Chapter 1
From X-Rays to Ion Beams: A Short History of Radiation Therapy

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Abstract Radiation therapy (RT) developed in several eras. Patients' needs for more effective treatment guided the efforts. The development of ion beam therapy (IBT) can be seen as a corollary in this continuous endeavor to optimize disease control while minimizing normal-tissue damage. It could not have materialized, however, without the curiosity, ingenuity, and perseverance of researchers, engineers, and clinicians who developed important enabling technologies.

1.1 Introduction

Prior to the advent of ionizing particle beams, medicine had few options for treating some malignant and benign diseases. Physicians' needs for new techniques to address these problems formed a vacuum, clearly demonstrated immediately following the discovery of X-rays in November 1895. By the first few months of 1896, X-rays were being used to treat skin lesions prior to any understanding of the beams' physical or biological characteristics. The driving force was, of course, patients' overwhelming need of treatment for uncontrollable and debilitating diseases.

Radiation medicine developed over four major eras: the era of discovery, from Röntgen's discovery to about the late 1920s; the orthovoltage era, from the late 1920s through World War II; the megavoltage era, which began with higher-energy linacs for therapy in the 1950s, and, with refinements such as intensity-modulated X-ray therapy (IMXT), is still ongoing. Within this scheme, the roots of IBT fall into the third or megavoltage phase, with the first treatment of humans in 1954.

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Only in the mid 1980s did a first hospital-based proton facility become feasible. These eras represent a continuum rather than a succession of distinct periods, but are a convenient way to assess the evolution of RT and IBT as a sophisticated part of it.

In each era, the fundamental impetus for improvements came from patients' needs for effective disease control while retaining or improving quality of life. These needs aroused the curiosity of physicians, physicists, and biologists, who, in their own ways in each of the eras, performed studies aimed at better understanding the tools they were working with and learning how to use them optimally for patients' benefit. A kind of teamwork occurred in all of the eras, although often no formal teams existed; an overarching goal – better patient treatment – guided the efforts. The development of ion beams is part of this process.

1.1.1 The Discovery Era

During this period of 30–35 years, the roots of RT were established. This era saw the discovery of the atom and various subatomic and electromagnetic particles; investigators strove to learn how to use them therapeutically.

The salient discovery was Röntgen's in 1895 [1], although X-rays were produced earlier – if unwittingly – by others [2]. His report was followed soon by Becquerel's on the phenomenon of radioactivity [3] and, in 1898, by that of the Curies on the discovery of radium [4]. Becquerel and Curie reported on the physiologic effects of radium rays in 1901 [5]. Such discoveries stimulated speculation that radioactivity could be used to treat disease [6]; indeed, X-rays were used to treat a patient with breast cancer in January 1896 [7]. By 1904, RT texts were available [8, 9]; reports of the use of X-rays and radium (curietherapy) occurred throughout the first decade of the twentieth century.

In retrospect, it is clear that lack of knowledge of the biological effects and mechanisms of actions of the new rays led to much morbidity and poor cancer control [10]. However, such outcomes led physicians to ponder better modes of delivery; radiobiologists to study the effects of the rays on cells; and physicists to investigate the properties of these newly discovered radiations. Physics research led to the discovery of radioactive isotopes, which later were used for intracavitary and interstitial therapy; the same research led ultimately to an understanding of the structure of the atom.

As the era progressed, biologists began to understand the relationship between time and dose on cell survival. A crucial discovery occurred when Regaud [11] and Coutard [12] studied alternative ways of delivering the total radiation dose. Until that time, treatment was generally administered in one or a few large doses. Regaud demonstrated that fractionated therapy would eradicate spermatogenesis permanently; Coutard later showed that applying external beam therapy similarly could control head and neck cancer without the severe reactions and late effects that single large doses caused. These findings established that normal cells are better

able to recover from radiation injury than cancer cells and led radiation therapists to employ dose fractionation.

During this era also, Coolidge developed a practical X-ray tube, allowing physicians to deliver higher-energy X-rays (180–200 kV) to deeper tumors [13]. Until then, X-rays were used mainly to treat superficial tumors. High-voltage transformers were also developed. Subsequently, physicists and engineers developed techniques to better measure the dose of radiation with X-rays.

The path to charged-particle therapy begins with Ernest Rutherford, whose work spurred understanding of atomic structure. Rutherford explained radioactivity as the spontaneous disintegration of atoms; he helped determine the structure of the atom; and he was the first to note that one element could be converted to another. A complete bibliography of Rutherford's works is available online, as part of a comprehensive site devoted to him [14]. The reader is referred to that source for publications relating to discoveries noted herein.

In 1896, Rutherford began to use X-rays to initiate electrical conduction in gases; he repeated the study with rays from radioactive atoms after Becquerel's discovery. In 1898, he discovered that two separate types of emissions came from radioactive atoms; he named them alpha and beta rays, the latter of which were shown to be electrons. He showed that some heavy atoms decay into lighter atoms, and in 1907 demonstrated that the alpha particle is a helium atom stripped of its electrons. He and Geiger developed a method to detect single particles emitted by radioactive atoms. He investigated whether alpha particles were reflected from metals, discovering that some alpha rays were scattered directly backward from a thin film of gold; a massive yet minute entity, the atomic nucleus, turned back some alpha particles. In 1911, Rutherford proposed the nuclear model of the atom. One of his students, Niels Bohr, placed the electrons in stable formation around the atomic nucleus; the Rutherford–Bohr model of the atom, with later modifications, became standard, and Rutherford scattering is still used today in basic and applied research.

Wilhelm Wien, in 1898, had identified a positively charged particle equal in mass to the hydrogen atom. In 1919, Rutherford demonstrated that nitrogen under alpha-particle bombardment ejected what appeared to be nuclei of hydrogen; a year later, he equated the hydrogen nucleus with the charged entity that Wien had discovered. He named it the proton.

The discovery of X-rays, then gamma rays, then the structure of the atom with electrons, protons, and neutrons marked the first era. It was one of physical and biological experimentation to determine and understand the characteristics of the newly discovered beam and the effects of such rays on cells and tissues. Especially following the work of Rutherford, radioactive elements were also identified and diligently studied, as well.

As treatment began with these new types of radiation prior to adequate knowledge of their characteristics and effects, errors were made and patients were injured. However, as knowledge and understanding increased during this era, two major divisions of radiation medicine – diagnosis and therapy – were developing; physicians were diagnosing many diseases and malignant tumors were being treated, some of them successfully.

1.1.2 The Orthovoltage Era

The period from roughly the late 1920s to 1950 encompasses this era. Patients' needs for treatment of deep tumors were addressed largely by radium-based intracavitary and interstitial irradiation, in the absence of deeply penetrating external beam sources. It was also a transitional period: physical developments that led to supervoltage (approx. 500 kV–2 MV) RT were being made [15]. During the 1920s, advances in physics and engineering led to increased understanding of subatomic particles and techniques for energizing and focusing them.

The first supervoltage X-ray tubes, built by Coolidge [16], were the basis of the linear accelerator, developed by Widerøe in 1927 and described in a German journal in 1928. E.O. Lawrence, despite knowing little German, used Widerøe's equations and drawings to conceptualize the cyclotron [17]. By the late 1920s, particle accelerators began to be constructed. Following the invention of the linear accelerator, devices operating on the principle of applying a potential difference were developed by Van de Graaff in 1929 [18] and by Cockcroft and Walton in 1932 [19, 20]. The cyclotron, also based on the principle of applying a difference in potential, was invented in 1930 by Lawrence and Livingston [21]. At Lawrence's laboratories at the University of California, Berkeley, accelerated particles were used to bombard atoms of various elements, forming, in some cases, new elements. Lawrence's brother, John, a physician, along with Robert Stone, pioneered neutron radiation for medical treatments [22].

Electron beam therapy became a practical and useful therapeutic option in 1940, when Kerst developed the betatron [23, 24]. The first machine produced 2 MeV electrons; later devices yielded up to 300 MeV. Medical research in particle therapy was largely sidelined during World War II, but high-energy physics investigations were spurred, notably in the effort to develop an atomic bomb. Some who worked on it, notably Robert R. Wilson, became instrumental in the development of IBT.

One major advance during this period was the synchrotron, conceived independently and at about the same time (1944–1945) by Veksler in the Soviet Union and McMillan in the United States. McMillan gave priority to Veksler [25]. The central concept was phase stability, by which high energies could be achieved without the need to build ever larger cyclotrons. Phase stability became the basis for all high-energy proton and electron accelerators thereafter. More importantly for medical use, the synchrotron made it easier to vary the energy of acceleration and thus the depth of penetration in tissue – needed for optimal radiation treatments. The first, the Cosmotron at Brookhaven National Laboratory, began operation in 1952 [17].

1.1.3 Megavoltage Era

The megavoltage era encompasses the years from about 1950 to 1985, although, as noted, in some respects it is still in progress. A major advance, in response to

the continuing need to treat tumors located in deep tissues, was the development of cobalt teletherapy machines and megavoltage linear electron accelerators. Cobalt teletherapy was capable of producing beams equivalent to approximately 1.3 MV X-rays. Electron linacs began to become clinically available as early as the mid 1950s [26], but widespread application occurred in the 1960s and 1970s. Their higher energies (4–6 MeV in earlier machines; 10–20 MeV in later units) made possible increased depth of penetration, greater skin sparing, and improved disease-control rates, which often doubled or tripled, through delivery of higher doses [27, 28]. There was still a major limitation, however, because the radiation sources, X-rays or gamma rays (cobalt), were difficult to control as they passed through tissue: they scattered laterally and passed beyond their targets, exiting patients opposite the point of entry and causing excessive radiation in normal tissues surrounding the tumors. To overcome this, radiation oncologists and medical physicists developed multifield treatment plans to spread unwanted radiation to larger volumes of normal tissue, thereby reducing the high dose to any one region. This tactic helped to reduce visible effects, but also increased the total dose delivered to normal tissues (volume integral dose). Doses sufficient to control many tumors were still unattainable because of continued acute complications and late effects caused by injury to normal tissues.

During this era, radiation medicine advanced as a discipline. Well-designed clinical studies demonstrated the efficacy of modern methods of delivering RT. One of the earliest was done by Gilbert Fletcher at the University of Texas M.D. Anderson Hospital; it demonstrated clearly that megavoltage treatment resulted in improved survival in cancer of the uterine cervix [29]. The founding of the American Society for Therapeutic Radiologists (ASTR) in 1966 (originally the American Club of Therapeutic Radiologists, founded in 1958) occurred partly as a means of encouraging careful studies such as those done by Fletcher. As time progressed, radiation therapists began to emphasize themselves primarily as radiation oncologists; in 1983, the organization became the American Society for Therapeutic Radiology and Oncology (ASTRO) [30].

In many respects, the megavoltage era is still in progress, although the development of higher-energy electron accelerators is quite mature. In recent years the emphasis in photon RT has been on conformal techniques, featuring computerized control and approaches such as IMXT. The intent, as has been true throughout the megavoltage era, is to deliver a more effective dose to the target volume while reducing the dose to tissues that do not need to be irradiated. One might think of it as the multiportal approach brought to its logical conclusion; indeed, the approach was anticipated by rotational arc therapy, popular for a time in the 1970s and 1980s. IMXT can conform the high dose to the target volume, but the modality employs a greater number of portals and thus traverses a greater volume of normal cells. IMXT beams are still composed of photons; their absorption characteristics in tissue remain unchanged.

1.1.4 The Era of Ion Beams

The groundwork for IBT was laid in 1946 when Robert R. Wilson wrote the landmark paper in which he proposed that protons accelerated by machines such as Lawrence's could be used for medical purposes as well as scientific investigations [31]. In a conversation with the author, Wilson said that his insight was inspired by the medical work that Lawrence and Stone had done at Berkeley. In the immediate postwar years, higher-energy accelerators were just becoming available. Wilson reasoned that protons, among the charged particles, offered the longest range for a given energy and were then the simplest and most practical for medical use.

Wilson's interest in the medical use of protons never ceased. When he was selected as first director of the National Accelerator Laboratory (later Fermilab), he encouraged the idea of a proton treatment facility. In 1972, Fermilab investigators proposed such a facility. However, physicians in the Chicago area advocated a neutron facility at the laboratory instead. After Wilson resigned the directorship in 1978, others at Fermilab, among them Miguel Awschalom, Donald Young, and Philip Livdahl, continued to believe in a patient-dedicated proton facility.

The first clinical use of a proton beam occurred at Berkeley in 1954 [32]; limited investigational proton treatment lasted for a few years afterward, until Berkeley scientists, notably Cornelius A. Tobias, began investigating biologically similar helium ions. Tobias was a nuclear physicist who, early in his career, became interested in applying physics to biology and medicine. His fundamental research interest was on the effects of ionizing radiation on living cells, and he, like Wilson, foresaw the advantages of therapeutic ion beams long before most radiation oncologists did [33, 34].

Proton therapy (PT) began to spread to other physics laboratories around the world. The second use of a physics research accelerator for PT occurred in Uppsala, Sweden in 1957. Physicians at MGH, led by a neurosurgeon, Raymond Kjellberg, began employing protons in 1961 for neurological radiosurgery; pituitary adenomas were first so treated at Harvard in 1963 [35], followed by fractionated PT for other malignant tumors in 1973 [36, 37], under the leadership of Herman D. Suit. Proton beam therapy began at Dubna, Russia (then USSR), in 1967; subsequently, other Russian facilities began operating at Moscow in 1969 and at St. Petersburg in 1975. The Japanese experience began in 1979, at Chiba; another facility opened at Tsukuba in 1983. At the Swiss Institute for Nuclear Research (now the Paul Scherrer Institute), PT commenced in 1985 [38].

The development of the world's first hospital-based proton facility began in 1970 at LLUMC with a feasibility study that revealed three major missing supportive developments that prevented optimal use of protons for patient treatments: computer competence, digital imaging (computerized tomography scanning), and computer-assisted treatment planning that could allow the physician to visualize the ionization pattern superimposed on the patient's anatomy and thereby plan treatments with the precision necessary to realize the benefits from these well-controllable charged

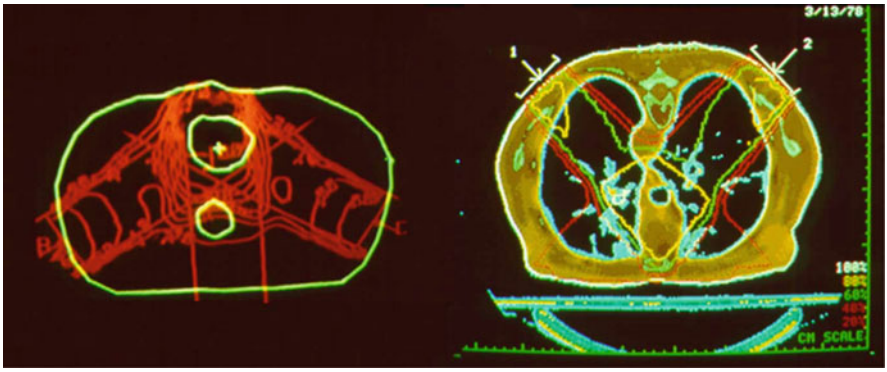

Fig. 1.1 Examples of data output from the computer-assisted treatment planning systems developed at LLUMC in the 1970s. The image from the first (ultrasound) planning system, for a patient treated in 1973, is shown at *left*; a planning image from the second LLUMC system, which employed CT scans, is shown at *right* for a patient treated in 1978. In addition to reproduction of the patient's anatomy, the CT-based system allowed assessment of density variations as the X-ray beams passed through tissue

particle beams (cf. Chap. 34 for details). Industry provided sufficient computer competence and the needed imaging technology by the early 1980s. LLUMC investigators began developing the concepts needed for computer-assisted radiation treatment planning in the late 1960s and completed the first unit, utilizing ultrasonography, in the early 1970s [39]. In the mid-1970s, this was converted to a CT-based unit, using one of the first GE scanners developed (Fig. 1.1). This system provided electron density data, which made possible placement of the Bragg peak precisely within the designated treatment volume [40]. Michael Goitein at MGH expanded the planning system to three-dimensional capabilities, thus providing excellent treatment-planning capabilities for heavy charged particles [41, 42]. The establishment of such planning systems provided one of the essential prerequisites for proton (and other heavy charged-particle) RT [43]. By 1984, all prerequisites for establishing optimal ion beam facilities for clinical use were in place. This was clearly recognized by some of the staff at Fermilab and at the MGH and LLUMC departments of radiation medicine.

The author approached the leadership of Fermilab, Deputy Director Philip V. Livdahl and Director Leon M. Lederman, who agreed to provide Fermilab support for developing a conceptual design for such a clinical facility; to continue with development of an engineering design; and to produce the accelerator, beam transport, and beam delivery systems for LLUMC to begin PT clinical trials (Figs. 1.2 and 1.3). A major turning point in PT, therefore, occurred in 1990, with the opening of the world's first hospital-based proton treatment center at LLUMC. This event occurred more than 20 years after the author and colleagues began to investigate and work toward developing such a facility [44, 45].

Protons were selected as the particle of choice at LLUMC because the relatively low LET of protons as compared to that of heavier ions would allow selective

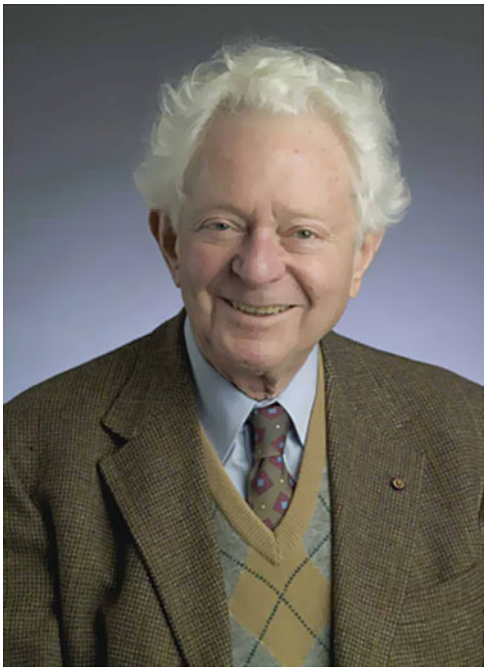

Fig. 1.2 Leon Lederman, Ph.D., Director of Fermilab from 1979 to 1989; recipient of the Nobel Prize for Physics in 1988. In 1986, Dr. Lederman approved Fermilab's collaboration with LLUMC in developing the world's first hospital-based proton treatment center

destruction of the invasive cancer cells growing among normal cells, as had been demonstrated for many years and documented by the worldwide data from using photons (X-rays). By this period, the RBE was known to be very similar for the two kinds of radiation. Loma Linda investigators realized that optimal applications and accumulation of meaningful clinical data could be made only in a facility designed to support patient needs and to operate within a medical environment, with access to a large patient volume and the supporting services available in a medical center. To date, over 15,000 patients have been treated at LLUMC.

Protons were not the only particles investigated for therapy. In the 1960s and 1970s, some physicists and radiation biologists were enthusiastic about the therapeutic possibilities of negative pi-mesons and ions heavier than the hydrogen nucleus. It was then not a given in the minds of many that the particle employed most commonly would be the proton.

Basing their suggestions on the pion capture phenomenon, Fowler and Perkins proposed pi-mesons for clinical use [46]. Pions were expected to become clinically desirable [47], and trials were conducted at three centers: Los Alamos National Laboratory, the Paul Scherrer Institute in Switzerland, and TRIUMF, in British Columbia, Canada. Although some successful outcomes were reported [48–50], in general, the anticipated clinical outcomes did not materialize.

Fig. 1.3 Two Fermilab personnel who helped make the hospital-based proton center at LLUMC a reality. Philip Livdahl (*left*) was Deputy Director of the laboratory in 1986, when the decision was made to proceed with the center. Livdahl had been a colleague of Robert Wilson; he shared Wilson's commitment to proton therapy. Lee Teng, Ph.D. (*right*), shown with the Loma Linda proton synchrotron under construction in the late 1980s, was the chief designer of the accelerator

Helium ion therapy was begun at Berkeley by Tobias and colleagues in 1957 [51]; some notable outcomes supervened [52–54]. Clinical studies with heavier ions were begun by Joseph R. Castro and associates in 1974 [55, 56]; Tobias elucidated the molecular and cellular radiobiology of the particles [57]. Advantages of heavy ions, though appealing theoretically, were not well-understood clinically; the Berkeley studies were undertaken partly to help develop this understanding. Several trials were conducted by Castro and colleagues; some clinical applications were studied, notably specialized indications such as bone sarcomas and bile duct carcinomas [58–60]. However, the cost of developing and delivering heavy ions eventually could not be justified by the relatively limited patient experience, as had been true in the pion trials [61]. Studies of heavy ions shifted to Japan and Germany, under the leadership of such individuals as Hirohiko Tsujii at Chiba and Gerhard Kraft at Darmstadt.

Today, several ion beam facilities operate around the world, including facilities in the United States, Japan, Germany, Russia, France, Canada, China, England, Italy, South Africa, South Korea, Sweden, and Switzerland. Most centers offer protons, but carbon ion therapy is available at HIMAC (Chiba) and HIBMC (Tatsuno) in Japan, and at HIT (Heidelberg), in Germany. The two latter centers offer both protons and carbon ions [62]. Thousands have been treated to date with carbon ion therapy [63, 64], but Eickhoff and Linz note that "systematic experimental studies to find the optimum ion have not yet been pursued" [65]. They speculate that ions with atomic numbers greater than 6 are "unlikely to undergo a clinical revival," but those with atomic numbers between 1 and 6 may be alternatives to carbon.

1.2 Perspective

The development of IBT was a response to the need to preserve normal tissue as much as possible, so as to lessen the side effects and complications that often barred delivery of sufficient dose levels to control tumors, even in the mature megavoltage era. Investigations by physicists and radiation biologists from the 1940s to the 1970s pointed to the superiority of charged particles in comparison to photon and neutron beams. Both Wilson and Tobias told the author that they found it easier to explain and demonstrate the advantages of protons and other ions to fellow scientists than to physicians. As evidence mounted, however, some physicians recognized the physical attributes of ions and were able to understand how these attributes would translate into clinical advantages beneficial to patients.

From the clinician's point of view, the advantages ultimately rested on the fact that ion beams are precisely controllable in three dimensions, while photon and neutron beams are less controllable in two dimensions and are uncontrollable in the third. The controllability of ion beams, in the hands of skillful physicians, provides a superior tool for cancer therapy and for dealing with difficult-to-treat benign diseases.

Curing patients who have solid tumors requires controlling those tumors at their site or region of origin. Normal-tissue damage, whether occasioned by surgical trauma or effects of radiation or chemotherapy, restricts the ability to ablate malignant cells.

Keeping the volume integral dose to normal tissues as low as possible is a fundamental issue in radiation medicine. Rubin and Casarett demonstrated that there is no "safe" radiation dose, in terms of avoiding sequelae in irradiated normal tissues [66]. Later, Rubin and colleagues noted a "cascade of cytokines" in mouse lung tissue exposed to doses that might be considered trivial, leading to pulmonary fibrosis [67]. Biological studies are now commonly finding other injury mechanisms.

Research, therefore, is always ongoing to develop new techniques to overcome these imposed limitations of normal-cell damage. Proton and other charged-particle beams are one outcome of such research.

Any radiation beam, regardless of the basic particle employed, can destroy any cancer cell – or any living entity – if the dose is high enough. Historically, therefore, the limiting factor in radiation medicine has been the normal cell and the need to avoid irradiating normal tissues, so as to permit normal-tissue repair and avoid treatment-compromising side effects. This was the fundamental reason behind dose fractionation and multiportal techniques. During the early years of radiation medicine, the major problem of practitioners was their inability to focus the invisible radiation beam precisely on the invisible tumor target.

Improvements in imaging technologies, along with computer-assisted, CT-based radiation treatment planning, enabled radiation oncologists to deliver precision external-beam radiation treatments to any anatomic site. This advance was limited, however, because conformity with photon beams, which has reached a high degree

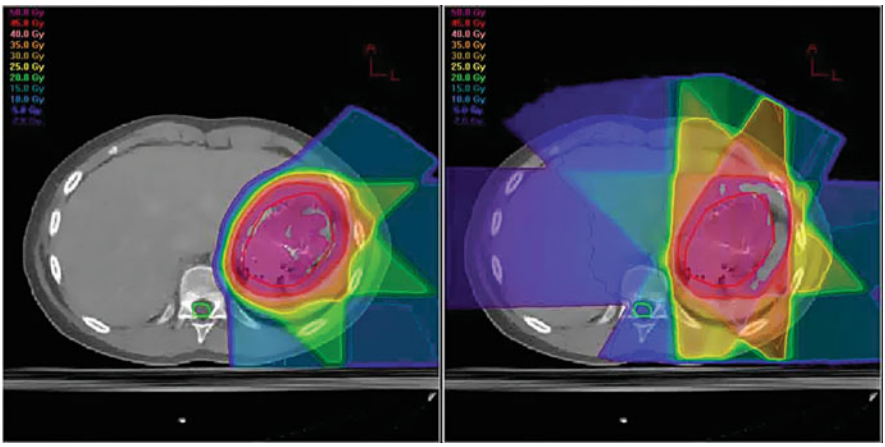

Fig. 1.4 An example of improved controllability needed to spare normal tissues from unnecessary radiation. A 3-field proton plan (*left*) is compared with a 6-field IMXT plan for treating a large liver cancer. Both modalities effect similar high-dose coverage of the clinical target volume (*red outline*), but the superior controllability of the proton beam enables the physician to avoid most of the normal liver tissue receiving low-dose irradiation in the IMXT plan

of precision with IMXT, requires a trade-off: an increased normal-tissue volume integral dose. Ion beams forming a Bragg peak offer a means to achieve the needed increased conformity – i.e., sparing a greater volume of normal tissue – (Fig. 1.4) because of their charge and increased mass.

Physicians using ion beams can now plan treatments to place the Bragg peak in targeted tissues and avoid unacceptable normal-tissue effects. Such capability is facilitated not only by precision therapy planning but also by precision positioning and alignment (cf. Chaps. 33 and 34). This creates a new focus for research and development in the upcoming era. Included in this era, one can expect studies on cell organelle effects with each particle and delivery technique used, and ultimately, biological dosimetry to be developed and merged with physical dosimetry for further improvements in treatment planning. We can also expect to use much more optical imaging fused with our more conventional imaging techniques to better understand the physiological attributes and biological effects of targeted cells and nearby normal cells following treatment. In future years, this increased understanding of cell physiology should help provide a more reasonable rationale for selecting the particle of choice, the fractionation schedule, and the total dose to use for each patient. Technological advances are also occurring in the development of radiosensitizers and radioprotectors, which will further enhance the physician's ability to optimize treatment.

This cyclical process, ongoing since Röntgen's discovery, should take us ever closer to an ideal treatment, wherein only "bad" cells are destroyed and "good" survive. Research will continue; the prime motivator, as always, will be the ongoing effort to meet patients' needs as optimally as possible.

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