Annals of Surgical Oncology, 4(6):516–522
Published by Lippincott–Raven Publishers

Educational Review

What a Surgeon Needs to Know About Radiation

Avraham Eisbruch, MD, and Allen S. Lichter, MD

Background: A better understanding of the physical and biologic principles of radiation oncology, along with improvements in the technical and clinical aspects of this field, have been gained in recent years. Some of these aspects are presented, with an emphasis on their relevance to the oncologic surgeon.

Results: Recent innovations have improved our ability to deliver high radiation doses safely and to increase the therapeutic ratio of radiation. They include the concurrent administration of radiation sensitizers and chemotherapy, altered fractionation schemes, and the conformal delivery of radiation using sophisticated imaging and planning tools.

Conclusions: The increasing efficacy of radiation, resulting from innovations described in this review and others, enhances the role of radiotherapy in the struggle against cancer.

Key Words: Radiation—Chemotherapy.

Radiation constitutes an integral part of the treatment of malignancies, as a single modality or as a part of combined modality treatment plans. In recent years, a better understanding of the biologic principles underlying the response of tumors to radiation and improved technical aspects of radiation delivery have emerged. We present some of the basic principles of the treatment of malignancies with radiation and recent advances in the field.

PHYSICAL BASIS OF RADIATION

Radiation interacts with biologic material by removing an orbiting electron from an atom, thus causing ionization (hence the term "ionizing radiation"). The energy dissipated by the ionizing event is enough to break strong chemical bonds, most importantly in DNA, leading to the biologic effect. The unit used to describe the amount of radiation quantifies the amount of energy absorbed per unit mass. This quantity is called "absorbed dose" and is measured in joules per kilogram. One joule per kilogram is one gray (Gy) which is the major unit used to express radiation dosage. A hundredth of a gray is the centigray (cGy), which is equivalent to the older unit, the rad. In clinical practice the most often used range of electromagnetic radiation energies are megavoltage: energies of more than 1 million electron volts (MeV). As the energy increases, the penetration of the radiation increases and the skin is spared because the electrons created during the interaction of photons and tissue travel a distance forward and achieve the full intensity only at some depth below the skin. The absorption of high-energy photons in bone is not different from that in the soft tissues. Lower energy radiation, used in the first half of the century, in the range of 125 to 250 kiloelectron volts (KeV), dissipates most of its energy at the skin surface and therefore is only used today to treat superficial skin cancers, or superficial rectal tumors in contact therapy. Even lower energies than these are used in diagnostic radiology, in which the absorption of energy in bone is higher than that in soft tissue, a quality that is well suited for diagnostic purposes.

BIOLOGIC BASIS

The important target of radiation in the cell is thought to be the DNA. It can be effected directly by radiation, or

Received August 22, 1996; accepted January 6, 1997.

From the Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan, USA.

Address correspondence and reprint requests to Dr. A. Eisbruch, Dept. of Radiation Oncology, University of Michigan Hospitals, 1500 E. Medical Center Dr., Ann Arbor, MI 48109, USA.

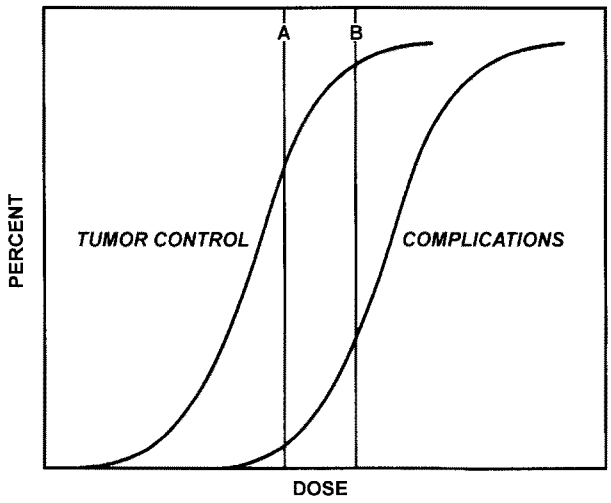

FIG. 1. The probabilities of tumor control and of complications versus dose. At lower doses **(A)** the probability of complications is low with a moderate chance of tumor control. Increasing the dose **(B)** may gain a higher chance of tumor control at the price of significantly higher complication risks.

more commonly, the photon may interact with water, the predominant molecule in the cell, to produce highly reactive free radicals that indirectly damage DNA. The damage to DNA exerted by radiation causes interference with the reproductive capability of the cell. An irradiated cell may still divide once or more until its progeny become reproductively sterile, and are eventually phagocytized by macrophages. As a consequence, the effect of radiation on tumor or normal tissue depends on the number of cells in active reproductive cycle and on the length of the regeneration cycle of the cells. Because cells are usually not directly damaged by radiation but sustain reproductive damage, tumors may only start to shrink after several weeks of radiation and completely disappear only at its completion or several weeks or months later. The effect on normal tissue is similar: skin or mucosal reactions are evident only several weeks after the start of radiation.

Most tumor and normal tissue have dose-response relationships that can be plotted as a sigmoid curve (Fig. 1). A minimum dose of radiation must be given before any response is seen, then the response to radiation increases slowly with an increase of dose. At a certain dose level the tissue or tumor response becomes exponential, with larger shrinkage of tumor or more damage to normal tissue following each unit increase in dose. Tumor control can only be achieved if complete response—the complete regression of tumor—is achieved. For larger tumors, higher doses of radiation are necessary to induce complete response and a high rate of tumor control compared with small tumors. For example, microscopic solid tumors (no gross residual disease after surgery) need 50–60 Gy for a high chance of local control. Tumors measuring 1 cm in their largest diameter need 60–65 Gy for control, and tumors measuring 3 cm need 70 Gy and larger tumors need higher doses (1). However, it should be noted that some tumor types that are very sensitive to radiation (e.g., lymphoma and seminoma) require significantly lower doses to achieve complete eradication; also, large variations in the responses of individual tumors within the same histologic classes may exist. For comparison, the radiation doses that cause a 5% chance of long-term complications for various organs are detailed in Table 1. It is evident that the doses required to eradicate most tumors are at the range where long-lasting normal tissue damage may occur. The total doses are given in the common fractionation of 1.8–2.0 Gy daily, over several weeks, five days a week. Dividing the radiation dose into a large number of fractions spares normal tissue by allowing repair of sublethal damage to occur between daily fractions. It also increases damage to the tumor as a result of reoxygenation between fractions (hypoxic cells are less sensitive).

Acute radiation effects occur in tissues that have high rates of turnover of cells: skin, the mucosa of the gastrointestinal tract, bladder and vagina, and hair follicles. Because the effect of radiation on these tissues depends on the balance between cell replication and death, the acute reactions are mainly affected by the time intervals between fractions (which allow cell repopulation) and to a lesser extent by the radiation fraction size (which determines how many cells are killed per fraction). Whenever an acute reaction occurs in the mucosa or skin, a small decrease in the fraction size or an increase in the time allowed between treatments (usually a several day break in radiation) permits rapid recovery. On the other

TABLE 1. *Radiation doses that may cause 5% and 50% complications rate in various organs*

Organ	Complication	Dose* producing a complication rate of 5%	50%
Testes	Sterility	1	2
Ovary	Sterility, menopause	6	10
Eye (lens)	Cataract	6	12
Lung	Pneumonitis	20	30
Kidney	Nephritis	20	30
Liver	Hepatitis	30	40
Heart	Pericarditis	40	50
Spinal cord	Myelitis	50	60
Small bowel	Obstruction	55	65
Large bowel	Proctitis	65	70
Brain	Necrosis	60	70
Bone and muscle	Necrosis	65	>70

* Doses in Gy; standard fractionation, 1.8–2.0 Gy daily.

hand, late tissue effects manifest as long-lasting complications after radiation. They include necrosis of soft tissue or bone, fibrosis, fistula formation between organs, ulceration, permanent damage to organs such as kidneys or spinal cord, and blindness due to irreversible damage to the optic nerves. These late effects primarily depend on the total dose of radiation and to a great extent on the size of each radiation fraction.

The difference between the characteristics of early and late radiation effects may be exploited in order to increase the therapeutic effect of radiation. One way is hyperfractionation, in which the overall treatment time remains unchanged (6 to 8 weeks) but radiation fractions are given twice daily and the dose per fraction is decreased. The aim is to reduce late effects by reducing the dose per fraction and, with an increased total dose, to achieve better tumor control. A different strategy is accelerated fractionation, in which two or more fractions of radiation are given daily and the overall radiation time is markedly decreased. The intent of accelerated fractionation is to reduce the chance of repopulation in rapidly proliferating tumors (Fig. 2).

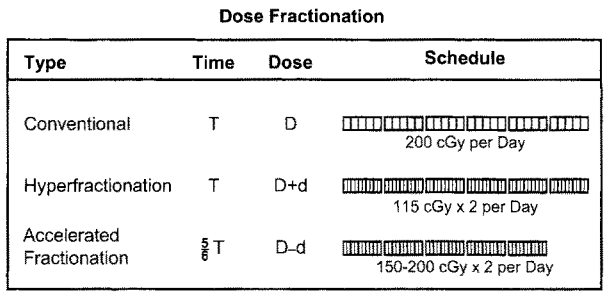

FIG. 2. Common fractionation schemes. In the conventional scheme, 1.8–2.0 Gy are delivered daily, five fractions a week; a total of 70 Gy is delivered in 7 weeks. In the hyperfractionation scheme a reduced dose is delivered in each fraction (1.1–1.2 Gy), twice daily, and the total dose may be increased due to the relative sparing of normal tissue from late toxicity. Accelerated fractionation strives to reduce the overall treatment time. Radiation according to this scheme is delivered twice daily throughout the treatment or at the end of the radiation course. Fraction size is 1.5–1.8 Gy, similar to the conventional fraction size. The total treatment time is reduced, and the total dose is the same as in the conventional scheme, or it may be reduced due to more severe acute tissue reactions.

TECHNICAL ASPECTS OF RADIATION

Achieving the best results in radiotherapy depends on delivering a homogenous, high radiation dose to a well-defined region that includes the tumor and tissue at risk for subclinical disease while minimizing the dose to the surrounding normal tissue. Several steps are used to achieve this goal. The first step is the determination of the target to be irradiated and the dose-limiting normal organs in the vicinity. The target encompasses the tumor and the areas at risk of subclinical disease, typically regional lymph nodes and tissue, which may be infiltrated with microscopic disease. The treatment planning process includes examination of alternative techniques of treatment and selection of the optimal treatment plan. This is done using a simulator, which reproduces the geometry of the treatment machine but uses low-energy radiation to produce diagnostic-quality radiographs that delineate the beam location relative to bony landmarks. The best beam distribution that will achieve homogeneity within the target volume and will minimize the dose to normal tissue is determined. These decisions are made by a team that includes the radiation oncologist, radiation physicist, and dosimetrist. After the optimal treatment plan has been accepted, simulator films are used to further modify the plan by allowing blocking of the parts of the beams that traverse through tissue not included within the target. Immobilization devices and marking on the patient's skin are used to ensure that the daily treatments are given in exactly the same way. After simulation, a dedicated computer is used to calculate the output of the radiation machine that is required to deliver each specified dose, and the patient is ready to start treatment.

Recent advances in external beam radiation include the development of three-dimensional radiotherapy treatment planning and delivery (2). In the traditional two-dimensional treatment planning, planar x-rays and single transverse slices of computed tomography (CT) scans or magnetic resonance imaging are used to define the target to be irradiated and the radiation beam arrangement. The new technique uses reconstruction of the CT data to display the tumor and normal tissue anatomy three dimensionally. Complex radiotherapy treatments can be planned that optimize dose delivery, enabling further restriction of the dose to the normal tissue, and escalation of the dose to the target beyond conventionally accepted doses (Fig. 3). Such dose escalation trials are currently being performed for brain, lung, and prostate cancer. Preliminary studies show that doses exceeding previously established thresholds for toxicity can be safely delivered using three-dimensional planning (3). During the next few years we may be able to assess whether higher tumor control is achieved with higher radiation doses.

COMBINED RADIATION AND CHEMOTHERAPY

Treatment programs that combine radiation and chemotherapy have taken into account the advantages of each modality, and the possible additive or even syner-

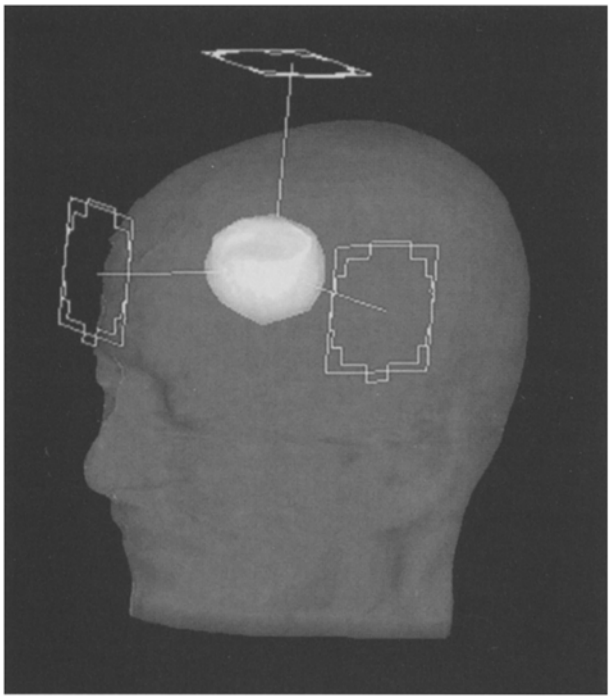

FIG. 3. Three-dimensional treatment planning of a brain tumor. After 3D reconstruction of images of the tumor and the surrounding normal organs, an arrangement of beams producing isodoses that conform to the target is determined using "beam's-eye view" techniques.

gistic effects of combining them. Radiation alone may fail to cure if unsuspected systemic metastases exist, if the tumor contains resistant tumor cells due to hypoxia, or if suboptimal radiation doses must be delivered due to dose-limiting normal tissue. The chemotherapeutic agents used should have proven efficacy against the tumor, so that they are potentially capable of controlling systemic disease. The toxicity of the chemotherapeutic agents and radiation should be independent and different. Chemotherapy may be given before or concurrently with radiation. Chemotherapy before radiation may reduce the tumor burden and the amount of hypoxic cells in the tumor, facilitating the effect of subsequent radiation. Certain chemotherapeutic agents have radiation-sensitizing properties and are therefore most suitable for concurrent combined treatment. Cis-platinum and 5-fluorouracil interfere with sublethal damage repair. Other chemicals may increase radiation effectiveness by preferentially killing cells that are more resistant to radiation. For example, hydroxyurea destroys cells in the more resistant synthesis phase of the cell cycle. Clinical examples of successfully combining radiotherapy and chemotherapy include pediatric cancer, notably Wilms' tumor and Hodgkin's lymphoma, where the use of effective chemotherapy may allow reduced radiation doses, thus limiting potential complications (4). In adult patients with squamous cell carcinoma of the anus, combined radiation and chemotherapy is as effective in eradicating tumor as radical surgery, while preserving the anus and rectum (5). Improved results when chemotherapy is delivered concurrent with radiation, compared with radiation alone, have been reported in advanced esophageal (6), lung (7), and extracranial head and neck cancer (8). In patients with head and neck cancer, tumors that respond well to chemotherapy have a high chance to be eradicated with radiation. A recent approach in the treatment of advanced, resectable laryngeal cancer relies on this observation: "Induction" chemotherapy is given and the patients whose tumors respond are referred for definitive radiation, thus sparing their larynx, whereas nonresponders undergo laryngectomy (9).

In patients with cancer of the gastrointestinal tract, such as that of the rectum, stomach, and pancreas, combined chemo-radiotherapy has been used mostly as an adjuvant to surgery. After surgery for advanced adenocarcinoma of the rectum, stage B2 and up, combined adjuvant treatment with radiation and 5-fluorouracil achieved superior local control and survival compared with chemotherapy alone, radiation alone, or no adjuvant treatment in randomized trials (10).

PRINCIPLES OF COMBINING RADIATION AND SURGERY

The rationale for combining surgery and radiation relates to the different pattern of failure resulting from these two modalities. In surgery, the gross resectable tumor can be removed, but in some cases, due to the inability to resect surrounding tissues containing microscopic tumor, the periphery of the surgical bed is at risk for tumor recurrence. On the other hand, radiation usually fails in the center of large tumors and not in their periphery, where the number of tumor cells is small and they are well oxygenated. Therefore, combining these modalities is a logical approach. Radiation may be given either pre- or postoperatively. Preoperative radiation may eliminate potential seeding of the tumor during surgery by rendering the seeded tumor cells inactive. It allows smaller treatment fields because the operative bed has not been contaminated with tumor cells, and in the case of unresectable tumors, it may reduce tumor volume sufficiently to allow resection. The disadvantages of preoperative radiation include the inability to select patients for radiation and plan radiation on the basis of the anatomic extent of disease, which may be apparent at surgery. It is difficult to effectively reirradiate if cancer is discovered at the margin of excision. Surgery is delayed by 4 to 6 weeks to allow for tissue recovery. Downstag-

ing of the tumor by radiation may inadvertently influence the selection of other adjuvant therapies that would otherwise be given.

Postoperative radiation has a number of advantages. The subgroup of patients who are most likely to benefit from radiation can be defined after the surgical exploration and the pathologic review. A higher radiation dose compared with preoperative radiation may be delivered safely. The target volumes and radiation doses can be tailored to the findings at surgery. A higher radiation dose will be delivered if macroscopic tumor was left behind or if the surgical specimen shows tumor involvement at its margin, and a lower dose if the surgical margins are negative for tumor cells but the surrounding tissues are suspected of harboring subclinical disease. There are some disadvantages associated with postoperative irradiation: the volume of normal tissue requiring radiation may be greater after the surgical procedure, and the tumor may be poorly oxygenated due to disruption of blood supply and therefore may be less sensitive to radiation. In cases involving abdominal surgery, postoperative adhesions may fix or reduce the mobility of small bowel loops, resulting in a higher risk of radiation damage. Due to the inhibition of the fibroblast migration by radiation, postoperative radiation should be delayed after surgery by 3 to 4 weeks, and healing of the surgical scars should be complete before radiation is commenced. Delaying the start of radiation much beyond this period may allow for tumor cell proliferation and potentially reduce the efficacy of radiation. It is uncertain which sequence, preoperative or postoperative radiation, is superior in each clinical setting. Many standard sequences were established due to historical rather than scientific reasons.

An additional approach to combining surgery and radiation is when limited surgical removal of the gross tumor is combined with a full course of radiation, sterilizing the site of maximum tumor burden. This approach is used when lumpectomy is followed with definitive radiation for the treatment of limited breast cancer. Removal of the gross tumor enables delivering moderate doses of radiation to the breast, thus preserving the organ with good cosmetic results (11). Limb preservation in soft-tissue sarcomas of the extremities relies on wide excision of the tumor followed with irradiation, achieving the same local tumor control that may be gained by amputation (12).

After surgery for sarcoma, breast, and certain head and neck tumors, the pathologic examination may show microscopic tumor at the edge of the resected specimen. This usually implies that the tumor cell burden left behind is higher than in cases where the specimen margins are negative. The outcome of postoperative radiation in these cases is less optimal, with a higher risk of tumor recurrence or poorer cosmetic results and more radiation-related complications due to the higher radiation doses that would be required. Reexcision of the tumor bed and achieving clear margins are recommended in these cases, whenever this is technically feasible (13).

Leaving radiopaque markers at surgery to delineate the tumor bed enables accurate definition of the target for radiation. This helps to avoid missing the target and restricts the tissue volume that receives high doses of radiation. In the conservation treatment of breast cancer, this practice may result in better cosmetic results (Fig. 4). In the postoperative irradiation of abdominal tumors, it may decrease bowel-related complications by decreasing the amount of bowel in the radiation fields.

PALLIATIVE ROLE OF RADIOTHERAPY

Radiotherapy is a powerful tool for controlling symptoms in patients with metastatic disease. Pain due to bony

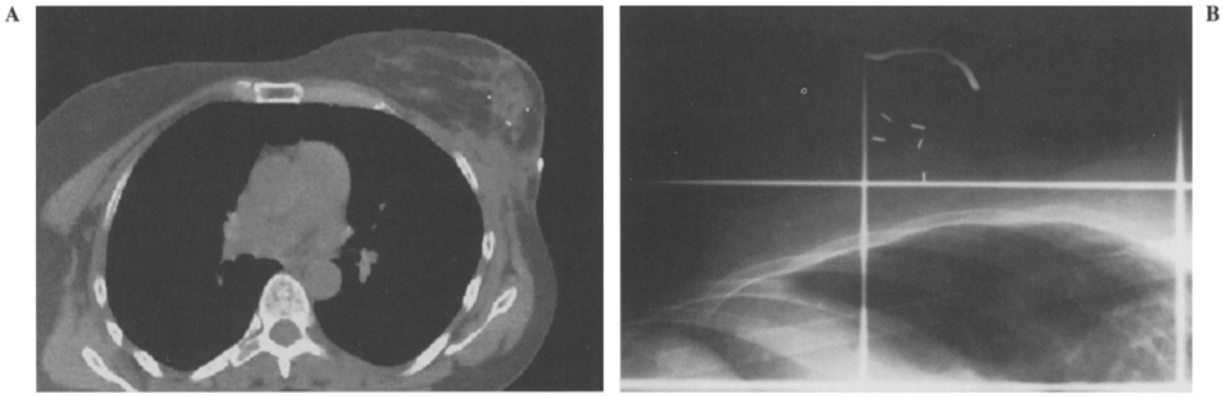

FIG. 4. Radiopaque markers left at the lumpectomy bed in a patient with breast cancer **(A)** are visible on the radiation simulation film **(B),** allowing accurate focal boost irradiation to the target. This will help avoid missing the target and will minimize the volume of breast tissue receiving a high dose.

metastases can be effectively treated if the cause of pain can be localized and identified with radiologic means and physical examination. A Radiation Therapy Oncology Group (RTOG) randomized study showed that doses of radiation of 8 Gy in one fraction, 20 Gy in five fractions, or 30 Gy in 10 fractions give equal response rates; about half of the patients receiving radiation achieved complete pain relief, and an additional one third had partial pain relief. Patients receiving the more protracted radiation course had their symptoms relieved for longer period of time (14). When the life expectancy of the patient is long, for example, in patients with breast cancer whose sole site of metastases is bone, a more protracted course of radiation may be advisable.

Radiation is usually recommended for symptomatic metastases only. However, lytic metastases in weight-bearing bones such as the femur, tibia, or humerus, also should be considered for irradiation regardless of symptoms to prevent future fracture. Before radiation starts, such bones with lytic metastasis that erode 50% or more of the cortex should be considered for internal or external fixation due to the high probability of subsequent fracture. If pathologic fracture occurs, internal fixation is then necessary to immobilize the bone, decrease pain and accelerate healing and ambulation of the patient.

Spinal cord compression due to metastases to the epidural space is most commonly caused by metastases to the vertebral body extending posteriorly to the spinal canal and invading the epidural space. If posterior laminectomy is performed, tumor resection anterior to the cord is minimal and radiation is usually required postoperatively. When a patient presents with sensory changes and weakness due to cord compression, steroids should be started and radiation should follow promptly, within 24 h. Such patients have a 50% chance of becoming ambulatory if treatment is started promptly (15). On the other hand, patients who present with paraplegia have a poorer outcome and their neurologic deficit is rarely reversible. The main benefit of radiation in such patients may be pain relief.

In patients with lung cancer, several palliative roles of radiation exist. In cases of lung atelectasis, an effective dose of radiation may be delivered to a limited volume, shrink metastatic hilar lymph nodes or an endobronchial mass, and permit reinflation of the lung. Pain and hemoptysis also may be effectively controlled with radiation. Malignant pleural infusion, on the other hand, requires radiation to the whole pleural surface. Because the tolerance of the whole lung to radiation is well below tumoricidal dose, pleural effusions cannot be treated effectively with radiation, nor can lymphangitic spread of solid tumors in the lung.

Brain metastases are usually multiple, and radiation to the whole brain frequently induces improvement in neurologic function and significant relief of symptoms such as headache. Twenty grays in 1 week or 30 Gy in 2 weeks are as effective for palliation as any other dose regimen. When a single brain metastasis is apparent, surgical removal of the metastasis followed by radiation is superior to radiation alone in disease-free and total survival (16). It is important to bear in mind that if the clinical picture is equivocal, the first site of metastatic disease should ideally have tissue confirmation of cancer before irradiation is delivered to eliminate the chance that a treatable benign condition, e.g., infection, exists.

SUMMARY

Radiation can effectively eradicate cancer. The dose required to cure microscopic or small volume disease is usually well tolerated by the normal surrounding tissue, and a high rate of cure with relatively low morbidity can be achieved. This is the rationale for adjuvant radiation being delivered before or after surgery, to reduce the risks of locoregional recurrences in high-risk patients. On the other hand, bulky tumors require radiation doses that approach or exceed the normal tissue tolerance. Recent innovations have improved our ability to deliver high radiation doses safely or to increase the therapeutic ratio of radiation. They include the concurrent administration of radiation sensitizers and chemotherapy, altered fractionation schemes, and the conformal delivery of radiation using sophisticated imaging and planning tools. These innovations and others increase the efficacy of radiation and its role in the struggle against cancer.

REFERENCES

1. Fletcher GH. Clinical dose-response curve of human malignant epithelial cells. *Br J Radiol* 1973;46:1–12.
2. Lichter AS, Sandler HM, Robertson JM, et al. Clinical experience with three-dimensional treatment planning. *Semin Radiat Oncol* 1992;2:257–66.
3. Sandler HM, McShan DL, Lichter AS. Potential improvement of the results of irradiation for prostate cancer using improved dose distributions. *Int J Radiat Oncol Biol Phys* 1992;22:361–7.
4. Donaldson SS, Link MP. Combined modality treatment with low-dose radiation and MOPP chemotherapy for children with Hodgkin's disease. *J Clin Oncol* 1987;5:742–9.
5. John MJ, Flam M, Lovalvo L, Mowry PA. Feasibility of nonsurgical management of anal canal carcinoma. *Int J Radiat Oncol Biol Phys* 1987;13:299–303.
6. Herskovic A, Martz K, Al-Saraaf M, et al. Combined Chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992;326:1593–8.
7. Dillman RO, Seagren SL, Propert KL, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in nonsmall cell lung cancer. *N Engl J Med* 1990;323:940–5.

8. Stell PM. Adjuvant chemotherapy in head and neck cancer. *Semin Radiat Oncol* 1992;2:195–205.
9. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med* 1991;324:1685–90.
10. Gastrointestinal Tumor Study Group. Prolongation of the disease-free interval in surgically treated rectal carcinoma. *N Engl J Med* 1985;312:1465–72.
11. Fisher B, Redmond C, Poisson R, et al. Eight year results of a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1989;320:822–8.
12. Rosenberg SA, Kent H, Costa J, et al. Prospective randomized evaluation of the role of limb-sparing surgery, radiotherapy and chemotherapy in the treatment of adult soft-tissue sarcoma. *Surgery* 1978;84:62–72.
13. Bell RS, O'Sullivan B, Lle FF, et al. The surgical margin in soft-tissue sarcoma. *J Bone Joint Surg* 1989;71:370–9.
14. Blitzer, PH. Reanalysis of the RTOG study of the palliation of symptomatic osseous metastases. *Cancer* 1985;55:1468–72.
15. Zevallos M, Chan PYM, Munoz L, et al. Epidural spinal cord compression from metastatic tumor. *Int J Radiat Oncol Biol Phys* 1987;13:875–81.
16. Patchell RA, Tibbs RP, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to he brain. *N Engl J Med* 1990;322:494–500.