125 Beams and the Rise of Radiation Therapy

The People, Landmark Discoveries, and Innovations that Shaped a Field

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Charles R. Thomas Jr.
Editors

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Foreword

As a patient whose cancer was cured with brachytherapy, I am honored to recognize *125 Beams* pioneered by Drs. Heard and Thomas and their colleagues as the first comprehensive history of over a century and quarter of radiation therapy. Their masterpiece not only chronicles the beams of ionizing radiation, it sheds beams of light on the efforts of innumerable radiation oncologists, medical physicists, dosimetrists, radiation biologists, and other scientists around the world who enabled radiation to become a treatment for half of all patients with cancer and for many noncancerous conditions. The latter include cardiac arrhythmias, soft tissue disorders (keloids, Peyronie's, and Dupuytren's disease), musculoskeletal disorders (osteoarthritis and osteoarthrosis, achillodynia, and heterotopic ossification), central nervous system abnormalities (arteriovenous malformations, trigeminal neuralgia, and seizure disorders), and eye conditions (Graves ophthalmopathy). In at least one European country, one in every five radiotherapy patients are receiving it for non-oncologic conditions.

To be to learn what Wilhelm Röntgen, Emil Grubbe, Marie Curie, Godfrey Hounsfield, William Coolidge, Gustav Bucky, Irvin I. Kirsch, AMS Kelman, and so many other radiation therapy pioneers accomplished in one volume is a crucial accomplishment by itself. Having been involved with the care of Japanese children, adolescents, and young adults who suffered the long-term adverse effects of ionizing radiation in Nagasaki and Hiroshima, I can personally attest to the value of understanding the communal history of radiation and the irony of using radiation therapy to treat what radiation caused in them. Going back to the future provides a better understanding of where we are now and which way to go in the future. With *125 Beams*, we can take off from here more effectively.

Access to radiotherapy is improving globally. Yet radiation therapy is not available to more than half of patients in lower-income countries. The evolution covered by the *150 Beams* treatise will also help treat this challenge and provide more direction and feasibility.

As a student, intern, resident, Fellow, mentor, teacher, attending physician, and professor, I also appreciate how *125 Beams* can be an invaluable teaching resource. Its beams can illuminate and educate all of us.

Clinical Research Professor
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Archie Bleyer

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History of Radiotherapy: 1895–1905

George Starkschall

1 Introduction

Not long after the discovery of x-rays by Roentgen in 1895 and the discovery of radium by Becquerel the following year, biological effects of the radiation emitted by these two methods were identified. In this chapter, we shall open the history book to the decade following these discoveries and gain a perspective on the use of radiation for the treatment of diseases during this period. The chapter will begin with a brief review of the physical properties of both the radiation generated in an x-ray unit and the radiation produced by the radioactive decay of radium. Special emphasis will be given to those properties that have been found to be useful in radiation therapy. Next, the chapter will identify some of the clinical applications of radiation in the treatment of various conditions. Sources of clinically useful radiation, both x-rays and gamma-rays, are described next. The next part of the chapter deals with the issues presented in the use of radiation for therapeutic purposes, particularly the quantification and the localization of radiation. We conclude the chapter by visiting a clinic around 1905 and observe how radiation is used in the clinic.

2 Physical Properties of Ionizing Radiation

This section provides a brief summary of some of the key properties of ionizing radiation that have application to radiation therapy. For more details, the reader is urged to refer to one of the standard texts on radiological physics. The radiation

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used in radiation therapy is ionizing electromagnetic radiation, that is, radiation produced by electric and magnetic fields that has sufficient energy to remove electrons from atoms. Hence, the term "ionizing radiation" is often used to identify this radiation. It is similar in nature to such forms of radiation as visible light, infrared and ultraviolet light, and radio waves, but its energy is much greater. The energies used in radiation therapy are greater than several thousand electron volts (keV) and may range up to 25 million electron volts (MeV), although in the early days of radiation therapy, energies tended to be on the low end of the spectrum. The beam produced by an x-ray machine was polyenergetic with reduced intensity at the low-energy component of the spectrum due to selective beam attenuation inside the x-ray tube.

Heavy elements, radium, in particular, also emanate ionizing radiation due to the instability of their nuclei. In the case of these heavy elements, however, the radiation is monoenergetic or at least consists of a small number of energy components. This radiation is somewhat higher in energy than the x-rays that were produced in a machine in the early days, although it should be pointed out that contemporary linear accelerators produce x-ray beams of greater energy than that produced by radium (or other radioactive sources). However, other than their energy spectra, the radiation produced via both mechanisms is the same,

Because the rate of decay of the radioactive nuclei, and hence, the decrease in the number of radioactive nuclei, is independent of everything other than the number of radioactive nuclei present, the fractional rate of change of the number of atoms present is a constant, enabling us to write the equation for the time dependence of the number of nuclei undergoing radioactive decay:

$$\frac{dN/N}{dt} = -\lambda$$

where N is the number of radioactive nuclei, dN/dt is the change in the number of nuclei, and λ is a constant, called the "transformation constant," that is characteristic of the particular decaying nucleus. The negative sign indicates that the fractional rate of change of the number of nuclei present decreases with time. Integrating this equation gives us an expression for $N(t)$, the number of nuclei present and undergoing radioactive decay as a function of time t:

$$N(t) = N_0 e^{-\lambda t}$$

where N_0 is the number of nuclei at the initial time ($t = 0$), and λ is the transformation constant.[1]

[1] Exponential behavior can be rigorously derived using statistical analysis from the assumption that each decay event is independent of any other decay event, but the derivation is beyond the scope of this book.

Regardless of the type of radiation, the intensity of radiation as it passes through absorbing material such as tissue obeys a depth dependence similar to the time dependence of the decaying nuclei, that is,

$$I(d) = I_0 e^{-\mu d}$$

where $I(d)$ is the beam intensity at a depth d below the skin surface, I_0 is the intensity at the surface of the patient, and μ is the linear attenuation coefficient, defined as the depth dependence of the fractional change in beam intensity, a function of both the energy of the radiation and the nature of the absorbing material.

3 Early Clinical Applications of Radiation

Shortly after x-rays were discovered, early experimenters observed cutaneous irritation in those regions exposed to the x-rays.[2] This observation led to great enthusiasm among clinicians, suggesting that x-rays be used in the treatment of disease.[3] Many publications appeared in the literature prescribing x-rays as a universal panacea.[4] It is important to note, however, that the potential risks and proper dosages of x-ray therapy were not well-understood at the time. As a result, many of these early therapeutic applications carried significant risks to the physician as well as to the patient and often resulted in unintended harmful effects. Despite these side effects, x-rays were used for various therapeutic purposes during this period.

X-rays were initially believed to have potential benefits for treating skin conditions, such as ulcers, infections, and certain dermatological disorders.[5] The affected areas of the skin were exposed to the radiation with the belief that x-rays could promote wound healing and alleviate skin problems. Early speculations proposed the use of x-rays to treat cancer.[6] Some researchers and clinicians believed that x-rays could potentially target and shrink tumors. X-rays were also applied to treat conditions like pain and arthritis. It was thought that the radiation could provide relief by reducing inflammation and discomfort in affected joints.[7] X-rays were used

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[2] Belot J., *Radiotherapy in Skin Disease,* Rebman Co, NY (1905), p 99.

[3] MacKee GM, *X-rays and Radium in the treatment of diseases of the skin*, Lea & Febinger, Philadelphia (1921).

[4] Belot, p 99.

[5] Pusey, Wm. Allen (1900). "Roentgen rays in the treatment of skin diseases and for the removal of hair" (https://books.google.com/books?id=EZPTAAAAIAAJ&pg=PA302),
Journal of Cutaneous Diseases Including Syphilis **18**: 302–318.

[6] Lederman M (1981). "The early history of radiotherapy: 1895–1939," Int J Rad Oncology Biol Phys **7**:639–648.

[7] Calabrese EJ, Dhawan G, Kapoor R, Kozumbo WJ (2019). "Radiotherapy treatment of human inflammatory diseases and conditions: Optimal dose," *Human and Experimental Toxicology* **38**:888–898.

to treat superficial lesions, such as skin tumors and certain growths. These applications were based on the belief that x-rays could selectively target abnormal tissue. X-rays were also used in attempts to remove unwanted hair.[8] The radiation was directed at hair follicles in the hopes of inhibiting hair growth. This application was not effective, and it posed a significant risk of skin damage. In some areas, the procedure was illegal.[9]

However, the lack of knowledge about safe dosages often led to radiation burns and injuries. Moreover, the limited understanding of the appropriate radiation dosage and potential harm led to inconsistent and sometimes harmful outcomes. Actual therapeutic benefits were questionable, and the potential harm from radiation exposure was significant. However, due to the limited control over dosage and the inability to precisely target the radiation, patients often experienced radiation burns and other adverse effects.

It is important to emphasize that the use of x-rays for therapeutic purposes during this period was marked by significant experimentation and a lack of understanding of radiation safety.[10] Early experimenters quickly observed that exposure to x-rays could cause burns and reddening of the skin. These effects were particularly pronounced in areas where the skin was exposed to high doses of radiation. The skin reactions were often painful and could lead to blistering, ulceration, and even the need for amputation.[11] Exposure to high doses of x-rays was found to cause temporary or permanent hair loss in the irradiated areas. This effect became evident in individuals who worked with x-ray equipment or underwent x-ray treatments without proper shielding. Prolonged or high-dose exposure to x-rays could lead to significant damage to underlying tissues. In severe cases, this could result in tissue ulceration, necrosis (cell death), and the formation of open sores that were difficult to heal. Researchers discovered that x-rays could cause damage to the lenses of the eyes, leading to the development of cataracts. Medical professionals who were involved in early x-ray procedures without adequate eye protection were particularly at risk. High doses of x-rays were found to have adverse effects on reproductive organs. Female ovaries and male testes were susceptible to radiation-induced damage, potentially leading to sterility or genetic mutations in offspring. Exposure to ionizing radiation could lead to changes in blood cells and bone marrow. Researchers noted decreases in red blood cells, white blood cells, and platelets following radiation exposure, which could lead to anemia, susceptibility to infections, and bleeding disorders.

Some of the most significant discoveries were related to the potential for delayed effects of radiation exposure. Researchers observed that individuals exposed to

[8] Herzig R (1999). "Removing roots: North American Hiroshima Maidens and the X-ray," *Technology and Culture* **40**:723–745.

[9] Bickmore H, *Milady's Hair Removal Techniques: A Comprehensive Manual.* Thomson Delmar Learning. ISBN 978–140,181,554, as cited in en.wikipedia.org/wiki/Hair_removal

[10] Belot, p 88.

[11] Gould GM, Lloyd JH, "X-ray Burns—Amputation of the Thigh, X-ray Burans; Their Nature and Treatment," *The Philadelphia Medical Journal,* 1:354 (1898).

x-rays had an increased risk of developing cancer, particularly leukemia and other malignancies. This realization sparked concerns about the long-term health risks associated with ionizing radiation. Exposure to x-rays could impair the body's natural healing processes, making it difficult for wounds and injuries to heal properly. This effect was particularly concerning for medical practitioners who were using x-rays for therapeutic purposes. Early researchers also speculated about the potential genetic effects of ionizing radiation. Some experiments on plants and animals suggested that radiation exposure could lead to hereditary changes in subsequent generations, raising concerns about the potential impact on human genetics.

Many patients and medical professionals experienced harmful effects, including radiation burns and tissue damage. It was not until later years that a more comprehensive understanding of radiation biology and dosimetry developed, leading to the establishment of safer and more effective radiation therapy practices.

These discoveries highlighted the need for caution and careful consideration when working with x-rays and other forms of ionizing radiation. As a result, radiation safety measures, protective equipment, and dose limits were gradually developed to minimize the risks associated with radiation exposure. Over time, these early observations and findings contributed to the establishment of radiation protection guidelines and standards that are still in use today.

4 Sources of Radiation

The x-ray tube, as we know it today, is based on the principles applied in the design of the x-ray tube by Coolidge in 1913. Prior to the invention of the Coolidge tube, early radiation therapy primarily used a Crookes tube as the source of x-rays.

A Crookes tube, also known as a Crookes–Hittorf tube, is a device that was used in early experimental physics to study the properties of cathode rays, which are streams of electrons. It was invented by Sir William Crookes in the nineteenth century and played a significant role in understanding the nature of these particles and their behavior in a vacuum. The Crookes tube is considered one of the precursors to the modern cathode ray tube (CRT) used in older television and computer monitors.

A Crookes tube consists of a glass envelope with most of the air evacuated from it, creating a partial vacuum. Inside the tube, there are two main electrodes: the cathode and the anode. The cathode is a metal plate or a filament made of a material like tungsten, while the anode is typically a metal disk. Both electrodes are connected to a high-voltage power source (Fig. 1). The key element in the operation of a Crookes tube is the partial vacuum inside the glass envelope. The tube is designed to have a very low pressure of gas or air (0.1–0.006 pascal), remaining inside.[12] When a high voltage is applied between the cathode and the anode, electrons are generated by ionization of the residual air in the tube. The emitted electrons form a

[12] https://en.wikipedia.org/wiki/Crookes_tube

Fig. 1 A Crookes tube. The disk on the left is the cathode while the electrode in the shorter side arm is the anode. Electrons striking the flat end of the tube produced x-rays

stream known as cathode rays. These rays are negatively charged and are attracted to the positively charged anode. In the absence of significant air molecules, cathode rays can travel in straight lines across the tube. To visualize the path of the cathode rays, a fluorescent screen can be placed at one end of the tube. This screen emits visible light when struck by the high-speed electrons. The path of the cathode rays can be observed as a glowing spot on the screen. By introducing external magnetic or electric fields, researchers can deflect the path of the cathode rays. This behavior helped scientists understand the nature of cathode rays as charged particles. When the cathode rays strike the anode, they can cause the anode to emit a faint glow due to the release of energy upon impact. This glow was one of the early indicators of the presence of cathode rays.

Although the Crookes tube was used to generate x-rays, its primary application was to study cathode rays and their properties. It was one of the earliest devices used to investigate the behavior of electrons in a vacuum. The cathode rays produced in a Crookes tube helped scientists understand the fundamental nature of electrons and their interaction with electric and magnetic fields. Unlike the Coolidge tube, it was not designed for the production of x-rays.[13]

Use of the Crookes tube as an x-ray source for radiotherapy had some severe limitations. While the Crookes tube provided a source of radiation, the ability to control and accurately measure the radiation dose was limited compared to modern standards. As will be discussed later in this chapter, dosimetry was not as precise as it is today, and treatment planning was based on general observations and trial-and-error. The Crookes tube also had limitations in terms of the quality and intensity of the x-rays it produced. The x-rays had lower energy compared to the x-rays generated by more advanced methods that were developed later. This limited the depth of penetration into tissues and could result in uneven dose distribution. Consequently, early radiation therapy using the Crookes tube was associated with significant risks and side effects due to the lack of precise control over the radiation dose and the

[13] https://en.wikipedia.org/wiki/Crookes_tube

potential for damage to healthy tissues. Patients undergoing radiation therapy experienced various adverse effects, including burns, skin reactions, and damage to surrounding organs.

The Crookes tube played a pioneering role in the early days of radiation therapy by providing a source of x-rays for medical treatment. While its use was associated with significant challenges and risks, it laid the foundation for the development of modern radiation therapy techniques that offer greater precision, dose control, and patient safety.

The cathode ray tube was not the only type of tube used clinically prior to the development of the Coolidge tube. Another example of a clinical tube was the Chabaud tube. In structure, however, it was similar to the Crookes tube, as was the "heavy anode" tube.[14]

Radiation was also delivered to the patient by implanting radioactive sources into the tumor or by placing the sources in contact with the tumor. Because of the short distance between the source and the tumor, the decrease in dose following the inverse square law spared much tissue distal to the tumor.

Radioactive sources used for brachytherapy were primarily natural radioactive materials. Radium was one of the most commonly used radioactive sources for brachytherapy in the early twentieth century. The radium isotope with a mass number of 226 (^{226}Ra) was the isotope used, emitting alpha, beta, and gamma radiation. Radium was often enclosed in small tubes or capsules and inserted into tumors or body cavities. The encapsulation attenuated the alpha and beta radiation. Radium, however, was very costly. Moreover, the initial decay of radium did not produce the therapeutically useful high-energy gamma rays; decay products further down the line generated the clinically useful gamma rays. In order to overcome the issue of the high cost of radium, radon gas (^{222}Rn), the initial decay product of radium, was encapsulated and could be permanently implanted into the tumor because of its short half-life of 3.8 days. It is important to note that the encapsulation methods used during this early period were limited in their ability to precisely control the radiation dose and distribution.

The early sources of radiation had several limitations and safety concerns compared to modern brachytherapy sources. The sources used in the early twentieth century did not provide precise control over the radiation dose, depth, or distribution within the tissues being treated. Handling and disposal of radium and other radioactive materials were not well understood, leading to significant radiation exposure risks for healthcare workers and patients. Many of the early sources had relatively short half-lives, which required frequent replacement and limited their usefulness for long-term treatments. The sources were often inadequately shielded, further increasing the risk of radiation exposure.

[14] Morton ER *A Textbook of Radiology*, EB Treat & Co, New York (1915) pp. 44–50.

5 Issues in Treatment

In the delivery of radiation for treatment, the two basic issues are how much radiation is being delivered to the patient and where it is being delivered. In the early days of radiotherapy, the amount of radiation delivered to the patient was determined by the geometrical and electrical parameters governing the delivery of the radiation, as units of measurement such as the roentgen had not yet been defined. Treatment records recorded such parameters as the tube current, the spark gap, the irradiation time, and the distance between the anode and the skin surface since clinicians were unable to measure the amount of radiation received. In 1902, Holzknecht developed the "chromoradiometer," an early method of dosimetry based on the effect of the radiation rather than the parameters related to the source of radiation.[15] His version used chemical dosimetry, in which the degree of discoloration of small discs of a fused mixture of KCl and Na_2CO_3 was measured. His units, called "H," were based on the degree of discoloration of the discs. The dose required to produce a light erythema skin reaction was determined to be "3H." The "radiometer," developed by Sabouraud and Noiré in 1904, was an improvement over the Holzknecht chromoradiometer. The Sabouraud–Noiré radiometer was based on the coloration of compressed barium platinocyanide. Yet another chemical dosimeter was developed by Kienböck, whose "quantimeter" used strips of silver bromide-impregnated paper to quantify the radiation exposure.[16]

It should be noted that dosimetric methods had not been standardized; all of these methods were concerned with scales used to relate chemical change to biological effects, for example, skin erythema, as a unit for dose had not yet been defined.

In the absence of accurate dosimetry, measurement of input parameters was used to attempt to ensure some level of consistency in radiation delivery. For example, as was noted earlier, a small level of air pressure was necessary in the Crookes tube to generate the electrons that ultimately produced x-rays. It was important to maintain a constant air pressure in the tube to ensure consistency in x-ray output and x-ray energy since both depend on the pressure in the tube. Lower air pressure yields lower output but also higher x-ray energy. Various tubes were designed to regulate the vacuum level inside the tube.[17]

The alternative to controlling the vacuum level is to measure the vacuum level. While this was not able to be done directly, several inventions measured potential across the tube.[18] For example, the spintermeter was a device placed in the x-ray circuit in parallel to the x-ray tube. When the current was turned on, a spark jumped between the two balls (Fig. 2). The balls were then separated until no spark could

[15] Glasser O. "The Evolution of Dosimeters in Roentgen Ray Therapy," Radiology 37 (1941).

[16] Cadogan M, "Robert Kienbðck," https://litfl.com/robert-kienbock/

[17] Belot p 39.

[18] Belot p 44.

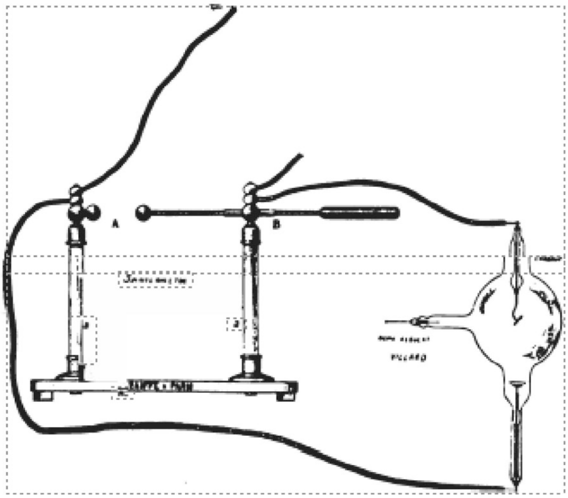

Fig. 2 The spintermeter used to measure potential across the x-ray tube. (Figure from Belot)

jump the gap. The distance of separation was then correlated to the potential across the tube.

The second issue in the delivery of radiation is localization. Ideally, once a region to be irradiated has been identified, the radiation will be delivered to that region and nowhere else. In the early days of radiotherapy, the x-ray tube was fixed on any available support; it had to be placed near the surface to be irradiated, and neighboring tissue was protected with lead sheeting. This localization method had several drawbacks; it was not reproducible, there was a high risk of operator exposure to stray radiation, there was also danger of electric shock if the tube was too close to the patient, and the lead sheeting was heavy and fatiguing. One solution to this problem was to enclose the entire tube assembly with an aperture to emit x-rays defined by a lead sheet with a small opening to allow the insertion of a Holzknecht dosimeter.[19]

6 Clinical Radiotherapy in 1905

In the period 1895–1905, the major application of x-rays for therapeutic purposes was to treat skin diseases. Freund and Schiff in Germany first suggested that x-rays could be used in the treatment of disease.[20] In the United States, Grubbe was the first

[19] Belot, p 63.

[20] MacKee, p 19.

to experiment with the medical use of x-rays,[21] and within several months, many articles appeared in journals regarding the successful treatment of skin disorders.

Still unknown was the mechanism that would explain the action of x-rays on tissue. Freund and Schiff believed it was the electrical discharge that caused the action. Tesla believed it was ozone generated by the x-rays. Finally, Kienbock demonstrated it was x-rays themselves that caused the radiation effects.[22] One of the difficulties in interpreting the results of these experiments was that other types of radiation with different properties, for example, cathode rays, were ejected from the Crookes tube in addition to x-rays.

The early treatment of disease was developed in Germany and Austria. During this period, much experimentation was done using human subjects, including patients and physicians. Alternatively, skin experiments were done on pigs. Clinicians also found that skin reactions also occurred when radioactive sources were placed close to skin, but this did not explain the mechanism for the reaction.

No record was kept addressing the amount of radiation received by the patient. As was mentioned earlier, absence of understanding of radiation dosimetry led to the determination of many input parameters. Figure 3 is an illustration taken from a patient record.

[21] *"Pioneer in X-Ray Therapy". Science. New Series.* ***125*** *(3236): 18–19. 4 January 1957. Bibcode:1957Sci...125T..18.*. https://doi.org/10.1126/science.125.3236.18. *JSTOR 1752791*. *PMID 17835363*.

[22] Belot, p 90.

First Page.

Name: Mr. Smith.

Address: 402 N. Y. City.

Referred by: Dr. N. Y. City.

Date: September 7, 1914. *Age:* 56. *Mar.:* *Sing.:* *Wid.:*

Occupation: Broker. *Nationality:* U. S. A. *Blond:* *Brunette:*

Duration of present eruption: 6 years. *Of disease:* 6 years.

Size: Dime. *Photograph No.:* 806.

Location—Distribution: Center of left cheek.

Diagnosis: Epithelioma (Basal cell).

Family History: Negative.

Past history: Very slow evolution. Has grown more rapidly during past six months. Lesion has never been treated excepting with mild ointments.

Laboratory findings: Small piece of lesion examined in skin department of Vanderbilt Clinic shows anatomical structure of basal-cell epithelioma. Biopsy No. 1, 220.

Present Condition: Lesion consists of a hard mass, elevated ¼ inch. Margin is composed of semi-translucent nodules. Center is crusted. Crust, when removed, shows underlying necrosis.

Second Page.

Date.	Formula.	Filter.	Areas.	Dose.	Remarks.
Sept. 7, 1914	$\frac{2 \times 7 \times 8}{8 \times 8}$	None	Lesion and surrounding skin	H2 S.D.	Curettage under cocaine; skin for ¼ inch outside of lesion treated.
Sept. 25, 1914	....	....	....	....	Mild second degree reaction; wet dressing of aluminium acetate.
Nov. 7, 1914	$\frac{2 \times 7 \times 5}{8 \times 8}$	None	Same as before	H1½ S.D.	Healing is complete; reaction has disappeared; no evidence of epithelioma; prophylactic treatment.
Jan. 15, 1915	....	....	....	....	Erythema after last treatment which lasted one week; clinical cure.
Jan. 22, 1918	....	....	....	....	No return of epithelioma; no sequelæ; almost imperceptible scar; photograph No. 870.

Fig. 3 Actual patient record of radiation treatment (Mackee)

7 Conclusions

In the 10 years from the discovery of x-rays until 1905, radiation therapy was mainly the province of dermatology because of the lack of penetrating ability of the low-energy x-rays produced by sources such as the Crookes tube. Localization of the treatment field was done visually and defined by the use of lead sheets with orifices to allow the passage of the x-rays. Treatment dosage was based on external parameters until such time as chemical dosimetric methods were incorporated in the clinic as ionization dosimetry was still in the future. Little was known about the mechanism for x-ray interactions with the patient as well as the long-term effects of the radiation treatments on uninvolved organs. It remained for later researchers and clinicians to incorporate such improvements into clinical procedures.

Radiant Pioneers: The Dawn of Modern Radiography (1905–1915)

Kamila Rawojć, Beata Malachowska, Oleg Belyakov, Chandan Guha, and Mansoor M. Ahmed

1 Introduction

From 1905 to 1915, the landscape of medical imaging was irrevocably altered by X-ray technology's advent and rapid evolution. This decade, rich in scientific exploration and discovery, marked a pivotal transition for X-rays from experimental curiosity to a cornerstone of medical diagnosis and treatment. The chapter delves into this transformative era, highlighting groundbreaking advancements such as the development of the Coolidge tube and enhanced imaging techniques that revolutionized X-ray production, detection, and application. It pays homage to the visionary pioneers, including Wilhelm Conrad Röntgen and other lesser-known figures, whose tireless endeavors propelled the field forward. By detailing their significant contributions, the narrative shapes an understanding of how these developments irrevocably altered medical diagnostics, paving the way for modern medical imaging practices used to diagnose and treat conditions ranging from bone fractures to tuberculosis and cancer.

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The key innovations, such as the Kienbock method for direct dosimetry and Coolidge's revolutionary work on X-ray tubes, are central to this narrative. These breakthroughs significantly advanced medical science by enhancing the accuracy of radiation dosage measurement and providing stronger, more consistent X-ray beams, which paved the way for today's sophisticated radiographic techniques. Moreover, the period was marked by in-depth case studies that provided critical insights into the long-term effects and challenges of X-ray treatments, particularly in cancer therapy. For instance, the documented treatment of sarcoma with X-rays in 1905 underscores the complexities and gradual progress in oncology, highlighting the persistent need for research and development in this field [1–3]. These studies helped to establish early safety standards and influenced ongoing enhancements in diagnostic accuracy and therapeutic efficacy.

This chapter not only chronicles the significant scientific achievements of this decade but also reflects on the broader implications of these developments for medical technology and patient care. By connecting these historical milestones to contemporary practices, it sets the stage for a deeper understanding of the dawn of modern radiography, illustrating a continuum of innovation from the early twentieth century to the present day. A timeline highlighting these pivotal innovations from 1905 to 1915 is presented in Fig. 1, providing a visual overview of this formative decade in X-ray history.

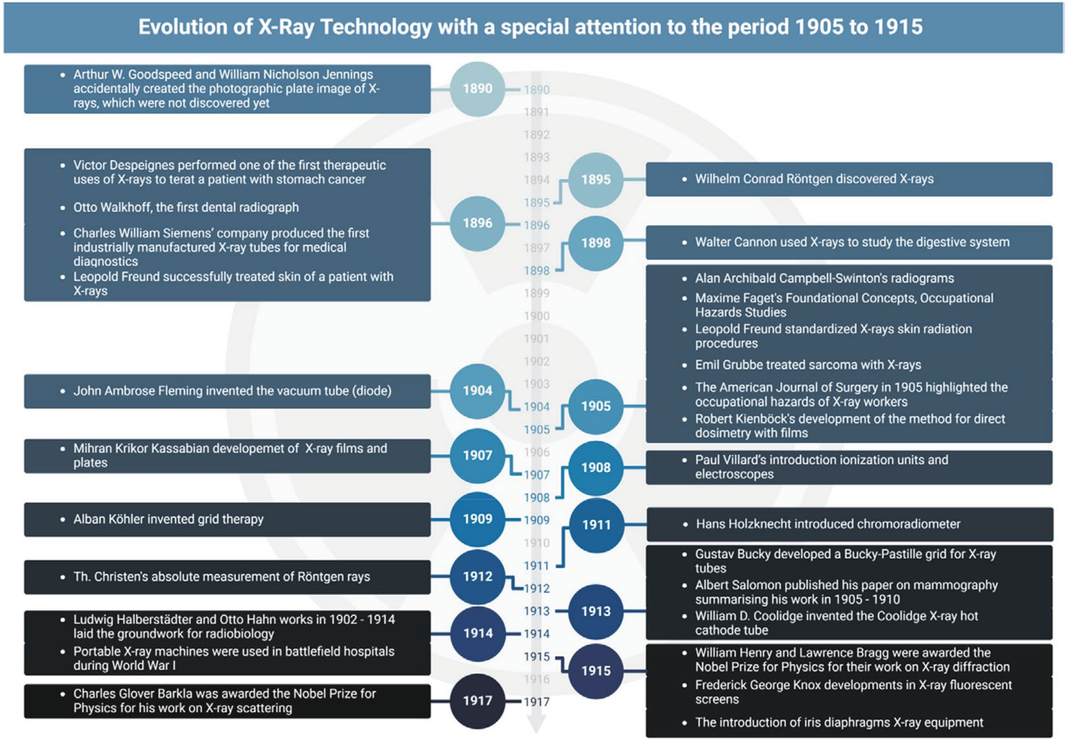

Fig. 1 Evolution of X-Ray Technology with a Special Focus on the Period 1905–1915. This timeline illustrates the chronological development of key milestones in X-ray technology from the discovery of X-rays in 1895 to the post-World War I era. Emphasis is placed on the critical decade between 1905 and 1915, showcasing pioneering contributions in diagnostic imaging, radiation therapy, dosimetry, equipment innovation, and safety awareness. The timeline integrates interdisciplinary advancements made by physicists, engineers, and physicians, highlighting innovations such as the Coolidge tube (1913), Bucky grid (1913), grid therapy (1909), and portable X-ray machines used in World War I. These milestones collectively underscore the foundational role this era played in establishing X-rays as a central modality in modern medical diagnostics and therapeutics

2 Evolution of X-Ray Technology: A Decade of Progress (1905–1915)

The decade from 1905 to 1915 marked a significant period of transformation in X-ray technology, featuring rapid advancements that reshaped medical diagnostics and treatment. In 1905, A.A. Campbell-Swinton introduced pivotal radiograms [1] that significantly advanced early radiography by enhancing image clarity and detail, thereby setting the stage for future medical imaging innovations. During this era, notable improvements in X-ray equipment, spearheaded by Campbell-Swinton, led to the production of more precise images while simultaneously reducing radiation exposure—crucial developments that greatly enhanced patient safety and diagnostic accuracy.

Alongside Campbell-Swinton, other important investigators significantly contributed to this era's transformation. American physiologist Walter Cannon utilized X-rays to pioneer studies of the digestive system, thereby opening new paths in medical diagnostics by allowing noninvasive observation of gastrointestinal processes. Concurrently, Otto Walkhoff was a trailblazer in applying X-rays within dentistry, effectively pioneering dental radiography. His work provided foundational techniques that greatly improved the accuracy and safety of dental treatments, marking a significant milestone in the field.

Physicists like Charles Barkla and William Henry Bragg significantly deepened the understanding of X-ray physics through their studies on X-ray scattering and diffraction, respectively. Their research provided crucial insights that enhanced the application of X-rays in medicine, particularly in improving diagnostic accuracy and safety. Similarly, engineers played a pivotal role in advancing X-ray technology; William Coolidge's invention of the Coolidge tube in 1913 markedly improved the design and operational safety of X-ray machines. In the same year, radiologist Gustav Bucky developed the Bucky-Pastille grid, which significantly enhanced radiographic image quality while simultaneously reducing patient radiation exposure [1–8].

The development of X-ray machines tailored for specific medical applications during this decade underscored the growing importance of this technology in healthcare. These advancements not only demonstrated the adaptability and versatility of X-ray technology but also marked a significant paradigm shift within the medical community. Moving away from more traditional diagnostic methods, such as invasive surgeries and manual examinations, to embrace X-rays improved the precision of diagnoses and the efficacy of treatments, thereby enhancing patient care significantly. This transition represented not just technological advancement but also a transformation in the approach to patient health and safety, setting new standards in medical practices.

This introduction sets the stage for this chapter to delve into specific technological advancements, examine important case studies, and assess the overall impact of these developments on medical science and radiography. Beyond merely documenting technological progress, this exploration recognizes the lasting influence of these early innovations on today's medical practices. The combined efforts of scientists, physicians, and engineers throughout this decade not only advanced the field but also reshaped it entirely, forging a new direction in medical history. As a result, X-ray technology has become an integral part of modern healthcare, reflecting a significant paradigm shift initiated by these early twentieth-century innovations.

3 Early Challenges and Discoveries in X-Ray Technology

The early twentieth century, particularly between 1905 and 1915, was a dynamic period marked by significant challenges and groundbreaking discoveries in X-ray technology. This era witnessed remarkable advancements that would fundamentally shape the future of medical imaging and treatment. Central to these advancements was the work of Th. Christen in 1912 on the absolute measurement of Röntgen rays [2]. His pioneering research was pivotal in enhancing the precision and efficacy of radiation therapy. By providing a method to accurately measure radiation dosage, Christen's innovation significantly improved treatment outcomes across various medical fields, setting new standards for therapeutic applications of X-rays.

During this time, the safety of X-ray operators and patients emerged as a pressing concern, highlighting the urgent need for rigorous safety measures. In 1911, Hans Holzknecht introduced the Holzknecht chromoradiometer, a revolutionary device that transformed the way radiation doses were measured and managed. This innovation not only provided a reliable method for quantifying radiation exposure but also laid the groundwork for standardized dosimetry practices [4]. The development of this technology was crucial in ensuring the safe and effective use of X-rays in medical diagnostics and treatment, paving the way for the adoption of comprehensive safety protocols in radiography.

The era also witnessed significant contributions from other researchers and physicians who furthered the advancement of X-ray technology. Notably, Gustav Peter Bucky, working in the early 1910s, developed the grid-controlled X-ray tube. This innovation greatly improved image quality by minimizing the effect of stray radiation, thereby enhancing both the clarity of radiographic images and reducing patient exposure to unnecessary radiation. Additionally, the early work of Maxime Faget laid foundational concepts that, although gaining prominence later, significantly influenced the development of radiological imaging and safety protocols. His contributions helped to shape the future directions of the field, underscoring the cumulative nature of scientific progress in radiology.

Research during this period expanded beyond the initial fascination with X-rays, delving into their practical applications in medicine. Studies began to reveal the significant potential of X-rays for diagnosing and treating bone fractures and joint diseases, providing clearer insights and more accurate treatment plans compared to previous methods. A chapter discussing the deleterious effects of the X-ray highlighted the comments of Dr. F. Tilden Brown, who called attention to the frequency of azoospermia in X-ray workers [9]. This report underscored the urgent need for improved safety protocols in radiographic practices, leading to heightened awareness and the gradual implementation of safer operational standards.

The exploration of X-rays for treating skin diseases and cancer by pioneers like Leopold Freund and Albert Salomon showcased their immense potential, marking a new era in medical therapeutics. In the early 1900s, Freund pioneered radiation treatment for various skin conditions, significantly advancing therapeutic approaches and patient outcomes. Meanwhile, Salomon's groundbreaking studies using X-ray imaging for breast cancer diagnosis enabled earlier detection and better understanding of tumor characteristics, vastly improving diagnostic accuracy. Together, their work demonstrated the versatility and transformative power of X-ray technology, leading to its widespread adoption in modern medicine.

Furthermore, the contributions of physicists like William D. Coolidge, who developed the Coolidge X-ray tube in 1913 [3], significantly enhanced the stability and control of X-ray emissions. This innovation represented a major advancement over earlier tubes by utilizing a vacuum and enabling precise control over X-ray intensity and focus. These improvements not only led to sharper and more reliable images but also reduced unnecessary radiation exposure, further solidifying the role of X-rays in a wide range of medical applications, from diagnosis to treatment planning.

This period of exploration and discovery not only advanced X-ray technology but fundamentally transformed it from a novel scientific discovery into a mainstay of medical diagnostics and treatment. The early twentieth century's blend of challenges and achievements in X-ray technology represents a remarkable confluence of scientific inquiry, technical innovation, and clinical application. These pioneering efforts laid a durable foundation that has continued to support and shape modern medicine. Today, the influence of these early developments is still evident as they inform ongoing advancements in medical technology, improving diagnostics, treatment, and patient care across the globe.

4 Advancements in Medical Applications of X-Rays (1905–1915)

The era from 1905 to 1915 was a transformative period in X-ray technology, marked by significant technological advancements that profoundly impacted medical practice. A monumental development was the invention of the high-vacuum Röntgen ray tube by W.D. Coolidge in 1913. This innovation dramatically improved the clarity and reliability of X-ray images, enabling more precise diagnostics and safer medical procedures [3]. The Coolidge tube's consistent and controllable X-ray output represented a drastic improvement over the previously used gas discharge tubes, facilitating more accurate diagnoses and setting new standards in radiographic imaging. By providing clearer images, this technology significantly reduced the risks associated with earlier X-ray techniques and improved the efficacy of treatments for various conditions, from bone fractures to internal diagnostics.

Simultaneously, the introduction of ionization units and electroscopes around 1908, pioneered by Villard, marked a significant stride in radiation measurement. These devices, critical for their ability to accurately quantify radiation doses, represented a technological leap forward. By measuring the ionization of air—an indicator of radiation intensity—these tools provided a more precise method for assessing exposure levels, enhancing the safety and effectiveness of radiation therapy. This advancement was pivotal, enabling clinicians to tailor radiation doses with unprecedented accuracy and significantly improving patient outcomes in radiation-based treatments.

In oncology, this period saw remarkable advancements in X-ray technology, notably the utilization of focused X-ray beams for tumor treatment—a novel concept at the time that represented a significant leap forward in cancer therapy. This era also witnessed an increase in clinical research, with numerous studies underscoring the efficacy of X-rays in treating various conditions, including pivotal work in postoperative breast cancer treatments. These studies demonstrated how targeted X-ray therapy could effectively shrink tumors and reduce recurrence, marking a major milestone in oncology and showcasing the therapeutic potential of this technology.

Rich in collaboration and discovery, this period benefited from the contributions of many brilliant minds. These pioneers—physicists, radiologists, and oncologists—worked together to forge new paths in medical science, significantly advancing our understanding and application of X-ray technology in medicine.

Leopold Freund, a physician in Austria, was recognized for performing one of the first documented treatments of a skin lesion with X-rays in 1896, underscoring the therapeutic potential of this new form of radiation. By 1905, he had standardized procedures for skin radiation treatments at his clinic, which significantly improved treatment outcomes and patient safety. Additionally, Albert Salomon, a German surgeon, was among the first to explore the use of X-rays in breast cancer diagnosis, laying the groundwork for modern mammography. His pioneering work, especially notable around the early 1900s, demonstrated the potential of X-rays in detecting tumors and helped establish diagnostic protocols still foundational today [10–13].

Gustav Peter Bucky, a German radiologist, was instrumental in enhancing the quality of X-ray images through the development of the grid-controlled X-ray tube. This significant advancement, crucial for diagnostic radiology and radiation therapy, utilized a grid to reduce scatter radiation, thereby improving image clarity and contrast. This enhancement was particularly beneficial in visualizing and targeting tumors more effectively, leading to more accurate diagnoses and optimized treatment planning [14]. Bucky's innovation marked a pivotal shift in medical imaging, setting new standards for precision in radiographic techniques.

Howard Atwood Kelly, one of the founding professors of Johns Hopkins Hospital, was a pioneer in the use of radium to treat cervical cancer. In the early 1900s, his innovative approach not only demonstrated radium's efficacy in shrinking cervical tumors but also opened new doors for its application in gynecological oncology, influencing future treatment protocols [14].

In France, Victor Despeignes, a physician, performed one of the first therapeutic uses of radiation by successfully treating a patient with stomach cancer using X-rays in 1896. This pioneering treatment showcased the therapeutic potential of X-rays, marking an early foray into the use of this new technology for cancer therapy. Despeignes' work laid foundational insights for the emerging field of radiation therapy, significantly influencing subsequent medical research and clinical applications [14].

Ludwig Halberstaedter and Otto Hahn made significant contributions to understanding radiation's biological effects in Germany between 1902 and 1914. Their pioneering research was instrumental in establishing the foundations of radiobiology, a field crucial for optimizing radiation therapy and ensuring proper radiation protection. Through their studies, they explored how radiation affects living cells and tissues, identifying key mechanisms that impact cell survival and mutation. This knowledge has been fundamental in developing effective and safe radiation treatments, significantly shaping the protocols and safety measures used in modern radiation therapy [14].

These scientists and physicians, among many others, were instrumental in the evolution of radiation therapy. Their collective work, marked by innovation, experimentation, and sometimes personal sacrifice, paved the way for developing more effective and safer radiation treatments. During this period, X-rays were also effectively used to diagnose and treat skin conditions, bone fractures, and joint diseases, showcasing the technology's versatility. The collective impact of these advancements was monumental, establishing X-rays as an indispensable tool in modern medicine and setting the stage for future innovations in medical diagnostics and treatment.

This era's contributions to the field of X-ray technology were foundational, significantly influencing the development of the sophisticated radiographic techniques that are now a staple in medical facilities worldwide. Their pioneering work not only revolutionized medical imaging and therapy but also laid the groundwork for continuous innovation, enhancing both the efficacy and safety of patient care.

5 Technical and Methodological Progress (1905–1915)

The decade from 1905 to 1915 heralded a transformational period in X-ray technology, marked by significant technical and methodological advancements. One of the most notable contributions was Robert Kienbock's development of the Kienbock method for direct dosimetry in 1905 [5]. This innovative technique utilized the blackening of photographic films by radiation to measure exposure, fundamentally changing the standardization of radiation dosage practices. The method revolutionized the way radiation dosages were quantified, significantly enhancing the precision of measurements. This, in turn, improved the safety and effectiveness of X-ray treatments, contributing to more reliable and consistent therapeutic outcomes across the medical field.

In the early days of X-ray therapy, Hittorf-Crookes tubes, the initial devices used for X-ray production, exhibited varying qualities that affected their usefulness. Eugene Wilson Caldwell noted these inconsistencies and advocated for a methodical assessment of each tube's focus using a wire grid. By positioning the grid 8 inches from the focal point, Caldwell could determine the clarity of the shadow produced. Tubes that produced clear shadows were selected for diagnostic imaging, while those with less precise focus were relegated to therapeutic uses, such as X-ray therapy. This practice significantly enhanced the efficacy and safety of X-ray applications by ensuring that only the most suitable tubes were used for imaging.

Eventually, complementing Kienbock's dosimetry innovation, the groundbreaking invention of the Coolidge tube in 1913 by William D. Coolidge marked a significant advance in X-ray technology. A pivotal figure in this evolution was Charles William Siemens, a German-born engineer whose substantial contributions to electrical engineering laid the groundwork for the high-powered X-ray tubes that would later become essential in radiation therapy. Siemens' advancements, particularly in enhancing the efficiency and safety of electrical systems, played a crucial role in developing more reliable and powerful X-ray machines. His work facilitated significant improvements in X-ray tube technology, enabling the precise control and high voltage necessary for effective radiation therapy, as later epitomized by the Coolidge tube.

In 1905, Georg Clemens Perthes introduced a groundbreaking method to harden X-rays through a metal layer, setting a foundational standard for deep radiotherapy. Building on this critical advancement, German radiologist and passionate photography enthusiast Alban Köhler significantly advanced the field in 1909 by developing grid therapy. This technique, designed to address critical challenges in the treatment of massive tumors with intact skin coverage, marked a substantial leap forward in therapeutic radiology.

Köhler's grid therapy involved the strategic placement of a specifically designed metal net or grid directly on the skin's surface during radiation treatments. He meticulously tested this method on a limited number of patients using 60–70 kV X-ray tubes. The X-ray tube's lead-shielded housing was positioned in front of a stiff grid composed of 1 mm^2 iron wires, woven 3.0–3.5 mm on center and tightly attached to the skin over a thin layer of chamois. This setup allowed precise irradiation of the tumor through numerous unshielded islets in the grid, effectively focusing the radiation where it was needed most while protecting the surrounding skin from excessive exposure.

Following the irradiation, the treated skin was carefully cleansed, disinfected, and bandaged, leading to the healing of necrotic points within several weeks—an outcome that was considered optimal for the era [15]. This method demonstrated not only the effectiveness of targeted radiation therapy but also introduced a safer approach to treating deep-seated tumors, significantly reducing the risk of severe skin damage, a common problem with previous radiation techniques.

Köhler's innovation in grid therapy not only addressed a crucial clinical challenge but also laid the groundwork for future advancements in radiotherapy. By achieving a more heterogeneous distribution of radiation doses, Köhler's approach allowed for higher overall radiation doses to tumors while minimizing damage to healthy tissues. His work exemplifies the early application of what would later evolve into techniques of spatial fractionation and modulation in radiation therapy, which are critical components in modern oncological treatments.

Köhler's grid therapy aimed to achieve spatial fractionation of X-rays, ensuring a more heterogeneous distribution of radiation while protecting the skin from unhealable damage. By meticulously refining aperture techniques and advocating for skin anemicization, Köhler significantly improved the therapeutic outcomes of radiation. His pioneering achievements not only propelled the field forward but also laid the groundwork for subsequent advancements in radiotherapy that are used until today. This innovative approach, now known as "spatially fractionated radiation therapy," has been readopted as an important modality for treating bulky tumors. It plays a crucial role in inducing abscopal effects, where localized treatment triggers systemic antitumor responses, and priming for immunotherapy, enhancing the effectiveness of cancer treatments by boosting the immune system's response to tumors [16]. This evolution of grid therapy underscores its lasting impact and continuing development in the field of oncological therapy.

Another notable figure in the advancement of medical technology was William David Coolidge, an American electrical engineer and physicist who revolutionized X-ray technology. In 1913, Coolidge introduced the Coolidge tube, a high-vacuum X-ray tube that significantly advanced the control and quality of X-ray generation. Unlike earlier tubes, which were inconsistent and difficult to manage, the Coolidge tube allowed for precise control over the emission of X-rays, making it possible to produce more consistent and higher-quality images. This invention marked a significant milestone in the fields of radiology and radiation therapy, greatly enhancing the safety and effectiveness of treatments across a range of medical disciplines. The reliable performance of the Coolidge tube also set new standards in the industry, influencing the development of various diagnostic tools and paving the way for future technological innovations in medical imaging.

Gustav Bucky, previously mentioned for his pioneering work in radiology, was also an accomplished engineer and inventor. In 1913, he developed the Bucky-Pastille grid, a device designed to reduce scattered radiation and significantly improve the clarity of X-ray images. This innovation was crucial in the diagnostic aspect of cancer treatment, enhancing the ability of radiologists to detect tumors with greater accuracy and facilitating more effective treatment planning. The Bucky-Pastille grid works by positioning a series of parallel lines that block scattered radiation, which would otherwise obscure the clarity of the diagnostic images. This reduction in noise allowed for sharper images, making subtle differences between healthy and affected tissues more distinguishable [14]. Bucky's development has had a lasting impact on the field of radiology, setting a standard that continues to influence modern imaging technologies and methodologies in cancer diagnosis and beyond.

John Ambrose Fleming, a British electrical engineer and physicist, was instrumental in the early development of electronic devices. His invention of the vacuum tube, or diode, in 1904 was a revolutionary advancement that paved the way for developing more sophisticated electronic equipment. The vacuum tube functioned as a crucial component in controlling electrical currents, which was essential for the later development of complex machinery, including those used in radiation therapy machines. This technology enabled more precise and controlled therapeutic applications, significantly improving the efficacy and safety of radiation treatments [14]. Moreover, Fleming's invention had a profound impact on various fields, laying the foundational technology for early computers, telecommunications, and broadcasting, thereby shaping the modern technological landscape.

Maxime Faget, an engineer whose most significant contributions would later revolutionize spacecraft design, also indirectly influenced advancements in radiation therapy. His pioneering work in developing heat shield technology for spacecraft introduced innovations in thermal control and precision engineering. These principles found a parallel in radiation therapy equipment, where managing heat and precise targeting are crucial for safety and efficacy. For example, the thermal management techniques adapted from Faget's aerospace designs helped improve the reliability and safety of radiation therapy machines, ensuring that they operate within safe temperature ranges while delivering precise doses of radiation. This cross-disciplinary influence underscores how advancements in one area of technology can contribute to critical improvements in completely unrelated fields.

The contributions of these engineers were crucial in overcoming some of the major technical challenges of early radiation therapy. Innovations in electrical engineering provided more reliable and controllable power supplies, essential for operating advanced radiation equipment. Breakthroughs in vacuum technology, spearheaded by the development of high-efficiency X-ray tubes, enhanced the quality and consistency of radiation doses administered during treatment. Additionally, advancements in radiation physics allowed for more precise targeting and minimization of radiation exposure to non-cancerous tissues, significantly improving treatment safety and outcomes. Collectively, these engineering achievements directly impacted the safety, precision, and effectiveness of radiation treatments, demonstrating the vital role of interdisciplinary collaboration in medical technology advancements.

Integrating engineering innovations into radiation therapy was pivotal to this era's progress, highlighting the indispensable role of multidisciplinary collaboration in advancing medical technology. Engineers worked closely with physicians and scientists to create a holistic approach essential for the field's advancement. This partnership enabled the translation of theoretical discoveries and medical advancements into practical clinical applications. For example, the development of precise radiation delivery systems that minimized exposure to healthy tissues was directly facilitated by engineers' expertise in mechanical and electronic design. This collaborative effort not only enhanced the efficacy of treatments but also significantly improved safety and patient outcomes, demonstrating the profound impact of combining diverse expertise to tackle complex healthcare challenges.

Moreover, this era saw the emergence of portable X-ray machines, a remarkable technological leap that expanded the utility of X-rays beyond conventional medical settings. These portable units, notably designed and deployed by Marie Skłodowska-Curie, brought crucial X-ray technology to diverse environments, including battlefield hospitals during World War I. Curie's pioneering work involved not only the adaptation of X-ray units into more compact and transportable forms but also organizing and equipping radiological cars, known as "petites Curies," to serve at the front lines. This innovation significantly broadened the scope of medical care and diagnostics, allowing for rapid and effective treatment of injuries in challenging situations, and transforming wartime medical response [14].

These advancements collectively represented a fundamental shift in radiography, both in terms of technological capabilities and their impact on medical practice and patient care. They laid the foundation for the sophisticated radiographic techniques of the modern era, such as digital imaging and computed tomography, which continue to evolve and improve. By firmly establishing X-ray technology as a cornerstone of contemporary medical diagnostics and treatment, this period marked the transition of X-ray technology from a novel scientific discovery to an essential tool in healthcare. These transformative years were instrumental in paving the way for future innovations and applications in medical imaging, enhancing everything from the speed and accuracy of diagnostics to the efficacy of treatment protocols, thereby significantly improving patient outcomes.

6 Diverse Applications and Long-Term Observations of X-Rays (1905–1915)

Between 1905 and 1915, X-ray technology witnessed significant expansion in its applications and understanding, marking a period of profound influence on medical science. Notably, advancements in X-ray equipment, such as the introduction of iris diaphragms by 1915, greatly enhanced the safety and efficacy of X-ray tubes. This particular improvement allowed for more precise control of X-ray beams, significantly reducing unnecessary radiation exposure for both patients and operators and improving the focus and sharpness of the resulting images. Furthermore, developments in X-ray films, plates, and fluorescent screens were pivotal in enhancing image quality. These advancements provided clearer, more detailed visualizations that were crucial for accurate diagnoses, enabling physicians to detect conditions with greater precision and confidence. Together, these technological enhancements not only improved diagnostic capabilities but also contributed to the overall safety of X-ray procedures, marking a critical phase in the evolution of medical imaging.

This improvement in equipment design, led by engineers like William D. Coolidge, who is renowned for his development of the Coolidge X-ray tube, significantly reduced radiation exposure for both patients and operators. The Coolidge tube represented a major technological breakthrough, providing more controlled and consistent X-ray emissions, which allowed for more precise imaging. This advancement not only improved the safety standards in radiographic practices but also enhanced the quality of the diagnostic images, thereby improving the accuracy of medical assessments and treatments. These enhancements have had lasting impacts, setting new benchmarks in the field of radiology.

In the realm of imaging technology, the pioneering work of Dr. Mihran Krikor Kassabian in 1907 and Frederick George Knox in 1915 was instrumental [7, 8]. They introduced significant improvements in X-ray films, plates, and fluorescent screens, which provided clearer and more detailed visualizations that were crucial for making accurate diagnoses. These advancements enabled physicians to detect and treat medical conditions with greater precision. Additionally, Arthur W. Goodspeed and William Jennings Morton played pivotal roles in refining the photographic techniques used in X-ray imaging. Their contributions significantly enhanced the clarity and utility of radiographic images, facilitating easier interpretation and more effective use of X-ray technology in clinical settings. Together, these innovators significantly advanced the field of radiology, improving diagnostic accuracy and paving the way for further innovations in medical imaging technology.

Incorporating X-ray technology into gastrointestinal diagnostics marked a significant milestone, primarily attributed to the pioneering work of Walter Cannon, an American physiologist. His groundbreaking studies, which involved using X-rays to observe the digestive process, revolutionized the approach to diagnosing digestive tract disorders. Cannon employed novel techniques, such as the administration of bismuth meals, which coated the digestive tract and made it visible on X-ray films, allowing for clear and noninvasive internal imaging [9]. This innovation significantly improved the accuracy of diagnoses and enhanced the ability to assess and treat various gastrointestinal conditions effectively. Furthermore, Cannon's work set the stage for further developments in medical imaging, continuing to influence the field by providing a foundation for more advanced diagnostic technologies.

Therapeutic applications of X-rays saw remarkable growth during this period, particularly in the treatment of various cancers. Pioneers like Leopold Freund and Albert Salomon explored the use of X-rays for treating skin diseases and breast cancer, respectively, laying important groundwork for understanding the therapeutic potential of this technology. Freund developed techniques for targeted skin irradiation, while Salomon's work in mammography provided a critical diagnostic tool that complemented therapeutic uses. Additionally, extensive case studies conducted by researchers such as Emil Grubbe on treating sarcoma and other complex cancers provided critical insights into the long-term efficacy and potential side effects of radiation therapy. These studies were crucial in shaping the understanding of the benefits and limitations of X-rays, highlighting both their curative potential and the risks associated with their use.

Such advancements were revolutionary, not only in treating and managing cancer but also in enabling clinicians to diagnose and plan treatments for gastrointestinal conditions with unprecedented accuracy. This integration of diagnostic and therapeutic capabilities of X-rays reduced patient discomfort and improved treatment outcomes, marking a significant evolution in medical practices.

In addition to diagnostic advancements, the therapeutic applications of X-rays during this period witnessed considerable growth, underscoring their versatility in treating a wide range of conditions from skin diseases to complex cancers. Notably, extensive case studies focusing on the treatment of sarcoma and other malignancies with X-rays provided critical insights into the long-term efficacy and potential side effects of radiation therapy. Researchers documented varying outcomes, which were instrumental in shaping an understanding of both the benefits and limitations of X-rays in medical treatment. These studies guided future research and clinical applications, laying the groundwork for the development of more refined radiation therapy techniques that are still in use today. This body of research has been pivotal in advancing our knowledge and shaping the protocols that ensure the safety and effectiveness of radiation treatments [8, 14, 17].

The cumulative impact of the diverse applications of X-rays during this pivotal decade underscored the technology's growing importance across various realms of medical science. This era of exploration and innovation not only introduced groundbreaking diagnostic and therapeutic techniques but also set the stage for future advancements in X-ray technology. As researchers and clinicians collaborated to push the boundaries of what was possible, they firmly established X-rays as an indispensable tool in modern medical diagnostics and treatment. The foundations laid during this period have continued to evolve, influencing current practices and driving further innovations in the field. The ongoing development of X-ray technology reflects its crucial role in enhancing the precision, safety, and effectiveness of medical care, maintaining its status as a cornerstone of contemporary healthcare.

7 Conclusion and Future Implications

As we retrospectively analyze the decade spanning from 1905 to 1915 in the realm of X-ray technology, it becomes undeniably clear that this was a defining period in the annals of medical science (Table 1). This era was marked by trailblazing advancements that laid the groundwork for modern diagnostic radiology and radiation therapy. The pioneering innovations and discoveries of this time catalyzed a transformation in medical diagnostics and treatment, introducing techniques and practices that have become cornerstones of contemporary healthcare. Innovations such as the Coolidge tube, portable X-ray machines, and refined radiation therapy methods have not only persisted but have also evolved, integrating with digital technologies and computational methods to enhance diagnostic accuracy and treatment efficacy. Looking forward, the continued refinement of these technologies promises further advancements, particularly in precision medicine and personalized treatment plans. As X-ray technology continues to advance, it will likely play an integral role in addressing complex medical challenges, pushing the boundaries of what is possible in both diagnostics and therapeutic procedures.

Table 1 Summarizing the discoveries and advancements in X-ray technology from 1905 to 1915: encapsulating the fundamental discoveries and advances across different aspects of X-ray technology during this crucial decade in medical imaging history

Section	Discoveries
Evolution of X-ray technology: a decade of progress (1905–1915)	A.A. Campbell Swinton's radiograms (1905), Walter Cannon's digestive system studies, Otto Walkhoff's dental radiography, Charles Barkla's X-ray scattering studies, William Henry Bragg's X-ray diffraction work, William Coolidge's Coolidge tube (1913), Gustav Bucky's Bucky–Pastille grid (1913)
Early challenges and discoveries in X-ray technology	Th. Christen's absolute measurement of Röntgen rays (1912), Holzknecht chromoradiometer (1911) by Hans Holzknecht, Gustav Peter Bucky's grid-controlled X-ray tube, Maxime Faget's foundational concepts, occupational hazards studies (1905), Leopold Freund & Albert Salomon's cancer treatment studies
Advancements in medical applications of X-rays (1905–1915)	W.D. Coolidge's Röntgen ray tube (1913), ionization units and electroscopes by Villard (1908), focused X-ray beams in oncology, Freund's skin lesion treatment (1896) & Solomon's breast cancer diagnosis, Bucky's grid-controlled X-ray tube, Howard Atwood Kelly's radium use in cervical cancer, Victor Despeignes' therapeutic radiation use (1896), Halberstaedter & Otto Hahn's radiobiology research (1902–1914)
Technical and methodological progress (1905–1915)	Kienbock's method for direct dosimetry (1905), Coolidge tube (1913) by William D. Coolidge, Charles William Siemens' electrical engineering contributions, Bucky's Bucky–Pastille grid (1913), John Ambrose Fleming's vacuum tube (1904), Maxime Faget's heat shield technology, emergence of portable X-ray machines
Diverse applications and long-term observations of X-rays (1905–1915)	Introduction of iris diaphragms (by 1915), advancements in X-ray films, plates, and fluorescent screens, Mihran Krikor Kassabian & Frederick George Knox's contributions (1907, 1915), Arthur W. Goodspeed & William Jennings Morton's photographic techniques, Walter Cannon's gastrointestinal diagnostics, Leopold Freund & Albert Salomon's therapeutic applications, Emil Grubbe's case studies on sarcoma treatment

The period from 1905 to 1915 was characterized by an interdisciplinary fusion of physics, medicine, and engineering, leading to remarkable breakthroughs in X-ray technology. These advancements were not merely incremental; they represented monumental leaps forward, reshaping the landscape of medical imaging and therapeutic approaches. The introduction of refined X-ray equipment, such as the Coolidge tube, provided more reliable and precise X-ray production. Standardized dosimetry practices emerged, allowing for the safer and more effective application of radiation therapy. Furthermore, the expanded application of X-rays in diverse medical treatments, from cancer to bone fractures, exemplifies the era's profound impact. These innovations laid the foundation for the sophisticated diagnostic and therapeutic techniques we rely on today, demonstrating the enduring influence of this pioneering decade in medical science [14].

Moreover, the challenges and limitations encountered during this pivotal decade, such as the initial underestimation of radiation hazards that led to health complications, underscored the critical importance of ongoing research in understanding and mitigating the long-term effects of radiation exposure. These historical insights have continued to guide and inform the evolution of radiological sciences, playing a crucial role in the development of stringent safety standards and protective measures that ensure patient safety remains paramount. Today, ongoing research efforts focus on refining imaging technologies and protocols to reduce radiation doses and enhance diagnostic accuracy, ensuring that the lessons learned from the past continue to influence and improve contemporary radiological practices.

Early success stories in radiation therapy emerged despite an incomplete understanding of how radiation affected cancer cells. Particularly, patients with skin cancers and superficial tumors often saw notable improvements, which underscored the potential of this nascent treatment modality. However, the early techniques for delivering radiation lacked precision, and the rudimentary nature of the equipment, by today's standards, sometimes led to significant side effects and complications, including severe skin reactions and damage to adjacent healthy tissues.

Despite these hurdles, the medical community recognized the urgent need for enhanced methods and more sophisticated equipment. This recognition spurred ongoing advancements in the field. Driven by the initial successes and the evident potential for improvement, researchers and clinicians worked to develop more refined radiation delivery techniques. These efforts aimed at minimizing exposure to healthy tissues and maximizing therapeutic effects on tumors, thereby reducing complications and improving patient outcomes.

The limitations in understanding radiobiology, particularly the mechanisms of radiation's impact on cells, posed significant challenges during this formative period. Clinicians often had to rely on a trial-and-error approach to determine effective treatment plans, navigating uncertainties about radiation dosages and their effects on different types of tumors. This era's work, however, was instrumental in building a foundation for the more precise and safe radiation therapy methods used today. Despite the rudimentary tools and limited scientific knowledge, the pioneering experiments of this time provided crucial data that helped to refine treatment protocols and improve patient safety. These early efforts laid the groundwork for a deeper understanding of radiobiological principles, which now guide the targeted and minimized use of radiation in cancer therapy, ensuring more effective and less harmful treatments.

Looking to the future, the legacy of this pivotal decade from 1905 to 1915 continues to resonate deeply within the field of radiology. The foundation laid during these years has not only withstood the test of time but has also spurred continuous innovation in medical imaging and radiation therapy. Today, as we stand on the cusp of new technological frontiers, such as the integration of artificial intelligence and precision medicine into radiology, the lessons learned and the progress made during that era remain integral to guiding future advancements. Innovations in imaging software, enhanced automation, and improved diagnostic accuracy directly trace back to early twentieth-century breakthroughs. This era, therefore, can be seen as the genesis of a journey towards ever more sophisticated, safe, and effective radiological practices. These advances are significantly enhancing patient care and medical outcomes, marking a continual evolution that promises to transform the landscape of healthcare further.

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A Community History of Radiation Therapy: Decade of 1915–1925

F. M. D. Brooks, L. Wairiri, and E. Ford

1 Introduction to the State of Radiological Physics Circa 1915 with Special Emphasis on the Life and Work of Marie Curie

The history of cancer therapies and the history of physics are intertwined, especially so in the decade of 1915–1925. This was a period in history when the structure of matter was beginning to reveal itself. The oil drop experiments of Robert A. Millikan and Harvey Fletcher had shown that electrons were particles with quantized charge (1909), and the gold foil scattering experiments of Earnest Rutherford and colleagues (1913) had revealed that atoms contained nuclei [1]. Alongside this, the nature of radiation was beginning to be understood and even used for therapeutic purposes. If much was already known in 1915, a great deal of the credit goes to one person, Marie Curie [2].

In 1915, Madam Curie was 48 years old and the recipient of not one but two Nobel prizes, one in physics and one in chemistry. The first, in 1909, made her the first woman to receive a Nobel Prize, while the second, in 1911, made her the only person to win two Nobel Prizes in the natural sciences. All of this is a testament to her enormous impact on physics and radiological sciences. If one wants to understand the developments in this era, one must understand the life and work of Marie Curie.

Madam Curie was driven by a curiosity to understand nature. As she began her independent scientific career in the late 1890s, her first investigations were into the strange phenomena of X-rays that Wilhelm Röntgen had discovered in 1895. In particular, she sought to better understand an apparently related phenomenon that

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Henri Becquerel had discovered merely months after Röntgen. He had found that photographic films left next to uranium ore would develop dark shadows. It was thought that invisible rays, similar to Röntgen's "X-rays," were causing this exposure. Madam Curie began to investigate this curious phenomenon. Her early experiments with uranium, and then another mineral ore of uranium-dioxide, revealed that there was likely a much more highly active element hidden among the uranium. Curie named this element "polonium." As Curie collaborated with her husband and scientific partner, Pierre Curie, to characterize the polonium, they discovered another element, radium, along the way. They showed that these elements were, themselves, by-products of uranium, and they invented a name for this process of transmutation of one element into another and the subsequent release of particles: "radioactivity."

As interesting as the Curies' discoveries were, it is equally as interesting to consider how these discoveries emerged and, especially, how Marie Curie played such a pivotal role [2]. What were the elements of her personality that enabled such revolutionary discoveries? What was it about her environment that allowed her, in particular, to contribute so meaningfully? Perhaps the first notable characteristic was Marie Curie's hard work and dedication. She had an incredible work ethic. One example of this is the laborious steps that she took to prove the existence of the new "mystery" element that she postulated. The radium was hidden in tiny amounts among the uranium ore, so she had to labor to extract it through physical and chemical refinement. She spent several years working at this until, finally, after refining over a ton of the uranium ore she was able to extract an amount of pure radium salt that could be measured and weighed; 0.1 gram.

A second key to Marie Curie's success was her ability to innovate and invent new techniques that would enable new discoveries. An example of this was her use of the electrometer; a novel device developed earlier by Pierre Curie and his brother. Marie Curie discovered that "rays" from the radium compounds would ionize air within the electrometer chamber and the current in the electrometer scaled linearly with the amount of material used. She had invented the first ionization chamber and could use it to measure what we would later call "activity."

While innovation, creativity, and hard work certainly drove Marie Curie's success, it is also important to recognize the environment that she worked in. As a female scientist in the early 1900s, she was not necessarily set up for success. For example, the French Academy of Sciences had not a single female member, so Curie was barred from presenting her work at their conferences based solely on her gender [2]. However, Mdm. Curie had something that most other female scientists at the time did not, supporters. And chief among them was Pierre Curie. He fully recognized her as an equal scientific partner, and he also understood that her accomplishments would not go unrecognized, unlike his own. The fact that he realized this had very real consequences. In 1903, Pierre Curie and Henri Becquerel were nominated for the Nobel Prize for the discovery of radioactivity and its link with radium.

Marie Curie was not named in this original nomination. However, a member of the Nobel committee, Magnus Gosta Mittag-Leffler, a Swedish mathematician, notified Pierre that Marie Curie was not named. Pierre complained to the committee and pointed out the equal importance of her independent work in this discovery. The Nobel Prize committee revised the nomination and added her name to it, making her the first woman to ever be awarded the Nobel Prize [3]. This is one of many illustrations of the environment and support that Marie Curie found herself in and which allowed her to thrive and make her contributions to science.

By 1915, this early work on radioactivity was a decade in the past but Madam Curie remained interested in the science and application of radioactivity. Pierre Curie, however, was no longer at her side. He had died in 1906 at the age of 46 in a collision with a horse-drawn carriage on the streets of his native Paris. In the midst of this personal tragedy, Mdm. Curie found a way to continue on, following the science and continuing to be supported by others around her. In the decade of 1915–1925, another major event would disrupt the life and work of Marie Curie and many others as well. World War I, the "Great War" in Europe, started in 1914 and lasted until 1918. During these years, scientific research in Europe slowed to a halt but the war was also an arena where Marie Curie and others demonstrated the application of radiological sciences as a life-saving intervention as we will see.

2 Use of Radiation for Oncology Purposes Circa 1915

Since the discovery of the X-ray by Röntgen in 1895, and radium by Marie and Pierre Curie in 1898, the scientific community was abuzz and eager to explore uses of radiation [4, 5]. This decade (1915–1925) was no different. Collaborations from notable figures (and unmentioned researchers) revealed some of the key principles of modern radiation therapy, including radiation fractionation and the oxygen effect, which were built upon and refined in later decades. More practical clinical uses of radiation at this time would include reinvention of radiation in the war period and expansions/refinements in cancer treatment. This decade also saw the expansion of radon use over radium due to the lower cost, leading to the rise of establishments such as the radon cow in Boston, in 1915 [6]. Although we cannot mention all collaborators and their work, as this would make an extremely long chapter, we aim to highlight some work that may have influenced modern radiation therapy.

Science is a continuum, and it would be impossible to attribute it to a singular decade. There will be some overlap and brief mention of the research work predating the chapter's years. We hope that you will continue through the rest of the book for the full detailed account.

The Principles of Radiation Effects in Tissue

Fractionation

Claudius Regaud and Henri Coutard are credited for their critical roles in the advancement of fractionation theory, though Coutard carries the title of the pioneer of radiation fractionation.

The Surrogate Model for Prolific Tumors and Normal Skin Tissue

There was debate around the idea of fractionation during this time. Many of the disagreements centered around high-dose single-fraction cures versus multi-fraction therapy. Some believed multi-fraction therapy to be inferior because it allowed cancerous cells to survive and required weeks of radiation that would cause further damage to normal tissue [7]. Conversely, the pro multi-fraction group based their support on the experiments conducted by Claude Regaud in 1919 [8]. Driven by scientific curiosity, Claudius Regaud conducted experiments with Thomas Nogier in a large subject, the ram, where they explored many different fractionation schemes. Regaud discovered that ram testes could be irradiated, resulting in sterilization, over the course of several weeks without exceeding scrotum skin tolerance. In particular, three doses, delivered 15 days apart, resulted in no damage to the scrotal skin [9, 10]. These findings contrasted with the results for a single high-dose fraction and would later be used to observe the idea of using multiple doses of radiation to malignant tumors and tissues, such as the skin. The single fraction sterilized the ram; however, the scrotum exhibited severe damage. In his design, the testes represented prolific cancer cells while the scrotum was an acceptable model for normal tissue. This outcome for the ram testes only occurred with fractionated treatment, thus Regaud concluded that only with fractionation could the appropriate dose be delivered that would provide curative treatment without exceeding the tolerance for normal tissue [11]. Though this topic would be greatly debated for over a decade after his results were published in 1922, Regaud's research played a vital role in the advancement of multi-fractionation theory. His work highlighted the skin-sparing effects of multi-fractionation and the relationship between radiosensitivity and resistance cycles in rapidly dividing cells and the favorable results from his technique.

The First World War (WWI) slowed down clinical and lab work. Experiments and applications regarding fractionation in cancer treatment began around 1922 by Henri Coutard. He used X-ray therapy in small doses over weeks (instead of one high-dose session) in patients with laryngeal, cervical, and skin cancer [12]. It was through these applications that it was noted that normal tissue recovered well while the tumor was sensitive and responded to radiation. By 1925, a landmark study on radiation for laryngeal cancer was conducted. The study included over 40 patients with early-stage laryngeal cancer who received 6000–7000 Roentgens (60–70 Gy) over 5–6 weeks and was pivotal in today's modern fractionation. It marked the first clinically documented study for radiation for cure of early-stage laryngeal cancer. A truly remarkable feat in this decade [13]. Even though the importance of fractionation could be seen, it was still poorly understood and optimized. The systematic modeling of fractionation and the establishment of standardized protocols did not occur until the 1930s, based on Edith Quimby's research. Trials using fractionation in cervical, prostate, and breast cancer would be used in the later years and are beyond the scope of this chapter.

The Oxygen Effect

The oxygen effect was another key discovery of the decade and remains a key principle of modern radiation biology. It was first described in 1921 on ascaris by Hermann Holthusen in Ascariasis eggs and later observed in 1923 by Edward Petry by observing how oxygen tension affected ionizing radiation effects on vegetable seeds [14–16]. This would lead to the hypothesis of oxygen acting as a radiosensitizer in tumor killing, a hypothesis that would later be developed as the oxygen fixation hypothesis by Peter Alexander in 1962, and is still an active area of continued research.

Radiation Techniques for Clinical Use

Expansions to Radon: The Radium Cow

By 1912, radium (^{226}Ra) became popular among physicians as a potential cure for cancer; however, its prohibitive cost placed it beyond the reach of most. William Duane, a close associate of Marie Curie, sought a more practical alternative and discovered what he termed "radium milk," later officially named radon, which was more accessible for use. Radon (^{222}Rn), a naturally occurring gas, had been investigated for use since the 1900s, but it is also a by-product of radium decay (^{226}Ra->^{222}Rn). It will decay to ^{218}Po with a half-life of 3.83 days. Because the half-life of ^{226}Ra is so much longer than that of ^{222}Rn (1600 years vs. 3.83 days) if radium is encapsulated, it creates daughter particles of ^{222}Rn and comes into equilibrium with these. The radon can then be "milked" from the encapsulated source. In 1915, Duane constructed Boston's first radium "cow," a device designed to extract radon gas from radium, enabling thousands of patients to receive treatment [17].

During WWI, the application of radon for wound healing made it more popular than radium. Further, for a time, radon would replace radium for use in cervical, prostate, and head and neck cancer brachytherapy in most hospitals. However, the surge in radon use would be short-lived as it would later be declared a villain, a carcinogen, by the turn of the century, details of which are beyond this chapter.

Advances in Brachytherapy

The story of brachytherapy started with a gift, back in 1903 when Pierre Curie (husband and partner of Marie Curie) gifted his friend Henri-Alexander Danlos some radium. Together they sought ways into which they could implant radium into tumors. This saw the development of early radium implant techniques for gynecological cancers by Dr. Margaret Cleaves (New York, 1913) where radium sources were inserted manually [18]. Unsurprisingly, these early methods of application saw uncontrolled exposure with no standardized dose and severe radiation side effects, including severe rectal, bladder, and vaginal damage from uncontrolled exposure. To address the dose inconsistencies and complications, cervical cancer brachytherapy systems were developed in various parts of the world, conveniently named after the city in which they were invented. The systems, Stockholm (1910), the Paris method (1919), and the Manchester method (1938) were a way to standardize consistent dose delivery.

The Paris method, developed by Claudius Regaud, Henri Coutard, and his associates at the Radium Institute, used an equal amount of ^{226}Ra in the uterus and vaginal applicators with treatment completed in a single fraction [19, 20]. They later adopted the method of using fractionation, incorporating Coutard's prior work, thus establishing fractionation's role in minimizing tissue damage. The Manchester method (1938), a pivotal technique in modern HDR brachytherapy, will be discussed in the relevant decades of the book.

Various applicators were used to deliver doses within close proximity of the tumor in the 1900s. The earliest versions of the applicators lacked shielding and delivered exceedingly high doses to both the tumor and normal surrounding structures. Physicians using these applicators were also exposed to high doses of radiation during procedures. Ernest Rutherford's pioneering work in the early 1900s laid the foundation for the concept of using sealed containers for radium to control exposure. And Robert Abbe was one of the first American physicians to implant radium in tumors, thus laying the groundwork for brachytherapy applicators for gynecological, prostate, and skin cancers [21].

Teletherapy

Many radiation oncology applications relied on brachytherapy approaches during this time period; however, treatment with external beam or teletherapy ("treatment at a distance") was also known and being explored. While linear accelerators and Cobalt beams would not appear until the 1950s, teletherapy was being explored in these early years with radium sources and with X-ray tubes. An important locus for research and development was Memorial Hospital in New York, which would later evolve into Memorial Sloan-Kettering Cancer Center [22].

In 1915, a medical physicist by the name of Gioacchino Failla (1891–1961) was hired as the first Director of Medical Physics and Chief Medical Physicist at Memorial Hospital [23]. In 1916, Failla was appointed to operate the radon plant to create radon seeds; however, his interest in radon far exceeded day-to-day plant operation responsibilities. Much of his career was dedicated to acquiring a deep fundamental understanding of the biology and physics of emitted radiation, and he led the first medical physics group in the United States to prioritize research related to understanding the biological impact of radiation exposure [23].

Just 2 years after his appointment, Failla developed the first external beam radium therapy device called the "radium bomb" or "radium elemental pack," shown in Fig. 1 [24, 25]. The device was a radium-based teletherapy unit that was designed to deliver radiation to treat cancer in the abdomen, brain, or chest. The "radium elemental pack" consisted of 4 Ci of radium housed in a lead cylinder that was lowered from the ceiling on a pulley device to rest within a few centimeters of the patient's skin [24]. Memorial Hospital was in possession of 9 grams of radium at the time, an incredibly valuable resource and more than any other place in the world at the time [26].

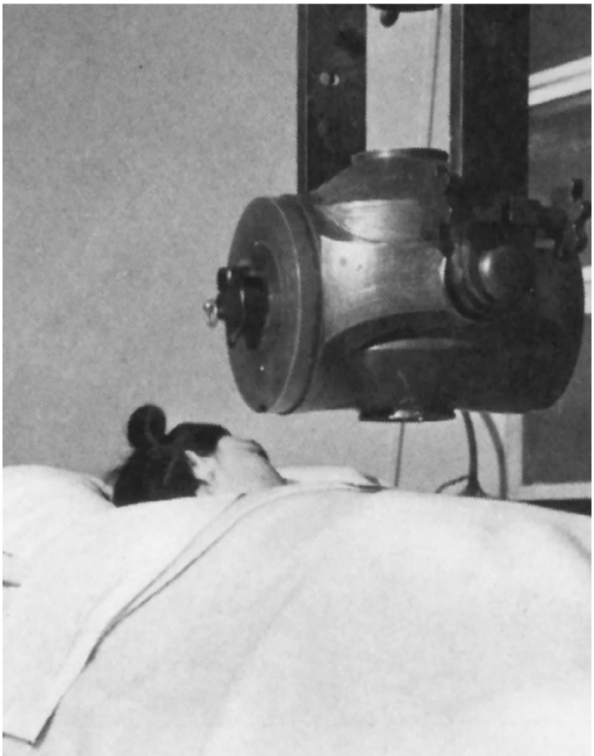

Fig. 1 A patient being treated with external beam radiation therapy using the "radium element pack" at Memorail Hospital

Development of Radiation Dose Standards

It is recorded that Failla was the first person to suggest that radiation doses should be expressed in terms of absorbed radiation energy [27]. He was also the first to estimate radium dose as a function of micro calories per cc of tissue in 1921 [9]. That same year, Edith Quimby (1891–1982), whom Failla hired as an assistant physicist in 1919, created radiation dose tables designed to select the appropriate dose to treat different types of cancer [28]. These tables provided an effective standard that could be easily adopted by clinics to provide a straightforward method for delivering effective radiotherapy. Quimby's standards eliminated the need for using complex algorithms unique to each patient. The following year, after his laboratory received an X-ray unit, Failla developed the first human phantom in the United States to study the effects of filtration and distance on X-ray fields in the body [29]. And after taking a sabbatical to earn his doctorate, with Marie Curie as his advisor and committee chair, Failla published protocols and equipment descriptions that focused on accurate dose delivery.

The work spearheaded by Failla and Quimby was instrumental in the development of radiotherapy techniques. What started as a temporary employment opportunity turned into a 40-year working relationship that would see an incredible amount of novel research. Failla and Quimby were colleagues until Failla's tragic death at the age of 70 in a car accident in 1961.

Emerging Case Reports, Clinical Trials, and Publications

Many clinical trials in Europe and America were performed during the decade 1915–1925, some of which are highlighted below. It would be impossible to document them all as we are limited to time and space. We, however, acknowledge that they all played a part in how radiotherapy exists today.

From 1915 to 1924, the Mayo Clinic documented patients who were treated with radium for cervical cancer. The list includes operable, borderline, nonoperable, and modified cases (patient who received any previous treatment). The study consisted of an impressive review of 1094 cases; 91.5% of which included follow-up data. Bowing et al. report that after 5 years, 75% of the patients who were in the operable group and 61.53% of the patients in the borderline group were still alive after 5 years. Unfortunately, only 21.49% of patients in the inoperable group and 24.82 patients in the modified group were still alive after 5 years. The results from this study highlighted the critical importance of early detection and diagnosis.

In 1917, "Radium Therapy in Cancer at the Memorial Hospital, New York" was published by Henry Harrington Janeway, the head of the radium department at Memorial Hospital at the time, providing a comprehensive documentation on radium therapy used for various cancers between 1915 and 1916. Disease sites included head and neck, genitourinary, and gastrointestinal cases; more specifically, uterine, cervix, esophagus, stomach, testes, and skin. Janeway published many articles throughout his career and became a renowned scientist in the therapeutic use of radium [30]. The American Radium Society sponsors an award in his honor, The Janeway Medal, which is presented based on an individual's contributions to the scientific community.

Henry Louis Hilgartner is credited with being the first to treat retinoblastoma with external radiation therapy in 1903 [31]. While the short-term results were described as excellent, there is no record of long-term follow-up. The first documented cure of retinoblastoma, with long-term follow-up data, was initially treated by Fredrick Herman Verhoeff, in 1917 [32]. The histopathology was recorded and published over 70 years later (Marcus et al) after the patient had passed away.

Radiation for Breast Conservation: Postsurgical Bed Irradiation

Sir Geoffrey Langdon Keynes (1887–1982) developed another notable technique. After returning from WWI, Keynes began working as a physician at St. Bartholomew's Hospital in London [33]. The high mortality rate, coupled with the lasting physical and psychological damage associated with radical mastectomies at the time, caused Keynes to question the standard of care; specifically, the "Halsted radical mastectomy [34]. William Halsted (1852–1922) was a prominent surgeon who advocated for other surgeons to locally resect all suspicious tissues, including the areola, nipple, breast tissue, chest wall muscles (pectoralis major and minor), and all axillary lymph nodes when performing radical mastectomies; the list expanded over time [35]. Keynes argued against what he ultimately considered to be mutilation and began experimenting with injecting tumors with 50 mg of radium. He observed significant changes in the tumor size and pliability, which fueled his conviction that only the cancerous tissue required removal. These findings supported his arguments that radical mastectomies might not be necessary.

Keynes began his trials shortly after starting at St. Bartholomew's Hospital. He spent several years investigating the impact of injecting radium chloride into breast cancer tumors, post-conservation surgery, on patient outcomes. Despite the very promising results that demonstrated equivalent survival rates to Halsted's radical mastectomy, it would be many years before the results of his work would gain serious traction in the oncology community.

Interstitial Prostate Treatment

Urologist Benjamin Barringer (1877–1953) is arguably the first person to use an interstitial technique to treat prostate cancer. He began his career at Memorial Hospital the same year as Gioacchino Failla, in 1915. By the time Barringer started, Memorial had already established a radon purification system thanks to the work of biophysicist William Duane (1760–1835). Duane built a radium emanation (first daughter product of radium decay) plant at Memorial based on his prior research work with Marie Curie and his experience building a radium emanation plant at Collis P. Huntington Hospital [37]. Berringer encapsulated the gas in glass capillary tubes that he used to insert into the posterior prostatic lobe, through the perineum, with 18-gauge needles [36]. He also delivered the treatment in a single fraction, 4–6 h long, repeated every several months depending on tumor response, instead of the common approach of delivering dose over several weeks. Other urologists used radium (much larger) capsules placed within a cavity (along the anterior rectal wall, urethra, bladder neck, and perineum) to the prostate over several weeks. Barringer's technique reduced the dose to the surrounding organs and allowed for greater dose to be delivered to the prostate [36].

Within a few years, Barringer began using glass encapsulated radon as permanent implants. Unfortunately, this new technique caused his patients a lot of pain when the necrotic tissue began to shed. However, once Failla determined that unfiltered beta particles were the issue, he developed a 0.3-mm-thick gold capsule replacement. The new casing filtered 99% of the beta particles and transmitted approximately 80% of the gamma rays. The implants contained approximately 1.5–2.0 mCi of radon and were placed to provide 4000 mCi-hr of treatment. This technique and the gold radon seeds were used for many decades [37].

Despite the initially favorable outcomes, the majority of his patients relapsed. To address this, Berringer experimented with external irradiation using Failla's radium bomb or a 200 kV tube. Skin reactions were the limiting factor in both cases. When he determined that the primary cause for a poor outcome was how advanced the disease was at diagnosis, Berringer began advocating for routine prostate exams for men over the age of 50 [36].

Research Programs and Training Programs

The Radium Institute

Numerous laboratories and investigators around the world were performing research on radiation and its biological effects during this time period, but arguably none were more important than the Radium Institute in Paris. First proposed in 1909, its focus was on the intersection of physics and biology and was founded on the principles and work from the Institute Pasteur and the University of Paris. In 1912, Dr. Claudius Regaud was appointed as the head of the cancer services department of the Radium Institute. Later the same year, Regaud crossed paths with Marie Curie, who had just received her second Nobel Prize, and he eagerly offered a laboratory to her and her colleagues to facilitate collaboration. Unfortunately, construction of the Radium Institute was completed at a rather inconvenient time, 1914, just before the beginning of WWI.

3 Use of Radiation and Irradiation During WWI (1914–1917)

WWI was a rather interesting time for the use and reinvention of radiation [38]. The works of Marie Curie and Claudius Regaud were rather prominent in this period. However, cancer research significantly slowed down. Radiation resources and applications were tailored to cater to the injured combatants, including those developed at the Radium Institute, which became a military hospital during the war [39]. Marie Curie resourcefully harnessed her expertise into organizing mobile X-ray units, known as “Little Curies,” which were deployed in 1914 during the Battle of Marne for use in the field so that surgeons could locate bullets and fractures more effectively.

Meanwhile, Claudius Regaud’s efforts were redirected to the establishment and oversight of various military hospitals. Regaud notably coordinated multidisciplinary teams for surgery and was appointed director at the School of War Surgery at the Hospital of “Bouleuse/Aubilly/Ste-Euphraise.” He also experimented with different fractionation schemes for delivering radium therapy to those suffering from various injuries, including gunfire or chemical burns, ulcerations, and frostbites wounds.

Radon was used in British and German military hospitals for similar types of injuries. Although the exact mechanism was not well understood or described, radiation was believed to stimulate the healing process and prevent infections in the body. Unfortunately, the liberal use of radiation during the war provided many opportunities to study its side effects. These consequences of unregulated radiation exposure and the emergence of radiation safety measurement are described later in this chapter.

After the hiatus in research during WWI, scientists were eager to get back to their work, as would be demonstrated in the accelerated number of innovations and clinical trials using radiation for cancer treatment.

4 Risk and Safety: What Was Known About Exposure Risks Circa 1915–1925?

There is much evidence supporting the numerous incidents of radiation-induced injury and death during the years leading up to 1915. However, there was a distinct disconnect between the individuals who suffered from radiation exposure and the scientific community and public at large. Early radiation workers, especially those serving during WWI, bore the tragic repercussions of prolonged or frequent radiation exposure without recourse for legal action. Several types of x-ray equipment, including x-ray vehicles, outfitted with an x-ray machine and darkroom equipment, powered by an electrical generator, were operated by unshielded medical workers. Conversely, during the same time period, medical professionals were extolling the virtues of radiation exposure, con artists joined the marketing campaign for their own gain, and the public accepted radium as the new "cure all."

During the early years of WWI, as radiation was gaining popularity as a novel and effective method for treating cancer, the notion that radiation was generally "good for you" became widely accepted as well. Companies marketed radium-infused drinking water, cosmetics, household cleaning products, and personal hygiene products. Licensed and fraudulent medical practitioners alike capitalized on this idea and radiation became known as a "cure all" for diseases or maladies and a natural enhancement to maintain good health. Fortunately, some companies made false claims regarding the radioactive contents of their products. Bailey Radium Laboratories, based in New Jersey, manufactured Radithor, a radioactive patent medicine, from 1918 to 1928 [40]. William J.A. Bailey owned the company and was the lead operator. It is reported that he dropped out of Harvard and was not actually a medical professional. Radithor, an expensive elixir selling for an estimated $1 USD per ounce, was created by mixing ^{226}Ra and ^{228}Ra with distilled water (Fig. 2: courtesy of ORAU [41]). Radithor was marketed as "perpetual sunshine" and as a "cure for the living dead," which frankly was a terrible foreboding to those who consumed it (ORAU). The elixir was also reputed to eliminate the effects of impotency. Unfortunately, a wealthy young man by the name of Eben Byers became well

Fig. 2 Radium drinking water from Standard Chemical Company contained two micrograms of radium. The label specifies the dose as "the entire contents of one bottle after each meal"

known for his enthusiastic consumption of the deadly product. It is recorded that Byers consumed nearly 1500 bottles [40]. At the time of his death, 5 years after his initial consumption, Byers had several types of cancer and had lost his jaw due to radiation poisoning. His body was buried in a lead-lined coffin and when exhumed over 30 years later, emitted over fifty times the amount of radioactivity that would be expected of the levels of ^{40}K that are naturally present in a human body [42].

Shoe stores appealed to customers with promises of a perfect fit based on images taken with their pedoscope (Fig. 3: [43]), a device that delivered over 1 Gy to individuals. These devices remained in use for decades even after medical knowledge was more readily available and in circulation; pedoscope units were equipped with warnings to limit use to no more than 2 R per 5 s exposure and children were not to receive more than 12 exposures per year (ORAU).

Unfortunately, also during this period, industrial manufacturers discovered that, when mixed with zinc, radium would glow bright green in the dark. This was an important discovery that led to the development and usage of radium paint to add nighttime visibility of clocks and other equipment. In 1914, amid the increasing demand at the start of WWI, the United States Radium Corporation (USRC) was founded and began employing young women as clock dial painters [44]. The young painters would mix their own paint using radium powder and various materials. Their hair, skin, teeth (from personal application), and clothes would glow as a result of the dust from the powder, thus earning them the nickname “ghost girls.” Painting the dials required exceptionally fine and precise brushstrokes. The young

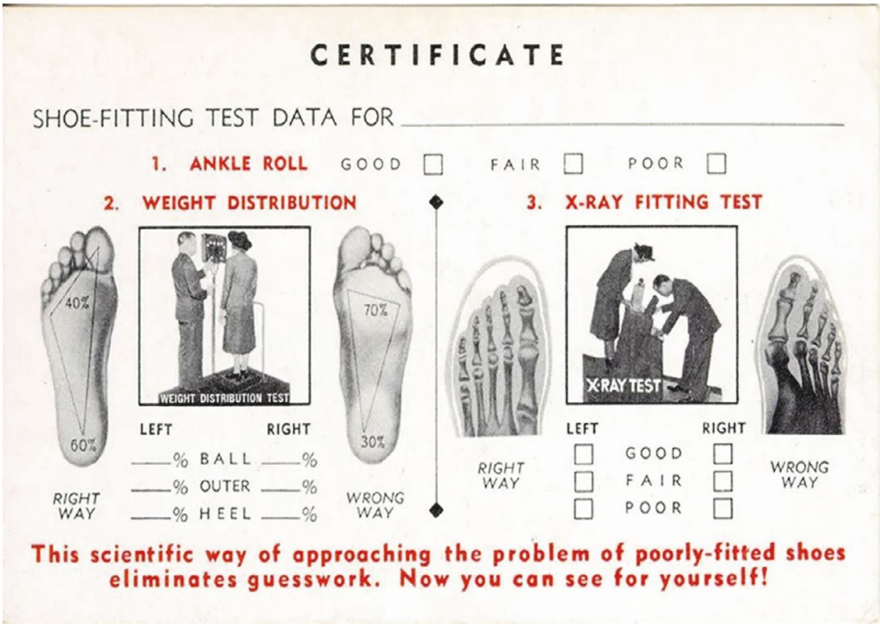

Fig. 3 Radium-based shoe fitting certificate

women were instructed to maintain a sharp brush tip by molding it with their lips and tongue. This practice required frequent brush shaping and subsequent radium ingestion. Despite the number of women who became ill, due to their occupation, the employers at USRP were adamant that the radium paint was so diluted that it was in fact “harmless.”

Meanwhile, the scientists and owners at USRC took great care to avoid radium exposure as they understood the real danger it posed to an individual’s health. Lead screens, tongs, and even masks were available for scientists working with the toxic material. Surprisingly, there is evidence that USRC provided written documentation detailing the harmful effects of radium, to the medical community while denying the hazardous impact of radium paint on the lives of their employees. They managed to keep the dangers to their employees a secret by compelling researchers, doctors, and dentists to deny the link between the deteriorating health of the dial painters and high radium exposure, and by falsifying reports that described how contaminated the working environment was [44].

Despite reports of cancer, radium jaw (necrosis of the jaw), anemia, bone fractures, oral lesions and ulcers, tooth extractions that failed to heal, suppressed menstrual cycles, and infertility (all signs of acute radiation syndrome) the USRC attributed the increasing number of health issues to the x-rays the young women were receiving to investigate their poor health. In 1922, Amelia “Mollie” Maggia was the first dial painter to pass away. It is reported that her jaw became fully detached from her face before her death. Many more young painters fell ill and died from radium poisoning after Maggia [45].

In spite of the growing amount of evidence against the safety of radium paint, the USRC continued to deny any responsibility to its employees, and continued to hire “medical professionals,” many of whom were inexperienced and, in some cases unlicensed, to spread false information in an effort to avoid legal repressions and insurance claims. In 1925, Frederick Flynn, a toxicologist from Columbia University, offered to examine Grace Fryer after she began investigating whether her declining health was linked to her work at the U.S. Radium Corporation (USRC). Flynn assured Grace that she was in good health, echoing the earlier diagnosis of his colleague. However, it was later revealed that Flynn was not a licensed medical professional and was actually serving as a vice president on USRC’s payroll [44].

Over the next several years after Maggia’s tragic passing, lawsuits were brought against the USRC. When the case was eventually settled, 6 years after Maggia’s death, most of the plaintiffs had passed away due to radium poisoning. Through their horrific suffering, the case of the radium girls brought much-needed attention to the plight of radium-exposed individuals and the need for standardized occupational and public safety guidelines.

You One may wonder how it could be possible that so many people could fall victim to radium poisoning when there were many scientific bodies that were aware of and produced guidelines for worker safety. Recall that media coverage was much different in the early twentieth century and the USRC compelled those in the scientific community to suppress the information. It took the sensational story of the radium girls, with over 50 deaths in a few years, and hundreds more who suffered from lifelong ailments, to galvanize the scientific community to act. This horrific tale motivated the community to be more intentional about raising public awareness that would later lead to federal guidelines and requirements. Many other organizations, labor laws, and new legal precedents, dedicated to radiation safety standards, were born from this case.

5 Professional Societies and Standards Bodies

It is important to note that during the early years of the war there were societies that recognized the importance of radiation safety and provided guidelines. For example, the British Röntgen Society published safety guidelines for x-ray operators in 1915, the British Association for the Advancement of Radiology and Physiotherapy (BARP), which became the British Institute of Radiology, was formed in 1917 [46, 47]. Boice et al. went on to report that the American Roentgen Ray Society established the first standing committee on X-ray protection in 1920, with protection guidelines that were in accord with those established by the British Röntgen Society. Next, the American Society for Radiologic Technology and the Society of Radiographers in the United Kingdom were founded in 1920. And in 1921, the British X-ray and Radium Protection Committee made recommendations to address the increase in use of radium in the clinical setting and worker safety. The American Registry of X-ray technologists gave the first radiation safety certification examination in 1922. In 1925, the First International Congress of Radiology (ICR) was held [47]. The ICR established an X-ray Unit Committee and was tasked with setting up an International Committee on X-ray Units; they would eventually become the International Commission on Radiological Units (ICRU).

This decade (1915–1925) also saw the formation of a number of professional societies that focused on radiological sciences, clinical practice, and standards. Starting in 1915, the Western Roentgen Society was founded in Chicago, and in 1920 this would become the Radiological Society of North America (RSNA) that is still active today [48]. Next, in 1916, the America Radium Society (ARS) was formed with financial support from a radium company and remains active [49]. Finally, in 1923 the American College of Radiology (ACR) was founded in California by Albert Soiland, an early pioneer of the specialty, who also successfully lobbied the American Medical Association to recognize radiology as a recognized medical subspecialty [50].

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1925–1935: Radiation Oncology's Collaborative Path from Empirical Applications to Biophysical Efficacy

Malcolm Heard

1 Introduction

During the decade from 1925 through 1935, there were several major events that had a global impact. The US stock market crash in October of 1929 led to the Great Depression over the following decade. The market crash also had an impact on global trade, employment, and political stability. The decade also experienced the rise of Fascism and Nazism in Italy and Germany, respectively. Similar movements also occurred in other countries, thus changing the political landscape globally. In addition, Japanese Expansionism destabilized Asia and impacted international relations. Despite events occurring within individual countries, they had an impact on the entire continent and caused chain reactions lasting decades. These events highlighted the ways the world had become interconnected. Economic shocks, political ideologies, and scientific discoveries in one place had significant effects globally.

Radiation oncology was also impacted by these global events. The Great Depression impacted funding for technological developments in several countries. While the rise of Fascism and Nazism resulted in the persecution of scientists and clinicians. This caused a loss of expertise in Europe and stunted the growth of radiation oncology in those countries. Despite these challenges, radiation oncology continued to advance as a promising treatment modality.

Henry S. Kaplan described the first 25 years of radiotherapy as the "dark ages" due to the considerable handicaps clinicians encountered [1]. There were no reliable methods to measure dose, the equipment was very temperamental, and the energies used for treatment were quite low in comparison to the megavoltage energies utilized "today" [1]. The decade from 1925 to 1935 saw technological developments in x-ray tubes allowing for more skin sparing while increasing the depth of treatment. There was continued development of brachytherapy techniques using radium

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and the application to new treatment sites. There was also evolvement in the fractionation patterns used for treatment as clinicians sought to improve the effectiveness of their treatments while minimizing side effects. Perhaps the most significant growth that occurred during the decade was the increase in international collaboration. The collaboration resulted in the establishment of scientific meetings, the birth of radiation dosimetry, and the establishment of an international unit of dosage.

2 Advancements in Radiation Technology

Evolution of X-Ray Machines

Many of the scientific and technological developments during the decade of 1925–1935 resulted in improvements in the precise delivery of modern radiotherapy. The First International Congress of Radiology was held in 1925 in London, England [2]. This meeting was the catalyst for significant technological growth during this decade. The British Institute of Radiology invited delegates from several countries to attend the meeting. The meeting included presentations of physics, electrotherapy, radio-diagnosis, and treatment by radium and x-rays. During the congress, there were several discussions on the need for more effective radiotherapy that could reach deeper tumors and effectively kill cancerous cells. Dr. Casman from Antwerp discussed using a multi-modality approach of x-rays, radium, and surgery to treat breast cancer [2]. Dr. Casman presented observations that x-rays alone may not be enough to ensure sufficient dose to the tumor, and the addition of radium tubes inserted into the tumor was effective [2]. Dr. E. H. Zweifel from Munich presented the experience of using radium and x-rays to treat cancer of the uterus [2]. There were several other clinical observations presented of insufficient tumoricidal dose at depth that resulted in an increase in tumor growth following treatment with x-rays and radium [2]. The meeting included discussions around treatment techniques, dosage, and the limitations of existing equipment in radiotherapy.

By 1925, radiotherapists were commonly using 200,000-volt x-ray tubes for treatment. In 1913, William D. Coolidge designed and produced the hot cathode tube that allowed for stable operation of the x-ray tubes at 200,000-volt potential. Coolidge also developed a 700,000-volt unit that was installed at New York's Memorial Hospital in 1932 [3]. Gioacchino Faila, a physicist at Memorial Hospital, used the new unit along with the 200,000-volt unit and radium sources to perform studies that compared the biological effects of each form of radiation [3]. Around the same time, General Electric X-ray Corporation partnered with Memorial Hospital to test a 900,000-volt machine for clinical treatments [3]. The size of the tube and generator required the construction of a separate building adjoining the hospital [4]. As a result, a lead-lined treatment room was constructed to protect hospital personnel [4]. The machine was typically operated at 700,000 volts when used to treat patients and provided more penetrating power compared to 200,000-volt machines [3]. The unit when operated at 700,000 volts and 5 milliamperes had an emission equivalent to 450 grams of radium [4]. This amount of radium would have cost $22 million dollars in 1932 [4]. Faila presented the results of his study at the Fourth International Congress of Radiology in 1934. Ralph Herendeen, chief of roentgenology at Memorial Hospital, and his colleagues used the newly developed technology to deliver 25,659 treatments in 1933 [3]. These advancements laid the groundwork for the megavoltage era several decades later.

Development of the International Unit of Dosage

One of the most significant discussions of the First International Congress of Radiology was the need to establish an international unit and standard for radiation. This development represented a critical juncture in ensuring both the efficacy and safety of radiation therapy. Participants of the Congress determined there was a need to develop a standard type of x-ray beam with a constant voltage apparatus as a first step in the determination of an international unit [2]. A resolution was adopted at the meeting to establish the International X-ray Unit Committee to study the question of measurement of this unit. Discussions also included the need for a standard machine capable of generating a constant voltage and current to help establish this unit of dosage [2]. This underscored the intertwined challenge of equipment standardization and the definition of a dose unit. In 1928, at the Second International Congress of Radiology, a provisional unit called a Roentgen, designated by the symbol r, was introduced as the international unit by the committee [5]. The concept of ionization produced in air became central to the definition of the roentgen. Failla presented his work in developing a standard open-air ionization chamber that was instrumental in establishing the provisional unit [6]. These chambers were designed to measure the ionization produced by the primary x-ray beam in a defined volume of air, avoiding secondary and scattered radiation effects [6]. This definition remained unchanged until 1937 at the International Committee for Radiological Units.

Innovations in Dosimetry

Leading up to the decade, clinicians often observed inconsistent outcomes in patients undergoing radiotherapy. Some patients experienced clear benefits, others found it ineffective, and some were harmed. This variability underscored the urgent need for accurate dosage measurement. Prior to this decade, attempts at dosimetry were made using thermometers or bolometers as a method to determine the total energy output of the radiation source and lacked direct clinical applicability [6]. Clinicians estimated the radiation dose for treatment by observing the time it took to cause epilation or erythema [6]. This continued for some time, even after the establishment of the Roentgen, as there was no methodology to determine the dose received by the patient's skin. Moreover, clinicians could not determine the dose at depth within the patient.

Physicists continued to make improvements in the accuracy of measuring dose using the ionization chamber. After the establishment of an international unit using a standard ionization chamber, several countries developed their own standards that enabled their secondary (national) standard to be calibrated. This allowed the countries to have traceability back to the international primary standard. International comparisons using these standard ionization chambers were very desirable at the time. The first versions of the standard chambers were heavy and difficult to transport, until a smaller version was developed in 1928 that enabled many countries to find 4–5% agreement between their national standards [6]. In 1930, L. S. Taylor further refined the design and developed a portable guarded-field ionization chamber [6]. This ionization chamber was used in a direct intercomparison between the United States, England, and German with an agreement of 0.5% [7].

Ionization chamber design improvements enabled clinicians and physicists to better understand radiation interactions within the body. Edith H. Quimby performed experiments to correlate the amount of radiation dose, Roentgen, required to trigger specific biological effects [8]. Physicists used ionization chambers to measure radiation absorption curves within the depth of a paraffin phantom [6]. Measurements of x-ray beam quality were also performed using concentric shells of copper surrounding ionization chambers [6]. By the time of the Second International Congress, the need for a standardized way to describe x-ray radiation was already recognized. At the Third International Congress, agreement was reached that the tube voltage and the half-value layer (aluminum or copper) should be used to describe an x-ray beam [9].

The development of ionization chambers also enabled the standardization of x-ray machines. The roentgen output was measured using an ion chamber, and this was correlated to an erythema dose [6].

Radiation Safety

As the ability to deliver radiation treatments improved, so too did the concern for personnel safety. As a result, clinicians and physicists developed better protection measures. Gioacchino Failla of Memorial Hospital observed changes in the skin and nails of personnel in the department, particularly individuals handling radium [3]. The lead-lined treatment room constructed at Memorial Hospital for the 700,000-volt unit contained 1–2 inches of lead in the walls, floors, and ceilings for the purpose of personnel protection [4]. Radiation protection was a significant priority to Failla; therefore, he and Edith Quimby implemented a personnel film badge program at the hospital in 1923 [3].

During the First International Congress Meeting, G. W. Kaye discussed the impact of scattered radiation from the x-ray unit and patients undergoing treatment and the need to protect the operator of the x-ray unit [2]. This was particularly important as many x-ray units being used had an open-bulb design that offered no radiation protection. V. E. Pullin presented instances whereof patients developed ulcers from the scattered radiation in rooms above an x-ray room [2]. F. L. Hopwood presented procedures developed to minimize exposure from radium. These included the use of leaded drawers and the placements of identification marks on needles to identify the intensity of the radium contained without the need to touch the needles [2].

The International X-Ray Unit Committee conceived at the First International Congress Meeting in London had their first meeting at the Second International Congress in 1928. They discussed the need to develop international regulations for protection in radiological work. This committee was renamed as the International Committee for Radiological Units in 1931 and later renamed as the International Commission on Radiological Units (ICRU) in 1950 [10]. The ICRU is still in existence today with the mission to advance the safe and efficient use of ionizing radiation by developing and disseminating international recommendations for its application in medicine, science, technology, and public protection. The ICRU publishes reports that are instrumental to the practice of radiation oncology. These include Reports 50, 62, 83, and 92, which detail recommendations on prescribing, recording, and reporting in radiation oncology. In addition, ICRU Report 51 defined quantities and units for the measurement and calculation in radiation protection.

An additional product of the Second International Congress was the formation of another committee titled the International X-ray and Radium Protection Committee (IXRPC) [11]. This group was transformed into a commission in 1934, held its first meeting in 1950, and was renamed the International Commission on Radiological Protection (ICRP) [11]. The purpose of this commission, still in existence, is to advance the science of radiological protection by providing recommendations and guidance on all aspects of protection against ionizing radiation for the public benefit. The ICRP provides recommendations for dose limits, including those for occupational exposure and public exposure.

3 Refining Radiation Delivery

The years spanning 1925–1935 represent a transformative phase in radiation oncology marked by increasing recognition of its curative potential and the refinement of techniques for delivering radiation. The introduction and development of both teletherapy and brachytherapy during this period were instrumental in broadening treatment options and improving outcomes for cancer patients.

Emergence of Radiotherapy

The advancements in technology resulted in the formal establishment of radiotherapy as a medical specialty in some countries. This was a significant step toward increased accessibility of radiation therapy. The Second International Congress discussed the importance of establishing clinics with individuals specially trained in radio-therapeutics [5]. This was further detailed during the Third International Congress of Radiology in 1931. Attendees noted the need for a centralized department of radiotherapy containing 50 beds, 4–5 grams of radium, and the needed x-ray equipment [9]. By the 1930s, radiotherapy was routinely used as a treatment for cancer in coordination with surgery. However, it was the utilization of radiotherapy for inoperable cancer that provided the most value to clinicians [9]. In addition, prophylactic irradiation had also been considered [9].

Brachytherapy Developments

Parallel to the advancements in teletherapy, the period between 1925 and 1935 witnessed significant innovations in brachytherapy, primarily utilizing radium as the radioactive source. Institutions like the Radium Institute in Paris under Regaud and the Radiumhemmet in Stockholm were at the forefront of developing and implementing these brachytherapy techniques. There were three primary schools of thought in radiotherapy, centered in Paris, Stockholm, and later Manchester, each with distinct approaches. Regaud and Forssell in Paris and Stockholm extensively utilized radium not only for uterine carcinoma but also for head and neck cancers, including tonsils and the oral cavity [12]. These practices involved placing radium sources directly within or near the tumor, allowing for high doses to the target while minimizing exposure to surrounding healthy tissues. The "Manchester technique," which gained prominence in the 1930s and beyond, represented an effort to combine the best features of the Paris and Stockholm methods, particularly in the treatment of carcinoma of the cervix using radium [11]. The Manchester technique involved a compromise between the low-intensity factor of the Paris method and the protracted overall treatment period of the Stockholm approach, indicating a refinement in the principles of dose rate and overall treatment time in brachytherapy [13].

Radiation Biology: Dosage and Fractionation Improvements

Significant advancements in the understanding of radiation biology, particularly the manipulation of dose and its temporal distribution through fractionation, were made during the decade. Clinicians experimented with various fractionations in teletherapy to improve the effectiveness of treatment. The shift from single-dose to fractionated regimens was a key turning point. In 1926, George E. Pfahler would write about a fractionation scheme called the "Saturation Method" [14]. This method involved giving an initial erythema dose to the tumor followed by repeat doses at short intervals to maintain the erythema dose. The smaller doses were needed to maintain the effect of radiation on the malignant cells undergoing cell division [14]. The rate at which the effectiveness of radiation decreases could be represented by a logarithmic decreasing function [12]. The rate of decline was a function of the x-ray energy, with higher energy x-rays having a more sustained effectiveness. Despite the advantages and positive clinical results, Pfahler did note this treatment technique required more time to deliver, resulting in a higher treatment cost and more opportunities for treatment interruption [14]. This early appreciation for the interplay between beam quality and the temporal dynamics of radiation response is a noteworthy precursor to later, more sophisticated radiobiological investigations into relative biological effectiveness (RBE) and linear energy transfer (LET).

Regaud and Ferroux proposed a therapeutic benefit for fractionated treatments from irradiations of ram testicles. More damage was observed in the coiled tubes within the testes when the same dose was delivered in 4 fractions rather than one [13]. Moreover, less damage was observed in the skin in the 4 fraction treatments [13]. Henri Coutard, working at the Curie Institute in Paris, used "protracted-fractionated radiotherapy," utilizing low-dose rates delivered continuously or in multiple daily fractions over extended durations, typically 4–6 weeks, for the treatment of head and neck cancers [13]. Many departments were unable to implement this low-dose rate technique due to large patient volumes. As an alternative, these departments would use higher dose rates. Coutard meticulously documented skin and mucosal reactions from the treatment of patients and published 5-year results of cancer treatments in the early 1930s [12]. These early attempts to optimize radiation delivery attempted to leverage the temporal aspects of radiation delivery despite a growing understanding of radiobiological principles.

4 Legacy of the Decade

The International Congress meetings served as important catalysts, not merely for the exchange of promising ideas but also for the establishment of fundamental principles and a collaborative framework that continues to shape the field to this day. The legacy of these international meetings extends far beyond the specific resolutions and agreements reached. They established a vital tradition of global collaboration and knowledge sharing that remains indispensable in radiation oncology. The international congresses provided the platform for the creation of a common language of dosimetry, fostered key collaborations in radiation protection, and cultivated a global community dedicated to the advancement of radiation oncology.

The ongoing efforts of organizations like the International Atomic Energy Agency (IAEA) continue to refine standards for dosimetry, treatment planning, and radiation safety. These modern initiatives are direct descendants of the foundational work initiated and championed at the early International Congresses of Radiology. The sense of a unified international community, dedicated to the advancement of the field for the benefit of patients worldwide, was fostered through these gatherings. The IAEA partners with radiation oncology professional societies all over the world to improve access to radiotherapy through its initiative Rays of Hope [15]. The organization also provides important guidance and protocols to ensure the establishment of safe, sustainable, and consistent practices in radiation oncology.

Edith Quimby: Pioneering Precision in Radiation Dosage

The work of Edith Quimby during this decade was instrumental in transitioning radiation oncology from an era characterized by empiricism toward a more precise and scientifically grounded discipline. Her pioneering work early in her career focused on quantifying the biological effects of radiation and development of practical dosimetry systems. She also had an influential role as an educator and advocate for medical physics. The following section will present a few of Quimby's contributions and achievements in the field of radiation oncology.

In 1919, Quimby joined the first research laboratory in the United States devoted to medical applications of radiation at the Memorial Hospital for Cancer and Allied Diseases in New York City as an assistant physicist under Dr. Gioacchino Failla, Chief Physicist and a former student of Marie Curie [8]. At a time when radiation measurements were rudimentary, Quimby conducted research to quantify different aspects of radio-biological effects of radium [8]. Quimby also introduced a dose preplanning system at Memorial Hospital designed to deliver a nonuniform dose distribution over a plane or volume of targeted tissue with the aim of increasing the dose at the center of the targeted tissue [8]. Quimby published dose charts to enable calculation of the amount of radium required to deliver a certain absorbed dose [8]. Quimby's work to experimentally determine erythema dose was instrumental to later work on RBE as she investigated differences between the radiation quality of beta and gamma radiation [8]. Her research findings and measurement standards were widely published and became essential references in the field. In 1940, Quimby was awarded the Janeway Medal of the American Radium Society, and the following year, she earned the Gold Medal of the Radiological Society of North America [8].

Quimby transitioned to Columbia University in 1941 and helped grow one of the first educational programs in Radiological Physics in the United States. She participated in collaborative studies with other Columbia researchers on the clinical applications of isotopes in treating thyroid disease, conducting circulation studies, and diagnosing brain tumors, thereby setting the foundations for the field of nuclear medicine [8]. Edith Quimby also made contributions outside of the clinic and education. She was a contributor to the Manhattan Project and served as an oral examiner for the American Board of Radiology [8]. Edith Quimby was an advocate for clinical medical physics departments in hospitals, the inclusion of a physics section in the ABR examination, and the professional rights of medical physicists [8]. In 1963, Quimby received the Gold Medal from the American College of Radiology, making her and Marie Sklodowska Curie the only two women to receive the award at that time [8]. She is also one of the founding member of the American Association of Physicist in Medicine (AAPM). In 1996, the AAPM established a lifetime achievement award in her honor. The award recognizes AAPM members whose careers have been notable based on their outstanding achievements.

As one of the twentieth century's most prominent researchers in medical physics and nuclear medicine, Edith Quimby's foundational contributions to radiation dosimetry, coupled with her dedication to education and professional standards, were instrumental in shaping the discipline.

Summary Despite the social, economic, and political challenges of this decade, radiation oncology experienced a significant transformation. Driven by the collaborative spirit fostered at the International Congresses of Radiology, the field moved toward greater scientific rigor. The adoption of the Roentgen as a global dosage unit, combined with progress in dosimetry and x-ray technology, allowed for a move away from experimentation toward more precise and effective treatment strategies. The pioneering work of individuals like Edith Quimby was instrumental in this shift, laying the foundation for modern radiation physics and dosimetry. Furthermore, the growing understanding of radiobiology and the exploration of fractionation techniques hinted at the future potential for optimizing treatment outcomes. This decade, therefore, stands as a testament to the resilience and ingenuity of the radiation oncology community, which, even amidst global turmoil, forged a path toward becoming a vital and increasingly sophisticated weapon in the fight against cancer. The seeds of modern radiation oncology, characterized by international collaboration, standardized practices, and a growing understanding of the fundamental science, were firmly planted during this transformative era.

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Radiotherapy in Transition: Scientific and Clinical Advances, 1935–1945

Angélica Pérez-Andújar and Erica L. Braschi

1 Introduction

The years between 1935 and 1945 were marked by the Great Depression in the United States that started during the early 1930s. The Great Depression had a significant impact on the entire United States, particularly affecting marginalized groups. In 1932, it was recorded that approximately half of the US African Americans were unemployed. This was very similar to what other minority groups were undergoing then. This situation exacerbated antiminority sentiments. White Americans were calling for African Americans to be fired from their jobs, and even unions were excluding minorities by requesting that antidiscrimination rules be kept from President Franklin D. Roosevelt's New Deal Laws [1].

In 1941, Japan attacked Pearl Harbor, initiating a chain reaction of events that changed the world. In 1942, President Roosevelt authorized the production of the atomic bomb. This same year, the Manhattan Engineer District was established to develop the nuclear bomb and, with this, the beginnings of the Manhattan Project and a revolution in physics with the creation of what we now know as high-energy physics. The Oak Ridge National Laboratory was founded in 1943, and the first experiments with plutonium occurred there. Plutonium was selected for experiments in the development of the atomic bomb. The experiments performed at the Oak Ridge National Lab on plutonium were done under the X-10 site, where the graphite reactor and processing plant were used for the initial experiments [2].

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Later, the Los Alamos National Laboratory became the center for the development of the atomic bomb, which was detonated on July 16, 1945.

Throughout this period, a need to establish standardized methods for measuring and prescribing radiation for patients emerged. There was also a need to stabilizing standards, regulate and ensure proper shielding in facilities with radioactive devices, and establish radiation limits for radiological workers. During this decade, there were advances in the use of radiotherapy to treat tumors of the central nervous system (CNS) and developments in the brachytherapy field.

2 Establishment of the International Commission on Radiological Units

In 1925, the International Congress of Radiology established the International Commission on Radiological Units (ICRUs). The commission was a response to the necessity for standardized radiation units applicable to X-ray radiotherapy and radium usage. The commission was originally formed by two members representing each country that participated in the International Congress of Radiology, with the expectation that one members was a radiologist and the other a physicist. Fifty countries participated in this meeting, which first took place in London, England [3].

In 1928, the Roentgen unit was introduced internationally for the first time [4]. It was defined as the International Unit of X-ray, and the letter R was designated to represent the unit. At the same time, it was established that the dosimeter should be the instrument used to measure X-ray radiation and that ionization chambers should be calibrated against a standard. In 1931, the commission set the first limits for radiation exposure among radium workers [5]. The recommendation included defining the working days as 7 h and the working week as no more than 5 working days. They also provided recommendations for X-ray medical workers. Moreover, these recommendations encompassed the location of X-ray facilities and guidelines regarding office infrastructure, such as windows, ventilation, wall colors, room temperature, square footage, electrical precautions, and film storage. The committee also provided recommendations concerning shielding in X-ray departments, specifying appropriate shielding to protect X-ray operators and indicating their positioning in the room during irradiation [5]. Additionally, a subgroup within the committee, was tasked with defining the standard for X-rays, which evolved to up to 1 MV during this decade.

3 Fractionation

The idea behind fractionation existed even before the 1930s. In 1910, Louis-Frédéric Wikham and Paul-Marie Degrais described that spacing radiation exposure can produce different effects [6]. They found that when a total dose is delivered in multiple intervals, the affected tissues can adapt to the radioactive impact or lose some of it. As a consequence, the fractions of dose will not yield an identical effect as the total dose [6]. However, it was much later that optimal fractionations for therapeutic radiation were established.

In 1930, German physician Leopold Freund proposed delivering doses in greater numbers of small fractions [7]. The origins of "conventional fractionation" date back to 1932 with the work of Henri Coutard. In Paris in 1932, Coutard presented his findings at the American Congress of Roentgenology, demonstrating that skin and mucosal reactions were dependent on dose, treatment time, and number of treatment sessions for pharynx and larynx cancers. This later became known as the time-dose factor concept [8]. He showed control of laryngeal cancer through the use of low-dose rates (2–3 h daily fractions) in treatment schedules lasting 4–6 weeks [9]. In 1937, Coutard reported a 23% success rate in treating head and neck cancer using this approach, commonly recognized as the "Paris technique" [10].

Also in the 1930s, people started differentiating between the influence of dose per fraction versus overall treatment time on normal tissue [11]. In 1933, Reisner conducted experiments measuring the progression of skin erythema on human thighs by administering varying doses per fraction while maintaining a constant total dose and overall treatment duration. He found a reduction in acute skin damage with smaller doses per fraction [12]. A few years later, in 1935, Friedrich Miescher presented results from his animal experiments on the impact of fractionation on the late radiation effects in rabbit skin. He observed that the primary factor influencing tissue tolerance was the dose per fraction, and there were indications that the overall treatment time did not affect the development of late reactions [13].

The work from Baclesse showed that delivering a lower dose per fraction could help delay the reaction time of normal tissues and allow for higher total doses to the tumor over time. Baclesse was a pioneer in the area of breast cancer treatment, using high doses delivered over a longer time with volume reduction during the treatment course [8]. Still, many different approaches to radiation schedules were being used in the 1930s and 1940s. There was a broad spectrum of total treatment durations, variations on dose per fraction, and sessions per day. There was little consensus on the most effective approach [13].

During this decade, the concept of "isoeffective" formulas was developed to compare different radiation schedules. At first, the focus was on managing various treatment durations, but eventually, it evolved into Magnus Strandqvist's formulation, which remained a predominant concept for many years [14]. In his monograph on the time factor in skin cancer treatment, Strandqvist asserted that the primary factors influencing local control and normal tissue damage were the total dose and overall treatment time [15]. This led to disregarding small fraction sizes' beneficial effects on normal tissue for approximately 40 years. Strandqvist's formulation of the relationship between dose and time gained broad acceptance as a theoretical advancement for several decades, although some critiqued it.

The discoveries made on this subject led to the adoption of Target Theory later in the 1940s as well as discoveries about radiation-induced cell killings in the 1950s based on mammalian cellular radiobiology [15]. After 20 years emphasizing total time as the most important parameter for the effects of radiotherapy, in 1967 Frank Ellis presented the first isoeffect formula, including the number of fractions in addition to overall time [15]. All of these discoveries, along with many more in the 1970s–1980s (including the linear-quadratic formula and BED concepts), contributed to what we now call dose fractionation.

4 Studies on Oxygenation in Radiotherapy

Researchers started exploring the idea that oxygen and hypoxic conditions played a role in cell response to radiation. JC Mottram spearheaded the importance of oxygen for tumor-cell radiosensitivity in England in the 1930s. During this time, non-animal experiments were conducted using "newly" discovered radiation. Mottram, Gray, and Read studied the effects of radiation on the broad bean, *Vicia faba*, at Mount Vernon Hospital. They showed that roots radiated at a temperature of 0 degrees Celsius (C) were more sensitive to the radiation than roots radiated at 24 degrees C. Radiation on roots in anaerobic conditions was even less sensitive. Later on, Mottram showed that roots were also more sensitive when immersed in 1/2000 molar hydrocyanic acid for 3 h. In contrast, those immersed for 5 h in 1/40 molar solution of urethane did not have an effect [16]. Although interesting, these findings were mainly experimental at the time and did not lead to many impactful discoveries on the effects of radiation itself.

Around the same time, Crabtree and Cramer described a series of in vitro experiments on cancer cells' susceptibilities to radium, specifically by manipulating the respiratory mechanism of the cell. They showed that anaerobiosis lowers susceptibility to radium, while other conditions, such as hydrocyanic acid and cold temperatures, increase susceptibility [17]. Building on the findings of Crabtree and Crammer, Mottram described exposing mice with tar warts to gamma radiation by applying a radium applicator to the warts from the outside, so that the deepest cells received less radiation than those near the surface. He suggested that the peripheral cells of carcinomatous masses are more sensitive to gamma radiation than central cells and attributed this to a richer oxygen supply near blood vessels. Furthermore, he proposed that cells with more oxygen supply are more radio-sensitive, while those under anaerobiosis are radio-resistant [18]. These were some of the first studies to describe oxygen as a radiosensitizer and hypoxic environments as radioresistant. This important discovery contributed to work being done in support of fractionation during this time period since hypoxic tumor cells could reoxygenate between fractions, improving the tumor cell kill.

5 Ernest Lawrence Nobel and the Invention of the Cyclotron

Ernest Lawrence invented the cyclotron in 1929 at the University of California (UC) Berkeley, a breakthrough that transformed the field of physics. The cyclotron gave rise to the field of high-energy physics [19]. Lawrence received the Nobel Prize for this invention in 1939. The invention of the cyclotron led to the creation of new radioactive elements and the acceleration of protons and light particles. The UC Berkeley group also pioneered using light ions, such as alpha particles, for radiotherapy. In 1931, The Lawrence Berkeley National Laboratory (LBLN) was found, and in 1936, Robert Wilson joined Ernest Lawrence's laboratory at LBLN as a PhD student. Robert Wilson led one of the Manhattan Project research groups at an early age [20]. He also worked on the design of a new cyclotron capable of accelerating particles up to 150 MeV. After his involvement in the Manhattan Project, Wilson proposed using protons for the first time for radiotherapy purposes given the characteristics of the proton's Bragg Peak and its sharp dose fall off [19].

Before then, there were no particle accelerators capable of producing particles at energies that could be used to treat patients [21]. His work opened the door to a new type of radiation that could be used to treat patients and whose characteristics could minimize the toxicity of organs near the treatment area. Proton therapy is used worldwide for cancer treatment, and pediatric patients benefit significantly from such techniques [22, 23]. He also suggested using light ions for radiotherapy purposes and carbons. Helium particles were eventually used at Berkeley for some time to treat patients, but its use did not continue [24]. The use of carbon ions for radiotherapy purposes, also proposed by Wilson, has been implemented in recent decades, but it has been mostly used in countries outside of the United States, like Japan [25].

Luis Alvares was another prominent figure who joined LBLN and the Ernest Lawrence Laboratory [26]. Alvares was born in San Francisco, but his family originated from Spain. He obtained his PhD in physics from the University of Chicago in 1936 and joined the Ernest Laboratory in 1936. At LBLN, he and Felix Bloch measured the neutron's magnetic moment for the first time. Alvares later joined the Massachusetts Institute of Technology (MIT) radiation laboratory, where he contributed to World War II radar projects, specifically a project related to the type of microwave used for plane identification. He eventually joined the Robert Oppenheimer Group on the Manhattan Project and was involved in the technique used to detonate the atomic bomb. Alvares was also involved in the development of the first proton linear accelerator. He obtained the National Medal of Sciences in 1963 and won the Nobel Prize in 1968.

6 Brachytherapy

During the early 1930s, Roentgen rays were used alone or in combination with radium implants for the treatment of cervical cancer [27]. In 1934, Irène Curie and Frederick Joliot made the groundbreaking discovery of artificial radionuclides, paving the way for a new era in brachytherapy. In 1935, they were jointly awarded the Nobel Prize in Chemistry for their synthesis of new radioactive elements. This laid the groundwork for radioisotopes used later on in place of radium-226 for intracavitary therapy, such as cobalt-60 (Co-60), gold-198 (Au-198), tantalum-182 (Ta-182), and cesium-137 (Cs-137), and eventually iridium-192 (Ir-192), which became the preferred clinical choice over previously mentioned sources.

Following World War I, Germany faced a shortage of radium for brachytherapy. In the 1930s, in Berlin, Chaoul collaborated with Siemens to develop the initial contact X-ray brachytherapy (CXB) machine as an alternative for treating uterine cervix carcinoma [28]. This machine delivered 60kVp X-rays with a short (4–5 cm) focus-to-skin distance (FSD). This allowed treatment to primarily skin tumors, as well as intraoral and intravaginal conditions, with minimal toxicity and high efficacy.

The Siemens system was replaced in 1945 by the Philips Company in Eindhoven under the name of RT 50. The RT 50 allowed delivery of a high dose rate (20Gy/min at the exit tube surface with a 4 cm FSD). This marked the first time a 30 Gy dose could be administered in under 3 min. The beam penetration was well-suited for superficial and thin tumors, and optimization was achievable through adjustments in the FSD or adding extra-filtration. This machine resulted in outstanding cosmetic outcomes and successful treatment of small skin, eyelids, and conjunctiva tumors [29]. The RT 50 proved invaluable, particularly during an era marked by Kaposi sarcoma in AIDS patients. It allowed treatment of 1–6 skin sarcomas in three sessions over 3 weeks. In 1946, Lamarque documented the utilization of the RT50 for trans-anal endoscopic irradiation in rectal cancer [30]. This machine maintained popularity until the close of the twentieth century when high-energy linacs and image-guided IMRT took precedence.

Also in 1945, a technique involving radon gas enclosed in gold “seeds” was pioneered at Memorial Sloan Kettering for internal radiation therapy. This innovative method utilized gold capsule filters to selectively block beta rays responsible for inflammation and skin burns while permitting the passage of gamma rays [31].

7 Juan Angel del Regato: Unveiling the Legacy of a Hidden Figure in Radiation Oncology

Juan del Regato was born, raised, and educated in Cuba and studied medicine at the University of Havana [32–36]. In the early 1930s, he left for the University of Paris when the University of Havana was closed due to political controversies. In Paris at the Radium Institute, he developed the del Regato localizer in 1934, the first light localizer used to indicate where a radiation beam strikes the patient. In 1937, he received his medical degree with a medal-winning thesis on successful radiotherapy of inoperable cancers of the maxillary antrum. He continued his work at the Radium Institute of Paris alongside people like Henri Coutard, Claudius Regaud, Marie Curie, Antoine Lacassagne, and Antoine Ceclere. In 1938, he came to the United States and brought with him the Parisian tradition of specialization, given that at this time in America, there were few physicians specializing exclusively in radiation therapy. He also brought an interest in research and medical education and integrated this into the practice. He served as a Research Fellow at the National Cancer Institute and as Radiotherapy Director at the Ellis Fischel State Cancer Hospital in Columbia, Missouri, during the 1940s.

Later in his career, he helped establish the first training program in the United States dedicated to training physicians in radiation oncology at Penrose Hospital. He also founded the American Club of Therapeutic Radiologists, which later became the American Society of Therapeutic Radiologists and, ultimately, the American Society for Radiation Oncology (ASTRO). He was a faculty member of the University of South Florida in Tampa, Florida, first as a Professor of Radiology, and later as Professor Emeritus of Radiology in 1981. He also received many awards and honors, including gold medals from the Radiologic Society of North America (1966), the American College of Radiology (1968), the American Society for Therapeutic Radiology and Oncology (1977), as well as the American Medical Association Scientific Achievement Award (1993).

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1945–1955: The Postwar Era

Eric Elder, Malcolm Mattes, and Richard Castillo

1 Introduction

On May 7, 1945, General Alfred Jodl signed the German Instrument of Surrender in Reims, France, on behalf of the German High Command, conceding unconditional surrender and ending the war in Europe. May 8, 1945, would thereafter be remembered as Victory in Europe, or VE, Day, marking the end of the deadliest conflict in European history [36]. As war in the Pacific continued, scientists in the United States carried on in urgent pursuit of atomic weapons development. The monumental and collective effort of approximately 130,000 military and civilian personnel employed at the peak of the Manhattan Project resulted in historic advancement of nuclear technology [80, 81].

The Nuclear Age would officially begin July 16, 1945; born in a remote region of the New Mexico desert, 210 miles south of Los Alamos, at the Trinity Test Site. At 5:30 am, a plutonium core bomb nicknamed the "Gadget" was successfully detonated, releasing approximately 21 kilotons of energy in the first-ever explosion of a man-made nuclear device [80, 81]. The successful Trinity Test provided invaluable data on the energetic yield, physical characteristics of the explosion fireball and ensuing shockwave, including photographic record of the now iconic "mushroom cloud," as well as radioactive environmental consequence of the resultant fission

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by-products. However, at this crucial moment in history, above all it showed that the plutonium implosion design was physically realizable and could therefore supplement the more theoretically robust uranium gun-type mechanism, which nevertheless could not be feasibly tested at the time due to a critical lack of enriched uranium. To this day, historians debate the necessity of atomic warfare levied against Japan versus military and political alternatives to end the war, balancing consideration of multiple avenues, including ground invasion of the Japanese mainland, partnership with the Soviet Union following their own potential declaration of war against Japan, and controlled demonstration of the nuclear destructive potential. Just some of the factors that illuminated this debate included the potentially catastrophic loss of life associated with a mainland invasion, concern over postwar administration of Japanese territory with the Soviet Union, and functional reliability of the nuclear arsenal within a global demonstrative setting.

Ultimately, following success at Trinity, President Truman authorized combat deployment of the atomic bomb. The first atomic weapon deployed in human history was dropped on August 6, 1945, over Hiroshima, Japan, just 3 weeks following the Trinity Test. "Little Boy" was an enriched uranium gun-type assembly, which detonated over Hiroshima at an altitude of approximately 1800 ft., yielding a 15-kiloton blast resulting in an estimated loss of life ranging from 70,000 to 140,000 within the first 4 months of the bombing. Three days later, August 9, 1945, "Fat Man," a 21-kiloton plutonium implosion-type assembly such as that demonstrated at Trinity was detonated approximately 1600 ft. over Nagasaki, Japan, resulting in an estimated loss of life ranging from 60,000 to 80,000 within the first 4 months of the bombing. The next day, Japan offered its surrender, and on August 15, 1945, Emperor Hirohito formally addressed the Japanese people via public radio broadcast. In his address, now known as the "Jewel Voice Broadcast," the Emperor refers directly to the atomic bomb, *"…Moreover, the enemy has begun to employ a new and most cruel bomb, the power of which to damage is indeed incalculable, taking the toll of many innocent lives. Should we continue to fight, it would not only result in an ultimate collapse and obliteration of the Japanese nation, but also it would lead to the total extinction of human civilization"* [74]. The Japanese Instrument of Surrender was signed on September 2, 1945, aboard the USS *Missouri* in Tokyo Bay [51].

The deadliest war in human history was over, but at an incredible cost [82]. Estimates of the catastrophic loss of life incurred in World War II range from 22.6–25.5 million military personnel and 37.6–55.2 million civilians dead [11]. Moreover, to this day, World War II remains the most expensive war in US history, with total national wartime expenditure between 1939 and 1945 estimated at over $4.1 trillion in FY2011 dollars [13]. Financial costs would continue to mount as the United States committed to subsequent international reconstruction efforts to re-establish world order and safeguard democracy in part by ensuring the successful rebuilding of war-torn economies and infrastructure in Western Europe. The Marshall Plan, or European Recovery Program, provided roughly $170 billion in FY2025 dollars between 1948 and 1951 toward recovery in Western Europe, with similar estimates for spending on reconstruction efforts in Japan and other Pacific nations [71].

The world would be forever changed following the war. And in the immediate aftermath, we begin to see transformational consequences stemming from the groundbreaking innovations borne out of necessity for an unparalleled collaborative war effort, and whose wartime trajectories would carry on with significant ramification to shape cultural and technological landmarks of the ensuing decade. The United States entered the war as a deeply racially segregated society. However, the sheer necessity for manpower gave rise to unprecedented inter-racial cooperation and collaboration across military, scientific, agricultural, and industrial efforts. Within the US Armed Forces alone, it is estimated that over one million African American men and women served during the war, comprising 10% of the total US military personnel [75]. The collective experience challenged deeply rooted racial stereotypes and coalesced renewed pride and newfound optimism into accelerated efforts in activism, setting the stage for historic strides toward civil rights in the years to come. Executive Order 9981, signed by President Truman in 1948, was one of the first major administrative milestones of the era, granting formal equality of treatment and opportunity in the Armed Forces, regardless of race, color, religion, or national origin [77]. The landmark Brown v. Board of Education Supreme Court decision issued on May 17, 1954, would formally declare racial segregation in public schools as violation of the 14th Amendment, and therefore unconstitutional [7]. Likewise, the unprecedented technological innovation central to the war's outcome would drive rapid and transformational advancement in medical science and technology in both long and near terms. It is estimated that approximately 1500 US patents were developed by contractors working on the Manhattan Project alone [15]. Furthermore, in the immediate aftermath of nuclear devastation, it was clear that the medical complexity of both acute and long-term effects of radiation exposure warranted urgent investigation. The US government established the Atomic Bomb Casualty Commission in 1946 to study the long-term medical and genetic effects of radiation exposure to atomic bomb survivors [61]. Epidemiological research of the population of atomic bomb survivors and their offspring continue to serve as the foundational basis for the modern understanding of radiation exposure risk and occupational safety in clinical practice [18].

Looking forward in 1945 meant balancing the wartime catastrophe with optimism borne out of its ending. November 20, 1945, marked the first of 13 trials held between 1945 and 1949 in Nuremberg, Germany, by the International Military Tribunal prosecuting war crimes and crimes against humanity carried out by German personnel and interests during the war. Within this same time span, between 1946 and 1948, Japanese leaders were prosecuted before the International Military Tribunal for the Far East on the same basis. The Nuremberg and Tokyo Trials were historically unprecedented for seeking and adjudicating individual accountability during times of war. These proceedings introduced and acted upon the concept of crimes against humanity, and furthermore were foundational for subsequent landmark actions including ratification of the 1948 Genocide Convention that codified the crime of genocide, and the 1950 Universal Declaration of Human Rights by the newly formed United Nations [1, 78].

As the international community sought accountability for the atrocities against humankind, and to further enshrine human rights as fundamental and universal, the world would concurrently be propelled into a new age of conflict. The Cold War was personified by the Iron Curtain that physically and ideologically divided Europe beginning in 1945 and was further shaped by a new international race for advancement and proliferation of ever-more destructive nuclear arms. The new age of nuclear armament began on August 29, 1949, following the successful detonation of the first Soviet Union atomic bomb, the RDS-1, at a test site in Kazakhstan. The 22-kiloton plutonium device was similar in energetic yield and design to the US bomb dropped on Nagasaki 4 years prior [72]. This was followed by the first-ever nuclear test conducted by the United Kingdom, which took place on October 3, 1952, off the coast of Western Australia. The plutonium device was detonated on board the frigate HMS *Plym*, with a reported yield of 25 kilotons [17]. The very next month, and just over 7 years since the dawn of the Nuclear Age itself, the modern era of thermonuclear weaponry arrived at Enewetak Atoll on the Marshall Islands. At 7:15 am local time, November 1, 1952, the United States successfully detonated the world's first hydrogen bomb, a two-staged implosion device nicknamed "Mike" yielding an estimated 10.4-megaton explosion [63]. Finally, on March 1, 1954, Castle Bravo became the largest ever thermonuclear detonation by the United States, yielding a 14.8-megaton explosion at Bikini Atoll in the Marshall Islands [65]. Predeployment underestimation of the yield by approximately a factor of three resulted in unintended radioactive fallout and radiological disaster for the region [73].

Within the overall span of one decade, nuclear weaponry was born, deployed in combat, and enhanced in energetic yield by three orders of magnitude. The devastation in combat, the significance of secondary risk associated with radioactive fallout, and the unpredictable nature of nuclear weapons testing were evident. These issues prompted British philosopher and mathematician Bertrand Russell to pen an essay warning of the existential threat levied by the modern thermonuclear weaponry and imploring all parties toward the peaceful resolution of conflict. The Russell–Einstein Manifesto, as it became known, was issued in July 1955 and signed by multiple prominent scientists of the time, including Albert Einstein. Fundamentally, the document appeals to our shared humanity in the shadow of a new common threat to our existence [14].

Against this backdrop, the modern age of megavoltage radiotherapy would be born.

2 The Linear Accelerator

"During the human struggle between British and the German Air Forces, between pilot and pilot, between anti-aircraft batteries and aircraft, between ruthless bombing and the fortitude of the British people, another conflict was going on step by step, month by month. This was a secret war, whose battles were won or lost unknown to the public, and only with difficulty comprehended, even now, to those outside the small high scientific circles concerned. No such warfare had ever been waged by mortal men" ([10], p. 381). So, Winston Churchill describes the herculean efforts to develop radar but the words apply, maybe even more so, to the creation of the atomic bomb. The scientific achievements of radar and the atomic bomb made the years of 1945–1955 monumental for medical therapy and physics.

Open hostilities in Europe and Asia began before the official outbreak of the European World War II (WWII). The aerial bombing of Spanish and Chinese cities in the Spanish Civil War (1936–1939) and the Second China-Japan War (1937–1945) was of great concern to former Pan American pilot Sigurd Varian. As a pilot, Sig was sure he could locate a target even at night or in overcast weather. This left cities defenseless to air raids in such conditions. He frequently discussed the problem with his brother Russell as they worked in their laboratory in their hometown of Halcyon, California. Russ started thinking and recognized from his knowledge of basic physics (B.A. Physics 1925, Stanford University), the only means of aircraft detection would be through radio waves. Furthermore, for adequate antenna size and resolution of smaller objects, the wavelength would have to be in the centimeter region [33].

At Stanford University, Professor of Physics William Hansen in the mid-1930s invented an unusually effective resonant microwave cavity, naming it a rhumbatron. Russ had been Bill's undergraduate classmate and graduate school roommate, and had knowledge of the rhumbatron. In early 1937, convinced the solution to Sig's concern somehow involved the rhumbatron, Russ and Sig approached Hansen and the head of the physics department to set up a research lab at Stanford. The university agreed to provide laboratory space and $100 a year for materials and supplies [33]. By the summer of that year, Russ had an idea in the middle of the night in which he visualized the movement and bunching of cars traveling at different speeds. By the end of 1937, brothers Russell and Sigurd Varian working with Hansen coupled the rhumbatron with the velocity modulation concept to create the first klystron [9].

On the other side of the Atlantic, at the University of Birmingham, the Stanford achievements were discussed at colloquia in the physics department, but the push in the United Kingdom for a 10 cm microwave source only began in earnest in 1939 on the eve of war. In November of that year, Henry Boot and John Randall combined the advantages of the klystron with the more favorable geometry of a primitive magnetron creating the modern magnetron [5]. Then, in February of 1940, Randall and Boot produced a magnetron capable of producing a 10 cm wavelength at 0.1 MW. Collaboration between Britain and the United States allowed for the transfer of the magnetron to the United States for production by American factories. The more compact and higher output magnetron became the microwave source for the allies in WWII. By 1944, magnetrons had reached about 2 MW, and by 1945 approximately 250,000 magnetrons had been supplied to the UK government alone [5]. The klystron reached only a pulsed output power of 30 kW during the war [32]. But the klystron acting as an amplifier, receiver, and superheterodyne detector proved equally instrumental in winning the war [33].

After the war, many scientists and engineers could return to their civilian research, but now with tools only previously imagined. But, while the conflict ended, the push for advancement did not, albeit now for scientific and humanitarian ends. An electron linear accelerator (linac) was developed in the 1930s but lacked the microwave source to accelerate the electrons [24]. WWII radar needs created powerful S-band frequency microwave sources with a 10 cm wavelength (3000 MHz frequency). Fortunately, this frequency proved to be optimal for high-energy linacs [43]. But for a linac to function optimally, the microwave frequency must match the resonant frequency of the accelerating waveguide. Therefore, the race was on to create a waveguide to match the microwave source and then improve the system to take it to higher and higher energies.

Many groups jumped into the race to develop these linacs, but two particular groups stood out among the competition: Hansen's group at Stanford University and D.W. Fry's group based at Telecommunications Research Establishment (TRE) in Great Malvern, UK [76]. Edward Ginzton (physics faculty member at Stanford University and later co-founder of Varian Associates with Russell and Sigurd Varian, William Hansen and others) and Craig Nunan (Varian Associates) document the back-and-forth race of the research efforts between the groups. In actuality, the two groups had little knowledge of each other's work until 1947 [32].

When designing their accelerating waveguides, both groups recognized the 1944 mathematical work of C. C. Cutler [12], showing that the introduction of circular irises forming a corrugated cylinder allows for the creation of a traveling wave with an axial electric field component and a phase velocity less than the velocity of light. This slowing of the phase velocity allowed for energetic bunches of electrons to "catch" the wave and "surf-ride" in an accelerating field and thus gain energy [84]. Thwaites and Tuohy point out the irony of the United Kingdom group first using the surfing analogy instead of the Californians [76]. With this idea of a corrugated traveling linear accelerator, the essential building blocks of the linac were available. Now to put it all together.

The TRE group, led by Fry, was the first to strike with a 40 cm long, 538 keV accelerator in November of 1946 [29]. Hansen's group at Stanford had been unaware of the work done in England, but had also been working on a traveling wave, magnetron-driven accelerator. By early 1947, they completed a 90 cm accelerator capable of producing 1.7 MeV electrons. Fry's group responded with a 2 m waveguide producing 3.5 MeV electrons in November of 1947. The same month, Hansen's group increased the accelerator waveguide to 3 m, creating 4.5 MeV electrons and later 6 MeV [32].

All of these linacs utilized magnetrons and traveling waveguides, but in 1947 Hansen and the Varian brothers formulated a plan to build a klystron a thousand times more powerful than the 30 kW WWII device. The 1947 proposal was demonstrated by 1949. After three additional years of work, the 30 MW klystron was really opening up the possibility of creating a compact medical accelerator in the range of 25 MeV [32].

Bringing these accelerators from the laboratory to the clinic was the next stage. The competition continued between the two groups but now with the additional support from physicians, government, and, for the British group, industry. In the United Kingdom, at the end of 1948, the British Ministry of Health coordinated the formation of three groups to produce a linear accelerator for clinical use. The linear accelerator team was led by Fry who still led the TRE group, which had been renamed the Atomic Energy Research Establishment (AERE). The other two groups were the Radiotherapeutics Research Unit of the Medical Research Council (MRC) and the Metropolitan Vickers Electrical Company [32]. The linac was the first of its kind to be built specifically for X-ray therapy. The linac, operating for the first time in December 1950, was a 3 m accelerating waveguide powered by a 2 MW magnetron capable of producing an 8 MeV X-ray beam at 100 cGy/min. Maximum field size was a 15 cm x 20 cm rectangle. While the accelerating waveguide was stationary, a rotatable 90° magnet was mounted at the end before hitting the target allowing for the direction of the X-ray beam to be changed [49]. The treatment table could be positioned vertically and laterally, allowing for a range of treatment angles. Installation of the linac began in June 1952 at Hammersmith Hospital, London. The first patient was treated on August 19, 1953 [32].

The isocentric gantry mount was conceived by P. Howard-Flanders in 1949 at MRC in Hammersmith while 4 MeV linacs were simultaneously commissioned by the Ministry of Health and being built by AERE. The 1-m-long accelerator, developed from the experience gained by the 3 m 8 MeV linac [49], could be mounted on a single or double gantry mount. The first double gantry unit, capable of 210° rotation, was installed at Newcastle General Hospital in August 1953 and the first single gantry unit, limited to 120° rotation, at Christie Hospital, in October 1954 [32].

The clinical efforts at Stanford began unknowingly with the hiring of Dr. Henry Kaplan as the head of the Department of Radiology for the School of Medicine in 1948. Stanford's School of Medicine was located in San Francisco at that time, but Dr. Kaplan heard of the linear accelerator work that was being done down the peninsula at the Physics Department on the campus. Dr. Kaplan met with E. L. Ginzton of Hansen's group at the Stanford faculty club to discuss Kaplan's ideas for a clinical linear accelerator. His criteria included a 6 MeV X-ray beam with a high dose rate, sharply defined fields, orientable, and easy to use. Kaplan's drive led the way and resulted in grants from the National Institutes of Health and the American Cancer Society by 1952 [32].

The creation of the machine Kaplan desired began in 1954 in Stanford's Microwave Laboratory. A 1 MW klystron was used as the microwave source as the high-powered klystron was still under development. The linac employed a 1.65 m accelerating waveguide mounted on a Van de Graff trunnion mount. This permitted a vertical travel of 120 cm and a little over 90° rotation of the accelerator. The maximum field size was 15 cm x 15 cm with an unflattened dose rate of 110 cGy/min. The linac was capable of producing a therapeutic electron beam as well. A 100 kVp rod anode could be inserted near the linac target position. Paired with an image intensifier, the anode could allow target localization, making this linac capable of image-guided radiation therapy (IGRT). However, the first treatment would have to wait until January of 1956 [32].

By the mid-1950s, therapy linacs were being manufactured by Varian Associates in California, High Voltage Engineering in Boston, Mullard and Vickers in the United Kingdom, Massiot in France, and Toshiba in Japan [59].

3 Radionuclide Production

Nuclear fission rapidly evolved from theory into practical applications as part of military weaponry, as a source of power, and as radioisotopes used for medical purposes [60]. After World War II, the Atomic Energy Commission (AEC) was established by the Atomic Energy Act of 1946, signed by President Harry Truman [48]. This Act turned the atomic energy program over to civilian authority, except for leaving military applications under the auspices of the Defense Department. The first reactor-produced isotopes were made available through the AEC from Oak Ridge National Laboratories (ORNL) in 1946 [44]. Gradually, the production of radionuclides for medical therapy and diagnosis developed, and in the 20 years that followed, over 111 PBq (three million Ci) of radioactivity were sold by Oak Ridge National Laboratory. In the latter 1940s, these nuclides included not only fission products, but also induced nuclides such as C-14, P-32, S-35, Na-24, Ca-45, and I-131 [69].

These newly available radionuclides were soon put into use in patients. In 1946, Sam Seidlin (a New York endocrinologist) published an article in *JAMA* (*Journal of the American Medical Association*) announcing a cure for thyroid cancer using I-131, involving the complete disappearance of multiple functioning metastases in a patient who had been diagnosed with thyroid cancer several years earlier. As early as 1948, P-32 was used for relief of bone pain associated with metastatic cancer, though at the expense of significant bone marrow suppression. In 1949, Ga-72 was first suggested for the diagnosis and therapy of osteogenic sarcoma [19].

Ra-226 was used as a standard for dose calculations and radiation safety precautions, but less commonly for medical applications as it was more radiotoxic than other brachytherapy nuclides if taken into the body, and it had a greater potential to cause source ruptures, resulting in the need for expensive decontamination measures [30, 31, 66]. These early radionuclides would be precursors to Cs-137, I-125, and Ir-192 used in modern brachytherapy.

The development of Co-60 teletherapy units was another important advancement in this period. Cobalt-60, produced by neutron irradiation of cobalt metal in a nuclear reactor, is a high-activity gamma-ray emitter, emitting 1.17 and 1.33 MeV gamma rays. Co-60 had several advantages over x-ray therapy linacs being developed at this time, which were lower energy and had high skin doses and a lack of deep penetration, which is necessary for tumors deep inside the body. Furthermore, the dose rates were such that the x-rays needed to be applied with fairly short treatment distances, which resulted in shallower depth of dose penetration. The outputs of x-ray tubes and generators were also quite variable, resulting in complications in their dose calibration [64]. Ra-226 was also an available gamma emitter with similar energy as Co-60; however, radium was difficult to produce in high-enough activities for external beam therapy. Furthermore, as part of its nuclear decay process, it emitted a radioactive gas, resulting in radiation safety concerns, and was prohibitively expensive [64]. Co-60 is also notable for having a relatively long half-life of 5.27 years compared to other gamma emitters. In 1949, Dr. Harold E. Johns of the University of Saskatchewan requested that the National Research Council (NRC) of Canada produce cobalt-60 isotopes for use in a cobalt therapy unit prototype. Two cobalt-60 apparatuses were then built, one in Saskatoon in the cancer wing of the University of Saskatchewan and the other in London, Ontario. Johns collected depth-dose data at the University of Saskatchewan that would later become the world standard [79]. The first patient to be treated with cobalt-60 radiation was treated on October 27, 1951, at the War Memorial Children's Hospital in London, Ontario [34, 41].

With the increasing use worldwide of greater quantities of radioactive materials with varied characteristics, there was a need for the full-time attention of specially trained professionals to develop standards for limiting the intakes of radionuclides and ensures the safety of their use [50]. The new profession of "Health Physics" was born to address this need. Karl Morgan, Director of the Health Physics Division at ORNL, led the development of these standards. Most of the early calculations of organ doses from internally deposited radioisotopes in the 1940s were based on early work of Marinelli [45] at Memorial Hospital in New York and on subsequent work with Quimby and Hine [46]. As chairman of the International Commission on Radiological Protection (ICRP) and National Committee on Radiation Protection and Measurements (NCRP) II Committees, Morgan and his team published the early limits on intake of radionuclides [55]. Programs for training, education, and research using radioisotopes were funded by the AEC, and the safety of these programs around the United States was inspected by AEC scientists and physicians [6]. The Atomic Energy Act of 1954 added licensing and regulations to AEC's authority, to a limited extent given the continued rapid evolution of the technology [48].

In summary, since the first reactor-produced radioisotopes were made available in 1946, there has been a rapid expansion of their medical use for a variety of diagnostic and therapeutic purposes. This evolutionary progress is a testament to the work of an interdisciplinary team of physicists, chemists, pharmacists, physicians, and engineers during these formative years of development, leading to the wide variety of radiopharmaceuticals used today in contemporary medicine.

4 Radiation Detection/Protection/Safety

Radiation protection became a more complicated task after the use of nuclear weapons due to new concerns about public safety from these weapons [83], and the wide variety of new radionuclides that could be produced with nuclear fission for emerging diagnostic and therapeutic medical purposes [47]. Frank Ellis published several scientific papers on biological dose-volume effects, tolerances of irradiated tissue

[20, 21], genetic risks from ionizing radiation [22], and medical aspects of radiation protection [23]. In 1946, Hermann Joseph Muller was awarded the Nobel Prize in Physiology or Medicine “for the discovery that mutations can be induced by X-rays.” In his acceptance speech, he reasoned that no threshold dose of radiation existed that did not produce mutagenesis, which led to the adoption of the linear no-threshold model of radiation on cancer risks. These scientific findings were further supported by clinical experiences related to hazards and toxicities experienced by radiotherapy departmental staff [35, 37, 47, 58].

The Atomic Energy Act of 1946 established the AEC to manage the United States atomic energy program [67]. However, this legislation was primarily oriented toward the desire to control nuclear materials, and less so on radiation safety. In 1946, the National Advisory Committee on X-Ray and Radium Protection was renamed to the National Committee on Radiation Protection, which later became the NCRP. Lauriston Taylor was designated the first chairman of the NCRP. The concerns about public safety from nuclear fallout had a rapid impact on radiation protection by increasing public awareness about the risks of exposure to ionizing radiation and prompting the NCRP and the ICRP to reassess its radiation protection recommendations.

Standards for radiation exposure were first developed in 1947. At this time, the permissible occupational whole-body dose was 3 mSv per week. However, assuming that a person was exposed at this weekly rate over a 50-year career, the accumulated dose would be approximately 7.5 Sv, which was considered a large lifetime dose in light of emerging evidence on the lasting effects of ionizing radiation [39]. The ICRP and NCRP subsequently adopted a threefold decrease in weekly dose and recommended a 50 mSv per year whole-body dose limit [39, 54, 56]. Additionally, permissible dose to a number of critical organs, including the gonads, lens of the eye, and the blood-forming organs, was also specified. The ICRP and NCRP also recommended that the general public, and minors, should be exposed to less than one-tenth of the limits for radiation workers [40, 53]. Over time, the concept of “tolerance dose” was replaced by “permissible dose,” for the ever-expanding number of radiation workers [52]. Furthermore, in 1952 the US Public Health Service (PHS) published the first edition of the *Radiological Health Handbook for Health Physicists*, and in 1953 developed the first comprehensive guide for inspection of diagnostic x-ray facilities, known as “the yellow book” [38]. The PHS also played an important role in radiation protection through professional trainings of PHS commissioned officers and other personnel in radiological health laboratories.

An important component of radiation protection was the development of the ability to reliably measure radiation [25, 70]. However, due to a lack of accurate commercial systems for personnel dosimetry during this time period, individual institutions developed their own methods of dosimetric detection and systematic record keeping [68]. At Middlesex Hospital in London, Frank Farmer created a variety of tools for this purpose, including a thimble-chamber dosimeter, fixed chamber integrating dosimeter [26], small condenser ionization chamber that could comfortably be inserted into body cavities [27], and feed-back amplifier for ionization currents [28]. At Hammersmith Hospital in London, Jack Boag described the saturation curve for an ionization chamber exposed to pulsed radiation [2, 3], as well as the ionization measurements of pulsed radiation beams at very high intensities [2], and ionization chambers for electron dosimetry [4]. By the 1950s, the use of ionization to measure X-ray intensity was well developed [62].

Initial work that led to the development of thermoluminescent dosimeters (TLDs) began in 1947 at the University of Wisconsin by Farrington Daniels [8]. Also in 1947, Hartmut Kallmann reported on the use of the first photoelectric scintillation detector [16, 42], which could relate pulse intensity to energy. This was followed in 1950 by Kallmann's discovery of liquid scintillation counting using a special solution of toluene and xylene. Scintillation counters, which measure the emission of visible light by substances exposed to radiation in portable survey meters, were further improved over time with the use of a photomultiplier tube to detect the emission of light, and with the use of thallium-activated NaI as a gamma spectrometer [57]. TLDs became more widespread in the 1960s, and various types of scintillation counters have been used for radiation measurement since then [8].

In summary, our understanding of the potential hazards of ionizing radiation has gradually advanced since the discovery of X-rays in 1895. However, after the use of nuclear weapons during World War II, the lay public demanded standardized guidance and recommendations for protection. The national and international scientific community responded by developing regulatory organizations that provided standards to protect occupational workers and members of the general public and assure the safe use of radiation and radioactive materials. Although these standards have continued to evolve over time, there has been relatively little change in the recommendations in contemporary practice from this foundational work.

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Nuclear World: A Decade of Medical Progress Under the Shadow of the Cold War: 1955–1965

Joseph Weygand

1 Introduction

Medicine is one of humanity's most ancient sciences, born out of our enduring struggle against the inevitability of death and driven by an instinct for survival. Throughout history, two constants have shaped our collective experience: conflict and disease. These relentless forces, rooted in our deepest fears, have been powerful drivers of scientific progress. While conflict has remained a persistent feature across time, one event in the mid-twentieth century profoundly altered our philosophical approach to it: the development of atomic weapons in Los Alamos, New Mexico. In August 1945, President Harry Truman authorized the use of atomic bombs on Hiroshima and Nagasaki, leading to the surrender of Emperor Hirohito [1] and ending hostilities in the Pacific Theatre of World War II [2]. However, this victory came at a cost. The erstwhile allies, the United States and the Soviet Union, soon found themselves on opposing sides, igniting a rivalry that would dominate most of the remainder of the twentieth century and trigger a perilous nuclear arms race.

Today, we call this period the Cold War—a term afforded by the clarity of more than a half century's hindsight. At the time, however, the threat of the conflict turning "hot" and escalating into open nuclear warfare was alarmingly real. The prospect of such a catastrophe, with estimates suggesting it could result in 100 million casualties in the United States within the first hour alone [3], led to widespread preparations. Schools routinely conducted duck-and-cover drills, instilling vigilance in children, while average citizens constructed fallout shelters and stocked them with essential supplies, bracing for the unthinkable.

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Yet, amid this era of profound existential anxiety—particularly in the period between 1955 and 1965, when the Cold War and the threat of nuclear annihilation reached their zenith—some of the most significant breakthroughs in radiation oncology began to emerge. This dynamic reveals a deeper, unexpected connection between conflict, disease, and humanity's relentless drive to overcome both. The very force that once embodied the ultimate threat—atomic power, with its immense potential for destruction—became the catalyst for groundbreaking advances in another field. Radiation oncology harnessed this formidable energy, redirecting it from its destructive origins to a life-saving purpose: the treatment and cure of cancer.

Typically, historical narratives focus on either conflict or disease as separate drivers of progress. This chapter, however, will interweave these stories, connected by a common thread: atomic energy. Between 1955 and 1965, the world teetered on the brink of nuclear annihilation. Yet, in this same period, scientists at Stanford repurposed atomic power to develop a transformative medical device—the linear accelerator—which would go on to save and prolong countless lives by revolutionizing cancer treatment. Meanwhile, across the Atlantic, a scientist in Zurich was harnessing applications of nuclear spin, laying the mathematical foundations for a technique that would eventually lead to magnetic resonance imaging (MRI). Today, MRI continues to be a powerful tool, propelling modern radiation oncology.

This chapter seeks to explore these intertwined narratives, examining how the tumultuous global landscape of the mid-twentieth century, marked by both conflict and disease, created an environment ripe for pivotal advancements in nuclear science and medical technology. It aims to show how, amid the tension of the Cold War, atomic energy emerged not only as a symbol of conflict but also as a force for hope, driving innovations that continue to shape the future of medicine.

2 An Era of Historical Transformation

The End of Empires: Decolonization and Independence Movements

One of the most profound developments between 1955 and 1965 was the dramatic reorganization of global geopolitics. During this period, the number of sovereign states surged by over 50%, driven primarily by the collapse of European colonial empires [4]. After centuries of dominance, colonial powers were forced to relinquish control, leading to a wave of independence movements across Asia, Africa, and the Middle East [5]. This era of decolonization reshaped the political landscape, as newly sovereign nations emerged from the shadow of foreign rule, determined to assert their autonomy and redefine their futures on the global stage. The process was not without its challenges; the road to independence was often fraught with conflict, negotiation, and the struggle to forge national identities amidst the legacies of colonialism. Despite formal independence, however, many of these nations continued to contend with economic and political pressures exerted by former colonial powers—a dynamic that laid the foundation for neocolonialism. Thus, while decolonization redrew borders and ushered in a new era of self-determination, the persistent influence of foreign powers through economic dependencies and strategic interventions often limited the sovereignty these newly independent states had fought so hard to attain.

The origins of European colonialism lie in the Age of Exploration. At the close of the fifteenth century, two landmark voyages—those of Christopher Columbus [6] and Vasco da Gama [7]—brought Europe into direct contact with lands that would become known as the Americas and established new maritime routes to Asia. These expeditions marked the beginning of a rapid expansion, led by the Spanish, Portuguese, and Dutch, as European powers sought wealth through trade with distant territories. What initially began as the establishment of trading posts soon evolved into a more exploitative form of colonization, driven by the pursuit of resources and strategic dominance. As the sixteenth through the nineteenth centuries unfolded, other European nations, including the British, French, Germans, Russians, and Italians, were eager to stake their claim in this global competition, extending their reach across most of the Americas, Asia, the Middle East, Oceania, and the periphery of Africa. The relative inaccessibility of Africa's interior initially limited European influence there, as much of the continent remained unexplored. This changed in the mid-to-late nineteenth century, following the expeditions of prominent explorers such as David Livingstone [8], Henry Morton Stanley [9], and Pierre de Brazza [10]. Their explorations charted the once-mysterious interior, paving the way for the "Scramble for Africa." With the continent now mapped, European leaders convened at the Berlin Conference in 1885 [11], where they brazenly partitioned Africa among themselves, as if slicing a cake, solidifying colonial dominance over the region.

European colonialism officially dissolved during the period this chapter covers (1955–1965), though its unraveling began much earlier. In late June 1914, Archduke Franz Ferdinand, heir to the Austro-Hungarian throne, was assassinated in Sarajevo by a Bosnian Serb nationalist [12]. What followed was a cascade of flawed diplomatic maneuvers [13], ultimately plunging Europe into the bloodiest conflict it had ever seen [14]. In the aftermath of this devastation, the 1919 Paris Peace Conference saw U.S. President Woodrow Wilson introduce his 14 Points, with the principle of self-determination of nations at its core [15]. This concept resonated powerfully with leaders in colonized nations, igniting nationalist aspirations worldwide. Over the following decades, the nonviolent resistance led by Mahatma Gandhi secured India's independence from Britain [16], Ho Chi Minh's nationalist forces drove the French from Indochina after their defeat at Điện Biên Phủ [17], and a determined, violent insurgency led by Dedan Kimathi, Jomo Kenyatta, and other Kikuyu nationalists in Kenya left the British struggling to maintain control [18]. The momentum for self-determination culminated at the Bandung Conference in 1955, where leaders from 29 newly independent nations across Asia and Africa gathered to discuss a united stance against colonialism and foreign domination [19]. This unprecedented display of Afro-Asian solidarity reinforced the weakening foundations of European imperial power and underscored the growing influence of postcolonial nations on the global stage, accelerating the decolonization movement worldwide.

The foundations of European colonialism were dealt a decisive blow in July 1956 with the onset of the Suez Crisis. The crisis began when Egyptian President Gamal Abdel Nasser nationalized the Suez Canal [20], a strategic waterway previously under British and French control. Nasser's move aimed to fund the Aswan High Dam and reinforce Egyptian sovereignty, especially after the United States and Britain had withdrawn financial support for the dam, partly in response to Nasser's strengthening ties with the Soviet Union. In October, a covert alliance between Britain, France, and Israel led to a coordinated invasion of Egypt, which mounted a determined defense. However, intense international condemnation from both the United States and the Soviet Union compelled Britain, France, and Israel to withdraw by March 1957 [21]. This withdrawal marked a landmark diplomatic triumph for Nasser, a substantial setback to European imperial influence, and an inspiring precedent for leaders across the developing world.

Following the Suez Crisis, the independence movement surged across Africa, Asia, and beyond, fueled by visionary leaders who sought not only liberation from colonial rule but also the reimagining of their nations. In West Africa, Kwame Nkrumah emerged as a powerful voice for self-determination. Under his leadership, Ghana gained independence from Britain in 1957, becoming the first sub-Saharan African nation to do so [22]. Nkrumah's vision extended beyond national freedom; he championed pan-African unity, envisioning a continent free from foreign domination and committed to collective progress [23]. His influence resonated deeply, inspiring neighboring nations and establishing Ghana as a symbol of African self-governance. In East Africa, Julius Nyerere led Tanganyika (which eventually merged with Zanzibar to form the modern nation of Tanzania) to independence in 1961, promoting *ujamaa*, a philosophy centered on African socialism and self-reliance, which he hoped would foster unity and economic resilience across the region [24]. Similarly, Léopold Sédar Senghor, a key figure in Senegal's independence from France in 1960, infused the decolonization movement with his vision of *négritude*, celebrating African heritage and emphasizing the cultural renaissance of formerly colonized nations [25]. Beyond Africa, leaders in Asia, such as Indonesia's Sukarno, who had hosted the Bandung Conference, continued to strengthen bonds among newly independent states, highlighting their shared struggle and the power of solidarity [26]. This wave of independence prompted a critical response from British Prime Minister Harold Macmillan, who, in his famous 1960 "Winds of Change" speech in Cape Town, acknowledged the irreversible tide of decolonization sweeping across Africa and Asia [27]. Macmillan's speech signaled a profound shift in British policy, affirming the inevitable end of colonial rule and the arrival of a new era marked by self-governance and autonomy across the formerly colonized world.

As the independence movement swept across Africa and Asia, a new phase emerged: the onset of neocolonialism. While colonial empires formally withdrew, they often left behind economic and political structures designed to sustain dependency. Nowhere was this struggle against residual colonial influence more evident than in Algeria, where a brutal war of independence raged from 1954 to 1962. This conflict, known as the Algerian Revolution [28], was marked by widespread violence, including torture, mass arrests, and severe civilian casualties, as Algerian nationalists fought fiercely against France's military power. Ahmed Ben Bella, a prominent nationalist leader and founding member of the National Liberation Front (FLN), became a symbol of the Algerian fight for sovereignty and self-determination. The French government's refusal to relinquish Algeria—viewing it as an integral part of France—resulted in a particularly vicious campaign to suppress the independence movement, with atrocities committed on both sides. The war not only sought to expel French military presence but also to dismantle France's economic and political control, underscoring the reality that freedom from foreign rule would require both military and economic independence. The Algerian Revolution thus became emblematic of anti-colonial resistance, highlighting the immense sacrifices required to secure true autonomy and inspiring other colonized nations facing similar struggles against neocolonial forces.

Meanwhile, in Francophone sub-Saharan Africa, French President Charles de Gaulle confronted rising demands for independence by offering a stark choice: either join the newly formed French Community with limited autonomy or break away entirely [29]. When Sekou Touré of Guinea chose full independence in 1958 [30], France responded by severing economic ties, withdrawing all French assets, and even stripping government offices of light bulbs. Though punitive, France's reaction underscored the neocolonial tactics that would pervade the continent, as former colonizers sought to maintain influence through economic pressure rather than military might. Economic dependency on former colonial powers became common across Francophone Africa, where states remained tied to French trade, currency systems, and development aid—structures that effectively prolonged foreign influence under a guise of autonomy. Portugal, however, resisted the wave of decolonization, clinging fiercely to its colonies in Africa. It launched costly military campaigns to suppress independence movements in Angola and Mozambique, viewing these territories as integral to the Portuguese state [31]. The resulting wars of independence, which extended into the 1970s, highlighted the contrasting approaches of European powers and underscored the tenacity of colonial ambitions, even in the face of growing global condemnation. Similarly, in Asia, the British response to Malaya's demands for independence reflected neocolonial ambitions, as they worked to secure favorable trade terms and military alliances, ensuring their continued strategic presence in the region [32].

One of the most glaring instances of neocolonial interference unfolded in the Congo. Originally seized in the mid-1880s as personal property by Belgium's King Leopold II, the Congo Free State served as a source of immense wealth for the monarch, largely through the ruthless exploitation of its rubber resources. Leopold's pursuit of profit, however, was marked by a regime of staggering brutality [33]. When international scrutiny eventually forced Belgium to assume formal control of the Congo, the colonial administration made only minimal investments in public infrastructure, prioritizing resource extraction over sustainable development [34]. When Congo declared independence in June 1960, Belgium promptly intervened by backing the secession of the mineral-rich Katanga province. Led by Moise Tshombe, Katanga's leaders collaborated with Belgian and Western interests eager to maintain access to the region's vast mineral wealth [35]. Just weeks later, the Belgian government and the CIA orchestrated a coup to overthrow Prime Minister Patrice Lumumba, whose vision for a unified and independent Congo was seen as a threat to Western influence in Central Africa. In early 1961, Lumumba was transported to Elisabethville, the capital of Katanga, where he suffered brutal torture and execution. His remains were then destroyed with sulfuric acid to erase any trace of his existence [36]. Today, Lumumba stands as a revered martyr and a powerful symbol of Pan-African resistance against neocolonialism and imperialism.

The destabilization set in motion by Lumumba's 1961 assassination opened the door for Joseph Mobutu, who seized power with backing from the West, positioning himself as a reliable ally during the Cold War. Mobutu's reign would evolve into a three-decade-long dictatorship, marked by rampant corruption, resource exploitation, and the consolidation of a kleptocratic state that drained the country's wealth [37]. His rule left the Congo economically ravaged and politically fractured, setting a precedent for the cycles of conflict that continue to this day. In the aftermath of Mobutu's downfall, regional power struggles over the Congo's vast mineral wealth have fueled ongoing violence, creating one of the most protracted and devastating conflicts in modern African history [38]. The Congo's journey from colonial exploitation to neocolonial interference and dictatorship remains a stark reminder of the enduring consequences of foreign intervention and resource-driven agendas [39].

In parallel to European neocolonial endeavors, the United States emerged as a significant player in the shaping of postcolonial societies, frequently exerting influence through covert operations and diplomatic pressure. The early 1950s saw the CIA orchestrate the overthrow of democratically elected leaders like Mohammad Mossadegh in Iran and Jacobo Árbenz in Guatemala, both of whom threatened American economic interests with their nationalization policies. Mossadegh's ousting reasserted Western control over Iranian oil, while Árbenz's removal preserved American agribusiness dominance in Guatemala, setting a precedent for interventions motivated by perceived threats to US interests abroad. In Indonesia, Washington similarly backed efforts to destabilize President Sukarno, whose push for nonalignment and a unique national vision raised American suspicions. The CIA's support for opposition factions in Indonesia prefigured a broader pattern of covert actions aimed at influencing political landscapes in the Global South, often with substantial consequences for domestic autonomy. Meanwhile, the removal of Lumumba in the Congo, discussed above, underscored the extent of US intervention in Africa, reflecting a broader pattern of influence that extended across continents. This inclination toward interference was further exemplified by the Bay of Pigs invasion in Cuba and deepening American involvement in Vietnam, both of which are explored in detail in subsequent sections. Collectively, these actions—driven by a blend of economic interests and realpolitik—revealed a distinctly American form of neocolonialism that sought to preserve strategic dominance while outwardly advocating for the sovereignty and self-determination of newly independent states.

The period from 1955 to 1965 marked an extraordinary surge in decolonization, as nations across Africa, Asia, and the Middle East emerged from centuries of foreign rule to claim sovereignty and self-determination. This transformative process was complex and multifaceted, with each newly independent state navigating the challenges of defining its identity and governance while contending with the entrenched legacies of colonial control. Leaders like Ghana's Kwame Nkrumah, Algeria's Ahmed Ben Bella, and Egypt's Gamal Abdel Nasser inspired their nations with visions of independence and dignity, signaling a broader shift toward Afro-Asian solidarity against imperialism. The 1955 Bandung Conference exemplified this united stance, as 29 nations came together to champion a postcolonial future. Yet, true independence was seldom straightforward; colonial powers frequently resisted or manipulated the transition, drawing out negotiations, fostering internal divisions, and setting economic dependencies that allowed them to maintain influence after formal withdrawal [40]. This intricate dance of empowerment and constraint paved the way for what would later be termed neocolonialism.

While flags and governance structures changed, former colonial powers retained leverage through economic dependencies, selective support of local elites, and influence over trade and foreign policy. This power imbalance was further underscored by the fact that only the most technologically advanced nations possessed nuclear capabilities—a stark reminder of a global hierarchy in which military dominance and nuclear monopoly were held as instruments of control. In some cases, as in the Congo, this covert interference turned violent, with Western interventions undermining leaders whose visions posed a threat to established interests. Nevertheless, the resilience of these newly independent nations reshaped the global order, embedding the principles of self-determination and anti-imperialism into international discourse. In a brief span of a decade, decolonization not only redrew the world map but also transformed the political consciousness of the era, introducing the struggle for genuine autonomy as a defining global issue. This quest for true sovereignty—economic, political, and, for some, even nuclear—continues to resonate today as developing nations strive for equitable development in a world where power dynamics remain as complex as ever.

A Dream for Racial Equality: The Civil Rights Movement in the United States

The struggle for equality and self-determination that defined the decolonization movements across Asia, Africa, and the Middle East also found a powerful parallel in the United States during the same period. While newly sovereign nations grappled with the legacies of colonial rule, African Americans and other marginalized groups in the United States launched their own campaigns to dismantle systemic injustices that had persisted for generations. Both movements shared a common vision: the pursuit of dignity, agency, and freedom from institutionalized oppression. Just as newly independent nations fought to redefine their place on the global stage, the Civil Rights Movement aimed to reshape the social and political landscape within the United States. Together, these movements underscored a broader global yearning for justice and equality, challenging entrenched power structures in pursuit of true liberation.

The origins of African slavery extend deep into history, beginning with the Arab slave trade, which saw the forced movement of East Africans across the Indian Ocean to the Arabian Peninsula and parts of Asia from as early as the seventh century [41]. However, the transatlantic slave trade, initiated in the fifteenth century, would reshape this brutal institution on an unprecedented scale. European powers—primarily Portugal, Spain, Britain, France, and the Netherlands—established and profited immensely from a transatlantic network that forcibly transported Africans to the Americas. By the seventh century, bustling slave ports had developed along Africa's western coast, with infamous sites like Gorée Island in Senegal and Cape Coast Castle in modern-day Ghana serving as major hubs. These coastal outposts, where enslaved individuals endured inhumane conditions while awaiting transport, represented only the beginning of a horrific journey known as the Middle Passage, where millions lost their lives to disease, malnutrition, and abuse [42]. As slavery became deeply embedded in the colonial economies of the Americas, European societies eventually began to grapple with its moral implications. By the late eighteenth century, abolitionist movements had emerged, with Britain leading the charge under figures like William Wilberforce [43]. British activism culminated in the passage of the Slave Trade Act of 1807, which banned the trading of enslaved people, and the Slavery Abolition Act of 1833, which legally ended slavery in British territories. Across the Atlantic, the United States continued to expand its reliance on slavery, but tensions over the institution escalated as abolitionist voices grew louder [44]. By the mid-nineteenth century, the country was fractured, and in 1861, the Civil War erupted [45]. Under the leadership of President Abraham Lincoln and Union General Ulysses S. Grant, the war ultimately turned in favor of the Union, leading to Lincoln's Emancipation Proclamation and the formal abolition of slavery with the 13th Amendment [46]. The conclusion of the Civil War in 1865 finally freed millions, ending centuries of sanctioned bondage and setting the stage for the long, complex struggle toward equality.

Despite the abolition of slavery in 1865, African Americans in the United States continued to face profound restrictions on their freedoms, which persisted well into the twentieth century. Freed from formal bondage, they were nevertheless subjected to oppressive laws and social customs that reinforced racial segregation, economic marginalization, and political disenfranchisement. The Reconstruction era brought fleeting advances in rights and representation, but the rise of Jim Crow laws in the South systematically dismantled these gains, enforcing a racial caste system designed to keep black Americans as second-class citizens [47]. This institutionalized inequality sparked a gradual evolution of black consciousness, as African Americans sought ways to assert their identity, rights, and dignity in the face of systemic repression. Figures like W.E.B. Du Bois, with his advocacy for higher education and equal rights [48], and Marcus Garvey, who promoted black pride and self-determination [49], became pivotal in shaping a growing movement that emphasized unity, resilience, and the fight for civil rights. By the mid-twentieth century, this rising awareness had laid the groundwork for a powerful, collective push toward equality—one that would define the Civil Rights Movement of the 1950s and 1960s, challenging the racial status quo and calling the nation to fulfill its promise of freedom and justice for all.

In 1955, the brutal murder of Emmett Till became a defining moment in the civil rights movement and a stark testament to the deeply entrenched racial hatred in the United States. Till, a 14-year-old African American boy from Chicago was visiting family in Money, Mississippi, when he allegedly whistled at a white woman, Carolyn Bryant. For this perceived transgression, he was abducted by Bryant's husband, Roy, and his half-brother, J.W. Milam. The two men tortured, mutilated, and ultimately killed Till before discarding his body in the Tallahatchie River. His mother, Mamie Till-Mobley, bravely insisted on an open-casket funeral to reveal the horrors inflicted upon her son. The haunting images of Till's body published in *Jet* magazine shocked the nation, underscoring the pervasive violence against black Americans and catalyzing widespread outrage and calls for justice [50]. Although his murderers were acquitted by an all-white jury, Till's death ignited a moral reckoning that would fuel the civil rights movement for years to come.

Just months later, the arrest of Rosa Parks in Montgomery, Alabama, marked another watershed moment. On December 1, 1955, Parks, a 42-year-old black seamstress and long-time NAACP activist, refused to give up her seat to a white man on a segregated city bus. Her quiet defiance led to her arrest, and her courage inspired the African American community in Montgomery to organize a citywide boycott of the buses. This boycott, led by a then-unknown preacher named Martin Luther King Jr., would last 381 days, crippling the city's public transit revenue and drawing national attention [51]. Through persistent nonviolent resistance, the boycott successfully pressured the U.S. Supreme Court to declare segregation on public buses unconstitutional. Rosa Parks' refusal to comply with discriminatory laws and the Montgomery Bus Boycott underscored the power of grassroots activism and set the stage for broader campaigns challenging racial injustice.

In 1957, the Little Rock Crisis in Arkansas brought the struggle for civil rights into stark focus, underscoring the fierce resistance to desegregation in the American South. Following the landmark *Brown v. Board of Education* Supreme Court decision of 1954, which declared racial segregation in public schools unconstitutional, nine African American students, known as the Little Rock Nine, sought to enroll at Central High School in Little Rock. Their attempt was met with vitriolic opposition, as Governor Orval Faubus deployed the Arkansas National Guard to block their entry, defying federal authority. The images of angry white mobs threatening the students, contrasted with their quiet determination, captured national attention and ignited public outrage. In response, President Dwight D. Eisenhower took the unprecedented step of federalizing the National Guard and deploying the 101st Airborne Division to escort the students into the school, demonstrating the federal government's commitment to upholding the rule of law. The Little Rock Crisis highlighted both the courage of ordinary citizens in the fight for civil rights and the depth of institutional resistance to change, serving as a critical turning point in the broader struggle for equality.

As the civil rights movement gained momentum, activists continued to challenge segregation through bold and direct actions, including the Freedom Rides of 1961. Organized by the Congress of Racial Equality (CORE), the Freedom Riders were an interracial group of activists who boarded interstate buses bound for the South to test compliance with recent Supreme Court rulings that outlawed segregation on public transportation. The Freedom Riders encountered violent resistance, particularly in Alabama, where mobs attacked them, and local authorities often refused to intervene. In Anniston, a bus was firebombed, and in Montgomery and Birmingham, riders were beaten severely by angry mobs. Yet, the Freedom Riders pressed on, highlighting the federal government's failure to enforce desegregation laws and compelling the Kennedy administration to intervene, ultimately leading to new regulations to enforce desegregation in interstate travel. The Freedom Rides showed the world the determination of the movement and exposed the violent lengths to which segregationists would go to uphold racial divisions [52].

Throughout these years, Dr. Martin Luther King Jr. emerged as a moral and strategic leader of the civil rights movement. Drawing on principles of nonviolence and civil disobedience, inspired by Mahatma Gandhi and rooted in his Christian faith, King advocated for peaceful resistance against oppressive systems. As president of the Southern Christian Leadership Conference (SCLC), he organized and participated in major campaigns such as the Birmingham Campaign and the Selma to Montgomery marches [53]. His speeches, including his famous "I Have a Dream" address at the 1963 March on Washington, galvanized public support for civil rights by envisioning a future of racial equality and justice. King's steadfast commitment to nonviolence, despite frequent arrests, personal threats, and the bombing of his home, made him a powerful symbol of resilience and hope for millions. His work was instrumental in achieving significant legislative victories, including the Civil Rights Act of 1964 and the Voting Rights Act of 1965, which dismantled legalized racial segregation and disenfranchisement in the United States.

While Martin Luther King Jr. championed nonviolence and integration, Malcolm X emerged as a powerful voice advocating for black pride, self-defense, and black nationalism. Born Malcolm Little, he adopted the surname "X" to represent his lost African identity and became a devoted member of the Nation of Islam, an organization that emphasized black empowerment and separation from white society. Malcolm's speeches and writings passionately condemned the injustices faced by African Americans and criticized the slow pace of civil rights reforms. His rhetoric, unfiltered and unapologetic, resonated deeply with black Americans frustrated by systemic oppression and brutality. Unlike the mainstream civil rights leaders, Malcolm questioned the feasibility of integration, instead encouraging African Americans to take pride in their heritage and to defend themselves "by any means necessary." As he became disillusioned with the Nation of Islam's leadership under Elijah Muhammad, however, Malcolm made a pilgrimage to Mecca in 1964, where he experienced a profound shift in perspective, advocating instead for racial unity and peace on a global scale. His message began to evolve toward a vision of equality that transcended race [54], but this shift made him a target for enemies both inside and outside the Nation of Islam. On February 21, 1965, Malcolm X was assassinated while delivering a speech at the Audubon Ballroom in Harlem, New York. His death silenced one of the most dynamic and influential voices of the movement, but his legacy endures, inspiring generations to embrace self-determination, pride, and the fight against racial injustice.

The Civil Rights Act of 1964 was a turning point, capping years of sustained efforts by leaders like Martin Luther King Jr. and Malcolm X, as well as by countless citizens who joined protests, boycotts, and marches to confront systemic racism. Their dedication laid the groundwork for legislative change that outlawed discrimination based on race, color, religion, sex, or national origin, marking an essential step toward equal rights in the United States. This achievement echoed broader global movements for independence and self-determination as newly decolonized nations worked to break free from the legacies of colonial rule. Together, these parallel struggles highlighted a shared pursuit of dignity and justice, demonstrating how local efforts to end discrimination were part of a larger, worldwide push for freedom and equality.

The Cold War

The Cold War was the defining geopolitical struggle of the mid-twentieth century, a global standoff that shaped every aspect of international affairs. Its roots lay in the tenuous alliance between the United States, Britain, and the Soviet Union during World War II, a partnership bound by necessity rather than trust [55]. As the Allied leaders, President Franklin D. Roosevelt, Prime Minister Winston Churchill, and Premier Joseph Stalin, met at Yalta, ostensibly to shape a cooperative postwar order, ideological rifts simmered just beneath the surface [56]. The Soviet Union, driven by security concerns and an expansive vision for socialism, sought to establish a buffer zone of communist states across Eastern Europe. Meanwhile, the United States viewed these moves as the first steps in a campaign of aggressive communist expansion, necessitating a policy of containment. This clash of ideologies took on new urgency as the Cold War extended beyond Europe. In 1949, Mao Zedong's forces claimed victory in China's civil war [57], establishing a communist government that initially aligned with the Soviet Union. This "red takeover" added a vast new theater to the struggle, fueling American fears of a global communist wave. The Korean War, which erupted in 1950, soon brought these fears to the battlefield. North Korea, backed by Soviet arms, launched an invasion of the South, drawing in US and United Nations forces to repel the advance. But when US-led troops pressed northward, China intervened with overwhelming force, driving the conflict into a bloody stalemate [58]. By 1953, an armistice had been signed, but the peninsula remained divided—a potent reminder of the Cold War's grim reality and the ever-present threat of escalation. By 1955, the world had polarized around these superpowers, each championing competing ideologies and weaponized by nuclear arsenals, propelling humanity into a precarious era marked by the constant specter of total annihilation.

The death of Joseph Stalin in 1953 marked a profound turning point for the Soviet Union, setting in motion a shift in leadership and strategy that would reverberate across the Eastern Bloc and beyond. After a period of political jockeying, Nikita Khrushchev emerged as Stalin's successor, and his rise ushered in a new phase of Soviet policy that was both bold and turbulent. Khrushchev condemned the excesses of Stalin's rule in his famous "Secret Speech" of 1956, signaling a partial thaw in the rigid repression of Stalinism [59]. Yet, his push for "peaceful coexistence" with the West was soon tested by the limits of Soviet tolerance for rebellion within its sphere of influence. In 1955, with West Germany joining NATO, the Soviet Union formalized its own military alliance with the Eastern Bloc through the creation of the Warsaw Pact [60], solidifying a defensive bulwark against the West and binding its satellite states more tightly to Moscow. The strength of this alliance would be starkly tested the following year when Hungary attempted to break free from Soviet control, fueled by a burgeoning demand for political reform and national independence. For a brief moment, it seemed that the Hungarian Revolution might succeed, as Soviet forces initially withdrew. However, Khrushchev could not afford to lose Hungary without risking a cascade of defections from the Eastern Bloc. Soviet tanks returned to Budapest, crushing the revolution in a brutal show of force that reaffirmed Moscow's resolve to maintain dominance in Eastern Europe. Meanwhile, Khrushchev also pursued a vision of Soviet progress that would project the USSR as a technological powerhouse on the world stage. This ambition culminated in 1957 with the launch of *Sputnik*, the first artificial satellite to orbit Earth [61], which shocked the West and marked a watershed moment in the Cold War. *Sputnik*'s success demonstrated Soviet scientific prowess and inaugurated the Space Race, adding a new dimension to the ideological competition between superpowers. Through these moves, Khrushchev redefined Soviet leadership, asserting the USSR's place as a formidable global power while reinforcing its hold on the Eastern Bloc, even as he flirted with a more diplomatic approach to the West.

While the superpowers vied for dominance, the People's Republic of China, under Mao Zedong's leadership, embarked on a turbulent path that would profoundly shape its society and global standing. In 1958, Mao launched the Great Leap Forward, an ambitious campaign aimed at rapidly transforming China's agrarian economy into an industrial powerhouse. Communes replaced traditional village structures, and collective farming was enforced with revolutionary zeal. Yet, the campaign was a catastrophic failure. Unrealistic production targets, coupled with widespread mismanagement, led to agricultural collapse and one of history's deadliest famines, claiming tens of millions of lives. As the nation reeled, Mao's grip on power wavered, only for him to reassert dominance with the Cultural Revolution in 1966. This radical movement sought to purge "bourgeois" elements from Chinese society, unleashing Red Guards who targeted intellectuals, officials, and perceived enemies of the revolution. Schools closed, historical artifacts were destroyed, and society was thrown into chaos. These years of upheaval solidified China's break with the Soviet Union, as ideological and strategic rifts deepened between the two communist giants. By the mid-1960s, China stood as a distinct force in global politics, its revolution shaping the aspirations of leftist movements worldwide even as the nation bore the scars of Mao's radical experiments.

As the Cold War deepened, fear and suspicion permeated American society, with anxieties over communism reaching a fever pitch. This period, often epitomized by McCarthyism, saw Senator Joseph McCarthy rise to prominence by claiming that communist spies and sympathizers had infiltrated key institutions in the United States [62]. His relentless accusations, though largely unfounded, played into the public's growing paranoia, leading to widespread investigations, blacklists, and ruined careers. The era was marked by loyalty oaths, public loyalty hearings, and an erosion of civil liberties as the hunt for communists spread to Hollywood, the State Department, and even the military. Behind the scenes, the Dulles brothers—John Foster Dulles, Secretary of State, and Allen Dulles, Director of the CIA—wielded immense power in the US government's global fight against communism. John Foster Dulles was a staunch advocate of "massive retaliation" and "brinkmanship," a strategy that brought the United States to the edge of conflict, believing that only a strong, unyielding stance would deter Soviet aggression. Meanwhile, Allen Dulles directed CIA operations that covertly supported anti-communist regimes and orchestrated coups to safeguard American interests and prevent Soviet influence. Together, the Dulles brothers were instrumental in shaping America's foreign policy, transforming it into a relentless campaign to contain communism wherever it seemed to appear. This climate of heightened vigilance and interventionism reflected a nation gripped by fear, its leaders prepared to go to extreme lengths to protect democracy, even at the expense of individual freedoms and national stability [63]. As the Cold War continued, these internal and external pressures fed into an enduring culture of fear and suspicion, leaving a lasting impact on American society and its role on the world stage.

The U-2 spy plane program emerged as a critical asset in the American intelligence arsenal, a high-stakes effort to monitor Soviet activities from altitudes previously believed to be safe from interception. These high-altitude reconnaissance missions allowed the United States to gather invaluable intelligence on Soviet military installations, nuclear capabilities, and missile development, thereby offering a rare glimpse behind the Iron Curtain in a time of profound mistrust. However, the program's covert nature reached a devastating turning point in 1960, when a U-2 aircraft piloted by Francis Gary Powers was shot down deep within Soviet territory, unraveling the secrecy of the operation and leading to a major diplomatic crisis. Powers' capture presented a propaganda windfall for Soviet Premier Nikita Khrushchev and embarrassed the United States on the global stage, as it became clear that American surveillance efforts were not only extensive but also vulnerable. This incident underscored the complex duality of President Dwight D. Eisenhower's foreign policy legacy. On one hand, Eisenhower had famously avoided direct military engagement whenever possible, ending the Korean War and refusing to yield to pressure from his Secretary of State to use nuclear weapons in conflicts like Dien Bien Phu and the Taiwan Strait. His reluctance to escalate conflicts into open warfare showcased a measured approach to military power. Yet, beneath this restraint lay a willingness to wield clandestine influence, often through the CIA, which gained unprecedented authority under his administration. In his quest to counter Soviet influence without overt military confrontation, Eisenhower approved covert actions that reshaped nations. These CIA operations not only sanctioned coups and assassinations but also set a precedent of interventionism that would permeate US foreign policy for decades. Eisenhower's presidency thus reveals a leader caught between his commitment to peace and a deepening dependence on covert aggression, a paradox that highlighted both his aversion to direct conflict and his readiness to engage in covert wars that cast a long shadow over global politics [64].

The election of John F. Kennedy in 1960 ushered in a new era [65], one charged with a sense of purpose to counter communism's spread. Kennedy entered the White House amid escalating fears over Southeast Asia, where communist leader Ho Chi Minh sought to unify Vietnam under socialism. American policymakers were increasingly gripped by the conviction that a communist Vietnam would trigger a domino effect, leading neighboring countries across Southeast Asia to fall under communist rule [66]. This fear, rooted in the doctrine that any foothold gained by communism posed a dire threat to regional stability, drove Kennedy's administration to deepen US involvement in Vietnam. Thousands of American military advisers were deployed to support South Vietnam's military under President Ngo Dinh Diem, whose authoritarian rule—particularly his harsh persecution of the Buddhist majority—alienated much of the population and undercut US efforts. By 1963, as Diem's government teetered, American officials tacitly supported a coup that resulted in Diem's assassination, plunging South Vietnam into political chaos and binding it more tightly to US support as it struggled against Ho Chi Minh's forces. This entanglement paved the way for a larger American commitment, one that would soon transform Vietnam into a deeply divisive conflict and ultimately claim the lives of tens of thousands of US soldiers [67]. Though Kennedy did not live to witness the full scope of the war, his administration had laid the groundwork for a tragedy that would unfold largely after 1965, leaving a profound scar on the nation and shaping its future course.

As the Cold War intensified, Berlin became a focal point of ideological and territorial contest, a city split in two that exemplified the division of Europe itself. At the end of World War II, Germany was divided into zones administered by the Allied powers—the United States, the Soviet Union, Britain, and France. This division extended to Berlin, which, despite being deep within Soviet-controlled East Germany, was also partitioned among the Allies. Initially, Berliners could move relatively freely across these zones, maintaining family connections and a semblance of normalcy in a city still scarred by war. Yet, as East and West Germany developed along opposing economic and political lines, Berlin became an escape route for East Germans yearning for the political freedoms and economic opportunities of the West. Throughout the 1950s, this flow of defectors turned into a flood, as hundreds of thousands fled the repressive regime in East Germany. This migration, which included skilled workers, intellectuals, and young professionals, threatened the stability of the Eastern Bloc, fueling East Germany's economic woes and jeopardizing the socialist vision that Soviet Premier Nikita Khrushchev sought to sustain. As pressure mounted, Khrushchev demanded a solution to the "Berlin problem." In August 1961, the East German government, with Soviet approval, began constructing a wall that would enclose West Berlin, physically severing it from the surrounding East German territory. Over the course of days, barbed wire gave way to concrete slabs, and a formidable structure rose, with guard towers and searchlights casting a shadow over the border. This Berlin Wall became a symbol of the Iron Curtain, a harsh reminder of the lengths to which the Eastern Bloc would go to prevent the spread of Western influence and the exodus of its own citizens. Tensions reached a dangerous peak that October, when an American diplomat was denied entry to East Berlin. In response, US military forces moved tanks to Checkpoint Charlie, the crossing point between East and West controlled by the American sector. Within hours, Soviet tanks arrived on the other side. The two superpowers stood at the brink of direct conflict, each tank barrel aimed across a line that had become more than a geographic border—it was a line between worldviews. For 16 tense hours, American and Soviet forces stared each other down, ready to fire at a moment's notice. Only a quiet agreement, brokered by officials on both sides, led to a gradual withdrawal, averting what could have been a catastrophic escalation. This showdown at Checkpoint Charlie underscored Berlin's status as a flashpoint, a stage on which the Cold War drama played out with breathtaking intensity [68]. Each side knew that Berlin was not just a city but a symbol, and neither could afford to lose face in this arena where East met West. The standoff marked a perilous chapter in the Cold War, a high-stakes prelude to the even more dangerous confrontation that would soon unfold in Cuba.

Cuba's rise as a Cold War flashpoint is deeply tied to its long struggle against foreign domination, a fight that began in earnest under the leadership of José Martí, the revered poet and revolutionary. Martí envisioned a Cuba free from colonial rule and foreign exploitation, rallying his people with calls for independence, dignity, and social justice. After a protracted battle, Cuba gained independence from Spain in 1898 [69]. Yet, Martí's dream of a truly sovereign Cuba remained elusive, as the island fell under the shadow of American influence. US businesses came to dominate Cuba's sugar industry, and American interests controlled much of the nation's economy, leaving ordinary Cubans in poverty and dependence. This economic entanglement, which saw wealth concentrated in foreign hands, sowed resentment that would eventually ignite revolutionary fervor. By the mid-twentieth century, Cuba was governed by Fulgencio Batista, a dictator propped up by US support, whose corrupt and oppressive regime only deepened popular discontent and fueled the drive for genuine independence that Martí had once championed.

In 1959, a young revolutionary named Fidel Castro, alongside his Argentine comrade Che Guevara, led a revolution that toppled Batista's government. Initially, Castro's aims were framed around reform and independence rather than ideology [70]. Yet, as he faced resistance and, ultimately, hostility from the United States, he began to gravitate toward the Soviet Union. For the United States, this shift was nothing short of a catastrophe. To have a communist ally of the USSR, a mere 90 miles from Florida's shores was unthinkable, a direct affront to America's long-standing dominance in the Western Hemisphere. Determined to contain what they saw as an existential threat, the United States launched the Bay of Pigs invasion in 1961—a covert attempt to overthrow Castro by training Cuban exiles to mount a rebellion. The operation was a disaster. Poorly coordinated and lacking popular support, the invasion was swiftly crushed, embarrassing the United States and pushing Castro further into the Soviet orbit [71].

With Cuba now firmly aligned with the USSR, Nikita Khrushchev saw an opportunity. In 1962, Soviet forces began secretly installing nuclear missiles in Cuba, aimed at countering the American missiles positioned in Turkey and bridging the nuclear gap between the two superpowers. For the United States, this was an intolerable threat. Reconnaissance photos revealed the missile sites, and President Kennedy faced the grim realization that American cities could now be reached by Soviet nuclear weapons within minutes. Thus began the Cuban Missile Crisis—the most dangerous 13 days in human history. With both nations bristling with nuclear arsenals capable of annihilating all life, Kennedy demanded the removal of the missiles and declared a naval blockade to prevent any further Soviet shipments. The world stood on the edge, watching the steady march toward catastrophe. Day by day, tensions mounted, as each message exchanged between Kennedy and Khrushchev could either defuse the situation or spark all-out war [72].

In a breathtaking show of brinkmanship, Kennedy and Khrushchev managed to avert disaster. A deal was reached: the Soviet Union would dismantle its Cuban missiles, while the United States, in a secret agreement, would withdraw its Jupiter missiles from Turkey. Humanity had skirted the abyss by the slimmest of margins. Had either leader chosen aggression over negotiation, had either man acted out of pride rather than caution, the result might have been catastrophic. Kennedy's measured diplomacy and Khrushchev's willingness to back down preserved a fragile peace [73]. In those tense days, the world was fortunate to have leaders willing to put humanity's survival above personal victory. In the end, the Cuban Missile Crisis underscored the peril of nuclear armament and the urgent need for restraint. The confrontation marked the peak of Cold War tensions, a crescendo that underscored the terrifying power of the nuclear age and the delicate balance upon which human survival rested.

3 Reflections on History

The mid-twentieth century was a paradoxical era of profound fear and unparalleled ingenuity. Caught in the grip of the Cold War, humanity faced the omnipresent specter of nuclear annihilation. Yet, the same existential dread that cast a shadow over the era also fueled an unprecedented drive for scientific progress. From the race to dominate space to the quest to harness atomic energy for medicine, geopolitical tensions often served as a crucible, forging breakthroughs that would shape the course of history. The Space Race, in particular, stands as a vivid illustration of how global anxieties can catalyze innovation, transforming political rivalry into a vehicle for scientific discovery.

The launch of *Sputnik* in 1957 marked a turning point in human history. For the first time, a man-made object orbited Earth, its rhythmic radio beeps resonating as a symbol of Soviet scientific prowess—and a stark reminder to the United States of its vulnerability in the technological hierarchy. While *Sputnik* induced widespread anxiety in the West, it also galvanized a renewed commitment to science and education. Within months, the U.S. Congress passed the National Defense Education Act, prioritizing mathematics, science, and engineering in American schools to cultivate the next generation of innovators. The newly created National Aeronautics and Space Administration (NASA) became a focal point of this effort, spearheading projects that would ultimately culminate in the *Apollo* moon landing in 1969 [74]. Beneath the public spectacle of rockets piercing the heavens lay deeper philosophical questions about humanity's relationship with science and technology. Could the tools forged for destruction also serve as instruments of exploration and discovery? The answer, as history shows, is complex. The same knowledge that enabled the intercontinental ballistic missile (ICBM) propelled spacecraft to escape Earth's gravity [75]. Liquid-fueled rocket engines, perfected under the looming threat of war, became the lifeblood of peaceful space exploration. These dualities reflect the tension inherent in scientific progress during the Cold War: innovation spurred by fear yet imbued with the potential for transcendent achievement.

The Space Race also underscored how national ambition and international rivalry could align with humanity's broader aspirations [74]. While the Soviet Union and the United States competed for supremacy, their efforts brought humanity closer to the stars. Satellites enabled unprecedented communication networks, transforming how the world shared information. Scientific instruments sent into space delivered insights into Earth's climate, atmospheric composition, and geology, laying the groundwork for modern environmental science. In this way, geopolitical competition not only advanced national agendas but also enriched collective knowledge, demonstrating the power of science to bridge the divides it was ostensibly created to serve. This interplay between existential fear and scientific progress was not confined to the cosmos. On Earth, similar dynamics unfolded in fields like nuclear medicine and radiation therapy. The profound unease surrounding atomic energy's destructive potential drove efforts to understand and control it, paving the way for its medical applications. In this context, the development of the linear accelerator for cancer treatment serves as a poignant counterpoint to the nuclear arms race. Where one application of atomic energy threatened annihilation, the other offered hope and healing.

Such dualities invite reflection on the nature of scientific progress itself. At its core, science is neither inherently good nor evil; it is a tool shaped by the intentions of those who wield it. The Cold War demonstrates how the same pressures that can lead to destructive escalation can also inspire humanity to reach beyond its limitations. The innovations of this era—whether in space exploration, nuclear technology, or medical imaging—reflect a relentless drive to understand and control the forces that define our existence.

As the chapter now turns toward the scientific advancements of the period, it is essential to recognize the interconnectedness of these achievements with their historical context. The breakthroughs in radiation oncology and medical imaging that emerged between 1955 and 1965 were not isolated events but part of a broader narrative. They were shaped by the same anxieties that launched satellites into orbit and spurred humanity to confront its deepest fears. This convergence of geopolitical tension and scientific ambition illustrates a profound truth: even in the shadow of destruction, the human spirit is capable of extraordinary creativity.

4 An Era of Scientific Transformation

The Clinical Linac: A Catalyst in the Evolution of Cancer Care

The clinical linear accelerator, commonly known as the linac, represents the most transformative advancement in the history of radiation oncology, revolutionizing how cancer is treated worldwide. Before the linac became a central feature in cancer treatment, the options for radiotherapy were constrained by the limitations of earlier technology. Radiotherapy began with devices like x-ray tubes and radium [76], which were effective to a certain extent but lacked the penetration needed for deep-seated tumors, often causing significant radiation exposure to surrounding healthy tissue. Although groundbreaking for their time, these early devices could only deliver low-energy radiation, which penetrated tissues superficially and was not ideal for tumors located deeper within the body. In the 1930s and 1940s, cobalt-60 units and Van de Graaff generators emerged, offering some improvement in energy and, as a result, depth of penetration. Still, they did not meet the clinical need for highly controlled, deeply penetrating beams that could target internal tumors precisely with minimal damage to surrounding healthy tissues. The clinical demand for more advanced tools laid the groundwork for the eventual creation of the linac, a development that would permanently reshape the field of radiation oncology [77–79].

In the late 1940s and 1950s, the Medical Research Council (MRC) in the United Kingdom and Stanford University in the United States independently pursued the development of high-energy linacs for clinical use in radiation therapy. At the MRC's Radiotherapeutic Research Unit at Hammersmith Hospital, physicist Louis Harold Gray and his team [80], collaborating with engineers from Metropolitan-Vickers, developed an 8 MV linac specifically designed for treating deep-seated tumors. This unit featured a 3-meter accelerating waveguide that utilized a 2 MW magnetron to produce therapeutic x-rays, with an electron beam deflected 90 degrees to hit the target, yielding treatment fields up to 20 cm^2 at a distance of 1 meter and dose rates of approximately 150 cGy per minute. After months of rigorous testing, this machine was used to treat its first patient on September 7, 1953 [81].

Meanwhile, at Stanford University, physicist Edward Ginzton and radiologist Henry Kaplan collaborated to develop a 6 MV linac that also relied on a klystron to power the device. The Stanford linac used a 1.65-m waveguide and was initially positioned in a trunnion mount originally used for Van de Graaff accelerators, allowing for motion but falling short of the full isocentric rotation targeted by later designs [81]. The machine became operational in January 1956, treating its first patient and demonstrating the feasibility of high-energy x-ray therapy in the United States [82]. Kaplan's vision of integrating linac technology into clinical practice proved influential, as the Stanford machine garnered attention nationwide and solidified interdisciplinary approaches between engineering and medicine, exemplifying the practical potential of linac systems in cancer treatment.

The landmark treatments delivered by the newly developed linacs at Hammersmith and Stanford spurred a wave of advancements in linac design and clinical applications through the 1960s and beyond. These first-generation linacs, though groundbreaking, had notable technical limitations. Early models were restricted by limited gantry movement and relied on large vacuum systems that required frequent recalibration and occupied significant space, complicating both installation and operation. By the early 1960s, ongoing innovations addressed these issues [83]. Enhanced gantry designs allowed full rotation around the patient for multi-angle irradiation, and the introduction of isocentric mounting systems allowed consistent beam alignment with the tumor from multiple directions, with a fixed isocenter. This setup supported higher doses to the tumor while sparing surrounding healthy tissue. Another key development was the achromatic bending magnet, which helped stabilize electron beams by maintaining a consistent trajectory, addressing energy variation issues common in early models [84]. By the 1970s, these advancements—including refinements in waveguide design and gantry rotation—had led to more compact and efficient linacs.

The introduction of the linac allowed fractionation to become a routine aspect of radiation therapy by enabling precise, flexible dose delivery that previous technologies could not support. Unlike cobalt-60 units, which emitted a continuous, fixed radiation dose, the linac could generate controlled, high-energy x-ray beams on demand. This capability facilitated the shift toward treatment regimens spread over multiple fractions. Moreover, linacs provided adjustable beam energy and multi-angle targeting, facilitating accurate and repeatable administration of fractionated doses. The flexibility to modify dose, angle, and timing transformed fractionation from a theoretical concept into a practical clinical approach. As linac technology advanced, fractionation strategies diversified to include options like hypofractionation, which delivers fewer, higher-dose treatments, and hyperfractionation, which employs more frequent, smaller doses, adapting to patient and tumor-specific requirements [85].

The adoption of linac technology accelerated in the 1980s, with installations expanding worldwide as linacs gradually replaced cobalt-60 units in many centers. Linacs offered enhanced flexibility in treatment planning, including variable beam energy and dose modulation, which enabled more adaptable treatment approaches across a range of cancer types. Advances in engineering also helped reduce manufacturing and operational costs, making linacs more affordable for a broader range of healthcare facilities. This increased accessibility brought advanced radiotherapy options to more patients, establishing the linac as a central tool in radiation oncology. In low- and middle-income countries (LMICs), the transition to linac-based radiotherapy is still underway [86]. Although cobalt-60 units remain prevalent due to lower upfront costs and simpler maintenance, efforts are being made to increase access to linacs in these settings. Programs in global health are focused on expanding linac infrastructure, building local expertise, and addressing technical challenges unique to LMICs, such as reliable power supply and maintenance support. As these transitions progress, linacs are becoming increasingly integrated into cancer care in LMICs [87], improving treatment adaptability and precision globally.

The development of the multileaf collimator (MLC) in the 1980s was a major advancement in radiation therapy as it enabled clinicians to shape radiation beams to fit the contours of tumors more precisely. By adjusting motorized leaves to create complex, customized beam shapes, MLCs provided a foundation for intensity-modulated radiation therapy (IMRT). IMRT advanced treatment precision further by allowing differential dose intensities within a single field, sparing surrounding healthy tissue while delivering higher, targeted doses to the tumor. This was particularly valuable for treating irregularly shaped tumors or those near critical structures. IMRT also introduced a significant change in planning methodology, moving from “forward” planning to “inverse” planning. Unlike forward planning, where beam configurations are manually defined, inverse planning allows dosimetrists to define the desired dose distribution first. Sophisticated algorithms, such as those first developed by Thomas Bortfeld, then calculate the optimal beam arrangements to achieve this distribution [88]. This shift allowed for complex, highly conformal dose patterns that were previously unattainable, enhancing both the therapeutic effectiveness and safety of radiation therapy. Through these advancements, the MLC and IMRT together marked a transformative period in radiation oncology as linac technology adapted to meet increasingly complex clinical needs.

In the 2000s, cone-beam computed tomography (CBCT) was integrated into linac systems, significantly enhancing image-guided radiotherapy (IGRT). This development, spearheaded by David Jaffray and colleagues, provided the ability to capture imaging directly before each treatment session, allowing for precise patient alignment verification [89]. CBCT addressed the challenge of setup variability by confirming the patient’s position relative to the planned target just before treatment, which reduced setup uncertainties and helped minimize unintended exposure to healthy tissue.

The clinical linac is the foundational technology in modern radiation oncology, offering high-energy, precisely controlled radiation that replaced earlier low-energy, fixed-output devices like x-ray tubes and cobalt-60 units. Initial applications at Hammersmith and Stanford demonstrated the linac’s ability to target deep-seated tumors with megavoltage beams, setting new standards for dose delivery and tumor penetration. The linac’s adaptable design has enabled critical developments over time, including the integration of multileaf collimators (MLCs) and the transition to intensity-modulated radiation therapy (IMRT), which improved dose shaping and allowed for advanced planning techniques. Later additions, such as image-guided radiotherapy (IGRT), provided alignment verification, enabling more consistent setup precision. These advancements have cemented the linac as a scalable, flexible platform in radiation oncology, meeting the field's needs for precision and reliability in diverse therapeutic contexts.

Nuclear Spin Meets the Fourier Transformation: Richard Ernst's Impact

Richard Ernst's development of Fourier transform (FT) nuclear magnetic resonance (NMR) spectroscopy revolutionized the efficiency and sensitivity of magnetic resonance techniques, transforming NMR from a slow, labor-intensive process into a fast and versatile tool. Born in Winterthur, Switzerland, in 1933, Ernst's passion for chemistry led him to ETH Zurich, where he earned a PhD in 1962 [90]. During this period, he focused on enhancing the sensitivity of NMR, which was still a fledgling technology. After completing his PhD, Ernst joined Varian Associates in California in 1963, where he and his colleagues worked to refine NMR techniques, making them essential for a wide range of scientific applications [91]. Ernst's innovations laid the groundwork for magnetic resonance imaging (MRI) , which adapted NMR principles to create detailed images of the human body. Today, MRI has become indispensable in radiation oncology, where its superior soft-tissue contrast allows precise tumor targeting and treatment monitoring, highlighting the far-reaching impact of Ernst's pioneering work.

The roots of NMR spectroscopy can be traced to the mid-1940s, when teams led by Felix Bloch [92] and Edward Purcell [93] independently demonstrated that certain atomic nuclei could absorb and emit radiofrequency (RF) energy when placed in a magnetic field. For this discovery, they received the Nobel Prize in Physics in 1952. The basic principle involves placing a sample in a magnetic field, which aligns nuclei with a magnetic moment (such as hydrogen-1). When an RF pulse is applied, these nuclei absorb energy, and as they return to their equilibrium state, they emit signals. By analyzing these signals, scientists could deduce information about the chemical environment around the nuclei [94], effectively revealing the structure of molecules. However, the early methods required sequential scanning of each frequency, making the process slow and limiting its applications to simpler molecules.

In the late 1950s, Ernst became increasingly focused on overcoming these limitations. During his doctoral research at ETH Zurich, he studied the mechanisms of NMR signal detection and sought ways to enhance sensitivity. His early work laid the foundation for his later breakthrough at Varian Associates. Joining Varian in 1963 [95], Ernst entered an environment rich with pioneering research in magnetic resonance. It was here that he, together with his colleague Weston Anderson, developed FT-NMR [96]. This breakthrough came as a response to the inefficiencies of continuous wave (CW) NMR [97], which required the slow scanning of individual frequencies. Ernst's approach involved using a broad-spectrum RF pulse that could excite all resonant nuclei at once, producing a complex signal known as free induction decay (FID). This signal could then be analyzed using the Fourier transformation [98], a mathematical technique that rapidly converted the data into a spectrum displaying all the component frequencies of the resonant nuclei simultaneously.

The innovative use of the Fourier transformation allowed Ernst and Anderson to bypass the slow, sequential scanning process, significantly increasing the efficiency and sensitivity of NMR. This advancement enabled the study of complex molecules like proteins and nucleic acids, which were previously challenging to analyze due to their size and complexity. FT-NMR quickly became an essential tool across various scientific fields, helping to unravel intricate biological structures and chemical compounds [99]. Ernst's contributions during this period, particularly his application of advanced mathematical techniques to physical chemistry, were instrumental in the evolution of NMR from a rudimentary technique to a robust analytical method.

While NMR was originally applied to chemical analysis, the core principles behind the technique would eventually be adapted to develop MRI. Unlike NMR, which identifies chemical structures, MRI harnesses magnetic resonance to create detailed images of the human body. The evolution of NMR to MRI was made possible through the use of gradient magnetic fields, which enable spatial encoding. In MRI, a patient is placed in a strong magnetic field that aligns the hydrogen nuclei (protons) in the body's water and fat molecules. When an RF pulse is applied, these protons absorb energy and are momentarily knocked out of alignment. As they relax back, they emit signals that vary depending on the properties of the tissues around them. By applying gradient magnetic fields, the emitted signals can be localized, allowing MRI systems to reconstruct precise three-dimensional images of the body [100].

Ernst's insight to apply FT principles to MRI [101] played a crucial role in advancing the technology from a theoretical concept to a practical diagnostic tool. While Paul Lauterbur, credited with the invention of MRI [102], initially employed a back projection-based technique [103] for image reconstruction, similar to the reconstruction used in CT [104], it was Ernst's FT methods that enabled faster and more accurate processing. The application of Fourier transformation facilitated the generation of clear, high-resolution images of internal tissues, making MRI capable of producing detailed views of soft tissues—such as the brain, muscles, and internal organs—that are often indistinguishable on other imaging modalities like CT [105]. Ernst's foundational work on FT-NMR allowed these complex signals to be acquired and interpreted efficiently, bridging the gap between experimental physics and clinical practice.

The development of MRI, enabled by these principles, has had a transformative impact on radiation oncology, where precise imaging is critical for effective treatment. Accurate identification of tumor boundaries, known as target delineation [106], is essential in radiotherapy, and MRI's superior soft-tissue contrast [107] allows for precise targeting, especially for tumors in challenging areas such as the brain, liver, and prostate. This precision permits radiation oncologists to deliver high doses directly to the tumor while minimizing damage to surrounding healthy tissues [108]. For example, in head and neck cancers [109], MRI can distinguish between different muscle groups and lymph nodes, enhancing the ability to target the tumor accurately. In prostate cancer, for example, MRI is now the gold standard for identifying both the primary tumor and any adjacent metastatic lesions, which is essential for devising effective treatment plans [110].

Beyond initial diagnosis and planning, MRI is also used to monitor the response to treatment [111]. By tracking changes in tumor size, morphology, and physiological characteristics, oncologists can adjust treatment strategies in real time, ensuring that therapy remains effective. These capabilities are directly linked to Ernst's advancements in FT-NMR, which allowed for the efficient acquisition and processing of magnetic resonance signals. Detailed imaging empowers oncologists to make informed decisions and refine treatment plans, adapting them as needed throughout the course of therapy.

A significant development in recent years has been the integration of MRI with linear accelerators (linacs), leading to the creation of MRI-guided radiation therapy systems [112–114]. Traditionally, radiotherapy relies on CT imaging for guidance, which often struggles to differentiate between soft tissues. MRI-guided linacs have changed this dynamic, enabling real-time imaging during radiation delivery [115]. This allows clinicians to see the tumor and surrounding structures as they administer treatment [116], particularly beneficial for managing tumors in areas that move during normal physiological processes, like breathing, or in tumors located close to radiosensitive structures, such as the pancreas. With real-time visualization, clinicians can adapt the radiation beam to follow the tumor's motion, reducing exposure to healthy tissue and minimizing side effects.

The ability to dynamically gate radiation delivery is particularly valuable for treating mobile tumors, which can shift position due to respiration or other movements. For patients with lung cancer, for example, MRI guidance ensures that the radiation beam remains focused on the tumor even as it moves, turning off the radiation beam when the target has moved out of the planned radiation field [117]. Similarly, in treating tumors near critical structures, such as the pancreas that is surrounded by radiosensitive organs such as the stomach, duodenum, and bowel [118], MRI-guided systems allow for more precise targeting, reducing the risk of collateral damage. These advances, which build on the principles Ernst established, exemplify how foundational scientific discoveries can lead to substantial improvements in clinical care.

Looking to the future, MRI's role in radiation oncology is set to expand further with the development of biologically guided adaptive radiotherapy. This approach utilizes functional MRI techniques, such as diffusion-weighted imaging (DWI) [119] and dynamic contrast-enhanced MRI (DCE-MRI) [120], to capture information about the biological characteristics of tumors, beyond just their morphological anatomy. By assessing parameters like blood flow, cell density, and metabolic activity [121, 122], functional MRI techniques can provide insights into how tumors are responding to treatment at a physiological level. These data can then be used to adapt and personalize radiation therapy, tailoring the dose to target more aggressive areas of a tumor or sparing regions that are responding well [123]. The concept of “dose painting,” where different parts of a tumor receive customized radiation doses based on MRI data, represents a shift toward more personalized medicine, promising more effective treatments with fewer side effects.

Such techniques offer the potential to significantly improve outcomes, particularly for cancers that have been difficult to manage with traditional methods. By providing detailed insights into tumor biology, biologically guided adaptive radiotherapy can help identify areas that are more resistant to treatment and require a higher dose while sparing healthy tissue [124]. Though still in the early stages of clinical application, this approach builds on the precision and adaptability introduced by MRI-guided systems, pointing toward a future where real-time imaging and individualized therapy become standard in radiation oncology. Additionally, functional MRI might open new opportunities to integrate radiotherapy with other treatments, such as immunotherapy or targeted drug delivery, potentially enhancing therapeutic outcomes.

The broader historical context of Ernst’s work reflects a period of rapid scientific and technological progress during the mid-twentieth century, driven in part by the pressures of the Cold War. Significant investments in nuclear research, aimed at developing new energy sources and military technologies, created fertile ground for breakthroughs across many fields [125]. While much of the initial impetus for this research was geopolitical, the scientific advances that emerged—such as improvements in magnetic resonance—found diverse and often life-saving applications. Ernst’s work, which made it possible to analyze complex molecular structures quickly and accurately, was one of the pivotal discoveries that set the stage for later developments in medical imaging and, eventually, the management of disease.

Today, MRI is a cornerstone of modern medicine, and its integration into radiation oncology highlights the enduring influence of Ernst’s legacy. MRI-guided systems, biologically adaptive radiotherapy, and the potential for personalized, real-time treatment are all rooted in the ability to process magnetic resonance data efficiently—a capability that Ernst’s FT-NMR helped refine. His work, although initially focused on the intersection between spin physics and chemistry, has had a profound and lasting impact across multiple domains, from research laboratories to clinical care. As radiation oncology continues to advance toward more precise, adaptive treatments, the principles Ernst established will remain central, demonstrating how fundamental discoveries can lead to meaningful and far-reaching improvements in patient care.

5 Reflections on Science

Science, at its essence, is a profound testament to human curiosity and resilience. It reflects our drive to understand, control, and ultimately improve the world around us. As this chapter has shown, the mid-twentieth century was a period of extraordinary scientific transformation, shaped by the paradoxical forces of fear and hope.

This duality—the capacity for science to both threaten and heal—underscores the ethical complexities inherent in progress.

Between 1955 and 1965, advances in atomic energy, medical imaging, and radiation oncology exemplified how scientific discoveries often arise from the tension between existential crises and the aspiration for a better future. The development of the clinical linear accelerator and advances in magnetic resonance imaging illustrate the power of interdisciplinary collaboration, where physicists, engineers, and clinicians merged their expertise to redefine what was possible in medicine. These innovations did not emerge in isolation; they were deeply rooted in their historical context, driven by the urgency of the Cold War and the broader quest to harness knowledge for the betterment of humanity.

The relationship between science and its historical milieu is not linear but deeply intertwined. The very technology that could obliterate cities in seconds also became a tool for saving lives, offering a poignant reminder that science itself is neutral—its impact shaped by the intentions of its creators. The same nuclear energy that fueled the arms races propelled breakthroughs in cancer treatment, transforming a symbol of destruction into one of hope. Similarly, magnetic resonance, born from the Cold War's push for technological superiority, evolved into one of medicine's most powerful diagnostic tools, demonstrating how even geopolitical rivalries can sow the seeds of progress.

As we reflect on this transformative era, it becomes clear that the true power of science lies in its adaptability and potential for reinvention. The mid-twentieth century taught us that moments of profound uncertainty often serve as catalysts for innovation. Yet, these advancements also highlight a critical responsibility: to wield scientific knowledge with humility and foresight, ensuring that its applications prioritize human well-being over short-term gains or destructive ambitions.

This chapter's exploration of science during a turbulent period invites us to consider the broader role of scientific inquiry in society. Beyond its technical achievements, science carries the potential to unite—bridging disciplines, nations, and ideologies in pursuit of shared goals. The enduring legacies of the linear accelerator and FT-NMR are not just in their technical brilliance but in their testament to collaboration, creativity, and the pursuit of solutions to humanity's most pressing challenges.

Ultimately, the story of science in this period is one of resilience. It reminds us that even in the shadow of potential annihilation, the human spirit can rise to transform fear into discovery, destruction into healing, and conflict into collaboration. As we look to the future, this legacy challenges us to approach scientific progress with both ambition and responsibility, ensuring that its trajectory continues to align with the betterment of humanity. In doing so, we honor the profound lessons of this transformative era, carrying its spirit forward into the challenges yet to come.

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The War on Cancer and Other Wars, 1965–1975

Kristi R. G. Hendrickson and Todd A. Swanson

1 Nixon's War on Cancer

The National Cancer Act of 1971 ushered in a renaissance in cancer care in America. Signed into law on December 23, 1971, it was championed by health activist and philanthropist Mary Lasker, who is credited with being instrumental in persuading Congress to pass the act. No stranger to scientific philanthropy, Lasker and her husband Albert had previously established the Lasker Foundation in 1942 to recognize scientists for their medical research. As of 2023, 86 Lasker Medical Research Award Winners have gone on to win the Nobel Prize [1]. Richard Nixon's signature on the bill strengthened the National Cancer Institute (NCI) at a time when cancer had become the second leading cause of death in America. In fact, at that time, only about one in two people diagnosed with cancer survived at least 5 years—compared to two of three people diagnosed with the disease today [2]. The legislation granted broad authority to the director of the NCI to establish new cancer research centers, support training programs for physicians, award research contracts, and promote collaborations between federal, state, local, and private entities. The act, which later became known as the "war on cancer," was introduced in President Nixon's State of the Union address with the declaration that "the time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease." The proposal included an additional $100 million (nearly $700 million in 2021 dollars) of federal funding for cancer [3]. Despite its wildly ambitious rhetoric of curing cancer in the time frame

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of those other scientific and technical advances and the fact that we are still fighting the "war on cancer," the legislation gave the field of Radiation Oncology a jolt at a time when a confluence of other activities was synergizing to advance the field.

2 Organizing the Troops

The late 1960s through the 1970s represented a period of maturation in the specialty of radiation oncology. Before this period, most practicing radiation oncologists were trained as general radiologists. Also, many physicians practicing radiotherapy in the United States were trained in Europe. Among those practicing, there was a recognized need to form a society to promote the professional interest of this burgeoning field.

Although a loosely cohesive American Club of Therapeutic Radiologists existed, 1966 saw the formalization of the American Society of Therapeutic Radiologists (ASTR). Seeking to include ancillary disciplines, the society offered associate memberships for radiobiologists, radiation physicists, nuclear medicine physicians, and tumor pathologists. Initially, ASTR held its annual scientific meeting in conjunction with the annual meeting of the Radiological Society of North America (RSNA). But by 1970, the society held its first independent meeting in Scottsdale, Arizona.

3 Structure and Function

The initial goals of the newly created ASTR were to promote the development of the field with respect to (1) standards of clinical practice, (2) teaching and training in radiotherapy, and (3) clinical and basic research [4]. The first objective was achieved through the formation of the Committee for Radiation Therapy Studies (CRTS), which set radiotherapy practice standards by outlining the recommended resources, facilities, and personnel with the publication of the "blue books." The divergence of radiotherapy from diagnostic radiology created a need for radiation oncology-specific training, as articulated in ASTR's second initial goal. The number of radiation oncology residencies tripled between 1960 and 1970, and by 1973, almost no one entering the field was trained first in general radiology [4]. The third goal to promote clinical and basic research led to the creation of the Radiation Therapy Oncology Group (RTOG) in 1968, with the CRTS playing a leading role in its formation. This national collaborative trials group, funded by the NCI, was essential for coordinating basic, clinical, and physics research in the United States. Between 1971 and 2014, the RTOG activated over 500 trials, accruing over 110,000 patients and resulting in over 1000 publications. Perhaps more importantly, the RTOG's efforts led to improvements in local/regional control and survival of scores of cancer patients [5].

Initially, the ASTR voted to designate the *Journal Cancer* as the official publication of the society in 1971. However, after four years, the membership of the society began to look for its own voice as a dedicated channel for the communication of radiation oncology issues. In 1974, the inaugural edition of the *International Journal of Radiation Oncology*Biology*Physics (IJOBP)*, now known affectionately as the Red Journal, began as the society's official publication. ASTR also felt the need to produce a textbook for the field. It so came to be the definitive text of radiation oncology, "*Principles and Practice of Radiation Oncology.*" [4].

4 Technological Advances

During the decade 1965–1975, radiation oncology and cancer care advanced by introducing the computed tomography (CT) scanner that facilitated imaging of tumors and 3D planning, and stereotactic radiosurgery as a treatment modality with the commercial release of the Gamma Knife.

5 CT Scanner

The three-dimensional internal imaging of tumors became a reality with the introduction of computed tomography (CT) in the early 1970s. Computed tomography refers to a computer-generated image generated by a narrow beam of low-energy X-ray radiation passing through the body while the source and beam of radiation rotate around the body. Detectors mounted opposite the radiation beam source measure the attenuated beam. Signal processing and analysis of the detected signals result in a cross-sectional image slice corresponding to a single rotation around the body or scanner bed. The body on the scanner bed also moves through the center of the scanner while the X-ray source and detector rotate, allowing multiple slices of the body or object to be acquired and built up into a fully three-dimensional image. This three-dimensional image provides substantially more detail of internal anatomy over a conventional two-dimensional X-ray (think "chest X-ray"). Normal structures of the body and abnormalities such as tumors can be located and visualized within a CT image.

The first commercially available CT scanner in 1972 was developed by British engineer Godfrey Hounsfield working at Electric and Music Industries (EMI) Laboratories, which also owned Abbey Road Studios, the recording studio of the Beatles and other prominent musical groups [6, 7]. His co-inventor, physicist Dr. Allan Cormack, shared the 1979 Nobel Prize in Medicine with Hounsfield. Hounsfield's aim was to invent a technology that would reconstruct a three-dimensional picture of a box with objects inside. Radiologist James Ambrose contributed to the transition of the prototype to medical applications. The first human patient was a woman suffering from a brain tumor. She was scanned on October 1,

1971. The scan took several hours to obtain the raw data for a single scan or "slice" and a few days to reconstruct the image from the acquired data.

The development of CT scanner technology and sophisticated image processing next led to the leap from two-dimensional radiotherapy planning to target tumors seen on X-rays or by physical palpation to more conformal radiotherapy planning techniques that utilized the three-dimensional knowledge of the location of internal tumors to target and the sensitive normal organs to avoid. Prior to the use of CT in radiotherapy planning, radiographic images were used to visualize the tumor relative to nearby anatomy, usually bony anatomy. Rectangular block shapes for open treatment fields were created with attenuating jaws within the treatment head of the radiotherapy device. The size of the rectangular field was customized to irradiate the tumor and block radiation to other tissues outside the collimated field. Dose calculations were completed by hand, using factors such as field size, radiation energy, and distance to the tumor from the external skin surface. By 1974, the first dedicated computational planning systems were introduced [8].

6 Positron Emission Tomography (PET)

The concept of positron emission tomography (PET) scanning can be traced back to the mid-twentieth century when researchers began exploring the possibilities of utilizing positron-emitting isotopes for medical imaging. The efforts involved physicists, chemists, engineers, and medical professionals from the University of Pennsylvania, UCLA, and the University of Washington, among others. PET scans offer the most specific and sensitive means of imaging molecular interactions in the body. Current PET scans are now used in tandem with CT scans; however, the development of the technology took place separately, nearly in parallel with the developments in CT imaging. Although PET scans are common in oncology practice now, the information gained from molecular imaging suggests new cancer-fighting techniques, such as biologically targeted radiotherapy. This section details some of the important milestones in the development of the PET scan between 1965 and 1975, culminating in its first use in humans.

In 1965, Dr. Michel Ter-Pogossian and his team of researchers at the University of Pennsylvania began experimenting with positron-emitting isotopes and optimal methods to detect and visualize their emissions. Initial experiments focused on studying brain metabolism, employing positron emitters like 13 N-ammonia and 11C-labeled compounds. [9] This early work demonstrated proof-of-concept for the use of this technology in human patients. The development of instrumentation for PET imaging followed. Between 1972 and 1973, Dr. Michael E. Phelps and his team at the University of Washington designed and constructed the first dedicated PET scanner (PETT II) [10]. The development of detectors capable of accurately capturing and localizing positron emissions marked a turning point in the evolution of PET technology.

It did not take long before Drs. Edward Hoffman and Michael E. Phelps collaborated to develop the first commercially available PET scanner [9]. By 1975, the successful imaging of various metabolic processes, including cancer and neurological disorders, and the commercial availability of PET scanners contributed to the widespread acceptance of PET as a diagnostic tool in the medical community. The proliferation of imaging technology went hand in hand with the proliferation of cyclotrons in medical centers, as required to produce the short-lived isotopes for nuclear medicine diagnostics and therapeutics [10].

In conclusion, the period from 1965 to 1975 witnessed a remarkable evolution in the development of PET scans. From early proof-of-concept experiments to the commercial availability of dedicated PET scanners, researchers made significant strides in overcoming technical challenges and demonstrating the clinical utility of PET imaging, setting the stage for its widespread adoption in subsequent years. Although PET scan information is currently integrated in modern radiation therapy, we have likely scratched the surface in the burgeoning era of molecular targeting and stereotactic ablative technologies for oligo-metastasis.

7 Gamma Knife

Undoubtedly one of the most productive technical achievements resulting from the marriage of radiation therapy and neurosurgery during 1965–1975 was the development of the Gamma Knife. Stereotactic radiosurgery delivers high-dose radiation to small targets in the brain, akin to a noninvasive surgery technique. In 1967, the first Gamma Knife device was constructed using 179 cobalt-60 sources in a hemispheric array by Swedish radiobiologist and medical physicist Borje Larsson of the Gustaf Werner Institute, University of Uppsala, and neurosurgeon Lars Leksell at the Karolina Institute in Stockholm. The first patient was treated in 1968 for a craniopharyngioma. The Elekta Corporation was founded by Leksell in 1972 to manufacture the Gamma Knife commercially.

This “non-bloody brain surgery” soon gained traction in the media. Leksell had estimated that three to five Gamma Knives would probably be enough to meet the demand of the world’s needs [11]. His prediction proved to wildly underestimate the explosive demand for such an approach. According to the National Centre for Stereotactic Radiosurgery, there are over 300 Gamma Knife Treatment facilities worldwide, as of this writing, with approximately 60,000 patients treated yearly. In 1975, the second-generation Gamma Knife unit was developed and released as a commercial unit and available worldwide. As systemic treatment continues to improve, brain metastasis remains a challenge, and no platform treats brain metastasis while sparing a maximum volume of normal brain better than the Gamma Knife.

8 Brachytherapy

The era of 1965–1975 saw innovations in brachytherapy, one of the original forms of radiotherapy that relied primarily on the isotope radium and its derivatives. New techniques for treating prostate, gynecological, and other cancer disease sites were developed. The Paris System, a dosimetric system that optimizes dose distribution for iridium-192 wires used in interstitial brachytherapy, was introduced by Pierquin and Dutreix [12].

9 Prostate Brachytherapy

Early prostate permanent implants were performed through a retropubic incision. This presented anatomical challenges for visualization contingent on the prostate size and variation of the public arch amongst patients. This approach also precluded assessment/dissection of the lymph nodes for adequate disease staging, in an era predating CT scans and prostate-specific antigen (PSA) for risk stratification. Seed placement was performed through trocars that were advanced to the rectal wall under palpation by the brachytherapist's finger inserted into the patient's rectum. Seeds were placed based on modeling of the patient's prostate based on intraoperative measurements, using calipers and normograms for loading peripheral dose. The postoperative assessment was based solely on orthogonal X-ray films. Results in these patients were poor, given the challenges of staging, imaging, and implant techniques [13].

However, in the early 1970s, incremental progress was made by physicians at Memorial Sloan-Kettering Cancer Center. The implants were performed via a retroperitoneal approach, allowing lymph node dissection for surgical staging. They began using ^{125}iodine permanent seeds instead of the commonly used ^{198}Au (gold) seeds. Iodine had the benefit of a lower energy and, hence, a tighter dose distribution, with only 2 cm of tissue beyond the seed receiving half the prescribed dose instead of 6 cm for ^{198}Au [13]. Additionally, with a longer half-life and the relatively slow growth of prostate cancer, it had the theoretical advantage in treatment allowing longer times for normal tissues to repair damage and leading to less acute toxicities.

Yet another significant development in the field of brachytherapy was the advent of the commercially available brachytherapy after-loader. Both high-dose and low-dose rate models were available. High specific activity sources, initially cesium-137 and iridium-198, were used; however, for shorter treatments ^{198}Ir was preferred. Patients were first implanted with plastic "conduits" in which the source would travel through on a guidewire. Electronic controls allowed movement within the conduit, stopping at planned intervals to mimic the dose distribution of a low-dose-rate permanent implant. Once implanted, the patient was transferred to a "hot room" and connected to the after-loader. The staff could then release the source from the radioactive shielding vault into the "conduits" via the guidewire using electronic controls in an outside control room. This greatly decreased the radiation exposure of staff, reduced treatment times, and allowed increased efficiency with greater patient throughout.

10 Radiobiology Contributions

While the physicians and physicists were making advances in their respective corners, the third pillar of the field of Radiation Oncology–the Radiobiologists–were pushing ahead with advances in their arena. Central concepts in the mechanism of radiation's damage at the cellular level were articulated. Researchers adapted techniques developed previously in cell culture lines to assess the effects on cell growth and reproduction of primary tissue derived from laboratory animals. In 1967, experiments were described whereby patches of irradiated skin exhibited nodule regrowth in the irradiation field that correlated with the number of stem cells, which were relatively resistant to radiation [14]. Similar experiments were performed with irradiated intestines, whereby the number of regenerating crypts allowed similar quantitative assessments of the number of stem cells present in the gut [13]. Not only did these experiments set the foundation for a more comprehensive understanding of the intrinsic radio-sensitivity of solid tissues, but these experiments were critical to the development of stem cell biology, which led to stem cell transplants in hematologic malignancies [15].

Attention then turned to quantizing the radiosensitivity of various tumors. In 1966. Suit et al. introduced the concept of tumor control dose 50% (TCD50). [16] This required the injection of tumor cells into numerous mice, allowing the tumors to grow to similar sizes, irradiating them with varying doses of radiation, and then assessing the animals for tumor recurrence locally. Plotting tumor control as a function of radiation dose allowed the determination of the TCD50 for various tumors. A similar metric was developed by other researchers using similar models, in which they measured volumetric changes in tumors, again as a function of dose, to develop yet another technique still used today– the tumor growth delay assay [17].

During this time, radiobiologists were exploring the benefits of fractionated radiotherapy and how doing so would confer a therapeutic advantage by selectively killing tumor cells while leaving normal cells intact. It was demonstrated that, when normal cells were irradiated, the sublethal damage could be repaired prior to the subsequent radiation fraction, whereas the rapidly dividing tumor cells could not. The unrepaired error in the tumor cells would lead to cell death, leaving the normal cells that had repaired the damage in the interval. The differences in progression through the cell cycle led to the redistribution of cells and the selective sensitivity of rapidly progressing cells. This, along with several other concepts, converged into what became an axiom of radiation therapy: the 4 R's. Together, differences in repair, redistribution, reoxygenation, and repopulation were conceived as the mechanisms for selective killing of tumor cells by fractionated radiotherapy [18].

It was understood that the tumor microenvironment was relatively hypoxic. According to the 4 R's, reoxygenation increases radio-sensitivity. This led to the search for ways to exploit strategies to improve oxygenation within tumors treated with fractionated radiotherapy. The use of radiotherapy in conjunction with hyperbaric oxygen (HBO) was an attempt to improve oxygenation in the target tissue [19]. Most of the human trials during this period did not show significant tumor control benefit and introduced formidable barriers to delivery, as HBO chambers for humans are limited to specialized centers. Worse yet, there were reports that, in cases of metastatic disease, HBO treatments promoted the rapid growth of disseminated disease. Other efforts to exploit reoxygenation within fractionated radiotherapy led to the development of compounds that mimicked oxygen's effects during radiation therapy. One such compound is misonidazole. Although this compound was impressive in vivo and even in small animal models, the compound has dose-limiting neurotoxicities in humans. Nonetheless, a later meta-analysis of 50 trials in six tumor sites (data from over 7000 patients) demonstrated an improvement of local control when nitroimidazoles (misonidazole and related agents) were added to radiation therapy [20].

11 World Events

Within the United States, the decade of 1965–1975 witnessed several significant events that challenged moral sensibilities, are still impactful today, and served as a constant backdrop to the war on cancer and the technological advances in Radiation Oncology and cancer treatments. The Cold War and Vietnam-American War were ongoing, and the fight for civil rights was underway. The atmosphere included a sense of uncertainty and fear with political events worldwide and a sense of optimism and hope with the gains in civil rights and advances in science and technologies. Don't forget, the quest to put a man on the moon was in progress.

The Vietnam-American War was a conflict in Southeast Asia that began in 1955 and lasted until the fall of Saigon in April 1975. It was a major conflict of the Cold War. While the war was officially fought between North Vietnam and South Vietnam, the North was supported by the Soviet Union, China, and other communist states, while the South was supported by the United States and other anti-communist allies, making the war a proxy war between the United States and the Soviet Union. Military involvement in the conflict was controversial among Americans, and opinions divided the nation. It lasted almost 20 years, with direct US military involvement ending in 1973. Estimates of total deaths as a result of the war vary, with one estimate at 791,000–1,141,000 Vietnamese deaths and 64,000 American and allied military deaths. It ended with Vietnam officially becoming a communist state by 1976 [21].

In 1967, Israeli and Arab forces battled during what is known as the Six-day War. It ends with Israel occupying the Sinai Peninsula, Golan Heights, Gaza Strip, and the east bank of the Suez Canal.

Also in 1967, Thurgood Marshall was sworn in as the first black U.S. Supreme Court justice. He served until his retirement in 1991.

The decade includes several devastating assassinations of prominent progressive leaders in civil rights and politics. Malcolm X was shot to death at a rally in Harlem, New York, in 1965, and Martin Luther King Jr. and Robert F. Kennedy were assassinated in separate incidents in 1968.

12 The Assassination of Martin Luther King Jr. (April 4, 1968)

Martin Luther King Jr., an African American clergyman and the leading civil rights leader of the time [22], was in Tennessee in support of striking African American city sanitation workers engaged in a walkout in protest of unequal wages and working conditions for African Americans. The assassination happened early in the evening when King went out onto the balcony of his hotel room. After being shot, he never regained consciousness and was pronounced dead at 7:05 pm after surgical attempts to save him. His funeral was held on April 9, 1968, with a crowd of over 300,000 attending. He was a Nobel Peace Prize laureate known for using nonviolence and civil disobedience in protests [23].

13 Other Civil Rights Events [24, 25]

The 1968 Summer Olympics are remembered for the medals presentation on the podium stand after the men's 200-m dash on October 16. Two African American athletes were among the medal winners. Tommie Smith won the gold medal, and John Carlos won the bronze medal. At the podium, they stood without shoes to signify the poverty of African American communities. They wore black scarves to signify black pride. When the American anthem played, they raised a fist in the air with a black glove in a salute to human rights. Many in the crowd booed the athletes. Fifty years later, similar protests by athletes indicate that the fight for civil rights is still a work in progress.

The Stonewall riot in New York City in 1969 marked the beginning of the gay rights movement.

Beyond the international wars and internal civil rights conflicts, technology allowed humankind to explore space outside Earth's thin atmosphere. In 1968, Apollo 8 astronauts were on the first mission to leave Earth's orbit and travel toward the moon. They were the first to witness the famous *Earthrise,* a color photo taken with the Earth partially black and appearing to rise over the moon's surface. In 1969, Neil Armstrong and other Apollo 11 astronauts became the first to walk on the moon. In 1975, the *Soyuz* and *Apollo* spacecrafts lifted off for a US–Soviet link-up in space.

The Woodstock Music Festival was held in August 1969. And on broadcast television, Sesame Street debuts. With less fanfare but no less impact, the Internet (ARPA) went online in 1969.

In 1973, the U.S. Supreme Court ruled on *Roe v. Wade*. In 1974, President Richard Nixon resigned his office, following the Watergate scandal and coverup.

14 Notable Contributions to Cancer Care

Physicians, physicists, and scientists from minority populations have been largely missing from the radiation oncology workforce since its split from radiology. There is also a clear lack of progress in representation in the field compared to other fields in more contemporary times. For instance, a 2020 *JAMA* study has found that, of senior radiation oncology faculty in the US academic medical departments, only 1.52% were black and only 1.3% of Hispanic, Latino, or Spanish origin in 2019. This trend has remained static from 2000 to 2019. However, disciplines that also participate in the care of oncology patients, that is, surgery, radiology, and internal medicine, all saw increases in the proportion of underrepresented minorities at the level of senior faculty during the same period [26]. As well, even as the incidence of cancer in blacks closely approximates that in whites and according to the 2020 US Census, blacks represent nearly 13% of Americans, approximately 3% of practicing oncologists are African American. Much of this lack of progress is attributed to the lack of mentors and role models in these roles, among the layers of obstacles to the education and training needed to enter these professions. The contributions of racial and ethnic minorities and women have been underrecognized throughout history including the 10 years of 1965–1975. These individuals faced formidable obstacles in pursuing education, research opportunities, and clinical practice roles. The accomplishments achieved are therefore even more remarkable. Here we highlight the contributions to cancer care of five African Americans whose impacts were felt in this 10-year period in history [27].

Eva M. Noles (1919–2015) was the first African American woman to train and graduate as a registered nurse in Buffalo, NY. Nursing was not always a career open to black women. In 1936, she applied to nursing school in Buffalo, NY, anyway, paving the way for others to follow. Graduating at the top of her class of 100 from The School of Nursing at Buffalo's E.J. Meyer Memorial Hospital, she was the first African American to graduate from the institution. Unfortunately, upon arrival at the graduation banquet, she was asked to leave because the hotel did not serve African Americans.

She became the director of nursing at Roswell Park Comprehensive Cancer Center in 1971, serving there for a career spanning some 30 years. She dedicated her life to nursing, education, cancer care, community service, and outreach.

Eva served on many local and national committees in nursing and community health. She founded the New York State Nurses Week in 1970, which has been celebrated ever since from May 24–30. Eva continued to inspire many people as an example of courage, determination, skill, and leadership.

Every year, Roswell Park awards the Eva M. Noles Scholarship to offer assistance with education-related expenses to eligible members of underrepresented groups who wish to pursue a career in health care [28].

Dr. May Edward Chinn (1896–1980) was the first African American woman to graduate from Bellevue Hospital Medical College and the first African American woman to intern at Harlem Hospital. Her father, William Lafayette Chinn, was a former enslaved person from the Cheyne (Chinn) plantation in Virginia, and her mother, Lulu Ann Evans, was a Native American from the Chickahominy Indian reservation near Norfolk, Virginia. As a physician, May provided medical care in Harlem for 50 years, starting her own private practice with other African American physicians. Her interest in early cancer diagnosis developed during these years, as she saw many patients who were very ill with terminal diseases, often late-stage cancer. She became a strong advocate of early cancer screening. May was then hired at the Strang Clinic to research cancer. Her work in cancer research helped in the development of the Pap smear, a test for early detection of cervical cancer. In 1975, she established a society to promote African American women to attend medical school [29].

As a radiologist, researcher, teacher, and community leader, *William Edward Allen Jr.* (1903–1981) achieved notable success in the field of radiology during its development in the 1930s. He was raised in Pensacola, FL, and received medical training at Howard University in Washington, D.C., and postgraduate training at the Homer G. Phillips Hospital in St. Louis, MO. He made considerable advances in shaping radiology as a science and profession and worked for the advancement of others as an educator and by developing funding for scholarships. Credited with being the first African American certified in 1935 by the American Board of Radiology. His examination took place in a Detroit Hotel where, because of his race, he had to take the freight elevator to the exam floor. He volunteered for the military service just before World War II. At the time, blacks were not welcome to serve as radiologists in the military, so instead, he accepted a position as a battalion surgeon. When a separate hospital military hospital staffed by African-American medical officers was established, he became the Chief of X-ray Services at the Ft. Huachuca, AZ facility. At the war's end, Dr. Allen was named Radiologist Consultant to the War Department.

After his return to civilian life, he turned to organizing scientific exhibits in the field of radiology. He became the first black member of the American College of Radiology (ACR) in 1940 and the first black fellow of the ACR in 1945. Dr. Allen established one of the first approved residencies in radiology for minorities in the late 1930s. In 1974, he was awarded a gold medal from the ACR in recognition of a career in which he overcame prejudice to become an exemplary clinical radiologist and educator. That same year, he was responsible for the first cobalt treatment unit introduced in Western Africa. Dr. Allen was the first African American to receive the

American College of Radiology's highest honor, the Gold Medal. William's career shaped the emerging fields of radiology and radiation oncology. His later research focused on nuclear medicine and radiation therapy in prostate tumors and cervical cancer [30, 31].

Dr. Carl Mansfield, MD, ScD, FACR, FASTRO, was born to a single mother in 1928. His mother worked as a housekeeper, and he was raised with the help of his grandparents. He attended one of the few medical schools open to African Americans at the time, Howard University School of Medicine. He pursued training in Radiology, while Radiation Oncology was beginning to diverge from Diagnostic Radiology, at Thomas Jefferson University Hospital. He was awarded several fellowships, including one that allowed him to obtain additional training in radiotherapy in the United Kingdom. This training earned him certification from the American Board of Radiology as well as the American Board of Nuclear Medicine.

He became the first African American Full Professor at Jefferson University and served as the Chief of the Division of Nuclear Medicine. Beyond the years of 1965–1975, he continued to be a successful innovator and leader, serving as Chairman of Radiation Oncology at the University of Kansas, Thomas Jefferson University, and the University of Maryland. He served as associate director of the Division of Cancer Treatment Diagnosis and Centers for the Radiation Research Program at the NCI. He also served as the first African American president of the American Radium Society.

Dr. Mansfield made significant contributions to the development of techniques for breast cancer radiation therapy, including intraoperative therapy and partial breast irradiation, at the level of clinical trial development. He staunchly promoted interdisciplinary care. He published more than 130 peer-reviewed articles along with two textbooks. He mentored hundreds of students, residents, and faculty throughout his career. His volunteering activities included spearheading the efforts to curb RJ Reynolds from marketing tobacco products in African American communities. He won numerous awards throughout his career for his professional and volunteer contributions. Dr. Mansfield's career as a radiation oncologist ultimately earned him the ASTRO Gold Medal, making him the first African American to earn this prestigious award [32].

Dr. Jane Cook Wright, MD, was born into a family of African American doctors, including her father Dr. Louis Tomkins Wright, one of the first African American graduates of Harvard Medical School, her paternal grandfather, a graduate of Meharry Medical School, and her step-grandfather, Dr. William Fletcher Penn, the first African American graduate of Yale Medical School. She attended the New York Medical College and completed her residency at Harlem Hospital, where she continued as a visiting physician while serving in a staff position with New York City Public Schools.

She then joined her father, who founded the Harlem Hospital Cancer Research Foundation. Together, they began their contributions to medical oncology, at a time when the field was in its infancy with only a few agents and no clear guidelines for their use. They contributed to the development of foliate agonists, like methotrexate, and adapted the use of Mustard Gas from the battlefields of World War I and II and its nitrogen mustard derivatives for the treatment of cancer. The duo were among the first researchers to combine agents in a specific order. The application of their work resulted in the remission of patients with a spectrum of cancers, including sarcoma, lymphoma, and leukemia.

After her father's death, she assumed the directorship of the foundation and then joined the New York University Medical Center. Here, she began her work correlating chemotherapy's effects on cell culture models and administration in patients, culminating in a seminal paper published in the *New England Journal of Medicine* [33].

She then pivoted to focus on service to the oncology community. She was among the seven people who conceived of and formed the American Society of Clinical Oncology (ASCO), for which she served as Secretary-Treasurer. She served on the U.S. National Cancer Institute's National Cancer Advisory Committee, which, with the signing of the National Cancer of 1971 by Richard Nixon, transitioned to a Presidentially appointed position. In 1967, Dr. Wright moved on to the New York Medical College to serve as associate dean, making her the highest-ranked African American woman at a nationally recognized medical institution.

These are only a few shining examples of those from underrepresented minorities in and around the field of radiation oncology from the period. Not to be ignored are the masses of unsung heroes who contribute daily to the field. Lastly, there are thousands upon thousands of underrepresented and underserved patient populations, whose participation in clinical trials has advanced the field of cancer care as we know it today.

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1975–1985: Women's Decade

Julianne M. Pollard-Larkin

> They have arrived like a new immigrant wave in male America. They may be cops, judges, military officers, telephone linemen, cab drivers, pipefitters, editors, business executives – or mothers and housewives, but not quite the same subordinate creatures they were before. Across the broad range of American life, from suburban tract houses to state legislatures, from church pulpits to Army barracks, women's lives are profoundly changing, and with them, the traditional relationships between the sexes. …1975 was not so much the Year of the Woman as the Year of the Women – an immense variety of women altering their lives, entering new fields, functioning with a new sense of identity, integrity and confidence.

- *TIME* Magazine article "Great Changes, New Chances, Tough Choices (January 5, 1976)
- https://www.cnn.com/2015/07/22/living/the-seventies-feminism-womens-lib/index.html

> I think I wanted to marry a doctor. But if I couldn't, I'd be one. And so I became one.

- Sucha Asbell, MD, FASTRO in an American Society for Radiation Oncology interview conducted on April 23, 2021 by Colleen Lawton, MD, FASTRO and H. Joseph Barthold, MD, FASTRO
- https://www.astro.org/About-ASTRO/History/History-Interviews/Sucha-Asbell

Women and other underrepresented researchers, scientists, doctors, and others saw a boon of activities that promoted their inclusion in numerous fields in the United States in the 1970s. Despite the US FDA recommending the exclusion of women of childbearing age from early-stage clinical trials in 1977 (which was overturned by the NIH Revitalization Act of 1993 that specifically called for the inclusion of women in clinical research), other 1970 laws came into place that provided legal protection for women in society and academia [1]. Most importantly, 1972's Equal Employment Opportunity Act that gave legal authority to reinforce the

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promises made in the original Civil Rights Act of 1964 [2]. This Equal Employment Opportunity Act gave the Equal Employment Opportunity Commission (EEOC) to sue noncompliant employers, made educational institutions subject to the 1972 act, increased the time for complainants to file charges against employers, and increased the number of employers covered by the original Title VII law [2].

The law that had some of the largest impact on gender equity within women's sports and beyond was Title IX of the Education Amendments Act of 1972. Title IX prohibits discrimination based on sex for educational programs receiving federal funding and is not limited to the scope of athletics despite having specific language dedicated to providing equitable athletic opportunities for athletes regardless of gender [3]. Due to these specific sports-related provisions, some have misinterpreted this law to be primarily focused on sports when that is not the intent nor factually sound. At the time that Title IX was enacted, only 1 out of 27 girls participated in sports; currently, that number is upward of 2 in 5 [4]! Medical school gender parity has been attributed in some circles to Title IX's far-reaching impact since in 1970, less than 10% of medical school students were women, and now that number has just surpassed 50% in recent years [4]. Title IX serves as a stopgap against sex or gender-based discrimination, harassment, or assault; however, it is not foolproof and now courts are faced with considering the broadening definition of gender and sex in society with relation to the protections conferred by Title IX.

However, it is in the context of this more legally inclusive landscape that several of the early women pioneers of radiation oncology found themselves being trained and establishing themselves in radiation oncology departments. One of those women being Dr. Sucha Asbell, MD, FASTRO and former secretary of the American Society for Radiation Oncology (ASTRO) [5]. Between 1971 and 1976, Dr. Asbell followed her brother into radiation oncology based upon his recommendation of the field, "He said it was a good field for a woman because there were not too many emergencies so you could have a better home life." Since she was the daughter of a family doctor and the sister of a radiation oncologist, it was no surprise that she followed in her brother's footsteps and eventually made a finding on racial disparities in prostate cancer patients' responses to Zoladex and Casodex [5]. When it came time to publish her findings, she discovered lots of unexpected roadblocks and rejection, until she reached out to one of the most well-known and ahead of his time gatekeepers and sponsors, Dr. James Cox, MD, FASTRO.

Dr. Cox led MD Anderson Cancer Center's Radiation Oncology division from 1995 to 2014 [6]. During his tenure at MD Anderson, Dr. Cox was responsible for helping grow its division of Radiation Oncology from about 29 faculty to 44, and his major accomplishment was being the brainchild and force (along with his wife and fellow radiation oncologist, Dr. Ritsuko Komaki, MD, other physicists and researchers at MD Anderson Cancer Center) behind the building of MD Anderson's Proton Therapy Center in 2006. Beyond his role transforming how we treat cancer with new technologies, Dr. Cox was a visionary when it came to building diverse, innovative teams with researchers, physicists, and doctors who came from a multitude of backgrounds that is reflective of his experiences as a doctor in the US Army's Walter Reed Hospital as well as his fellowship at the Institut Gustave Roussy in

Paris. He helped herald in a new, modern climate of inclusion in the Radiation Oncology Division at MD Anderson, which has been maintained to this day under its current leadership. Few radiation oncology departments can boast 12% of its academic clinical faculty being Black or African American, 7% identifying as Hispanic and 27% identifying as Asian, but this was true of MD Anderson in a 2019 survey, and this continues with its current group of faculty. These statistics are quite remarkable given that the Deville et al. 2020 paper declares that only 1.5% of all full-time radiation oncology faculty in the United States identify as Black [7].

Mentorship and more importantly, sponsorship, the ability to not only offer career advice for trainees and colleagues, but to also offer junior physicians and trainees opportunities for growth and leadership beyond their reach is something that came naturally to Dr. Cox, and that is perhaps partly to blame on one of his most critical mentors and sponsors, Dr. Juan del Regato, MD.

Dr. Cox moved to Dayton, OH, early on in his formative years and grew to become not only a great high school football player but a brilliant young scholar as well [6]. After excelling in high school, James (known as "Jim" by those close to him) took his talents to Kenyon College and double-majored in biology and chemistry but switched to pre-med after hearing a guest lecturer speak about physiology. He graduated from Kenyon as magna cum laude and then entered the University of Rochester Medical School where not only he met his first wife, Christa, he discovered radiation oncology while doing a 1-year clinical research fellowship project at Penrose Cancer Center under the mentorship of the aforementioned Dr. Juan del Regato, MD, in 1963 [6, 8].

Dr. Juan del Regato is a Cuban-born forefather of radiotherapy who was trained internationally among the likes of Coutard and Lacassague. Notably, he even worked in the same Radium Institute as Madam Marie Curie [9]! He was born to a father who worked as a photographer and projectionist and a mom who had Mayan roots. His father's understanding of photography and lighting helped his dad develop a preliminary interest and understanding of the basic concepts behind radiation physics and due to that he became friends with physicians who performed x-rays and treatments [9]. While growing up, del Regato's father praised physicians in their island nation home and planted the seed to study medicine in his son's mind. Del Regato studied medicine at the University of Havana from 1926 to 1930, and while studying, he worked as a radiotherapy technician to earn extra money. When his university closed in 1930 due to political upheaval, the Cuban League of Cancer gave Regato funding to train as a radiotherapy physician in Paris under the tutelage of a fellow Cuban-trained physician, Dr. Francisco Dominguez-Roldain.

Before leaving to study in Paris, del Regato had already familiarized himself with using a 220 kV General Electric Coolidge tube to treat cervical cancer patients and offer palliation to advanced-stage patients at the center he trained at in Cuba [9]. Impressively, he also had taught himself some rudimentary French in the 18 days before his trip to France. When his mentor asked him upon his arrival in Paris if Regato spoke any French, he responded with "I understand it better than I speak it" in passable French. This thoroughly surprised his Professor Regaud, who was the director of the Radium Institute of the University of Paris at the time. At the institute, del Regato was also able to train under the originator of the radiotherapy "Coutard method," Dr. Coutard, who was one of the first to show the medical community that external beam radiation was useful for treating head and neck cancer [9]. During his 6 years training as a radiation oncologist and getting certified in Radiophysiology and Radiotherapy from the University of Paris, del Regato had developed a design for an early version of what we now refer to as the field light for linear accelerators that allows for a light source to indicate on a patient's skin the open-field shape where the radiation would enter on a patient. This device is and was super useful in helping ensure a radiation patient is setup appropriately on the treatment table.

Dr. del Regato received the Faculty of Medicine Silver Medal for his thesis that he defended. His dissertation work focused on the 10 cases of maxillary sinus carcinoma he treated with radiotherapy under Dr. Coutard [9]. By 1937, he had finished all necessary training to receive his medical certifications in Radiophysiology and Radiotherapy from the University of Paris [9]. It was toward the end of this medical training that Dr. del Regato was able to introduce his concept for what he coined the "Regato Localizer" to a young trainee from Scotland, Jean Riach. This localizer, as mentioned earlier, was used to identify the limits of the x-ray field with the open light from the x-ray tube [9]. He was also instrumental in making some key findings on "peculiar dental caries" in his early pharynx cancer cases that he was able to write up and have published in *Surgery, Gynecology and Obstetrics* [9].

His graduation with his medical degrees was well-timed. In the same year, an American pathologist, Dr. Max Cutler, reached out to Dr. Coutard in hopes of him running a radiotherapy department of a cancer hospital he was proposing to build in the Midwest. Dr. Coutard liked the idea and agreed to come, he then invited his trainee the newly degreed Dr. del Regato. Dr. del Regato agreed, and they all met up in Chicago in 1938. Coutard admitted later on that had del Regato not agreed to come, he would not have taken the opportunity himself.

Upon arrival to the Chicago Tumor Institute that was founded by Dr. Max Cutler, a young Dr. del Regato was introduced to all of the staff and was pleased to meet an attractive, blonde nurse whom he adoringly remembered having a popular-at-the-time short page-boy haircut [9, 10]. The young nurse, Inez, later became his wife. The initial staff of the Institute included Dr. Cutler as the director, esteemed British surgeon, Sir Lenthal Cheatle, Drs. Coutard, Bushke, Cantril, Rosenthal, and del Regato, as well as an assistant [9]. With this list of leaders of early radiotherapy all on board for this endeavor, the Institute was able to offer some of the first and only radiotherapy educational refresher coursework for those interested [9]. Despite the great training that was offered by the center, the center was fraught with financial hardships and several of the initial staff members quickly left for other pursuits as opportunities arose.

Dr. del Regato moved onto Washington, DC, for the next 20 months to work alongside radiation oncologist Dr. Edwin Merritt. Merritt had a unique problem to solve. He was in the early phases of pursuing a regimen for transvaginal roentgen therapy, but his patients were experiencing problems with necrosis. Dr. del Regato helped him change his treatment from a monotherapy approach to a complementary approach alongside external beam irradiation and with a lower 140 kV setting. He also managed to create a new speculum that was more successful in sparing parts of the vagina during transvaginal treatment delivery [9].

After DC, Dr. del Regato was able to work at the Ellis Fishel Cancer Hospital. This facility was renowned at the time due to its wide array of patients, large staff, and treatment resources. Dr. del Regato really got his academic grounding as an attending at this center. One of his major contributions included reorganizing how they maintained all patient records for all of their patients [9]. Prior to his arrival, patient records were collections of loose-leaf paper with handwritten notes, charts, observations, and other items. There was no official order to the patient charts nor was there a quality control process to ensure that only pertinent information was maintained in the chart. Dr. del Regato changed all of that. Under his leadership, he had the institutional staff to remove all unnecessary documentation from the patients' chart [9]. He also had them type out of the important notes so that they could easily be read by other staff later. The other major accomplishment of his was introducing the role of transvaginal radiotherapy in conjunction with external beam radiation for cervical cancer, and he also introduced the concept of using external beam radiation for endometrial cancer.

Dr. del Regato's largest contribution to the field of radiation therapy happens to be the *Cancer* textbook he wrote alongside Dr. Lauren Ackerman [9]. This textbook went on to educate and be the primary resource for several generations of oncologists. After becoming a research fellow for the National Cancer Institute, he moved on to two different director positions; he was director of radiotherapy for the Ellis Fischel Cancer Institute and the Penrose Cancer Hospital in Colorado Springs before settling in the University of South Florida and ultimately becoming a renowned physician with the Veterans Administration before retirement [10]. Dr. del Regato's legacy lives on in the careers, and the impact of the trainees he taught who has now led the field after him, including Drs. Jim Cox, Larry Cun, Frank Wilson, Winona Mackey, and others [10, 11].

Another physician in radiation oncology who was impacted by an early leader in the field is Dr. Sarah Donaldson. She grew up with her hardworking mother after her parents divorced when she was quite young [12]. Young Sarah developed her mom's sense of dedication, duty, and service that was forged by the World War II era she was raised in. Despite having a small household, Sarah had an array of cousins nearby that she grew up with. She spent her formative years in public schools in Oregon where she excelled in class, was well liked, and even a cheerleader [12]. Notably, her high school, Grant High School, is the same school featured in the critically acclaimed film *Mr. Holland's Opus* [12].

After high school, she excelled in college and finished a nursing program since she had always had an interest in the field. Her first nursing job at the department of surgery at the University of Oregon serendipitously placed her on the path to working alongside a young Dr. William S. (Bill) Fletcher, who at that time had just finished all of his surgical training and was a new surgical instructor trying to begin a surgical oncology program [12]. Soon Sarah became responsible for being Dr. Fletcher's assistant, organizing the tumor board meetings, measuring his patient's clinical data, managing all aspects of his clinical research, and even preparing the new chemotherapy drugs such as 5-fluorouracil for infusion [12]. Beyond taking care of his clinical patient work, she was also placed in charge of running her own research experiment where she transplanted amelanotic melanoma tumors into hamsters and treated the patients with chemotherapy and radiation therapy. It was during this busy time that Dr. Fletcher became aware of the medical potential evident in then-nurse Sarah.

Years into their working together, Dr. Fletcher began to prod Sarah to pursue bigger goals in medicine beyond her current role as a nurse. She fought him and maintained that she was happy as she was. However, Dr. Fletcher was able to get her to take a series or pre-medical school prerequisite classes such as physics and organic chemistry in order to help better run his experiments. Each class he suggested that she took, she passed and quickly amassed all necessary didactic training to pursue applying for medical school. When he explained that she could now apply to medical school, she balked. She thought that she at 24 years old was too old to apply for medical school, that she had little chance of getting in since she was a woman and there were few if no programs for women, that she lacked the financial resources to pay for medical school, and that she was not academically qualified for the rigors of medical school training [12]. That did not stop Dr. Fletcher. He reminded her that in his role he had a firm understanding of the aptitude necessary to succeed in medicine and that she had displayed that in her time working for him and in all of the classwork that she had conquered. Next, he knew something that she did not, that there were programs such as the one he had graduated from himself, Dartmouth Medical School, that were finally accepting women and were looking for strong women candidates. He even knew that the Oregon department would be able to cover some of the expenses as needed for her training. Later on, when it was time for Sarah to travel to a funding agency to get funding renewal for her hamster study, he was able to get her to visit eight different medical schools over the course of 10 days. During this trip, while relaxing outside the Hanover Inn watching the football team practice under a cerulean blue sky, Sarah fell in love with Dartmouth [12].

Good timing too, Dartmouth sent her an acceptance letter just 2 weeks after her trip; and when Sarah lacked the $50 deposit, she called Dr. Fletcher, and he ensured that the department covered the cost [12]. This was a common occurrence throughout Sarah's budding career; when she encountered a challenge or difficult decision, she reached out to Dr. Fletcher and consulted him. His wisdom and influence helped her forge her own new broader horizons for herself. With his guidance, she went from seeing herself as a nurse to comfortably taking her path to becoming a surgeon in radiation oncology just like her mentor and advisor. She graduated from his program as one of the first women to be able to in a time when almost no female mentors who understood her unique path existed. However, through her connection and training under Dr. Fletcher, this was no deterrent for her.

Sarah loved her experience in Dartmouth Medical School. Due to the lack of living spaces or facilities of any kind for women, all of the six women in that class were housed together in a former Dartmouth president's home where they were able to study with each other and encourage each other. During her rotations, she excelled in what many consider the hardest rotation, surgery. This was due to her years of being the assistant of Dr. Fletcher during his procedures. Over the years, he had taught her how to tie surgical knots, start IVs, and even do biopsies [12]. Therefore, she was well-trained and able to easily excel in an area where most of her colleagues were fraught with difficulty regardless of gender. She performed so well that she was accepted as a house surgical officer at Brigham when there had only been one previous woman house surgical officer. That previous surgical officer had been Dr. Tenley Emma Albright, a former Olympic medal-winning figure skater [13]. Dr. Albright's trajectory served as motivation for Sarah. After her surgical rotation, Sarah decided to get more in-depth training in medicine by doing a medical internship at the University of Washington under a Dr. Petersdorf [12].

In 1968, Sarah graduated from Harvard Medical School and had to decide on a specialty. The newly degreed Dr. Donaldson did what she always did when faced with an important career decision; she called out to Dr. Fletcher and asked for his advice [12]. Without hesitation, he encouraged her to choose his field. And as was common with Dr. Donaldson, she equivocated and admitted how little she understood about radiation and isodose curves. He told her to just hire a good physicist to overcome those issues. With that decision solved, he helped her connect with a past colleague of his to get training in radiation oncology at Stanford.

And that first foray to Stanford began a multidecade career at their radiation oncology department where she eventually became chief of their radiation oncology service and director of mentoring for the radiation oncology department. She finished her residency at Stanford in 1972 and served as president of the American Society of Radiation Oncology in 1991 [13, 14]. She is now seen as one of the leading experts in pediatric radiation oncology and is a founding member of the Children's Oncology Group and the Childhood Cancer Survivor's Study [13].

Around the same time that Dr. Donaldson was entering her radiation oncology residency at Stanford, Dr. Ivy O. Brooks, the first Black woman radiation oncologist in America, was appointed as chief of the radiology service at the Tuskegee VA (Veterans Administration) Medical Center. Dr. Brooks was born in Brooklyn on June 21, 1916, and followed a lifelong dream of wanting to become a doctor [15]. She got her BS from New York's Hunter College as well as an MS from Columbia University. Given that she was doing all of her educational training during World War II, it is worth noting that she worked as a dietitian at a hospital in Harlem and was a nurse and lieutenant in the Women's Army Corps [15]. Right after getting her medical degree at the famous historically Black medical school, Meharry Medical College, she got trained in diagnostic radiology at the VA in Tuskegee before going to the VA in New Jersey for training in radiation therapy. She was a pioneer in a field that was still being forged and was followed by several other notable past Black and African American radiation oncologists [15].

Florence Chu was another notable woman in radiation oncology who happened to be influenced by Dr. del Regato's career. Florence grew up in Shanghai and graduated from the National College of Shanghai in 1942 [16]. After college, she had a major decision to make, which specialty would she focus on for her medical training. She was concerned about not being able to have enough time with her "dear husband," so she chose to pursue radiology over surgery [16]. In 1948, Dr. Chu applied to three different US-based radiation therapy programs. Surprisingly, she was accepted by all three programs. And just like was the case with Dr. Donaldson, Dr. Chu reached out to one of her trusted mentors, Dr. Gottlieb, who was her mentor during her diagnostic radiology fellowship at the City Hospital of New York, to decide between the programs, and he encouraged her to choose Memorial Sloan Kettering Cancer Center hands-down despite the fact that they offered her no stipend [16].

Memorial Sloan Kettering Cancer Center (MSKCC) was the nation's first cancer hospital and was established in 1884 [16]. The center was originally named New York Cancer Hospital but developed its iconic "MSKCC" name in 1945 when 2 General Motors tycoons (Alfred P. Sloan and Charles F. Kettering) decided to make an impact on treating cancer [17]. New York Cancer Hospital beat the rest of the medical community by installing two low-voltage x-ray machines by 1902 to treat and image patients. By 1903, the hospital had already treated 84 patients, and the staff was able to note the effectiveness of treating lymphoma patients with radiation [17].

When Dr. Chu arrived as a special fellow in radiation therapy at MSKCC in 1949, there were only two radiation therapists, the chair of the radiation therapy department, Dr. Ralph Phillips, and another special fellow trainee [17]. The staff might have been paltry, but the technical equipment was in great supply. The department had a 1-MeV x-ray unit, two low-voltage kV units, and eight 250-kV units [17]. Within a couple of years, a 24 MeV betatron capable of high-energy photons and electron beams was added to the center. The doctors were excited to exploit the physical characteristics of electron beams with their shorter range in material compared to photons because of their higher exit dose [17]. The MSKCC team considered focusing on treating patients who could most benefit from electron treatments, those being advanced breast and head and neck cancer patients [17].

Consequently, Dr. Chu was promoted to leading the breast program in 1955. This opportunity allowed Dr. Chu to treat over 1000 patients in a decade with new complex, modern treatment planning techniques that accounted for inhomogeneities [17]. MSKCC was leading radiation oncology by pioneering these electron treatments, and several radiation oncologists came by to learn their techniques, which led to Dr. Chu and her team presenting at several national conferences and giving refresher courses at the Radiological Society of North America meeting. Her connection to her MSKCC departmental leaders gave her access to the group that created the American Club of Radiation Therapists (ACRT), which eventually became known as the American Society for Therapeutic Radiology and Oncology (ASTRO) [17]. That group included MSKCC's own Dr. Nickson and Dr. Juan del Regato. Dr. Chu was one of the first 100 founding members of ACRT.

In 1976, Dr. Chu was selected to be the chairperson of the radiation therapy department at MSKCC [17]. By the time Dr. Chu became chair of the department, the betatron was 25 years old and all 5 of their other treatment units needed to be replaced [17]. It took her and the department 6 years to upgrade all of their treatment units. Meanwhile, she worked closely with her team of radiation oncologists and physicists to support them as they developed new treatment platforms and technology. MSKCC's physicist KC Tsien created an original computer-based treatment planning system meant to help design the cobalt-60 treatment plans but was eventually utilized for brachytherapy treatments as well as other photon and electron beam treatments [17]. This computer system was used to send computed isodose distributions to several other outside institutions [17]. Based on Dr. Chu's recommendation to Memorial's Medical Board, MSKCC was allowed to create the nation's first brachytherapy service [17]. Finally, in 1984, Dr. Chu retired from her position as the first woman chair of a large radiation oncology department.

At the same time that Dr. Chu assumed the role as chair, another woman radiation oncologist that left an indelible mark on radiation therapy and radically changed how we treat breast cancer rose to prominence, Dr. Mildred Vera Peters [18]. By the time she graduated from medical school, she showed a preference for her middle name and was going by the moniker "Vera" instead of her given first name [18]. She was an exceptional student and enrolled at the University of Toronto at the age of 16, where she studied physics and math [18]. With the help of all six of her other siblings covering the financial costs, she was able to matriculate into the University of Toronto's medical school and graduate in 1934 as one of only 10 of the women in the medical school class out of a total of 115 students [18]. Poignantly, the year prior to her graduation from medical school, Vera's mother succumbed to metastatic breast cancer [18]. This tragic event would have an impact on her future clinical research interests.

In her 2-year surgical residency program at Toronto's St John's Hospital, she was able to work alongside the physician who had treated her mom's breast cancer with radiation therapy, Dr. Gordon Richards [18]. Dr. Richards was a formidable figure in radiation oncology at the time; he was the first president of Canada's National Cancer Institute and the developer of the first radiology training program in Canada [18]. Under his guidance, Dr. Peters was able to write a landmark paper highlighting the effectiveness of radiotherapy in treating Hodgkin's lymphoma [18]. She reviewed the overall survival rates of lymphoma patients treated with radiation over a 20-year period of time and showed 50% 5-year overall survival rates [18]. Her follow-up paper in 1956 received endorsement from a prominent radiation oncologist, Dr. Henry Kaplan from Stanford, and thereafter the medical community considered radiation therapy to be the standard-of-care treatment option for localized Hodgkin's lymphoma [18].

Dr. Peters' most lasting gift to medicine was her work in breast cancer. Since 1898, when Dr. William Halsted created a radical mastectomy procedure for breast cancer patients named after him [19]. This surgery was extensive, if not life-altering, for the patients who had it, it required removal of more than just the tumor, but removal of the breast, nipple, skin, axillary lymph nodes, and even the chest wall muscles too [19]. All of this tissue was removed since the widely accepted medical belief of the early nineteenth century was that the more tissue removed, the higher the chance for survival and cure of the disease [19]. Dr. Peters changed all of that with her 1953 paper on the largest dataset on the Radiotherapy Institute of Toronto's breast cancer patients [19]. Before she began her research, in 1948 Dr. McWhirter had compared their mastectomy patients and found that simple mastectomy had "equally as good five- and ten-year survival" rates as radical mastectomy [19]. This information created a trend in physicians pursuing the less aggressive simple mastectomy for more patients. Dr. Peters decided to investigate if radiation helped in these cases.

After McWhirter's findings, more patients began to get treated at the Radiotherapy Institute of Toronto who had refused radical mastectomy and were coming for treatment after limited surgeries. Dr. Peters noted that the "impetus to change to the most conservative treatment (lumpectomy) was provided by a handful of patients and a few missionary surgeons. The patients were rebels against radical surgery ... insisting on removal of the lump, nearly always done against [their] surgeon's wishes" [19]. Quickly, Dr. Peters' reputation grew as the kind physician willing to treat these patients in as compassionate a manner as possible [19].

Therefore, it was appropriate that Dr. Peters was the proper choice in physicians to exhaustively review the records on 7000 patients who had been treated at Princess Margaret Hospital between 1935 and 1960. Each of the patients had received mastectomy alone, radiation alone, or both radiation and mastectomy. Surprisingly, she uncovered that there was no difference in 5-year survival between any of the treatment groups! This was a huge finding at the time. Dr. Peters' paper on this work was published in 1967; then she spoke on it a year later at the National Cancer Conference in Denver, Colorado [19]. However, it was her talk on her data at MD Anderson Hospital in Houston, Texas, in 1969 where a surgeon heard her data and changed their surgical approach to be a more conservative one as reported by radiation oncologist Dr. Eleanor Montague from MD Anderson [19].

Several physicians contested her work when it was first published and presented given the near century of radical mastectomy alone being the treatment of choice for breast cancer. Dr. Peters did not concede; instead, she performed an even larger retrospective analysis of 8000 breast cancer patients from Princess Margaret Hospital [19]. And once again, after matching the patients for age, tumor size, and treatment year, she found no statistical difference in overall survival among the resulting study patients who were treated with excision and breast irradiation, radical, or modified radical mastectomy with radiation [19].

In 1977, Dr. Peters was able to publish the culmination of all of her breast cancer work in the *International Journal of Radiation Oncology Biology and Physics* [20]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B.06 began accruing patients in 1976 to test her assertions. B.06 was a randomized study of 2000 patients with stage 1 or 2 breast cancer treated with lumpectomy with and without radiation and patients treated with total mastectomy with and without radiation. In 2002, the 20-year follow-up report showed no significant difference in disease-free or overall survival between any of the three groups [19]. Dr. Peters' work was officially confirmed! And her final recorded statement in literature was maintained, "As more and more conservative studies ripen, as more and more concerned physicians observe the adverse effects of excessive treatment, as more and more women become armed with knowledge, mastectomy, in early breast cancer, may become as old-fashioned as bloodletting" [19].

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1985–1995: The Power of Computers

Meral Reyhan and Salma Jabbour

The hair was big, the colors were bright, and the shielding blocks were heavy. In 1985, radiation treatment was primarily carried out with either Co-60-based treatment units or linear accelerators. Regularly shaped fields were created with two pairs of secondary collimators, which could move independently. Irregularly shaped fields were created using customized beam-shaping blocks. A low melting point alloy, Lipowitz or Wood's metal, consisting of 50% bismuth and 26.7% lead, was utilized to make these blocks, which were approximately 7.5 cm thick to reduce transmission to about 3% [1].

At the time, radiation treatment fields were designed using a 2D (conventional) simulator, which was designed to mimic the geometry and motion of the treatment equipment with a diagnostic x-ray source in the head. Patients were placed on the simulator's table, immobilized, and moved so the treatment area would be located at the isocenter of the simulator. Fluoroscopic or static x-ray imaging was performed, often with the graticule in place. From the images, the internal anatomy could be outlined and transposed onto a cross-sectional outline of the patient's external contour. The fields were determined based on the target location and healthy tissue from those images. The isocenter was known and often used as the reference point for MU calculations. The fields were shaped using a block-cutting machine that simulated the geometry of treatment. The machine consisted of a light box tabletop in conjunction with a vertical arm attached to a hot wire. The shape of the shielding block was indicated on a radiographic film, which was placed on the light box and traced with the vertical arm, carving a shape in a Styrofoam block using the hot wire. The orientation of the radiograph would be in the beam's eye view to ensure that when mounted the orientation was accurate. The pieces of cut

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Styrofoam were removed, a tray was mounted using nails to the Styrofoam, and the metal alloy was poured into the holes [1].

Safety was a major concern for both workers and patients. Some hospitals installed special exhaust systems to mitigate the risk of inhaling vapors from the metal alloy. The clinical blocks, often weighing over 25 pounds, had to be mounted and removed from the treatment unit by radiation therapists, putting the workers at risk of strains from lifting the blocks while standing in awkward positions. Dropping or falling blocks were also a major safety concern for patients and therapists [2]. Modern photon therapy techniques have moved away from using shielding blocks to shape fields; however, Lipowitz metal is still used in radiation oncology for custom electron field shaping. The weight and thickness of the apertures made out of this material are significantly less.

The concept of multileaf collimation was originally developed by the Japanese in the 1960s and 1970s; however, it was not clinically adopted due to large leaf widths and the desire for small treatment field sizes. Bjarngard et al. developed computer-controlled radiotherapy, customizing a Siemens Mevatron XII in the late 1970s, where the gantry, jaws, collimation rotation, couch rotation, and dose rate were computer-controlled. It was not until the computer revolution of the 1980s and 1990s that these technologies became a reality for treatment outside of academic hospitals [3].

1 Computer Revolution

In 1985, the United States Department of Defense and Energy built the CRAY-2. It was the fastest and most powerful computer ever built with the ability to perform 1.9 billion floating point operations per second. Compared to a modern cell phone, it was 5000 times slower. Around this time, C++ emerged as the dominant object-oriented programming language. Also in 1985, the NSF formed the NSFNET, linking five supercomputers across the United States together. Eventually, many regional educational networks joined, helping boost the popularity of Internet protocols. In 1989, HL7 was introduced as a data interchange protocol for health care, introducing standards for clinical, financial, and administrative information for health care computer systems. By 1990, Windows released its first successful version of its operating system (OS) compatible with DOS, Windows 3.0, which supported large graphical applications and allowed multiple applications to run simultaneously. Also, in the 1990s, CERN programmer Tim Berners-Lee prototyped the "WorldWideWeb," utilizing a server, HTML, URLs, and the first browser connected to the Internet. By 1991, the NSF's policy changed and commercial restrictions were lifted from the Internet [4]. Radiation oncology was one area of medicine that benefited greatly from these major improvements to both computational hardware and software.

2 Computers in Treatment Planning

Radiation oncology was one of the areas of medicine to really adapt to computers, so much so that the International Commission on Radiation Units and Measurements (ICRU) published report 42 in 1987 in response to the fact that computers "completely changed the approaches" to treatment planning. The report even noted the risk that it would be "rapidly outdated" due to the "rapid evolution of computer technology." The report covered nearly all aspects of treatment planning, including beam data acquisition, patient data acquisition, computation of absorbed dose in a patient, practical treatment planning, presentation of calculation results, graphic representation of dose distributions, recording, monitoring, automatic set-up, and documentation of treatment, and quality assurance [5]. This report parallels modern treatment planning practices closely, while the treatment planning algorithms have improved the principles found in this report remain used today. By 1993, as the treatment planning computers and software improved, updated guidelines for commissioning and quality assurance of treatment planning computers were published with recommended tests to ensure file integrity and system reproducibility and suggestions for manpower considerations for all the new testing [6].

3 Computed Tomography and Simulation

The computer revolution of the times had a major impact on computed tomography (CT). By 1990, continuous gantry rotation CT (slip-ring technology) and patient transport during data acquisition was commercially available. The helical, or spiral as it was called at that time, data acquisition reduced scan time, allowing for acquisition of 3D volume data within a single breath-hold [7]. Due to these advancements in CT technology, radiation oncology departments started to introduce CT simulation. Publications on CT simulation during the mid-1980s ranged from topics of cost-effectiveness versus improvement in cure rate [8] to initial clinical results of virtual simulation [9]. In 1986, a paper was published describing a method for "conversion of Hounsfield number to electron density," which led to treatment planning systems using Hounsfield Units for heterogeneity-based calculations. By 1987, Nagata et al. reported over 800 patients with CT simulation-based treatment plans had better tumor control and survival [10]. At the time, "a matrix plane of 128 × 128" was regarded as "the minimum required to obtain the desired dose calculation accuracy" [5] compared to the 512 × 512 matrix size utilized today. By 1994, the "average time" for a volumetric CT simulation was 74 min with contouring taking about 80 min (36 of those minutes for target contouring), 78 min for treatment planning, 53 min for plan evaluation/optimization, and 58 min for verification simulation. Approximately 1500 scans per year were necessary for the operation of the device to be cost-effective [11]. Presently, radiation simulation is performed on multidetector CT simulators, which utilize multiple rows of detectors to capture multi-slice data simultaneously. Additionally, dual-energy CT, MRI, and PET/CT are being incorporated into radiation oncology departments for simulation. The addition of CT simulation in radiation oncology in the late 1980s and early 1990s led to more conformal treatment planning techniques.

4 3D Conformal Radiation Therapy

In the mid-1980s, 3D conformal radiation therapy (3DCRT) moved from concept to practice. One of the main research goals during the time was "the need to improve local tumor control, while minimizing treatment related toxicity" [12]. This goal was accomplished with 3D treatment planning, conforming "the spatial distribution of the high radiation dose to the shape of the tumor contour while concomitantly decreasing the volume of the surrounding normal tissues receiving high radiation doses" [12]. This goal still guides treatment planning today. CT simulation, in combination with 3D treatment planning software and computer-controlled multileaf collimation, made 3DCRT a reality at the time. The transition from conventional simulation to 3D CT simulation was facilitated by improvements in 3D treatment planning software. Treatment targets and organs at risk could be delineated in greater detail from the CT scan compared to conventional simulation. The practice of contouring normal organs and tumors is still performed today and is moving toward automation due to gains in computer vision algorithms. The beam's eye view (BEV) generated in 3D treatment planning software allowed determination of the best gantry angles for treating a target while sparing organs at risk. A digitally reconstructed radiograph (DRR) could be generated from the CT data to help with treatment field design [13]. DRRs are still used for treatment field development, but are now also used to guide patient setup during pretreatment imaging. Finally, evaluation of these sophisticated 3D treatment plans was performed quantitatively using dose volume histograms (DVH) [14]. The DVH is still reviewed during the treatment planning process, both as part of the physician's initial treatment plan review, the physics chart check review, and during department-wide planning rounds.

In response to the popularity of 3DCRT, Emami et al. published a collaborative manuscript funded by the National Cancer Institute on the tolerance of normal tissues to therapeutic irradiation [15]. While research has progressed since Emami's publication and the tolerance values have changed, routine evaluation of treatment plans based on normal tissue tolerances, "clinical goals," is daily practice. From 1991 to 1995, Dr. Fuks at Memorial Sloan Kettering Cancer Center shared his experience with 3DCRT through a series of papers ranging in topics of the biologic basis of 3DCRT to applications in prostate, lung, and nasopharynx cancers [12, 16–32]. Around the same time, at the Karolinska Institute, a stereotactic body frame was developed, which was able to reproducibly setup 90% of patients within 5–8 mm [33]. Starting in 1991, the first stereotactic radiation therapy (SRT) was delivered to an extracranial tumor. Straight secondary blocks were used to collimate 4–8 non-coplanar treatment beams. Treatment was given in 1–4 fractions with total dose dependent on cancer type (intrahepatic tumors, liver, retroperitoneal and skeletal, and thoracic cavity metastases) [34]. Commercial vendors now sell immobilization equipment for stereotactic body radiation therapy (SBRT), which is routinely performed in 1–5 fractions for various forms of cancer (prostate and lung among the most common).

5 Multileaf Collimation and Intensity-Modulated Radiation Therapy

In 1984, Brahme patented the multileaf collimator for radiation therapy [35]. The device consisted of 32 pairs of leaves made from high density and atomic number, driven by individual motors that could move the leaves in and out of the radiation field. It was subsequently commercialized by Scanditronix (Fig. 1). Multileaf collimation remained controversial well into the 1990s due to the differences in the isodose distributions particularly in the penumbral region compared to those generated by traditional blocks. One approach was having two treatment delivery systems, with one system dedicated to treatment plans utilizing the MLCs, eliminating the need to remove the MLC system between patients. The need for automated transfer of the MLC leaf positions from the treatment planning system to the treatment unit was another limitation [1]. Compared to the MLCs of the late 1980s and 1990s, modern systems have significantly more (120–160 leaves) and smaller leaves (commonly 0.5 cm, but ranging from 0.25 to 1 cm in thickness). Additionally, the older MLC systems were often retrofit to the head of the linac, whereas modern linacs have them built directly into the machine head.

By 1988, a new approach to treatment planning with MLCs was presented where optimization of stationary and moving beam irradiation was proposed, inverse planning [36]. The idea was to treat patients with nonuniform fluences, optimized to deliver high dose to the target and spare radiation to the organs nearby. The MLC could be used to deliver intensity-modulated treatment fields. Subsequently, a myriad of improvements to the optimization algorithms and delivery techniques were published [37–40]. One approach was to treat the patient with multiple fields, where each field could be divided into a set of subfields irradiated with uniform intensity, “step and shoot” [41]. Another approach, “sliding window,” involved the opposing leaves moving simultaneously and unidirectionally with independent velocity as a function of time [42]. In 1995, Yu et al. published a technique called intensity-modulated arc therapy, which used moving MLC leaves similarly to “step and shoot,” but also rotated the gantry during treatment [43]. While the algorithms to create treatment plans based on “step and shoot” and “sliding window” have changed, the use of the MLCs to produce nonuniform fluences is widely used today in intensity-modulated radiation therapy (IMRT).

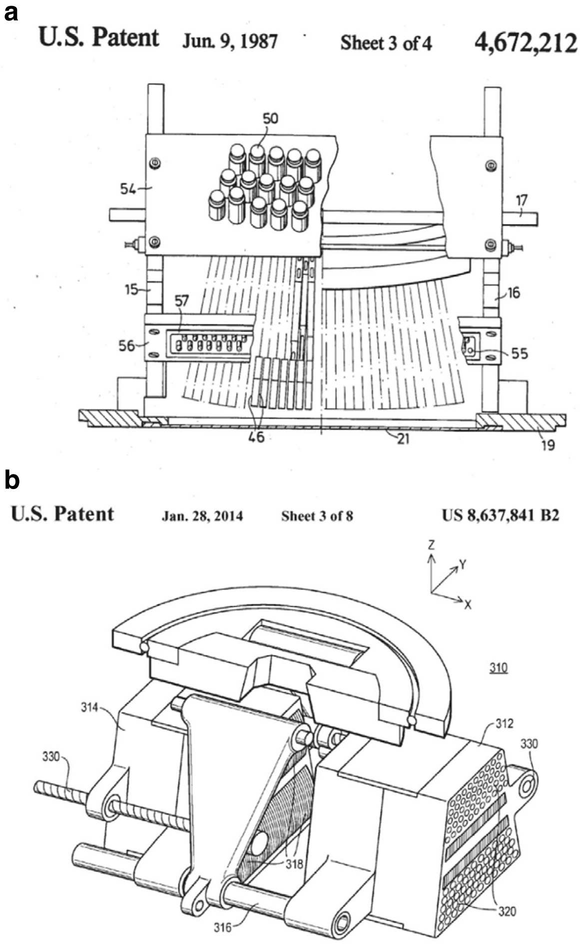

Fig. 1 (**a**) The first commercially available "multileaf collimator" from Brahme and Scanditronix's US patent filed in 1985 [56]. (**b**) Modern multilayer MLC from Varian's US patent filed in 2014 [57]

6 Tomotherapy

Tomotherapy was introduced as a form of IMRT where the patient was treated slice by slice, similar to CT imaging. The NOMOS Corporation introduced a version of tomotherapy where the couch moved one or two slices at a time serially during treatment [44]. The company produced a binary MLC, MIMiC, and a treatment planning system, Corvus, for the creation of optimized treatment plans. When used together, the system was referred to as "Peacock." The MIMiC was a binary MLC system attached below the linac's collimation with 20 pairs of leaves made of tungsten, capable of creating a 1 or 2 cm openings at the isocenter [45]. The first patient (recurrent retropharyngeal cancer) was treated with Peacock IMRT at Baylor College in March 1994 [46]. The Peacock system was the first commercialized IMRT system and optimization-based treatment planning system that received FDA clearance in 1996. One of the issues with this design was the potential mismatch between adjacent slice pairs, which was necessary for long target volumes.

Mackie et al. introduced helical tomotherapy with continuous couch motion, which would help minimize hot and cold dose spots at the junctions between slices due to the continuous longitudinal motion of the patient during treatment [47]. The linear accelerator was attached to a slip ring gantry with a kV x-ray source at a right angle to the accelerator. The system would be capable of diagnostic CT imaging prior to treatment to ensure correct patient positioning and proposed that the treatment plan could be modified in subsequent fractions based on the pretreatment CT imaging—plan adaptation based on daily imaging [45]. Mackie's original paper also proposed the IMRT concomitant boost, "it may be better to deliver both the primary field and the larger regional field for the full treatment duration to increase repair of normal tissues encompassed by the regional field or to provide more tumor cell killing at the same probability of normal tissue damage" [47]. The concomitant or integrated boost is routine treatment technique for many treatment sites. Initially in 1994, Mackie's group partnered with General Electric Medical Systems (GEMS) to build the first clinical prototype. The system was to be based on the GEMS HighSpeed CT gantry/couch and their 4MV linac, but it was not until 2001 that the first TomoTherapy unit at the University of Wisconsin was built [45]. The commercialization and popularity of both serial and helical tomotherapy demonstrated to the major radiation therapy vendors the importance of this emerging treatment technique.

7 Accidents in Radiation Oncology

While the computer revolution undoubtedly led to great gains in radiation oncology, there were also accidents. Between 1985 and 1987, the Therac-25 overdosed six patients, resulting in serious injury and death. The Therac-25 was developed by the Atomic Energy Canada Limited and CGR as one of the most sophisticated linacs of its time. In earlier versions of the linac, mechanical safety interlocks and positioning guides helped prevent radiation exposure if there was an issue with patient positioning or position of internal components of the linac. These hardware-based safety controls were largely replaced by software for the Therac-25. A turntable that housed the X-ray target (used for photon treatments) and steering magnet (used for electron treatments) was not in the proper location for the treatment of these patients; the electromechanical lock used in prior version of the linac had been replaced by a software check that proved unreliable. The patients were treated with roughly 100 times the intended dose of radiation to a very narrow field [48, 49]. Detailed analysis of the accidents was performed and ultimately the IEC set new standards for life cycles of medical device software and guidance on using software of unknown pedigree [50]. The Therac-25 is often used for case study in computer ethics, software engineering, and health informatics courses, highlighting overconfidence in computer programming and failure to investigate user claims. Incident learning systems are now common in most radiation oncology departments; users can submit and review radiation events that occur in their department, helping improve overall safety. Also, during these years, the world experienced one of its biggest nuclear disasters; the nuclear reactor in Chernobyl exploded on April 26, 1986. These negative events brought radiation back into the public eye.

8 Radiation Biology

1985–1995 were prolific years of discovery in radiation biology. Dr. Withers at the UCLA published a series of papers that shed light on fractionation, early and late responding tissues, clonogen repopulation, treatment volume and tissue tolerances, and investigated the dose response for several body sites. The "Biological Basis for Altered Fractionation Schemes" looked at differences between early and late responding tissues, concluding that using "doses of less than 2 Gy, only 5 times per week may not be in the patient's best interest because of tumor regeneration late into therapy" [49]. By systematically reviewing literature and retrospective reviewing charts of 500 patients with oropharyngeal cancer, Withers et al. demonstrated rapid tumor regrowth during extensions of treatment between 5 and 8 weeks, concluding that radiation of the head and neck should not be delayed during treatment [51]. Modifications to dose fractionation because of treatment breaks and holidays for patients with head and neck cancer are commonly practiced today because of Withers' findings. Withers et al. defined functional subunits of tissue structurally or functionally that could be arranged in parallel or series. The parallel arrangement gave "rise to graded dose responses, where as in series they gave rise to threshold binary, or quantum responses" [52], a concept still taught today. In the middle of the Cold War, 1989, Withers et al. published a review paper describing "typical human symptoms in reaction to prompt total-body ionizing radiation" in the event of a nuclear attack [53]. In a study of patients with adenocarcinoma of the rectum and rectosigmoid, it was shown that postoperative adjuvant radiotherapy was beneficial in decreasing local recurrence rate utilizing total doses greater than 50 Gy to the entire target volume, using treatment plans with multiple fields followed by field reduction after 45–50 Gy [54]. In 1995, Withers et al. published a paper looking into the dose–response relationship for subclinical disease, specifically validating a model for metastatic cell burden. The group was able to establish that 50 Gy in 2 Gy fractions achieved high control rates [55]. These papers had major impacts for radiation biology and radiation oncology treatment helping to scientifically establish dose fractionation schemes.

The late 1980s and early 1990s were a fruitful time for innovation in radiation oncology. The innovation was largely driven by the computer revolution at the time. The power of computers transformed radiation therapy from 2D treatment with heavy metal blocks to shape the fields designed on a conventional simulator to helical 3D CT-based treatment planning using techniques of stereotactic radiation therapy, 3D conformal treatment, and intensity-modulated treatment using MLCs to shape the fields (and fluence).

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History of MRI in Radiation Oncology 1995–2005

Saffanat Sumra, Hedvig Hricak, and Lisa Singer

1 Introduction

From diagnosis to treatment, magnetic resonance imaging (MRI) has revolutionized radiation oncology. For example, MRI has facilitated the early diagnosis of small, asymptomatic brain metastasis, allowing for early treatment. MRI has provided guidance for highly focal and ablative treatments, enabling many patients to undergo alternatives to whole-brain radiotherapy. In extensive-stage small-cell lung cancer, the use of MRI for brain surveillance has provided an alternative to the side effects of prophylactic cranial irradiation. In cervical cancer, MRI provides image guidance for brachytherapy, a treatment that improves local control and survival. Diagnosis of prostate cancer, liver cancer, breast cancer, and numerous other cancers has been improved by MRI, often facilitating earlier and/or more conformal and effective treatments. For some cancers, synthetic CT, derived from MRI data, has enabled patients to avoid unnecessary CT simulations. For other cancers, MRI simulation in the treatment position has enhanced data obtained from CT, improving radiotherapy treatment plans. Technical advances in MRI and radiotherapy treatment delivery have enabled the development and implementation of MRI-guided external beam

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radiotherapy with MR-linacs. None of these advances would be possible without advances in nuclear magnetic resonance (NMR) and the creation of the first whole-body human MRI scanner in 1977 (Fig. 1).

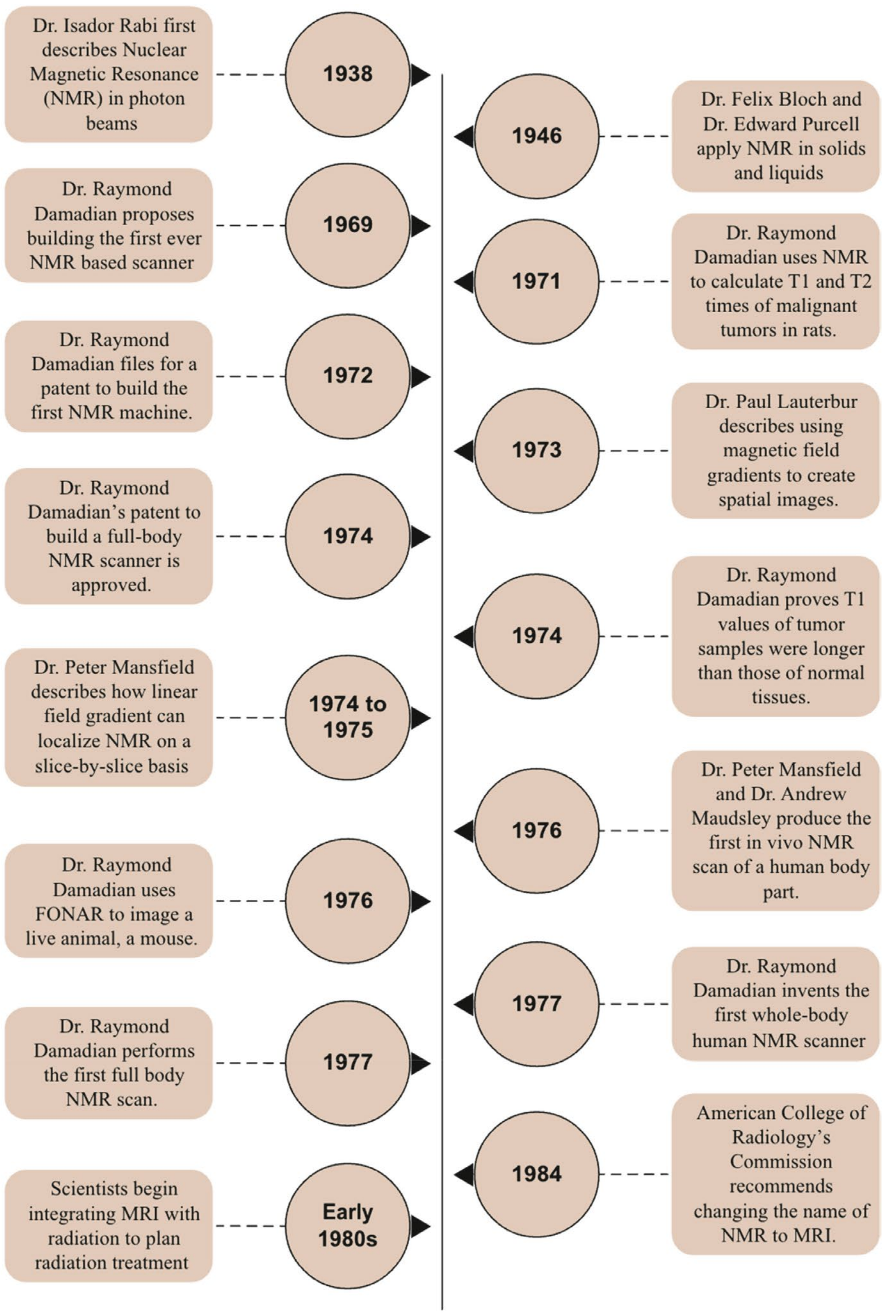

Fig. 1 Timeline of the history of MRI developments from the early 1930s to the early 1980s

2 Early Developments in Nuclear Magnetic Resonance

The foundations of MRI are rooted in the discovery of nuclear magnetic resonance (NMR) spectroscopy in the mid-twentieth century. NMR is an analytical technique used in biomedical research to study the structure of molecules. It uses the properties of the atomic nuclei of atoms, such as hydrogen and carbon, to describe the local environment of that atom. Dr. Isidor Isaac Rabi, an American physicist and a professor at Columbia University, studied the magnetic properties of atomic nuclei and began researching molecular beams in the 1930s. In 1938, Rabi conducted an experiment in which he passed a beam of atoms through an external magnetic field, which led to the discovery of magnetic resonance. Magnetic resonance refers to the phenomenon where atomic nuclei absorb and re-emit electromagnetic radiation when in a magnetic field. Rabi later went on to receive the Nobel Prize in Physics in 1944 for developing the "magnetic resonance method" of measuring the magnetic properties of the atomic nuclei [1].

In 1946, Dr. Felix Bloch and Dr. Edward Purcell further expanded on the development of NMR to identify the structure of molecules beyond gases, such as those of solids and liquids. Bloch was a Swiss physicist conducting research at Stanford University, and Purcell was an American physicist at Harvard University. Bloch applied a constant magnetic field to a sample of liquids and solids to observe that the nuclei in the sample emitted radiation [2]. Purcell worked on a similar experiment wherein he applied radiofrequency pulses to a sample nucleus placed in a magnetic field, which would cause the nuclei to deviate temporarily from their initial alignment and then return to their original alignment while emitting those radiofrequency signals [3]. Both Purcell and Bloch were awarded the Nobel Prize in Physics in 1952 for their development of NMR as a tool for analytical purposes in the study of the molecular structures of a variety of substances, including solids and liquids [4]. These contributions laid the foundation for NMR to be used in basic science research and the study of the structures of live organs and tissues.

3 Transition from Applications in Basic Science to Medicine

Although initially limited to applications in basic science research, NMR proved useful in clinical settings. In 1969, Dr. Raymond Damadian pioneered the introduction of NMR in medicine in a request addressed to the Health Research Council of the City of New York. Damadian was an American physician who worked at the State University of New York (SUNY) Medical Center as a professor and researcher. In this letter, Damadian outlined how nuclear magnetic resonance could be used in developing a full-body scanner to image the human body, and he envisioned how this technique could have "powerful applications in anti-cancer technology" that could "bring us very close to the total eradication of the disease" [5].

4 Pioneers of MRI: Raymond Damadian, Paul Lauterbur, Peter Mansfield

Damadian first used NMR to calculate the spin–lattice relaxation time (T1) and the spin–spin relaxation time (T2) of malignant tumors. Both T1 and T2 are parameters measured by NMR, which describe the behavior of nuclear spins within the sample nuclei in a given magnetic field. In a paper published in 1971, Damadian reported how both the T1 and T2 values for malignant tumors were longer than the T1 and T2 values of nonmalignant tissues—a distinction that indicated the potential of NMR to identify cancerous tissues and thus be used as a diagnostic tool for cancer [6]. Damadian conducted these initial experiments on rats, and other labs conducting similar experiments were able to confirm that the T1 and T2 values for cancerous tissues were indeed longer. Eager to put his ideas into action, in 1972, Damadian filed for a patent for an "Apparatus and Method for Detecting Cancer in Tissue," which described the workings of the first NMR machine that he envisioned [7].

Around this time, Dr. Paul Lauterbur, an American chemist and a professor at Stony Brook University in New York, was one of the first scientists to leverage NMR signals to produce images. In 1973, he published a report describing how magnetic field gradients can be used to create spatial images. Lauterbur called this technique zeugmatography, which comes from the Greek word "zeugma," and published the first true MR images of tubes filled with water and other liquid samples [8]. Although Lauterbur did not use zeugmatography on living organisms, he also noted the possible application of using NMR as an imaging technique to study tissues, including the "in vivo study of malignant tumors" [8].

Dr. Peter Mansfield is another scientist who played a critical role in the development of MRI. Mansfield was a British physicist and professor at the University of Nottingham who, between 1974 and 1975, worked on describing how linear field gradients could be used to localize NMR on a slice-by-slice basis. He selectively focused on a specific slice using a magnetic gradient and visualized the distribution of particles or "spins" within that slice [9]. This allowed for the creation of visual images based on how these particles are distributed in that particular part of the object. In 1976, Mansfield and his then-graduate student Andrew Maudsley produced the first ever in vivo MRI scan of a human body part, a human finger [10].

In 1974, Damadian conducted a large study on 104 human tumor samples and 181 normal tissue samples and was able to prove that the T1 values of the tumor samples were much longer than those of the normal tissues [11]. Labs across the country subsequently produced data that confirmed Damadian's claim that pathologists could use NMR as a diagnostic tool to detect malignancy [12]. Subsequently, in 1974, Damadian was granted the patent that he had submitted 2 years ago, and in 1976, Damadian used the FONAR technique (*F*ield f*O*cusing *N*uclear m*A*gnetic *R*esonance) to image a living mouse [13]. The FONAR technique primarily relied on using T1 and T2 values from tissues to visualize the internal structures of the organism and obtain tissue images. In 1977, Damadian invented the first whole-body human MRI scanner, which used FONAR. He and his two postdoctoral students, Dr. Michael Goldsmith and Dr. Larry Minkoff, were able to perform the first full human body scan the same year [14].

Both Mansfield and Lauterbur were awarded the Nobel Prize in 2003 for developing the foundational ideas of MRI, which continues to transform radiation treatment planning today [15]. Damadian's work developing the first full-body MRI scanner has profoundly impacted medicine and the ability of radiation oncology to harness the advantages of MRI.

5 Limitations and Challenges of MRI in Clinical Practice

The history of MRI in medicine, including in radiation oncology, is defined by the persistence of many scientists and physicians who continued to advocate for its use despite initial resistance to its acceptance in the wider medical community. Damadian, for instance, advocated for the potential of MRI to be used as a tool to diagnose cancer, but this idea was not free of controversies and prompted speculation for multiple reasons. Some researchers pointed out the fact that there was still a significant overlap between the relaxation times of normal and malignant tissues. Others mentioned how Damadian had mainly compared the relaxation times for malignant tissues with normal tissue as opposed to inflammatory tissues, which also had longer T1 and T2 times [12].

The adoption of MRI in clinical practice required that it add value to the standard of care, which at the time of MRI's introduction was, in many cases, computed tomography (CT). A CT scan is a type of imaging technique that relies on using X-rays to produce cross-sectional images of the body being imaged, and it was first developed in the early 1970s, with the first CT scanner being built in 1971 by Sir Godfrey Hounsfield, an English engineer [16]. When Lauterbur first published his paper describing the principles of using NMR for imaging, CT had been in use as the standard-of-care imaging technique for about a decade. Both CT and MRI had advantages and disadvantages compared to each other in terms of their application in a clinical setting [12].

In general, MRI did not employ the use of ionizing radiation when imaging the subjects, and the soft-tissue contrast of MRI images was also greater than that of CT. For instance, clinicians were able to visualize blood vessels well with MRI without the use of intravascular contrast agents. In addition, images of superior quality could also be obtained in more than one plane—transaxial, coronal, sagittal, etc. On the other hand, it was much more difficult to detect bone destruction using MRI compared to CT—an issue that continues to persist even today [16]. CT images were also produced with higher spatial resolution than that of MRI, and compared to the length of time it took to get an MRI (5–10 min), CT images were produced much more quickly within a span of a few seconds. With MRI, it was also important that there was little to no physiological motion as they could degrade the images. While this degradation was a possible event in the case of CT scans, it was much less likely to happen [17, 18].

6 A Change in Name: From NMR to MRI

In 1984, the American College of Radiology's Committee on Nuclear Magnetic Resonance recommended changing the name of NMR to MRI (magnetic resonance imaging) [19]. Dr. Alexander Margulis was part of this committee and mentioned how the shift in the nomenclature aimed to make the name more socially acceptable and dissociate it from the term "nuclear," which gave it a rather threatening appearance [20]. This renaming marked a critical step in NMR's journey toward broader acceptance to be used as an imaging and diagnostic tool in medicine.

7 Integrating MRI with Radiation: Introducing MR-Guided Radiation Therapy

The history of MRI in the context of radiation oncology is important because some of the very first applications of MRI in medicine were confirmed by its use in examining cancer and delineating the regions where radiation could be delivered with greater specificity. Radiation first became a more conventional part of cancer treatment between the early to mid-twentieth century, being used in treatments for a wide number of conditions such as prostate cancer, lung cancer, and breast cancer. In the early twentieth century, radiation therapy often manifested itself as radium therapy, which involved the application of radium directly within or near the tumor site, thus lacking targeted delivery to the tumor. The use of MRI to guide radiation delivery in real time is called MR-guided radiation therapy and utilizes an MR-linac, which aims to ensure targeted delivery of radiation to the malignant tissues [17]. MR-linacs also enable online adaptive radiotherapy, or adjustment of the radiation plan to daily changes in the tumor or the nearby normal organs, while the patient is on the treatment table. When MRI is not used in radiation planning and delivery, CT is often used both to outline areas of the tumor for the targeting of radiation and for the assessment of daily tumor set-up. As outlined in Table 1, compared to CT, MRI excelled at showing soft tissues. CT images, on the other hand, provided more detailed images with higher spatial resolution and higher resolution images of the skeletal system (Table 2). MRI can also be utilized in radiation planning with treatment on a non-MR-linac, or for offline adaptive radiotherapy, or replanning outside the MR-linac system.

Table 1 Summarizes the differences between CT and MRI from 1985

	Computed tomography (CT)	Magnetic resonance imaging (MRI)
Use of radiation	Uses X-rays (ionizing radiation)	Does not use ionizing radiation
Image contrast	Lower contrast, especially in soft tissues	Higher contrast, superior visualization of soft tissues
Imaging speed	Faster (few seconds)	Slower (5–10 minutes)
Spatial resolution	Higher spatial resolution	Lower spatial resolution
Bone detection	Better at detecting bone destruction	More challenging to detect bone destruction
Imaging planes	Typically, in one plane (transaxial)	Multiple planes (transaxial, coronal, sagittal)
Motion sensitivity	Less sensitive to physiological motion	More sensitive to physiological motion
Primary use in clinical care	Standard-of-care imaging technique	Emerging as an alternative with advantages in soft-tissue visualization

Table 2 Summarizes the differences between CT and MRI in the present day (2023)

	Computed tomography (CT)	Magnetic resonance imaging (MRI)
Use of radiation	Uses X-rays (ionizing radiation)	Does not use ionizing radiation
Image contrast	Improved contrast (including in soft tissues)	Continued higher contrast, superior visualization of soft tissues
Imaging speed	Remains faster	Improved speed and reduced scan times
Spatial resolution	Improved spatial resolution with advanced CT scanners	Improved spatial resolution with ongoing developments in MR simulators
Bone detection	Still superior for detecting bone structures	Advances in bone imaging, but challenges persist compared to CT
Imaging planes	Now visualizes in multiple planes	Continue to visualize in multiple planes
Motion sensitivity	Continued lower sensitivity to physiological motion	Ongoing improvements to minimize sensitivity to physiological motion
Primary use in clinical care	Essential in diagnostic and treatment planning	Continuing to gain widespread acceptance for use in diagnostics and treatment planning

8 Early Case Studies of MRI Use in Radiation Therapy

Prior to the idea of integrating both CT and MRI to plan radiation therapy, the feasibility of MRI alone being used as a tool in radiation treatment planning was tested by multiple labs in the early 1980s. One of the first such studies was led by Dr. Peter Bloch, who, in 1983, showed how MRI (then still called by its former name, NMR) scans were essential for delineating the boundaries of localized cancer [21]. He confirmed Damadian's conclusions of taking advantage of differences in relaxation times between normal and malignant tissues, thus aiding in treatment planning.

Bloch primarily emphasized how NMR scans were able to provide information about hydrogen concentration in tissues, which is crucial for planning a specific type of radiation therapy called neutron therapy.

MRI further proved to be a useful form of imaging in studying central nervous system (CNS) tumors, providing detailed anatomical data to deliver radiation to these tumors. In both the brain and other organs, CT continues to be valuable in providing information on electron density needed for dose calculation [22, 23]. Stereotactic radiosurgery (SRS) for brain lesions can be performed with MRI data and without CT information to calculate dose due to dose estimates derived from the brain's water composition [24]. Today, synthetic CT derived from MRI data can also be used to estimate dose, without CT, for other cancers such as prostate cancer.

In 1987, Dr. Benedick Fraass at the Cedars-Sinai Medical Center published a study that used MRI to plan radiation treatment for a total of 15 patients. All of these patients underwent both CT and MRI scans for treatment planning, with MRI studies following the standard CT-based treatment. After comparing data from both CT and MRI, Fraass concluded that MRI could not replace CT due to the inferior resolution of its images compared to those produced by CT [25]. As indicated by earlier studies conducted by other scientists, these MR images also lacked information on electron density, which was needed for precise radiation dose calculations. However, the study did mention that although MRI could not replace CT, it could still be used with CT as it provided superior sensitivity to detect lesions and direct imaging in multiple planes. It was also easier to acquire axial, sagittal, and coronal images using MRI. So, the researcher concluded that the most sensitive radiation treatment planning would involve leveraging the strengths of both CT and MRI.

Ultimately, imaging techniques like MRI and CT allow for the radiation treatments to be personalized, increasing confidence of treatment planning by better outlining the patient anatomy. Since the initial experiences utilizing MRI in radiation oncology, improved MR sequences, as well as the development of improved synthetic CT algorithms, have enabled MRI, in some cases, to replace CT entirely in radiation treatment planning.

9 MRI Today and Future Prospects

Today, MRI scanners are utilized in radiation oncology to guide both brachytherapy and external beam radiotherapy treatment planning. MRI simulation enhances, or in some cases via synthetic CT, replaces, CT simulation. The improved soft-tissue contrast of MRI enables MRI-guided brachytherapy for cervical and prostate cancers. For stereotactic radiosurgery, MRI provides critical information regarding radiotherapy targets. In both offline and online adaptive radiotherapy, MRI guides replanning in response to changes in tumors or normal tissues. MRI also presents costs to the healthcare system regarding the financial cost to install and operate an

MRI and the time and training costs to operate, interpret, and integrate the data safely. The future growth of MRI in radiation oncology will depend on the ability of evidence supporting its use to outweigh these costs. In a field where target visibility is critical, this future is bright.

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The Shaping of Contemporary Radiation Oncology (2005–2015): A Focus on Clinical Practice and Technological Advancements

Kim C. Ohaegbulam and Malcolm Heard

1 Introduction

The period from 2005 to 2015 saw significant developments in radiation oncology, including the adoption of advanced treatment technologies and modalities and major progress in standardization. The increasing sophistication of treatment planning and delivery demanded a greater focus on standardization, particularly in the critical step of target and normal tissue delineation, resulting in the development of consensus guidelines and anatomical atlases with the explicit goal of improving consistency across different centers and facilitating clinical trials and normal tissue complication research. These efforts aimed to minimize variability that would influence dosimetric parameters that could impact treatment decisions.

The decade also witnessed the widespread adoption and technical maturation of image-guided radiation therapy (IGRT). This technology significantly impacted the professional roles and responsibilities within the radiation oncology team and necessitated the need to establish new standard operating procedures and treatment delivery tolerances for IGRT practices.

Alongside the rise of IGRT, this decade saw the continued development and expansion of hypofractionation and stereotactic body radiation therapy (SBRT) techniques, distinctly recognized from conventional fractionation methods. SBRT applications broadened to encompass various extracranial sites, including lung, spine, liver, and prostate cancers. The complexity and precision of these treatments also underscored the need for standardized approaches, leading to the development of additional consensus guidelines for target volume definition. There was also a

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continued emphasis on understanding and mitigating normal tissue effects, a critical aspect of delivering safe and effective radiation therapy.

Furthermore, more advanced delivery techniques became commercially available and implemented in clinics. This included volumetric-modulated arc therapy (VMAT), requiring the development of new commissioning and quality assurance protocols to ensure accurate, reliable, and safe use. The rapid pace of technological change brought a heightened awareness of patient safety and the importance of robust quality assurance processes.

In essence, the decade from 2005 to 2015 was a period of integrating and refining complex technologies like IGRT and SBRT, implementing advanced delivery platforms, and building the essential infrastructure—standardized contouring, and robust quality assurance (QA)—needed to support the delivery of increasingly precise and potentially hypofractionated radiation treatments. The collective efforts highlighted the dedication across the field to enhance targeting accuracy, expand treatment options, and, crucially, ensure the safety and quality of patient care amidst rapid technological evolution.

2 The Evolution of Clinical Practice Guidelines and Consensus Statements in Radiation Oncology: Foundations of Modern Practice

The development of Clinical Practice Guidelines (CPGs) and Consensus Statements between 2005 and 2014 represents a transformative period in radiation oncology that established the foundation for our evidence-based practice today. These early structured approaches to standardization have matured into comprehensive frameworks that guide virtually every aspect of contemporary radiation oncology practice.

Origins and Early Development of Radiation Oncology Guidelines

The formal development of radiation oncology guidelines gained significant momentum during 2005–2014, responding to an increasing recognition that standardization was essential to ensure quality care. The Interagency Steering Committee on Radiation Standards in 2005 highlighted the need for “facilitating consensus on acceptable levels of radiation risk” and “promoting consistent risk-assessment and risk-management approaches” in radiation protection standards [1]. This marked a pivotal shift from primarily experience-based practices toward systematically developed, evidence-based recommendations.

During this formative decade, professional organizations like the American Society for Radiation Oncology (ASTRO) began developing formal guideline programs that would eventually become cornerstones of clinical practice [2–4]. A systematic review published in 2020 documented a remarkable increase in guideline publications over time, showing virtually no guidelines published from 1995–1999 compared to 65 from 2015–2019 [5]. This exponential growth had its foundation in the 2005–2014 period, which established the methodological approaches and institutional frameworks for guideline development that continue to evolve today.

Addressing Clinical Problems and Evidence-Based Practice

The early guidelines addressed significant variations in clinical practice by providing standardized approaches based on the best available evidence. They served as critical tools for translating complex research findings into practical clinical recommendations, particularly important during a period of rapid technological advancement in radiation oncology.

The methodologies used to develop recommendations also matured significantly during this period. By the end of this era, literature reviews (50%) and image-based methods (45%) had become the predominant approaches to guideline development [5]. Panels developing these guidelines typically included a median of 10 physicians, with 70% of panels representing multidisciplinary expertise [5], reflecting the increasingly collaborative nature of oncologic care.

Guidelines played an especially important role in areas where high-level evidence from randomized controlled trials was lacking. Consensus statements provided expert opinion on best practices based on available evidence, offering clinicians practical guidance while acknowledging limitations in the existing literature. By 2014, these consensus processes had become increasingly sophisticated, often employing modified Delphi approaches to systematically develop recommendations when empirical evidence was insufficient [6].

Perhaps most importantly, these guidelines began transforming radiation oncology from a specialty characterized by significant practice variation to one with increasingly standardized approaches based on shared evidence. This standardization not only improved the consistency of care but also facilitated meaningful comparisons of outcomes across institutions and clinical trials, accelerating the pace of quality improvement.

Patient Safety and Medical-Legal Risk Reduction

Patient safety considerations became increasingly central to radiation oncology guidelines during 2005–2014. The ALARA principle (As Low As Reasonably Achievable) emerged as a cornerstone of radiation safety guidance, emphasizing "the importance of minimizing radiation exposure to the lowest possible level while obtaining images of sufficient quality for accurate diagnosis" [7, 8]. This principle extended beyond diagnostic imaging to therapeutic applications, informing dose optimization strategies in treatment planning.

Guidelines developed during this period began explicitly addressing risk management considerations alongside clinical recommendations. The standardization of practice offered significant protection against medical-legal risks by establishing clear standards of care. When practitioners followed guideline-recommended approaches, they had stronger medicolegal defenses for their clinical decisions.

The importance of qualified professionals in ensuring radiation safety was emphasized in guidelines from this era, noting that "radiation safety in medical imaging relies on the expertise of qualified professionals, including radiologists, radiologic technologists, and medical physicists" [7, 8]. This focus on professional qualifications and standards would later expand to encompass all aspects of radiation oncology practice, including treatment planning, delivery, and quality assurance.

Legal risks associated with clinical trials and standard practice were also beginning to be addressed more systematically. For example, analysis of legal considerations in clinical trial remuneration noted that "the only way to attain legal certainty about a particular remuneration agreement involving beneficiaries of federal programs... is to preemptively seek an OIG advisory opinion" [9]. This growing attention to legal aspects of practice eventually became integrated into comprehensive risk management approaches in guidelines.

Standardized Contouring Guidelines and Target Delineation

One of the most significant contributions of guidelines from this period was addressing the substantial variation in target volume delineation. The systematic review published in 2020 noted that "variation in contour delineation among providers is common and can affect the resulting plan quality and patient outcomes" [5]. Reviews of prospective clinical trials for radiation therapy quality assurance demonstrated that "variations in target volume delineation can result in increased treatment toxicity and decreased survival," with documentation that "major deviations in target delineation occurred in up to 13% of radiation therapy plans across 5 different trials" [5].

In response to this challenge, consensus guidelines with recommendations for contour delineation emerged as an essential solution. Studies demonstrated that utilization of guidelines and contouring atlases can reduce variation in delineation of both target volumes and organs at risk (OARs) with additional evidence that these improvements in contour delineation can improve predicted tumor control and normal tissue complication probability [5].

Disease sites receiving the most attention in contouring guidelines during this period included head and neck (24%), gastrointestinal (12%), and gynecologic (12%), reflecting areas where standardization was deemed most critical. These early efforts laid essential groundwork for the highly refined contouring guidelines we use today, which now extend to virtually all disease sites and incorporate multimodality imaging approaches.

Despite their proven benefits, the review by Lin et al. notes underusage of consensus guidelines with barriers, including unfamiliarity and access. This recognition led to improved dissemination strategies that matured in subsequent years, including the development of electronic atlases, integration with treatment planning systems, and expanded educational efforts.

Effect on Treatment Decisions and Outcomes in Specific Cancer Sites

Head and Neck Cancers

Head and neck cancers represented 24% of contouring guidelines by 2020 [5], making them the most extensively addressed disease site in standardization efforts. These guidelines were particularly important given the complex anatomy and proximity of critical structures in the head and neck region [10]. The standardization of nodal-level delineation and primary tumor target volumes significantly reduced geographic misses while optimizing normal tissue sparing [11]. The integration of functional imaging, particularly PET-CT, into target delineation was also a key advancement addressed in guidelines from this era [12].

Gynecologic Malignancies

For gynecologic malignancies, guidelines began addressing the integration of image-guided brachytherapy with external beam radiation therapy, establishing approaches that would eventually become standard of care for cervical cancer treatment [13]. The transition from point-based to volume-based brachytherapy planning represented a paradigm shift that required careful standardization through guidelines [14]. The development of contouring standards for organs at risk in the pelvis also significantly advanced the safe implementation of intensity-modulated radiation therapy for gynecologic cancers [13].

Gastrointestinal Cancers

In gastrointestinal cancers, guidelines helped standardize approaches to complex treatment planning for sites like pancreatic cancer and rectal cancer, where the proximity of critical normal structures to target volumes demanded careful balance of tumor control and toxicity considerations [15–18]. The evolution of neoadjuvant treatment approaches, particularly for rectal cancer, necessitated clear guidelines on target volume modification based on treatment response [19].

Lung Cancer

Guidelines for lung cancer during this period addressed the implementation of four-dimensional CT simulation, management of respiratory motion, and standardized approaches to elective nodal irradiation [20, 21]. The integration of PET-CT for target delineation was a significant advance that required careful standardization through guidelines, particularly for stage III disease treated with definitive chemoradiation [22–24].

Methodologies Used to Develop Consensus and Contouring Guidelines

Developing robust consensus guidelines and statements during this era was a rigorous process driven by recognized experts in the field, typically convened by professional societies. Some of the societies that make contributions in this area include the American Brachytherapy Society (ABS), the American Society for Radiation Oncology (ASTRO), the Radiation Therapy Oncology Group (RTOG), the Canadian Association of Radiation Oncology (CARO), and the European Organisation for Research and Treatment of Cancer (EORTC). The methods used in developing these guidelines typically included the following: a review of existing literature, input from clinical experts, and consensus building. The ABS panels used to develop guidelines for vaginal cuff brachytherapy and locally advanced carcinoma of the cervix using high-dose-rate brachytherapy utilized relevant reviews of published literature [14, 25]. The published literature included previously published guidelines from professional societies, medical literature, and clinical trials. The results were used to develop recommendations on all aspects of the guidelines, including patient selection, QA, dosimetry, fractionation, and techniques. In some instances, a systematic literature review was used in developing guidelines as done by the panel appointed by ASTRO that developed guidelines for palliative radiotherapy for bone metastases [26]. Beyond the literature, the clinical experience and current practices of the expert panel members was integral to formulating the guidelines. The appointed groups were typically practitioners that had extensive clinical experience and research in the topic of interest [14, 25, 26]. Through a series of conference calls, meetings, and discussions, panel members worked to identify established practices, controversial topics, and reach consensus on recommendations. Sometimes controversy or insufficient evidence existed, and the panel declined to make specific recommendations [25]. Consensus building was an important part of the development of the contouring guidelines that became prevalent during the decade.

The advent of three-dimensional conformal RT (3D-CRT) and intensity-modulated radiation therapy (IMRT) fundamentally changed how target volumes and OARs were defined, shifting from two-dimensional field edges to sophisticated three-dimensional delineations on cross-sectional imaging like CT and MRI. This transition highlighted significant variability among practitioners in contouring. To address this, expert panels developed consensus contouring guidelines and atlases for various anatomical sites, often motivated by the needs of multi-institutional clinical trials. Examples of contouring guidelines developed or updated during the decade are shown in the following table.

Author/ reference	Title
Hall et al. [27]	Development and validation of a standardized method for contouring the brachial plexus: preliminary dosimetric analysis among patients treated with IMRT for head-and-neck cancer (**2008**)
Kong et al. [28]	Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus (**2010**)
Lim et al. [13]	Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive of treatment of cervix cancer (**2011**)
Gay et al. [29]	Pelvic normal tissue contouring guidelines for radiation therapy: A radiation therapy oncology group consensus panel atlas (**2012**)
Cox et al. [30]	International spine radiosurgery consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery (**2012**)
Goodman et al. [15]	Radiation therapy oncology group consensus panel guidelines for the delineation of the clinical target volume in the postoperative treatment of pancreatic head cancer (**2012**)
Grégoire et al. [31]	Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines (**2014**)
Jabbour et al. [32]	Upper abdominal normal organ contouring guidelines and atlas: a radiation therapy oncology group consensus (**2014**)
Wu et al. [33]	Expert consensus contouring guidelines for intensity modulated radiation therapy in esophageal and gastroesophageal junction cancer (**2015**)

Development of the contouring guidelines typically involved the following: case selection, expert contouring, quantitative analysis, refinement and atlas generation, then validation and generalizability. Case selection required the selection of representative patient cases for use, often requiring the cases that had the appropriate imaging information [i.e., computed tomography (CT) simulation, magnetic resonance imaging (MRI), positron emission tomography (PET), etc.]. Panel members independently contoured the volumes of interest and/or organs-at-risk (OAR). The contours were aggregated and assessed using quantitative analysis to determine the interobserver variability. The Simultaneous Truth and Performance Level Estimation (STAPLE) algorithm was often used to generate preliminary consensus contours for the panel to review [13, 29, 30, 32, 33]. The panel reviewed and addressed variability deemed significant to define the generalized set of contours. Written guidelines and image atlases (made available online) were then developed. In addition to helping standardize clinical practice, the guidelines and atlases served as teaching aid and references in radiation oncology.

Guidelines from this period outlined numerous technical specifications essential for safe and effective treatment delivery, particularly for techniques like high dose rate (HDR) brachytherapy, IMRT, and SBRT. Technical specifications were developed for applicator usage in HDR. This included guidelines for applicator selection, insertion, and imaging [14, 25]. Acceptable dose and fractionation schemes, often normalized to 2 Gy per fractions equivalence (EQD2) for comparability, were also provided for HDR treatments of cervix and vaginal cuff [14, 25]. A critical aspect was the specification of dose limits for OARs to minimize toxicity. Standardization of OAR contouring with atlases directly supported efforts to refine normal tissue dose constraints. The developed guidelines also stressed the roles and responsibilities of team members in the treatment process which was particularly important as new treatment techniques were being introduced. In particular, the guidelines emphasized the roles of the medical physicists being responsible for key QA activities within the department. The guidelines often referenced specific task groups published by the American Association of Physicist in Medicine (AAPM). Guidelines were helpful in encouraging interdisciplinary collaboration and communication within the radiation oncology department. This was a necessity to safely and effectively implement many of the complex treatments introduced during this decade.

Contemporary Impact and Future Directions

Looking back, it is clear that the guidelines and consensus statements developed during 2005–2014 laid the essential groundwork for current practice. The methodological rigor for guideline development has continued to improve, with recent guidelines exemplifying sophisticated approaches now employed, including “consensus scope definition by focus group discussion; evidence gap identification by a scoping review of guidelines and literature reviews; evidence review and synthesis by a systematic review of experimental and observational studies” [34].

The consensus panels have become increasingly multidisciplinary, reflecting the team-based approach that characterizes modern oncology practice. Recent consensus panels include not only radiation oncologists but also “clinical oncologists (4), radiologists (3), a nuclear medicine specialist, medical physicists (2), and dosimetrists (2),” ensuring multiple perspectives contribute to recommendations [25].

3 The Evolution and Clinical Impact of Stereotactic Body Radiation Therapy and Image-Guided Radiation Therapy

The development of stereotactic body radiation therapy (SBRT) and image-guided radiation therapy (IGRT) between 2005 and 2014 marked a transformative era in radiation oncology. These technologies redefined precision in tumor targeting, enabling high-dose ablative treatments while minimizing toxicity to surrounding tissues. This period laid the foundation for modern paradigms in managing early-stage malignancies, oligometastatic disease, and inoperable tumors.

Historical Origins and Technological Evolution

The groundwork for SBRT was established in the 1990s, but its clinical adoption accelerated during the mid-2000s. A pivotal 2006 phase II trial by Timmerman et al. demonstrated the efficacy of SBRT (60–66 Gy in three fractions) for stage I non-small cell lung cancer (NSCLC), achieving 95% 2-year local control in medically inoperable patients [35]. However, this study also revealed critical limitations: centrally located tumors (<2 cm from the proximal bronchial tree) had a 27.3% rate of grade 3–5 toxicity compared to 10.4% for peripheral lesions [35]. These findings prompted refined patient selection criteria and dose constraints for central tumors, shaping subsequent protocols.

Concurrently, Japanese researchers pioneered hypofractionated regimens. The 2007 study by Onishi et al. analyzed 257 patients treated with SBRT (18–75 Gy in 1–22 fractions) and established the biological effective dose (BED) threshold of ≥100 Gy as critical for optimizing local control [36]. For BED ≥100 Gy, 5-year local recurrence rates were 8.4%, versus 42.9% for BED <100 Gy [36]. This dose–response relationship became a cornerstone of SBRT planning.

The Radiation Therapy Oncology Group (RTOG) 0236 trial, published in 2010, validated these findings in a multi-institutional setting. Patients with peripheral T1-T2N0 NSCLC received 54 Gy in three fractions, achieving 97.6% 3-year local control and 40% 5-year overall survival. Notably, 27.3% experienced grade 3 toxicity, underscoring the need for rigorous normal tissue constraints [37]. This trial standardized SBRT delivery and facilitated its integration into national guidelines.

Clinical Applications in Medically Inoperable and Oligometastatic Disease

Inoperable Early-Stage NSCLC

By 2010, SBRT had become the standard for inoperable early-stage NSCLC. The 2013 RTOG 0618 trial expanded its application to operable patients, testing 54 Gy in three fractions for peripheral tumors. With 2-year primary tumor control of 92.3% and only 16% grade 3 toxicity, it demonstrated SBRT's feasibility even in surgical candidates [38].

Furthermore, a pooled analysis of two randomized trials demonstrated an estimated overall survival at 3 years was 95% in the SABR group compared with 79% in the surgery group [39], demonstrating SABR could be an option for treating operable stage I NSCLC.

Oligometastatic Disease

The concept of metastasis-directed therapy gained traction during this period. A 2012 prospective study of SBRT for ≤5 oligometastatic lesions reported 2-year local control of 87% and freedom from widespread distant metastasis (FFDM) of 52% [40]. These results catalyzed the design of phase III trials like the 2014 SABR-COMET, which later confirmed survival benefits in oligometastatic settings [41].

Efficacy in Key Disease Sites

Prostate Cancer

Early adoption of prostate SBRT emerged from hypofractionation studies. The 2013 phase II trial by Katz et al. used 35–36.25 Gy in five fractions, achieving 98% 5-year biochemical control with <5% grade 2+ genitourinary toxicity [42]. These regimens capitalized on prostate cancer's low α/β ratio (~1.5 Gy), enabling biological dose escalation equivalent to 90 Gy in conventional fractions.

Brain Metastases

While intracranial SRS predates SBRT, technological synergies during this period enhanced both modalities. The 2014 JLGK0901 study validated single-fraction SRS (18–22 Gy) for 1–10 brain metastases, showing 88% 1-year local control and <5% symptomatic radiation necrosis [43]. IGRT advancements, such as cone-beam CT for frameless setups, reduced marginal misses from 8% to <2% [44].

IGRT's Role in Margin Reduction and Toxicity Mitigation

The interplay between SBRT and IGRT was pivotal. Several studies in lung SBRT cases demonstrated that daily cone-beam CT reduced planning target volume (PTV) margins from 10 to 5 mm [45–47], leading to possible reductions of grade ≥2 pneumonitis. Similarly, in prostate cancer, intra-fractional ultrasound tracking enabled PTV reductions from 10 to 3–5 mm, lowering rectal toxicity [48]. Moreover, the 2011 phase I/II trial by Garg et al. used daily cone-beam CT for spinal SBRT, achieving 90% pain control with 3% myelopathy [49].

PTV Margins and Target Coverage

Margin protocols evolved iteratively during this era. Several guidelines for lung SBRT recommended:

- 5 mm axial/10 mm longitudinal margins without IGRT
- 3 mm isotropic margins with daily CBCT.

These adjustments preserved >95% target coverage while reducing mean lung dose [50–52]. For prostate cancer, several studies advocated 5 mm margins posteriorly and 3 mm elsewhere when using fiducial markers [53–55].

Technical Advancements that Enabled the Wider Adoption of SBRT

SBRT fundamentally changed the paradigm of delivering ablative radiation doses in just a few fractions to targets outside the brain. Its ascendancy during this era was not merely a clinical preference but a direct consequence of the maturation and integration of several key technical advancements within medical physics and engineering. Some of the key reasons for the clinical viability of SBRT were IGRT, motion management techniques, and improved treatment planning techniques. The clinical adoption of SBRT also required an improved understanding of the radiobiological implications of such large doses per fraction.

SBRT often targets small volumes that may move due to respiration or other physiological processes. Two-dimensional portal imaging was insufficient for treatment positioning. SBRT requires patient positioning to be based on the target volume, or a reliable surrogate. This necessitated the integration of advanced imaging systems into the treatment room, with the capability of imaging soft tissue. Technologies like kilovoltage (kV) cone-beam CT (CBCT) and megavoltage (MV) CBCT directly mounted on linear accelerators became widely available during this decade [44]. Non-radiation-based systems were also available, including ultrasound, electromacnetic tracking systems, and camera-based systems [44]. The ability to accurately and precisely localize the target before or during delivery became principal. This directly impacted the treatment margins used for treatment [56].

Treatment of targets in the lung and liver required implementation of motion management techniques. Vacuum bags or stereotactic body frames were used [57]. Also, respiratory management techniques were implemented, which included active-breathing control devices, breath-hold protocols, radiation beam gating, and real-time tumor tracking of implanted fiducial markers [57]. These techniques were required to ensure the high dose from SBRT treatments was consistently delivered to the moving target volume.

SBRT is characterized by delivering a high dose per fraction with steep dose gradients falling off rapidly outside the target volume. This required advanced treatment planning software and delivery systems capable of creating these dose distributions. While 3D-CRT was used for some early SBRT applications like lung primaries [57], IMRT, including techniques like VMAT, became commonly used for SBRT due to their ability to achieve the necessary dose conformality and sparing of nearby organs at risk. IMRT and VMAT achieve the dose distributions required using inverse planning algorithms that can dynamically determine the shapes of the multi-leaf collimators on the linear accelerators.

Normal Tissue Complications Models and Dose Constraints

SBRT delivers large doses in a few fractions, resulting in a high BED. The radiobiological effect of these hypofractionated, high-dose treatments on both tumor and normal tissues differs significantly from conventional fractionation (typically 1.8–3.0 Gy per fraction) [57, 58]. The use of high doses per fraction increased the demand for image guidance, as misalignment can result in underdosing the target or overdosing surrounding normal tissues. With VMAT and IMRT's complex radiation dose distributions, a larger amount of normal tissue was exposed to low doses, even in conventional fractionation. As a result, there was a need to update the "Emami" [59] dose constraints that were used for decades. In 2010, the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) summary papers were published. QUANTEC systematically pooled published peer-reviewed clinical data in a way to be useful for practitioners. QUANTEC provided organ-specific dose/volume/outcome data and recommended dose limits for a wide range of critical structures [60]. These limits are typically expressed as dose-volume histogram (DVH) constraints, such as the maximum dose to a small volume of an organ or the volume of an organ receiving a certain dose. QUANTEC was primarily for conventionally fractionated treatments. A similar compilation for hypofractionated/SBRT treatments was provided by the AAPM in Task Group Report TG101 [58].

QUANTEC-derived constraints, along with guidelines from clinical trial cooperative groups like RTOG and EORTC, became integral to the treatment planning process. Radiation oncologists and dosimetrists used treatment planning systems to delineate target volumes (GTV, CTV, PTV) and organs at risk (OARs) with the assistance of atlases or published guidelines. Once contours were defined, the treatment planning software calculated the dose distribution and generated DVHs for both targets and OARs. QUANTEC constraints and/or trial protocol guidelines were used to evaluate the plan, ensuring that normal tissue doses were within acceptable limits while still achieving adequate target coverage. This process was widely adopted by clinics during this decade.

4 QA and Commissioning of Advanced Radiation Delivery Systems Including IGRT

The need for rigorous and precise QA and commissioning procedures became more important than ever with the introduction of IMRT/VMAT and SBRT. The consequences of small errors became far more significant than with conventional, larger-field, fractionated treatments used in the past. This would become publicized in a New York Times article published in 2010 [61]. The period between 2005 and 2015 saw the physics community address the need to ensure the safe and accurate delivery of these increasingly complex treatments through the development of new commissioning and QA procedures.

The introduction of VMAT marked a significant leap forward in delivery efficiency and conformality. This treatment delivery was an incremental capability beyond static field IMRT. It involved the simultaneous and continuous variation of gantry speed, dose rate, and beam aperture during an arc or multiple arcs. New commissioning methods were required to verify the accurate and reliable operation of the system under these complex, dynamic conditions. IMRT and VMAT treatments utilize the multileaf collimator (MLC) to provide a dynamic beam aperture. Ling et al. [62] developed key tests involving evaluating the accuracy of MLC position during gantry rotation, the linacs ability to accurately vary and control dose rate and gantry speed. Dosimetric comparisons were made between calculated and measured dose distributions for representative test cases [62]. Bedford and Warrington [63] developed tests for beam flatness and symmetry at variable dose rates, as well as tests to evaluate the cumulative dose delivered during VMAT delivery. These commissioning tests aimed to harmonize with existing guidance documents for IMRT implementation previously published by the AAPM [63]. Future refinements and improvements were made to the commissioning process for VMAT in the following years.

The complexity of VMAT delivery also necessitated the development of new patient-specific QA methods. Patient-specific QA became necessary with the introduction of IMRT treatments. Medical physicists explored various measurement devices and comparison methodologies [64]. Common methods involved absolute point dose measurements using ionization chambers, relative dose measurements using radiographic film, and dose measurements using arrays of ionization chambers or diodes. Initially, the patient-specific QA process was very laborious and often required multiple measurements to verify the safety of treatment plans. New QA devices were eventually developed that resulted in a more efficient QA process.

As mentioned previously, IGRT became widely adopted during this decade. IGRT implemented various imaging technologies into the treatment room and onto the linear accelerator. The technologies included electronic portal imaging devices (EPIDs), CBCT, in-room CT, ultrasound, camera-based systems (surface guidance), and hybrid systems. The EPID provided MV planar imaging and was mounted onto the linac. EPID has limited contrast and limited applicability for IGRT applications. CBCT, using kV or MV, provided volumetric imaging of the patient undergoing treatment. In particular, the kV CBCT provided excellent contrast and proved useful for IGRT. Systems like CT-on-rails provided conventional quality CT images with the patient in the treatment position. This provided clinicians with diagnostic quality CT images that could be used to verify anatomy. However, this required a treatment vault with adequate space for a linac and a CT system, which was not common in radiation oncology departments. Ultrasound systems were a separate unit within the treatment room that could provide localization of soft tissues, particularly in the abdomen and pelvis. Surface guidance was implemented using cameras mounted within the treatment room to track the patient's surface in real time. Hybrid systems implemented multiple imaging modalities within a single linac. One commercially available hybrid system utilized 2 x-ray sources mounted orthogonally to perform stereoscopic imaging [44]. The technical abilities of each system enable different functionality in the clinic; therefore, appropriate commissioning and QA were required. IGRT provided clinicians with precise target localization and setup correction just before or even during dose delivery. As a result of these systems, there was increased confidence the delivered dose distribution consistently matched the planned highly conformal distribution on a fraction-by-fraction basis.

5 Conclusions

The 2005–2014 period represents a formative phase in the development of clinical practice guidelines and consensus statements in radiation oncology. These guidelines transformed practice by addressing everyday clinical problems, enhancing patient safety, standardizing target delineation, and improving treatment outcomes across disease sites.

The methodological approaches established during this era have evolved into the sophisticated, evidence-based guidelines that guide our practice in 2025. While early guidelines primarily translated existing evidence into recommendations, contemporary guidelines increasingly identify knowledge gaps and drive research priorities, creating a dynamic relationship between practice standardization and evidence generation.

Perhaps most importantly, these guidelines have democratized quality care by establishing clear standards that can be implemented across practice settings. This has reduced variations in care quality that previously depended heavily on individual physician experience and institutional practices. As we look ahead, the foundation established during 2005–2014 continues to support ongoing refinement of guidelines that adapt to emerging technologies and evolving evidence, ensuring that radiation oncology remains at the forefront of evidence-based cancer care.

Furthermore, the decade cemented SBRT and IGRT as pillars of precision oncology. Landmark trials established dose-response relationships, toxicity profiles, and technical standards that remain relevant presently. By enabling curative-intent treatment for inoperable patients and refining therapeutic ratios across disease sites, these technologies exemplify the translation of technical innovation into measurable survival gains. Their legacy persists in ongoing efforts to integrate artificial intelligence and molecular imaging into adaptive SBRT platforms.

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History of Intensity-Modulated Radiotherapy: From Sequential Tomotherapy to Volumetric-Modulated Arc Therapy 2015–2023

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1 Introduction

It is hard to imagine that modern intensity-modulated radiotherapy (IMRT) originated from the design of missing tissue compensators. As early as 1960, it was recognized that a patient's body is not a perfect cylinder or square, where opposed beams from anterior-posterior (AP/PA) and lateral directions can form a uniform, rectangularly shaped dose distribution. In 1976, Heedee W. R, a familiar medical physicist name and the previous editor-in-chief of the *Journal of Medical Physics*, published a paper called "Tissue compensating filter for cobalt 60 teletherapy" in *Am. J. Roentgen* [1]. In 1970–1991, many of our pioneer medical physicists published papers in the investigations of how to fabricate compensators [2, 3] from using measuring rods, topographic cameras, and computed tomography (CT). In the early 1990s, applying CT to treatment planning, Mageras [4] from the Memorial Sloan Kettering Cancer Center (MSKCC) proposed an iterative beam model calculation for dose compensator design. The concept of a dose compensator, not a missing tissue physical compensator, heralded the predawn of IMRT. Weeks and Sontag [5] proposed to use a nonlinear least-square optimization to design a 3D compensator, an early concept of inverse planning. The most complicated compensator design in 1990 was a so-called computer-based compensator, yet fabrication of a 3D compensator was labor-intensive and/or expensive (such as using a computerized milling machine), and it was difficult to apply such compensators to every patient.

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2 Brief History of IMRT Concept

The advent of computer-controlled multileaf collimators (MLCs) opened a new and exciting horizon in radiotherapy. With MLC, it is possible to modulate x-ray beam intensity without a compensator and shape the fluence pattern in any shape without physical blocks. In 1990, Djordjevich published a paper called “Optimal design of radiation compensators,” presenting an optimization method that took into account the dose constraints to the normal sensitive structures while having an optimal dose distribution in the target volume [6]. In the mid-1990s, MLC was not as ubiquitous as it is nowadays, and most linear accelerators (Linac) were not equipped with MLC. An add-on MLC for small field sizes [micro-multileaf collimators (mMLC)] was developed by Brain-lab [7], and another add-on MLC (see Fig. 1) was designed for fan-beam intensity modulation, inspired by CT technology [8, 9]. In the mid-1990s, modern Linacs came with MLC for large fields, thus enabling cone-beam intensity modulation [9, 10]. In 1995, Cedric Yu [11] proposed a concept of intensity-modulated arc therapy (IMAT), which was the inception of modern volumetric-modulated radiotherapy (VMAT).

With optimization algorithms and patient-specific CT images at hand, clinically implemented IMRT was reported in 1996 by Clifton Ling from MSKCC [12]. The first IMRT used an in-house developed inverse planning system for a

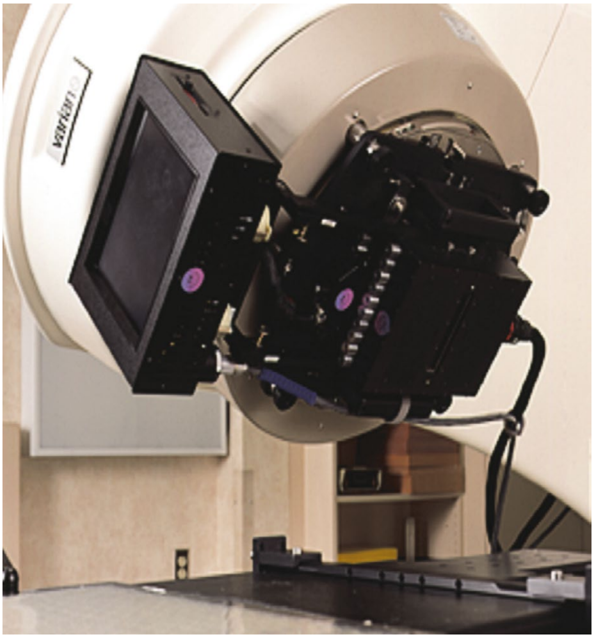

Fig. 1 An add-on collimator for early sequential tomotherapy delivery

boost plan of 9 Gy in five fractions for a prostate case after the initial 72 Gy in 40 fractions. Early clinical outcomes on 35 HN patients were reported by Sultanem et al., from the University of California San Francisco (UCSF) [13], using a poor man's IMRT method [partial transmission block, step-and-shoot fixed gantry IMRT, and sequential tomotherapy (Peacock System)]. This clinical outcome report laid the evidence that IMRT can increase dose to the gross tumor with significant sparing of the salivary glands. The paper reported an impressive 100% of the local-regional progression-free rate and 94% of 4-year overall survival.

In the late 1990s, it was recognized that IMRT planning and delivery were time and labor-intensive and, as a result, not all patients could be treated with IMRT. At the time, one optimization routine took 5 hours, a treatment session took about 45 minutes, and there was no established contouring guideline. For example, when planning for head–neck (HN) cancer, the normal tissue contours included the spinal cord, brainstem, optic nerves and chiasm, mandible, and parotid glands. Without modern imaging-guided radiotherapy (IGRT), the PTV margins were generous, 0.6–0.8 cm for the prostate and 0.5 cm from the clinical target volume (CTV) of HN tumors. With limited treatment machine time, only one IMRT plan could be added each week at UCSF (equipped with four Linacs at the time). After debating at each morning chart round to select the most suitable patients, it was determined that patients with advanced nasopharyngeal cancer had priority. Furthermore, these selected patients had to pass a simulation test (three repeated simulation images, 15 minutes of each interval) to demonstrate that they could endure 45 minutes of treatment without movement. Figure 2 is an impressive film dosimetry image in a

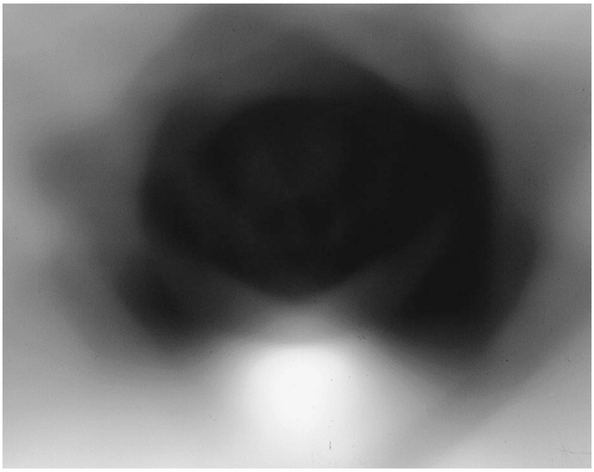

Fig. 2 A film image captured during IMRT QA for an HN case using a phantom

transverse plane of a phantom IMRT plan for an HN patient with visible sparing of the brainstem/spinal cord and parotid glands.

Now, intensity-modulated radiation therapy (IMRT), especially volumetric-modulated arc radiotherapy (VMAT), has become a standard of care for many disease sites. As such, the typical treatment time (defined as beam-on time) has been reduced to 2–5 minutes, a drastic reduction from 45 minutes in the late 1990s. Clinical results from the past two decades have shown improvements in local tumor control and/or reduction of treatment toxicities for prostate cancer, head and neck cancer, and other types of cancer [14–16]. It is also recognized that the success of IMRT critically relies on the accurate delineation of the tumor volume [17] and surrounding normal tissue. Missing dose constraints to the surrounding normal tissue could lead to unexpected treatment toxicity. An early report from the MD. Anderson Cancer Center [18] showed toxicity in the beam path, such as oral mucositis and occipital scalp epilation. Lee et al.'s report observed skin toxicity from five consecutive HN patients treated with extended IMRT fields to include neck and supraclavicular nodal volumes [19]. For typical HN tumors, they recommended that tumor volume be 3–5 mm away from the patient's skin surface to prevent the optimizer from unintentional dosing to the superficial regions. At Cleveland Clinic, for each cancer treatment site, a standard list of normal tissues and their associated dose constraints is established as the initial planning guideline, while each attending radiation oncologist has discretion to provide patient-specific dose constraints of OARs. Table 1 lists an example of OARs and dose constraints for a typical oropharynx case.

Recent applications of AI-based contouring have improved the efficiency and consistency of normal tissue delineations. With multiple imaging modalities, such as the magnetic resonance (MR) and positron emission computed tomography (PET/CT), tumor volume delineation is more accurate and less subjective. Organ motion, change in patient anatomy, and the tumor response to the radiotherapy call for real-time adaptive treatments. In-room image, real-time treatment planning, and efficient workflow on adaptive treatment are still in development.

Table 1 An example of planning dose constraints for a typical oropharynx case

Normal tissue	Dose constraints	Variation acceptable
BRAINSTEM	Max dose 2500 cGy	Max dose 3500 cGy
BRAINSTEM_PRV3	Max dose 3500 cGy	Max dose 4000 cGy
CHIASM	Max dose 500 cGy	Max dose 1000 cGy
COCHLEA_L	Mean dose 500cGy	Mean dose 1000 cGy
COCHLEA_R	Mean dose 500 cGy	Mean dose 1000 cGy
OARPHARYNX	Mean dose 4500 cGy	Mean dose 5000 cGy
ESOPHAGUS	Mean dose 2500 cGy	Mean dose 3500 cGy
GLOBE_L	Max dose 500 cGy	Max dose 700 cGy
GLOBE_R	Max dose 500 cGy	Max dose 700 cGy
LARYNX	Mean dose 3000 cGy	Mean dose 3500 cGy
LENS_L	Max dose 500 cGy	Max dose 700 cGy
LENS_R	Max dose 500 cGy	Max dose 700 cGy
LIPS	Mean dose 700 cGy	Mean dose 2000 cGy
MANDIBLE	105% RX < 1 cc	105% RX < 5 cc
OPTIC_NRV_L	Max dose 500 cGy	Max dose 1000 cGy
OPTIC_NRV_R	Max dose 500 cGy	Max dose 1000 cGy
ORAL_CAVITY	Mean dose 3000 cGy	Mean dose 3500 cGy
PAROTID_L	Mean dose 2400 cGy	Mean dose 2600 cGy
PAROTID_R	Mean dose 2400 cGy	Mean dose 2600 cGy
PITUITARY	Mean dose 300 cGy	Mean dose 300 cGy
SPINAL_CORD	Max dose 3500 cGy	Max dose 3800 cGy
SPINAL_CORD_PRV5	Max dose 3800 cGy	Max dose 4000 cGy
SUBMANDIBULAR_L	Mean dose 3900 cGy	Mean dose 3900 cGy
SUBMANDIBULAR_R	Mean dose 3900 cGy	Mean dose 3900 cGy
*SUPRAGLOTTIC	Mean dose 4500 cGy	Mean dose 5000 cGy
TRACHEA	Mean dose 2500 cGy	Mean dose 3500 cGy
BRACHIAL_PLEXUS_L	Max dose 6300 cGy	Max dose 6600 cGy
BRACHIAL_PLEXUS_R	Max dose 6300 cGy	Max dose 6600 cGy
HYPOPHARYNX_AVOID	Mean dose 5000 cGy	Mean dose 5500 cGy
THYROID	V30 < 60, V45 < 50	

3 IMRT Treatment Planning

Principle of Inverse Planning

Prior to inverse planning, a conformal plan is created manually by a planner who manually designs the beam shape of each beam and its associated beam weight. A typical three-dimensional conformal plan includes 4–7 beam directions. The goal of this manual planning process is to form a desirable 3D dose distribution conforming to the planning target volume (PTV), thus sparing the surrounding tissue. The algorithm of inverse treatment planning was first proposed by Brahme in 1988 [20]. In inverse planning, planners do not manually design beam shapes but specify the desired dose limits (or constraints) for the PTVs and pertinent OARs after defining the orientation and energies of all beams, which is similar to the manual planning, or forward planning. Figure 3 shows the difference in workflow between the inverse planning and forward planning. In inverse planning, the computer optimization algorithm divides each uniform beam into many small beamlets (or rays, or pencil beams) and then iteratively alters the intensities of beamlets until the composite 3D dose distribution best conforms to the specified dose objectives. Figure 4 shows a set of intensity maps from seven beam directions for a prostate case [9]. After the optimal beam intensities and resulting dose distribution have been determined, the computer must then calculate the sequence of MLC leaf motions that will achieve this in the most efficient way.

Leaf Sequencing

The “leaf sequencer” is an algorithm within the IMRT planning system that translates the beam intensity pattern produced by the inverse planning system into an instruction set describing how to move the MLC leaves during beam delivery. Depending on the specific inverse planning system being used, the result of optimization may be either continuous 2D intensity profiles or discrete 2D intensity

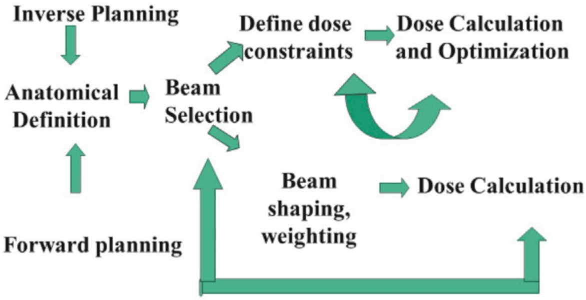

Fig. 3 A diagram for a typical workflow of forward and inverse planning processes

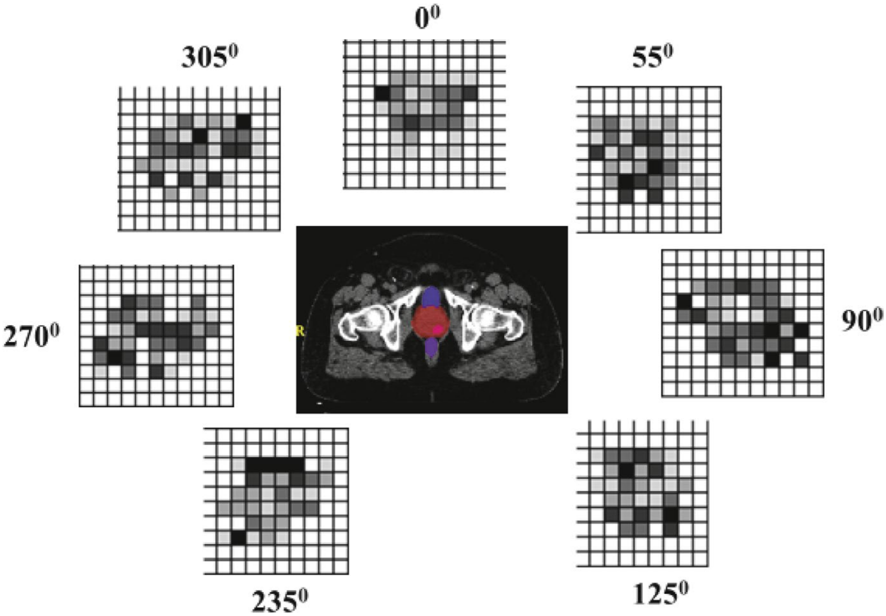

Fig. 4 Intensity patterns from seven step-and-shoot beam angles for a prostate case

matrices with discrete resolution (such as 10 × 1 mm spatially with 5% intensity steps). The term "dynamic delivery" (often referred to as sliding window) delivers a continuous 2D intensity profile, whereas static delivery (often referred to as "step-and-shoot") results in discretized intensity patterns. The dynamic delivery requires MLC leaves moving from one position to the next while the radiation beam remains on. Static delivery requires the radiation beam to be paused or off while MLC leaves move from one position to the next. Some Linac systems (e.g., Varian and Elekta) that allow MLCs to carry the dynamic delivery refer to their MLCs as dynamic MLCs. Some Linac systems (e.g., Siemens) that can only carry the static delivery refer to their MLCs as static MLCs [21]. In theory, the dynamic MLCs can behave as the static MLCs but not the other way around. Figure 5 shows a double-wedge-type intensity pattern to be delivered with dynamic MLC and static MLC [21]. On the left panel of Fig. 5 for dynamic MLC, the MLC positions (X-axis) are slowly sliding from left to right while the dose index in Y-axis increases. On the right panel of Fig. 5 for step-and-shoot delivery, the MLC positions remain stationary (as vertical lines on the right panel) for the static delivery.

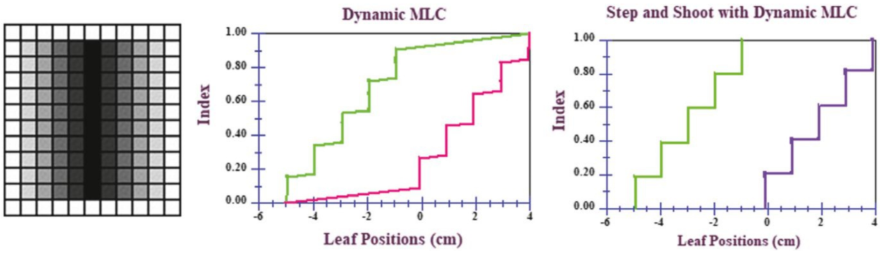

Fig. 5 An illustration of delivery an intensity pattern on the left using sliding window and step-and-shoot delivery method with dynamic MLC

Direct Aperture-Based Optimization

The typical beamlet-based or fluence-based inverse planning optimization often results in complex IMRT plans, which prolongs the treatment time and dramatically increases the number of monitor units (MUs) [22]. The complexity of IMRT plans originated from the use of fluence-based optimization and from the separation of leaf sequencing from the optimization, referred to as a two-step process. During leaf sequencing, the computer program may generate many small area segments (or sub-fields) to not significantly deviate from the initially optimized plan. The use of these small area segments in IMRT plans significantly reduces the overall efficiency of radiation.

To control the complexity of IMRT plans, most commercial planning systems provide options such as choosing coarse intensity levels during leaf sequencing, selecting a leaf sequencer that can provide an optimal delivery efficiency for the specific delivery method (e.g., sliding window or step-and-shoot), or utilizing smoothing filters during optimization [23–25]. However, the effectiveness of these methods in controlling complexity of an IMRT plan is limited, often resulting in significant deteriorations in plan quality.

Instead of using the two-step process, direct aperture optimization (DAO) directly optimizes weights and leaf positions with a predetermined number of MLC shapes permitted for each beam [26, 27]. DAO is a one-step optimization process that eliminates the separate step of leaf sequencing in two-step optimization and allows users to have direct control of the complexity of IMRT plans.

IMAX and VMAT

Cedric Yu et al. [11] proposed the concept of intensity-modulated arc therapy (IMAX) in the mid-1990s. In this method, 2D intensity-modulated (IM) beams at many equally spaced gantry angles are approximated by a superposition of multiple shaped radiation fields with uniform intensity. The increments of intensity level are delivered by individual arcs, with leaf positions changing with gantry angle to produce the shaped fields. Volumetric arc therapy (VMAT) stemmed from IMAX has been widely implemented clinically today, reducing the total number of MUs and total delivery time (i.e., beam-on time) while improving plan quality. Delivering VMAT requires simultaneously moving the MLC leaves and gantry while adjusting dose rate. VMAT achieves a greater degree of freedom for the generation of conformal dose distribution. Given the increased freedoms in MLC speed, gantry speed, and dose rate, VMAT plans are more conformal than conventional fix-gantry IMRT plans. Figure 6 compares a VMAT plan to a fix gantry step-and-shoot IMRT plan on the same patient [28].

Knowledge-Based Planning

As discussed above, the key to IMRT planning is the use of an inverse planning process to find an optimal balance between delivering the adequate prescription dose coverage to the planning target volume (PTV) and sparing critical and normal tissues. Even with many technological improvements, finding a clinically optimal IMRT plan for a specific patient is still a time-consuming and iterative process, often resulting in large variations in plan qualities among different institutions and planners [29–31]. The large variations in plan quality are partly due to planning objectives being the simplified dose and volume histograms and not explicitly specified on the spatial relationship between the organs-at-risk (OARs) and PTVs of a specific patient. Another reason is due to the use of a gradient descending algorithm. For a DVH-based objective function, a gradient descending algorithm may find a solution trapped in a local minimum rather than the global minimum [32–34]. Because of these limitations, progressive adjustments in the planning objectives are often used by experienced planners to create clinical IMRT plans. However, extensive manual progressive adjustments increase the planning time and the outcomes are highly dependent on the planner's skills and experience.

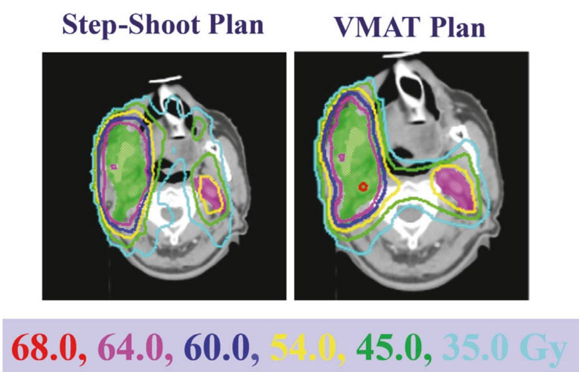

Fig. 6 Comparison of dose distributions for an HN case planned with step-and-shoot IMRT and VMAT

To reduce variations in plan quality and accelerate the IMRT planning process, several advanced treatment planning tools have been developed and implemented clinically. One method, the automatic planning (AP) tool developed by the Pinnacle^3 treatment planning system (Philips Radiation Oncology Systems, Fitchburg, WI), is designed to mimic the manual process by an experienced planner, automatically adjusting and adding planning objectives progressively after each run of optimization. A total of six optimization runs is programmed in the AP planning according to the initial planning goals entered by planners. Based on the resultant dose distribution from the previous optimization, cold spots and hot spots inside PTVs are automatically contoured and dose objectives for these newly created contours are added to the planning objectives in the next run optimization. In each run optimization, the AP planning progressively reduces the dose objectives to each OAR while maintaining the dose coverage to PTVs. The AP planning saves time for the planners, who do not need to attend to the planning while running AP, but it does not reduce the planning time completely [35, 36].

The second method is knowledge-based planning (KBP) (Eclipse Treatment Planning System, Varian), which uses the dose and volume endpoints achieved from previous IMRT plans as planning dose objectives for a new patient with a similar anatomic site [37–39]. More specifically, using machine learning algorithms, a cancer-specific model can be built based on the training dataset that is comprised of anatomic and dosimetric information of prior patients. The model predicts patient-specific dose–volume histograms (DVH), which are input as the planning objectives for the new patient [39, 40].

Instead of developing a predictive model from a database, another approach to KBP, called PlanIQ, was developed by Sun Nuclear Corporation (Melbourne, FL). For a specific case with both input contours and planning CT, PlanIQ calculates a set of feasibility dose–volume histograms (FDVH), depending on a feasibility value (f-value from 0 to 1) that a planner specified. The algorithm of FDVH predicts dose outside the PTVs using empirical high gradient dose spread functions (HGDS) to account for the effect of penumbra and low-dose spread kernels (LDS) to account for beam attenuation and out-of-field scattering, while assuming full-dose coverage to the PTV. The details of the algorithm were described by Ahmed et al. [41]. This tool has been integrated into the Pinnacle^3 TPS v. 16.2 (Philips Healthcare Inc., Cleveland, OH) in 2021. The patient-specific FDVH predictions can guide planners to achieve a clinically feasible plan without using a trial-and-error process to search for achievable planning dose objectives [42].

The third approach, called multicriteria optimization (MCO), is commercially available in both the RayStation treatment planning system (RaySearch, Stockholm, Sweden) and Eclipse Treatment Planning System. This method creates a set of trade-off plans for a single clinical case for clinicians to select the best compromised plan for each specific patient according to trade-offs between the dose coverage of the target volume and sparing of sensitive structures [43–45].

These advanced planning tools are useful to produce plan quality similar to or better than manual plans, thus improving plan consistency. Comparing auto-planning (AP), knowledge-based planning (KBP), and multicriteria optimization

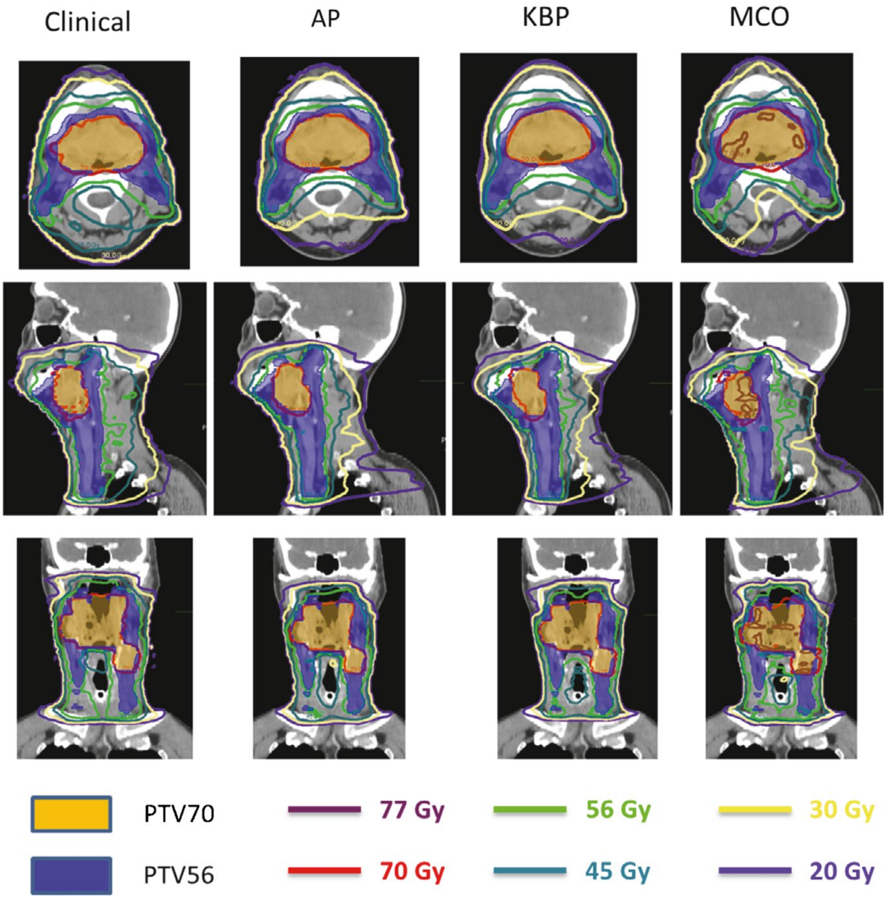

Fig. 7 Comparing isodose distributions from clinical, AP, KBP, and MCO plans for a head and neck patient

(MCO), Lu et al. [46] found that, for difficult cases such as HN cancer, advanced planning tools can further reduce radiation dose to numerous OARs while delivering adequate dose to the tumor targets. Figure 7 compares the clinical plan for an HN case with auto-planning (AP), knowledge-based planning (KBP), and multicriteria optimization (MCO) plans [46].

4 IMRT Treatment Delivery

The early IMRT delivery method included the use of custom-designed 3D physical compensators, which were fabricated using a computer-controlled milling machine to cut either the compensator itself or a negative mold of the compensator to be filled with Cerrobend or similar type of material. This "poor-man's" approach can be implemented without a significant capital investment as it does not require an MLC, which was considered a "cutting-edge" technology. This delivery method requires additional personnel time and space for fabricating the filters, prolonged the treatment time for entering the treatment room, and inserting the physical compensators into each field during treatment. Physical compensators also harden the beam, generate scattered radiation, and increase both skin doses and doses outside the field.

With MLC equipped in most modern linear accelerators, the "poor-man's" IMRT delivery described above was gradually phased out. Modern IMRT delivery methods can be categorized into two broad types: fixed gantry and rotation gantry delivery. As shown in Fig. 8, the fixed gantry delivery methods can use both static and dynamic MLCs as partially described in the previous section. In the step-and-shoot technique, after the dose from the first subfield is delivered, the beam is turned off, the field shape is reset by the MLC, the second incremental dose is delivered, etc. Initially, the concept of step-and-shoot was easier to be accepted and was believed to be safer and more accurate because each subfield was verified. The delivery time, however, was longer for the step-and-shoot method. For example, the beam pausing between each segment can be as long 3–5 seconds. Given that the number of steps or field shapes in the sequence could be 50–100 or more, the cumulative beam idle time could be 3–10 minutes, while the early maximum dose rate was 400–600 MU/min. Dynamic MLC delivery gradually gained popularity, especially after many phantom QA tests and treatment logfile analyses. Another issue encountered early for some Linacs was the ramp-up time after turning beam off and on. Ramp-up time affected beam delivery accuracy [47]. Thus, depending on operational design of a specific Linac, physicists often set the smallest permissible MU per segment to 5 MU in the treatment planning system to minimize the impact of ramp-up time. Besides the issue of beam ramp-up time, communication loss between the beam console and MLC control computer could be up to 50 milli-seconds in old Varian Linacs (before Truebeam Linacs). This communication lag caused over-shooting (delivering more MU than expected) of the first segment and under-shooting (delivering less MU than expected) of the last segment [48]. This phenomenon was also observed in dynamic MLC delivery. To minimize this effect, physicists set IMRT delivery to a moderate dose rate of 400 MU/min while asking planners to carefully control the total number of segments, especially the number of segments associated with small MUs.

Instead of only delivering IMRT with fixed gantry, IMRT can also be delivered in an arc fashion or dynamic gantry. As shown in Fig. 8, while the gantry is rotating around patients, the radiation beam can be modulated in either cone-beam or fan-beam configuration. A dynamic MLC or a specially collimated bimodal MLC is required. Cone-beam arc therapy with dynamic MLC has evolved into today's volumetric-modulated arc therapy (VMAT), taking advantage of the capability of modulating gantry speed, MLC speed, and dose rate. When the mechanical speed limits of MLC or gantry are reached, reducing the

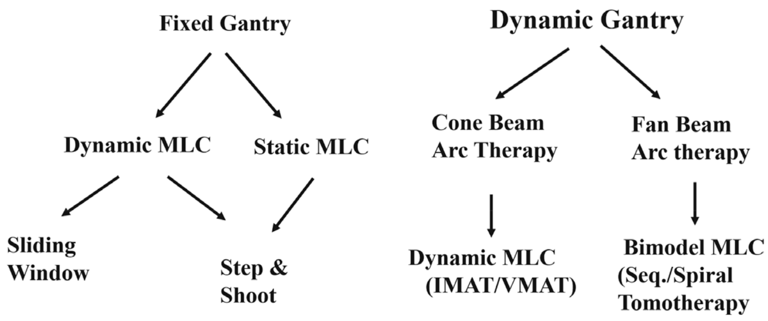

Fig. 8 Summary of IMRT delivery methods

dose rate can effectively further reduce the speed of MLC or gantry. The inability to continuously adjust dose rate in Siemens Linacs prohibited their implementation of VMAT delivery.

Another technologically different approach to IMRT beam delivery is tomotherapy, wherein a rotating fan-beam (broad in the transverse direction, but narrow in the superior–inferior direction- approximately 0.5–2.0 cm beam width in this direction) is intensity modulated with a bimodal MLC. The bimodal MLC contains 20 leaf pairs, with each leaf pair having only two positions: completely open or completely closed. Figure 9 shows an example of intensity patterns for the bimodal MLC. The transit time of a leaf from its fully open to closed position is about 20–30 ms. The beam intensity produced by each leaf is determined by the fraction opening time of the leaf. The beam intensity is usually modulated every 5° while the gantry is rotating around the patient. Figure 9 shows an example of intensity patterns for the bimodal MLC. The nominal maximum fan beam field size is 2 × 20 cm. Using this bimodal MLC, the early IMRT delivery was implemented by adding the MLC to a conventional Linac developed by a commercial company (Peacock System, designed by Nomos Corp, Sewicky, PA). Compared with today's VMAT delivery, one can see that this early IMRT delivery was limited by its field size, only suitable for primary HN tumors and prostate cancer. Depending on the superior–inferior extension of the PTV, therapists needed to enter the treatment room to manually move the table position from one position to the next using a digital micrometer from a special crane that controlled the precise movement of the conventional couch. This manual table position was another limitation of this early IMRT delivery, significantly prolonging the treatment time to 30–45 minutes. Historically, this type of treatment delivery is referred to as sequential tomotherapy, which has gone out of practice in most cancer treatment centers.

To improve the delivery efficiency from sequential tomotherapy, Rock Mackie from the Univ. of Wisc group developed a dedicated tomotherapy machine in early 2000. Similar to the concept of a conventional spiral CT scanner, the dedicated tomotherapy machine integrated a 6MV FFF beam with a bimodal MLC, described above. Simultaneous with the beam rotation and MLC leaf openings and closings, the treatment couch automatically translates through the treatment gantry donut to

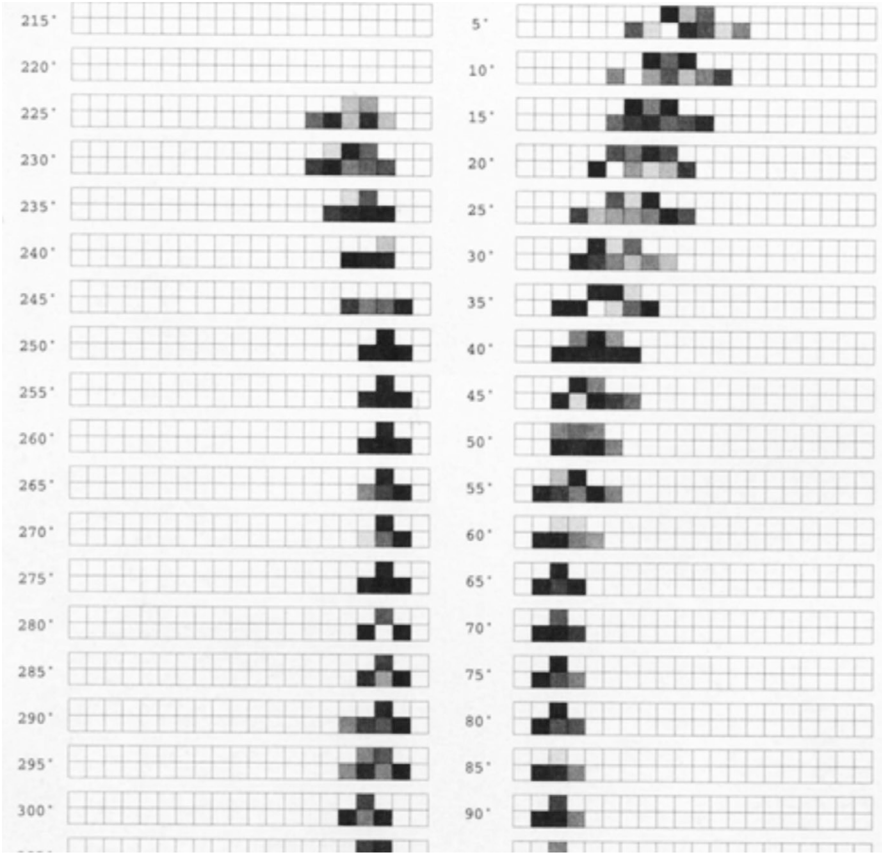

Fig. 9 shows an example of intensity patterns for the bimodal MLC

facilitate 3D dose delivery. The patient is treated with a spiral fan beam. By having the constant gantry rotation as well as constant table movement, spiral tomotherapy improves the delivery efficiency compared with sequential tomotherapy. An innovation that comes from tomotherapy is the synergy of imaging guidance using megavoltage fan-beam CT. Spiral treatment also enables tomotherapy to treat very long, large fields such as cranial spine treatment.

5 Concluding Remarks

In this chapter, we reviewed 30 years of IMRT development history. With increased radiation dose conformity to the tumor volume, geographic miss was a concern in the early days. This heralded more frequent and volumetric imaging guidance, thus leading to the widespread use of on-board cone-beam CT. Given the high-quality imaging in kilo-voltage cone-beam CT, this method of IGRT became the standard of care, equipped in most modern Linacs. The routine clinical use of IMRT and IGRT, and excellent clinical outcomes in reducing normal tissue toxicities, enables many centers to confidently introduce shorter treatment courses with high daily dose of stereotactic body radiotherapy.

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