

Recent Advances in Radiation Therapy

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Recent advances have improved the effectiveness, decreased the complications, and expanded the implications of radiation therapy. These advances include three-dimensional conformal radiation therapy, intensity-modulated radiation therapy, stereotactic radiotherapy, brachytherapy, and radioimmunotherapy. Each of these modalities has improved radiation targeting, thereby limiting radiation exposure of healthy tissues. The way radiation therapy is administered has also changed. Although traditional external beam radiation therapy is administered daily over several weeks, stereotactic radiotherapy may be administered as a one-time treatment. Radioimmunotherapy is administered intravenously. Contemporary radiation techniques also have distinct toxicity profiles. The high radiation doses employed during stereotactic radiotherapy have been associated with obliteration or obstruction of tubular structures, such as bronchi and bile ducts, limiting its use near these tissues. Radioimmunotherapy may be complicated by anaphylactic reactions during and following infusions. As more patients are diagnosed with cancer and as these patients live longer, primary care physicians will increasingly care for those who have received radiation therapy. (*Am Fam Physician*. 2008;78(11):1254-1262, 1263-1264. Copyright © 2008 American Academy of Family Physicians.)



ILLUSTRATION BY FLOYD HOSMER

► **Patient information:** A handout on radiation therapy, written by the authors of this article, is provided on page 1263.

Radiation therapy has a pivotal role in the treatment of cancer. Indications for radiation therapy (*Table 1*) range from definitive treatment of localized tumors to palliation of symptoms from widely metastatic disease. In certain circumstances, radiation therapy has disease control rates comparable with those of surgery, but with less morbidity. For instance, many advanced laryngeal cancers are treated with radiation and chemotherapy instead of with laryngectomy, allowing most patients to retain their voice after treatment.^{1,2} In some patients, radiation therapy can be used before surgery, allowing for a more limited, safer, and more effective surgery. Since the 1980s, the use of regional radiation after local excision (lumpectomy) of early-stage breast cancer has spared thousands of women the morbidity and disfigurement of a mastectomy.³⁻⁵

The principal limitation of radiation therapy is radiation exposure of healthy tissues. Radiation toxicities, such as cognitive dysfunction, esophagitis, and myelosuppression, depend on the irradiated organs and on the

radiation dose and scheduling. Traditionally, radiation oncologists have limited adverse effects by reducing the dose of radiation or by spreading the dose over multiple administrations (i.e., dose fractionation). Over the past decade, advances in radiation planning and delivery have markedly improved the ability to focus radiation on target tissues, sparing nearby healthy tissues. *Table 2* summarizes modern radiation therapy modalities.

Radiation Principles and Modalities

The underlying principle of radiation therapy is the destruction of malignant tissues while minimizing damage to normal tissues within a treatment field. Ideally, this would be accomplished by avoiding normal tissues altogether, but the relatively crude targeting of traditional radiation techniques does not permit such precision. Instead, a therapeutic ratio is achieved by making use of the different radiosensitivities of normal tissues and tumors. Ionizing radiation kills cells by causing DNA strands to break and cross-link. In general, normal cells are better

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Radiation therapy should not be administered during any trimester of pregnancy.	C*	5
Initial use of a plain, nonscented, lanolin-free hydrophilic cream is helpful for patients experiencing radiation skin reactions.	C	41
Amifostine (Ethyol) may be considered to decrease the incidence of xerostomia in certain patients undergoing fractionated radiation therapy to the head and neck region.	B	38
For most women with stage I and II breast cancer, breast-conserving therapy with lumpectomy, axillary lymph node dissection, and whole breast radiation therapy is equivalent to mastectomy with axillary lymph node dissection.	A	4, 5
Dental examination and treatment are important before starting radiation therapy, especially for patients with head and neck cancer, and should continue throughout treatment and follow-up.	C	39
Patients with low-risk prostate cancer may be treated with radiation therapy or surgery.	B	30, 31

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

**—Although there are no randomized controlled trials, clinical trials of radiation therapy in pregnancy are unlikely to be completed because there is overwhelming evidence that radiation is teratogenic.*

Table 1. Applications of Radiation Therapy

<i>Application of therapy</i>	<i>Principle</i>	<i>Common examples</i>
Primary (all patients)	Compared with surgery, radiation offers improved or equivalent tumor control with less morbidity Outcomes and toxicities are similar between radiation and surgery; therefore, both require an individualized assessment and discussion of the patient's condition and preferences	Anal cancer, head and neck cancer (e.g., laryngeal, oropharyngeal) Cervical and prostate cancers, acoustic neuroma, meningioma
Patients medically unfit for surgery	Cardiac, pulmonary, or other chronic disease precludes surgery, but not radiation therapy	Endometrial and lung cancers
Anatomically unresectable cancers	Close proximity to critical structures (e.g., blood vessels) precludes surgery, but not radiation therapy	Bladder, pancreatic, and skin cancers
Preoperative	Shrinks the tumor, facilitating subsequent surgical resection	Esophageal and rectal cancers
Postoperative	Decreases risk of local or regional tumor recurrence; treats areas with a known tumor if there is gross residual disease or positive surgical margins after resection	Breast, endometrial, gastric, pancreatic, and rectal cancers; malignant glioma; sarcoma; seminoma
Palliative	Relieves bony pain	Breast, lung, prostate, renal, other cancers that are metastatic to bone
	Stops or limits bleeding	Gastrointestinal, genitourinary, and lung cancers
	Relieves luminal (airway, biliary, gastrointestinal) obstruction	Lung and colon cancers

NOTE: The above categorizations are generalizations, and this table does not include an exhaustive list. Any therapy choice must be discussed between the patient and an oncologist.

able to repair this damage to DNA than are cancer cells. Administering relatively small daily doses of radiation over several weeks permits healthy cells to recover between sessions, while causing cumulative damage to tumor cells. Dose fractionation has been the central paradigm of treatment delivery in radiation oncology.⁶

External beam radiation therapy, or teletherapy, accounts for almost 90 percent of radiation treatments. This technique involves the delivery of electromagnetic

radiation (e.g., x-rays, gamma rays) or particulate radiation (e.g., electrons, protons) from a linear accelerator or radionuclide source, such as cobalt-60. Alternatively, in brachytherapy, a radiation supply—usually contained in seeds, rods, or liquid—is placed within the patient.

Shortcomings of Traditional Radiation Therapy

Until the 1980s, radiation oncologists devised treatment plans using plain radiography, which rarely

Table 2. Modern Radiation Therapy Modalities

<i>Modality</i>	<i>Description</i>	<i>Indications/uses</i>	<i>Administration</i>
External beam radiation therapy			
Three-dimensional conformal radiation therapy	CT or MRI is used to target tumors while minimizing radiation exposure of healthy tissues	Most solid tumors	Daily outpatient treatments (as short as one to two minutes each), administered Monday through Friday for two to seven weeks; overlying skin may be marked with freckle-size tattoos or colored ink marks to guide the radiation beam; a mesh face mask or body mold may be used to immobilize the patient
Four-dimensional radiation therapy	Computer-assisted tracking or gating of CT images of moving targets	Tumors that are susceptible to movement, most commonly in the lung, liver, pancreas, or breast	Similar to three-dimensional conformal therapy; for gating, patients may be asked to hold their breath while the radiation beam is activated
Intensity-modulated radiation therapy	The radiation beam is divided into components ("beamlets"), which permits sparing of normal tissues	Tumors surrounding or adjacent to normal critical structures, most commonly head and neck or prostate cancers	Similar to three-dimensional conformal therapy, although individual treatments may last more than 30 minutes
Stereotactic radiosurgery (e.g., Gamma Knife)	Multiple radiation beams converge on target tumor, delivering high-dose radiation to the tumor, but little to surrounding tissues	Intracranial lesions, such as brain metastases, meningiomas, acoustic neuromas, arteriovenous malformations, and trigeminal neuralgia	Single treatment; to ensure proper patient positioning and immobility, a positioning frame is secured to the patient's skull, then attached to the radiation source; treatment lasts 45 to 60 minutes
Stereotactic body radiation therapy (e.g., Cyberknife)	High-dose radiation delivered using robotic guidance	Treatment of spine tumors, localized lung cancer, and other tumors in patients who are not candidates for surgery	Most commonly delivered as three to five fractions; during treatment, a robotic arm containing the radiation source (a linear accelerator) rotates around the patient to deliver radiation from multiple positions; each treatment lasts up to two hours; positioning may be accomplished using fiducial markers placed beforehand or using a rigid body frame
Internal radiation therapy			
Temporary brachytherapy implant	A radiation source is placed within or near the tumor target and is subsequently removed	Cervical cancer, sarcoma, vaginal cancer, oral cavity cancers	Catheters (smaller) or applicators (larger) are placed in body cavities or tissues; subsequently, the radiation source is placed within these devices; the patient may be hospitalized in a private room during treatment (radiation source is left in place throughout treatment), or the patient may undergo outpatient treatment for up to several weeks (radiation source is removed between treatments)
Permanent brachytherapy implant	A low-dose rate (i.e., long half-life) radiation source is placed within or near the tumor target	Prostate cancer	Radioactive seed implants are inserted into target tissue through a catheter under local or general anesthesia; initially, the patient may be required to limit social contacts after placement for up to one month; implants are never removed, but radiation dissipates within six months
Systemic radiation therapy	Systemically administered radioisotopes target tumor cells	Iodine-131 for thyroid cancer; strontium-89 and samarium-153 for painful bony metastases; yttrium-90 ibritumomab tiuxetan (Zevalin) and iodine-131 tositumomab (Bexxar) for non-Hodgkin lymphoma	Administered intravenously or orally; inpatient or outpatient, depending on specific treatment; patients are required to follow radiation precautions (careful disposal of body fluids, including urine, sweat, and tears; hand washing; condom use) for one week after treatment

CT = computed tomography; MRI = magnetic resonance imaging.

visualized a tumor directly. This treatment approach was associated with uncertainties, inconveniences, and toxicities. Because only an approximate location of the cancer could be determined, the radiation field needed

to include a generous margin. For example, in prostate cancer therapy, the treatment volume usually included portions of the gastrointestinal and genitourinary tracts. This led to radiation proctitis (characterized by fecal

urgency and rectal pain and bleeding) in up to 40 percent of patients⁷; sexual dysfunction in up to 50 percent of patients⁸; and urinary complications (e.g., incontinence, hematuria, strictures) in up to 10 percent of patients.⁹ Because radiation was typically administered over 30 or more daily fractions (fractional doses), the location of the target tumor varied throughout treatment. Slight changes in patient position were inevitable, and shifting rectal contents altered the prostate's anatomic position. In some patients, such organ movement led to underdosing of the target tumor and increased relapse rates.¹⁰

Modern Radiation Therapy Techniques EXTERNAL BEAM RADIATION THERAPY

A series of incremental technologic advances has improved the targeting of external beam radiation therapy. Computed tomography (CT) and magnetic resonance imaging (MRI) have largely replaced plain radiography in radiation treatment planning. Because CT and MRI permit the direct visualization of soft tissue structures, tumors can be precisely located, instead of approximated. These detailed images have been directly integrated with computer-based modulation of the radiation beam outline, a technique known as three-dimensional conformal radiation therapy. Contemporary imaging modalities, such as CT and MRI, have also been directly incorporated into radiation delivery machines, allowing for frequent confirmation of the tumor and patient positioning throughout the course of treatment. This approach, which may be applied to a number of radiation therapy techniques, is called image-guided radiation therapy (Figure 1). If critical healthy structures, such as nerves or vessels, are adjacent to or surrounded by the target tumor, the radiation beam may be subdivided into multiple component beams ("beamlets"), each of which may be modified individually; this technique is called intensity-modulated radiation therapy¹¹⁻¹³ (Figure 2). Figure 3 illustrates a modern radiation treatment plan using intensity-modulated radiation therapy techniques.

With three-dimensional conformal radiation therapy for prostate cancer, urinary and rectal toxicity rates have decreased substantially compared with conventional external beam radiation therapy¹⁴; these complications



Figure 1. Image-guided radiation treatment unit. Daily imaging of the radiation target permits ongoing modification of the radiation plan to accommodate changes in patient and tumor positions.

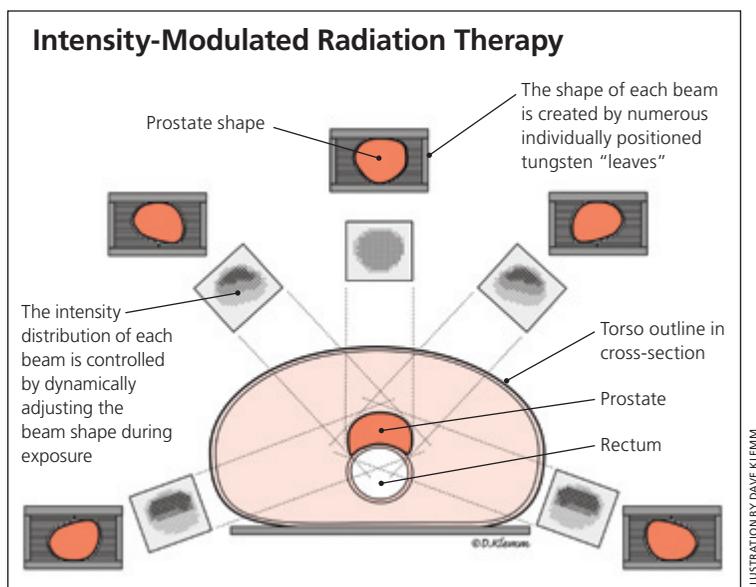


Figure 2. Concept of intensity-modulated radiation therapy for prostate cancer. Each radiation treatment is divided into separate beams. Each beam, subdivided into multiple "beamlets", delivers a unique pattern of radiation. The highly conformal radiation dose maximizes radiation to the tumor while minimizing exposure of healthy structures (e.g., the rectum).

have declined even further with intensity-modulated radiation therapy.^{11,12} Tumors susceptible to repeated movement, such as those in the lungs, may be tracked and targeted with rapidly acquired anatomic images (four-dimensional radiation therapy).^{15,16}

STEREOTACTIC RADIOTHERAPY AND RADIOSURGERY

Despite substantial improvements in tumor targeting, technologies such as three-dimensional conformal and intensity-modulated radiation therapy are prone to the inherent uncertainties and limitations associated with

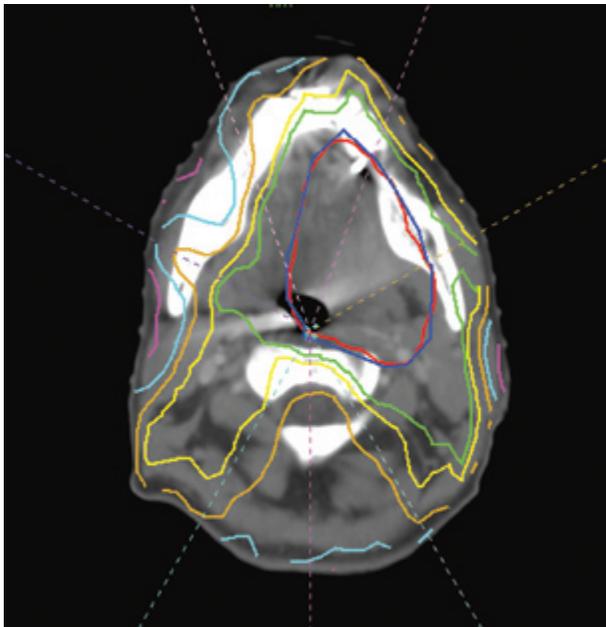


Figure 3. Modern radiation treatment plan using intensity-modulated radiation therapy techniques. The panel shows an axial computed tomography image used to plan radiation delivery for an oropharyngeal tumor. The colored lines represent isodose lines, depicting areas that receive a certain percentage of the radiation dose. These plans spare critical tissues, such as the parotid glands, the toxicities (e.g., xerostomia) of conventional modalities.

dose fractionation. If the target tissue was immobile and its localization highly dependable, normal tissues would receive minimal radiation, thus decreasing or eliminating the need for fractionation. A single treatment is more convenient than six weeks of daily sessions. A one-time, high-potency radiation dose also provides greater tumor kill rates than an equal or higher radiation dose divided over multiple administrations because there is less opportunity for cancer cells to repair damage to DNA.

This is the concept behind stereotactic radiosurgery, a specialized type of external beam radiation therapy. Stereotactic radiosurgery (*Figure 4*) has primarily been used as an alternative to surgery for the treatment of intracranial lesions, such as brain metastases, arteriovenous malformations, acoustic neuromas, trigeminal neuralgia, and meningiomas.¹⁷⁻²¹ The brain is an ideal location for this approach because there is essentially no internal organ movement. The Gamma Knife stereotactic radiosurgery system involves attaching a positioning device (i.e., a stereotactic frame) directly to the patient, then to the treatment unit. Outside the brain, stereotactic body radiation therapy also relies on patient immobilization equipment for accurate targeting of tumors. The

Cyberknife is a linear accelerator mounted on a robotic arm that provides more than 1,000 radiation beam orientations. It has been used to treat tumors in the lung, liver, spine, kidney, prostate, and pancreas.^{22,23} Although stereotactic radiation is often more effective than conventional radiation, the high radiation doses required for these treatments can lead to distinct radiation toxicities. Tubular structures, such as bronchi and bile ducts, are particularly prone to damage, which may manifest as luminal obliteration and obstruction.²³

BRACHYTHERAPY

With brachytherapy, the radiation source is permanently or temporarily placed within the patient, near the target tumor. For example, permanent iodine-125 radiation seed implants have become an established treatment for early-stage, low-risk prostate cancer. Temporary brachytherapy, administered via intracavitary catheters or larger applicators, is used to treat gynecologic malignancies, such as cervical cancer. Balloon catheters, filled with liquid radioisotopes, are used to limit local recurrence after the initial treatment of breast cancer and brain tumors; they are placed during surgical resection, then removed after several days.^{24,25}

SYSTEMIC RADIATION THERAPY

If adequate targeting is feasible, internal radiation may be administered systemically. Because thyroid tissue naturally concentrates iodine, iodine-131 may be given

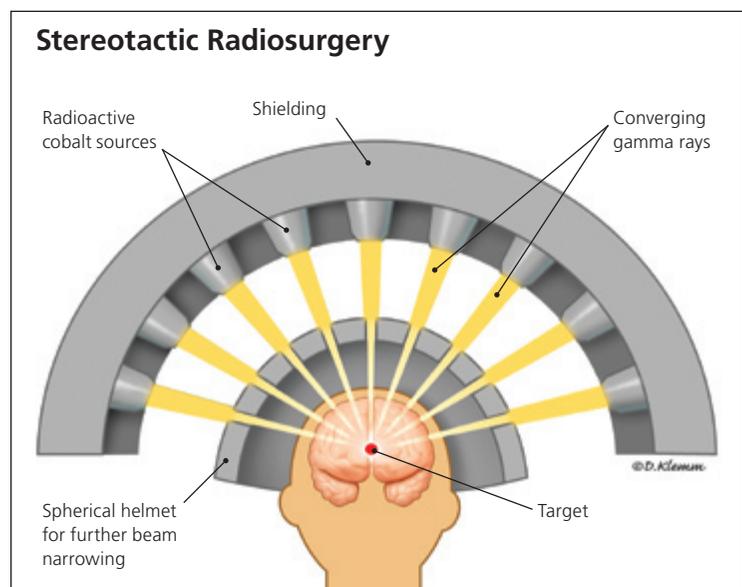


Figure 4. Concept of Gamma Knife stereotactic radiosurgery. Multiple separate small beams of radiation converge at the tumor target.

orally to treat localized and metastatic thyroid cancer²⁶ or benign causes of hyperthyroidism. Although this treatment almost always leads to hypothyroidism requiring thyroid hormone replacement, other organs are not affected. Similarly, the radioisotopes strontium-89 and samarium-153, which have affinity for bone, have been used to palliate painful skeletal metastases from prostate, breast, and lung cancers.²⁷ More recently, radioisotopes have been attached to monoclonal antibodies that target cancer cells (i.e., radioimmunotherapy) to treat non-Hodgkin lymphoma. Because these antibodies may be recognized as foreign proteins, patients must be closely monitored for infusion reactions.

Treatment Approach

CHOOSING RADIATION THERAPY

Radiation therapy may be presented to the patient as one of multiple treatment options. These options, which require multidisciplinary consultation and counseling, vary somewhat among diseases. For instance, localized prostate cancer is often treated with radical prostatectomy or radiation therapy. Rectal toxicities occur more commonly with radiation, whereas genitourinary complications occur more commonly with radical prostatectomy. Surgery lasts hours and provides immediate tumor removal, but has operative risks and discomforts. Radiation therapy lasts almost two months, and maximal prostate-specific antigen response does not occur until more than one year later²⁸; however, no incision is required. Despite these differences, surgery and radiation therapy generally have similar outcomes and overall complications. Therefore, in the absence of medical comorbidities precluding surgery, the selection of treatment modality depends highly on patient preference.²⁹⁻³¹ In contrast, for most patients with locally advanced laryngeal cancer, the choice of radiation versus surgery is more straightforward. Both treatment modalities have similar disease control rates^{1,2}; however, because total laryngectomy leads to the inability to speak, most physicians and patients opt for radiation, when feasible.

The selection of a specific radiation technique is also highly individualized. The improvements in imaging and dose distribution that characterize three-dimensional conformal radiation therapy and intensity-modulated radiation therapy make these techniques particularly suitable for tumors in the vicinity of critical normal structures, such as with prostate cancer and head and neck cancer. Stereotactic body radiation therapy appears to be effective in the treatment of early-stage lung cancer in patients who are not medically fit to undergo surgery; however, excessive toxicities preclude its use for tumors

located within 2 cm of the proximal bronchial tree.³² In addition to anatomic considerations, patient geography and economics also contribute to this decision. Although stereotactic and intensity-modulated radiation therapies are now available in most major metropolitan areas, they are typically not available in rural areas or smaller cities. For prostate cancer treatment, intensity-modulated radiation therapy may cost up to \$50,000, compared with \$10,000 to \$25,000 for conventional external beam radiation therapy.^{33,34}

RECEIVING RADIATION THERAPY

After an initial consultation with a radiation oncologist, the patient undergoes a treatment planning session (i.e., simulation). During this session, freckle-size tattoos or colored ink marks may be placed on the skin to guide the orientation of the radiation beam during treatment. A body mold or mesh face mask, to assist with patient immobilization, may be custom-fitted. Fractions are then delivered daily, Monday through Friday, for two to seven weeks depending on tumor type. Rarely, two smaller fractions may be administered daily (hyperfractionated radiation). For conventional external beam radiation therapy, each fraction takes only one to two minutes to deliver. For intensity-modulated radiation therapy, which requires frequent reorientation and reconfiguration of the radiation beam, it may take more than 30 minutes to deliver a fraction. Stereotactic radiation, which may be delivered as a single treatment or as three to five fractions administered every two to three days (for nonintracranial lesions), may take more than 45 minutes per fraction.

The radiation treatment itself is painless. However, discomfort may occur from attachment of a frame to the skull during stereotactic radiosurgery or from insertion of a catheter or applicator during brachytherapy. Patients undergoing external beam radiation therapy are not radioactive because the source of radiation remains outside the body; radiation exposure occurs only when the beam is turned on during the treatment session. In contrast, the radiation source is implanted within patients receiving brachytherapy. Temporary brachytherapy techniques may require hospitalization in a private room during the treatment course. Patients receiving radioimmunotherapy have circulating radioisotopes that are cleared from the bloodstream over several days. Although outpatient treatment is an option, patients receiving radioimmunotherapy must take radiation precautions (hand washing; careful disposal of body fluids, including urine, tears, and sweat; and condom use) for one week. With permanent brachytherapy devices, patients may be

Table 3. Potential Toxicities of Radiation Therapy

<i>Healthy tissue at risk</i>	<i>Toxicities*</i>	<i>Monitoring/prevention</i>	<i>Treatment</i>
Brain			
Optic nerves, chiasm, lens, retina	Late: blindness, optic neuritis, cataracts, retinal atrophy	—	Cataract removal
Brainstem	Acute: edema Late: motor and sensory dysfunction, stroke, radionecrosis	Follow-up MRIs	Corticosteroids
Brain tissue	Acute: edema, fatigue, nausea Late: radionecrosis, memory loss	Follow-up MRIs	Corticosteroids Surgery for persistent, symptomatic necrosis
Hair	Acute/late: alopecia	—	Scalp protection when outdoors
Head and neck			
Salivary glands	Acute/late: xerostomia	Amifostine (Ethyol; an intravenous cytoprotective agent), ³⁸ smoking cessation, gargling often with salt or baking soda solution	Saliva substitutes; saliva stimulants (sialogogues, such as pilocarpine [Salagen])
Mucous membranes	Acute: mucositis Late: dysphagia	Smoking cessation	Topical anesthetics (viscous lidocaine [Xylocaine]), systemic analgesics
Teeth and gums	Acute: infection, decay Late: osteoradionecrosis	Dental evaluation and treatment (e.g., extraction of diseased teeth) before starting radiation and throughout follow-up ³⁹	Hyperbaric oxygen
Pharyngeal muscles	Late: swallowing dysfunction, speech problems	Jaw muscle exercises	Speech and swallowing therapy
Thyroid	Late: hypothyroidism	Thyroid-stimulating hormone tests every six to 12 months after completion of radiation therapy	Thyroid hormone supplementation
Thorax			
Lungs	Acute: pneumonitis Late: loss of lung capacity, fibrosis	Smoking cessation	Acute: corticosteroids; chronic: supplemental oxygen, pentoxifylline (Trental), vitamin E
Heart	Late: pericarditis, coronary artery disease	—	Coronary stents, cardiac surgery
Esophagus	Acute: esophagitis Late: esophagus stricture	—	Topical or systemic analgesics Esophagus dilatation
Spinal cord	Late: paralysis, myelitis	—	Corticosteroids
Abdomen			
Liver	Late: liver damage	—	—
Stomach	Acute: nausea, vomiting Late: ulceration	Antiemetic agents Proton pump inhibitors	Antiemetic agents Proton pump inhibitors
Small bowel	Acute: nausea, vomiting, diarrhea Late: small bowel obstruction	Antiemetic agents	Antiemetic agents, antidiarrheal agents (e.g., loperamide [Imodium])
Kidney	Late: renal failure	—	—

(continued on next page)

required to limit social contacts, particularly with children and pregnant women, for up to one month after implantation. Although the implants are never removed, the radiation dissipates within six months.

FOLLOW-UP

Because 75 percent of patients receiving radiation are treated with the intent to cure the cancer,³⁵ family physicians are likely to care for these patients not only

before and during their radiation treatment, but also in the years after treatment. Thus, an understanding of radiation toxicities (*Table 3*³⁶⁻³⁹) will assist in the treatment of these patients.⁴⁰ Localized skin changes and fatigue occur in many patients receiving external beam radiation therapy. Other adverse effects of radiation therapy depend largely on the anatomic site. Common toxicities include diarrhea, nausea and vomiting, mucositis, xerostomia, hair loss in the treatment area, and

Table 3. Potential Toxicities of Radiation Therapy (continued)

Healthy tissue at risk	Toxicities*	Monitoring/prevention	Treatment
Pelvis			
Rectum	Acute: proctitis, rectal bleeding Late: rectal bleeding, rectal stricture	Sitz baths	Hydrocortisone cream Rectal dilatation
Bladder	Acute: cystitis, incontinence, urinary frequency, bladder spasms Late: urethral stricture, bladder contracture	—	Alpha blockers (e.g., tamsulosin [Flomax]), urethral dilatation for strictures
Vagina	Acute: vaginal dryness and irritation Late: vaginal stenosis or stricture	Lubrication during sexual intercourse	Vaginal dilatation
Ovaries, testes	Late: infertility	Sperm or egg preservation	—
Prostate	Acute: urinary obstruction	—	Alpha blockers
Sexual function (men)	Late: impotence	—	Phosphodiesterase inhibitors (e.g., sildenafil [Viagra]), penile implant
Bone marrow	Acute/late: myelosuppression	Weekly blood counts	Erythropoietin therapy Myeloid growth factors (e.g., granulocyte-colony-stimulating factor)
Extremities			
Joints	Late: scar tissue accumulation, loss of motion	—	Physical therapy, surgery
Lymph nodes	Late: lymphedema	—	Extremity wraps, physical therapy

MRI = magnetic resonance imaging.

*—Toxicities resulting from damage to normal tissues during the course of radiotherapy. These effects generally occur when the target organ receives a dose of radiation above a specific threshold (tolerance dose). Fatigue and skin changes may occur in all areas. By decreasing radiation exposure to normal tissues, modern radiation therapy techniques have reduced, but not eliminated, these toxicities.

Information from references 36 through 39.

sexual and urinary changes. Plain, nonscented, lanolin-free hydrophilic cream can help patients who have radiation skin reactions.⁴¹ Most acute toxicities resolve within the two months after the completion of radiation therapy, although some persist indefinitely.

Late toxicities may appear years after the completion of radiation therapy and, as with acute toxicities, vary by radiation field and dose. Late effects may include lymphedema, joint problems, xerostomia, infertility, cognitive changes, and, rarely, secondary malignancies. Men and women wishing to have children after receiving pelvic radiation may consider sperm or egg preservation before starting treatment. Because radiation is teratogenic in all stages of pregnancy, birth control is essential for women who could become pregnant.^{5,42} Follow-up after radiation therapy, which consists of regular physician visits, radiologic studies, or serum tumor markers, focuses on toxicity management and detecting cancer recurrence.

Figure 1 courtesy of Elekta Corporation.

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REFERENCES

- Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahnoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. *J Natl Cancer Inst.* 1996;88(13):890-899.
- Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med.* 2003;349(22):2091-2098.
- Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med.* 2002;347(16):1227-1232.
- Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and

Radiation Therapy

- lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347(16):1233-1241.
- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Breast cancer. 2008. http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf. Accessed October 10, 2008.
 - Coutard H. Principles of x-ray therapy of malignant diseases. *Lancet*. 1934;2:1-8.
 - Perez CA, Hanks GE, Leibel SA, Zietman AL, Fuks Z, Lee WR. Localized carcinoma of the prostate. Review of management with external beam radiation therapy. *Cancer*. 1993;72(11):3156-3173.
 - Hamilton AS, Stanford JL, Gilliland FD, et al. Health outcomes after external-beam radiation therapy for clinically localized prostate cancer. *J Clin Oncol*. 2001;19(9):2517-2526.
 - Halperin EC, Schmidt-Ullrich RK, Perez CA. Overview and basic science of radiation oncology. In: Perez CA. *Principles and Practices of Radiation Oncology*. 4th ed. Philadelphia, Pa.: Lippincott Williams & Wilkins; 2004:1-95.
 - de Crevoisier R, Tucker SL, Don L, et al. Increased risk of biochemical and local failure in patients with distended rectum on the planning CT for prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005;62(4):965-973.
 - Zelefsky MJ, Fuks Z, Happersett L, et al. Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. *Radiation Oncol*. 2000;55(3):241-249.
 - Xia P, Pickett B, Vigneault E, Verhey LJ, Roach M III. Forward or inversely planned segmental multileaf collimator IMRT and sequential tomotherapy to treat multiple dominant intraprostatic lesions of prostate cancer to 90 Gy. *Int J Radiat Oncol Biol Phys*. 2001;51(1):244-254.
 - Daly ME, Lieskovsky Y, Pawlicki T, et al. Evaluation of patterns of failure and subjective salivary function in patients treated with intensity modulated radiotherapy for head and neck squamous cell carcinoma. *Head Neck*. 2007;29(3):211-220.
 - Soffen EM, Hanks GE, Hunt MA, Epstein BE. Conformal static field radiation therapy treatment of early prostate cancer versus non-conformal techniques. *Int J Radiat Oncol Biol Phys*. 1992;24(3):485-488.
 - Shirato H, Shimizu S, Kunieda T, et al. Physical aspects of a real-time tumor-tracking system for gated radiotherapy. *Int J Radiat Oncol Biol Phys*. 2000;48(4):1187-1195.
 - Vedam SS, Keall PJ, Kini VR, Mohan R. Determining parameters for respiration-gated radiotherapy. *Med Phys*. 2001;28(10):2139-2146.
 - Rades D, Bohlen G, Pluemer A, et al. Stereotactic radiosurgery alone versus resection plus whole-brain radiotherapy for 1 or 2 brain metastases in recursive partitioning analysis class 1 and 2 patients. *Cancer*. 2007;109(12):2515-2521.
 - Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases. *JAMA*. 2006;295(21):2483-2491.
 - Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases. *Lancet*. 2004;363(9422):1665-1672.
 - Maruyama K, Kawahara N, Shin M, et al. The risk of hemorrhage after radiosurgery for cerebral arteriovenous malformations. *N Engl J Med*. 2005;352(2):146-153.
 - Régis J, Metellus P, Hayashi M, Roussel P, Donnet A, Bille-Turc F. Prospective controlled trial of Gamma Knife surgery for essential trigeminal neuralgia. *J Neurosurg*. 2006;104(6):913-924.
 - Timmerman RD, Kavanagh BD, Cho LC, Papiez L, Xing L. Stereotactic body radiation therapy in multiple organ sites. *J Clin Oncol*. 2007;25(8):947-952.
 - Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol*. 2006;24(30):4833-4839.
 - Vicini F, Beitsch PD, Quiet CA, et al. Three-year analysis of treatment efficacy, cosmesis, and toxicity by the American Society of Breast Surgeons MammoSite Breast Brachytherapy Registry Trial in patients treated with accelerated partial breast irradiation (APBI). *Cancer*. 2008;112(4):758-766.
 - Chan TA, Weingart JD, Parisi M, et al. Treatment of recurrent glioblastoma multiforme with GliSite brachytherapy. *Int J Radiat Oncol Biol Phys*. 2005;62(4):1133-1139.
 - Jonklaas J, Sarlis NJ, Litofsky D, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. *Thyroid*. 2006;16(12):1229-1242.
 - Bauman G, Charette M, Reid R, Sathya J. Radiopharmaceuticals for the palliation of painful bone metastasis. *Radiation Oncol*. 2005;75(3):258-270.
 - Crook JM, Choan E, Perry GA, Robertson S, Esche BA. Serum prostate-specific antigen profile following radiotherapy for prostate cancer: implications for patterns of failure and definition of cure. *Urology*. 1998;51(4):566-572.
 - Wilt TJ, MacDonald R, Rutks I, Shamlivan TA, Taylor BC, Kane RL. Comparative effectiveness and harms of treatments for clinically localized prostate cancer [published correction appears in *Ann Intern Med*. 2008;148(11):888]. *Ann Intern Med*. 2008;148(6):435-448.
 - Paulson DF, Lin GH, Hinshaw W, Stephani S. Radical surgery versus radiotherapy for adenocarcinoma of the prostate. *J Urol*. 1982;128(3):502-504.
 - National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Prostate cancer. 2008. http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf. Accessed October 10, 2008.
 - Timmerman RD, Park C, Kavanagh BD. The North American experience with stereotactic body radiation therapy in non-small cell lung cancer. *J Thorac Oncol*. 2007;2(7 suppl 3):S101-112.
 - Konski A, Watkins-Bruner D, Feigenberg S, et al. Using decision analysis to determine the cost-effectiveness of intensity-modulated radiation therapy in the treatment of intermediate risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2006;66(2):408-415.
 - Konski A, Sherman E, Krahn M, et al. Economic analysis of a phase III clinical trial evaluating the addition of total androgen suppression to radiation versus radiation alone for locally advanced prostate cancer. *Int J Radiat Oncol Biol Phys*. 2005;63(3):788-794.
 - American Society for Therapeutic Radiology and Oncology. Fast facts about radiation oncology. <http://www.astro.org/PressRoom/FastFacts/documents/FFRT121.pdf>. Accessed August 14, 2008.
 - Gunderson LL, Tepper JE. *Clinical Radiation Oncology*. Philadelphia, Pa.: Elsevier; 2007:1-74.
 - National Cancer Institute. Radiation therapy and you. <http://www.cancer.gov/cancertopics/radiation-therapy-and-you>. Accessed August 13, 2008.
 - Hensley ML, Schuchter LM, Lindley C, et al. American Society of Clinical Oncology clinical practice guidelines for the use of chemotherapy and radiotherapy protectants. *J Clin Oncol*. 1999;17(10):3333-3355.
 - Keefe DM, Schubert MM, Elting LS, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer*. 2007;109(5):820-831.
 - Small W Jr, Woloschak GE. *Radiation Toxicity*. New York, NY: Springer; 2006.
 - Bolderston A, Lloyd NS, Wong RK, Holden L, Robb-Blenderman L. The prevention and management of acute skin reactions related to radiation therapy. *Support Care Cancer*. 2006;14(8):802-817.
 - Pereg D, Koren G, Lishner M. Cancer in pregnancy. *Cancer Treat Rev*. 2008;34(4):302-312.