MAURIE MARKMAN, MD, EDITOR

Trends in radiation oncology: a review for the nononcologist

ANURADHA KOKA, MD, AND ROGER M. MACKLIS, MD

SUMMARY Fifty percent of cancer patients will undergo radiation therapy for either cure or palliation. This paper reviews the basic principles, practice, and future trends.

KEY POINTS Newer machines produce higher voltages and permit treatment of deeper tumors than earlier ones did. ■ How to deliver a higher radiation dose to the tumor without harming surrounding, normal tissue is the topic of ongoing research. Current practice is to divide the radiation dose into daily treatment fractions and to use multiple coplanar fields. Future practice likely will use smaller, more frequent doses and noncoplanar fields, planned with the help of computed tomography and stereotaxy. ■ Whereas brachytherapy once required operators to handle radioactive sources directly, radiation oncologists can now implant brachytherapy catheters, which are after-loaded by automated devices that permit a higher dose to be delivered. ■ Technological innovations are permitting more patients to be treated, and treated more effectively.

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From the Department of Radiation Oncology, The Cleveland Clinic Foundation.
Address reprint requests to A.K., Department of Radiation Oncology, T28, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

THE AMERICAN CANCER Society estimates more than 1.2 million people in the United States will be found to have cancer in 1995. Approximately half of them will undergo radiation therapy for either cure or palliation. Most physicians, whatever their specialty, will come into contact with patients who have undergone, or will undergo, radiation therapy. This article offers a brief overview of the basic principles of radiation oncology for physicians whose training may not have included a formal rotation in radiation oncology.

PRINCIPLES, HISTORY

The basic-science roots of radiation oncology include both physics (as it applies to electromagnetic radiation and radioisotopes) and radiation biology—the study of the response of cells and organisms to radiation. Radiation is emitted in the radioactive decay of certain naturally occurring and man-made unstable elements, and also in the collision of charged particles, such as electrons, with matter, as in a linear accelerator. An important part of clinical radiation physics involves quantitating and documenting the physical characteristics of radioactive emissions and beams. This entails detailed calibration studies, performed by radiation physicists and dosimetrists. The old unit of absorbed dose of radiation was the rad (0.01 J/kg); the new, SI unit is the Gray (Gy; 1 J/kg). Because 1 rad = 1 cGy, it is easy to convert between the new and old units.

The first radiation therapy treatment was given in January 1896, less than 3 months after Wilhelm Conrad discovered x-rays and less than 3 weeks after he presented his paper regarding this discovery. The first cancer patient was treated for a locally advanced breast malignancy. The first cure of a malignant disease (basal cell epithelioma) by radiation was documented in 1899. Henri Becquerel discovered the first naturally occurring radioactive material when he found that uranium salts darkened unexposed photographic plates. Marie and Pierre Curie discovered polonium in July 1898 and radium in December of the same year. Pierre Curie's animal experiments with Henri Becquerel set the stage for many subsequent discoveries concerning the effects of radium and similar compounds on normal tissue.

During the 1920s and 1930s workers found that large, single doses of radiation have significant acute and chronic effects on tissue, effects that played a major role in the damage to normal tissue that occurs after radiotherapy. Regaud and Coutard established that splitting large single doses into smaller daily doses or "fractions" ("fractionating the treatment") significantly decreased late tissue toxicity while producing essentially the same tumor response. One of the main reasons for this important observation is that most types of cells are capable of repairing a certain amount of radiation-induced damage. Single, large doses overwhelm the DNA damage-repair mechanisms and thus permit only minimal repair of damage, but smaller fractions permit repair to occur. In general, normal cells have a greater capacity to repair such damage than cancer cells do, contributing to the favorable therapeutic ratio of fractionated treatment.

One of the major clinical limitations of radiation oncology in its early days was the depth to which radiation could penetrate without damaging the skin. Early machines produced low-energy x-rays, in the range of 50 to 100 kV, which deposit their energy superficially, producing high skin doses. These units were very unsatisfactory for treating most types of tumors.

As the energy of the radiation beam increases, so does the depth of beam penetration and the skin-sparing potential. In the 1950s, cobalt-60 units came into widespread use. Emitting rays with an average energy of 1.2 MV, cobalt-60 machines deposit maximum energy 0.5 cm below the skin. However, at a depth of 10 cm, most of the energy has been delivered, leaving treatment of deeper tumors a persistent problem.

In the 1960s and 1970s, technological advances led to the development of clinical linear accelerators capable of producing higher-voltage beams—from 4 to 20 MV. Each accelerator is designed to deliver one, or at the most, two energy levels. The choice of energy depends on the depth of the tumor. For example, head and neck cancers require energies in the range of 4 to 6 MV; pelvic tumors usually require 10 MV or more. Superficial tumors are treated with electron beam radiation.

CURRENT PRACTICE

Patients are treated either supine or prone. Treatment fields (the volume of the body to receive radiation) are arranged to give maximum tumor coverage with minimal normal-tissue coverage. This usually necessitates from one to four treatment fields. Special configurations of opposed fields tend to even out the dose of radiation to an area and minimize dose variation across an expanse of tissue. An example of this is the initial field arrangement for the treatment of lung cancer (*Figure*). In breast cancer, a wedged technique is used, in which shoe-horn shaped metal wedges are used to compensate for the differences in tissue depth that the radiation has to pass through. With a "four-field box" technique, often used to treat pelvic tumors such as cancer of the prostate, endometrium, or cervix, the aim is to further spread out the dose by adding lateral fields. A single field may be used in the treatment of vertebral metastases and other relatively superficial tumors.

All but the simplest cases require detailed planning, which involves simulating the treatment with imaging machines. A simulator is architecturally similar to a linear accelerator but is equipped with a fluoroscope rather than a megavoltage x-ray unit. The fluoroscopy unit allows radiographic landmarks and radio-opaque surgical clips to be used to map out the appropriate radiation treatment fields. Custom lead-alloy blocking is used to shield uninvolved normal tissues. Dosimetric parameters are then cal-

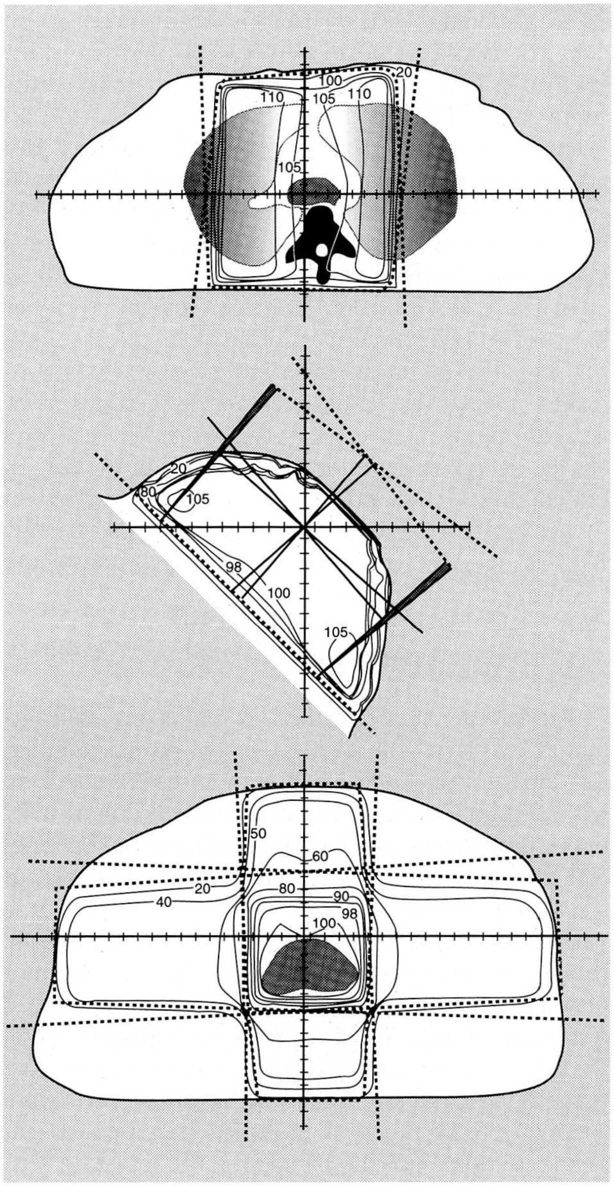

FIGURE. Top, an example of isodose curves for an anterior-posterior and posterior-anterior arrangement for the treatment of lung cancer. Numbers represent percent of radiation dose; dashed lines outline radiation fields. Middle, an example of isodose curves for treatment of a breast for breast conservation. Wedges are being used to compensate for the different tissue depths. Bottom, an example of isodose curves for a four-field arrangement (anterior-posterior, posterior-anterior, right lateral, and left lateral) for the treatment of prostate cancer.

culated to deliver the prescribed dose of radiation to the tumor volume.

The technical sophistication of radiotherapy treatment planning has advanced in parallel with advances in imaging and computer technology. Computed tomography (CT), commonly used in treatment planning at the Cleveland Clinic, generates information that is entered directly into a treatment-planning computer. The tumor (or "target") volume is defined, slice by slice, and radiation beam arrangements, blocking of normal tissues, weighting of beams, and optimal treatment energies are then manipulated electronically in order to achieve maximum tumor dose with minimal exposure to normal tissue.

For some very complex cases, current technology is moving towards three-dimensional treatment planning, in which beams can be aimed from any angle but come to a focus in the tumor, at the center of the treatment field. Because beams overlap only within the target volume, a higher dose can be given to the target while keeping the dose to normal tissues low. The disadvantage is that such noncoplanar field arrangements tend to deliver a low dose of radiation to a larger overall volume of tissue than simpler, coplanar beam arrangements.

The dose of radiation necessary to achieve tumor control in various clinical situations follows some basic principles. Fletcher and Shukovsky addressed the interrelationship of biological dose, tumor size, and control by radiation in their classic paper published in 1975. As one might expect, a significantly higher dose is needed to sterilize a 5-cm mass compared with a microscopic tumor. In general, the major limitation to delivering higher doses is the tolerance of surrounding, normal tissue.

BRACHYTHERAPY

Brachytherapy is the use of radioactive sources placed within the patient either temporarily or permanently. This technique has been used extensively in the treatment of cervical cancer, where we continue to follow many of the principles established by Patterson and Parker in the 1940s. Today we use computers to aid in determining the placement and loading of radioactive sources, the duration of the treatment, and radiation doses to the tumor and to surrounding, normal tissues.

Initially, brachytherapists used "live" sources (such as needles containing radium), which they placed by hand, a procedure that exposed them to considerable amounts of radiation. Now virtually all brachytherapy procedures are done with "afterloading" devices. In general, empty catheters are placed in the tumor bed at the time of surgery. These are then "afterloaded" with live sources once the patient has left the operating room. This allows more time for careful placement of sources and dose calculation, without the continual pressure of working with live sources, and significantly decreases the radiation exposure for all personnel.

In recent years, research has focused on the development of automated afterloading devices that house a radioactive source on a guide wire within a lead safe. The afterloading unit is connected to catheters placed within the patient. It is then programmed to automatically move the radioactive source to the end of each catheter for a specified time calculated to deliver the desired radiation dose. This can all be controlled remotely, thereby reducing operator exposure. The latest afterloading units have very-high-activity sources, enabling rapid delivery of dose. These high-dose-rate machines can deliver a highly localized dose of 1000 to 2000 cGy in about 15 to 20 minutes. This approach reduces the need for inpatient hospital admissions for many brachytherapy treatments.

RADIATION THERAPY IN PALLIATIVE CARE

Cure is the desired goal for all patients. Unfortunately, not all cancer patients can be treated with curative intent. Radiation oncologists often find they have a role in palliating a patient with an incurable, widely metastatic malignant disease. A general principle is to treat only those sites that are causing problems (or that have the potential to do so in the near future). In a patient with a diffusely positive bone scan reflecting metastatic disease, not all sites of uptake are treated: treatment is generally confined to symptomatic sites, pain being the most common symptom. However, asymptomatic, weight-bearing long bones are often treated to prevent a pathologic fracture. Lung tumors causing bronchial obstruction can be treated with either external-beam radiation, or, if an endobronchial tumor is present, with brachytherapy. Symptomatic brain metastases are treated in an attempt to reverse, or at least prevent, deterioration of neurological function. Asymptomatic brain metastases are treated to prevent neurological deficits and thereby maintain quality of life. The focus of palliative treatment is usually quality of life, as the treatment itself is unlikely to prolong survival significantly.

ADVANCES IN RADIATION ONCOLOGY

Much of the thrust of research in radiation oncology is aimed at increasing the dose through improved targeting, altered fractionation, or combined modality approaches employing radiation therapy, chemotherapy, and surgery. Clinical studies continue, with the goal of increasing the dose delivered to the tumor without increasing the toxic effect on normal tissue.

One approach is to alter the fractionation schedule by giving several, lower doses per day instead of one, larger, daily dose. The time between treatments is usually at least 6 hours, as radiobiological experiments indicate this interval is necessary for most cellular repair to occur. "Hyperfractionation" schemes are currently being tested in prospective randomized trials. The Radiation Therapy Oncology Group is currently enrolling patients with head-and-neck cancer into a four-armed study. To date, only one prospective, randomized study (from the European Organization for Research and Treatment of Cancer, in patients with oropharyngeal tumors of stage II or higher, excluding those arising from the base of the tongue) has shown a statistically significant benefit for hyperfractionation vs standard fractionation. Other studies have shown no difference in local control or survival, though hyperfractionation may offer some advantages in specific subsets.

Stereotactic radiosurgery has been performed at the Cleveland Clinic since 1989. The Leksell Gamma Knife, developed in Sweden, was the first unit designed for stereotactic radiosurgery. This unit contains 280 cobalt-60 sources that are focused on the treatment target. More recently, linear accelerators, which do not need cobalt-60 sources, have been adapted for clinical use. Beams of radiation are focused on an intracranial target, which has been localized using computed tomography or angiography or both, depending on the nature of the tumor, with a stereotactic head frame for reference. Lesions such as acoustic neuromas, arteriovenous malformations, and benign or malignant tumors can be treated with this technique. Limitations include the size of the lesion (generally less than 3 cm in maximum diameter), and in the case of metastatic disease, the number of metastatic sites that can be treated. This technique is often used to treat lesions in locations where surgery would pose the risk of significant morbidity, such as close to the base of skull and brain stem. The advantage of radiosurgery compared with conventional external-beam radiation therapy is the ability to target the lesion precisely with very rapid fall-off of radiation dose from the target area. This allows one to minimize the volume of normal tissue receiving radiation.

The next phase of stereotactic treatment will be to extend the capability to accurately focus on small tumors outside the cranium. The first generation of such technology is a prototype machine called the Neurotron 1000, produced by the Accuray Company (Santa Clara, Calif). This machine has a 6-MV linear accelerator mounted on a robotic arm; powerful image-processing technology verifies the patient's position and obviates the need for a stereotactic frame as is currently used in stereotactic radiosurgery. Six centers in the United States have received preliminary approval for testing this machine, including the Cleveland Clinic.

Three-dimensional treatment planning employs computed tomographic images to help plan noncoplanar beams, which are focused on the target volume. At the Cleveland Clinic, this approach is being used for the treatment of pancreatic cancer, where dose is limited by the tolerance of normal tissue in the bowel, kidneys, and liver. Using this treatment approach, the dose to the pancreas can be escalated without unacceptable morbidity. Currently, there are a number of national and single-institution studies looking at three-dimensional treatment planning for a number of malignant diseases, including lung and prostate cancer.

Another approach is to attach radioactive atoms to a monoclonal antibody directed against a specific cancer cell. This approach has been tried in a number of tumors, including non-Hodgkin's lymphomas. The testing of more-specific antibodies and the development of methods to reduce the dose to sites of blood pooling (such as the heart and liver) continue.

Intraoperative radiation therapy allows one to visualize the area of concern precisely, move critical organs (such as the bowel) out of the radiation field, and direct the radiation beam away from fixed, critical structures such as the spinal cord. Intraoperative treatment can be given with a dedicated linear accelerator that produces a range of electron energies and is permanently housed in an appropriately shielded operating suite. An alternative approach is to use intraoperative brachytherapy. In this situation, catheters can be placed at the time of surgery and radiotherapy delivered via a high-dose-rate unit positioned within a specially shielded operating room.

Since the 1950s, when the curative role of radiation therapy in Hodgkin's disease was first appreciated, radiation oncologists have continued to investigate how to cure malignant diseases. In certain situations, radiation alone is still the primary treatment: early-stage head-and-neck cancer, early-stage cervical cancer, skin cancers, and some lymphomas. However, most curative attempts now focus on combined-modality treatment, using a combination of surgery, chemotherapy, and radiation therapy. A multimodality approach is being used to explore how to preserve organs that would otherwise be lost. Currently, oncologists routinely employ a multimodality approach in sarcomas of the extremities, anal cancers, and early-stage breast cancer for cure and organ preservation. Organ-preservation protocols for locally advanced rectal and head-and-neck cancers are ongoing at the Cleveland Clinic; multimodality protocols for lung and esophageal cancers are also in progress.

SUGGESTED READING

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