Introduction to Radiotherapy and Standard Teletherapy Techniques

Ehsan H. Balagamwala\textsuperscript{a} · Abigail Stockham\textsuperscript{a} · Roger Macklis\textsuperscript{a} · Arun D. Singh\textsuperscript{b}

\textsuperscript{a}Department of Radiation Oncology, Taussig Cancer Institute and \textsuperscript{b}Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, Ohio, USA

Abstract

Radiation was first discovered in the late 19th century by Wilhelm Roentgen and has since been used extensively to treat a variety of cancers. Over the last century, we have developed an extensive understanding of the physical properties of radiation as well as radiation biology. Technological advances in the last few decades in medical imaging and radiotherapy delivery have led to the development of highly complex radiation delivery systems such as intensity modulated radiotherapy, which can be utilized to conformally treat complex tumor shapes while minimizing radiation dose to the surrounding normal tissue. To completely appreciate the application of radiotherapy for ophthalmic cancers, it is important to have a basic understanding of radiation therapy. In this chapter, we will discuss the fundamentals of radiation and radioactive decay, the mechanism of tumor cell damage leading to tumor cell apoptosis, as well as radiation and treatment parameters that are relevant for an ophthalmic oncologist. We will also discuss the concept of tissue tolerance which is of critical importance when prescribing radiation treatment as well as introduce the principles of three-dimensional conformal radiotherapy and intensity modulated radiotherapy.

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Radiation was first described as ‘X-rays’ by Wilhelm Roentgen in 1895 while he was experimenting with the discharge of electricity in vacuum tubes. Henri Becquerel, Marie Curie and Pierre Curie built on the understanding of radiation a few months later when they described the emission of radiation by uranium [1]. These discoveries in the late 1890s and early 1900s not only revolutionized the scientific community’s understanding of physics, but also medicine as X-rays were used to treat cancers as early as 1896. Soon after this external application of X-rays for therapeutic intervention, radon was implanted into tumors introducing the concept of brachytherapy. Advances over the last century have furthered radiation physics, radiation biology,
and the therapeutic application of radiation in the management of ophthalmologic malignancies.

Each decade of the early 20th century ushered in new technological capabilities in radiation technology. Low-voltage X-ray machines, used the treatment of superficial malignancies, were introduced in the 1920s. In 1932, the first cyclotron was engineered at the University of California at Berkley, which led to the advent of charged particle radiotherapy. Further technological progress occurred in the 1950s with the development of the first cobalt-60 unit. Development of the cobalt-60 radiotherapy unit in 1951 was significant for both its eventual commercial availability and dosimetric characteristic of the averaged 1.25 MeV gamma rays emitted upon the decay of the radionuclide. During the same decade, another option for teletherapy was developed. The linear particle accelerator (linac) accelerates electrons, which allows for generation of megavoltage electron and photon beams, which are used in the treatment of ophthalmologic malignancies. The first modern high-energy linac was manufactured in Hammersmith Hospital in London in 1953 [2]. The first patient in the United States to undergo treatment with a linac was a 2-year-old boy with retinoblastoma, treated at Stanford Medical Center in 1956 [3].

In more recent decades, advancements in medical imaging, such as CT and MRI in the 1970s and 1980s, as well as patient immobilization, have led to the development of sophisticated and more precise radiation therapy techniques. Techniques such three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiotherapy (IMRT) developed in parallel in the 1990s and early 2000s. Over this same period of time, stereotactic radiosurgery (SRS), which was first developed in 1953, was modernized with the GammaKnife® [4] and linac-based SRS was pioneered. All of these techniques allow therapeutic quantities of energy deposition and absorption to a defined target, while minimizing damage to normal surrounding tissue. This chapter will focus on reviewing the basic principles of radiation therapy and standard radiotherapy techniques, such as 3D-CRT and IMRT, used in external beam radiotherapy. The next chapter will continue the current discussion with an introduction to more advanced radiotherapy techniques, including SRS and heavy ion therapy. Brachytherapy will then be discussed in the next two chapters.

Basic Principles of Radiotherapy

The unique characteristics of each element are a function of its atomic structure, i.e. the number and configuration of electrons, protons and neutrons. The atom is held together by strong subatomic bonds. When these bonds are disrupted, energy is released. This may occur as a result of external radiation or may occur when an atom undergoes radioactive decay. Radiation is the propagation of this energy through space or matter. It can take the form of electromagnetic waves, energetic particles or both. Radiotherapy exerts its effect on tissues as a result of the interaction between ra-
Radiation and molecular composition of living cells. When radiation is of sufficient energy it can break chemical bonds between molecules, which generates ions and free radicals. These, in turn, induce damage by oxidizing DNA and other cellular contents critical for the viability and/or replication of cells [5].

Dual Nature of Radiation

Radiation can be in the form of electromagnetic waves, particles or both.

Electromagnetic Radiation

Electromagnetic (EM) radiation is a form of energy that exhibits wave-like behavior as it travels through space. Energy is transmitted at the speed of light (c), with an inverse relationship between the wavelength (λ) and frequency (ν): c = νλ. EM radiation has a broad range of wavelengths ranging from $10^{-13}$ m (ultra-high-energy X-rays) to $10^7$ m (radio waves). Visible light constitutes a very small band on the EM spectrum: $4 \times 10^{-7}$ to $7 \times 10^{-7}$ m (fig. 1). As the wavelength gets shorter, EM radiation gains the ability to ionize particles. Photons generated by linacs for use in radiotherapy have wavelengths in the range of $10^{-11}$ to $10^{-13}$ m [6].

Particle Radiation

Particle radiation refers to the energy carried by subatomic particles such as negatively charged electrons, positively charged protons, and uncharged neutrons. These particles are accelerated in either linacs (electrons) or cyclotrons (protons and neutrons) to clinically relevant energies. Upon introduction into a medium, they impart their energy to that medium in a manner specific to the characteristics of the particle beam and the medium [6].

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**Fig. 1.** The electromagnetic spectrum. High-frequency, small wavelength radiation is utilized in radiotherapy to treat tumors. Depending on the energy of the radiation, it can be optimized for diagnostic imaging versus use for therapeutics.
Radioactive Decay

Certain naturally occurring and synthetic elements exist in a high-energy, unstable state. These elements transform to a more stable, low energy state through a process called decay. The excess energy is emitted in the form of radiation. Multiple types of radiation can be emitted during radioactive decay. The three most clinically relevant type of radiation include positively charged alpha particles (helium nucleus), negatively charged beta particles (electrons) or electrically neutral gamma-rays. An important parameter in radioactive decay is half-life ($T_{1/2}$). The $T_{1/2}$ of a radioactive source is the time required for half the source to decay and is unique to each radionuclide. For a selected radionuclide, the treatment time increases as the source decays. The $T_{1/2}$ and the radiotherapeutic characteristics intrinsic to each radionuclide may influence which radionuclide is selected for a particular clinical therapy. Radioactive decay is utilized in cobalt-60 teletherapy units, GammaKnife radiosurgery (GKRS) and brachytherapy [6]. A variety of other radioactive sources are utilized in radiotherapy, most commonly utilized in brachytherapy. Brachytherapy refers to placement of a radiation source within or close to the tumor.

Ionizing and Nonionizing Radiation

When radiation passes through a medium, energy can be transferred from incident form of radiation to the atoms that compose the medium. Transfer of energy can result in both ionizing and nonionizing effects. Only ionizing radiation is clinically relevant. Ionization occurs when a neutral atom or molecule acquires a positive or negative charge, most frequently as a result of ejection of electrons. These ions interact with cellular components, including DNA, which affect cellular function and mitosis. Ionizing effects tend to dominate when higher energy (i.e. short wavelengths) radiation is utilized [5].

Mechanism of Radiation-Induced Cellular Damage

The most well-understood target of ionizing radiation is DNA. DNA damage, with subsequent cellular dysfunction and mitotic inhibition, occurs as a result of direct damage, indirect damage, or a combination of direct and indirect damage. Direct DNA damage refers to interaction between the incident form of radiation and cellular DNA, which results in single- or double-strand breaks which impair cellular function and preclude replication. This results in permanent senescence, cell death, or mitotic catastrophe and inability to replicate. Direct DNA damage predominates when large particle radiation, i.e. protons or alpha particles, is utilized (fig. 2) [5].

Indirect DNA damage is mediated by the formation of hydroxyl ions by radiation which, in turn, create DNA strand breaks. Hydroxyl ions are generated when radia-
tion overcomes the binding energy of the hydrogen and oxygen molecules of water, resulting in hydroxyl and oxygen ions. Indirect DNA damage predominates when photons or electrons are utilized.

**Teletherapy Sources**

Teletherapy, contemporarily referred to as external beam radiotherapy, denotes delivery of radiation from an external source at a distance. In modern clinical radiation oncology, a linear accelerator or a cyclotron is used to generate and deliver external beam photon or particle radiotherapy. While it may be used for standard teletherapy, cobalt-60 is most frequently utilized as a part of the GKRS system.

**Cobalt-60 Unit**

A cobalt-60 unit houses a radioactive cobalt source that emits gamma-radiation as cobalt-60 decays to nickel-60. Cobalt-60 has a $T_{1/2}$ of 5.27 years. As the source ages, the quantity remaining in the cobalt-60 state versus the nickel-60 state declines, thus, the time required to deliver a certain amount of radiation increases. The average energy of the $\gamma$ photon beam is 1.25 MeV. In modern practice, cobalt-60 is most often utilized as part of the GKRS system, which houses 201 cobalt-60 sources targeted at a single point (fig. 3). GKRS is one form of stereotactic radiosurgery utilized for the management of ophthalmic tumors.