Chapter 1

Introduction and History of Proton Therapy

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1.1 Introduction

Soon after the discovery of x-rays by Roentgen in 1896, the radioactivity by Henri Becquerel in 1896, and the extraction of radium and polonium by Madame Curie in 1898, the new field of scientific investigation now known as radiation science took place. For their discoveries, Roentgen, Becquerel, and the Curies were awarded Nobel prizes in subsequent years. Figure 1–1 shows the scientists who made modern radiation science possible so it could benefit mankind.

Most of the modern fundamental radiation physics discoveries took place in the early 20th century. The pace for high-energy beams was growing rapidly during the

Figure 1–1 (a) Wilhelm C. Roentgen, (b) Henri Becquerel, and (c) Marie and Pierre Curie.

early part of the century, with a 10-fold increase in beam energy every six years between 1920 and 1960 [1]. The design of high-energy devices led to many discoveries and created a vast network of basic and fundamental research that spilled over to the medical sciences. Proton beam therapy is one such area that is a product of early innovation.

The medical use of radiation was immediately realized after the discoveries of x-rays and radioactivity. Today, the majority of cancer patients receive combined treatments, including surgery, chemotherapy, and radiation therapy. Nearly 40% of all patients receive radiation therapy at some point during the course of their cancer treatment. Over the last decades, treatment techniques have evolved, and radiation therapy has become more complex with the introduction of computerized treatment planning in the 1980s and the introduction of image guidance in the last decade, to name just two examples. Furthermore, different radiation modalities have been introduced over time. The dominant aim when introducing new modalities was to increase dose conformity (e.g., the introduction of protons or heavy ion therapy) or the increase in biological effect (e.g., the introduction of neutrons and heavy ion therapy).

As an introduction to this book, this chapter seeks to provide historical perspective. More details on some of the historical aspects can be found in several publications [2–4]. Chu [5] has provided detailed educational materials for the evolution of particle beams leading to the current status. A concise description is provided here as a segue for this book.

1.2 The Discovery of the Proton

Ernest Rutherford (Figure 1–2a), a British physicist working on alpha particle scattering, showed that there is a positive charge at the core of every atom, i.e., the nucleus. For this discovery, he received Nobel prize in chemistry in 1908. During alpha particle irradiation of nitrogen gas, he was amazed to see that in every experiment he was able to get a positive charge, which he later named a proton based on the Greek word *proto*, which means first. His intuitive views led to the following equation:

$$N^{17} + \alpha = O^{17} + H^{+} \tag{1.1}$$

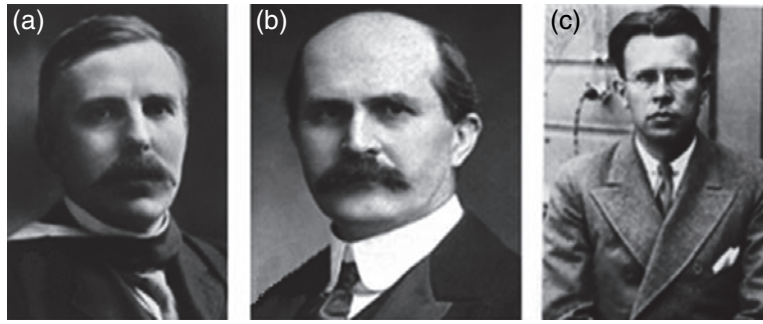

Figure 1–2 (a) Ernest Rutherford, (b) William H. Bragg, and (c) Ernest Orlando Lawrence.

This equation is significant in terms of the building blocks of the periodic table, indicating the first and primary particle in every nucleus. In 1919, he concluded that the positive charge associated with his experiment was nothing but the nucleus of a hydrogen atom, and he coined the term "proton." He also postulated that the nucleus might contain a type of neutral particle, which was discovered later by Chadwick in 1932 and is known as the neutron. A detailed discussion on the modern understanding of the proton and its composition in terms of quarks can be found elsewhere [6].

1.3 The Stopping Power Concept by Bragg

William Bragg (Figure 1–2b), an Australian physicist, was trying to understand the ionizing property of alpha particles. He investigated the ionization produced in air and how far these particles traveled. He published his experimental findings on the stopping power of radiation in gases [7,8]. These elegant findings are still valid and define ionization, stopping power, and range with values very close to today's values. To honor his contribution to the field of ionization, showing the large increase in energy deposition at the end of a particle beam's range, the curve is known as the *Bragg peak* curve. Details on stopping power and range are presented in Chapter 3, and its clinical consequences in are covered in chapters 4 and 5.

1.4 The History of Particle Accelerators

1.4.1 Cyclotrons

During the atomic age of the early 1900s, there was a competition focused on gaining high-energy radiation beams. In the summer of 1928, a young faculty member named Earnest Orlando Lawrence (Figure 1–2c) left Yale University to join the University of California–Berkeley to work on a collaborative project with a chemist and a mechanical engineer. This association turned out to be very fruitful because Lawrence was

able to make significant gains in particle acceleration. He was able to build a device 11 inches in diameter to slingshot a proton beam to very high energy. He called this device a "cyclotron," i.e., a device that accelerated particles in a circle [9]. To increase the energy, he started the design and construction of cyclotron with a larger diameter. In 1936, he was able to build a 37-inch cyclotron to accelerate deuterons and alpha particles to energies of 8 MeV and 16 MeV, respectively. This was a golden age for radiation experiments and an era of artificial radioactivity [10]. The desire to achieve higher-energy particle beams led to the development of even bigger cyclotrons. In 1939, a 60-inch cyclotron was built, for which Lawrence was awarded the Nobel prize in physics in 1939. Lawrence collaborated with many eminent scientists of the time, including medical doctors. He died at the early age of 57 in 1958, but he left a legacy of cyclotron physics that has created a new avenue to understand the nature and use of these beams for medical purposes.

The success of the cyclotron for accelerating high-energy charged particles led to the understanding of nuclear physics by breaking the nucleus and creating artificial isotopes, which were first discovered by Irène Joliot-Curie in 1934. This created a desire for most academic institutions to acquire such a machine to produce the isotopes that were finding applications in astrophysics, nuclear physics, and in medicine for diagnosis and therapy. Harvard University started a program in 1935 and other universities—like Princeton, Massachusetts Institute of Technology (MIT), Yale, and Cornell—also pursued acquiring cyclotrons.

1.4.2 The Use of Cyclotrons for Medical Use

The potential of using proton beams for cancer treatment was suggested in 1946 by Robert Wilson [11]. His suggestion to use protons (he also extended his thoughts to heavy ions) was based on the physics of protons—with their finite range in tissue resulting in a Bragg peak as they slow down during penetration in tissue. The physics of proton beams was well understood at that time. Furthermore, the tools to generate high-energy proton beams were in place, i.e., the cyclotron [12] and the synchrotron [13]. Wilson's paper triggered a series of radiobiological experiments using proton beams in the early 1950s. Tobias, Anger, and Lawrence published their work on biological studies on mice using protons in 1952 [14]. It didn't take long for the first patient treatments to happen, which ultimately led to the proton therapy uses we have today.

With the popularity of the Berkeley laboratory for the development of the cyclotron—plus the atomic and nuclear research during World War II via physics and chemistry experiments—medical use of radiation also become a necessity. Most influential universities in the world had joined the research efforts to design machines to accelerate particles. Harvard University built its first cyclotron in 1937 for nuclear physics research. One of Lawrence's graduate students, Robert Wilson, joined Harvard University in the midst of the war. He wrote the classic paper convincing all that the Bragg peak associated with a proton beam could be used for patient treatment [11]. Figure 1–3 shows the Bragg curve that was advocated by Wilson. Soon after the war, Berkley used a 184-inch cyclotron to treat the first patient with a proton beam in

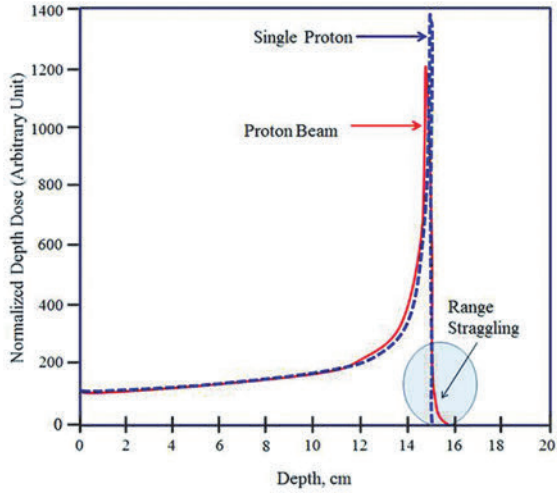

Figure 1–3 Depth–dose curve of a proton beam, showing a large peak and the end of range now known as Bragg peak. Also range straggling is shown when many protons form a beam. Adapted from reference [11].

1954, and then with He^{++} in 1957. Uppsala University in Sweden treated its first patient with a proton beam in 1957. After the war, Harvard decided to install a second cyclotron (the first one was sent to Los Alamos for war research) to be used for nuclear physics and, later, treating patients. In fact, the first patient was treated at Harvard on May 25, 1961, for neurosurgical irradiation. The Harvard Cyclotron Laboratory (HCL) in Cambridge, Massachusetts was originally built for nuclear physics experiments. A detail historical account of the HCL is provided in a book by Wilson [15]. It includes a long list of references and detailed seminal and historical landmarks in the evolution of proton beam therapy in Boston.

1.4.3 Synchrotrons

Based on the theory of relativity, particles gain mass as energy is increased. Consequently, the regular cyclotron fails to accelerate particles as they become out of sync in the cavity. A different approach was needed, and it was attempted early on in 1949, soon after World War II. Chapter 6 provides details of particle acceleration. For heavy charged particles, a synchrotron was developed. The detailed characteristics of a synchrotron are provided by Adruini et al. [16]. Currently several centers in Japan, the United States, and Germany are running particle beam therapy based on synchrotrons.

1.4.4 Clinically Based Accelerators

With the success of high-energy physics research, the University of Chicago and Femilab decided to investigate proton beams for neutron production, and these two

facilities became the most important places for neutron physics research. However, later research on proton beams for medical use became more interesting compared to neutron research. Uppsala University in Sweden also started working on a cyclotron for nuclear physics and later moved to patient treatment. In 1957, Uppsala University built a synchrocyclotron capable of producing 185 MeV protons that was used for fractionated radiation treatment. The clinical results related to neurological treatments were reported in 1963 [17]. The medical use of proton beams also started in Dubna, Russia in 1967; Chiba, Japan in 1979; and Somerset West, South Africa in 1993. Most of these facilities were mainly used for physics research, but some beam time was given for clinical work. The first dedicated facility for particle therapy was built in South Africa. In the United States, the first dedicated hospital-housed facility was built in 1990 at Loma Linda Medical Center in California. Today, dedicated accelerators for proton therapy are commercially available from several vendors.

1.5 The Evolution of Proton Therapy

The seminal paper by Wilson did more than introduce the idea of using protons for cancer treatments. It also described how the beam could be shaped to conform to a target by utilizing a rotating wheel of variable thickness to generate a spread-out Bragg peak (SOBP), although this term was not used until much later [11,18].

The first patient was treated with protons at the Lawrence Berkeley Laboratory (LBL), Berkeley, California in 1954 [19]. However, proton beams were utilized very differently compared to modern-day proton treatments using Bragg peak. In fact, a 340 MeV proton beam was used, penetrating the patient and using the plateau region of the depth-dose curve with a cross-firing technique, i.e., similar to rotational treatments today. The Bragg peak was not utilized because of the inability to predict the range accurately. Targeting of radiation therapy beams was done based on bony landmarks alone. Due to these limitations, protons were applied to treat the pituitary gland for hormone suppression in patients with metastatic breast cancer. Between 1954 and 1957, 30 patients were treated using large, single-fraction doses [19]. In the late 1950s, fractionated delivery (three times a week) was introduced [20].

Not long after the first patient treatments at the LBL, patient treatment started in 1957 at the Gustav Werner Institute in Uppsala, Sweden on their 185 MeV cyclotron [21–23]. The fractionation regimen of administering high doses per fraction had to be chosen because of difficulties in securing beam time at the cyclotron. Other than at LBL, the Bragg peak was adopted using large fields from range-modulated beams [22,24,25]. A rotating wheel technique was applied to produce SOBPs [26–28]. Thus, this was the first use of proton therapy along the lines suggested by Wilson. At the Gustav Werner Institute, range modulation to produce a SOBP was pioneered by using a ridge filter [22,29,30]. Pre-clinical work toward the introduction of proton therapy at the Harvard Cyclotron Laboratory (HCL) started in 1959 [31]. The 160 MeV beam offered sufficient range to reach most sites in the body [32,33].

1.5.1 The 1960s

The number of patients treated with protons was still very low in the 1950s and early 1960s. Thanks to radiobiological experiments at LBL, there was awareness of the potential difference in radiobiological effect when comparing protons with conventional radiation. Several groups thus engaged in experiments to deduce the relative biological effectiveness (RBE) of proton beams using *in vitro* as well as *in vivo* endpoints (see Chapter 5). A significant number of mice experiments were done at LBL [34], and chromosome aberrations in bean roots were studied at Gustav Werner Institute [35]. A large radiobiology program was launched at the HCL starting with studies on mortality in mice [36] and skin reactions on primates [37], followed by a series of *in vitro* and *in vivo* experiments, building the basis for today's practice of using a clinical RBE of 1.1 [38–41].

Patient treatments were refined as well. The HCL began with the treatment of intracranial lesions using single fractions with small beams using a single scattering technique to broaden the beam. The first patient was treated in 1961 [31]. The Gustav Werner Institute (Sweden) was instrumental in the development of proton radiosurgery. By 1968, 69 patients had been treated for intracranial lesions [17,42]. In the same time period, a large clinical proton therapy program was started at the HCL in collaboration with the Massachusetts General Hospital (MGH) using the Bragg peak for radiosurgery. Due to a funding problem associated with physics and space radiation research at the HCL, the proton therapy program was in danger of being terminated in the late 1960s, but it eventually survived due to grants from the National Cancer Institute (NCI) in 1971 and the National Science Foundation in 1972.

Early adopters of proton therapy came from the Soviet Union. A facility in Dubna at the Joint Institute for Nuclear Research (JINR) started proton therapy treatments in 1967, followed by the Institute of Theoretical and Experimental Physics (ITEP) in Moscow in 1968 [43–47]. The program at ITEP was the largest of these programs and allowed treatments with up to 200 MeV protons, which was used mainly in combination with a ridge filter to create depth–dose distributions.

1.5.2 The 1970s

By the 1970s, various beam delivery techniques to produce an SOBP and a broad beam were in place. The beam broadening was mainly done with a single scattering foil, which limited the achievable flatness, field size, and beam efficiency. The introduction of the double-scattering technique was another milestone, as it allowed achieving parallel beam, producing a flat dose distribution with high efficiency [48]. The idea was based on existing devices for heavy ion and electron beams [49].

The program at HCL increased in size in the early 1970s. By 1975, 732 patients had undergone pituitary irradiation alone [50]. Thus, the program at HCL was the largest in existence and was formally established as MGH Radiation Oncology in 1973, starting with the treatment of a four-year-old male with a posterior pelvic sarcoma. The treatment options were expanded toward using protons for skull base sarcomas and head-and-neck region carcinomas using fractionated proton therapy [51]. Treatment of melanoma started in 1975 [52] after tests had been made using monkeys

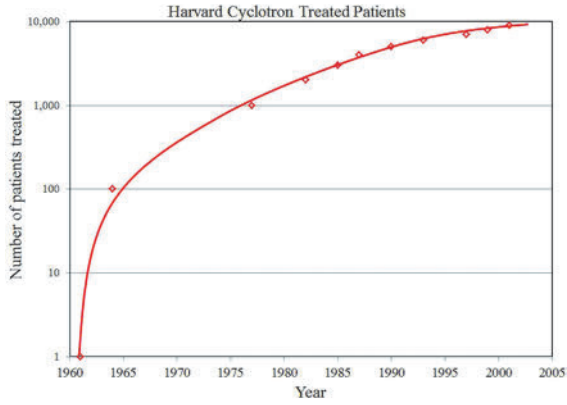

Figure 1-4 Patient treated at HCL over time indicating the growth and popularity of for patient treatments. Data adapted from reference [15].

[53,54]. The first prostate cancer treatments were done in the late 1970s at the HCL [55]. Instrumental for the further advancements of proton therapy was the award of a large research grant by the NCI in 1976 to MGH Radiation Oncology. This allowed extensive studies on medical, biological, and physical aspects of proton therapy. Figure 1–4 shows the growth of the patient numbers at MGH through HCL. It shows close to 10,000 patients were treated before the implementation of a commercial machine at the MGH.

The Russian proton program also expanded. A nuclear physics research facility near St. Petersburg in Gatchina started treating mainly intracranial diseases using Bragg curve plateau irradiation with a 1 GeV proton beam in 1975 [56]. Also at the ITEP facility, the majority of treatments irradiated the pituitary glands of breast and prostate cancer patients using the plateau of the Bragg curve [43,57], but by 1981, 575 patients with various indications had been treated with Bragg peak dose distributions [43].

At the end of the 1970s, Japan joined the proton therapy community. In 1979 the National Institute of Radiological Sciences (NIRS) at Chiba started treatment using a 70 MeV beam [58]. However, of the 29 patients treated between 1979 and 1984, only 11 received proton therapy alone. Most patients received a boost irradiation of protons following by either photon or neutron therapy.

The 1970s also saw plenty of research toward more precise treatment planning. Imaging for diagnosis and planning was done with x-rays and later with CT. Thus, the imaging modality used photons just as the therapeutic treatment beam. With protons it was realized clearly that additional information was desired because of the impact of density variations for each beam path [51,59,60]. The early targets for proton therapy were mainly pituitary adenomas and arteriovenous malformation, which could be visualized on x-rays using contrast material to visualize the vasculature [42,61]. The

treatment of sites in heterogeneous areas, such as the head and neck region, would require additional information to obtain densities in the beam path [59]. When CT imaging became available in 1973, it was adopted in proton therapy planning before it eventually was used in conventional therapy [62–64].

1.5.3 The 1980s and 1990s

Major efforts on not only establishing proton therapy, but on improving its delivery and efficacy, were launched in the 1980s and early 1990s in several continents. Examples are the start of proton therapy at the Particle Radiation Medical Science Center in Tsukuba (Japan) in 1983, the Paul Scherrer Institute (PSI) (Switzerland) in 1984, the facility at Clatterbridge (UK) in 1989, in Orsay (France) in 1991, and at the iThemba Labs (South Africa) in 1993. By July 1993, 12,914 patients had been treated with proton therapy. Nearly half of these patients were treated in Boston at the HCL and 25% in the Soviet Union. During the same time, the radiobiological consequences of proton therapy were being explored [65].

The proton therapy community was very active in research, particularly for treatment planning. The reason was twofold. First, most proton centers were located at a research laboratory and second, proton therapy made it necessary to look into more precise planning and delivery in order to utilize its theoretical dosimetric advantage (see Chapter 2). The first computerized treatment planning program was developed for proton therapy [66–69]. Other developments included the beams-eye-view and the dose–volume histogram. New ways for patient positioning were developed because the finite beam range required a more precise patient setup [70].

Research also focused on new delivery methods. A method using rotating dipoles instead of a scattering system in order to produce a uniform dose distribution was considered [48]. Similarly, a technique called wobbling, using magnetic fields to broaden the beam without a double scattering system, was developed at Berkeley for heavy ion therapy to reduce the material in the beam path that led to secondary radiation in double scattering systems [71]. Already in the late 1970s and early 1980s there were studies on the clinical implications of pencil beam scanning [68,72]. The basic concept of using beam scanning in three dimensions for clinical proton beam delivery dates back to 1977 [73]. It was well understood that scanning not only increased the beam efficiency due to fewer beam shaping absorbers in the treatment head, but also the sparing of structures proximal to the SOBP due to variable modulation [68]. The value of beam scanning was recognized in the late 1970s and early 1980s. Spot-by-spot delivery using scanning and conforming the dose to a target volume was first introduced at NIRS using a 70 MeV beam. The main motivation for this technique was to improve the range of the beam by removing a scattering system. Initially two-dimensional scanning was applied in combination with a range-modulating wheel [58]. Later, three-dimensional scanning was developed using two scanning magnets and an automatic range degrader to change the spot energy [58, 74–77]. Various studies on scanning techniques, such as spot scanning and continuous scanning, were done in the early 1980s at LBL, and continuous scanning in three dimensions without collimator was introduced in the early 1990s [78].

While the early applications of proton therapy were driven by what could be treated safely, it later became clear that proton therapy had clear niches where it had advantageous outcomes compared to photon therapy [79]. Clinical efficacy of proton therapy was demonstrated in otherwise poorly manageable diseases, e.g., for chordoma and chondrosarcoma of the skull base and the spine [79,80]. In addition, choroidal melanomas became the most commonly treated tumor at the HCL [81]. Overall, by the mid 1980s the majority of proton treatments were intracranial radiosurgery treatments [82,83].

In the 1980s, all of the existing centers were based at research labs, which had several significant disadvantages. Nursing staff and clinicians had to travel from their hospital, and patient care other than treatment—such as diagnostic imaging and often also treatment planning—had to be done off-site with personnel not necessarily familiar with the treatment operation. Most importantly, treatments had to compete for beam time with research, and the patient numbers were thus very limited. A major milestone would be the building of the first hospital-based facility.

1.6 Evolution of Machines for Hospital-based Proton Therapy

The first hospital-based facility started treatments in 1990 at the Loma Linda University Medical Center (LLUMC) in California [84]. Their synchrotron was developed in collaboration with Fermilab [85], and the gantries were designed by a group from the HCL [86]. The hospital-based facility at Loma Linda would soon not only treat the biggest share of proton therapy patients, it would also signal that proton therapy was ready for prime time and had made it from research labs into the health care environment. But still, all facilities up to this time had been developed and financed in part by research money. Furthermore, the facilities had all unique designs.

In the late 1990s, the first commercial proton therapy equipment from a vendor was installed at the MGH, financed in part by funds from the NCI. With its first treatment in 2001, MGH transferred its proton therapy program from the research environment at the HCL to the main hospital campus. Conversion of an existing physics cyclotron for medical use added a third facility in the United States at Indiana University in early 2000. This facility included a lot of indigenous advances, such as uniform scanning [87], which is now being used in commercial systems [88].

Subsequently, the number of patients treated with protons increased significantly, and so did the interest of the radiation oncology community. Today more than 100,000 patients have been treated with proton therapy. Figure 1–5 shows the number of patients and the number of facilities as a function of time. It shows exponential growth in both machines and the number of patients being treated worldwide.

The growth of proton therapy has caught the interest of many vendors seeking to provide therapy solutions. Some of the systems in the world have been built locally, like the ones at Loma Linda, PSI (Switzerland), and MPRI (Indiana). However, there are now more than 10 commercial vendors in the fray to provide particle beam therapy. New acceleration technologies based on dielectric wall acceleration [89,90], laser plasma acceleration [91–93], and linear accelerators are works in progress, and

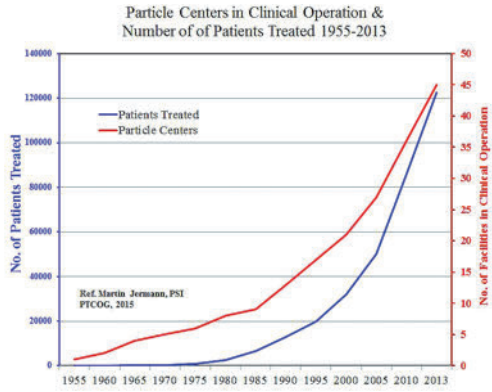

Figure 1–5 The number of patients treated (left axis) and the number of facilities in operation (right axis) from 1955 to 2014. (Courtesy of Martin Jermann, PSI, Switzerland.)

hopefully these techniques could provide badly needed compactness and cost reduction in particle beam therapy.

1.7 Historical Review of Beam-modifying Devices

1.7.1 Beam Broadening for Passively Scattered Delivery

As most proton beams from accelerators are relatively narrow, they are hard to use for large tumors and thus require broadening of the beam. Most centers initially used single scattering foils for broadening. This technique can only achieve a flat beam profile for treating relatively small lesions, and it lacks efficiency. Based on the idea of scattering foils used in electron therapy [49], the double-scattering technique was introduced in proton therapy by Koehler et al. in 1977 [48]. By choosing various materials for the first and second scatterer, it became possible to produce homogeneous lateral dose distributions in clinically acceptable sizes. The design requires a combination of materials with high and low atomic numbers to ensure broadening of the beam while maintaining uniform stopping power [94,95]. The double-scattering technique is being used today at all proton therapy centers treating large lesions without the use of beam scanning. In fact, a better term would be triple-scattering as the range modulator (see below) adds another component of the scattering system. For small lesions—such as in radiosurgery or for the treatment of ocular melanoma—single scattering systems are being used.

1.7.2 Beam Broadening by Scanning (Uniform Scanning)

The beam can also be broadened by a magnetic sweeping system. The idea of using rotating dipoles instead of a scattering system was already proposed in the 1970s [48].

The principle of magnetic beam scanning emerged already in the early 1960s when the idea to magnetically deflect proton beams for treatment was first published [22]. The system was not meant to scan the tumor with individual beamlets, as in beam scanning, but to replace the scattering system using a sweeping magnetic field. The principle was developed at Berkeley and led to uniform scanning or wobbling [71]. It was adopted and implemented at Indiana University in uniform scanning by magnetically sweeping the beam in the horizontal and vertical directions with specialized magnetic fields with a given frequency to provide uniform wide-field proton beam [88]. A description of uniform scanning is reported by Farr et al. [87]. An intercomparison of uniform scanning with commercial systems shows similar characteristics [88]. This technique provides unique treatment capabilities and reduced neutron dose compared to double scattering systems [96–98].

1.7.3 Depth Modulation for Passively Scattered Delivery

Modulator Wheel and Ridge Filter

Early uses of proton therapy had been done mainly without beam modulation. For the treatment of pituitary adenoma and hormonal disorders, the beam penetrated through the patient so that the Bragg peak itself was not used, as one was mainly interested in the favorable lateral penumbra of proton beams [19,20]. Another reason why the Bragg peak was not utilized lay in the limited imaging and, thus, planning capabilities to localize a tumor for treatment. The design of the rotating wheel—consisting of steps of variable thickness for creating a spread-out Bragg peak (SOBP)—was first published in 1975 by Koehler et al. [28,48]. It was later combined with the double scattering technique to provide uniform dose distributions for a certain treatment volume [48].

Uppsala University was first to describe the use of ridge filters to form an SOBP for depth modulation when treating relatively large tumors [22]. Ridge filters are comb-like devices with variable vertical thickness. Figure 1–6 shows several types of devices that are used to create an SOBP [99]. Modern treatments using passive scattering beams still use one of these forms of beam modification. Institutional variations have been adopted to provide uniform doses in depth [100].

1.7.4 Pencil Beam Scanning

Even though the concept of magnetically sweeping technology was known in particle beam, its usage for pencil-beam scanning did not get implemented soon. The pencil-beam scanning concept has a lot of merits because it reduces secondary dose (e.g., neutrons) and allows better dose conformity proximal to the target (see Chapters 23 Treatment Planning for Intensity-modulated Proton Therapy). The clinical implications of beam scanning were analyzed in the late 1970s and early 1980s [68,72]. In 1990 it was developed conceptually at PSI for spot scanning [101]. Pencil-beam scanning was implemented in a Moscow hospital in 1994 [102] and was refined further at PSI as shown by Pedroni et al. [103]. In parallel to intensity-modulated radiotherapy (IMRT), it was realized that intensity-modulated proton therapy (IMPT) can be imple-

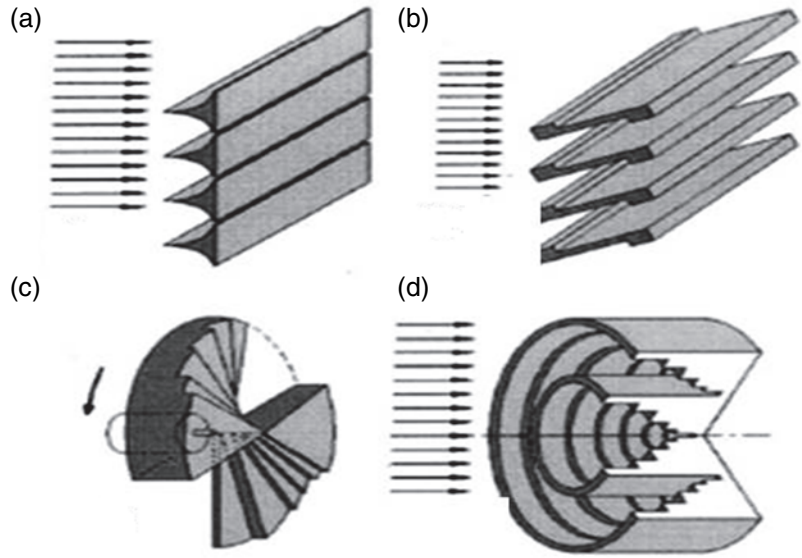

Figure 1–6 Various types of devices for creating an SOBP. (a) and (b) grating type, (c) propeller wheel, and (d) spiral ridge filter. (From reference [99]).

mented with pencil-beam scanning [104,105]. Proton beam scanning and its use in IMPT is currently being performed in Boston and Houston [104,106–109], and other centers are contemplating using it with help from vendors. The concept of beam scanning promises significant improvements in dose conformity (depending on the spot size), and many vendors are moving toward offering solutions for beam scanning only.

1.8 Current Technology

Proton therapy was introduced initially to improve target dose conformity. Today, mainly due to IMPT, the advantage in target dose conformity is not maintained for all sites. There is an advantage certainly for head and neck cancers. What still is and always will be advantageous when using protons is the advantage in integral dose, i.e., proton therapy reduces dose to most critical structures. Because each photon dose distribution can be duplicated by stacking individual pristine Bragg peaks, it is mathematically clear that the integral dose with protons is independent of the proton or photon treatment technique.

The debate about the place of proton therapy in radiation oncology is tied to health care costs [110–113]. If proton therapy would cost the same as photon therapy, it would be unwise to treat with the extra integral dose that photon treatments cause.

This assumes that the dose bath is not advantageous because of the uncertainties in defining the correct target location. A detailed discussion of clinical perspective by a clinician is provided in Chapter 2.

Furthermore, for many treatment sites, the dose reduction to organs at risk achievable with protons may not matter in terms of toxicities. It is here, where the debate about the pros and cons of clinical trials starts [114–117]. Prostate cancer is in the center of this controversy [117,118], while the clinical significance of the integral dose advantage is undisputed in the pediatric patient population [119]. Clinical trials to prove the efficacy and justify the cost are the subject of debates [113,120–123]. Randomized clinical trials are currently ongoing specifically for prostate, lung, and breast treatments. Hopefully this can be resolved in future by compiling all the clinical data that are being accumulated.

Proton therapy technology and delivery will change significantly in the years to come. More and more centers are moving toward beam scanning. The capability of intensity modulation will offer dose-sculpting capabilities that are impossible to achieve with photon beams. Furthermore, the field of proton therapy is expected to catch up with photon therapy when it comes to in-room imaging. Cone-beam CT is still not standard in proton therapy.

1.9 Historical View of the Particle Therapy Organization PTCOG

As particle beams became clinically relevant, the exchange of ideas and the dissemination of knowledge were needed. An ad hoc committee was formed and called the Proton Therapy Co-operative Group (PTCOG). The name was later changed to Particle Therapy Co-operative Group [124]. The first meeting of around 30 people was held in Boston on September 18, 1985. Later it was held nearly every six months with nearly 50 people. It was later rotated throughout various centers that had particle beams, including the United States, Canada, Germany, France, England, Japan, South Africa, Switzerland, and Sweden [5]. Starting in 2007, PTCOG has been held once a year, with the location based on voting by a steering committee. A growing population of attendee (close to 900 recently) attend separate educational and scientific meetings. This transition took place at PTCOG-47 which was held in Wanjie, China in 2007. The PTCOG provides a vast amount of educational information that can be accessed from its website [124]. In 2013, PTCOG started to publish the *International Journal of Particle Therapy* (IJPT) at http://www.theijpt.org/. PTCOG keeps track of the number of patients treated worldwide and of new centers that are operational and being planned. By the end of 2013, over 122,000 patients have been treated with particle therapy, with the majority of them treated with protons.

1.10 Summary/Conclusion

Proton beams have been utilized in research for over 100 years, and their clinical application is growing steadily since the first treatment in 1954. The physical characteristics are well suited to spare normal tissues and provide uniform and maximum dose to tumor. The popularity of proton therapy is growing at an exponential rate as shown in Figure 1–5 with a growth of the number of facilities and the number of

patients treated worldwide. The increasing number of scientific publications indicates maturity and acceptability in most institutions, even though the financial burden is hampering widespread utilization. As the technology is rapidly improving, many vendors are aiming at providing more cost-effective treatments. There are still many challenges in the areas of infrastructures, understanding biology, treatment planning, motion management, post-treatment verification, and clinical outcome where the proton community has to muster its energy.

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