

RADIATION IN THE TREATMENT OF CANCER

The prognosis for someone diagnosed with cancer is not as dire as is commonly believed. Many cancers—to name but a few, early-stage cancer of the larynx, childhood leukemia, and Hodgkin's disease—are highly curable. Unfortunately, others, such as pancreatic cancer, generally offer a miserable prognosis. Most cancers have a curability that lies somewhere between those extremes.

Early in their development, malignant tumors are generally well localized. As most cancers develop, they tend to spread to neighboring lymph nodes and, as metastases, to noncontiguous organs. When the disease is confined, a local treatment such as surgical excision or radiation therapy is indicated. If the tumor is inaccessible or is intimately entwined with a vital anatomic structure, or if regional spread has occurred, surgery may not be a viable option: In those cases, radiation therapy and chemotherapy offer better outcomes. Combination therapy—the use of two, or even all three, of the approaches just mentioned—is now commonly used to treat both the local and the systemic components of the disease.

The longer a patient has a viable malignant tumor, the more likely the cancer is to “break out” as a metastasis, which, in general, seriously compromises the outcome of treatment. The possibility of a breakout makes local control critical to achieving long-term survival and is an important impetus to improving local therapy.

Overly aggressive surgery or chemotherapy or very high doses of radiation can, with high probability, eradicate a cancer, but at the cost of causing unacceptable injury to normal tissue. A specific goal in improving the technology of radiation therapy is to reduce the probability of such morbidity. Achieving that goal may allow delivery of higher doses with an associated increase in the chance of controlling the tumor.

Radiations used for cancer treatment

Research in physics has contributed directly and indirectly to cancer therapy over the past century. Only months after their discovery, x rays were used to treat a patient with breast cancer. The use of protons in radiation therapy is another dividend from physics research. Other

The art of cancer treatment is finding the right balance between tumor control and injury to normal tissues.

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heavy particles, such as neutrons, light ions (particularly carbon and neon), and pi mesons have also been used for radiation therapy: With the exception of pi mesons, which did not live up to their promise, they continue to be investigated for their clinical potential. These particles all have somewhat different bio-

logical effects on cells. Because of the complexity introduced by their different biology, we do not consider heavy particles other than the proton in either this introduction or in the next two articles.

At present, the most common radiotherapy treatment uses high-energy x rays. Figure 1 shows a modern medical therapy machine. Shaped beams of x rays are directed toward the patient. The beams pass through the patient, undergoing near-exponential attenuation as they interact with tissues, and deposit dose along the way. (The strength or dose of radiation is characterized by the energy imparted per unit mass. The unit of dose is the gray; $1 \text{ Gy} = 1 \text{ J/kg}$.) It is the interactions of secondary electrons, set loose by the primary interactions of the x rays, that are the dominant cause of the molecular disruptions that eventually lead to cell death.

Protons differ from high-energy x rays in that they can deliver radiation dose up to an energy-dependent depth, and virtually none beyond it, whereas x rays continue to penetrate with near-exponentially decreasing intensity. Figure 2 compares the distribution of dose with depth for 15-MeV peak-energy x rays and 200-MeV protons. One noteworthy feature is the low x-ray dose in the first few millimeters due to the lack of secondary electron buildup. The resulting skin sparing can have beneficial clinical consequences not shared by protons, particularly for shallow targets.

Why does radiation work?

Radiation can cause lethal damage to cells. Secondary electrons create highly reactive radicals in the intracellular material. The radicals can chemically break bonds in the cellular DNA, causing cells—both the malignant cells one is trying to render inactive and cells in the normal tissues that one wishes to spare—to lose their ability to reproduce. The higher the dose, the greater the probability of killing cells.

Two main strategies help to assure that normal tissues and organs continue to function after a treatment with radiation. The first rests on what is apparently a small but favorable difference between the radiation response of normal and malignant cells. That difference can be exploited to preserve the normal cells that permeate the tumor and the nearby tissues that are included in the target volume (that is, the region that includes demonstrable disease; possible subclinical extension of that disease, delineation of which is one of the radiotherapist's arts; and a safety margin for organ and patient motion and

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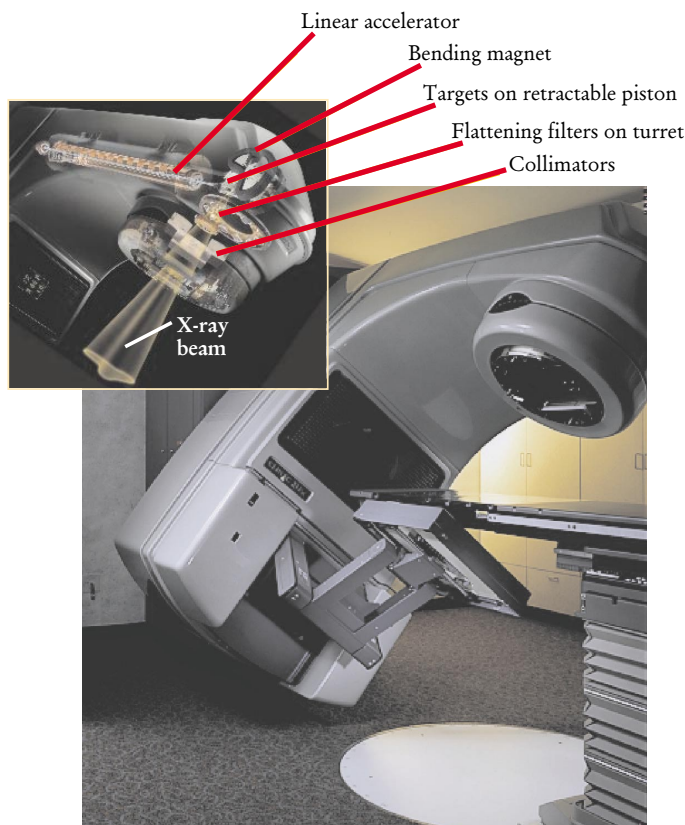


FIGURE 1. A MODERN RADIOTHERAPY TREATMENT machine. X rays are produced by bremsstrahlung when electrons, accelerated by a linear accelerator to energies between about 4 and 25 MeV, strike a thick target. The x rays are then shaped by a contoured flattening filter that makes uniform the originally spread-out, but forward-peaked, x-ray flux. The accelerator, beam transport system, and beam-shaping devices are all mounted on a so-called gantry that can rotate a full 360° about a horizontal axis. It typically takes about a minute to complete a rotation. The patient lies on a couch, mounted here on an accordion structure. The couch can move in all three translational directions and can also rotate about a vertical axis through the point at which the central axes of all beams cross. With the appropriate combination of gantry and couch adjustments, the radiation beam can be pointed at the tumor along almost any direction. The traylike object extending from near the bottom of the machine is an imaging detector. (Courtesy of Varian Medical Systems.)

technical uncertainties). The reasons for the differential response are complex, not fully understood, and even controversial. The varying responses are probably due less to differences in intrinsic cellular radiosensitivity than to differences in genetic machinery activated by radiation, in DNA repair kinetics, and in the mechanisms of cell repopulation. And those favorable differences are somewhat counterbalanced by tumor-protective factors such as the relative desensitization of tumor cells which occurs if, as appears often to be the case, they are less well oxygenated than normal tissue.

To further the beneficial difference, dose is usually delivered in small daily increments called fractions; this strategy, as compared with single-dose radiation delivery, is generally thought to improve the therapeutic advantage substantially. Consequently, in conventional radiotherapy, from 30 to 40 daily fractions of approximately 2 Gy each are delivered. These fractions are typically delivered once a day, with a two-day weekend break, so that a course of radiotherapy will typically last from six to eight weeks.

The second main strategy for minimizing morbidity is to reduce the dose delivered to normal tissues that are spatially well separated from the tumor. The next two articles describe some of the approaches that are being investigated to achieve this goal.

Multiple treatment beams

A single radiation beam of, say, x rays, leads to a higher dose delivered to the tissues in front of the tumor than to the tumor itself (see figure 2). In consequence, if one were to give a dose sufficient to control the tumor with a reasonably high probability, the dose to the upstream tissues would likely lead to unacceptable morbidity. A single beam would only be used for very superficial tumors, where

there is little upstream normal tissue to damage and the skin-sparing properties of x rays help. For deeper tumors, one uses multiple cross-firing beams delivered within minutes of one another: All encompass the tumor, but successive beams are directed toward the patient from different directions to traverse different tissues outside the target volume. The delivery of cross-firing beams is greatly facilitated by mounting the radiation-producing equipment on a gantry, as illustrated in figure 1.

Multiply directed beams markedly change the distribution of dose, as is illustrated in figure 3. As a result, with modern radiotherapy equipment and techniques, the dose outside the target volume can often be quite tolerable even when dose levels within the target volume are high enough to provide a substantial probability of tumor control.

Volume effect

The distribution of dose within the volume of a tumor or a normal organ can dramatically affect how the irradiated tissue responds. Radiotherapists generally agree on several points concerning tumors.

- The larger the tumor, the greater the dose needed to control it. Larger tumors compromise treatment in another way: Their greater volume means that more normal tissue is harmfully irradiated.
- Tumors should be irradiated as uniformly as possible. Dose inhomogeneity is inefficient and tends to lead to higher normal-tissue doses for the same tumor-control probability.
- The dose within a tumor, though, doesn't have to be perfectly uniform. It might be appropriate, for example, to deliver a somewhat reduced dose to a part of a tumor that is closely adjacent to a sensitive normal structure so that the dose received by the structure is tolerable.

For normal tissues, there is no incentive for uniform irradiation—indeed, quite the opposite. For many organs, the inclusion of just a part of the organ in the high-dose volume greatly increases tolerance. Thus, an important aspect of planning treatments is to arrange dose distributions so that critical organs near the target are at least partially avoided.

Intensity modulated radiation therapy

So far, we have assumed that the radiation beams are nearly uniform over their cross-section. Beam uniformity, in fact, has historically been a goal of radiotherapy. However, more

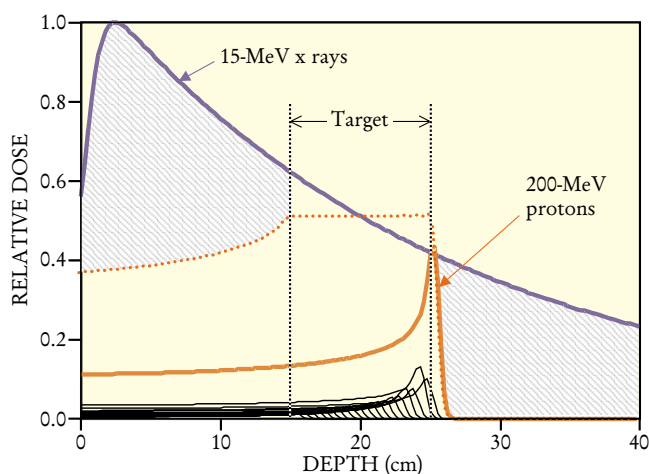


FIGURE 2. DEPTH-DOSE CHARACTERISTICS of typical x-ray and proton beams. The blue curve shows the initial rapid rise in dose and subsequent near-exponential attenuation of 15-MeV peak-energy x rays. Protons gradually lose energy due to electromagnetic interactions until they near the end of their range. At that point, energy losses due to ionization increase rapidly. The rapid terminal energy deposition gives rise to a so-called Bragg peak, beyond which the protons come to rest. The solid red curve shows the Bragg peak of a 200-MeV monoenergetic proton beam. Such monoenergetic beams give dose distributions too narrowly spread in depth to treat most tumors, which are typically many centimeters in diameter. In practice, the distribution is spread out by superposing a sequence of monoenergetic beams of suitably weighted flux. The dotted red curve shows such a distribution, with a spread-out Bragg peak (SOBP). The monoenergetic components leading to the distribution are shown in black. The x-ray and SOBP proton beams have been normalized to deliver the same dose at the center of the target volume. The shaded areas indicate the dose savings achieved with protons.

than a decade ago, Alan Cormack (fresh from inventing the CT scanner), Anders Brahme, and one of us (Pedroni, working with pi-meson therapy) independently suggested that the use of nonuniform beams could improve dose distributions over what was possible with uniform beams.

The idea was motivated by the observation that, in CT reconstruction, one deduces from a series of projections of an object what the internal structure of that object is. The mathematics can be inverted to estimate, in the case of radiation dose, what set of radiation intensities would produce a given dose distribution in the patient. This approach leads to highly nonuniform beams. The original idea has two flaws. The first is that many of the intensities so computed are negative—an unphysical result. The second is that there is no general way of specifying a priori a physically possible end result for which all the computed intensities would be nonnegative.

The basic idea of allowing nonuniform beams, however, has proven enormously fruitful. A workable computational approach is to use optimization algorithms that iteratively adjust the beam intensities so that the resulting dose distribution maximizes some score function. The search for those optimal beams is computationally intensive and therefore poses interesting technical challenges. The still bigger challenge, though, is to find score functions that give a viable measure of clinical goodness. Increasingly, researchers are investigating biophysical models of the dose response of both tumors and normal tissues and are beginning to use them to help determine such score functions.

Intensity modulated radiation therapy, as treatments featuring nonuniform beams are called, has been most intensely developed, and recently used, for x rays. However, it is equally appropriate for other radiation modalities, including protons. With charged particles one has an extra degree of freedom: One can also vary the intensity as a function of penetration or, equivalently, of energy.

Clinical requirements

To be clinically useful, a new technology must satisfy a number of requirements in addition to being effective. Above all, it must be safe. The medical community strives to make treatment safer than jumbo-jet travel in terms of the allowable probability of fatality. A new technology must be efficient. That is, the effort to implement it must be consonant with the realities of busy clinical life. It must

also be affordable. These constraints form an important part of the challenge in developing the new technologies discussed in the following two articles.

As different as those technologies are, they share the identical goal—the optimal tailoring of dose to the target volume and the minimization, or optimal distribution, of the dose delivered to normal tissues outside that volume. The history of radiotherapy in the past century has been one of a series of incremental technical developments, all sharing that same goal. The effort continues. ■

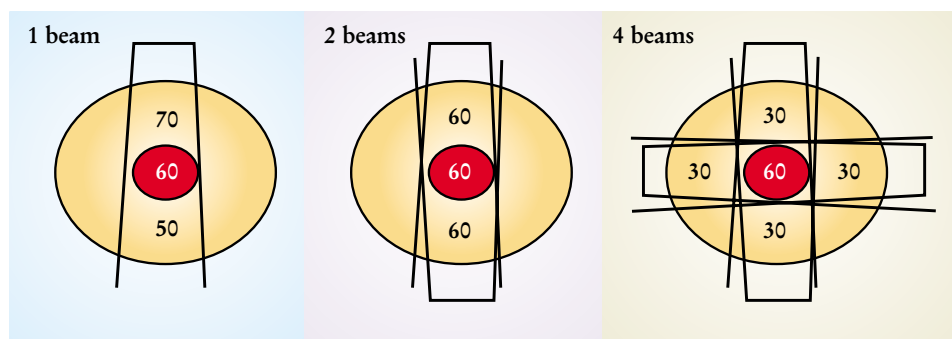


FIGURE 3. THREE X-RAY BEAM ARRANGEMENTS, each normalized to deliver 60 gray (60 J/kg) to a target. From left to right, the schematics show doses for a single beam, two beams pointed from opposite directions, and beams coming from the four compass directions. The dose outside the target volume, here shown only approximately, is successively reduced as the number of beams increases. In a complementary way, however, the volume outside the target that receives an appreciable dose increases as the number of beams increases.