Section 1

Scientific Foundations

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Basic Concepts of Clinical Radiation Oncology

Hannah Yoon, Karan Shah, William Small Jr, Minesh P. Mehta and John P. Hayes

Introduction

Radiation oncology is the practice of utilizing ionizing radiation to treat both malignant and benign diseases. It requires comprehensive medical knowledge coupled with advanced skills in clinical oncology, physics, and radiation biology. In 2017, radiation oncologists are integral team members of modern multidisciplinary care, working in conjunction with specialists in medical oncology, surgical oncology, diagnostic and interventional radiology, pathology, and the entire spectrum of subspecialties involved in oncologic care. The specialty can trace its history back over 100 years, yet as the role it plays continues to change, the primary mission remains the same – to enhance the health of the patient with cancer, and improve the specialty for the benefit of future patients.

To consider the scope of oncology, one can start with an acknowledgement of the extent of the socioeconomic impact. In the United States, deaths from cancer are exceeded only by those resulting from heart disease. In 2017, approximately 1,688,780 new cancer cases will be diagnosed (not including carcinomas in situ or non-melanoma skin cancers), and about 600,920 Americans will die of cancer [1]. It is estimated that 50–60% of patients afflicted with cancer will receive radiation therapy, either for cure or palliation. Radiation oncology is therefore a medical specialty of major importance. Such a specialty demands a working knowledge of the clinical and biologic course, both treated and untreated of various cancers, knowledge of the various stages of the diseases, and knowledge of the efficacy and toxicities of different methods of treatment. It necessitates an understanding of the clinical application of the physical and biologic aspects of ionizing radiation, and an awareness of the significance of rehabilitation and follow-up. The prognosis of patients with malignant diseases depends on many factors, both disease-related (cell type, tumor grade, extent of the primary disease, and presence or absence of regional or distant metastases), and patient-related (comorbidities, performance status, etc.). Consequently, a refined appreciation of palliative care, hospice care, quality of life issues, and end-of-life issues is paramount in this field. Furthermore, since oncology encompasses hundreds of different diseases, with differing natural histories, distinct biologic behaviors, modes of tumor growth and spread, and characteristic responses to radiation therapy, the therapeutic management and results will therefore differ greatly.

Planning and Preparation

The optimal use of radiation therapy requires meticulous planning, preparation, and implementation. First, the goal of treatment needs to be established, be it curative, palliative or to enhance local control in a non-curative patient. For most patients, radiation therapy is a local or local-regional treatment, and therefore, designing treatment starts with the recognition of the known and potential extent of the disease. Hence, the clinician must recognize both the grossly evident disease as well as adjacent areas at risk for harboring subclinical spread, and consider treatment, keeping in mind the normal tissues or organs that will be irradiated.

A thorough history and physical examination, along with a review of diagnostic studies such as laboratory values, plain films, ultrasound, mammograms, CT, MRI, and PET or PET/CT scans, precedes the first planning session. In certain cases of head and neck cancer, gynecologic cancers and genitourinary cancers, an examination under anesthesia may add critical information about the extent of the disease. Except for a few situations in which biopsy is considered impractical or potentially harmful, histologic confirmation of malignancy should be
obtained before treatment. This requirement, of course does not extend to the management of benign disease processes with radiotherapy.

Simulation is where the patient is positioned for radiation therapy, a support/immobilization platform often made, and imaging studies obtained that will be used to direct treatment. Most radiation therapy plan calculations today are based on CT data sets that allow three-dimensional (3D) reconstruction of individual patient anatomy. A four-dimensional (4D) CT can also be obtained to account for changes in tumor location during respiration. The definition of both the diseased and normal structures follows, and is primarily an image-based exercise, but incorporates essentially every imaging technique available, and therefore significant familiarity with the specialty of radiology is a key requirement for radiation oncology. Techniques of treatment are then developed and optimized in virtual reality. Today’s advanced computer systems enhance the radiation oncologist’s ability to compare options, quantify target and normal tissue doses, and create complex distributions of radiation energy that have been customized for each patient. Dose distributions are optimized so as to maximize the dose to the target and minimize the dose to the adjacent normal structures; in modern practice, these dose distributions can be reduced to mathematical representations such as dose–volume histograms, mean doses, maximum doses, and so on, which can be correlated with predicted toxicities, allowing, effectively for ‘multicriteria’ optimization, to generate the best possible treatment plan for a patient. In parlance that the patient can understand, treatment is designed to “hit what we want to hit, and miss what we don’t want to hit.”

With few exceptions, most external beam radiation therapy is given with megavoltage linear accelerators with energies ranging from 4 to 25 MV. Superficial areas such as the skin may be treated with low-energy x-rays (e.g. 50–100 kV) or electron beam therapy. The basic physical properties of radiation are reviewed in Chapter 3.

Radiation doses are quantified in units called Gray (Gy), that represent the energy absorbed within the tissue. Prescribed doses are based on accepted standards of normal tissue tolerances, which were historically developed from observation and, more recently, from quantifiable dose–response analyses.

### Radiation Therapy in the Clinic

Radiation therapy is used as primary, curative treatment, as palliative treatment, and as adjunctive therapy (most commonly to surgery), yet often in combination with chemotherapy, targeted molecular therapies, and now also immune-modulating therapies. Additionally, it can be combined with either tumor-radiosensitizing drugs, or normal tissue-protecting radioprotectors, or physical methods which enhance the effectiveness of radiation therapy, ranging from tissue displacement devices to local and regional hyperthermia, and potentially to alternating electrical field antimitotic therapy. Palliative treatment may be given with the hope of relieving symptoms and/or prolonging survival. Palliative doses of radiation may be more limited, and risks therefore minimized. In less common cases, radiation can be administered for benign diseases, such as heterotopic ossification, keloids and pterygium. Radiation therapy with curative intent may require doses that carry significant risks of permanent morbidity. These treatments may be prolonged and taxing due to acute toxicities, both local and systemic. As with any cancer therapy the goals of treatment – be they curative or palliative – need to be weighed against potential side effects and risks.

The effects of a given dose of radiation on malignant tumor tissue varies with multiple factors, including the total dose administered, the time over which it is given, and the amount that is administered during each treatment (called the fraction, hence, fractionation). Tumor responses to any given dose sequence vary, although generalization based on previous study helps determine expectations. Some cancers, such as lymphomas and germ cell tumors, are considered radioresponsive as doses ranging from 24 to 45 Gy given with standard daily fractionation of 1.8–2.0 Gy result in high rates of local control; in fact, in some modern regimens doses as low as 4 Gy are employed in certain situations. Most other cell types require higher doses, on the order of 60–70 Gy or beyond, to obtain reasonable rates of local or local-regional control. Some cell types (e.g., renal cell carcinoma) are notoriously capricious in their response, while others (e.g., melanoma, glioblastoma, pancreatic carcinoma, and anaplastic thyroid cancer) often require prohibitive doses to try to eradicate gross, or even microscopic, disease.

Other than cell type, the primary determinant of the likelihood of eradicating disease at a given site is the volume of disease, sometimes called the tumor burden. Although a dose of 60–70 Gy may lead to the sterilization of a 1 cm squamous cell carcinoma on 90% of occasions, the same tumor is much less likely to be eradicated if it is 3–4 cm, and will recur in most instances if it is 5–6 cm or larger and treated with standard fractionation external beam therapy alone. Recognizing this, alternative paradigms of treatment have been developed. Examples used at specific disease sites are reviewed in later chapters.

The **therapeutic index** or **window** is the balance of risk and reward that accompanies all treatment decisions in oncology, as there is no condition, nor any treatment, without risk. Outcomes are never guaranteed. Simply put, the ideal treatment separates the likelihood of benefit as far as possible from the probability of damage.
or dysfunction. Although theoretically logical and definable, this combination is notoriously difficult to define, and achieve.

**Combining Radiation Therapy with Surgery**

Surgery and radiation therapy may be competitive or complementary in the treatment of localized or locally and regionally limited malignancies. Each has its merits, indications and limitations, all of which are site- and diagnosis-specific. Radiation therapy can offer the advantage of controlling disease in situ, thus avoiding removal of useful, even critical organs, thereby preserving the function of these vital organs. Examples of organ-sparing treatment that preserve function in a high proportion of patients include the treatment of cancer of the larynx and anal canal cancers. In early-stage lung cancer, treatment with stereotactic body radiotherapy can obviate the need for a lobectomy (especially in patients with significant cardiopulmonary compromise), preventing morbidity from invasive surgery. Surgery may provide an expeditious alternative without functional or cosmetic compromise, and can provide treatment for lesions that are notoriously difficult to eradicate with acceptable doses of radiotherapy. Rather than considering these alternatives in a hierarchical way, each can be supported based on its applicability in a given clinical setting.

In the management of locally advanced carcinomas, the failure of surgery to cure the disease may be due to its inability to remove unrecognized microscopic tumor (subclinical disease) at the periphery of resection, thus resulting in a marginal recurrence. Tumor seeding in the wound and metastases via lymphatic or hematogenous routes are additional means to account for therapeutic failures of surgery. In contrast, radiation therapy may be unable to sterilize bulky tumors because of the volume of malignant cells, or because of relatively radioresistant cells (e.g., hypoxic cells) that may comprise a component of large tumors. Tumor cells that are well-oxygenated, well-nourished, and therefore more radiosensitive, may be more common at the periphery of the cancer. Radiation therapy failures are thus often central rather than marginal. Distant failures, be they from lymphatic or hematogenous spread, are also the bane of both surgery and radiotherapy.

Thus, it can easily be seen how the spatial strengths of radiation therapy and surgery can be complementary.

**Preoperative Radiation Therapy**

The aims of preoperative radiation therapy are to eradicate subclinical disease around the primary site and in the lymph nodes, or to convert technically inoperable tumors into operable ones. Preoperative treatment has been found to decrease the risk of iatrogenic scar implants as well as marginal and regional (nodal) recurrences, and in some cases, the incidences of distant metastases [2].

The disadvantages of preoperative radiation include: (i) the full extent of the primary tumor or regional spread may never be known due to the response to treatment; (ii) the risk of postoperative complications such as wound healing may be increased; (iii) the delay until surgery may create a great deal of anxiety; and (iv) if there is significant radioresistance the opportunity for surgical cure may be lost.

The doses employed in preoperative radiation therapy are usually moderate, on the order of 45–50 Gy over five weeks [3–5]. Surgery is usually performed one to two months later to allow healing of any inflamed tissue, facilitating visualization and resection. Examples of this approach include the treatment of head and neck cancers, rectal tumors, and soft-tissue sarcomas. Lower doses (e.g., 25 Gy in five fractions) followed by immediate surgery have been used in the treatment of rectal cancer, and more recently in mesothelioma, with similar success [6–8]. Some protocols have used preoperative treatment to gauge responsiveness of the disease, avoiding surgery when possible, often with the advantage of potential organ preservation [9,10].

**Postoperative Radiation Therapy**

Postoperative radiation therapy is used in an effort to eradicate residual disease at the periphery of the surgical bed, in the unresected regional lymphatics, and to prevent recurrence in the scar [11,12]. Time is required for adequate healing before postoperative radiation therapy can begin, usually at least three to four weeks. Doses are commonly 50–66 Gy for completely resected tumors, while subtotal resection requires higher doses that are often equivalent to those used for inoperable situations. Although exceptions include primary CNS malignancies, planned subtotal resection must be used selectively as the benefit of postoperative radiation therapy in these cases may be marginal.

The question of whether to use preoperative versus postoperative radiation therapy is unresolved in many cases. Each method has its advantages and disadvantages, proponents and opponents. The decision should be driven by evidence-based data whenever possible, individualizing for each patient and, very importantly, should include consideration of the experience of the treating clinicians.

**Combining Radiation Therapy with Chemotherapy**

Commonly used chemotherapeutic agents that exert cytotoxic or cytostatic effects on neoplastic cells include vinca alkaloids, alkylating agents, antimetabolites, epipodophyllotoxins, platinoids, and taxanes. Many of these drugs cause damage during specific phases...
of the cell cycle, while other agents such as platinum and alkylators are non-cell cycle-specific. Multi-agent chemotherapy regimens with different mechanisms of action may help overcome drug resistance through either additive or synergistic outcome.

Chemotherapy alone is rarely efficacious in tumor eradication or cure. However, the combination of chemotherapy with radiation in clinical trials for many sites of cancer has demonstrated improved local control, decreased distant metastases, and improved overall survival. At the present time, chemotherapeutic agents such as cisplatin, 5-flourouracil, gemcitabine, temozolomide, paclitaxel and docetaxel are often combined with radiation to treat head and neck, lung, CNS, breast, gastrointestinal, gynecological, and genitourinary cancers.

The interaction of radiotherapy and chemotherapy may be additive or synergistic, and various mechanisms of interaction have been theorized. Spatial cooperation is a condition in which various agents may be used to target tissue in spatially different areas (local versus distant), or within the same tumor mass but in areas with different environmental factors. Independent cell kill explains how two therapies at full dose can produce a greater tumor response than with either agent alone. A third theory – debulking – explains that radiotherapy can more effectively kill cells after chemotherapy is employed to shrink the tumor beforehand, as there are fewer tumor cells remaining. Finally, enhanced tumor response explains how chemotherapy can inhibit radiation-induced DNA damage repair, and also kill cells that are resistant to one modality of treatment [13]. Optimally, the combined treatment should be lethal to tumor cells but nontoxic to normal tissue.

Biologically, oxygen plays an important role in modulating the radiation response via reactions downstream of toxic free radical production, and this interaction is the mechanism of action of several radiosensitizing chemotherapeutic agents. Tirapazamine functions specifically on radiation-resistant hypoxic tumor cells, by converting itself into a highly reactive free radical under hypoxic conditions. Mitomycin functions in a similar fashion to damage hypoxic cells.

Combining Radiation Therapy with Biologic Agents

Molecular agents may enhance radiation sensitivity and cell killing by improving tumor oxygenation, inhibiting angiogenesis, promoting cell arrest, and activating apoptosis [14]. Similarly, there is a strong preclinical rationale for combining radiotherapy with anti-angiogenic therapies. Emerging preclinical data and some early clinical results have provided insights into how immune checkpoint inhibitors could potentially be combined with radiation, with the latter effectively acting as a ‘stimulatory vaccine’, a relatively novel role for radiotherapy [15–17].

Combining Radiation Therapy with Hormonal Agents

The use of hormonal agents either as monotherapy or part of multimodality regimen has implications for the treatment of breast, prostate, uterine, thyroid, and carcinoid tumors. These agents can directly bind to a hormone receptor, thereby either inhibiting (agonizing) or enhancing (antagonizing) the effects of the specific hormone. Alternatively, these molecules can exert their actions by binding to a receptor upstream or downstream in the hormonal pathway.

The use of hormonal agents is widely prevalent in the treatment of prostate cancer. In 1941, Huggins and Hodges first showed that bilateral orchiectomy results in a significant decrease in circulating testosterone levels within hours after the procedure, and thereby represented an effective, fast therapy to treat prostate cancer. In later years, the use of androgen deprivation therapy (ADT) – either as luteinizing hormone-releasing agonists or antagonists – has replaced surgical interventions and other pharmacotherapy agents, such as diethylstilbestrol, cyproterone acetate, and ketoconazole. Luteinizing hormone-releasing hormone (LHRH) agents can effectively reduce circulating testosterone levels by 90% [18].

The use of ADT in combination with radiation therapy for prostate cancer has shown to improve treatment-related outcomes, including local control, disease-free survival, time to the development of metastases, biochemical control, and overall survival in multiple Phase III randomized trials [19]. Furthermore, several investigators have proposed radiobiology synergism between ADT and radiation therapy, including enhanced apoptosis, decreased tumor hypoxia, and prostate volume reduction (improving radiation therapy delivery and reducing adverse effects) [20–22].

Radiosensitivity and Tumor Control Probability

Clinically, ‘radiosensitivity’ is often used interchangeably with ‘radioresponsiveness.’ In radiation biology, the former term refers to the innate sensitivity of the cells to radiation. As shown in the dose–response cell survival

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curves in Figure 1.1, the radiosensitivity for various normal and malignant mammalian cell lines is related to the slope of the curve that shows increasing cell death with increasing dose [24].

Factors influencing radiosensitivity include the ability to repair damage that does not immediately cause cell death (sublethal damage repair), the cell’s location in the cell cycle (most sensitive in G2 and M, least in G1), the degree of oxygenation or relative hypoxia, the dose rate, fractionation, total dose, and the quality of radiation.

**Fractionation and Fraction Size**

The effects of a single dose of radiation energy on mammalian cells are more pronounced than those produced by the same amount of energy delivered in divided doses. Because of this, a higher total dose is necessary to obtain the same amount of cell kill whenever an identical amount of radiation is given in multiple smaller doses. Therefore, *fractionation* – or the breaking up of the total dose into multiple smaller doses – may seem counterproductive when considering the goal of tumor eradication. However, tumors and normal tissues are intimate, and what might be desirable for the tumor can be hazardous for the normal tissues.

The benefit of fractionation is based on the fact that normal tissues can accept a certain amount of radiation energy, and avoid death, if the damage they incur is repairable. As the cell has avoided death the damage is called *sublethal*, and the corrective process is termed *sublethal damage repair*.

Most commonly in the clinic, treatment is given once a day, five days a week. This allows for the repair of sublethal damage by normal tissue, as this process normally requires less than 24 h, and some may be completed in as little as 4–6 h [25, 26]. Malignant cells are frequently much less efficient or incapable of similar sublethal damage repair. Standard fractionation external beam radiation therapy schedules try to take advantage of this difference. As such, a course of treatment may require higher total doses over five to eight weeks than would be necessary if given in smaller amounts over two or three weeks.

Fractionation also allows for changes in the tumor environment that may improve the effectiveness of subsequent treatments. An example of this is the death of well-oxygenated cells causing a reduction in tumor size, leading to a better oxygenation of previously hypoxic cells, which thereby increases their radiosensitivity. Another example is *redistribution*, during which the cell progresses from a radioresistant phase of the cell cycle to a more radiosensitive phase, such as M phase.

Conventional radiation therapy is generally given with one fraction per day, five days per week. The total dose prescribed is dependent on a number of factors, including the presence of gross versus microscopic disease, whether it is being given in a preoperative or postoperative setting (postoperative situations generally require a greater dose), and the nature of the surrounding normal tissues. Such programs were derived from empiric observations in the clinic, yet may not be the actual best treatment course for many human cancers. Altered fractionation schedules vary the dose and frequency of administration to try to take advantage of additional factors beyond sublethal damage repair, and have become part of the normal lexicon of radiation oncology.

**Linear Energy Transfer (LET) and Relative Biologic Effectiveness (RBE)**

In trying to understand why one type of radiation energy is more effective in causing cell death than another, characteristics of energy, mass, and charge need to be
considered. In simple terms, the greater the mass of a particle, the more damage it is likely to inflict along its path. Charged particles are more likely to interact over a short distance than are uncharged particles, while the energy of the radiation (expressed in electron volts) affects the location where these interactions will occur. Energy is deposited in the cell along that path of the particle, and their subsequent effects will be produced at that point or within a very short distance. Therefore, mass, charge, and energy combine to express the quality of any given type of radiation energy used in the clinic. The resulting concept is referred to as the linear energy transfer (LET).

LET is designated as the average energy deposited in each unit of length; it is measured in electron volts per micrometer (eV μm⁻¹) or kilo-electron volts per micrometer (keV μm⁻¹). Protons, fast neutrons and other forms of particulate radiation have dense ionization (energy deposition) along their paths, and therefore high LET. Photons and megavoltage electrons (which, although charged, have a relatively small mass) have more sparse ionization, and therefore a low LET.

Biologic damage to cells is related to LET. In general, high-LET radiation is more likely to produce substantial damage in a given volume of living matter, regardless of other factors. This is true for both normal and malignant cells. Because high-LET energy can cause such severe effects, there is little chance for the repair of sublethal damage, and therefore the benefits of fractionation are minimized. Again, damage to malignant and normal tissue may be similar, so the benefits of high-LET radiation can only be accrued if there is spatial separation of the targeted tumor and nearby critical normal structures.

Relative biologic effectiveness is a term used to describe comparisons of radiation quality against a benchmark of 200 kV x-rays as the standard. For cobalt-60 x-rays and low-megavoltage photons, the RBE approaches one, whereas higher-LET radiation has RBEs up to 3.5. Although extremely high-LET radiation deposits large amounts of energy in a given space, its RBE reaches a ceiling after maximum lethality has been reached.

The RBE of electrons, which are charged but consist of low mass, is similar to that of low-LET photons, typically 0.85 to 0.9.

Oxygen Enhancement Ratio

In most biologic systems under both normal and malignant conditions, the effects of radiation are greater when the cells are well oxygenated. Poorly oxygenated cells (i.e., hypoxic cells) comprise 10–20% of tumor cells [23]. It has been shown that regions more than 150–180 μm distant from functional capillaries often contain hypoxic cells [27]. These cells are viable and can proliferate, yet may be relatively resistant to the effects of radiation due to the lack of oxygen. The difference in radiosensitivity under oxygenated conditions is in the neighborhood of two- to threefold; this is known as the oxygen enhancement ratio (OER).

In order for oxygen to be a radiation sensitizer, it must be present in the cells during irradiation. The mechanism of oxygen enhancement is believed to be through radiation-induced free radicals that initiate a chain of events that begin with DNA damage and finally results in biologic damage. High-LET radiation operates in a more direct manner, so the OER is either low or non-existent for these types of radiation.

Clinical situations where hypoxic cells are likely to exist, such as bulky tumors or anemia, have been associated with poorer outcomes with standard treatment [28]. However, attempts to overcome cellular hypoxia – including transfusions, hyperbaric oxygen, and hypoxic cell radiosensitizers – have been disappointing for the most part.

Radiocurable Tumors

Clinically ‘radioresponsiveness’ is judged by the extent of regression of the gross tumor before surgery, or the extent of residual disease found during pathologic analysis. The sensitivity of various cancers is determined by many factors, including cell type and the growth kinetics of the individual cancer. The kinetics of growth include the rate of proliferation and cell loss from factors such as apoptosis, and adequate vascular and connective tissue support. Human tumors are extremely complex, and the aggregate of cell growth and tumor represents an enormous biologic disorder; consequently, there is a wide range of factors that affect a given tumor’s response. In spite of this tremendous variability, some types of cancer respond to radiation therapy more consistently than others (as noted above), and are commonly cured with tolerable doses associated with limited long-term sequelae. That is, radiocurability means that the tumor–normal tissue relationship is such that a dose of radiation energy can be delivered to eradicate the growth without leading to organ dysfunction. In these cases, the therapeutic window is open; in other words, there is a good separation between the likelihood of tumor sterilization and the risk of damage. Importantly, radiocurable tumors may be innately sensitive, or they may have normal sensitivity but be limited in extent (i.e., early stage), and therefore in a radiocurable state.

Examples of radiocurable tumors include:

1. Non-melanoma skin cancers (basal and squamous cell carcinomas).
2. Epithelial cancers of the head and neck.
3. Carcinoma of the uterine cervix.
4. Carcinoma of the prostate.
6. Seminoma of the testicle and dysgerminoma of the ovary.
7. Medulloblastoma, pineal germinoma, and ependymoma.
8. Retinoblastoma.
9. Choroidal melanoma (treated by proton beam therapy or plaque brachytherapy).

Technological Advances in Radiotherapy

During the past 25 years, the field of radiation oncology has undergone significant changes due to advancements in technology and a better understanding of how radiobiological principles can be utilized. Altered fractionation — that is, changing the dose of radiation per treatment — and the frequency of the treatments, including multiple doses of radiation per day, has become a commonplace regimen. Combining chemotherapy with radiation therapy, either sequentially or concurrently, has also become a standard approach for numerous disease sites. A brief review of some of the technical advancements in radiation therapy is provided in the following sections.

Intensity-Modulated Radiation Therapy (IMRT)

Classically, when external beam radiation therapy was utilized, the radiation therapy technique was determined by first considering the tumor location and the surrounding normal structures, and then selecting the direction, energy, and number of beams to be used so as to provide optimal coverage of the target with the least exposure of the adjacent normal structures. The distribution of radiation with this approach is manipulated by changing the field size or weighting, adding blocking to protect normal structures, and adding other devices such as wedges that act as tissue compensators to re-distribute the energy. This is known as forward treatment planning.

More recently, using advances in computer technology and equipment engineering, a different paradigm has been developed termed inverse treatment planning. Here, the radiation oncologist designs treatment by first establishing the dose parameters for the target tissues as well as the normal organs. Priority or rank is given to each contoured object. A computer program is allowed to proffer solutions for how the radiation therapy can be given to meet the desired goals. Multiple possibilities are considered and numerous iterations are evaluated. This assessment is optimized by the use of dose–volume histogram analysis, a technique whereby the critical normal tissue doses are quantified. Only after finding an acceptable distribution of the radiation is a technique chosen.

The delivery of IMRT is achieved either via a step-and-shoot (static) or a sliding window technique (dynamic IMRT). In the static method, the beam is off while the multileaf collimator (MLC) adjusts their proper shape, whereas in the latter method the beam is continuously modulated by moving the MLC. IMRT plans are highly conformal with the optimal sparing of organs at risk, especially with coverage of concave-shaped targets. However, IMRT plans tend to have higher overall monitor units (MUs) and increase low-dose radiation to the surrounding tissues.

An extension of IMRT is that of volumetric modulated arc therapy (VMAT), which combines gantry rotation, dynamic MLC movement, and changes in dose rate to create highly conformal radiation dose distributions. VMAT plans can use a single 360° arc or multiple arcs for treatment delivery, or a helical, CT-like delivery approach. The major advantage of VMAT over traditional IMRT is the reduction in treatment delivery time with a possible decrease in integral dose; for highly complex targets, it is also more likely to produce greater tumor dose conformality [29].

Image-Guided Radiotherapy (IGRT)

Moving from the planning phase to treatment requires an exact implementation of the chosen technique of treatment. This may be achieved in several ways after first confirming that the patient’s position is correct within the support platform that has been created during simulation. The direct observation of superficial tumors with a clinical set-up of the overlying field may be used in cases of cutaneous or superficial malignancies, although most patients receive radiation therapy for more deep-seated locations. Plain film images of each field or beam have been used for decades. Here again, with advances in technology, there has been a fusion of diagnostic imaging into therapy such that treatment may be directed based on CT scans obtained with the patient in the treatment position. The radiation oncologist might utilize megavoltage or cone beam CT scans to directly visualize the target, making adjustments based on the immediate location of the target, while adjacent normal tissues can be seen and taken into consideration. Surrogates such as fiducial markers that are placed in or near the tumor may be used to assess the focus of the radiation therapy. Other systems include (but are certainly not limited to) ultrasound-guided imaging, 3D optical surface monitoring, infra-red or optical marker tracking, and radiofrequency-beacon-guided modalities. Image-guided radiotherapy (IGRT) is thus the use of real-time imaging for treatment localization during radiotherapy.

The information gathered from IGRT can be used to modify treatment plans. During a typical six-week treatment course, changes in tumor volume, patient anatomy and patient positioning can significantly affect the location and volumes of both the target and organs at risk.
Hence, image-guidance can help identify these interfraction patient variations, which may lead to re-planning, re-simulation, or both. This process, termed adaptive radiotherapy, refers to adjusting the radiation delivery based on anatomic changes. Adaptive radiotherapy can be combined with functional imaging, such as \(^{18}F\)-FDG-PET, to differentially boost residual tumor or radioresistant intratumor regions. This latter technique is termed dose-painting. IGRT combined with adaptive radiotherapy allows for dose escalation to the target, while sparing organs at risk [30–32].

**Stereotactic Radiosurgery (SRS)/Stereotactic Body Radiation Therapy (SBRT)**

In 1951, Lars Leskell, a Swedish neurosurgeon, first introduced the concept of delivering high doses of radiation to treat brain lesions. SRS delivers a large dose per fraction (usually single or three to five fractions) to treat focal brain lesion(s), while minimizing toxicity to the surrounding normal tissues due to a sharp dose gradient. More recently, stereotactic body radiation therapy (SBRT), an extension of SRS to treat extracranial metastasis, has been made possible by the advances in real-time image guidance. SBRT can be used to treat focal lesions in the lung, spine, liver, pancreas, kidney, and prostate [33,34].

**Particle Beam Radiotherapy**

Although radiation therapy most commonly utilizes uncharged packets of energy called photons, it may also be given with charged particles such as electrons or protons, or uncharged particles such as neutrons. These particles have different advantages in their physical qualities, and thus their distribution within tissues as well as their biologic effectiveness also differ.

In proton therapy, the main advantage is spatial distribution, which potentially can deliver high doses to areas that would otherwise need a more conservative approach. This is most evident when considering tumors in close proximity to dose-limiting tissues such as the eye, brain, and spinal cord. With protons, there is also minimal exit dose beyond the target area. Carbon ions may provide a similar dose gradient with increased biologic effectiveness. Importantly, expertise in these forms of radiation is needed as increased conformity carries the risk of missing the intended target. That is, the avoidance of normal structures carries an increased risk of inadequate coverage of the malignancy. Another axiom: “Don’t miss what you want to miss if you don’t hit what you need to hit.”

Neutrons can be helpful in treating slower-growing tumors. They do not carry a spatial advantage as other particles may, but their radiobiologic effectiveness is greater and this can be advantageous when treating relatively unresponsive (‘radioresistant’) tumors. The lack of spatial advantage leads to a limited clinical potential due to difficulties in delivering adequate doses to the tumor without taking potentially prohibitive risks to adjacent structures. One approach to addressing this problem has been the use of boron-neutron capture therapy (BNCT). For this, a boron-containing compound is preferentially concentrated in the tumor, which is subsequently irradiated with neutrons. The interaction of the neutrons with the boron leads to a release of alpha particles (heavy, positively charged particles) and lithium nuclei. Both of these have very short ranges and so can interact preferentially with the immediately adjacent cells, causing significant damage to the tumor. This type of treatment has been used in malignant brain tumors [35].

**Brachytherapy**

Brachytherapy or ‘short-distance’ therapy is defined as the placement of sealed radioactive sources near the tumor. Historically, radium was used but now sources that are safer and have more practical characteristics, such as iodine, palladium, iridium and cesium, are used. Brachytherapy occurs in three forms: (i) in the first type, molds or plaques are placed on the skin or mucosa of a superficial lesion; for example, eye plaques have been used to treat retinoblastoma, ocular melanoma, and pterygium; (ii) in interstitial implants, catheters containing radioactive sources or seeds are placed within soft tissue; prostate interstitial implants can be an elegant and highly effective example of this; and (iii) in intracavitary implants, radioactive sources are placed in a body cavity; for instance, vaginal brachytherapy is often used in the adjuvant treatment of endometrial cancer.

Brachytherapy implants can utilize either temporary or permanent implantation of the source of radioactivity. Temporary implants, either low-dose rate or high-dose rate, typically utilize afterloading systems whereby the radioactive material is loaded into a previously placed holding device that was designed specifically for the purpose. Examples of this include treatment for endometrial and cervical carcinomas. In each case the devices are inserted into and secured in the endometrial cavity and/or vagina with the radioactive sources added later. This enables the clinician to minimize personal exposure to radioactivity.

In permanent implants, radioactive sources are placed into tissue and their activity allowed to progressively decay while in the body. Once the compound’s energy has dissipated, the inert source remains.

**Intraoperative Radiotherapy**

Despite intraoperative radiotherapy (IORT) technology having been in existence for the past three decades, the
technique has gained increasing popularity during recent years. This is partly due to the success of the TARGIT- A trial, a multi-international, randomized, prospective Phase III non-inferiority trial, in which early-stage breast cancer patients were randomized to whole-breast radiotherapy versus targeted IORT to the tumor bed, using low-energy x-rays (kV range) [36].

IORT is delivered to the surgical bed after removal of the tumor (primary or recurrent setting) under anesthesia. The theoretical advantage of IORT is a higher therapeutic ratio by maximally sparing/shielding normal tissues and delivering a large single-fraction dose to the tumor bed to improve local control. IORT can be used as monotherapy, but is more often used in combination with external-beam RT (± chemotherapy). Currently, intraoperative machines using electrons, low-kV photons and 192Ir high-dose rates exist in the marketplace [37].

Unsealed Sources

Unsealed radioisotopes have been used for the treatment of malignancies for many decades. In this type of treatment the radiopharmaceutical is delivered either alone or in conjugated form, orally or parenterally, to the patient. Examples include phosphorus-32, iodine-131, yttrium- 90, strontium-89, and samarium-153, all of which decay by high-energy beta-particle emission. While the very first radiopharmaceuticals typically had intrinsic tendencies to accumulate in a target organ or site, they were of limited potential use due to their hematopoietic toxicity. More recently, a new wave of research has led to the development of biologic molecular targeted radiopharmaceuticals that optimize the delivery of cytotoxic agents to specific body cell types, by manipulation of the immune system.

Radioimmunotherapy is commonly used to treat non-Hodgkin’s lymphoma that has proved refractory to other treatments. Two compounds have recently been approved by the Food and Drugs Administration (FDA) which consist of murine monoclonal anti-CD20 antibodies attached to radioactive isotopes; these are yttrium-90 ibritumomab tiuxetan (Zevalin®) and iodine-131 tositumomab (Bexxar®). Prior to treatment, the patient must undergo a hematopoietic work-up to ensure that he/she will tolerate treatment without significant toxicity, and also to determine the appropriate dosage. Patients can be discharged shortly after both types of therapy [38–41].

Radiopharmaceuticals have also been shown in multiple studies to significantly palliate pain caused by bone metastases, albeit without improving survival. They are most often given as second-line therapies for patients who have failed other local palliative treatments. Contraindications to treatment include poor hematopoietic reserve, impending pathologic fracture, spinal cord or nerve root compression, significant extra-osseous extension of disease, extensive bony destruction, and poor uptake of lesions on bone scan. Strontium-89 (Metastron™) is indicated in metastatic prostate cancer, while samarium-153 (Quadramet®) has been shown to accumulate preferentially in osteoblastic lesions rather than in normal bone. After injection, all bodily fluids should be monitored. Radium-223 has recently been shown to palliate symptoms and prolong survival in metastatic prostate cancer [42].

The thyroid gland’s innate ability to absorb and sequester iodine can be utilized to deliver radioactive iodine-131 for certain disorders. Radioactive iodine treatment may be indicated for benign disorders such as hyperthyroidism and toxic nodular goiter, or as adjuvant therapy to ablate residual thyroid tissue after thyroidec- tomy for differentiated thyroid carcinoma. Indications for adjuvant treatment include high-risk features such as large tumor size, multifocal disease, thyroid capsule, vascular, or soft tissue invasion. The standard postoperative activity delivered two to six months after thyroidec- tomy is 30–100 mCi. Iodine-131 is also given for recurrent or metastatic thyroid carcinoma, and an activity of 150–250 mCi is indicated.

Phosphorus-32 can be delivered as radioimmunotherapy in two distinct forms. In its soluble state, it accumulates in bone marrow, spleen and liver, and is hence useful to treat hematopoietic disorders such as polycythemia vera and thrombocytosis. In its colloid state, phosphorus-32 accumulates in intracavitary surfaces and is useful to treat malignant ascites, pleural effusions, and ovarian and endometrial carcinoma [43–46].

Hyperthermia

The addition of heat to radiotherapy can enhance the cell-killing potential of a given dose of energy. The mechanism of action is multifactorial and includes, but is not limited to, the inactivation of proteins that may be involved in DNA repair necessary for cell survival. Hyperthermia is also complementary to radiotherapy in that the S phase of the cell cycle, typically a relatively radiosensitive time, is sensitive to hyperthermia. In addition, hypoxic cells (which are relatively radioresistant) are nevertheless heat-sensitive due to the acidic pH of nutrient-deprived cells at the border of viability. It is not known if the combination of heat and radiation has a synergistic or additive effect. Regardless, this therapeutic combination may be a useful option for superficial tumors such as locally recurrent breast cancer. Historically, technologic limitations made heating deep-seated tumors difficult [47]. However, a Dutch randomized trial comparing radiotherapy with or without deep hyperthermia showed dramatic improvements in complete response rates with the latter, associated with a survival benefit. Newer-generation deep hyperthermia devices are coupled with in vivo
magnetic resonance imaging (MRI) to provide precise thermometry, and this combination is beginning to generate renewed interest [48].

**Radiation Complications**

The deposition of radiation energy into tissues leads to both immediate effects and potentially delayed reactions. The former is referred to as the *acute reaction*, while the latter is best described as *chronic toxicity*. It is important to understand that acute effects – that is, temporary side effects – are different from permanent changes. The latter are what most would call damage, and these are the true risks of treatment, more accurately described as treatment complications.

Acute toxicities are expressed as a function of the tissues or organs exposed, the total dose, and the time over which it is given. These side effects are *probable*, normally temporary, and are the result of both cell depletion in normal tissues and inflammatory reaction. Healing occurs when the injured tissue repopulates the lost cells, and the body’s defense reaction resolves. The time course over which this occurs is usually weeks to months for both the development of the reaction as well as the recovery.

The late toxicity of radiation therapy results from damage primarily to the vasculoconnective tissues and slowly proliferating parenchymal cells, leading to an increase in cell loss, that results in fibrotic replacement-associated tissue dysfunction. Examples include subcutaneous fibrosis and osteoradionecrosis, among others.

The probability of a long-term complication such as these is most commonly associated with larger fraction sizes and/or higher total doses. Looking again at the idea of therapeutic window, as seen in Figure 1.2, expresses this idea graphically [49].

Trying to increase the probability of tumor control from 90% to 95% by increasing the total dose from point A to point B will lead to a proportionately greater increase in the risk of late damage. In practice, the data – and therefore the position of the two curves – is never so clearly defined. Just as importantly, individual patient responses are never obliged to follow previous patterns, so there is always a risk of damage in any situation. This concept should never be forgotten.

Radiation oncologists must counsel patients regarding the risks of treatment, acknowledging that subcutaneous fibrosis, chronic enteritis or proctitis, and transverse myelitis result in substantially different quality of life repercussions. In the case of palliation, there is usually minimal tolerance for risk, while in curative treatment it is reasonable to accept a finitely low level of risk, especially when options for management of the complication are available. The difficult decisions arise when palliative treatments have a significant risk of organ damage due to previous therapy or pre-existing comorbidities, or when even high-dose radiation therapy is unlikely to provide much chance of cure. Although a clinician’s experience can be invaluable, there is no substitute for communicating the realities of the situation to the patient and their loved ones, and cooperatively reaching an agreement on how best to proceed. As much as the field of radiation oncology relies on quantifiable measurements of physics and statistics, it is the clinical art of implementation that brings the value to the patient.

**References**


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