Vision 20/20: Proton therapy

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The first patients were treated with proton beams in 1955 at the Lawrence Berkeley Laboratory in California. In 1970, proton beams began to be used in research facilities to treat cancer patients using fractionated treatment regimens. It was not until 1990 that proton treatments were carried out in hospital-based facilities using technology and techniques that were comparable to those for modern photon therapy. Clinical data strongly support the conclusion that proton therapy is superior to conventional radiation therapy in a number of disease sites. Treatment planning studies have shown that proton dose distributions are superior to those for photons in a wide range of disease sites indicating that additional clinical gains can be achieved if these treatment plans can be reliably delivered to patients. Optimum proton dose distributions can be achieved with intensity modulated protons (IMPT), but very few patients have received this advanced form of treatment. It is anticipated widespread implementation of IMPT would provide additional improvements in clinical outcomes. Advances in the last decade have led to an increased interest in proton therapy. Currently, proton therapy is undergoing transitions that will move it into the mainstream of cancer treatment. For example, proton therapy is now reimbursed, there has been rapid development in proton therapy technology, and many new options are available for equipment, facility configuration, and financing. During the next decade, new developments will increase the efficiency and accuracy of proton therapy and enhance our ability to verify treatment planning calculations and perform quality assurance for proton therapy delivery. With the implementation of new multi-institution clinical studies and the routine availability of IMPT, it may be possible, within the next decade, to quantify the clinical gains obtained from optimized proton therapy. During this same period several new proton therapy facilities will be built and the cost of proton therapy is expected to decrease, making proton therapy routinely available to a larger population of cancer patients. [DOI: 10.1118/1.3058485]

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I. ABBREVIATED HISTORY OF PROTON THERAPY

E. Rutherford proposed the existence of protons in 1919;[1] however, it was not until 1955 that the first patients were treated with proton beams at the Lawrence Berkeley Laboratory (LBL) in California.[2] In the years between 1919 and 1955, two events occurred that had an important impact on proton therapy. First, in 1930, E. O. Lawrence built the first cyclotron, paving the way for future particle accelerators with energies high enough for cancer treatment applications. In 1946, Robert Wilson then proposed that because of their physical properties, beams of protons would be advantageous for the treatment of deep-seated cancers stating, "It will be easy to produce well collimated narrow beams of fast protons, and since the range of the beam is easily controllable, precision exposure of well defined small volumes within the body will soon be feasible."[3] Wilson also described the use of a rotating wheel of variable thickness, i.e., a range modulation wheel (RMW), interposed in a proton beam as a method of adding together several Bragg peaks of variable energies and weights in order to spread the proton stopping region in depth to deliver a uniform dose to an extended target volume. Figure 1 illustrates the concepts proposed by Wilson.

Further progress in proton therapy was rather slow in the 35 years following the first patient treatments at LBL. During this time, patients were treated in a few research facilities, notably in the United States, Sweden, and Russia, where the methods and techniques for proton therapy were further refined and new technology was developed. The clinical results obtained in these research facilities demonstrated the feasibility and efficacy of proton therapy. In 1990, the modern era of particle therapy then began when the first hospital-based proton therapy facility was opened at the Loma Linda University Medical Center (LLUMC) in California.[4] Now there are approximately 25 facilities around the world treating cancer patients with proton beams with more than 55,000 patients treated.[5]

II. PROTON BEAM DELIVERY TECHNIQUES

In order for the reader to understand the material in the following sections, it is necessary to understand the various methods used to deliver proton radiation therapy, which fall into two general categories: passive scattering and spot scanning (also called pencil beam scanning) techniques. A basic overview of the techniques is given here; for further reading, good general descriptions can be found in the literature.[6,7]

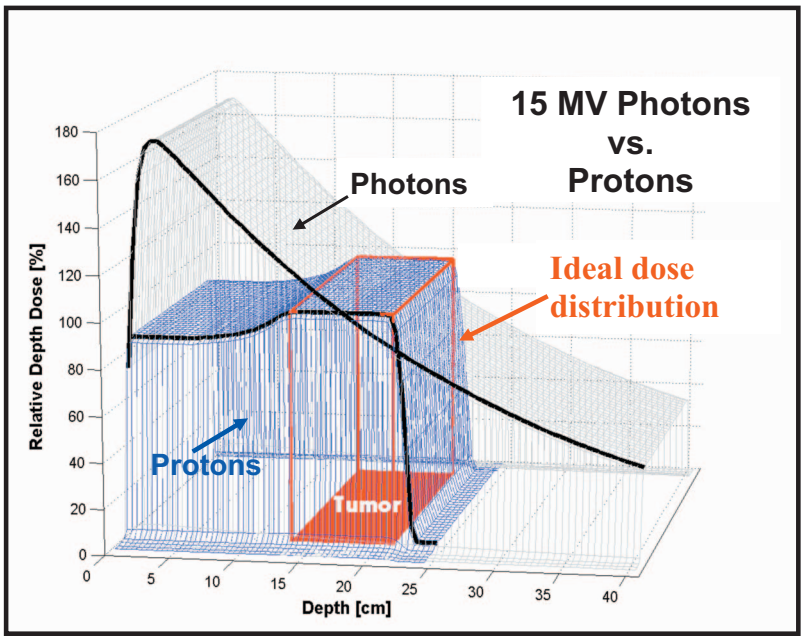

FIG. 1. Comparison between the depth dose curves for 15 MV photons and a proton spread-out-Bragg peak (SOBP). A "target volume" is shown in red. Shown also in red lines is an "ideal dose distribution" for the target volume, which provides uniform, maximum dose to the target volume and zero dose outside the target volume. The proton dose distribution approaches the ideal case to a much greater extent than does the photon dose distribution. Notably, the proton dose stops abruptly distal to the target volume and delivers less dose to the region proximal to the target volume.

The *passive scattering technique* uses scattering devices in the treatment delivery nozzle [usually double scatterers for large fields and single scatterers for small (e.g., radiosurgery) fields] to spread the beam laterally and an RMW or ridge filter[7] to create a spread-out-Bragg peak (SOBP) in the target volume. Between the nozzle exit and the patient surface, a treatment field-specific collimator is used to shape the field laterally to conform to the maximum beams-eye-view extent of the target volume and a range compensator is used to correct for patient surface irregularities, density heterogeneities in the beam path, and changes in the shape of the distal target volume surface. The size of the SOBP is chosen to cover the greatest extent in depth of the target volume. The SOBP size is constant over the entire target volume; therefore, in general, there is some pull back of the high dose region into normal tissues proximal to the target volume (Fig. 2). Because several treatment fields are usually used, each directed from a different angle, this high dose pull back into normal tissue is not additive over all fields. In principle, the use of an RMW to obtain an SOBP in passive scattering techniques modulates both energy and beam intensity. However, this should not be confused with intensity modulated proton treatment (IMPT) achieved with beam scanning techniques as described below.

The second type of beam delivery utilizes *spot scanning techniques* (also often called *pencil beam scanning*). Figure 3 illustrates how a target can be scanned by placing Bragg peaks throughout the volume by the use of scanning magnets and energy changes. Energy changes in scanning techniques can be carried out with various methods including: (1) energy changes in the accelerator when a synchrotron is used; (2) energy changes made with an energy selection system when a cyclotron is used; or (3) either of the above methods plus energy absorbers in the treatment nozzle.

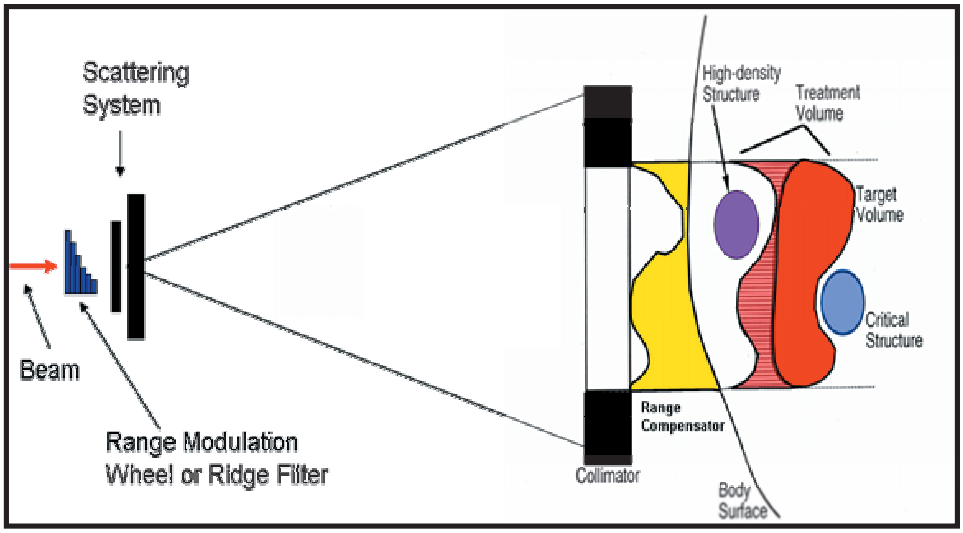

FIG. 2. Diagram of a typical passive scattering system. The range modulation wheel (or ridge filter) creates the SOBP; the double scattering system spreads the beam laterally; and the collimator and range compensator shape the beam to the lateral extent and distal surface of the target volume. The size of the SOBP is chosen to cover the greatest extent of the target volume and, where the target volume is smaller, the high dose is pulled back into normal tissues proximal to the target volume.

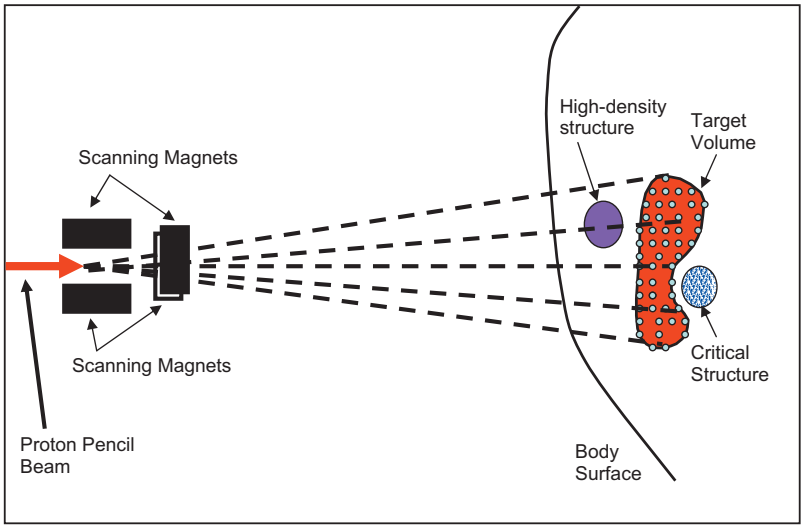

FIG. 3. Diagram of a typical pencil beam scanning system. Two sets of scanning magnets scan the beam in a 2D pattern: the beam range is adjusted by changing the beam energy entering the nozzle. In the usual case, all spots for the deepest range are scanned, the energy is changed, and all spots with the new range are scanned, etc., until the entire target volume has been scanned. In pencil beam scanning, the high dose region can be confined to the target volume and no high dose spills over into normal tissue.

Currently, no standard definitions exist for the various techniques used to deliver scanned beam proton treatments. For this paper, we will use the definitions given below.

Scanning techniques can be used to spread the beam laterally to generate large uniform treatment fields instead of using passive scattering techniques; this is designated as "uniform field scanning." This scanning technique is often called "wobbling;" however, this name was originally applied to a different technique developed at the Lawrence Berkeley Laboratory[7] and it is misleading to apply the term here. In uniform field scanning, collimators and range compensators are still required to shape the treatment beam laterally and distally to the target volume. The primary advantages of uniform field scanning are that large field sizes (up to about 40 cm $\times$ 40 cm or so) are feasible and, because of the absence of a double scattering system, protons are used more efficiently and fewer secondary neutrons are produced. An additional advantage is that the deliverable proton range is greater because there is no range loss in the scattering system: the additional range is typically 1–3 gm/cm^2 depending on the beam energy and field size. However, the disadvantages of uniform field scanning are that the resultant dose distributions in patients are essentially the same as those achieved with passive scattering techniques and a higher sensitivity is introduced to target motion errors than is present in passive scattering techniques.

Additional techniques used in scanned beam treatment delivery are those that use the results of optimization techniques in treatment planning to achieve a desired dose distribution (usually uniform) in the target volume. Objective functions can be used to optimize spot patterns for single treatment fields. This technique would appropriately be called "single optimized uniform field" but it has become customary to define this as "single field uniform dose," or SFUD, and this designation will be used throughout. An SFUD treatment plan consists of one or more individually optimized fields.

Another technique for delivering scanned beam proton therapy is IMPT, which is analogous to intensity modulated photon treatments that have been called IMRT but, which we will call IMXT. IMPT is defined as the simultaneous optimization of all Bragg peaks from all fields with or without additional dose constraints to organs at risk (OAR), such that, when all fields are delivered to the patient, their combination results in a desired dose distribution in the target volume and OARs. Figure 4 shows an IMPT treatment plan having four nonuniform fields optimized to deliver a uniform target dose when all fields are delivered. The desired dose distribution in the target volume may be uniform or nonuniform, depending upon the treatment goals—for example, the treatment goal may be to deliver a simultaneous boost dose in which case the resulting dose distribution would be nonuniform. Even when the treatment goal is to deliver a uniform dose distribution, there are usually low-level hot and/or cold spots in the dose distribution. It should be noted that IMPT is characterized by variations in intensity and energy

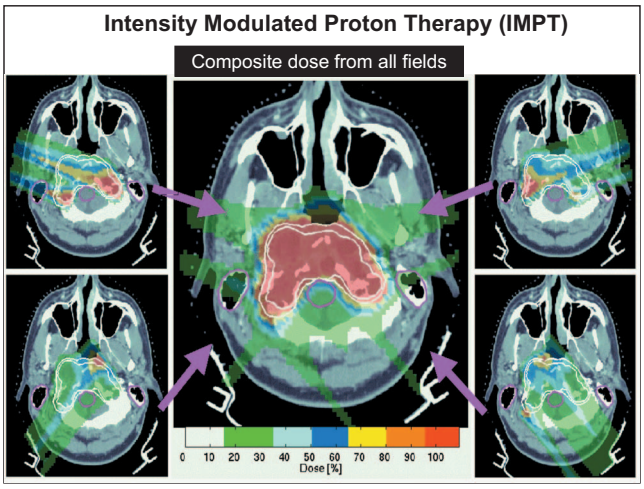

FIG. 4. Illustration of intensity modulated proton therapy. Four nonuniform fields have been optimized to deliver a uniform dose to the target volume. The dose scale applies only to the central figure showing the composite dose (courtesy of A. Trofimov and A. Chan, Massachusetts General Hospital, Department of Radiation Oncology).

rather than variations in intensity alone as is the case for IMXT. IMPT permits realization of the full potential of particle beams to provide highly localized dose distributions for cancer treatment; however, as stated elsewhere in this paper, more research and development is required in order to reduce treatment errors in IMPT, especially those related to uncertainties in treatment planning calculations of proton ranges in tissues and errors arising from target motion during treatment delivery.

Spot scanning is usually achieved by one of two methods: discrete spot scanning or dynamic raster spot scanning, which are described later in this paper.

To be clear, passive scattering, "uniform field scanning," and SFUD techniques, even though they may have components of energy and/or intensity modulation, do not comply with the definition for IMPT used in this paper.

III. REASONS FOR INTEREST IN PROTON THERAPY

Robert Wilson's observations on the potential advantages of proton therapy for cancer treatment created interest among clinical scientists and led to the hypothesis that highly localized dose distributions achieved by proton beams would result in higher probabilities for local control and disease-free survival, and lower probabilities for normal tissue damage. This hypothesis remains the motivating force for clinical studies in proton therapy. It is important to note that the advantages of a proton dose distribution hold true for every beam used in a treatment plan and, for treatments of equal complexity in terms of such factors as technique, number of beams, and beam directions, etc., protons will almost always have superior dose distributions to photons. An exception is when skin sparing is clinically important as photons offer more skin-sparing benefits than protons. It is also important to note that, in some clinical situations, the advantage of protons may be reduced by errors caused by proton range uncertainties in the treatment plan or by target motion during treatment delivery.[8,9]

Several developments occurred in the decade or so before the early 2000s that generated increased interest in proton therapy. These events took place in a number of areas including medical physics, clinical results, reimbursement, technology, and changes in the proton therapy equipment marketplace.

III.A. Medical physics developments

Between the mid-1980s and mid-1990s, medical physicists developed methods to fully utilize medical imaging and to calculate three-dimensional (3D) treatment plans for external beams of photons, electrons, protons, and light ions. In addition, inverse planning and optimization techniques were developed that made it possible to calculate treatment plans for intensity modulated radiation therapy. These developments led to a large number of treatment planning comparisons including those for:

- Conformal photons vs. conformal, passively scattered protons,
- IMXT vs. conformal, passively scattered protons, and
- IMXT vs. IMPT.

Many treatment planning studies have been published[10–14] all of which had the general conclusion that, when photon and proton treatment plans with comparable complexity are compared, protons provided superior dose distributions. These results were obtained from the analysis of dose volume histograms (DVHs) for both target volumes and normal tissues. In particular, the integral dose in the proton treatment plans was two to three times less than the integral dose in the photon plans.[14] These results obtained from treatment planning comparisons provided strong evidence of the potential for proton beams to deliver dose distributions that could improve clinical results if those dose distributions could be realized in actual cancer treatments.

III.B. Clinical results

Several published reports have confirmed that the use of proton beams results in improvements in both local control and normal tissue complications over those achieved with photon beams; however, these comparisons were predominantly made against historical photon controls.[15–17] It should be noted that many of these results were obtained from proton treatments carried out in research-based facilities with horizontal, passively scattered beams, limited energies, and restricted flexibility in the complexity and types of treatments that could be carried out. Further, the number of patients treated in a given disease site was relatively small and, thus, the analysis of these studies often did not produce statistically significant results. It should also be noted that during the mid to late 1990s, no patients had been treated with IMPT techniques; therefore, the best achievable dose localization for proton beams had not been realized.

Based on these preliminary results, it was reasonable to conclude that, should patients be treated with proton beams in modern, hospital-based facilities with improved treatment technology and improved treatment techniques, additional clinical gains could be achieved.

III.C. Reimbursement

Until the late 1990s, proton treatment delivery had not been assigned procedure codes by the American Medical Association. Billing was carried out using special procedure codes, which were evaluated by Medicare and third-party insurance carriers on a case-by-case basis. Therefore, reimbursement for proton therapy could be, and often was, denied. With no assurance of reimbursement, there was no financial incentive in the private sector for building new facilities. Both LLUMC and Massachusetts General Hospital (MGH) proton treatment facilities were financed with institutional and government funding.

In the late 1990s, MGH and LLUMC successfully applied to the American Medical Association (AMA) for proton-specific treatment delivery procedure codes. Medicare and

private insurance carriers then assigned payment rates to the new procedure codes. Moreover, when Medicare set rates for proton treatment delivery, they stated that proton treatments were *not considered to be investigational*. The achievement of reimbursement provided financial incentives for the private sector to finance, build, and operate proton therapy facilities, with the expectation that they could realize a reasonable return on investments. Current reimbursement rates for proton therapy delivery remain attractive; however, one should not expect that these rates will persist in the long term.

III.D. Advances in technology

Research laboratories where proton therapy was being carried out have continued to improve proton therapy techniques and develop new technologies for the acceleration, transport, and delivery of proton therapy. In the private sector, manufacturers have developed isocentric gantries, compact cyclotrons, medical synchrotrons, and advanced treatment delivery systems.[18] Superconducting technology has been used to develop smaller and higher energy cyclotrons[19] and the efficiency of cyclotrons in terms of beam extraction and power consumption has been substantially improved. Robotics have been introduced into proton therapy systems resulting in improved efficiency in the management of patient transport, patient treatment positioning, treatment appliances, and imaging systems.[20,21] In addition, proton capabilities have been developed for commercial treatment planning and data management systems.

Vendors have made major improvements in treatment delivery techniques during the past decade. New technologies include: (1) beam scanning techniques; (2) "universal" nozzles that have the ability to deliver both passive scattering and spot-scanning treatments; (3) RMWs installed permanently in the nozzle that produce variable SOBPs by a combination of beam gating and beam intensity variation; (4) advanced treatment control and safety systems; (5) improved imaging systems; and (6) multileaf collimators.

A noteworthy technological achievement was made at the Paul Sherrer Institute in Switzerland where techniques for proton pencil beam scanning were developed and implemented. This technology was first used for SFUD treatments and then extended to IMPT treatments.[22,23] Several vendors now offer advanced proton therapy systems that have U.S. Food and Drug Administration (FDA) 510(k) clearance. These achievements have matured proton therapy into fully integrated, modern radiation therapy systems that provide advanced cancer treatments in state-of-the-art hospital settings.

III.E. Increased vendor options

Until 1990, all proton therapy took place in research-based facilities with equipment developed by the clinical researchers and engineers who worked in those facilities. The lack of a sizable market was a disincentive for manufacturers to spend large sums of money to develop proton therapy equipment. The confluence of factors during the 1990s and early 2000s discussed above created a more favorable climate for vendors and there are currently several companies marketing proton therapy systems and offering systems that provide both protons and carbon ions for cancer therapy. New proton/carbon systems based on superconducting technology have been developed that will make it possible to build more compact isocentric gantries and accelerators for hospital-based systems. In addition, companies have been formed to develop and operate proton therapy facilities and others offer various levels of consulting (e.g., feasibility studies, marketing studies, business plans, technology evaluation, staffing and operating plans, etc.). The success of new hospital-based proton therapy projects like those at the University of Florida/Shands Cancer Center in Jacksonville, Florida and The University of Texas M. D. Anderson Cancer Center in Houston, Texas has demonstrated that these complex, expensive facilities can be built on time and on budget, and can rapidly reach targeted patient treatment capacity in order to satisfy ambitious clinical programs and business plans.

III.F. Summary

All the factors discussed above have contributed to greatly increased interest in proton therapy in the United States and worldwide. In fact, there has been such an explosion of interest in proton therapy during the past 3 years that one could argue that the current enthusiasm is overheated. There is an indication that some institutions seeking proton therapy facilities are doing so without critical evaluation of the clinical role of proton therapy and the relatively large financial, clinical, and personnel commitments required for developing and operating these facilities. Moreover, there is an acute shortage of trained proton therapy staff and few training programs. Therefore, institutions that are building new proton therapy facilities may have a difficult time recruiting trained, proficient staff for clinical operations.

IV. FUTURE PROSPECTS

Based on the current trends, the events that may occur in particle therapy during the next decade are listed below:

IV.A. Clinical studies

MGH and LLUMC have carried out dose escalation studies for prostate cancer.[24] Recently, the National Cancer Institute approved funding for a P01 grant application submitted by MGH and M. D. Anderson Cancer Center (MCACC) to conduct clinical studies in proton therapy with the objective of applying advanced proton radiation planning and delivery techniques to improve outcomes for patients with nonsmall-cell lung cancer (proton dose escalation and proton vs. photon randomized trials), liver tumors, pediatric medulloblastoma and rhabdomyosarcoma, spine/skull base sarcomas, and paranasal sinus malignancies. It is expected that the University of Florida and University of Pennsylvania facilities will also be participating in multi-institutional clinical studies.

There is an ongoing discussion in the radiation oncology community regarding the appropriateness of prospective, randomized clinical trails comparing protons with photons. The basic argument is that the dose distributions of protons will always be superior to those for photons when both modalities are optimized and one cannot justify randomized clinical trials of protons vs. photons because there would not be equipoise between the two arms of the trial.[25,26] Whether or not one supports the concept of randomized clinical trials for protons, it is difficult to argue against the need for additional clinical data; it is not feasible to draw statistically meaningful comparisons between photon and proton treatment techniques without data acquired through carefully controlled clinical studies in an expanded range of disease sites.

Research programs will also be directed toward the reduction of treatment errors in proton therapy treatment planning and treatment delivery, especially those related to uncertainties in the calculation of proton ranges in inhomogeneous tissues and errors arising from target motion during treatment delivery.

IV.B. Lower costs for proton therapy

Currently, proton therapy is more expensive than photon therapy. In 2003, Goitein and Jermann estimated the relative costs of proton and photon therapy, concluding that, with some foreseeable improvements, the ratio of costs (protons/photons) was likely to be about 1.7.[27] However, these estimates are probably outdated. Reimbursement rates currently make it possible to develop and operate proton therapy facilities with a reasonable profit margin. In the future, it is likely that reimbursement rates for proton therapy treatment delivery will decrease as capital costs of current facilities will be spread among more patients as these facilities reach full-capacity operations.

In addition, the overall costs of proton therapy will be reduced as proton therapy procedures become more efficient and patient throughput increases. Increased patient throughput will make it possible to spread the capital costs of proton therapy among a larger number of patients and the cost per patient will decrease. Improved efficiencies can be realized in the following ways:

- Using treatment setup rooms outside the treatment room will increase patient throughput, especially for pediatric patients who require anesthesia, which currently requires these patients to spend more time in the treatment room than patients who do not require anesthesia;
- Using faster, automated imaging techniques for patient positioning both outside and inside the treatment room;
- Using robotics both outside and inside the treatment room for transferring and positioning patients, for moving imaging devices, and for handling treatment appliances;
- Using improved accelerator, beam transport, and treatment delivery technologies, which will reduce the time currently required to change energies and to switch the beam from one room to another;
- Using IMPT techniques, which have the potential to decrease treatment times as fewer patient appliances (field-shaping collimators and range compensators) will need to be manually inserted and removed for each treatment field. It will also be possible after the treatment setup procedure for the first treatment field to treat all subsequent fields in a treatment session containing coplanar fields without re-entering the treatment room;
- Potentially using larger and fewer fractions (hypofractionation) in proton therapy than are currently used in photon therapy. Proton therapy spares normal tissues to a much greater extent than is possible with photon beams, making hypofractionation potentially effective. With reduced numbers of treatment fractions, the cost to patients for a course of therapy will decrease; and
- As the demand for proton therapy increases, more facilities will be built and more equipment manufacturers will enter the market. Competition between manufacturers should drive down the cost of particle therapy systems. Further, rapid growth of proton therapy facilities, spurred by strong market acceptance, will allow manufacturers to sell more systems (i.e., high business startup and technology development costs for proton therapy systems can be spread among larger numbers of systems).

IV.C. Advances in technology

New developments, many already underway, will have an impact on proton therapy.

IV.C.1. Single-room proton therapy systems

There is an increasing interest in smaller proton therapy facilities that are better suited for community hospitals and large private practices. Several vendors are developing the technologies necessary for "single-room solutions" for proton therapy systems. Single-room proton therapy systems have been stated to have the following advantages:

- They provide a lower-cost option for implementing proton therapy.
- All or most components (accelerator, beam transport, energy selection, and beam delivery) can be mounted on a rotating gantry or very near the gantry, thus, reducing the size of the complete proton therapy system enough that it can be installed in its entirety (or nearly so) in a single treatment room.
- There is no competition with other treatment rooms for proton beams because each room has its own accelerator.
- If multiple rooms are used, the entire proton treatment capability is not lost if the accelerator goes down, as is the case when one large accelerator generates beams for several treatment rooms.

Single-room systems may have the following disadvantages, however:

- The costs of these systems may not necessarily be

cheaper per treatment room as compared to large systems using single accelerators to feed several treatment rooms.
- Additional rooms may have to be installed if demand for proton therapy increases in a location with a single-room system. If several treatment rooms are eventually needed, the cost effectiveness of the single-room concept may be lost; for example, an additional accelerator will be needed for each treatment room. Maintaining multiple accelerators will also increase maintenance costs.
- Because of the pulse structure of some accelerators (e.g., synchrocyclotrons) chosen for the proposed systems, it may be difficult to use spot scanning techniques to deliver IMPT treatments.[28] IMPT could be delivered using a multileaf collimator; however, this method may have problems such as poor efficiency in the use of protons and increased neutron production.
- These systems are new, and, thus, their operability, reliability, and maintainability are not known.

IV.C.2. Accelerator development

Advances in accelerator technology are also expected. Several developments already underway show considerable potential to provide a new generation of more compact, more efficient, and less expensive accelerators for proton therapy. Some developments will improve upon current technologies, while others will provide entirely new types of accelerators, some of which are highlighted here. Flanz[29] has provided an excellent overview of new accelerator technologies.

IV.C.2.a. Superconducting cyclotrons and synchrocyclotrons. Cyclotron and synchrocyclotron development has resulted in more compact systems with increased energy. These gains have been achieved by the use of new accelerator designs and the application of superconducting technology. Figure 5 illustrates how the weight of cyclotrons/synchrocyclotrons has deceased since 1995. Notably, the accelerator energy has increased while the weight/size of the accelerators has decreased. At the current reduced weights of approximately 20 tons, accelerators can be installed on isocentric gantries and rotated around patients, eliminating large and expensive beam transport systems.[19,30] There is at least one vendor marketing a one-room proton therapy system based on this concept. Such systems will be particularly attractive to small community hospitals and large radiation oncology private practices.

IV.C.2.b. Fixed field alternating gradient (FFAG) accelerators. To date, most particle therapy facilities have used isochronous cyclotrons, and synchrotrons for particle acceleration. However, FFAG accelerators may be able to replace both cyclotrons and synchrotrons for hadron therapy. FFAG accelerators combine many of the positive features of cyclotrons and synchrotrons with fixed magnetic fields as in cyclotrons and pulsed acceleration as in synchrotrons. FFAG accelerators have the following potential advantages:

- FFAG accelerators can be cycled faster than synchrotrons, limited only by the rate of the radiofrequency (RF) modulation. Higher duty factors will permit higher average beam currents and high repetition rates for spot scanning. Fixed fields require simpler and cheaper power supplies and are more easily operated than synchrotrons.
- With respect to fixed field cyclotrons, nonscaling FFAG accelerators allow strong focusing and, hence, smaller aperture requirements, which leads to low beam losses and better control over the beam.
- FFAG accelerators (like synchrotrons) have a magnetic ring that allows beam extraction at variable energies rather than just a single energy, as in a cyclotron.
- Their superconducting magnets and compact size make FFAG accelerators attractive for proton therapy applications.
- Because of the possibility of changing energy and location with each spot and having a repetition rate of about 100 Hz, spot scanning with FFAG proton beams can be carefully controlled in three dimensions.

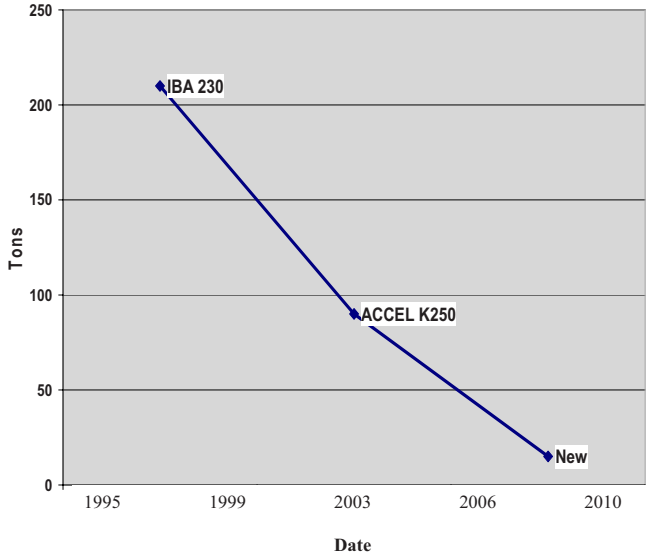

FIG. 5. This graph indicates how the weight (and, therefore, the size) of clinical cyclotrons has decreased since 1995. The IBA 230 room temperature cyclotron was the first cyclotron to be installed in a hospital-based proton therapy facility. More recently, the ACCEL K250 (now the Varian/ACCEL K250) has been installed in two European facilities. "New" superconducting cyclotrons will weigh about 10% of the IBA 230.

The FFAG concept was developed in the 1950s in Japan, Russia, and the United States.[31] The first electron FFAG accelerator as developed in the late 1950s and several others were built in the early 1960s. In the 1980s, proposals for FFAG-based neutron spallation sources were unsuccessful due to the perceived complexity of the magnets. In scaling-type FFAG accelerators, the magnetic field has to be nonlinear with zero chromatic beam optics. Because the magnets are complex and expensive to manufacture, the resulting cost has limited their use in medicine. However, new magnet designs have been made possible by 3D magnetic field simulation codes and large-scale computers. In addition, for a proton FFAG, a broad band and high gradient RF cavity is required. A new type of RF cavity developed at the High

Energy Accelerator Research Organization (KEK) in Japan[32] made it possible to overcome these problems, and in 1999, the first proton FFAG, was built at KEK in Japan.[33] This machine was the proof of principle (POP) for proton FFAG accelerators and was named POP-FFAG. After the success of POP-FFAG, a 150 MeV FFAG accelerator was developed at KEK. To date, several FFAG accelerators have been built in the energy range 150–250 MeV and others have been proposed.

The nonscaling FFAG accelerator was invented in 1999.[34] This accelerator's magnet design provides a variation of orbit length with energy, which can be arranged to greatly compress the range of the orbit radii and, thus, the magnet aperture, while maintaining linear magnetic field dependence. In addition, the small apertures and linear fields allow simplification and cost reduction compared with scaling FFAG accelerators. Keil *et al.* have proposed a hadron cancer therapy system using a nonscaling FFAG accelerator and gantry composed of nonscaling FFAG cells.[35] This accelerator will accelerate carbon ions up to 400 MeV/μ and protons up to 250 MeV.

IV.C.2.c. Laser acceleration. Proton laser acceleration is achieved by focusing a high-power (approximately 10^{15} W) laser on a thin target such as a 5 μm-thick titanium foil, or multilayer targets, such as 100 nm-thick aluminum hydrogen. To achieve proton energies of 200–250 MeV with adequate intensities, focused short laser pulses to intensities of 10^{22} W/cm^2 or higher are required.[36] The short ($\sim 30-80\times 10^{-15}$ sec) laser pulse width produces a high peak power intensity that causes massive ionization in the target, expelling a large number of relativistic electrons. The sudden loss of electrons gives the target a high positive charge and this transient positive field accelerates protons to high energies. The resultant proton beams have a broad energy spectrum; therefore, a magnetic spectrometer must be used to select a narrow energy band for patient treatment. This selection process throws away about 99.5% of the beam, and, thus, the energy selection system must be heavily shielded against neutrons resulting from proton losses in the spectrometer.

Achieving the energy and beam intensity required for proton therapy is a major challenge. Groups in several countries are working on proton laser acceleration;[36–38] however, because of the technical difficulties, it is not expected that the current development efforts will be able to achieve the required beams even for treatment of ocular melanomas ($\sim$70 MeV at a dose rate of approximately 10–12 Gy/min) over the next 5–7 years.

IV.C.2.d. Dielectric wall accelerators. Conventional accelerator cavities have an accelerating field only in their gaps, which occupy only a small fraction of the cavity length, and have an accelerating gradient of approximately 1–2 MeV/m. In contrast, dielectric wall accelerators (DWAs) have the potential of producing gradients of approximately 100 MeV/m. In a DWA, the beam pipe is replaced by an insulating wall so that protons can be accelerated uniformly over the entire length of the accelerator, yielding a much higher accelerating gradient. The DWA uses fast-switched high-voltage transmission lines to generate pulsed electric fields on the inside of a high gradient insulating (HGI) acceleration tube. High electric field gradients are achieved by the use of alternating insulators and conductors and short pulse times. An electric field propagates down the bore of the accelerator, pushing the proton "packet" in front of it. The system will produce individual pulses that can be varied in intensity, energy, and spot width and, therefore, should be suitable for IMPT applications.

The enabling technologies for DWA are the high gradient insulator, fast SiC switching, and new dielectric materials. The DWA technology is being developed at the Lawrence Livermore Laboratory,[39] with a full scale prototype proton therapy system expected to be operational in approximately 4 or 5 years. The private sector partner for this development is TomoTherapy[40] and the first prototype is expected to be installed at the University of California Davis Cancer Center.

IV.C.3. Pencil beam (spot) scanning techniques

Most patients who have been treated with proton beams have been treated with passive scattering techniques. Modern passive scattering systems are much more efficient and versatile than the systems used before hospital-based facilities were developed, and additional advances have continued to the present time. Recently, there has been an effort to develop multileaf collimators (MLCs) for passive scattering applications; however, to date, proton MLCs have been less than optimal (e.g., they have small field sizes, and, for some, their size does not permit positioning the MLC close to the patient surface, resulting in large air gaps that degrade the lateral penumbra of the treatment beam).

To date, only a handful of facilities are using beam scanning techniques for particle therapy. During the next decade, the development and refinement of beam scanning systems will continue. Importantly, pencil beam scanning makes it possible to deliver IMPT treatments, which provide a substantial dosimetric improvement over passive-scattering techniques. Analogous to IMXT, IMPT enables further optimization of dose distributions for proton therapy.

Scientists at the PSI in Switzerland developed a spot-scanning system where an energy selection system, one set of scanning magnets (for 1D scanning), and couch shifts are used together to deliver pencil beam Bragg peaks to a target volume.[22] The magnet and energy selection system are used to scan a section of the target volume, the couch is shifted, then another section is scanned. In this way, the target volume can be scanned in three dimensions. This scanning system has been used to deliver both SFUD and IMPT treatments.

More recent scanning systems use two sets of scanning magnets to scan the beam in a plane perpendicular to the nozzle axis (for 2D scanning). The target volume is divided into energy layers (highest to lowest energy), and each layer is sequentially scanned with pencil beams.

The treatment is carried out by moving the beam spot throughout each of several energy layers in a target volume.

The spot can be moved dynamically (i.e., continuously) in a raster or line pattern or by a discrete spot scanning method, where the beam is cut off between spots and the dose at each spot is varied to achieve the prescribed dose pattern. In dynamic raster scanning, either the scan speed or beam intensity, or both, are varied to produce the intensity distribution prescribed by the treatment plan.

A fundamental challenge for proton therapy using scanning techniques will be to develop methods to reduce or eliminate treatment uncertainties caused by range errors or target motions. Errors due to target motion during the delivery of scanned treatment fields are a problem for several treatment situations, particularly, for the treatment of lung tumors. Currently there are two primary ways to reduce motion errors: (1) beam gating, where the beam is turned off when the target has moved out of the target position for which the treatment plan was calculated;[41] or (2) repainting spots, repainting layers, or repainting the entire treatment volume (in this context, repainting means to scan a particular spot position, layer, or volume two or more times). Errors in target motion can be reduced in proportion to the number of repaintings. In addition, repainting of spots and layers can be done in a straightforward manner using treatment planning and beam delivery methods that have already been developed. However, rapid repainting of the entire volume will require a considerable amount of new technology to be developed for beam delivery, primarily in the area of very rapid scanning and energy changes. When combined with repainting, beam gating increases the complexity of treatment delivery. Furukawa *et al.* have proposed a design for a heavy-ion radiotherapy system that addresses this problem.[42] Bert *et al.* have proposed a system in which pencil beam positions, as well as the beam energy, are changed according to the tracked target motion to reduce motion errors.[43] A considerable amount of development effort is currently being directed toward decreasing the errors due to range uncertainties and target motion errors when spot scanning techniques are used and one can expect that good solutions will be found to reduce these errors during the next decade.

IV.C.4. Treatment planning calculations

IV.C.4.a. Monte Carlo treatment planning. Conventional proton treatment planning using pencil beam algorithms has been the mainstay of treatment planning using passive-scattering techniques. However, calculations by pencil beam algorithms can have appreciable errors in some situations, notably when there are tissue interfaces or inhomogeneities in the beam path or when metallic implants are present adjacent to or in the target volume. Monte Carlo (MC) calculations have the potential to increase the accuracy of dose calculations in those instances where pencil beam algorithms have difficulty. MC treatment planning has been developed for proton therapy applications.[44–46] However, MC calculations are time intensive and are not used routinely, although they can be useful in benchmarking pencil beam calculations. Within the next few years, MC calculations may become faster and more efficient and, therefore, can be used more routinely in treatment planning. MC calculations have also been quite useful in calculating data used in commissioning proton treatment planning systems[47,48] MC calculations can decrease the time required to commission a treatment planning system by eliminating a large number of measurements, especially in the case of spot beam scanning where approximately 100 energies need to be commissioned.

It is reasonable to expect that, with future developments, particularly in the area of increasing the speed of MC calculations, MC will play an increasing role in proton treatment planning.

IV.C.4.b. Optimization for IMPT treatment planning. Protons are much more sensitive to tissue inhomogeneities in the beam path than photons and current optimization algorithms do not accurately account for the errors resulting from range uncertainties and changes in scattering conditions caused by such inhomogeneities. For passive-scattering techniques, such uncertainties are partially offset by expanding the margins around the clinical target volume or by using internal target volumes determined from 4D CT treatment planning scans. In IMPT, the dose distribution is sensitive to the uncertainties in each individual beam of the potentially several thousand Bragg peaks used in the treatment plan, and uncertainties in the spot placements can result in unacceptable hot and cold regions in the target volume. One approach to improving IMPT treatment planning is to include errors in the optimization calculations in such a way as to ensure that the treatment plan predicts actual dose distributions more reliably. Work in this area is underway and these approaches have the potential to improve the accuracy and robustness of IMPT treatment plans.[49]

IV.C.5. Positron emission tomography (PET) for treatment verification

Ideally, one would have a method available to measure proton dose distributions delivered to patients either online during treatment or offline immediately or soon after treatment. Such treatment verification would make it possible to correct the treatment plan after the first treatment session or to make corrections during the course of treatment. Such adjustments may be necessitated by changes in the patient's weight or changes in the tumor's size, shape, or position during treatment. Positron emission tomography (PET) is a potentially useful tool for validating the fidelity of the treatment plan delivery.

PET can verify treatment delivery by detecting annihilation γ-rays arising from the decay of small amounts of β^+ emitters such as ^{11}C, ^{15}O, and ^{10}C produced by nuclear fragmentation reactions between the primary charged particle and the target nuclei in the irradiated tissue. Particle treatment delivery verification can be achieved by comparing the measured β^+ activity distribution with an expected pattern calculated by treatment planning or by MC calculations of the expected β^+ activity. In particular, PET techniques offer the potential to detect and quantify range uncertainties in treatment planning calculations.

Physicists at MGH and elsewhere[50–53] have been exploring the use of PET imaging, both offline and online, for

treatment verification. The preliminary results look promising and it is expected that with further development, this technique will become an important tool for verifying particle treatment plan delivery.

IV.C.6. Proton CT

The idea of using proton beams for imaging has been around for some time. In his seminal papers on the application of photon absorption in radiology, Cormack pointed out the possibility of using heavy charged particles in CT applications.[54,55] In 1968, Koehler demonstrated that 160 MeV protons could produce images on radiographic films that had much better contrast than those produced with photons.[56] Cormack and Koehler published a study on proton CT in 1976.[57] In the late 1970s and early 1980s, Hanson *et al.* published a series of papers on proton CT including one of the earliest studies of human specimens.[58] In addition, Schneider *et al.* conducted studies on the use of proton radiography as a quality assurance tool for proton treatment planning.[59,60] These studies, including measurements taken on an animal patient, concluded that inaccuracies in treatment planning as a result of incomplete modeling of multiple Coulomb scattering effects and errors in proton stopping powers derived from photon CT scans could result in sizeable deviations in predicted versus measured proton dose distributions. Zygmanski *et al.* demonstrated the feasibility of using proton cone-beam CT to determine proton stopping powers for materials of various densities.[61] In 2004, Schulte *et al.* at the LLUMC proton therapy center reported on a conceptual design for a proton CT system for applications in proton radiation therapy.[62]

Currently, most proton treatment planning dose calculations use a pencil beam algorithm that accounts for tissue inhomogeneities by means of pathlength (water equivalent depth) scaling based on relative stopping powers. Hounsfield numbers obtained from x-ray treatment planning CT scans are converted to proton stopping powers using measured relationships between Hounsfield numbers and the relative stopping powers for materials closely matched to human tissues such as soft tissue, fat, lung tissue, soft bone, and hard bone.[63] These conversions are frequently inexact, which can lead to errors in the calculation of proton ranges in patients of approximately 3% or more of the proton range. These errors could be substantially reduced by the direct measurement of relative proton stopping powers using proton CT techniques.

There are, however, also errors in proton CT data. For instance, limitations in the spatial and density resolution of proton CT arise from various sources: multiple Coulomb scattering in the patient leads to spatial uncertainties in the CT image and energy loss straggling due to momentum spread of the beam entering the patient and proton range straggling in the patient can cause errors in density resolution. In addition, secondary protons arising from nonelastic nuclear interactions can lead to noise in the proton CT images. Recent studies have demonstrated that density resolutions of 1%–2% are possible with proton CT techniques, which can be achieved with proton doses of 10 mGy or less, comparable to or better than doses stated for cone beam CT with kilovoltage x-ray beams.[64]

With the widespread use of isocentric gantries in proton treatment facilities, further development and study of proton CT and cone-beam CT are anticipated. Development of new high-bandwidth silicon strip detector systems will also make proton-by-proton data collection feasible. Individual proton tracking techniques will make it possible to measure the position of each particle's track and each particle's energy deposition,[65,66] which will greatly increase the spatial and energy resolution of proton CT measurements.

IV.C.7. QA systems for scanned proton beams

Implementing scanned proton beams for cancer treatment has generated the need for a new class of quality assurance (QA) systems that permit rapid and accurate 2D and 3D data acquisition. QA systems for scanned proton beams must also be adaptable to the timing structure and energy stacking of pencil beam scanning beam treatment delivery. In contrast to dosimetric measurements for passive scattering methods, when pencil beam scanning techniques are employed, the dose measured at a point in the phantom can be obtained only by collecting the detector signal during the entire scan sequence. In many cases, it is also necessary to characterize a single pencil beam, which places additional requirements on the measuring system.

In 2000, Jäkel *et al.* described QA procedures and methods for a treatment planning system used for scanned ion beam therapy.[67] In 2005, Pedroni *et al.* reported on aspects of dosimetric methods used to characterize the scanned proton beams at PSI in Switzerland[68] including ionization chambers, films, and a charged-coupled-device (CCD) camera coupled with a scintillating screen. In addition, Pedroni *et al.* have used a linear array of 26 ionization chambers and the CCD system to verify scanned dose distributions. In 1999, Karger *et al.* described a 24 ionization chamber planar array used for the QA of heavy ion beams.[69] More recently, Nichiporov and Solberg reported on two ionization chamber array systems: a 128-chamber planar array designed to measure beam profiles in fields up to 38 cm in diam and an array of 122 small-volume multilayer ionization chambers used for depth-dose measurements in clinical proton beams.[70] Users of these ionization chamber array systems have agreed that these systems provide considerable time savings in dosimetry measurements. Unfortunately, the ionization chamber arrays described above were developed in house at research facilities and are not commercially available. As more proton treatment facilities implement scanning techniques and the demand for appropriate dosimetry systems increases, vendors may be encouraged to develop similar commercial devices.

A dosimetry system utilizing a CCD camera plus scintillating screen[71] has been shown to be useful for measuring proton fluences in air, and by placing absorbers in front of the screen, relative dose delivered at depth. Pedroni *et al.* stated that the CCD system works well for conducting rela-

tive dosimetry measurements to compare treatment planning calculations with the dose distributions delivered by the proton scanning system.[68] A similar CCD system has also been used at the M. D. Anderson Proton Therapy Center to measure fluence patterns in air at the isocenter for single spots, uniform spot patterns, and for spot patterns calculated for a SFUD prostate treatment delivery. However, CCD camera-based proton dosimetry systems are not readily available, but they can be made in house without undue difficulty.

Other dosimetric systems such as radiochromic films,[72,73] alanine detectors,[73] and polymer gels[74] can be used for QA measurements. However, the use of these systems is limited because of saturation effects in the proton stopping region and because they are not real-time instruments. These systems continue to be investigated, and it is expected that they will, in time, become more widely used.

IV.C.8. Carbon ions

There is a growing interest in using carbon ions for cancer therapy. The rationale for using carbon ions is that in addition to their highly localized physical dose distributions, which are quite similar to those for proton beams, carbon ion beams are high linear energy transfer (LET) in their interactions in tissues. High LET provides increased relative biological effectiveness (RBE) and a low oxygen enhancement ratio (OER); therefore, carbon ions may be more effective than protons in treatment situations where cancer cells are anoxic or hypoxic.[75–77] Carbon ion facilities in Japan (HIMAC-Chiba and HIMC-Hyogo) and Germany (GSI, Darmstadt) have treated approximately 5,000 patients to date[5] and a hospital-based facility is being constructed at the DKFZ/German Cancer Research Center/University of Heidelberg, which will commence patient treatments in 2009. New facilities are being built in Japan, Italy, and Germany and are in an advanced stage of planning in Austria and France. Most of these carbon ion facilities will also have the ability to treat patients with proton beams. There are at least three institutions in the United States that are contemplating proton/carbon ion facilities—at this time they are all planning to start with protons only and, at a later date, add carbon ion capabilities, but there are several impediments to the development of carbon ion facilities in the United States: (1) carbon ion systems do not have FDA clearance; (2) there are no procedure codes or reimbursement rates for carbon ion treatments; and (3) carbon ion facilities are much more expensive than proton facilities. The current financial climate, high costs of construction, and unfavorable foreign exchange rates are also strong financial disincentives for building carbon ion facilities.

In addition, the clinical value of carbon ions has not been sufficiently demonstrated; however, clinical results are promising.[15] It is certain that investigations of both protons and carbon ions, and clinical comparisons between the two particles will be carried out during the next decade as more facilities are opened that have the capability of treating patients with both types of particles.

V. CONCLUSIONS

Proton therapy is in the midst of a remarkable transition. During the next decade, important advances in proton therapy treatment delivery, treatment planning, and quality assurance systems will be made that will improve proton therapy's efficiency, robustness, and accuracy. It is also expected that the cost to patients will decrease, making proton therapy more financially competitive with photon therapy.

IMPT treatments will become available for routine use in an increasing number of facilities, and methods will be developed to improve the accuracy and precision of this treatment modality. With the availability of advanced IMPT techniques, it may be possible to quantify the clinical gains obtained from optimized proton therapy and to compare the clinical outcomes of photons and protons using the best dose distributions for both modalities.

It will be necessary to develop methods to make proton treatment plan calculations more accurate and to verify that treatment plans are actually realized in the delivery of proton treatments. It is not meaningful to compare protons with photons unless we can demonstrate that the superior dose distributions of proton treatment plans can actually be delivered to patients.[78]

More hospital-based, state-of-the-art proton therapy facilities will be built and increasing numbers of patients will be treated. As stated by Schultz-Ertner and Tsujii, "The potential of particle therapy can only be exploited if a full integration of particle therapy into clinical environments and interdisciplinary treatment strategies is sought and if new medical and technologic advances are properly incorporated into the total treatment process."[15]

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