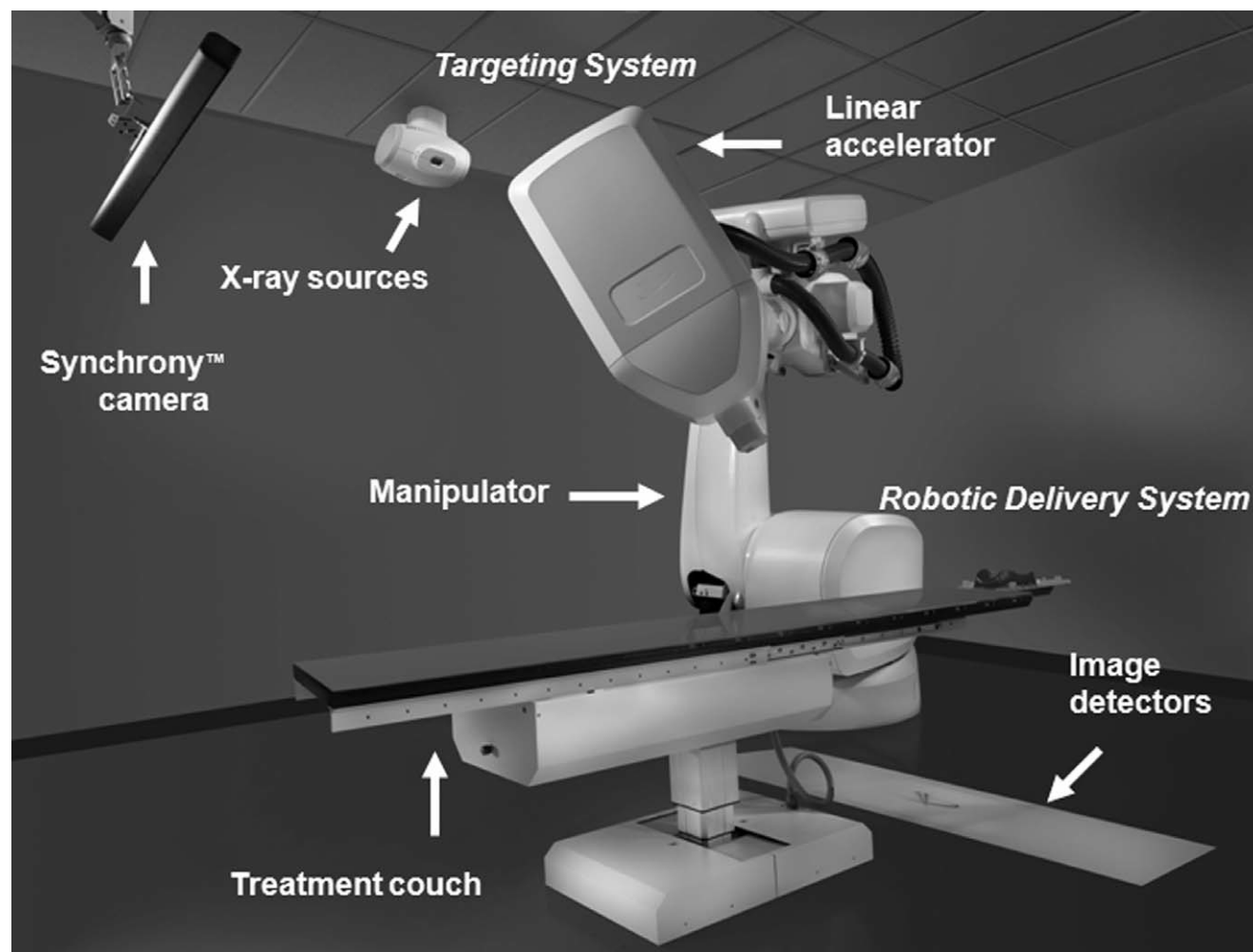


FIGURE 15.2 Cyberknife Robotic Radiosurgery system. The Synchrony camera incorporates fiber optic sensing technology that tracks respiratory motion so that intrathoracic lesions can be tracked accurately throughout treatment.

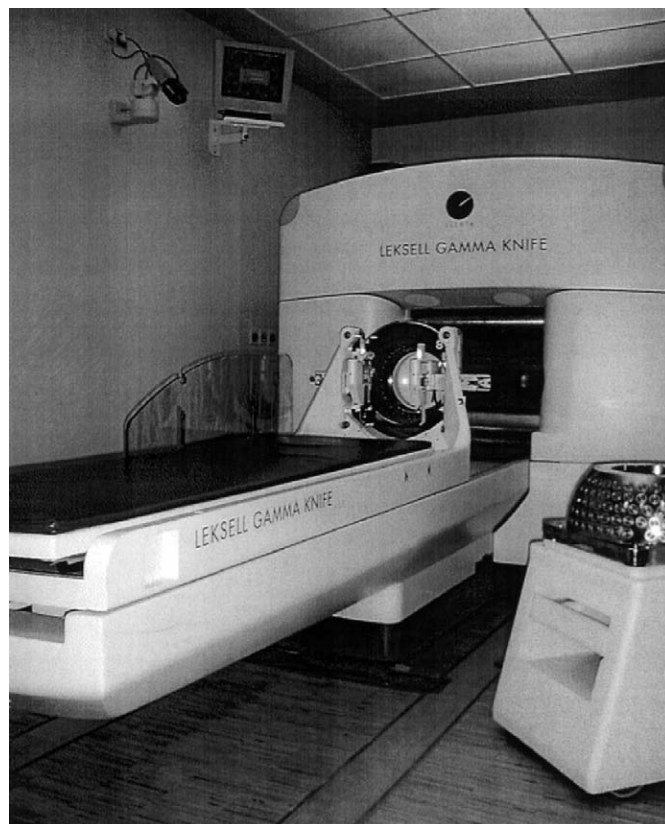


FIGURE 15.3 Gamma knife radiosurgery.

geometric distances from an x-ray radiolucent target can be performed.⁹

The Gamma Knife is a self-contained unit with 201 cobalt-60 sources arranged in a hemispheric array such that the emitted beams of radiation reach a common point of intersection (Fig 15.3). It was designed only to treat intracranial and skull base lesions. The overall time of radiation delivery varies depending on the prescribed dose, but it generally ranges from 15 to 45 minutes. The mechanical accuracy of radiation delivery with use of the Gamma Knife is less than 0.3 mm of variation, due to use of a stereotactic head frame.

High-quality radiation therapy can provide excellent local tumor control for either definitive treatment or palliation. The hallmark of good-quality radiation therapy is adequate tumor coverage while minimizing the risk of injury to normal tissue. This can be achieved by a team of physicians, physicists, nurses, dosimetrists, and therapists who can work as a team to deliver the correct dose to the tumor in the appropriate dose per fraction.

The role of radiation therapy in the management of painful conditions will be discussed further under “Radiation Strategies” in Chapter 21.

Complications of Radiation Therapy

Damage to normal tissues remains the most important limiting factor in the treatment of cancer by radiation therapy. Patients may experience symptoms associated with damage to normal tissue during the course of therapy for a few weeks after therapy or months or years later

TABLE 15.2

EARLY EFFECTS ASSOCIATED WITH RADIATION THERAPY

System	Effects
Hematological	Anemia, leucopenia, thrombocytopenia
Gastrointestinal	Gastritis, enteritis, proctitis, esophagitis, oral mucositis
Respiratory	Radiation pneumonitis
Urologic	Cystitis
Dermatologic	Erythema, pruritus, desquamation
Other (constitutional)	Fatigue

(Tables 15.2 and 15.3). Delayed progression of late effects for 20 to 34 years after therapy has been described.¹⁰ The pathological processes of radiation injury begin immediately after radiation exposure, but the clinical and histologic features may not become apparent for some time. Symptoms may be caused by cell death or wound healing initiated within irradiated tissue, and may be precipitated by exposure to further injury or trauma. Radiation injury is commonly classified as acute, consequential, or late effects, according to the time before appearance of symptoms. Acute (early) effects are those that are observed during the course of treatment or within a few weeks after treatment. Consequential effects (sometimes called consequential late effects) appear later, and are caused by persistent acute damage. Late effects emerge months to years after radiation exposure. Acute radiation damage is most prominent in tissues with rapidly proliferating cells, such as in epithelial surfaces of the skin or gastrointestinal tract. Symptoms develop when functional cells are lost as part of normal tissue turnover and are not replaced because of damage to the stem-cell compartment. Late effects may occur in tissues with a slow turnover of cells, such as subcutaneous tissue, fatty tissue, muscle, brain, kidney, and liver, and in sites of slow turnover within tissues that contain rapidly-proliferating cells, such as the wall of the intestine.

TABLE 15.3

LATE EFFECTS ASSOCIATED WITH RADIATION TREATMENT

System	Effects
Hematological	Myelofibrosis
Gastrointestinal	Mucosal stricture and fistula; xerostomia; loss of taste
Respiratory	Radiation pneumonitis
Urologic	Radiation nephritis, sterility
Dermatologic	Fibrosis, late ulceration, pigmentation
Musculoskeletal	Osteoradionecrosis (mandible, femoral head); muscle contractures
Neurologic	Plexopathy, myelitis, cognitive impairment
Other	Secondary tumors
Other (constitutional)	Fatigue

Significant musculoskeletal complications can result from radiation therapy and include muscle fibrosis and atrophy, fractures, and limb length discrepancy. Higher radiation doses (>60 Gy) can result in more pain and larger doses per fraction may lead to more muscle and soft tissue damage. Progression of injury may continue for as long as 10 years.¹¹ Hormone therapy, chemotherapy, radiation therapy, and castration all directly or indirectly damage bone and lead to loss of bone mass. Bone mineral density is usually measured by dual energy x-ray absorptiometry (DEXA) and this is considered the “gold standard” when performed at the femoral neck or total hip.¹² Bone densitometry results are often reported as t-scores, which represent the difference in the number of standard deviations (SD) between the individual’s bone mineral density (BMD) and the mean value for a group of young adults of the same sex. Normal bone mass is defined by the World Health Organization as BMD within 1 SD of young adult mean (t-score ≥ 1); osteopenia as increased bone loss, with bone mass between 1 and 2.5 SD below normal (t-score); and osteoporosis as bone mass >2.5 SD below normal (t-score >2.5).¹³ For every SD by which BMD is below peak bone mass, fracture risk approximately doubles.¹⁴

Xerostomia is a common side effect encountered by patients receiving radiation to the oral cavity because of the proximity to the salivary glands. It can be transient or permanent, depending on the radiation dose. Evidence shows that mean doses of less than 26 Gy to the parotid glands may avoid permanent xerostomia.¹⁵ Radiation mucositis (radiation-induced mucosal injury) usually occurs 2 to 4 weeks into treatment and abates 3 weeks to 2 months after the completion of radiation. Acute mucositis can be painful, and pain issues need to be addressed immediately to allow the patient to continue to eat. To minimize the chance of secondary infection, most radiation oncologists recommend baking soda mouthwash. If secondary infections (most often thrush) occur, appropriate antibiotic treatment is initiated. Topical anesthetic mouthwashes provide pain relief for 10 to 30 minutes and may help with eating. Many patients require narcotic analgesia for adequate pain control. Mucositis often causes significant swelling, which may be managed by nonsteroidal anti-inflammatory drugs (NSAIDs) or steroids. Usually, mucositis resolves 4 to 6 weeks after radiation is completed, but occasionally it can last for several months, necessitating close surveillance. Late complications of EBRT for base of tongue cancers include soft-tissue necrosis/ulceration, osteoradionecrosis (ORN), and xerostomia.¹⁶ The mandible is among the bones most frequently affected by irradiation. ORN of the mandible is a serious late complication of high-dose radiation therapy for tumors of the oropharynx and oral cavity. The diagnosis of ORN is principally based on the clinical picture of chronically exposed bone. Radiological symptoms include decreased bone density with fractures, cortical destruction, and loss of spongiosa trabeculation. Numerous factors that may be associated with the risk of ORN include treatment-related variables (for example, total radiotherapy dose, biologically effective dose, photon energy, brachytherapy dose rate, combination of external beam irradiation and interstitial brachytherapy, field size, fraction size, volume of the mandible irradiated with a high dose), patient-related variables (eg, deep parodontitis, preirradiation bone surgery, poor oral hygiene, alcohol and tobacco abuse,

bone inflammation, dental extraction after radiotherapy) and tumor-related factors (tumor size or stage, proximity of the tumor to bone, anatomic tumor site).¹⁷ Primary management of postradiation bone lesions include conservative modalities such as saline irrigations, antibiotics during infectious episodes, topically applied antiseptics, gentle sequestrectomy and removal of visibly loosened bone elements as well as treatment with hyperbaric oxygen. Surgery is reserved for persistent ORN and includes radical resection of the lesion (sequestrectomy, hemimandibulectomy, and so on) with reconstruction.

The risk of injury to the intestine is dose limiting during abdominal and pelvic radiation therapy. Delayed bowel toxicity is difficult to manage and adversely impacts the quality of life of cancer survivors. The rectum is the area most often affected by pelvic radiation for treatment of prostate and cervical cancer. The acute symptoms are diarrhea from loss of integrity of the epithelium and increased secretion of mucus. The most frequent but relatively uncommon late effects include increased stool frequency, urgency, spotting of blood, and partial incontinence. Much less common are ulceration, severe bleeding, pain, stricture, severe incontinence, and fistula. Treatments for rectal complications include: oral anti-inflammatory agents, pain management, stool softeners, intrarectal steroids, transfusions (for bleeding), and dilatation of strictures. For serious or refractory complications, hyperbaric oxygen or surgical intervention with temporary or permanent colostomy may be required. Hyperbaric oxygen therapy significantly improved the healing responses in patients with refractory radiation proctitis.¹⁸

Pelvic radiation causes chronic fibrosis and progressive endarteritis in poorly oxygenated bladder submucosal and muscular tissues, with eventual tissue scarring.¹⁹ This can lead to bladder mucosal sloughing and symptomatic hemorrhagic cystitis. Delayed radiation-induced hemorrhagic cystitis may appear more than ten years after pelvic radiotherapy. Traditional treatment methods include bladder irrigation, cauterization, oral or intravenous agents, intravesical chemical instillation, iliac artery embolization, urinary diversion, and cystectomy. However, no single treatment has resulted in satisfactory symptom control in most patients. Hyperbaric oxygen therapy may be a good primary option for the management of hemorrhagic cystitis.²⁰ One hundred forty-five (76%) of 190 reported patients demonstrated complete or partial symptomatic improvement with hyperbaric oxygen therapy, even among those who had failed multiple previous medical, cystoscopic, or intravesical therapies.²¹ Chong et al.¹⁹ reported that delivery of hyperbaric oxygen therapy within 6 months of the onset of hematuria was associated with an increased therapeutic response rate, even in patients with a history of clot retention. In patients with persistent pelvic radiation-induced toxicity (proctitis/cystitis, long-standing vaginal ulcers and fistulas, long-standing skin injuries), hyperbaric oxygen was both safe and effective.²²

CHEMOTHERAPY AND BIOTHERAPY

Chemotherapy consists of drugs that may be given with curative or palliative intent. Adjuvant therapy refers to additional treatment, usually given after surgery.

Adjuvant chemotherapy is given after surgery or radiation therapy in an attempt to prevent tumor recurrence. Its goal is to treat residual micrometastatic disease. Adjuvant chemoradiation is intended to prevent local or regional recurrence. It may be used in patients with positive surgical margins. Adjuvant chemotherapy reduces the rate of recurrence of some tumors, especially ovarian, breast, osteogenic sarcoma, colon cancer, and Wilms tumor. Neoadjuvant therapy, by contrast, is given before surgical resection and/or in addition to radiation therapy specifically for tumor reduction. The most common reason for neoadjuvant therapy is to reduce tumor size before surgical resection.

The majority of chemotherapy is delivered systemically, but regional therapy can also be used. The purpose of regional chemotherapy is to deliver higher concentrations of chemotherapy while minimizing systemic toxicity. Examples of regional administration include intraperitoneal and neuraxial. Chemotherapy is given neuraxially either by lumbar puncture or through an Ommaya reservoir attached to a ventricular catheter. Common intrathecal agents are methotrexate and cytarabine. Hepatic artery delivery of floxuridine (FUDR) via an implanted system in the treatment of colorectal liver metastases represents the largest application of hepatic artery therapy. Most trials have suggested an improvement in both overall and progression-free survival with hepatic artery infusion therapy.²³ Dose-limiting toxicity associated with hepatic artery infusion is related to hepatobiliary sclerosis, which has been reduced with the addition of dexamethasone as part of the treatment.

Chemotherapy for responsive tumors such as lymphoma, small-cell lung cancer, germ cell tumors, and possibly breast cancer may achieve pain relief. Chemotherapy regimens utilizing a combination of agents having different modes of action and exhibiting different forms of toxicity are more likely to cure than single-agent therapy. This is believed to be related to the low probability of double resistance to two drugs which is much less than the risk of single-drug resistance. Since the fraction of cells killed is proportional to the dose employed, maximally tolerated drug doses are indicated. The development of resistant tumor cell clones is related to single drugs, low doses, and long intervals between chemotherapy cycles. High-dose chemotherapy accompanied by autologous hematopoietic stem cell transplants is indicated for the treatment of high-grade non-Hodgkin lymphoma (relapsed) and acute myelocytic leukemia when an allogeneic donor is not available. Some have employed this approach for stage IV breast cancer in remission and to complete the adjunctive therapy of high-risk primary breast cancer.

Emerging evidence has suggested that the capability of a tumor to grow and propagate may be dependent on a small subset of cells within the tumor, termed *cancer stem cells*.²⁴ In an animal model, cancer stem cells have the capacity for unlimited self-renewal, as well as the ability to initiate and drive tumor progression. Thus, they would seem the most probable candidates responsible for tumor chemoresistance and recurrence. Before the recognition of cancer stem cells, cancer treatment was traditionally based on the assumption that human cancer cell populations were homogeneous. It was thought that resistance to treatment occurred because malignant cells survived chemotherapy and radiation or avoided immune surveil-

lance of endogenous cytotoxic T cells and natural killer cells.²⁵ The concept of cancer stem cells may have profound implications for our understanding of tumor biology and for the design of novel treatments targeted toward these cells. Current therapeutic strategies now include targeting the cancer stem cell.²⁵

Patients with metastatic solid tumors have typically been treated with palliative chemotherapy. However, there are situations where metastatic disease is potentially curable. Metastatic testicular cancer, gestational choriocarcinoma, Hodgkin disease, and high-grade lymphomas are potentially curable with chemotherapy.²⁶ A common feature of such curable tumors is that they arise from cells that undergo major genetic rearrangements or recombination as part of their normal physiology. The absence of further genetic and epigenetic changes in genes that regulate apoptosis, DNA repair, and senescence allows these cells to maintain their intrinsic sensitivity to chemotherapy. This process allows the cells, when challenged with chemotherapy, to undergo the natural apoptotic pathways that contribute to their intrinsic qualities of chemosensitivity and high curability.

Traditional chemotherapeutic agents are cytotoxic drugs that are either cell cycle-specific or cell cycle-nonspecific. Antimetabolites such as 5-fluorouracil (5-FU), gemcitabine, and methotrexate are more active on the S phase of the cell cycle. Vinca alkaloids and taxanes work on the M phase of the cell cycle. Cell cycle nonspecific agents such as the anthracyclines (doxorubicin, idarubicin) form free radicals that result in DNA strand breaks. However, these agents are known to have cumulative cardiotoxicity. The camptothecins (irinotecan, topotecan) inhibit topoisomerase I and cause single-strand DNA breaks. The platinumums (cisplatin, carboplatin, oxaliplatin) crosslink DNA and inhibit DNA synthesis and transcription. Of note, some agents such as 5-FU can exacerbate symptoms of systemic lupus erythematosus.²⁷⁻²⁸

With advances in molecular and cellular biology, anti-neoplastic therapy has become more refined. Imatinib (Gleevec) is a tyrosine kinase inhibitor that targets an oncogene and platelet derived growth factor. It has been used successfully in the treatment of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumor (GIST). Other tyrosine kinase inhibitors include erlotinib (Tarceva) which is used for lung and pancreas cancer, and sunitinib (Sutent) which is used for renal cell carcinoma and GIST. Bortezomib (Velcade), a proteasome inhibitor, is used for multiple myeloma.

Biotherapy utilizes biologicals and biologic response modifiers in the treatment of cancer. Tumors express a wide variety of proteins that can be recognized by the immune system. The immune system of the human organism comprises the innate system cells and the adaptive immune cells. The innate system includes hematopoietic cells, mast cells, basophils, monocytes, dendritic cells, and macrophages. Adaptive cells include CD4⁺ T cells, CD8⁺ T regulatory cells, and B cells. Biotherapy approaches to cancer treatment aim to protect and reactivate patients' adaptive immunity against tumor cells.²⁹ In healthy individuals there is a T helper 1 (Th1) and T helper 2 (Th2) balance, but during microbial-induced inflammation, pathogens induce an overproduction of Th2 cytokines that inhibit adaptive responses against a pathogen.³⁰ Tumor cells may induce increased Th2 cytokine levels that

TABLE 15.4

IMMUNE THERAPIES FOR CANCER

Established Therapies	Indication
Monoclonal Antibodies	
Rituximab (Rituxan)	Non-Hodgkin lymphoma, chronic lymphocytic leukemia
Ibritumomab tiuxetan (Zevalin)	Non-Hodgkin lymphoma
Tositumomab (Bexxar)	Non-Hodgkin lymphoma
Alemtuzumab (Campath)	Chronic lymphocytic leukemia
Gemtuzumab (Mylotarg)	Acute myelogenous leukemia
Trastuzumab (Herceptin)	Breast cancer
Cetuximab (Erbix)	Colorectal cancer
Panitumumab (Vectibix)	Colorectal cancer
Bevacizumab (Avastin)	Colorectal, lung
Immune Adjuvants	
Bacilli Calmette-Guerin	Superficial bladder cancer
Imiquimod (Aldara)	Basal cell carcinoma, vulvar intraepithelial neoplasia, actinic keratosis
Cytokines	
Interferon- α , interleukin-2	Melanoma, renal cell carcinoma
TNF- α	Soft-tissue sarcoma, melanoma
Supportive Therapy	
G(M)-CSF (filgrastim)	Myelosuppressive chemotherapy
Leucovorin	Methotrexate rescue
Prophylactic Immune Therapy	
Hepatitis B virus vaccine	Hepatocellular carcinoma
Human papillomavirus vaccine	Cervical cancer

(Adapted from Dougan M, Dranoff G. Immune therapy for cancer. *Annu Rev Immunol*. 2009;27:83-117.)

can serve as indicators for the existence of tumors.³¹ Polarized Th1 cells produce interleukin (IL)-2, IL-12, and interferon- γ . Polarized Th2 cells and hematopoietic cells produce IL-4, IL-5, IL-6, IL-10, and IL-13.²⁹

Established therapies employ a variety of manipulations to activate antitumor immunity including passive immunization with monoclonal antibodies, the introduction of adjuvants into the tumor microenvironment, and the systemic delivery of cytokines (Table 15.4).³² These various immunotherapeutic strategies include cytokines, therapeutic vaccines based on tumor cells or dendritic cells, monoclonal antibodies, and adoptive immunotherapy (T cell transfer or allogeneic hematopoietic cell transplantation). Biologic response modifiers have an established role in the treatment of certain cancers (eg, IL-2 in renal carcinoma, interferon as adjunctive therapy in melanoma, bacillus Calmette-Guérin [BCG] as local therapy for bladder tumors). The majority of biological agents in clinical use are cytokines. Examples of these agents include interferons, interleukins, hematopoietic growth factors, and tumor necrosis factor. Hematopoietic growth factors in use include granulocyte colony stimulating

factor (G-CSF or filgrastim) and granulocyte macrophage colony stimulating factor (GM-CSF or sargramostim), which stimulate the production of white blood cells. These agents facilitate host recovery from severe chemotherapy-induced myelosuppression, and permit an increase in the dose intensity of standard chemotherapeutic agents.

Monoclonal antibodies can be used as carriers to deliver drugs or toxins to tumor cells. Antibody structures are manipulated to facilitate selective interaction with host immune effectors. Monoclonal antibodies targeting non-Hodgkin lymphoma, *HER-2/neu* highly expressing metastatic breast cancer, colorectal cancer, acute myelogenous leukemia, and B-cell chronic lymphocytic leukemia are currently in use. For example, rituximab (Rituxan) is used in the treatment of non-Hodgkin lymphoma and trastuzumab (Herceptin) for metastatic breast cancer whose tumors express *HER-2*. There is also interest in the use of vaccines as active-specific immunotherapy for cancer treatment. Human papillomavirus vaccine is used as a prophylactic cervical cancer vaccine. Many strategies for generating therapeutic responses to cancer have been attempted. Of these the most promising include antigen-specific vaccines, dendritic cell vaccines, and whole tumor cell vaccines.³² However, in spite of advances in the understanding of tumor immunology, the realization of effective therapeutic cancer vaccines to date has been below expectations.³³

Oral Mucositis

Treatment of cancer is increasingly more effective but is associated with short- and long-term side effects. Oral side effects remain a major source of illness despite the use of a variety of agents to prevent them. One of these side effects is oral mucositis. Oral mucositis may produce oral discomfort and pain, poor nutrition, delays in drug administration, increased hospital stays and costs and, in some patients, life threatening infection.

Patients receiving chemotherapy and/or radiation therapy often develop oral mucositis, which can significantly complicate cancer treatment. The risk of oral mucositis increases as a function of the type of cancer therapy used, with the lowest risk occurring with “gentler” chemotherapeutics such as gemcitabine (Gemzar) and the higher risk occurring with more aggressive agents such as 5-FU and cisplatin and/or radiation therapy.³⁴ Mucositis is commonly encountered with drugs affecting DNA synthesis (S-phase-specific agents such as fluorouracil, methotrexate, and cytarabine). Mucositis may limit the patient’s ability to tolerate chemotherapy or radiation therapy, and nutritional status can be compromised. It may drastically affect cancer treatment as well as the patient’s quality of life. The incidence and severity of mucositis will vary from patient to patient. It will also vary from treatment to treatment. It is estimated that there is 40% incidence of mucositis in patients treated with standard chemotherapy and this will not only increase with the number of treatment cycles but also with previous episodes.³⁵ Similarly, patients who undergo bone marrow transplantation and who receive high doses of chemotherapy have a 76% chance of getting mucositis. The overall incidence of oral mucositis and xerostomia is approximately 80% in patients with squamous cell carcinoma of the head and neck

who are treated with radiation therapy directed at the oral and pharyngeal regions.³⁶ The exact pathophysiology of mucositis is not known, but it is thought to be divided into direct and indirect mucositis. Chemotherapy and/or radiation therapy will interfere with the normal turnover of epithelial cells leading to mucosal injury; subsequently, it can also occur due to indirect invasion of gram-negative bacteria and fungal species because many chemotherapeutic agents will cause changes in infection resistance.

Oral mucositis is typically diagnosed based on the clinical appearance, location, timing of oral lesions, and use of certain types of therapy known to be associated with mucositis. Other common conditions can have a similar clinical presentation to oral mucositis and may confuse the differential diagnosis. They include oral candidiasis, herpes simplex virus, and graft-versus-host disease in transplant patients. Chemoradiation-induced mucosal injury (mucositis) is the result of a complex series of biological and cellular events that take place predominantly in the submucosa with the epithelium being the target tissue.³⁷ Radiation and chemotherapy create both DNA and non-DNA damage. Clonogenic cell death of the basal epithelial cells occurs as a consequence of DNA strand breaks. The products of this stage then set in motion a cascade of biological and cellular occurrences in the submucosa that ultimately results in death of basal epithelial cells.

Several scoring systems have been devised to assess the severity of oral mucositis and its treatment, but no one scale is uniformly employed. The two most common scales are those proposed by the World Health Organization and the National Cancer Institute Common Toxicity Criteria (Tables 15.5 and 15.6).

Topical drugs such as local anesthetics, analgesics, and coating drugs have been used in cancer patients to manage mucosal pain. Epstein et al. reported that the use of an oral rinse of doxepin in the management of pain from oral mucositis produced a reduction in oral pain by more than 50% with an extended duration of action.³⁸ In a follow-up study in oncology patients only, 90% of 51 patients reported a reduction in pain after rinsing with doxepin.³⁹ Pain reduction was highly statistically significant in the first 15 minutes after rinsing with doxepin ($P < .0001$) and at the height of pain reduction, the average patient reported 70% less pain compared to baseline ($P < .0001$). Four hours after rinsing, 19 patients (37%) still reported continuing pain reduction on the visual Analog Scale (VAS) ($P = .012$). Doxepin suspension (5 mg/mL) was

TABLE 15.5

WORLD HEALTH ORGANIZATION SCORING CRITERIA FOR ORAL MUCOSITIS

Grade	Observation
0	Normal
1	Soreness with or without erythema; no ulceration
2	Ulceration and erythema; patient can swallow a solid diet
3	Ulceration and erythema; patient cannot swallow a solid diet
4	Ulceration and pseudomembrane formation of such severity that alimentation not possible

TABLE 15.6

**NATIONAL CANCER INSTITUTE
COMMON TOXICITY CRITERIA VERSION 3
SCORING CRITERIA FOR ORAL MUCOSITIS**

Mucositis Functional/Symptomatic Score	
Grade 0	No mucositis
Grade 1	Able to eat solids
Grade 2	Requires liquid diet
Grade 3	Alimentation not possible
Grade 4	Symptoms associated with life-threatening consequences
Mucositis/Stomatitis Clinical Score	
Grade 0	No mucositis
Grade 1	Erythema of the mucosa
Grade 2	Patchy ulceration or pseudomembrane
Grade 3	Confluent ulcerations or pseudomembranes
Grade 4	Tissue necrosis

prepared in an oral rinse containing 0.1% alcohol and sorbitol. Patients rinsed with 5 mL of the solution in their mouth for 1 minute and expectorated.

Worthington et al. reported on interventions used for preventing oral mucositis in cancer patients receiving treatment.⁴⁰ Four interventions were identified where there was more than one trial contributing to a meta-analysis finding a significant difference: amifostine, Chinese medicine, hydrolytic enzyme, and ice chips. Three of these, amifostine, hydrolytic enzymes and Chinese medicine were assessed in patients with head and neck cancer, and ice chips in two studies were used on patients having chemotherapy treatment with bolus dose 5-FU, and in a third study patients received the single-agent melphalan. Clarkson et al.⁴¹ reported on interventions used for treating oral mucositis. The evidence was weak and unreliable that allopurinol mouthwash, granulocyte macrophage-colony stimulating factor, immunoglobulin, or human placental extract improved or eradicated mucositis. There was no evidence that opioids administered by patient-controlled analgesia (PCA) were better than continuous infusion for controlling pain; however, less opioid was used per hour, and duration of pain was shorter with PCA only.

Graft Versus Host Disease

The hallmark of bone marrow transplantation is the reinfusion of marrow-derived hematopoietic stem cells to reconstitute hematopoiesis following conditioning with high-dose chemotherapy and/or radiation. Allogeneic hematopoietic stem-cell transplantation (HSCT) is a curative therapy for hematological malignancies and inherited disorders of blood cells, such as sickle cell anemia. Mature $\alpha\beta$ T cells that are contained in the allografts reconstitute T-cell immunity and can eradicate malignant cells in the recipient. Unfortunately, these T cells recognize the recipient as “nonself” and employ a wide range of immune mechanisms to attack recipient tissues in a process known as graft-versus-host disease (GVHD). Despite advances in the procedure and post-transplantation immunosuppressive therapy, more than half of HSCT recipients develop GVHD which remains a major cause of morbidity and mortality.⁴² GVHD is characterized by the development

of features reminiscent of various autoimmune or immunologic disorders, such as scleroderma, Sjogren syndrome, chronic immunodeficiency, and bronchiolitis obliterans. GVHD usually involves the skin, eyes, oral cavity, gastrointestinal tract, liver, and lungs. Symptoms typically present within 2 years following HSCT and are historically identified as limited or extensive.

Acute GVHD occurs within the first 100 days post-transplant and is clinically graded according to skin, liver, and gastrointestinal involvement. Manifestations can include more inflammatory and acute-type features such as erythematous rash, mucositis, diarrhea, transaminitis, and bronchiolitis obliterans with organizing pneumonia (BOOP), or can be more fibrotic and chronic in nature such as sclerotic or lichen planus-type skin changes, fasciitis, sicca syndrome, esophageal strictures, and bronchiolitis obliterans. In addition to these more commonly involved systems listed above, many other organ systems can be affected. Factors such as thrombocytopenia, extensive skin involvement, weight loss and chronic diarrhea have previously been established as risk factors for and prognostic indicators of GVHD. Standard GVHD front-line therapy typically consists of cyclosporine with corticosteroids but only approximately 70% of patients respond.⁴³ Current treatment options for GVHD include intense immunosuppression, which in turn has associated side effects, an increased risk of infective complications, and a potential for increased relapse of hematological malignancy. Strategies to prevent GVHD include T-cell depletion, immunosuppression, gut decontamination, and appropriate donor selection.⁴⁴ Cyclosporin and/or methotrexate have formed the basis of many GVHD prophylaxis strategies.

Postdural Puncture Headache and Chemotherapy

In oncology, dural puncture is a commonly performed invasive procedure for diagnostic lumbar puncture and intrathecal chemotherapy. The overall incidence of post-dural puncture headache (PDPH) after intentional dural puncture varies from 0.1 to 36%; the highest incidence of 36% is found after ambulatory diagnostic lumbar puncture using a 20- or 22-gauge standard Quincke spinal needle.⁴⁵ Unintentional dural puncture with large Tuohy needle (16 and 18 gauge) is typically associated with a 75% to 85% incidence of PDPH.⁴⁶ In this study, 48% were classified “severe” and, in 49%, the headache presented within 24 hours of dural puncture.⁴⁶ Headaches appear to occur more frequently in women than in men and more commonly in young adults and in patients prone to headaches. Spinal needle tip and design play a significant role in the development in PDPH. Apan et al.⁴⁷ demonstrated in an *in vitro* model in situations of varying pressures that the least amount of leak occurred with small diameter (25-gauge and 26-gauge) pencil point needles, such as the Whitacre needle.

The classic description of PDPH is that of a frontal or occipital headache that is present or aggravated by assuming the upright position and essentially disappears when returning to the supine position. The pain may be throbbing in nature, often radiates to the neck, and is extremely variable in severity. Other symptoms include nausea, vomiting, neck stiffness, and ocular and auditory disturbances (photophobia, diplopia, hypoacusia, tinnitus), and, rarely

cranial nerve palsies. The onset and duration of PDPH can be extremely variable. Most occur within 48 hours of dural puncture and are self-limited, lasting only days.

Although not universally accepted, most investigators favor the “leakage theory” as an explanation for PDPH. Theoretically, leakage of cerebrospinal fluid (CSF) through the dural rent causes decreased CSF pressure and volume, followed by gravity-dependent downward sagging of the brain resulting in traction on the pain-sensitive vascular structures around the brain. However, the amount of CSF leak, as demonstrated on magnetic resonance imaging (MRI), has not been shown to correlate with the incidence of headache⁴⁸ and some patients with typical features of PDPH may also have normal CSF pressures.⁴⁹ The other major mechanism thought to be responsible for PDPH is cerebral vasodilatation due to loss of CSF.⁵⁰ The successful use of epidural blood patch for the treatment of PDPH is based on the assumption that the injection of autologous blood at the site of the lumbar puncture seals the leaking rent. However, because of the relatively rapid effect of the patch in relieving the headache (often within 1 hour), the injected blood also may affect pressure dynamics within the CSF and effectively reverse cerebral vasodilatation associated with CSF leak rather than stop additional CSF flow. On the basis of these findings, Boezaart et al.⁵⁰ proposed that PDPH is probably a vascular-type headache and that epidural blood patch relieves the headache by its vasoconstrictive action.

Current treatment strategies (which do not have good-quality outcome evidence) for PDPH include oral or intravenous caffeine, theophylline, sumatriptan, adrenocorticotrophic hormone, epidural saline, and epidural blood patch. The gold standard for treatment of PDPH in symptomatic patients is epidural blood patch. Persistent symptomatic relief can be expected in 61% to 75% of patients with the initial epidural blood patch.⁵¹ Patching with nonblood solutions, although initially effective, seems to be associated with a higher incidence of headache recurrence.

Several techniques have been tried in an attempt to reduce the incidence of PDPH. The maintenance of the supine position after dural puncture is ineffective. The use of prophylactic epidural blood patches is controversial. Scavone et al.⁵² noted no difference in either a decreased incidence of PDPH or the need for therapeutic epidural patch when a prophylactic epidural blood patch was administered to parturients after inadvertent dural puncture with an epidural needle. However, in this study of 64 parturients who incurred an accidental dural puncture, prophylactic epidural blood patch did shorten the duration of PDPH symptoms.

In our practice, patients who present with PDPH with functional limitations typically receive an epidural blood patch after we ascertain that there is neither neutropenia nor thrombocytopenia. If a patient's headache recurs, a second blood patch is done, preferably under fluoroscopic guidance to ensure accuracy of placement of the blood. In patients with refractory headaches, a short course of steroids may then be considered if medical circumstances allow. With truly refractory headaches, it is important to eliminate the possibility of intracranial subdural hematoma with a computed tomography (CT) scan.⁵³

SURGERY

Surgery plays an important role in diagnosis, staging, and treatment of cancer. It also contributes to cancer prevention, structural and functional reconstruction with rehabilitation, and palliation of symptoms. The surgeon responsible for treating a patient with newly-diagnosed cancer has four tasks: (1) obtaining a biopsy for tissue diagnosis, (2) being involved in adequate staging of disease, (3) obtaining consultation with medical and radiation oncologists for adjuvant therapy, and (4) the appropriate timing of the surgical resection. Surgeons are also involved with the treatment of relapses or recurrence and may also play a role in the relief of symptoms caused by specific problems, such as visceral obstruction, unstable bone structures, and compression of neural tissues. Various surgical disciplines (eg, general surgery, orthopedic, neurosurgical, urologic, plastic, and reconstructive) may participate in the care of the cancer patient. Surgery is and has been the main treatment modality for solid tumors. Surgeons performing radical oncologic procedures have traditionally been involved with surgeries such as pelvic exenteration, abdominoperineal resection, limb amputation, liver resection, and esophagogastric resection. The basic principles of surgical oncology involve local tumor excision, regional lymph node removal, the management of local or regional recurrence, and the possibility of surgical resection of distant metastases.

Surgery for breast, colon, and lung cancer have become more conservative in the last 30 years of the twentieth century. Mastectomy (either radical or modified radical) had been the mainstay of the treatment of stage I and stage II breast cancer until the late 1970s. Although mastectomy still may be appropriate for some patients, breast conservation has become the preferred method of treatment, particularly for appropriately selected patients with early-stage breast cancer.⁵⁴ Organ-sparing surgery, laparoscopy, robotics systems, and image-guided ablation techniques have enabled surgeons to develop specifically tailored treatments for patients with urologic cancers.

Surgery is an important factor in tumor treatment outcome. Differences in the quality of surgery are significant contributors to wide variations in outcome of local treatment of most solid tumors.⁵⁵ For example, the influence of adequate surgical margins on the risk of recurrence is well established in the treatment of osteosarcoma⁵⁶⁻⁵⁸ and soft-tissue sarcoma.⁵⁹ Surgical treatment is preferable for sarcoma and most commonly is performed in specialized centers.⁶⁰ Local recurrence after breast preservation may be the result of inappropriate patient selection or inadequate surgery and may contribute to the increased risk of breast cancer recurrence. Lymphatic mapping and sentinel lymph node biopsy have become a promising alternative to axillary lymph node dissection with its associated morbidity.⁶¹ The best chance of curing esophageal cancer requires surgery that removes the entire tumor and the draining lymph nodes with adequate proximal and distal margins.⁶² Integration of γ probes into surgical oncologic procedures is becoming more established. A γ probe can facilitate localization of radio-labeled parathyroid glands.⁶³ γ probe-guided localization of nonpalpable breast cancers is highly accurate when the radioactive tracer used for sentinel node identification is injected close

to the primary tumor.⁶⁴ Surgery is the preferred treatment option for otherwise healthy patients with pancreatic cancer without metastases. Tumors of the pancreatic head and the periampullary region can be resected using pancreaticoduodenectomy (with or without preservation of the pylorus), whereas a distal pancreatectomy can be performed for tumors of the pancreatic body and tail. In most cases, a splenectomy has to be performed when tumor localization and surgical technique do not permit preservation of the splenic vessels. Primary melanomas are now excised with narrower surgical margins of 1 to 2 cm. Sentinel-node biopsy is recommended as a nodal staging procedure in patients with tumor thickness of 1 mm and more, but the prognostic impact of this procedure has not yet been demonstrated.⁶⁵ The technique of retroperitoneal lymph node dissection is routinely performed in many gynecological cancer centers as a staging procedure or as part of surgical management of cervical and endometrial cancers. This procedure can be performed laparoscopically or as an open procedure. Extensive pelvic surgical procedures such as pelvic exenteration can also be performed laparoscopically.⁶⁶ Included in the advantages for laparoscopic surgery are cost-efficiency based on the reduction of hospital stay and recovery time.⁶⁷ Minimally-invasive approaches have revolutionized surgical care, significantly reducing postoperative pain and recovery time, with marked improvements in cosmetic outcome. Surgical advances in neuro-oncology for brain tumors have centered around technological advances that enable the fusion of preoperative structural and functional imaging datasets, the use of intraoperative MRI scanning, and awake craniotomy and cortical mapping as means to maximize resection, minimize postoperative morbidity, and improve survival times.⁶⁸

Robotic surgery has the potential to transform laparoscopic surgery by providing instruments with distal ends that mimic the intricate movements of the human hand while at the same time providing the surgeon with a high-definition, 3D view of the operative field. Advantages over laparoscopy include a 3D vision system, wristed instrumentation, and ergonomic positioning for the surgeon while performing surgical procedures. The only FDA-approved system in the United States is the Da Vinci system. Robotic-assisted laparoscopic surgeries in gynecology include benign hysterectomy, myomectomy, tubal reanastomoses, radical hysterectomy, lymph node dissections, and sacrocolpopexies.⁶⁹ Laparoscopic-assisted and robotic-assisted urological procedures have been performed for radical cystectomy⁷⁰ and cystoprostatectomy.⁷¹

Only 10% to 20% of patients with primary and colorectal metastatic liver tumors are candidates for curative surgical resection.⁷² Even after presumptive curative treatment, tumors recur commonly in the liver. The majority of patients with primary or metastatic hepatic tumors are not candidates for resection because of tumor size, location near major intrahepatic blood vessels precluding a margin-negative resection, multifocality, or inadequate hepatic function related to coexistent cirrhosis. Radiofrequency thermal ablation (RFA) of primary, metastatic, and recurrent liver tumors can be performed under percutaneous, laparoscopic, or open intraoperative ultrasound guidance. The local recurrence rate at 2 years was statistically significant in favor of RFA over

percutaneous ethanol injection for treatment of hepatocellular carcinoma.⁷³

The decision to proceed with major surgery in patients with advanced cancer requires judgment of the patient's expected survival time, overall fitness for major surgery, and the anticipated morbidity of the proposed procedure. The decision to pursue a major surgical intervention is often controversial when it is not likely to be curative and has symptom relief as its only objective. This form of palliative therapy most often involves patients with later stages of disease. Although the development of metastatic cancer usually indicates incurable disease, curative surgical resection can be accomplished in rare instances: the primary lesion must be controlled; there must be the potential for complete resection of the metastases; there must be no other equally effective or better antitumor therapy available; metastases should involve only one organ; one should anticipate reasonable postoperative function; expected survival should be better than if left untreated; and the patient must be able to tolerate the surgical procedure. Rarely, excision of the primary tumor is indicated in the presence of unresectable metastatic disease. Locally advanced tumor can be very painful and unsightly, can interfere with vital functions such as breathing and swallowing, and produce complications such as bleeding and local infection. Surgical judgment is critical in such situations.

Multidisciplinary management of cancer is more effective than sequential monotherapies and results in more cures and improved organ and overall function preservation. Surgery is suitable for local and regional disease and may result in cures in early stages of cancer, especially when there is an early detection policy. In patients with localized but extensive tumors, surgery may prove valuable in improving the quality of life and potentially in prolonging life.

Surgical oncology is not recognized universally as a distinct discipline within surgery. Surgeons who regard themselves as surgical oncologists fall into two broad but distinct categories: those who regard themselves as general surgical oncologists, able to operate on most tumors and who have a minimal practice in benign pathology; and those who are anatomically specific and treat patients with complex disorders. As the treatment of patients with cancer becomes progressively more complex and multidisciplinary, various organizations have attempted to set guidelines and standards for care. For example, in 1998, three colleges (the American College of Surgeons, the American College of Radiology, and the College of American Pathologists), the American Cancer Society, and the Society of Surgical Oncology reported on standards for diagnosis and management of invasive breast cancer.⁷⁴ The American Board of Medical Specialties (ABMS) comprises 24 medical specialty member boards and is responsible for overseeing the certification of physician specialists in the United States. The primary function of ABMS is to assist its member boards in developing and implementing educational and professional standards to evaluate and certify physician specialists. Of the recognized surgical specialties, only obstetrics and gynecology has subspecialty certification in oncology care (gynecologic oncology).

As a field of distinct expertise, surgical oncology is relatively new. The Society of Surgical Oncology defines

guidelines for surgical oncology fellowships and approves 19 programs across the United States. The objective of the fellowship is to expand basic surgical knowledge and experience obtained during residency to develop skilled surgeon-investigators who will become recognized experts in the field of surgical oncology. The Society has 1,927 members in 48 states and 43 foreign countries. Membership consists of surgeons, scientists, and other health care providers who are significantly involved in oncologic patient care. This specialty is not recognized by the American Board of Medical Specialties (ABMS).

The National Cancer Institute's (NCI) Surgical Oncology Fellowship Program trains surgeons committed to academic careers in surgical oncology. The program instructs surgical oncologists in a combined modality approach to the evaluation and treatment of cancer patients that includes primary surgical treatment, chemotherapy, immunotherapy, and radiation therapy, and provides a solid basis for the conduct of clinical and laboratory research. This program is a 2-year training program of which 6 months of the first year are dedicated to clinical training in surgical oncology with rotations on various clinical surgical services. Eighteen months are spent in one of the laboratories of the Surgery Branch dedicated to basic science and translational research. Surgical oncology is not recognized as a subspecialty in all European countries. A major objective of the European Society of Surgical Oncology is to promote education in cancer surgery. Worldwide, other regions are also moving towards the development of a subspecialty in surgical oncology. Advancement in this area will improve the surgical aspects of care of the oncology patient.

STENTING AND DRAINAGE PROCEDURES

Neoplastic visceral obstruction occurs because of direct tumor infiltration or compression or metastatic involvement of lymph nodes. Obstructions of the gastrointestinal, hepatobiliary, and ureteric systems are the most common in patients with advanced cancer. The signs and symptoms of visceral obstruction are organ specific and therefore bowel obstruction, pain, jaundice, and renal insufficiency or failure may occur. Relief of the obstruction takes priority over other treatments in hopes of improving symptoms and palliating the disease process. The clinical presentation of ureteral obstruction due to advanced pelvic or abdominal malignancy can be a slow process with vague and nonspecific symptoms, such as flank discomfort or lethargy, or it may present as acute obstruction with intense pain, nausea, and vomiting. Unrelieved obstructive uropathy may result in uremia, electrolyte imbalances, and persistent urinary tract infections. Treatment of ureteral obstruction is challenging. Many patients in need of stenting are poor surgical candidates. The two common methods for urinary diversion after obstructive malignancy are retrograde ureteral stenting and percutaneous nephrostomy. Both techniques can result in leaking, tube movement, and tube dislodgment, and stenting may not completely resolve the secondary problems or it may not relieve obstruction. Stent insertion is typically performed under fluoroscopic guidance. Although intrinsic ureteral

obstruction is highly amenable to endoscopic ureteral stents in cases of intrinsic obstruction (stone disease, ureteral strictures, or ureteropelvic junction obstruction), the incidence of stent failure is significantly higher in cases of extrinsic compression, particularly when accompanied by hydronephrosis.⁷⁵ Percutaneous tubes are generally placed under ultrasound or CT guidance. Difficult clinical situations may require alternative procedures such as palliative cutaneous ureterostomy, percutaneous anterograde ureteric stent placement, and a combined anterograde and retrograde technique.

Common causes of malignant biliary obstruction include pancreatic cancer, cholangiocarcinoma, and metastatic disease, either intrahepatic or from lymphadenopathy. The majority of these patients will not undergo surgical resection of the obstructing tumor due to either the advanced nature of the disease or the significant morbidity associated with surgery. The insertion of internal biliary stents (plastic or metal) by endoscopic or percutaneous methods is common practice for the palliative management of obstructive jaundice caused by malignancy, and most surgeons prefer this to the use of external biliary drains.⁷⁶ For the treatment of malignant biliary obstructions in patients with pancreatic carcinoma, endoscopic biliary drainage is the option of first choice.⁷⁷ Drainage at endoscopic retrograde cholangiopancreatography (ERCP) compared to percutaneous drainage is safer and more successful than percutaneous drainage.⁷⁸ Gastrojejunostomy is the most commonly used palliative treatment modality for malignant gastric outlet obstruction. Endoscopic stent placement may be associated with more favorable results in patients with a relatively short life expectancy, whereas gastrojejunostomy is preferable in patients with a more prolonged prognosis.⁷⁹ Because gastric outlet obstruction is a frequent feature of advanced pancreatic carcinoma, self-expandable metal stents (SEMS) allow this problem to be managed relatively simply by endoscopy rather than surgical bypass.⁸⁰ Phillips et al.⁸¹ showed that SEMS effectively palliate gastric outlet obstructions that result from upper gastrointestinal malignancies. Stents and laser treatment have a place in both upper gastrointestinal and rectal obstruction due to advanced malignancy.⁸²⁻⁸⁴ Colonic stents potentially offer effective palliation for patients with malignant bowel obstruction, and a "bridge to surgery" for those in whom emergency surgery would necessitate a stoma. SEMS placement may result in the avoidance of surgical resection in patients with metastatic disease. The presence of metastases at the time of surgery is an independent predictor of operative mortality in colorectal surgery⁸⁵ and stenting also has the potential benefit of avoiding surgery and possible stoma formation, even on a temporary basis, in these patients. Preoperatively, failure of contrast to pass through an obstructive bowel lesion is a predictor of technical failure of SEMS insertion.⁸⁶ Patients with locally unresectable tumors may benefit particularly from endoscopic placement of SEMS.⁸⁷

Malignant pleural effusion can be the first sign of cancer or of its recurrence. Approximately 50% of effusions are malignant and only a minority benefit from suitable systemic treatment. Effusions can recur rapidly and often are disabling. Most patients with malignant pleural effusion are symptomatic; common presenting complaints are

shortness of breath, cough, chest pain, and a sense of fullness within the chest. Treatment is directed toward relief of these symptoms. When thoracentesis is repeated frequently over a number of months to treat dyspnea, the resulting depletion in ions, fluid, and proteins contributes to the deterioration in the patient's general condition. No more than 1500 mL of fluid should be removed by thoracentesis at a single session. Pleurodesis (adhesion of the parietal and visceral pleura) is the symptomatic treatment of choice and should be considered as early as possible in the course of chronic malignant pleural effusions. Intrapleural instillation of chemicals is done via thoroscopy in an attempt to produce pleurodesis. Various agents including tetracycline, doxycycline, minocycline, bleomycin, fluorouracil, and talc have been used for chemical pleurodesis. Talc is generally insufflated to the lung surface through a thoracoscope under general anesthesia. Safran et al.⁸⁸ described an outpatient pleurodesis with 4 grams of talc through a 14 French pigtail catheter. Once drainage had diminished to less than 100 mL/day, the patient returned for sclerotherapy. Sclerotherapy was accomplished by instillation of 50 mL of 1% lidocaine followed by 4 g of talc slurry and 20 mL of saline solution flush. It was thought to cause pleural symphysis as a result of reactive pleuritis.⁸⁹ Of the agents used for pleurodesis, talc appears to be the most effective.⁹⁰ No more than 5 grams of talc should be used for pleurodesis.⁹¹

Malignant ascites can lead to abdominal distention, nausea, early satiety, anorexia, and in severe cases, respiratory compromise. It is associated with a variety of tumors, especially, breast, bronchus, ovary, stomach, pancreas, and colon.⁹² Paracentesis and diuretics are the most commonly used measures for treatment.⁹³ Frequent drainage may be necessary to relieve pain and discomfort. Sonographically-guided paracentesis is commonly used for palliation of symptomatic malignant ascites. Permanent percutaneous catheters may prevent the need for repeated paracentesis, although there is potential for infection. Peritoneovenous shunts have also been recommended for the treatment of refractory ascites.⁹⁴ These shunts are designed for continuous drainage of ascites into the systemic circulation and can be placed surgically or percutaneously. Early use of this system (all placed surgically) has been discouraging, with reported morbidity rates of 60% to 70%, shunt-related mortality rates of 10% to 35%, and shunt patency rates of 20% to 40%.⁹⁵⁻⁹⁶ However, with the development of radiological interventional techniques, a shunt system can now be placed percutaneously. Using this technique, better results have been reported, particularly if patients with a history of variceal bleeding are excluded.⁹⁴ Becker et al.⁹⁷ provided guidelines on the management of symptomatic malignant ascites in advanced cancer (Table 15.7).

ANTIBIOTICS FOR PALLIATION

The goals of antibiotic use in terminally ill patients are sometimes to prolong life, and always to relieve symptoms. Treatment for cystitis does not usually prolong life, but may relieve the patient from painful dysuria and troublesome polyuria. Antibiotics may also have pain-relieving effects when the source of pain involves

TABLE 15.7

GUIDELINES FOR THE MANAGEMENT OF SYMPTOMATIC MALIGNANT ASCITES IN ADVANCED CANCER

1. Paracentesis is indicated for those patients who have symptoms of increasing intra-abdominal pressure. Available data show good, although temporary relief of symptoms in most patients. Symptoms like discomfort, dyspnea, nausea, and vomiting seem to be significantly relieved by drainage of up to 5 L of fluid.
2. When removing up to 5 L of fluid, intravenous fluids are not routinely required.
3. If patient is hypotensive or dehydrated or known to have severe renal impairment and paracentesis is still indicated, intravenous hydration should be considered. Infusion therapy is not sufficiently studied. The only investigated therapy in malignant ascites is infusion of dextrose 5%. There is no evidence for efficacy of concurrent albumin infusions in patients with malignant ascites.
4. To avoid repeated paracenteses, peritoneovenous shunting may be considered. Major complications (pulmonary edema, pulmonary emboli, clinically relevant disseminated intravascular coagulation, and infection) have to be expected in about 6% of patients.
5. There are no randomized controlled trials assessing the efficacy of diuretic therapy in malignant ascites. The available data are controversial and there are no clear predictors to identify which patients would benefit from diuretics. The use of diuretics therefore should be considered in all patients, but has to be evaluated individually. Patients with malignant ascites due to massive hepatic metastasis seem more likely to respond - to diuretics than patients with malignant ascites caused by peritoneal carcinomatosis or chylous ascites.
6. Choice of diuretics is not evaluated. As available data suggest that the efficacy of diuretics in malignant ascites depends on plasma renin/aldosterone concentration, aldosterone antagonists like spironolactone should be used, either alone or in combination with a loop diuretic.
7. Dose regimens of diuretics are not evaluated in patients with malignant ascites. There is no evidence to diverge from standard clinical practice. Therefore dosage should be performed according to manufacturer's instructions and package inserts.

(From Becker G, Galandi D, Blum HE. Malignant ascites: Systematic review and guideline for treatment. *Eur J Cancer*. 2006;42:589-597.)

infection, as illustrated by the treatment of pyonephrosis and osteitis pubis. Delayed breast cellulitis is primarily related to a bacterial infection in the setting of impaired lymphatic drainage and may appear months after completion of radiation therapy in patients undergoing breast conserving therapy (primarily lumpectomy and radiation therapy).⁹⁸ It is characterized by the late onset of breast erythema, edema, tenderness, and warmth. Delayed breast cellulitis may be treated conservatively with antibiotics to cover β -hemolytic *Streptococci spp.* and *Staphylococcus aureus* for 10 to 14 days. Terminally ill patients are susceptible to infections during the final phases of their care.⁹⁹ Infections increase symptom burden and decrease quality of life. Urinary and respiratory infections dominate. First-line therapy in cases of urinary sepsis, trimethoprim, cephalexin, and amoxicillin are effective agents. Cotrimoxazole and amoxicillin are effective agents for respiratory infections. Head and neck cancer patients who receive radiation therapy are at risk for *Candida* colonization in the oral cavity.¹⁰⁰ *Candida* species are the most common fungal pathogens isolated from the oral cavity. *Candida* species are responsible for all but exceptional examples of oral fungal infection. Oral candidiasis is relatively common occurring in approximately 25% of patients receiving radiation therapy for head and neck cancer.¹⁰¹ Previously *Candida albicans* was the most common pathogen, but non-*albicans Candida* (in particular *Candida glabrata*) is emerging as a relatively common cause of oropharyngeal candidiasis in head-and-neck cancer patients.¹⁰¹⁻¹⁰² The infections can be acute or chronic, pseudomembranous ("thrush") or atrophic (erythematous). Oropharyngeal candidiasis manifests clinically as acute pseudomembranous, acute atrophic, chronic atrophic, chronic hypertrophic/hyperplastic, and angular cheilitis. Infection is marked by oral pain and/or burning and can lead to significant patient morbidity. As an opportunistic organism, *Candida albicans* is extremely responsive to any process resulting in immunosuppression. Oral nystatin, clotrimazole, and fluconazole are

the usual treatments. Fluconazole in doses of 100 mg/day is predominantly used to treat oropharyngeal candidiasis. Development of resistance to fluconazole in these patients has become a growing concern and usually is correlated with the degree of immunosuppression and the total dose of drug. If resistance to fluconazole does occur, its occurrence may be due to the presence of yeasts other than *C. albicans*, which are less susceptible to fluconazole.

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