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* Authors are listed alphabetically by their first names.

Chapter 1

Radiation Physics, Dosimetry, and Treatment Planning

Wilhelm Roentgen discovered X-rays in 1895 while experimenting with a gas-filled cathode tube; Henri Becquerel discovered radioactivity in 1896 while experimenting with uranium salts. Soon after these discoveries, radiation was used to treat cancer and other diseases. To effectively use radiation, it is important to understand its basic properties, which are addressed in this chapter.

Fundamental Physical Quantities

Mass, energy, charge, and force all have key roles in radiation physics.

Mass

Mass is the amount of matter within any physical object. Mass is measured as weight, and the standard international (SI) unit of mass is the kilogram (kg), represented by a lump of platinum-iridium alloy kept in Paris, France. In the much smaller realm of atomic physics, weights are expressed as atomic mass units (amu or u). An amu is equivalent to one-twelfth the mass of one atom of carbon (the C^{12} isotope).

Einstein's theory of relativity ($E = mc^2$) suggests that mass (m) can be converted into energy (E) as a function of the speed of light squared (c^2). One amu of mass is converted into 931 MeV of energy. The mass of a moving object, its "relativistic mass," is larger than its mass at rest because the kinetic energy associated with its motion adds to the resting mass.

Energy

Energy is the ability of a system to perform work. There are two types of energy: Potential energy and kinetic energy. One electron volt (eV) is the energy acquired by an electron when it moves across a potential difference of 1 V. One million eVs are designated by MeV.

Charge

Electric charge is the property of matter that causes it to experience a force in the presence of an electromagnetic field. Charges are positive or negative with an electron being the smallest unit of negative charge (−1) and the proton being the smallest unit of positive charge (þ1). The SI unit of charge is the coulomb (6.25×10^{18} elementary charges).

Force

A force is an interaction that can change the direction or velocity of an object. The coulomb force (electromagnetic force) is the force between two charged bodies. Protons and electrons are held together by the Coulomb force. Gravitational force is the attraction between two masses. It is a very weak force unless the masses are very large. The strong force holds particles together in the atomic nucleus (protons, neutrons, and quarks) and, on a smaller scale, holds quarks together to form nucleons. It is the strongest known fundamental physical force, but only acts over distances of 0.8 fm (nucleons) and 1e3 fm (formation of nuclei). The weak force is the force that is responsible for particle decay processes (beta decay) and is approximately one-millionth of the strong force.

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Chapter 6

Intensity Modulated and Image Guided Radiation Therapy

Intensity-modulated radiation therapy (IMRT) is an advanced form of conformal therapy that delivers high doses of radiation to target volumes while minimizing exposure to normal tissues. Conformal refers to multiple beams with directions and aperture shapes chosen to conform the radiation dose to a three-dimensional (3D) target volume constructed using 3D imaging modalities [1,2]. IMRT improves the dose conformality further by using mathematical optimization of clinical objectives, such as the dose prescribed to the tumor and dose-volume constraints of normal tissues. Mathematical objectives and computer optimization are used to determine beam intensity distributions, resulting in a highly conformal dose distribution. Typically, a dynamic multileaf collimator (MLC) is used to deliver the intensity-modulated radiation treatment [3,4].

Target Volumes, Margins, and Dose Volumes

- Target volumes: Currently, physicians use the International Commission on Radiation Units and Measurements (ICRU) reports 50, 62, and 83 [5e7] definitions for different target volumes (Fig. 6.1).
  - Gross target volume (GTV) is the gross disease seen clinically or in imaging studies and includes primary gross tumors, nodal gross tumors, and metastatic gross tumors.
  - Clinical target volume (CTV) is the clinically suspected extension of the tumor beyond the gross disease.
  - Internal target volume (ITV) is the CTV and a margin to account for the internal movement of the CTV.
  - Planning target volume (PTV) is the margin needed for the uncertainty of the setup error for the patient.
  - Organs at risk (OAR) volume has also been defined by the ICRU as the margin added to the OAR for the uncertainty of setup error for the patient to create a planning organ at risk volume.
  - Tissues not defined as CTV or OARs are considered to have remaining volume at risk.
  - Treated volume is the area enclosed by an isodose line specified by the physician/planner, and irradiated volume is the volume enclosed by the 50% isodose line.

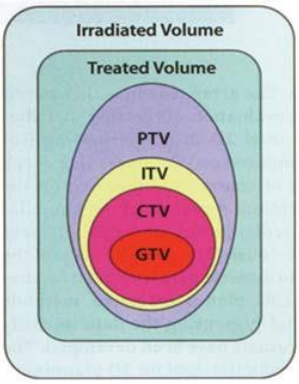

FIGURE 6.1 Different target volumes as defined by the International Commission on Radiation Units and Measurements (ICRU). *Reprinted from Shepard DM, Cao D, Afghan MK, et al. An arc-sequencing algorithm for intensity modulated arc therapy. Med Phys 2007; 34:464e470; Levitt SH, Purdy JA, Perez CA, Vijayakumar S. Technical basis of radiation therapy: practical clinical applications, fourth edition, Fig. 9.13, p. 188, © 2006 with permission of Springer Science and Business Media.*

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Chapter 9

Proton Radiation Therapy

Over the past few decades, proton beam therapy (PBT) has emerged as an important tool for cancer treatments. More and more commercially available proton canters are now available for clinical use. This chapter will discuss the rationale, clinical indications, techniques, and toxicity profiles of PBT.

Proton Beam Depth Dose

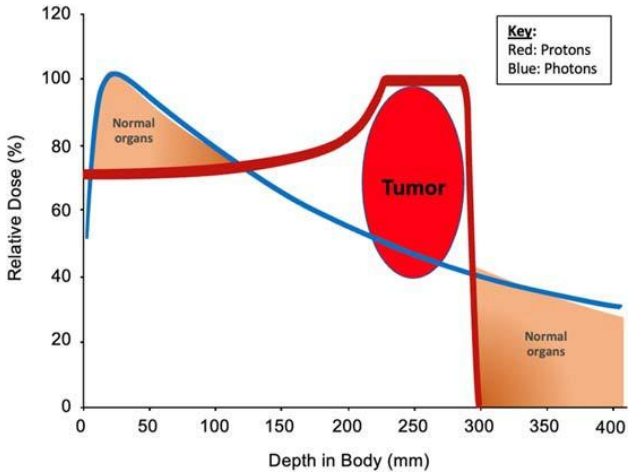

FIGURE 9.1 In a typical treatment plan for proton therapy, the spread-out Bragg peak (SOBP, red plateau over "tumor") is the therapeutic radiation distribution. The SOBP is the sum of several individual Bragg peaks at staggered depths. The depth-dose plot of an X-ray beam (blue line) is provided for comparison. The tan area represents additional doses of X-ray radiotherapyдwhich can damage normal tissues and cause secondary cancers.

Protons are heavy-charged particles that have mass, possess a positive charge, and, as such, interact differently with matter than photons. Protons do not change direction appreciably while traveling through matter but generally interact with matter by undergoing inelastic collisions with atomic electrons. In this process, they give up a portion of their energy with each collision (without changing direction appreciably). Hence, a mono-energetic proton beam continues to lose its energy while traveling through tissue, and the rate of energy loss increases with decreasing proton energy, resulting in most of the dose deposition occurring at the end of the range in a sharp Bragg peak [1].

Absorbed dose beyond the Bragg peak is negligible [1e3]. The depth of the Bragg peak is dependent on the incident proton beam energy. To deliver a uniform dose to a target volume, the proton energy is tuned and varied to superimpose multiple Bragg peaks across the target, resulting in a region of relatively uniform dose called the spread-out Bragg peak (SOBP). Proximal to the target, the SOBP delivers less of a dose than that given at the target dose (low entrance dose). Distal to the target, the SOBP delivers a negligible dose (the minimum exit dose). A single photon beam, on the other hand, delivers a higher dose proximal to the target and a lower, but nonnegligible dose distal to the target. Protons therefore have a dosimetric advantage over photons, delivering a less integral dose to normal tissues for the same tumor dose. Furthermore, most proton treatment plans require only one to three beams. Proton and photon beam depth dose charac- teristics are illustrated in Fig. 9.1.

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Chapter 11

Artificial Intelligence in Radiation Therapy

The past decade has been a golden age for artificial intelligence (AI), with an explosive amount of research and development. AI has rapidly transformed the way we live, work, and interact with the world around us and ushered us into a new era of possibilities and innovations. In the evolving landscape of AI, one of the most promising and consequential areas of application is medicine.

This chapter will introduce the basic concepts and current methods of AI and discuss the applications and roles of AI in radiation oncology.

Basic Concepts of AI

AI refers to the simulation of human intelligence in machines for performing tasks that typically require human intelligence, such as those ranging from understanding natural language and recognizing images and patterns to making decisions and solving problems [1]. There are many frequently encountered concepts in the realm of AI, such as machine learning (ML) [2], deep learning (DL) [3], natural language processing (NLP) [4], and large language models (LLMs) [5]. Fig. 11.1 is plotted to briefly illustrate the relationship of these concepts.

- AI is an overreaching concept that encompasses a broad spectrum of techniques with the primary goal of making machines capable of learning and reasoning.
- ML is an important subset of AI methods that enable machines to learn from data, aiming at improving machines' performance over time without being explicitly programmed.
- DL is a subset of ML methods that focus on artificial neural networks (ANNs) with multiple layers and complex feature extraction. ML and DL are the foundations of many applications in radiation oncology.

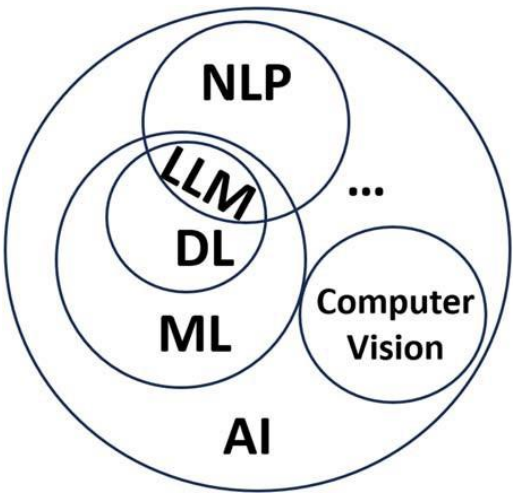

FIGURE 11.1 Relationship of example AI concepts.

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Chapter 12

Immunotherapy

Immunotherapy has become an increasingly critical component in the management of various malignancies. In fact, several large prospective studies have shown significant clinical benefits. Studies are now underway to assess the potential synergism between these agents and traditional chemotherapeutics, surgery, and radiation therapy. Radiation therapy has the potential to enhance the efficacy of immunotherapeutic agents. Following is a discussion regarding immunological principles and the biological rationale for the use of immunotherapeutics, along with the key immunotherapy studies that have led to the approval of a number of these agents for clinical use.

Immune System Components

Anatomy of the Immune System

The bone marrow contains hematopoietic stem cells and is the site of development of all blood cells except T cells, which are produced in the thymus through positive and negative selection. Lymph nodes are the site of antigen presentation within the lymphatic circulation, while the spleen is the site of antigen presentation from the blood.

Cells of the Immune System

The innate immune system: The innate immune system is comprised of dendritic cells, natural killer cells, macrophages, neutrophils, eosinophils, basophils, and myeloid-derived suppressor cells. It provides immediate defense through nonspecific recognition of foreign pathogens or tumors, thus providing immediate defense, but does not provide long-lasting immunity.

The adaptive immune system: The adaptive immune system is made up of CD4 T cells, CD8 T cells, B cells, and regulatory T cells, which provide specific recognition of foreign antigens or tumor-associated antigens by the immune system. It is characterized by an initial weaker response and a stronger memory response upon rechallenge. The large variety of T cell receptors (TCR) and B cell receptors (BCR) occur through somatic DNA recombination events (VDS recombination) initiated by the RAG gene.

The Immune Synapse

The immune synapse between antigen-presenting cells (APCs) and adaptive immune cells defines the immunologic response, as represented in Fig. 12.1. The immune synapse between the APCs and cognate T cells requires two signals for an effective immune response:

- Signal 1: Presentation of a specific peptide antigen by the major histocompatibility complex (MHC) on the APC to the cognate TCR on the T cells.
- Signal 2: The danger signal is provided by APCs to alert the immune system via the interaction of costimulatory molecules, the suppression of immune checkpoints, and the release of proinflammatory cytokines. APCs recognize the danger via pathogen-associated molecular patterns during foreign pathogen invasion or damage-associated molecular patterns during immunogenic cell death.

Immune checkpoints provide suppressor signals to the T cells during immune recognition, which limit excessive immune responses or auto-immune responses; they are often utilized by tumors to suppress antitumor immune responses, and the most effective cancer immunotherapy targets these checkpoints using antagonists. Examples of immune checkpoints include programmed death 1 (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTL-4), Tim3, and LAG3.

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Chapter 16

Primary Brain Cancers

The estimated incidence in the US of primary brain cancer is 25,400, with an estimated 18,760 deaths in 2024.

Primary brain cancer incidence peaks in childhood and again after age 60 and has been increasing. The major brain sites are the cerebrum, diencephalon, brain stem, and cerebellum. The brain and spinal cord together form the central nervous system (CNS). CNS tumors are locally invasive, even though cerebrospinal fluid dissemination and drop metastases can occur along the spine, they are uncommon. Extraneuraxial metastases are extremely rare.

Workup

Risk Factors

- Neurofibromatosis
  - a NF1: astrocytoma, optic glioma, and malignant peripheral nerve sheath tumors
  - b NF2: meningioma, vestibular schwannoma, other cranial nerve schwannoma
- Von Hippel-Lindau disease: Hemangioblastoma
- Tuberous sclerosis: Subependymal giant cell astrocytoma (SEGA)
- Turcot's syndrome: Medulloblastoma, glioblastoma
- Li-Fraumeni syndrome: glioma
- Multiple endocrine neoplasia type 1: Pituitary tumor
- Ionizing radiation: meningioma and high-grade glioma
- Chemical vinyl chloride formaldehyde: High-grade gliomas

Symptoms and Signs

- Majority are asymptomatic
- Seizures, headache, nausea, vomiting, blurred vision, diplopia, weakness, ataxia, memory loss, change in personality, and language/speech difficulties (dysarthria)
- Enlarged head size in children (cephalomegaly).

Investigations

- CBC, CMP, and CSF cytology are helpful in medulloblastoma, ependymoma, choroid plexus tumors, pineal and supra-sellar tumors (including germinoma)
- Stereotactic biopsy
- Molecular testing by tumor type (IDH, 1p/19q codeletion and/or ATRX for oligodendrogliomas, BRAF for PAs, BRAF V 600 E for pleomorphic xanthoastrocytomas, MGMT methylation and IDH1 status for gliomas, H3K27M for diffuse midline gliomas or brainstem gliomas)
- MRI with and without gadolinium contrast; MR spectroscopy; MR perfusion; and MRA may be necessary prior to surgery

Circumscribed Astrocytic Glioma

The World Health Organization (WHO) 2021 classification divides circumscribed astrocytic gliomas into the following:

- Pilocytic astrocytoma (PA) – grade I, not IDH mutation, have BRAF alteration

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Chapter 21

Genitourinary Cancers

Renal Cancer

The estimated incidence of renal cancer in the US is 81,610, with an estimated 14,390 deaths in 2024.

The right and left kidneys are located between the 11th ribs and the third lumbar vertebrae in the retroperitoneal fatty tissue. The left kidney resides slightly higher than the right in the posterior abdominal wall. The kidneys and renal pelvis lymphatics drain to the renal hilar, paraortocaval, and paraaortic (PA) nodes. Right-sided cancers drain to the interaortocaval, whereas left-sided cancers drain to aortic nodes.

Workup

Risk Factors

- Smoking, analgesic abuse (containing phenacetin)
- Obesity, hypertension
- Von Hipple Lindau disease
- Family history

Symptoms and Signs

- Occasionally, constitutional symptoms such as malaise, fever, night sweats, and weight loss
- "Classic triad" of abdominal pain/flank pain, flank mass, and hematuria
- Paraneoplastic syndromes such as erythrocytosis and hypercalcemia
- A physical exam should note flank mass, any supraclavicular lymph node (LN), organomegaly, and lower extremity edema.

Investigations

- CBC, CMP, LDH, urinalysis, and urine cytology
- Consider needle core biopsy (for surveillance or ablative therapy or if a second primary is suspected); otherwise, tissue diagnosis is obtained from nephrectomy
- CT or MRI abdomen/pelvis with and without contrast (bone scan, brain MRI, if indicated), PETCT scan

TNM Staging (Renal Cancer)

Primary Tumor (T)	
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
T2	Tumor larger than 7 cm in greatest dimension, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional Lymph Nodes (N)	
N0	No regional lymph node metastasis

Continued

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Chapter 27

Radiation Emergencies and Common Indications for Palliative Radiotherapy

Brain Metastases

The estimated incidence metastatic brain cancer in the US is between 170,000 and 200,000 cases in 2024.

The most common brain tumors are intracranial metastatic tumors. They are primarily located in the cerebral hemispheres along gray and white matter junctions which comprise the vascular border zone. Occurrences within the cerebellum or brainstem are less common. Frequent sites of primary malignancy are lung (48%), breast (15%), melanoma (9%), and colorectal (5%).

Workup

Symptoms and Signs

- Generalized headache, which may worsen with positional changes
  - Vomiting, secondary to increased intracranial pressure (ICP),
  - Difficulty with vision, hearing, speech, and memory.
  - Changes in personality
  - Numbness, tingling, weakness, motor difficulty, and loss of balance
- Focal or generalized seizures

Investigations

- CBC, CMP
- Biopsy of primary and/or metastatic lesion for tissue diagnosis
- CT head with and without contrast followed by MRI brain with and without contrast
- CT chest, abdomen, pelvis
- PET/CT scan if patient has no history of malignancy

Treatment

Asymptomatic: close observation with initiation of steroids only if symptomatic vasogenic edema occurs. Anticonvulsive prophylaxis is not needed.

Symptomatic vasogenic edema: dexamethasone should be initiated.

a For mild–moderate symptoms, provide a total dose of 2–8 mg of dexamethasone daily
b For severe symptoms, provide dexamethasone 10 mg IV loading, followed by 2–4 mg every 6 h
c Proton pump inhibitor should be used for gastric prophylaxis throughout duration of steroid use. If steroids duration is anticipated to exceed 28 days, opportunistic infection prophylaxis with trimethoprim-sulfamethoxazole, atovaquone, or pentamidine should be provided
   - If impending cerebral herniation is a concern, recommend neurosurgical consult for consideration of shunt placement and other management such as use of mannitol or glycerol IV
   - If seizure is a presenting symptom, recommend antiepileptic management. For generalized seizures, use levetiracetam, phenytoin, carbamazepine, or phenobarbital. For partial seizures, may consider levetiracetam, valproic acid or carbamazepine. Serum anticonvulsant level should be monitored for selected agents such as phenytoin.

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