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RADIATION THERAPY PHYSICS

The treatment of cancer by radiation therapy is being pursued at the Johns Hopkins Medical Institutions in the recently established Oncology Center. The radiobiology and physics of radiation therapy, as well as the radiation sources and their calibration, are described.

INTRODUCTION

In response to needs expressed by the scientific and medical communities, the United States Congress passed the National Cancer Act in 1971. Through this legislation, Congress committed the resources necessary to assure a continuing national program of research into the causes and treatment of cancer. The vehicle of implementation chosen by Congress was the establishment of regional comprehensive cancer centers, to be selected by the National Cancer Institute on the basis of competitive grants and located at major academic research institutions across the country. These 20 centers serve as the backbone of the national research effort and provide a regional focus for all aspects of cancer prevention, detection, and care.

Through the leadership of Dr. A. H. Owens, Jr., a comprehensive oncology center was established at The Johns Hopkins University in 1973. The Johns Hopkins Oncology Center is located at the East Baltimore campus and is an integral part of the Johns Hopkins Medical Institutions. The physical plant, dedicated in April 1977, includes three floors of research laboratories where basic cancer research is carried out, a 56-bed inpatient wing that also supports clinical studies, and a major radiation therapy wing, perhaps the most modern and comprehensive radiation therapy facility on the east coast. The Center also maintains a major outpatient service and an outreach program in support of nearby community hospitals.

The Applied Physics Laboratory played an important role during the early planning phases of the Oncology Center. It was evident that the quality of research and patient care could be enhanced by introducing certain high-technology equipment and systems into the Center. Through J. T. Massey, then Director of Biomedical Programs at the Laboratory, and R. J. Johns, Director of the Department of Biomedical Engineering at the School of Medicine, a number of important initiatives were set in motion. A major physiologic monitoring system serving the entire patient wing was conceptualized, procured, and implemented by J. B. Oakes, L. Raum, and me. This activity ultimately broadened substantially and led to the formation of the Oncology Center Clinical Engineering Group under my direction. Further, a comprehensive computer-based system to support the Center's research and patient care needs was developed. This project led to the design and implementation of the Oncology Center Clinical Information System by B. I. Blum, a data management system that has become a model for other oncology centers. All these activities continue to be fully operational after five years and are critical elements in the Center's day-to-day clinical operations.

In July 1975, through an institutional interdivisional assignment, I was appointed Director of Radiation Physics by S. E. Order, Director of Radiation Therapy. This appointment was prompted by immediate technologic concerns surrounding the specification, installation, and certification of the Center's new therapy linear accelerators. My general assignment was to develop necessary staff and resources and initiate an academic program of radiation physics responsive to the clinical, research, and teaching needs of the Center.

This article is based on my experiences at the Johns Hopkins Oncology Center in a post that I held for five years.

BACKGROUND

The treatment of cancer in the United States has become largely an interdisciplinary endeavor involving three major therapy modalities: surgery, chemotherapy, and radiation therapy. Combined modality treatment strategies have been widely accepted within major oncology research centers as holding the greatest promise for extending survivability and for producing curative treatments. Research sponsored by the National Cancer Institute and other agencies certainly reflects this philosophy.[1] Some notable successes are evident, such as with Hodgkin's disease, where complete surgical delineation of disease, followed by aggressive courses of radiation therapy and possibly of chemotherapy have elevated the five-year survivability, nominally considered curative, to over 90% for early-stage disease. Similarly, surgery or radiation therapy or both, followed by an aggressive regimen of chemotherapy, has markedly improved the disease free survival of breast cancer patients.

In many forms of cancer, progression of the disease is characterized by cells migrating from the primary tumor to other organs in the body where they

initiate secondary (metastatic) tumors. In such cases of systemic dissemination, chemotherapy must necessarily be invoked as the most appropriate treatment. Surgery and radiation therapy, on the other hand, are more efficacious for local tumor control, that is, those situations where the cancer is an isolated, well-defined tumor mass. The rationale for combined therapy, then, is to achieve local control, either through surgical excision or through radiation, and then to attack possible systemic disease with chemotherapy agents (which themselves are given in combination and which are more efficacious because of local control).

The great potential of radiation therapy resides in its ability to achieve local tumor control and ultimate cure of disease while preserving organ function. This option is not always available when local tumor control is achieved by surgical resection. Therefore, in the early stages of disease we frequently find that radiation therapy is the preferred treatment of choice (e.g., in cancer of the uterus of young females). It is also evident that radiation patients typically suffer much less apparent trauma to achieve the same end result than do surgical patients. An additional benefit of radiation therapy derives from its much more favorable cosmetic result in treating superficial lesions and particularly in the treatment of breast cancer.

Radiation therapy has become an invaluable treatment modality in modern cancer therapy largely because of the extensive clinical research conducted by radiation therapists. Through this process, therapists have formulated concise therapy protocols for all major cancers according to the stage of disease. National review groups (such as the Radiation Therapy Oncology Group) have been established to monitor and systematically upgrade these protocols based on long-term survival data. As a result, an impressive body of knowledge has evolved that permits therapists to prescribe treatments optimized for maximum survival probability. The protocol system systematizes treatments and assures patients of the greatest chance of cure while maintaining the highest quality of life.

Other disciplines have made major contributions as well. Concomitant with the therapists' clinical research, radiobiologists have advanced the basic science of radiation therapy. Research on the mechanisms of cell kill and on the effects of radiation on homogeneous cell populations and on complex biological systems has provided a coherent framework to enhance the effectiveness of radiation therapy and to broaden its armamentarium.

Throughout the evolution of radiation therapy, physicists and engineers have also played a major role. Advances in the technology of radiation sources, the development of precision dosimetry instrumentation, and basic research into the interaction of ionizing radiation and matter, all essential to the advancement of clinical radiation therapy, were made by physical scientists and engineers. Progress in these areas within the last two decades has had a profound impact on radiation therapy by greatly enhancing the speed and accuracy of treatments and the breadth of its application.

RADIOBIOLOGY

There is no cell, healthy or otherwise, or tumor for that matter, that cannot be killed by radiation. The basic problem of curative therapy is that tumor cells are embedded in healthy tissue, which has a maximum dose tolerance limit. Necrosis of the healthy tissue, i.e., tissue death, will result if the tolerance level is exceeded, leading ultimately to extreme consequences for the patient. The correct strategy is to eliminate all tumor cells while preserving as many healthy cells as possible, a most important distinction. Figure 1 shows the dilemma. Here we have plotted the probability of effect versus dose[2] for a tumor embedded in healthy tissue. Clearly, the therapist is in a trade-off situation in that enhancing the probability of cure also enhances the probability of necrosis of normal tissue. For example, a therapist may prescribe a dose level corresponding to an 80% cure probability, implying a 20% recurrence probability, and accept a 10% probability of necrosis. Depending on circumstances, the therapist may elect to be more aggressive or less aggressive. Ideally, therapists optimize treatment parameters (such as the type of radiation and time-dose fractionation) so that, for a given probability of cure, the ratio of the probability of cure to the probability of normal tissue necrosis (called the therapeutic ratio) is maximized. However, the curves shown in Fig. 1 depend on many factors, such as stage of disease and tumor type, size, and location, and there are conditions when the curves will lie very close together with nearly equal probabilities for cure and necrosis. (For example, tumor sites that have been previously irradiated have a reduced radiation tolerance.) In these situations, the therapist has no recourse. The prospect for successful radiation

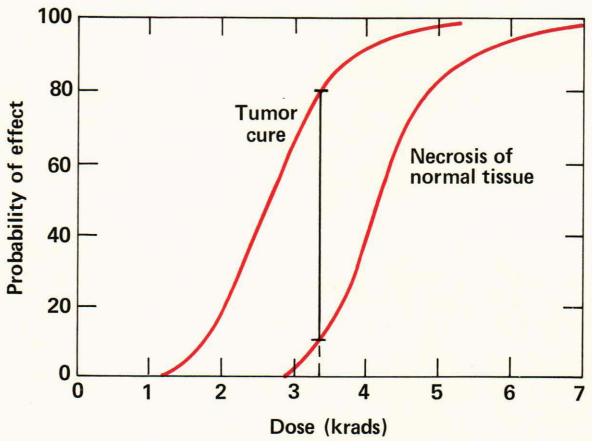


Figure 1 — Dose-response curve for a tumor embedded in healthy tissue. Prescribed dose of 3400 rads gives 80% cure probability and 10% probability of necrosis of normal tissue.

therapy is poor in such cases, and alternative therapies need to be examined. Many other factors, such as the patient's age and general health, intervene in the scenario so neatly described above, making the real world much more complicated.

To limit the growth of a tumor and ultimately to kill it, it is presumably necessary to eliminate all proliferating tumor cells. This is accomplished most effectively by disabling the cells' reproductive capacity. The end result is the same as killing the cells outright. A tumor cell that cannot replicate, even though it is otherwise intact and functional, poses no threat. Hence, to achieve tumor control, it is only necessary to be concerned with proliferative viability or, alternatively, with "reproductive death." Proliferative viability is gauged by a cell's capacity to produce clones. Simply stated, success in replication implies cell viability; lack of success implies cell death.

The mechanisms by which ionizing radiation causes reproductive death in mammalian cells are not completely understood. It is known that there are a number of critical sites within the cell nucleus, most likely associated with chromosomal DNA, where the breaking of chemical bonds results in cell damage. Available data for moderate and weakly ionizing radiation suggest that at least two biophysical events, i.e., "hits," are necessary to cause irreversible cell damage. Radiobiologists have hypothesized single site-multiple hits (two or more) and multiple sites-multiple hits (one at each site) target models, and apparently both are credible. Damage of this nature, which is irreparable, expresses itself initially as reproductive death and ultimately, during attempted mitosis, as actual cell death.

Cell damage is produced by two known ionization processes. Incident primary radiation produces a cascade of secondary electrons with sufficient range to migrate through the cell's cytoplasm and intranuclear fluid. Some of these electrons find their way to a critical site, initiate an ionizing event, and damage the cell. In a less direct process, the secondary electrons ionize intracellular water and by chemical reaction cause the formation of the highly reactive hydroxyl radical (OH). These radicals diffuse to critical sites within the nucleus, react, and damage the cell. This indirect process is apparently responsible for most of the damage observed in mammalian cells, although for heavy or charged primary radiation, the direct process assumes a greater significance.

Isolated biophysical events within the cell do not necessarily result in permanent damage. Survival data give strong evidence of sublethal damage occurring in a fraction of a cell population irradiated with low-energy X rays. Many of these cells invoke a self-repair mechanism so that, within hours of the ionizing event, they are completely normal. Laboratory experiments have demonstrated the ability of Chinese hamster cells to go through repeated sublethal damage-repair cycles without loss of metabolic or reproductive integrity. Unfortunately, the repair process is not infallible. Chromosomes fragmented by radiation can recombine in many ways, producing mutations of the original cell. Scientists have linked these anomalies to the carcinogenic nature of radiation, an ultimately ironic consequence of its use in medicine.

The cell survival curve (Fig. 2) is used by radiobiologists to quantify the sensitivity of a population of cells to ionizing radiation. *In vitro* techniques are usually used to develop these data, although *in vivo* techniques have been developed for a number of specific cell types. A large number of viable cells are counted and plated onto petri dishes containing appropriate nutrients. Under controlled conditions and in the absence of radiation, a constant fraction of these cells will replicate. After the plating process, the cells are immediately exposed to different amounts of radiation and are incubated. The surviving fraction of cells is then determined as a function of the dose by counting the number of viable colonies on each dish.

The logarithmic nature of the cell survival curve means that a given increment of the dose will reduce the surviving fraction of cells by a constant factor. Radiobiologists have adopted the $1/e$ dose increment (D_0), corresponding to a 37% fractional reduction, for comparing sensitivity data. This parameter describes the linear portion of the curve.

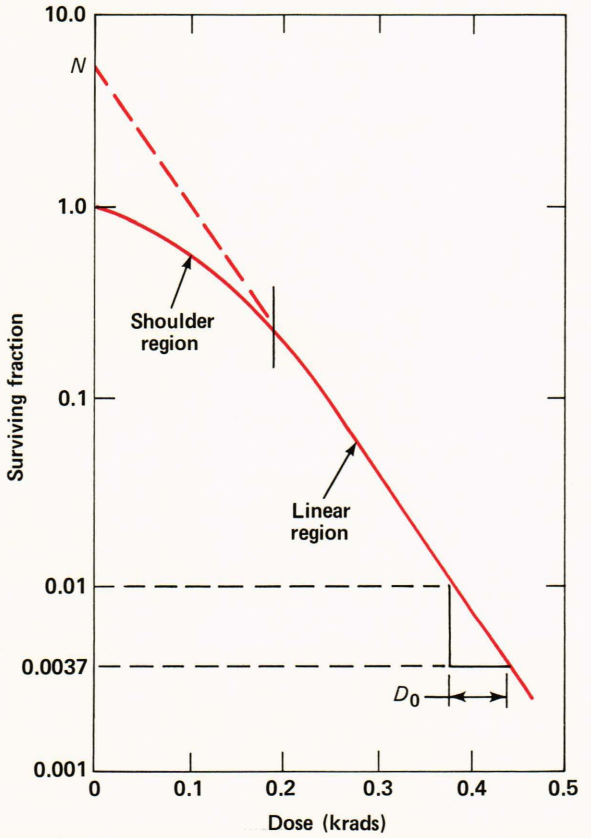


Figure 2 — Mammalian cell survival curve. A dose increment of 600 rads reduces the surviving population by 37%. The D_0 extrapolation number N is a measure of the shoulder width.

The cell survival curve for X rays and other types of radiation frequently exhibits a gradual shoulder at low dose levels. In this range, incremental increases in dose are apparently less effective in killing cells than had the same increase occurred at a higher total dose. These observations formed the basis for the multiple hit target model hypotheses alluded to above. Experiments have also demonstrated that the shoulder region is highly repeatable if several hours are allowed to elapse between successive irradiations. This observation is consistent with the notion of sublethal damage and repair.

The damage inflicted on a cell population by ionizing irradiation occurs with essentially equal efficiency for both normal cells and tumor cells. In general, little distinction can be made between the two, which would suggest that the cancer cells are intrinsically more susceptible to radiation. Further, even if tumor cells could be selectively identified, the highly randomized nature of spatial ionization events precludes the precise targeting necessary to kill only tumor cells. If a tumor embedded in healthy tissue is irradiated, both types of cell will incur sublethal damage and undergo processes of self-repair. Apparently, the normal cells are better at it. Also, radiation-damaged tumor cells or mutations are susceptible to attacks from the body's immunological system, which further diminishes their relative numbers. By fractionating the total dose in smaller amounts over a period of time, a differential effect will accrue to the disadvantage of the tumor. Ideally, a tumoricidal dose will be delivered before the tolerance limit for healthy tissue is reached.

The concept of relative biological effectiveness is of principal importance in radiation therapy. A review of cell survival data shows that equal quantities of ionizing radiation do not produce equal biological effects. For example, in single-dose treatments (Fig. 3), a dose of 270 rads of densely ionizing radiation (e.g., neutrons) produces a 0.003 surviving fraction, whereas 430 rads of sparsely ionizing radiation (e.g., 250-kilovolt X rays) are required to produce the same effect. The ratio of these two doses shows that the neutrons are 1.6 times more effective than the X rays in producing the same relative biological effect (1.6). For low dose levels, i.e., on the shoulder, the relative biological effectiveness of the densely ionizing radiation is even greater. Radiobiologists have standardized the use of 250-kV X rays as the reference for relative biological effectiveness measurement.

A course of fractionated radiation therapy may run five days a week for three or four weeks, with tumor dose fractions of 150 to 200 rads applied each day. In a typical regimen, a single dose fraction barely moves off the survival curve shoulder, and ample time is allowed between treatments for cell repair mechanisms to be effective. Accordingly, the degree of repair must be accounted for to make a valid comparison of therapies using the same energy radiation but different fractionation schedules. As shown in Fig. 4, fractionated therapy requires a greater total dose to produce the same biological result than does a single-dose treatment. Further, the phenomenon is accentuated if the dose per fraction is decreased. Conversely, the fewer the number of fractions to achieve a given total dose, the greater will be the relative biological effect. Comparisons of therapies using different qualities (a catch-all term that describes the electromagnetic or particulate nature of the radiation, mass, charge, energy, etc.) of radiation must also account for the relative biological effectiveness phenomenon. The relative biological effectiveness of

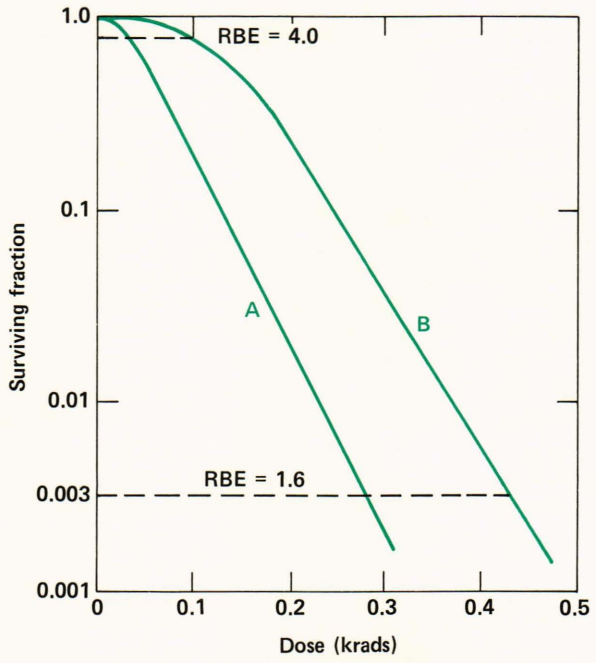


Figure 3 — Relative biological effectiveness, single dose. (A) Densely ionizing neutrons. (B) 250-kilovolt X rays. To achieve a 0.003 surviving fraction, a dose of type A radiation 1.6 times smaller is required.

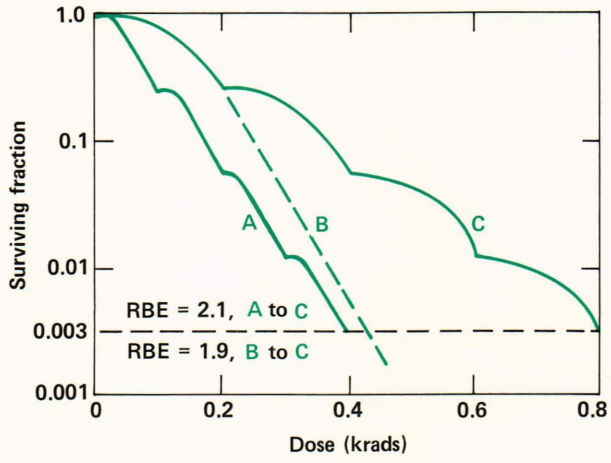


Figure 4 — Relative biological effectiveness, fractionated dose. (A) Densely ionizing neutrons, fractionated dose. (B) 250-kV E rays, single dose. (C) 250-kV X rays, fractionated dose.

neutrons, for example, increases markedly either with the total fractionated dose or with the number of fractions. The relative biological effectiveness phenomenon is of critical importance in developing new candidate sources for radiation therapy.

The total picture of cell kill and cell survival is influenced by many other factors. It is known that the sensitivity of a particular cell varies with its phase in the mitotic cycle and is maximized just prior to and during mitosis. This observation provided radiation therapists with a rational basis for dose fractionation. It is also known that different biological systems exhibit markedly different radiation sensitivities. Cells that have a short mitotic cycle appear to be more radiosensitive than less proliferative cells, although they may simply express the end result faster. Some slowly dividing systems, in fact, exhibit considerable radiation resistance. Further, evidence indicates that a cell's oxygenation has a profound effect on its radiosensitivity. This phenomenon has strong implications in cancer therapy, where many tumors are partially hypoxic and therefore relatively radioresistant. A strong thermal radiosensitization process is also evident in some cell lines. Several decades of increased radiation-induced cell kill can be achieved by elevating certain cell populations' temperature by a few degrees centigrade. While thermal energy itself is toxic to tumor cells, there is a strong synergistic relationship between thermal energy and radiation. Considerable research is under way on both hyperthermia and oxygenation sensitizers. Finally, we note major discrepancies in dose response between *in vitro* and *in vivo* laboratory data and the same tumors treated clinically, an apparent paradox that is not well understood.

Interested readers will find Refs. 3 and 4 excellent detailed reference texts on radiobiology.

INTERACTION OF IONIZING RADIATION WITH MATTER

High-energy X rays and gamma rays are by far the most common forms of therapeutic radiation in use today. An analysis of the interaction between electromagnetic radiation with matter at therapeutic energies requires consideration of three different attenuation processes (Fig. 5): photoelectric absorption, Compton scattering, and pair production. The relative importance of these processes varies both with beam energy and with properties of the irradiated medium, such as density and atomic number. However, a common result of each of these processes is the production of energetic secondary electrons that interact with matter more strongly than do the incident photons. These electrons decay through numerous excitation and ionization events, ultimately transferring all their energy to the surrounding medium. In an elemental volume, it is the interactions produced by secondary electrons, rather than the direct primary beam ionization events, that are chiefly responsible for the phenomenon of absorbed dose.

The process of photoelectric absorption (Fig. 5a) occurs only at relatively low photon energies. In water, for example, it is not significant above about 50 kiloelectronvolts (keV). In this process, an X-ray photon of energy $h\nu$ interacts with an inner shell electron of an atom and is totally absorbed. The photon absorption causes the ejection of a photoelectron with energy

$$E_e = h\nu - \bar{E}, \tag{1}$$

where $\bar{E}$ is the associated binding energy. In tissue, typical binding energies are $\bar{E} = 0.5$ keV, so most of the photon's energy appears as photoelectron kinetic energy. The atom also emits a 0.5-keV photon when the electron vacancy is filled, but this photon is quickly absorbed. Within its range of significance, the photoelectric process varies inversely with the cube of both atomic number and photon energy. The former relationship accounts for the absorption dif-

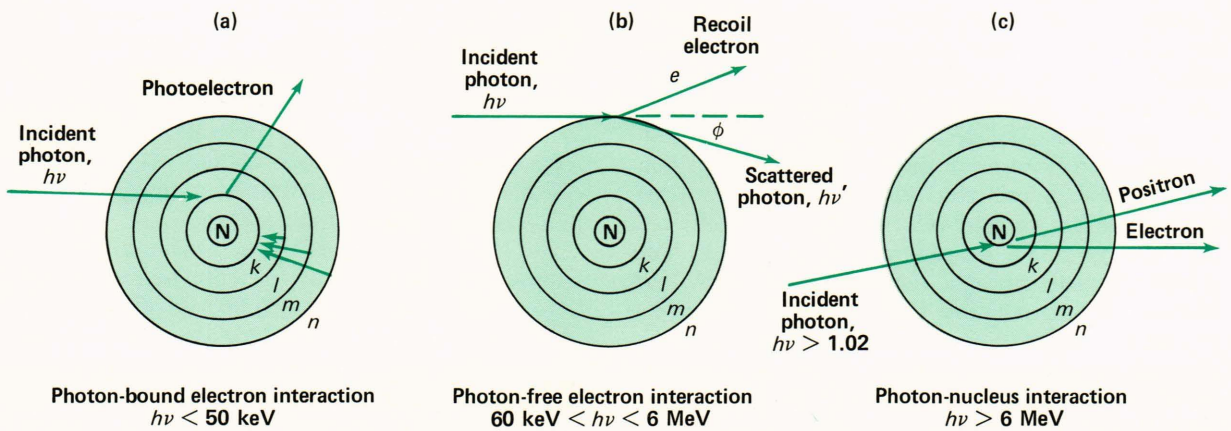


Figure 5 — Attenuation processes. (a) Photoelectric absorption, (b) Compton scattering, and (c) pair production.

ferential between soft tissue and bone exhibited by diagnostic rays. (Diagnostic X rays are typically in the 80 to 125 keV range.)

Compton scattering (Fig. 5b) is a phenomenon that is significant over the entire range of therapeutic beam energies. Between 60 keV and 4 megaelectronvolts (MeV), this process is dominant in water and accounts for over 90% of the interactions. Compton scattering occurs when a high-energy photon collides with an outer ring (i.e., essentially unbound) electron. The photon's energy is converted into electron kinetic energy by this process, causing it to recoil. The electron then transfers its energy to the medium through a prolonged series of secondary ionization and excitation events. (A 1-MeV photon scattered by the Compton process converts essentially all of its energy into electron kinetic energy. Assuming an average 34-electronvolt (eV) ionization energy per event for biological tissue, the decay process will involve about 30,000 interactions.) The photon continues to exist after the collision, but it is scattered through an angle ϕ and its energy is reduced.

From conservation of energy and momentum considerations, the energy of the electron (E) and the photon ($h\nu'$) can be computed as a function of scatter angle ϕ after the collision; that is,

$$E = h\nu\left(\frac{\alpha(1 - \cos\phi)}{1 + \alpha(1 - \cos\phi)}\right), \quad (2)$$

$$h\nu' = \frac{h\nu}{1 + \alpha(1 - \cos\phi)}, \quad (3)$$

where α is the incident photon energy divided by the rest energy of an electron.

As the incident photon energy increases, it is evident that the energy of the recoil electron increases and in the limit approaches $E \rightarrow h\nu$.

The Compton process involves electrons that are essentially free and therefore is independent of atomic number. However, the effect does depend on electron density (electrons per gram), a parameter with small variability for different biological materials. In radiation therapy, where the Compton process dominates, soft tissue and adjoining bone will receive nearly the same dose even though their mass densities differ.

The third energy attenuation process of significance is electron-positron pair production (Fig. 5c). The process occurs at relatively higher energies when an X ray passes in proximity to an atomic nucleus and interacts, and a particle pair is generated. The phenomenon has a threshold energy of 1.02 MeV, the rest energy of the particle pair. In water, the effect becomes significant above 6 MeV and, at 25 MeV, pair production and Compton scattering are comparable phenomena. The positron produced in the interaction rapidly combines with a nearby electron, causing an associated pair of 0.511-MeV annihilation photons to be produced. Pair production absorption is observed to increase linearly with atomic number. An excellent summary of these interactive processes is given in Ref. 5.

On an atomic scale, the electrons produced by the processes described above cause ionization events that either directly or indirectly produce cell damage. The manner in which ionizing radiation deposits energy on a microscopic scale is also extremely important. As noted above, equal amounts of energy deposited by different sources or in different time frames may result in widely different biological effects. A principal factor in the relative biological effectiveness phenomenon is the rate with which the primary radiation loses energy along its track. Dif ferent types of radiation (i.e., qualities) have different intrinsic capacities to produce ionization. The significance of these differences becomes evident if viewed on a scale comparable to cell size. Current models hypothesize that incident photons or particles produce a distinct track through the matter and that ionization events occur in proximity to the track.

The spatial rate at which energy is distributed along the track, called the linear energy transfer, establishes the probability of multiple hits within a cell and therefore is a determining factor in the relative biological effectiveness. Ordinary X rays produce relatively infrequent events along their track (sparsely ionizing) and have linear energy transfer values on the order of 1 keV/micrometer. Neutrons are more efficient ionizers because of their mass and associated recoil protons and, at 15 MeV, have a transfer value of about 10 keV/micrometer. Alpha particles that are both heavy and charged may have transfer values on the order of 1000 keV/micrometer.[4] These large differences in linear energy transfer translate directly into correspondingly large differences in energy deposited within individual cells, thereby contributing to the relative biological effectiveness phenomenon.

To develop the concepts of dose distribution useful in radiation therapy, it is necessary to consider the interaction of radiation with matter on a macroscopic scale. This interaction is best studied by a monoenergetic point source of ionizing photons irradiating a semi-infinite slab of water at a fixed distance, by convention 1 meter (Fig. 6). All important properties of the treatment beam can be studied in detail by using this model. In practice, dose measurements in such a "water phantom" are made in great detail and are extrapolated to predict the dose distribution in patients irradiated in a similar manner. It is instructive to examine the dose distribution along the axis of a regular (square or rectangular) beam.

The absorbed dose measured within an elemental volume along the axis arises from two contributing factors: the direct primary beam ionization and ionization produced by secondary scattered electrons. The former contribution decreases exponentially from the surface and is independent of field size. The latter contribution is determined by the scatter volume surrounding the elemental volume and the

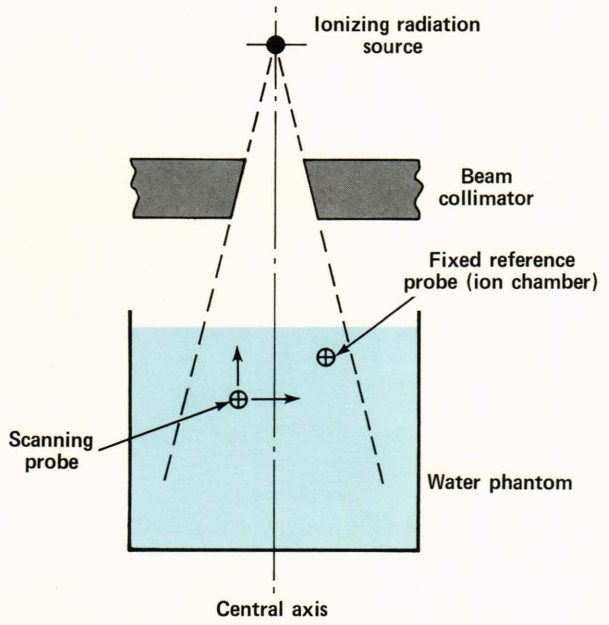


Figure 6 — Beam-scanning configuration patterns are measured by taking the ratio of the scanning ionization probe to the fixed ionization probe to eliminate temporal variations. Readings are normalized to the maximum dose level.

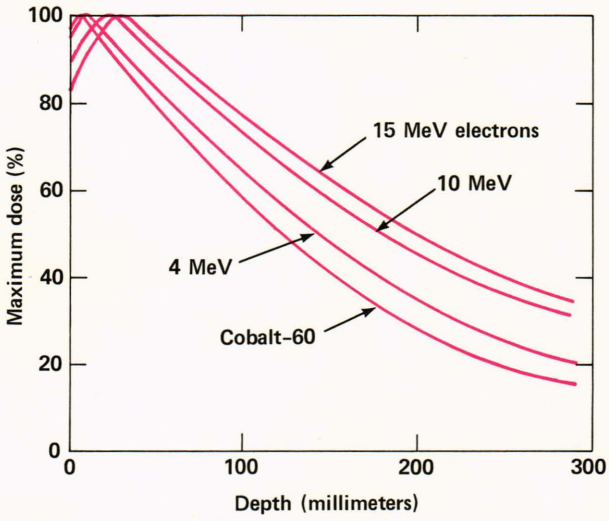


Figure 7 — Percent of depth dose, cobalt-60 and X-ray beams of 4, 10, and 15 MeV, normalized to maximum dose.

strength of the primary beam. This relationship, which is field-size dependent, starts small, increases to a peak, and diminishes at depth. The depth dose relationship for a number of therapy sources is shown in Fig. 7. As the energy of the beam increases, it becomes more penetrating and therefore more favorable for deep therapy.

An important phenomenon of dose buildup occurs near the surface of the irradiated medium (Fig. 8). Incident photons initiate primary recoil electrons and secondary scatter electrons that migrate in the forward (beam) direction. As a result, an elemental volume near the surface will witness relatively few scattered electrons either coming to rest or in transit. The contribution to absorbed dose from the scattered electrons is therefore diminished. The primary beam must penetrate into the medium for a distance equal to the maximum range of initial recoil electrons before sufficient secondary electrons are generated to achieve an equilibrium condition (i.e., the net flow of electrons out of the elemental volume is zero). Consequently, the depth of maximum dose does not occur at the surface but rather builds up to the peak a short distance into the medium. The depth of maximum dose increases with energy, occurring at 0.5 centimeter depth for 1.25-MeV (cobalt) gamma rays and 1 centimeter depth for 4-MeV X rays. Low-energy therapy machines (e.g., 250 keV) have essentially no build-up region, and the maximum dose occurs on the surface. This produces severe radiation burns on a patient's skin, a very troublesome phenomenon in early radiation therapy. The skin-sparing benefits of high-energy radiation gave considerable impetus to its use in therapy.

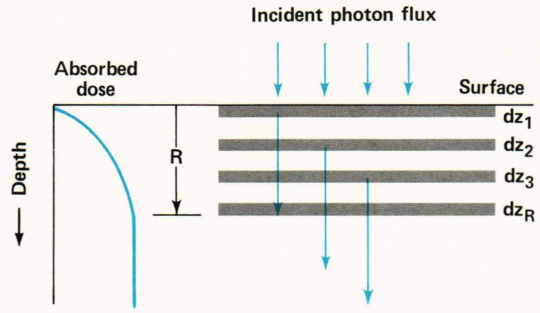


Figure 8 — Dose build-up region. The electron range *R* (in centimeters) equals one-third the electron energy (in MeV, approximately) up to depth *R;* the number of primary interactions in each slab *dz* is assumed constant. The absorbed dose is proportional to the total number of electron tracks in each elemental volume. Therefore, the absorbed dose function increases monotonically to depth *R,* where electronic equilibrium is established.

RADIATION SOURCES

Physicists and engineers have developed a broad array of electronic and isotopic sources for use in clinical radiation therapy. Most of the treatments in modern radiation therapy facilities are conducted by using external beams or teletherapy sources. Prior to 1950, all isotopic teletherapy machines used radium-226, which was extraordinarily costly ($20,000 per gram) and which, in the quantities required, suffered from considerable self-absorption. However, in 1951, the Canadians produced a new isotopic source, radioactive cobalt-60, by activating cobalt-59 in a nuclear reactor through high neutron flux bombardment. This source proved to have many advantages over radium, which soon led to its widespread use. Cobalt-60 has a very high specific activity, that is,

radioactive disintegrations per gram, and provides therapists with an intense point source of ionizing radiation. It produces gamma ray emissions at 1.2 and 1.3 MeV, yielding all the clinical benefits of high-energy therapy. New source activities of up to 6000 curies are available that produce clinical dose rates in excess of 125 rads/minute at conventional treatment distances (Fig. 9). The cobalt-60 isotope has a physical half-life of 5.3 years, which causes clinical sources to be replaced on an approximately three-year cycle. Cobalt-60 has proven to be an extremely reliable source of radiation and is relatively easy to handle. The development of cobalt teletherapy was a dramatic technologic breakthrough that resulted in an extremely rapid growth in clinical radiation therapy.

Since the very earliest days of radiation therapy, major research and development efforts have been under way in industry to develop electronic X-ray sources in the megavoltage range. The clear advantages of high-energy therapy and the need for more flexible, easily controlled sources provided impetus to this activity. The first electronic sources used for therapy were simply extensions of the diagnostic X-ray technology. This approach ran into difficulty above 200 keV photon energy because of component (rectifier) failure resulting from the necessary high voltages. New conceptual techniques were required to reach the megavoltage range (imagine a 10 million volt power supply). The Van de Graaff generator was used to produce 2-MeV X rays for therapeutic use in several centers. However, these units never gained widespread acceptance. Approximately 20 years ago, high-energy linear accelerators were introduced into therapy clinics, and since then they have undergone a continuing series of improvements. The basic structure of a linear accelerator (Figs. 10 and 11) is a resonant waveguide (S band) coupled to a microwave power amplifier. Electrons injected into the waveguide are coupled onto the electromagnetic wave and

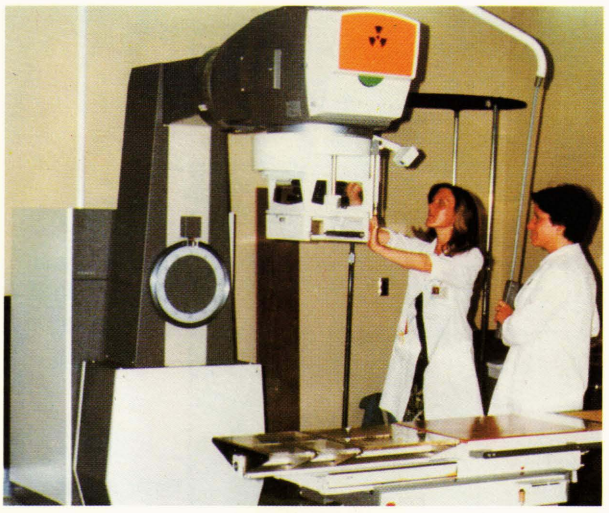


Figure 9 — The Siemens Gammatron cobalt-60 machine. Technologists are setting up the machine for patient treatment by preadjusting beam collimators.

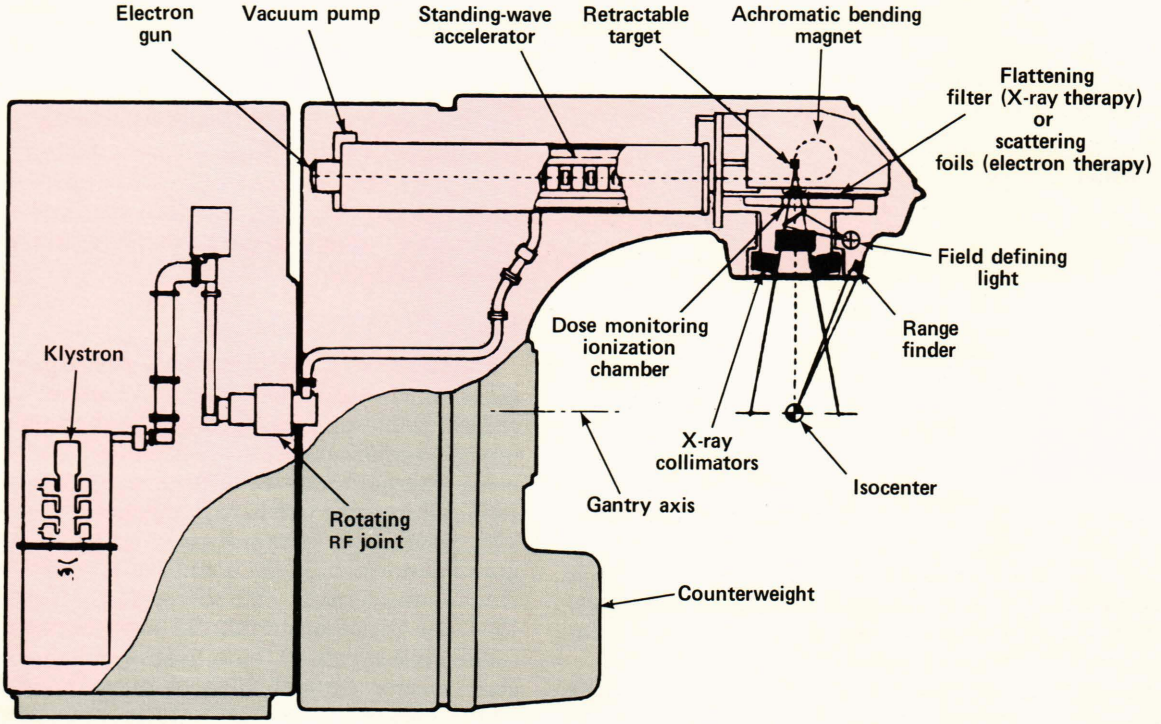


Figure 10 — Varian CLINAC-20, major subsystems. A dual-mode high-energy linear accelerator produces 15-MeV X rays or 6-, 9-, 12-, 15-, and 18-MeV electrons.

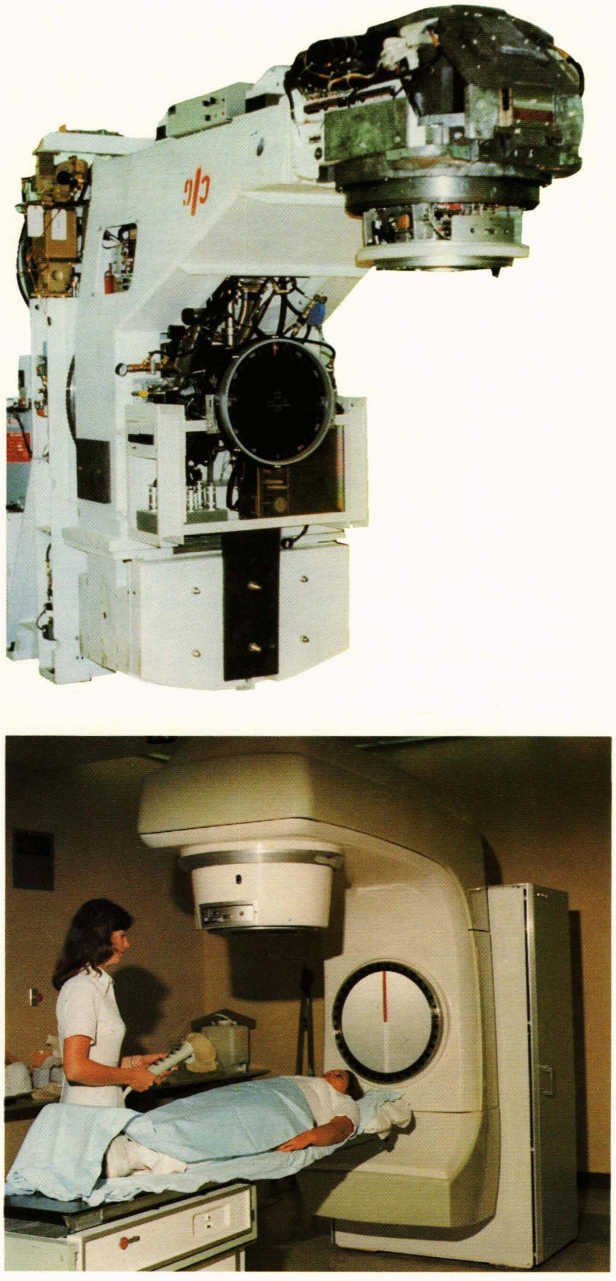


Figure 11 — (top) The Varian CLINAC-20. The complexity of clinical linear accelerators is reflected in the six months average time to complete installation, calibration, beam scanning, and certification for patient use. This photograph was taken at the conclusion of the installation phase. (bottom) Varian CLINAC-4 certified for patient use.

propagate through the structure, increasing in velocity. The X rays are produced when the electrons collide with a tungsten (or other high atomic number metal) target. The standing wave configuration is quite efficient and permits electrons to be accelerated to megavolt energies in very short (meter) distances. The development of a standing wave linear accelerator that was compact and reliable was a second notable breakthrough in radiation therapy. Linear accelerators are now found in all major facilities; they range from 2 to 18 MeV in energy and have become the principal teletherapy radiation source.

The beam-forming apparatus of teletherapy machines contains the omnidirectional radiation field by means of a heavily shielded radiation "head" that encloses the source. A high-density (depleted uranium) adjustable collimator is embedded in the head, which projects a regular (rectangular) beam outline onto the patient. Typical therapy beams range up to 40 square centimeters at a treatment distance of 1 meter. To facilitate treatments, the configuration of the source should allow the tumor to be irradiated from any direction. This has been achieved with an isocentric geometry, a configuration adopted for most teletherapy sources, where the source is cantilevered on the arm of a mechanical gantry and is rotated in a precision circle in a plane normal to the gantry axis. This configuration facilitates multiple fixed-port therapy, rotational therapy, and other complex source distributions.

SOURCE CALIBRATION

Surely the most critical activities carried out by a radiation physicist in a therapy department are those tasks associated with source calibration. In a year, many thousands of treatments take place on a single machine in a busy therapy department. It is imperative that the prescribed tumor dose levels be delivered with high accuracy. For some tumors, underdosing by 10% is known to result in a marked increase in recurrences, while in others, overdosing by 10% is known to result in very serious side effects. Of further significance is the importance of calibration on the transfer of information. Protocols developed at one institution cannot be used at other facilities unless machines at both institutions are calibrated absolutely.

The most direct way of quantifying levels of ionizing radiation is through a measurement of "exposure," a unit that denotes the ability of the radiation to ionize air. Exposure is measured by collecting the charged particles produced by irradiating a known mass of air at standard temperature and pressure under conditions of electronic equilibrium. Sources are calibrated in exposure units by means of a "standard ionization chamber" where 1 roentgen = 1.6×10^{12} ion pairs per gram of air. Since the average ionization energy of air molecules is 34 eV, a radiation beam producing 1 roentgen exposure will deposit 86.9 ergs per gram or 0.869 rad. This factor relates exposure measurements to absorbed dose in air. To achieve electronic equilibrium, the physical length of the chamber must equal (at least) the maximum range of the secondary electrons. This requirement places a practical limit on the use of the roentgen to energies less than 3 MeV.

The calibration of therapy machines in major departments is almost always referenced directly to a secondary standard ionization probe and electrometer (Fig. 12) calibrated at the National Bureau of

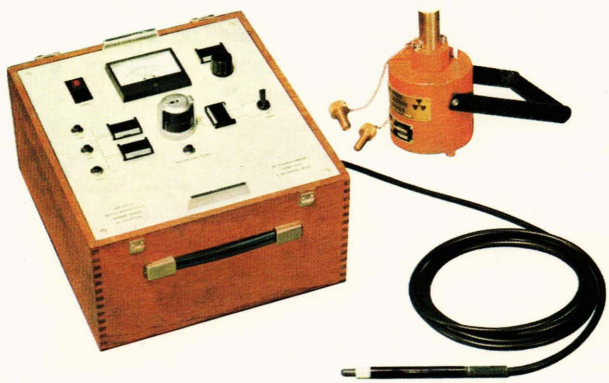


Figure 12 — National Precision Laboratories secondary standard. The ionization chamber and probe have a basic sensitivity of 100 picocoulombs per roentgen. The check source is a constant strontium-90 source enclosed in a lead cylinder and is used to verify the stability of the standard.

Standards. The ionization probes used for machine calibration are small (volume approximately 0.3 cubic centimeter) thimble chambers, standard ionization chambers being too unwieldy. Typically, Baldwin-Farmer model 2502/3 or Keithley model 616 electrometers are used with a measurement sensitivity of 10^{-12} coulomb. To achieve the conditions essential for a valid calibration, which, at the National Bureau of Standards, is done with cobalt-60 radiation, the probes are fitted with special build-up caps. The thickness and composition (density, atomic number) of these caps are such as to emulate an "air wall" chamber so that the air volume inside will achieve a condition of electronic equilibrium.

Radiation physicists are primarily concerned with measuring the absorbed dose in tissue or in a tissue equivalent medium such as water. The Bragg-Gray cavity theory provides the necessary relationship between ionization produced in a small (essentially nonperturbing) air-filled cavity embedded in a medium and the energy that is absorbed by the medium. Simply, $E = JWS_A^W$, where J is the ion pairs produced per gram of air (standard temperature and pressure) in the cavity, W is the average energy per ionization event (ergs per ion pair), and S_A^W is the stopping power ratio (water to air).

The stopping power of a medium (see Ref. 6 for the Bethe-Block formulation) relates the loss of kinetic energy of an electron traversing a material to the material's atomic number. The stopping power ratio relates the relative energy deposited in two different media (e.g., water, air) for the same electron flux.

Clinical dose rates are calibrated in a tissue-equivalent medium (water) and are computed by

$$D = \frac{RCC_\lambda}{T} ,$$

where R is the electrometer reading, C is the National Bureau of Standards calibration factor relating measurement reading to roentgens, C_λ is the factor relating exposure to absorbed dose (relative to cobalt-60 energy, which is the National Bureau of Standards standard), and T is the electrometer integration time.

Precision dosimetry is a major problem in radiation therapy physics. The measurement is indirect; i.e., we wish to measure energy density in tissue and instead we measure charge in air. Further, the measurements are quite sensitive to the ambient conditions and beam energy. Simplification and refinement of dosimetry techniques remain major goals of radiation physics research.

The procedures for maintaining calibration on a heavily used machine are quite detailed. At the Johns Hopkins Oncology Center, which is typical of most large institutions, "absolute" calibrations are made every three months using a National Bureau of Standards-calibrated secondary standard electrometer. (Constant checks are usually done with a constant-output strontium-90 source.) A series of measurements is taken in a water phantom at a specified depth (10 centimeters) under exact conditions of source distance (100 centimeters) and field size (10 × 10 centimeters). Multiple readings are corrected for temperature and pressure conditions and are averaged. These absolute calibration measurements are the most precise measurements performed by the radiation physicist and are the basic reference for all treatments. To validate source calibration, additional measurements are made each week in a polystyrene phantom, which is also cross-referenced with the secondary standard. Further, constancy checks are made each morning with solid-state detectors to verify that the machine's output has remained constant for a given set of test conditions. This check is very effective in detecting hidden electronic or mechanical failures that would occur, for example, if the source-to-patient distance indicator were to malfunction. Finally, on an annual basis, external agencies such as the Radiation Therapy Oncology Group or other major teaching and research institutions are invited to verify the calibration dose rates using their own equipment.

By following these detailed procedures, the calibration of the five major therapy machines at the Johns Hopkins Oncology Center was maintained within 2% of absolute accuracy over a five-year period.

COMPUTER-AIDED TREATMENT PLANNING

To be certain that radiation therapy treatments will be effective and relatively free from undesirable side effects, therapists must be concerned with the total dose distribution within the patient. Accordingly, patients who receive radiation therapy must first undergo an extensive treatment planning process. There

are certain practices or goals common to all good radiation therapy treatments. First, it is imperative that the entire tumor be encompassed by the treatment portals. Hence, the tumor volume, that is, the volume receiving the prescribed dose, is in fact the true tumor volume plus a small margin (approximately 0.5 centimeter). Second, the dose delivered to the tumor volume should be uniform throughout the volume. Ideally, the degree of inhomogeneity should not exceed 5%. Third, the dose delivered to surrounding healthy tissues should be minimized. Finally, therapists often must deal with maximum dose tolerance limits imposed on critical organs in the vicinity of the tumor, organs that will be irradiated unavoidably. An excessive incidental dose to the spinal cord or to the eyes, for example, will result in severe problems for the patient. While the aforementioned treatment goals are all highly desirable practices, some compromise is often necessary.

When the practice of radiation therapy was developing, therapists were provided with dose rate versus depth data for their teletherapy equipment by the equipment vendor. These "canned" data were derived from a single set of water phantom measurements for different field sizes and treatment distances and were universally applied to all equipment of a similar make. Dose calculations assumed patients were homogeneous, and patient curvature was accounted for by very approximate methods.

In recent years, computer-aided treatment planning has added immeasurably to the therapist's knowledge of dose distribution. While a straightforward modeling process is involved, physicists must first gather considerable detailed data about the treatment beams. In the beam scanning process, the teletherapy machine is made to irradiate a flat water phantom at a distance of 1 meter. A precision ionization probe scans through the water automatically and measures the beam profiles at various depths. Measurements are made relative to a second fixed ionization probe to eliminate temporal variations, and all measurements are normalized relative to the maximum dose. Of particular importance are the relative dose-versus-depth profile along the beam central axis, the beam flatness profile, and the penumbra region (sources are not infinitesimal and collimators are not perfect). On a particular machine, such data are measured for as many as 100 fields. Typically, beam profiles (Figs. 13 and 14) are measured in 2-centimeter linear increments from 2 × 2 centimeters to 40 × 40 centimeters. Data are obtained for open fields and four sizes of wedged fields (wedged fields are produced by placing a linear amplitude taper over the open field). Also, high-aspect (length to width) fields used in special treatment are measured. All profile data are sampled spatially in great detail and are digitized and stored in a computer file. These data are used with various rules of geometric field size equivalence and interpolation to generate the beam profiles for intermediate-sized beams as they would appear in a homogeneous water phantom.

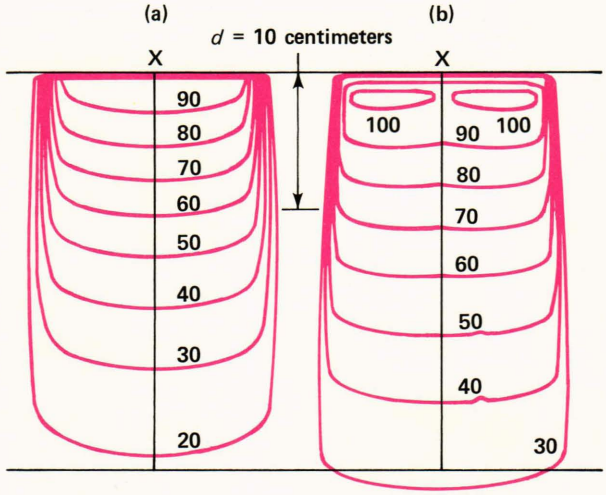
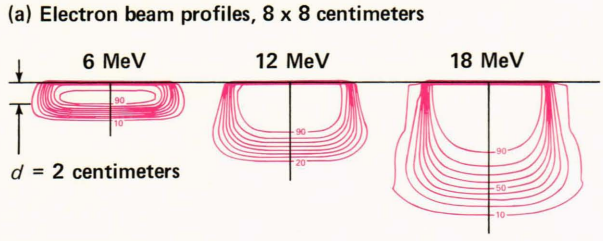


Figure 13 — Treatment beam profiles. (a) Siemens Gammatron cobalt-60, energy = 1.25 MeV. (b) Varian CLINAC-18 linear accelerator, energy = 10 MeV. Data normalized to maximum dose levels that occur at d_{max} = 0.5 centimeter in (a) and d_{max} = 1.5 centimeters in (b). The linear accelerator is more penetrating, has a flatter profile, and has a smaller penumbra than the cobalt device.



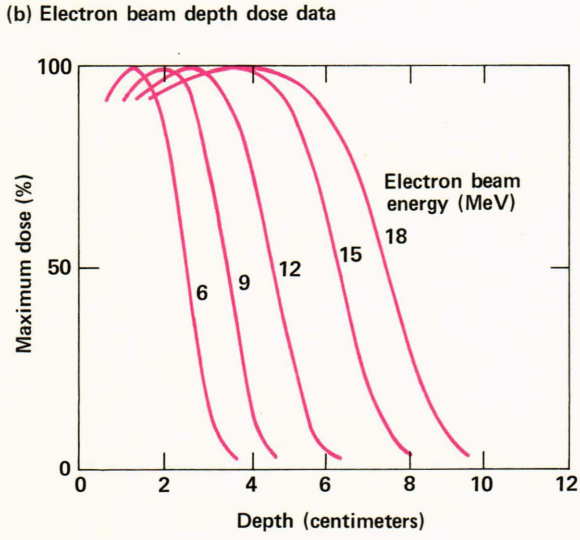


Figure 14 — Electron beam therapy. High-energy linear accelerators such as the CLINAC-18 and the CLINAC-20 are dual-mode units and produce high-energy electron beams for therapy as well as X rays. The range (in centimeters) of electrons in tissue is roughly one-third of the energy (MeV). The dose versus depth relationship is nearly flat up to the electron range and then falls off rapidly. As a result, large doses can be given to superficial or near-surface lesions while completely sparing underlying tissue.

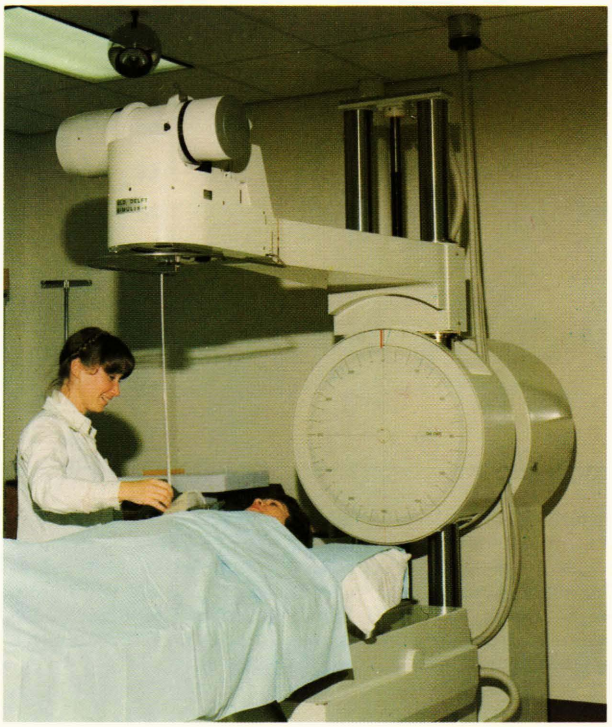


Figure 15 — Technologists require certain critical information to set up a patient properly for treatment on a teletherapy machine. Basic data, such as gantry angle, field size, and tumor depth, are required to be sure the tumor volume is encompassed and the treatment optimized. This information is obtained before treatment starts on a therapy "simulator." The machine uses a standard X-ray radiation source in a configuration that emulates the therapy source. The diagnostic quality images produced on the simulator allow visualization of the tumor volume and facilitate the setting of necessary treatment parameters.

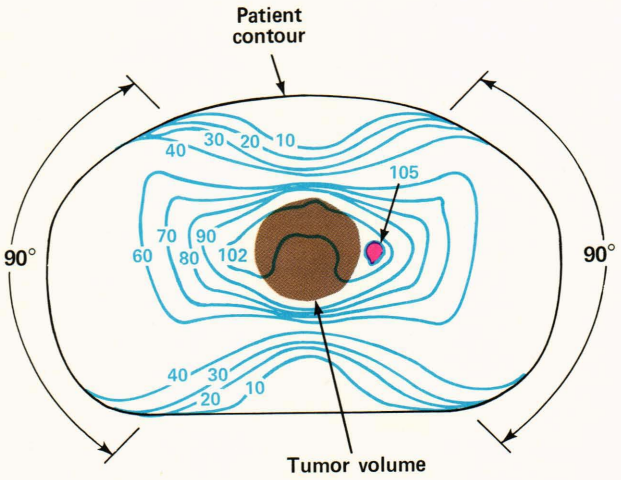


Figure 16 — Computer-aided treatment planning is used here as rotational arc therapy. An 8.5-centimeter-square beam is rotated through two arcs (45° to 135° and 225° to 315°). Isodose lines are normalized to the center of the tumor volume (i.e., dose per 100 rads at isocenter). Much of the tumor is covered by the 102% isocontour. The distribution has a "hot spot" of 105%.

Special algorithms are required to compute dose distributions for irregular fields.

Prior to the first treatment, usually during the process of simulation (Fig. 15), the patient contour is measured, digitized, and entered into the computer. The tumor volume and critical organs are located within the contour by the therapist, and the contour is located relative to the radiation source (i.e., relative to the machine isocenter). Different treatment prescriptions (gantry angle, field sizes, etc.) are simulated by mathematically projecting the beams onto the patient contour. The resultant dose distribution is then calculated. This modeling procedure works extremely well for multiple fixed-port therapy or rotational arc therapy (Fig. 16). Isodose curves for various prescriptions are presented to the therapist, who selects the optimum curve.

Computer-aided treatment planning advanced considerably with the development of diagnostic computerized axial tomography (CAT). These machines produce excellent cross-sectional images of patients with submillimeter resolution and excellent contrast sensitivity. CAT scanners generate patient contour information, as well as images of internal organs. It is now possible to assign electron densities to different biologic structures (tissue, fat, bone, and air) visible in the CAT scan, permitting a much more refined calculation of dose distribution. Isodose curves, homogeneity factors, and critical organ dose levels, for example, are computed as a routine part of the treatment plan. Further, automatic optimization techniques are being developed based on prescribed homogeneity and maximum dose constraints (at various points). This process results in the generation of five or six optional plans for consideration by the therapist.

FUTURE DIRECTIONS

Many of the more promising research areas in radiation therapy are tightly coupled to advances in technology. A Swedish firm, Scanditronix, Inc., recently announced a new type of machine, the Microtron, for X-ray and electron therapy. This machine uses a single large evacuated disk to accelerate electrons to high energies via the synchrotron principle. The electrons, whose energy increases with radius, are picked off and distributed to a number of different therapy rooms simultaneously. Beam transportation and focusing are accomplished by means of a series of bending magnets and focusing magnets. The Microtron provides a much simpler source of electrons capable of serving a multiplicity of therapy rooms. The electron beam energy is continuously variable, and maximum energies of 25 MeV have been achieved. A Microtron is currently being installed in the Clinical Center, Department of Radiation Therapy at the National Institutes of Health, Bethesda, Md.

The use of high-energy X rays, gamma rays, and even electrons is commonplace. Truly dramatic improvements in the effectiveness of radiation and tele-

RADIATION THERAPY TREATMENTS OF MEDULLOBLASTOMA

Radiation therapy treatment of medulloblastoma, a lesion occurring near the base of the brain, requires extensive use of computerized treatment planning. The treatment protocol for medulloblastoma calls for both total brain irradiation and total spine irradiation (see figure). Because of the high degree of dose homogeneity required and the extended three-dimensional nature of the tumor volume, the treatment geometries tend to be very complex, making the use of computerized planning imperative.

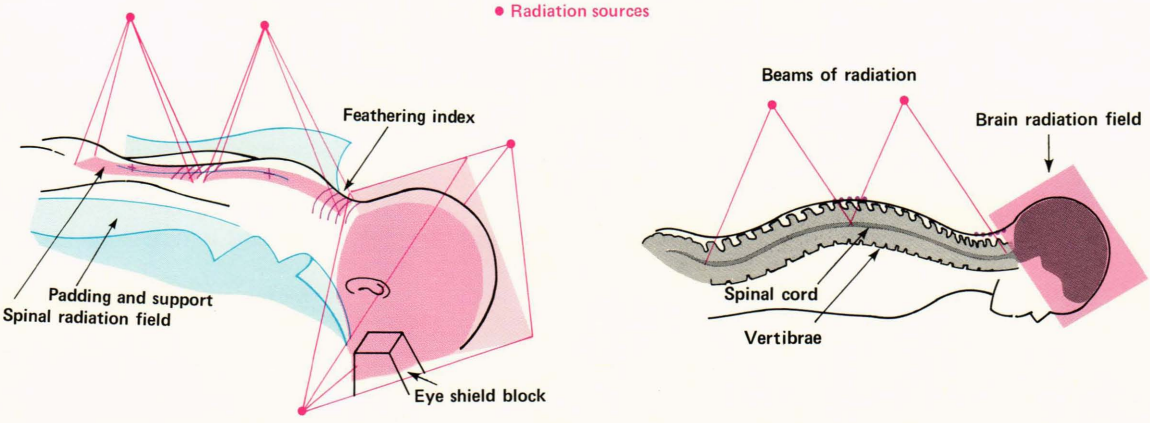
The total brain irradiation is accomplished with parallel-opposed bilateral fields, taking care to shield the patients' eyes from direct radiation. The dose distribution produced by such irregular fields is complex; special algorithms have been developed that compute direct radiation dose and scatter radiation dose separately in order to predict accurately the resultant brain midline dose distribution.

Total spine irradiation is accomplished by using multiple adjoining fields with sufficient total length to encompass the entire spine. Because of the large length-to-width aspect of these fields, conventional dose prediction methods fail and the spine dose must be computed from a special subset of measured beam data. Beam divergence requires that special provisions be made in order to accommodate the overlap area at the junction of the bilateral brain fields and the upper spine field. When viewed in its full three dimensionality, this is a very troublesome problem. If the two spine fields abut at the posterior level of the spine, a section of the cord will receive twice the prescribed dose due to the divergent beam overlap, possibly resulting in a cord transection. If the fields abut at the anterior level, a cold region will occur resulting in a less than tumoricidal dose being delivered to a small section of the cord. Simular circumstances obtain at the brain field-upper spine field juncture.

A process of field "feathering" has been introduced to resolve the problem. This process calls for separating adjacent fields by a 1 centimeter gap and shifting the edge of each field by 1 centimeter per day on consecutive treatment days. The process is repeated on a four day cycle. The result is a spatially averaged dose distribution where large excursions have been eliminated.

The total dose distribution for the entire treatment must be computed accounting for its three dimensionality and the feathering process. Under the guidance of M. D. Wharam, a series of complex treatment planning algorithms was developed at the Johns Hopkins Oncology Center by R. E. Sterner, now at APL, which helped to generate distributions homogeneous to better than ±5% over the entire tumor volume.

Medulloblastoma is a lesion found predominantly in teenagers and young adults. Its successful treatment is a lengthy and extremely demanding task requiring close cooperation among the therapist, technologist, and physicist. Most important, however, is the courage and resolve of the patient. The patient illustrated in the figure is shown in the treatment position. Because of the need for high geometrical precision, the patient must be set up in custom-made fixtures designed for complete immobilization. On any single day, he or she will receive both the bilateral brain irradiation and the spinal irradiation. Such treatments, which often require more than an hour for setup and irradiation, are repeated daily for a period of several weeks. Note the feathering index reference marks drawn on the patient's neck.



Treatment planning of medulloblastoma, showing orientation of the patient relative to the radiation sources.

therapy treatments from these sources should not be realistically expected. However, there are some new particle therapies that appear to have definite advantages and that are being vigorously pursued. Neutrons, for example, are known to have an enhanced relative biological effect and are much less dependent upon time-dose fractionation than are X rays. Two major firms, the Cyclotron Corporation (U.S.) and Scanditronix, are marketing isocentric neutron teletherapy machines. The heart of these machines is a high-capacity positive ion cyclotron. These units produce a 100-microampere beam of either protons or deuterons, transported and focused via large magnets, that collides with a beryllium target located in the head of a rotating gantry. The proton-beryllium interaction yields a high flux of energetic neutrons at therapeutic dose rates. Facilities for neutron therapy are quite extraordinary (9-foot-thick concrete primary radiation barriers) and costly, and will be much less widespread than X-ray therapy facilities. However, it is certain that neutron therapy will be available at several centers.

A continuing area of research at major particle accelerator facilities involves the use of esoteric particles (e.g., pi-mesons and heavy ions) for cancer therapy.[7] Pi-mesons are negatively charged, have a mass intermediate to those of an electron and a proton, and are unstable, decaying in about 10^{-8} second. The advantage of pi-mesons, as with other heavy charged particles, is that they have an essentially constant depth-dose relationship until the very end of their range, where the absorbed dose increases dramatically to a large peak and then falls off rapidly (Fig. 17). This results from strongly enhanced energy transfer mechanisms at lower particle energies. By varying the incident beam energy, particles can be "tuned" to deposit their energy within the tumor volume, thereby minimizing effects to the surrounding tissue. Production of pi-mesons in quantities sufficient for therapy is a very difficult technical problem. The large particle accelerator at Los Alamos has been used for this purpose, and some clinical data are being gathered. However, it is not certain that pi-mesons will ever become useful clinically because of beam generation problems.

The use of radiolabeled antibodies, research being pioneered by S. E. Order at the Johns Hopkins Oncology Center, is a method for targeting atoms of radioactive materials directly onto the surface of tumor cells. The technique is maximally efficient. Antibodies produced to target selectively on tumor cells will carry a radioactive tag, such as iodine-131. The radionuclide releases its energy in close proximity to the tumor cell, enhancing the kill probability. Assessment of this new therapy requires the use of positron-emission tomography and other sophisticated imaging systems and advanced dose modeling techniques, some of which will be carried out at the Applied Physics Laboratory.

Clinical researchers at the National Institutes of Health under E. Glatstein are developing protocols for intraoperative radiotherapy using the variable-energy Microtron. In this procedure, the diseased organ is exposed via surgery in the therapy room and is subjected to direct massive dose levels. This method sidesteps problems resulting from irradiating surrounding healthy tissue and permits much more aggressive therapy.

Intensive research is under way in the use of hyperthermia to exploit the synergistic response that results from the combined use of thermal energy and ionizing radiation. The problems of generating, controlling, and monitoring localized volumes of increased temperature *in vivo,* initiated by either radio frequency microwave or ultrasonic sources, are very difficult technical challenges. This therapy has been successfully demonstrated on superficial tumors.

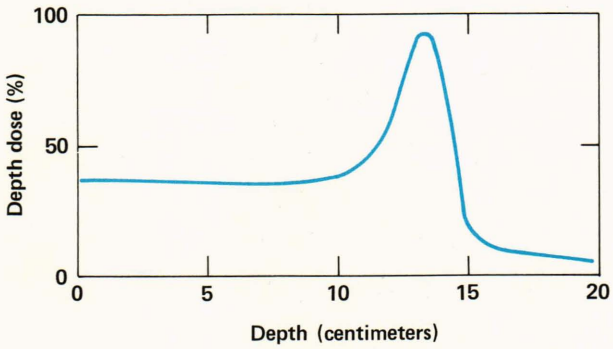


Figure 17 — Depth dose distribution of monoenergetic negative pi-mesons. Other heavy charged particles (protons, ions) have a similar distribution.

Figure 18 — The Johns Hopkins radiation therapy wing under construction. The high-energy and high-flux levels of the therapy machine demand extraordinary shielding measures. To protect technologists and the general public, the Varian CLINAC-20, which produces 15-MeV X rays at rates up to 300 rads/minute, requires 8 inches of steel embedded in 66 inches of concrete. The radiation barriers in the Johns Hopkins Oncology Center reduce ambient radiation levels to a factor of 10 less than national regulations. Technologist exposure is comparable to that produced by natural background.

Finally, we note the future impact of computer-aided treatment planning. The use of higher resolution CAT scans, nuclear magnetic resonance imaging, and positron-emission tomography will optimize radiation therapy dose planning to a much finer degree. Certainly, full three-dimensional dose planing with millimeter-scale resolution is in the near future.

It is clear that ionizing radiation will continue to play a major and increasingly significant role in cancer therapy as new biomedical research unfolds and as the technology brought to bear by physicists and engineers advances (Fig. 18).

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