CHAPTER 2

Principles of radiation therapy

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

How radiation works

IONIZING RADIATION

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

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

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

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

PHOTON-TISSUE INTERACTIONS

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

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

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

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

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

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

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

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

ELECTRON BEAMS

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

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

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

MEASURING RADIATION ABSORPTION

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

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

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

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

How radiation is delivered

TREATMENT MACHINES

Linear accelerators

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

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

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

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

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

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

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

TABLE 1: Depth dose characteristics for clinical radiotherapy beams

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

kV(p) = kilovolt (peak)

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

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

PRETREATMENT PROCEDURES

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

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

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

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

TREATMENT PLANNING AND DELIVERY

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

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

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

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

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

BRACHYTHERAPY

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

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

TABLE 2: Physical characteristics of commonly used radioisotopes

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

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

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

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

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

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

Remote afterloading brachytherapy

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

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

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

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

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

Recent advances in planning and treatment

CT SIMULATION

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

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

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

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

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

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

CONFORMAL RADIATION THERAPY

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

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

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

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

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

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

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

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

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

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

PROTON THERAPY

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

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

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

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

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

STEREOTACTIC RADIOSURGERY

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

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

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

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

SUGGESTED READING

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