Chapter 2

THE DEVELOPMENT OF RADIOTHERAPY: PHYSICS, TECHNOLOGY, METHODS

Summary

Radiotherapy was introduced in Sweden already before the turn of the century, ie, a few years after the discovery of x-rays and radioactivity. Pioneering contributions were made by Forssell, Berven, Heyman, Sievert, and Strandqvist in general radiotherapy, gynecologic radiotherapy, dosimetry, teleradium methods, and radiation biology. Technological advancements, along with nearly 100% followup of treatment effects, created a foundation for compiling early empirical experience in a methodologically sound specialty.

Therapeutic radiology in Sweden was distinguished from diagnostic radiology already in 1917, at which time the specialties of general and gynecologic radiotherapy were founded. These specialties later developed into general and gynecologic oncology.

Progress during recent decades has been characterized by access to better equipment such as telegamma devices and accelerators for external radiotherapy, and new radionuclides, eg, for remote controlled local application. With CT (computed tomography) and MRI (magnetic resonance imaging), SPECT and PET (tomography using gamma radiation and positron-irradiated nuclides), and ultrasound diagnostics, the anatomic basis for individual dose planning has radically improved. Dosage can now be planned with high precision and visualized in three dimensions using advanced computer programs. Technical safety has increased with improved methods for in vivo dosimetry and computer-controlled verification of all parameters for every treatment. It is now possible to deliver the intended radiation dose to a benign tumor without causing serious side effects. Important research fields include the impact of different fractionation schedules on the effects of radiation and how radiotherapy can best be combined with other forms of therapy such as surgery and chemotherapy.

Introduction

In 1895, Wilhelm Conrad Röntgen described the radiation that bears his name, Henri Becquerel discovered natural radioactivity in 1896, and Marie and Pierre Curie succeeded in isolating the radioactive element radium in 1898. These discoveries were quickly applied to medical diagnostics and treatment. Clinical experience, physical and technical advancements, and radiation biology research during the decades that led up to World War II helped establish a stronger scientific foundation for treatment methods using ionizing radiation.

Progress has been rapid since World War II, eg, new sources of radiation, artificial radionuclides, and physical accelerators for electrons and other charged particles are now available. Treatment devices, methods, and technologies have advanced considerably, which, along with expanding knowledge in clinical and radiation biology, has resulted in major progress in both curative and palliative radiotherapy. This chapter, as reflected by the list of references, focuses mainly on developments in Sweden. The initial 50 years are summarized in a brief introductory history, while the more extensive developments during the 50 years since World War II are presented in greater detail.

History: the first 50 years

Soon after the physical discoveries of the 1890s, researchers were able to observe changes in body tissues that had been irradiated by x-rays or radiation from radioactive substances. Such observations inspired physicians to use these newly discovered physical agents to treat malignant and benign disorders.

External radiotherapy

Quite naturally, skin lesions became the first targets for radiotherapy. Already in 1899, Dr. Thor Stenbeck in Stockholm used x-rays to treat basal cell cancer at the tip of a woman's nose. The tumor was irradiated daily for three months, and tissue reactions were carefully observed. The patient was symptom-free and could be presented as the first cancer patient in the world to be cured by radiotherapy—at the Second International Radiology Congress held in Stockholm in 1928, ie, approximately 30 years after treatment (1).

During the early years, radiotherapy progressed purely empirically, based on observable changes in tissue. Morbid changes in skin, the mouth, the throat, and other accessible body cavities were the most common target areas for

radiotherapy. Early x-ray tubes were primitive and supplied by open high voltage wires. Later, tube voltage could be increased and the devices could be completely enclosed and made more reliable. Until the 1950s, external radiotherapy was given mainly using x-rays generated by voltages up to 200 kV. In England and the United States, devices were developed that could deliver x-rays at higher energies (approximately 1 MeV) and a few clinics had access to such equipment (2). With support from the Norwegian Red Cross, a van de Graaff generator of 1.5 MeV was built in Bergen and became operational in 1942 (3).

Radium has appropriate characteristics for some radiotherapy. However, radium was expensive and not available in sufficient quantities. It was used mainly in local applications with small, encapsulated sources (eg, for treating uterine cancer). So-called teleradium cannons were also developed (4–7) that utilized gamma rays for external irradiation of, eg, tumors in the head and neck region. This method, compared to 200 kV x-rays, involves lower energy absorption in bone and cartilage and is somewhat milder to the skin, hence advantageous. Teleradium methods developed relatively successfully in Sweden despite short treatment distances (which meant relatively low dosage at depths), long treatment times (often more than one hour), and limitations in individually adapting the dose distribution (8).

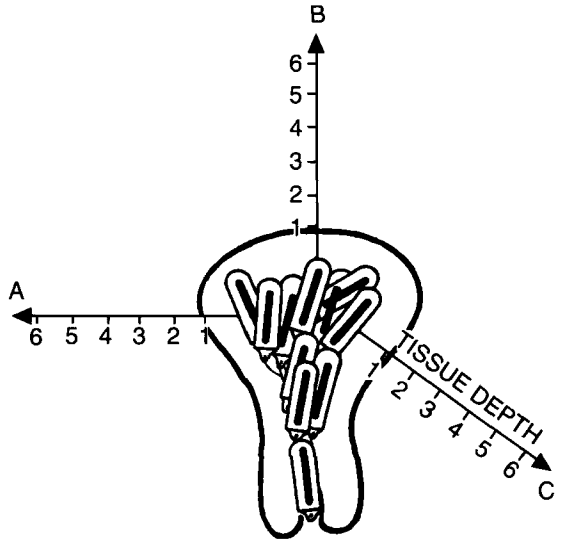

Fig. 1. The principle for the "packing method" by Heyman, for intracavitary treatment of uterine cancer. By completely filling the cavity with capsules containing radium, two objectives are achieved. The cavity is expanded whereby the thickness of the wall is reduced, particularly the tumor-infiltrated portions. Furthermore, each segment of the cavity is irradiated at close range with a high local dose and rapid dose reduction in the uterine wall, which lowers dosage to adjacent organs (16).

Dosage

Until the mid-1920s, a general biologic dosing unit (Skin-Erythema-Dose) was developed based on radiation-induced skin redness. X-ray equipment was calibrated to this unit by testing the skin of the physician or staff. However, this biologic calibration was highly unreliable, which became clear when radiation was measured by physical methods (9). Here the measure was based on ionization in air, which provided the basis for the Röntgen unit "R" or "r". This unit was accepted at the 1928 Congress in Stockholm and served as the most important dosing unit for several decades. At this time in Sweden, a mobile, dose measurement service was introduced. Later, a Swedish standards laboratory for radiation dosimetry was founded, and served all Nordic countries for decades (10). Rolf Sievert developed a measurement method, the condenser chamber method, which enabled dose measurements in vivo. The method could be used to measure doses in patients receiving external and intracavitary therapy, and in radiation-protection measurements for staff (11). This instrument is usually referred to as the Sievert Chamber.

Local application of radiation sources—brachytherapy

Treatment based on gamma radiation from radium (Ra) also developed empirically from the beginning. Metal tubes or needles containing radium salt were applied to the skin and in body cavities, or were surgically inserted in tumor tissue (interstitial therapy). Applications with radium, which has a long half life (approximately 1 600 years), usually required treatment times of several hours to several days. Radiation doses near these implants were determined by the geometric form of the radiation source and container, and by the abatement of radiation with the square of the distance. In 1921, Sievert published theoretical and numeric estimates of these relationships (12).

Treatment times for local radium applications were determined empirically at first, and dosage was defined in mg Ra hours. Tables were compiled to show the number of mg Ra hours required to treat a particular surface or a particular volume. Edith Quimby in the United States and Paterson and Parker in England developed rules and tables for calculating treatment times and for achieving the appropriate dose distributions.

Local radium treatment was used mainly for tumors in the skin, lip, mouth, throat, and uterus. Methods in gynecologic radiotherapy were particularly successful. After initial work by Forssell (13), Heyman developed methods which, internationally, formed schools referred to as the "Stockholm method" (14) for cervical cancer and the "packing method" (15) for uterine cancer. These methods were further developed by Kottmeier (Fig. 1).

Radiation biology

Early research established that different organs and tissues reacted differently to irradiation. In general, cell

populations that divided quickly were found to be more radiosensitive. The therapeutic effects on a particular tissue or cancer type also appeared to depend on factors other than the total physical radiation dose. The total treatment time, intensity of radiation (dose rate), number of radiation treatments, and interval between treatments became important parameters for study. Different schools in Stockholm, Paris, and Manchester advocated different time schedules for radiotherapy and discussed the importance of these radiobiologic parameters.

Basic experimental work was done by Sievert and Forssberg among others concerning the importance of time factors (17–19). The relationship between total radiation dose, treatment time, and the effects on skin in fractionated treatment of skin and lip cancer were studied by Strandqvist. His work (20) paved the way for later attempts toward identifying the radiobiologic relationship in external and interstitial radiotherapy, and intracavitary radiotherapy with fractionated and prolonged single treatments. Since the 1960s, Strandqvist's model has been successively replaced by newer formulas which better express the relationship between fractionation schedules and biologic effects.

Followup

To study both the immediate and late effects of radiation in cancerous and adjacent healthy tissues, it soon became clear that radiotherapy patients should receive periodic followup. In 1917, King Gustaf V asked Gösta Forssell, the grand old man of Swedish radiology, what he wished for in support of cancer care. He asked that Radiumhemmet's patients be reimbursed for their travel costs in conjunction with followup visits. Based on this perceptive wish, cancer care in Sweden benefited early from patient registers. These registers played a major role in the of advancement of radiotherapy, eg, method development.

An important initiative was later taken by Heyman who, in 1928, actively promoted internationally accepted staging as recommended by the League of Nations' Health Committee in 1935. In 1937, he introduced the "Annual Report", a periodic review of treatment methods and results for gynecologic cancer. The "Annual Report" now has a broad international readership and is still edited from Sweden (21).

Radiation protection

Many early pioneers in medical radiology suffered radiation injuries. This situation demanded action. The International Commission on Radiation Protection (ICRP), which was formed at the second Radiology Congress in Stockholm in 1928, helped establish the norms. Increasingly stringent requirements have been developed to protect healthcare staff from radiation. It was relatively easy to meet the safety requirements for external radiotherapy by equipping radiation treatment rooms with fully shielded walls. Patients are left alone, but remain under visual observation. Earlier, radiotherapy was problematic for children who required an attendant. However, this problem has been solved by, eg, anesthesia and TV-monitoring.

As early as 1903, radiation protection problems for staff were observed in conjunction with radium treatments. A patient bearing radium is an unshielded radiation source who exposes staff to irradiation when radium applicators are inserted and removed, and when patients require care during the course of treatment. The problem was particularly pronounced in gynecologic brachytherapy where relatively large radium doses were used and the treatment times were approximately one day using the Stockholm method, approximately three days using the Manchester method, and approximately one week using the Paris method. These difficult radiation protection problems have been solved satisfactorily only in recent decades.

Radiation injuries or other undesirable side effects in radiotherapy patients were also observed early, and resulted in increasingly stringent indications for radiotherapy. Thus, eg, radiotherapy treatments that had been common for certain benign diseases early in the history of radiotherapy were strictly limited or discontinued.

Developments after World War II

World War II interrupted international developments in radiotherapy, but also created new opportunities for technical advancement.

The production of new radionuclides in nuclear reactors, and the construction of physical electron and particle accelerators that were operationally reliable enough for use in clinical radiotherapy, opened new opportunities for improving treatment. Also, the public's understanding of radiation and its effects have changed radically. Unfounded trust in the miraculous characteristics of radiation has shifted to an often equally unfounded mistrust of even the most beneficial applications, eg, within medicine. This mistrust is rooted in the threat of nuclear weapons, accidents involving nuclear power stations and other facilities, and often a lack of knowledge about our "natural" radiation environment.

External radiotherapy

In many situations, the application of external radiotherapy with voltages up to approximately 200 kV has three main disadvantages:

- high dosage to the outer layer of skin may cause undesirable early and late skin reactions
- insufficient penetration of tumors deep in the body

- high absorption in bone, often leading to inhomogeneous dose distribution and brittle bones.

The limitations were known as early as the 1930s. Different methods such as multifield techniques, rotation, pendulum, and convergence irradiation were used in attempts to reduce the effects of these limitations. Methods were also developed to use photon radiation (x-rays or gamma radiation) at high energies and sufficient intensity, eg, the facility in Bergen mentioned above.

Telegamma equipment

Cobalt 60—a reactor-produced, gamma ray nuclide—became available in large quantities during the 1950s. Cobalt 60 devices made it possible to replace teleradium cannons, enabling a considerable reduction in treatment times and further advancements in technology (22, 23). New, powerful radiation sources permitted the use external gamma radiation at treatment distances of 50 cm to 100 cm (24). Hence, the disadvantages of conventional x-rays could be eliminated and new indications for radiotherapy could be tested. These so-called telegamma devices are relatively simple and operationally reliable. The radiation source, which must be replaced on occasion (usually following one half life, which is approximately 5 years for cobalt 60) represents a relatively low operational cost. A disadvantage is that the radiation source is often so large that the geometric penumbra reduces the edge sharpness of the radiation field. The size of the radiation source can be reduced by using a higher specific activity, which also increases the price. Telegamma devices are available at most radiotherapy departments, and are fully adequate for many applications.

A special type of radiotherapy was used in radiosurgery of small volumes in the central nervous system. The method was developed in Sweden by Leksell and associates and usually involves a single treatment of a small, stereotactically localized tumor in the brain. This procedure can be performed with high precision. A special device was developed (the gamma knife) for this purpose, which has approximately 200 cobalt 60 sources distributed over a large spherical sector, each one carefully collimated toward the center of the sphere. Patients are fixed with geometric precision on a treatment table which is placed in the sphere so that the target volume in the patient's head coincides with the radiation volume (25). This method has received major international interest and promoted Swedish export of the radiation equipment and an advanced computer-based three-dimensional dose planning method. Similar methods have been developed based on high energy x-rays from an linear accelerator instead of a cobalt 60 pendulum or rotational irradiation. Recently, this technique has also been applied to larger tumor volumes and other sites (26).

Electron accelerators

The first electron accelerators used in radiotherapy were van de Graaff generators, resonance transformers, and betatrons. As early as the 1930s, several radiation therapy centers used accelerators built "in house". During the 1940s, some electron accelerators were marketed for industrial radiography, which led to demand for similar equipment for radiotherapy. These devices enabled x-ray treatments using photon energies in the MeV range, and in certain cases (especially the betatrons) high energy electron irradiation. Relatively low radiation intensity, limited maneuverability, sometimes deficient operational reliability, and relatively high maintenance costs resulted in these types of accelerators giving way, in the 1970s, to linear accelerators. During the 1950s, several manufacturers began developing microwave-based linear accelerators, the devices which now dominate the market.

A noteworthy Swedish contribution to the field has been the microtron, an electron accelerator based on principles developed in the 1940s, and which was developed for practical applications at the department of accelerator technology at the Royal Institute of Technology in Stockholm (27). Several medical microtrons in the 10 MeV to 20 MeV range are installed at clinical departments world wide. A further development is the so-called "race-track" microtron that produces electrons with energies up to 50 MeV, a prototype of which has been available since 1986 in Umeå, Sweden. This device, in conjunction with established technology, will open new opportunities for treatment (28).

Electron accelerators offer high energy x-rays, 5 MV to 50 MV of high intensity from a small focus. Even at a treatment distance of 100 cm, the treatment times are normally less than 1 minute, and the beam is characterized by high tissue penetration, high homogeneity, and sharp field boundaries. Many new treatment methods that use high energy photons have been developed in recent years. Mainly, they provide a more homogeneous dose distribution, even in complicated tumor volumes, and a better definition of radiation dosage to adjacent critical organs. A special application for high-energy photons is whole-body irradiation in conjunction with bone marrow transplantation. This method, however, requires technical adaptation of both the treatment room and the equipment.

Most of the accelerators mentioned can also be used for high-energy electron irradiation. Because of the limited penetration of this radiation, it is often suitable for treating relatively superficial cancers, eg, in the head and neck, when it is necessary to avoid irradiating underlying normal tissue. Other applications of electron radiation include postoperative treatment of breast cancer (to protect underlying lung tissue) and total-skin irradiation for mycosis fungoides (Chapter 6, Section 13).

The accelerators are substantially more complex than telegamma devices and more expensive to purchase and

operate. They also require extensive control programs and internal detectors to check field homogeneity and radiation intensity.

The treatment table is an integrated part of radiotherapy equipment. It must permit irradiation of the patient from virtually all directions, and the radiation may not be influenced by supporting structures. The treatment position of the patient must be precisely reproduced on repeat radiotherapy visits; often 40 to 60 occasions.

The risk for error associated with manual adjustment of the 10 to 15 parameters for each treatment is not negligible. To assure medical/technical safety, modern devices often use a "check and confirm" system. A computer registers and documents all settings during the first treatment. This computer has the capacity to block radiation during subsequent treatments if the settings deviate beyond the margins selected.

Measuring radiation dosage in vivo is important for confirmation and to indicate necessary adjustments. This is done with display semiconductor detectors or integrated TL-detectors (thermoluminescence).

Dose planning

Telegamma devices and accelerators required new methods for planning and delivering radiotherapy since it is often impossible to directly observe the reaction of tissue during treatment. Dose distribution has been measured in homogeneous media and in tissue-equivalent phantoms, and methods have been developed to correct for irregular body contours and inhomogeneous tissue. Special devices have been constructed to shape and adapt the radiation beam to the individual patient. With x-ray irradiation up to 200 kV, the shape of the radiation field can be simply modified by placing rubberized, lead shields directly on the patient's skin. When using high-energy photons from telegamma devices or accelerators, the field must be defined by individually-shaped blocks of lead alloy, approximately 10 cm-thick, attached to the treatment head of the device. An example of this technique would be radiation for Hodgkin's disease (Chapter 6, Section 12). With high-energy photon radiation and an individualized field design, a relatively homogeneous radiation dose can be achieved for all major lymph node regions, often curing the disease (Fig. 2).

Dose planning was first introduced based on two-dimensional patient images using manual methods and dose distribution diagrams measured in water. The patient image was drawn using a mechanical contour device, anatomic atlas, and possibly measurements from x-ray images perpendicular to each other. Semi 3-dimensional planning was done for treatment areas with major variations in contour or anatomy, eg, the head and neck region, by drawing several images. Increasingly advanced methods are being developed to correctly adapt to body contours and non-homogeneous tissues (Fig. 3).

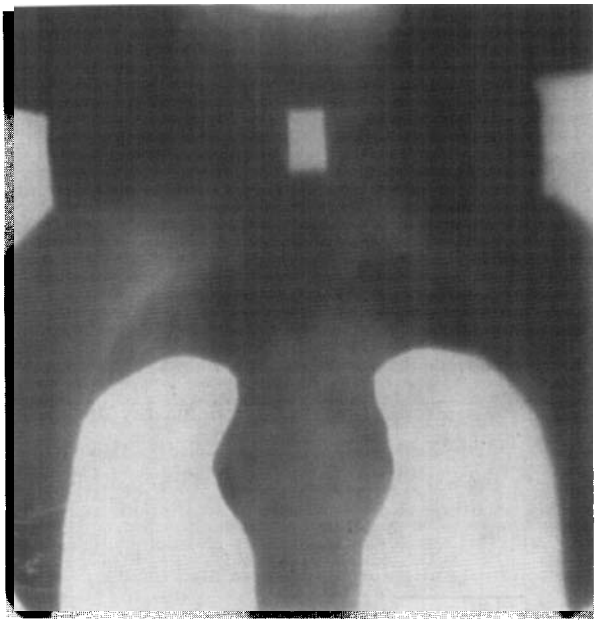

Fig. 2. Example of a mantle field for total nodal irradiation for Hodgkin's disease. The irregular field form for each individual patient is created by constructing an approximate 10 cm-thick block of heavy metal, at an appropriately reduced scale, fitting in the rectangular radiation beam. Note that radiation is shielded from the lungs, shoulder, larynx, and mouth. Radiation is directed from two opposing fields, usually with different blocks for the anterior and posterior fields since the anatomy varies between the abdominal and back positions.

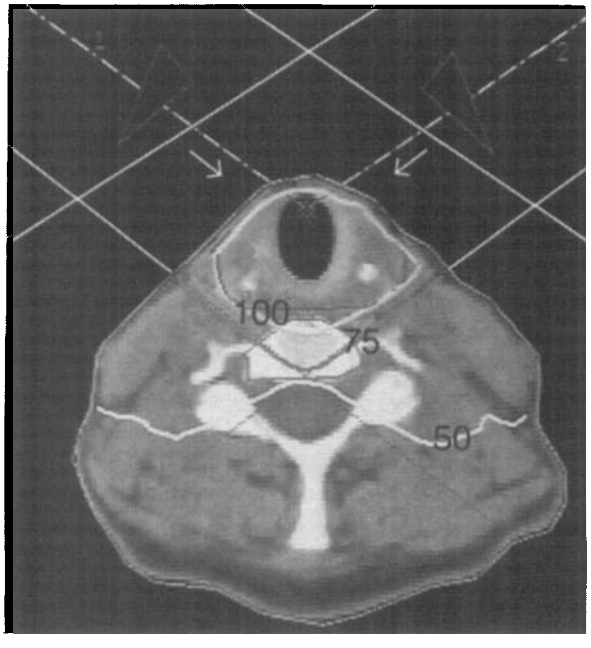

Fig. 3. Dose plan for radiotherapy of vocal cord cancer with two opposing radiation fields from a linear accelerator. Shown on the CT section are the tumor area and the dose distribution represented by isodose curves for 50%, 75%, and 100% of the tumor dose.

The precision required to establish the appropriate radiation dose for a tumor, and the acceptable dose for surrounding risk organs, is substantially higher than the precision normally required for medical doses. Some newer studies suggest that a dose deviation of 1% may cause a change in the tumor response of 2% to 5%. The therapeutic range, ie, the difference between the radiation dose needed to obtain the desired effect on the cancer, and the dose that causes intolerable side effects, is often quite small. In practice, dose variation within the target volume is usually held below 10%.

Local application of radiation sources—brachytherapy

Since the 1950s, many countries have seen a major decline in the use of radium for, eg, interstitial applications. This phenomenon is due in part to problems involving radiation protection, and in part due to introduction of improved technology for external radiation.

The success of intracavitary gynecologic radium therapy has been difficult to build upon. Nevertheless, new radiation sources have been developed to replace radium. This has generated renewed interest in local applications, which sometimes have dosimetric and radiobiologic advantages. Interstitial treatment is usually delivered by artificial radionuclides cobalt 60, cesium 137, or iridium 192. Treatment times may vary from several days with a single treatment at low dose rates (intensity) to minutes or less with repeated treatments at high dose rates. Another type of interstitial treatment uses short-lived gamma-irradiating nuclides such as iodine 125 or gold 198 encapsulated in biologically inert material and left in the tumor tissue following application. This method has recently been tested, eg, for prostate cancer (Chapter 6, Section 8).

To improve radiation protection during local radium treatment, Strebel proposed (already in 1903) surgically placing a tube in cancerous tissue through which radioactive sources could be quickly inserted and removed. This procedure, referred to as "afterloading", was introduced during the 1950s, but was not widely used until after new radionuclides with highly specific activity became available during the 1960s.

Afterloading may be manual or by remote control. In the latter case, the patient is attached (during the entire treatment time) by flexible tubes to a device equipped with a shielded container to which the radioactive material can be automatically returned when staff need to approach the patient. The first device of this type was constructed and tested clinically at Radiumhemmet in the 1960s (30).

Several commercial afterloading devices are now available. Highly active material can be handled using this method, the treatment time is shortened, and a higher treatment capacity is achieved. For radiobiologic reasons, prolonged irradiation lasting several days (which is typical for radium therapy) must be replaced by multiple fractions at a high dose rate.

Metabolic radiotherapy

Accessibility to artificial radionuclides has created opportunities in metabolic radiotherapy. An ideal therapeutic approach would be if the tumor or organ to be irradiated could sufficiently and selectively take up a radioactive substance from the blood stream. Such is the case with radioactive iodine, which concentrates in the thyroid and in some thyroid tumors, and is used to treat hyperthyroidism and selected cases of thyroid cancer (31, 32).

Various scintigraphic methods have been developed to assess the concentration and release of radionuclide uptake. The first whole body scintigraphic apparatus was constructed at Radiumhemmet (33) and is now produced industrially.

Other radionuclides with therapeutic applications are phosphorus 32 for polycythemia vera and strontium 89 for bone metastases.

Therapeutic dosage

The radiation dose that should be directed toward the defined target volume (Chapter 3) is determined after considering several factors. Important factors include, eg, if treatment is curative or palliative, tumor location and stage, tumor histology, the assumed radiosensitivity, and the risk for side effects.

For small, surface tumors, eg, skin and lip cancer, treatment may involve a few fractions given within the course of several days, and a total dose of 30 Gy to 45 Gy. For larger and more deeply situated solid tumors, treatment is usually given 5 days per week up to a total dose of 50 Gy to 75 Gy. For most solid tumors, there is a narrow margin between the dose needed to sterilize the tumor and the dose that causes irreversible tissue damage. Therefore, only limited volumes can be effectively treated, and very thorough dose planning is required. Some malignancies have a much higher radiosensitivity, eg, malignant lymphoma, seminoma, and dysgerminoma, and a substantially lower dosage can be delivered while concurrently permitting treatment of larger tissue volumes. An extreme example would be whole-body irradiation in conjunction with bone marrow transplantation for leukemia patients, where a single or fractionated treatment of approximately 10 Gy is given (Chapter 6, Section 17).

Radiosensitivity of organs near the tumor is also of major importance. The smooth musculature in the uterus accepts high radiation doses, which explains, at least in part, the favorable results from intracavitary radiotherapy for cancer in the cervix and the body of the uterus.

In comparison, the radiation doses delivered to tumors are 1 000 to 10 000 times greater than the annual radiation

dose to which we are normally exposed. In Sweden, it is estimated that the population, on average, is exposed to an annual dose which is the biologic equivalent of approximately 0.005 Gy from natural sources, and approximately 0.001 Gy from all artificial sources. Radon in dwellings dominates the former group and medical diagnostic radiology dominates the latter, in both cases contributing approximately 80% of the dose. Detailed regulations apply to staff who work near radiation. The threshold values for staff exposed to radiation in their work have been successively reduced, and currently average 0.015 Gy per year over a prolonged period, however up to 0.050 Gy may be acceptable for a single year.

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