Present Status and Future Developments in Proton Therapy

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Abstract. Within the past few years, interest in proton therapy has significantly increased. This interest has been generated by a number of factors including: 1) the reporting of positive clinical results using proton beams; 2) approval of reimbursement for delivery of proton therapy; 3) the success of hospital-based proton therapy centers; and 4) the availability of modern, integrated proton therapy technology for hospital-based facilities. In the United States, this increased interest has occurred particularly at the level of smaller academic hospitals, community medical centers, and large private practices; however, interest from large academic centers continues to be strong. Particular interest exists regarding smaller and less-expensive proton therapy systems, especially the so-called “single-room” systems. In this paper, the advantages and disadvantages of 1-room proton therapy systems will be discussed. The emphasis on smaller and cheaper proton therapy facilities has also generated interest in new proton-accelerating technologies such as superconducting cyclotrons and synchrocyclotrons, laser acceleration, and dielectric-wall accelerators. Superconducting magnets are also being developed to decrease the size and weight of isocentric gantries. Another important technical development is spot-beam scanning, which offers the ability to deliver intensity-modulated proton treatments (IMPT). IMPT has the potential to provide dose distributions that are superior to those for photon intensity modulation techniques (IMXT) and to improve clinical outcomes for patients undergoing cancer therapy. At the present time, only two facilities - one in Europe and one in the United States - have the ability to deliver IMPT treatments, however, within the next year or two several additional facilities are expected to achieve this capability.

Keywords: proton therapy, cancer treatment, proton accelerators, proton therapy technology

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INTRODUCTION

Among major cancer sites (head and neck, gastrointestinal, gynecologic, and genitourinary tracts; lung, breast, lymphoma, skin, bone, soft tissue, and brain) treated with radiation therapy, approximately 35% of deaths from cancer are caused by the inability to locally control the tumor. The primary cause of failure of local treatment is the inability to deliver a lethal dose of radiation to the tumor cells; the reasons for this problem include:

- Inability to determine the exact location and extent of tumor cells and their routes of spread
- Failure to properly diagnose and treat the disease
- Presence of radio-resistant tumor cells
- Proximity of dose-limiting normal tissues and organs

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Limitations in the dose distribution of radiation beams used for treatment

The solutions to the above problems are multifaceted and complex. We will focus on the last two problems, which can be addressed to a great extent by the use of radiation beams having highly localized dose distributions that permit the delivery to the target volume of sufficiently high dose of radiation to eradicate the tumor and at the same time irradiate adjacent normal tissues at a level that does not exceed their tolerance threshold.

Proton beams have the characteristic Bragg peak in their depth-dose distribution. By proper energy/dose modulation and beam-shaping, proton beams can provide a dose distribution in a patient that is highly conformal to the tumor target and thereby has the potential to deliver a high dose of radiation to the tumor, a low dose to normal tissues proximal to the tumor, and no dose distal from the tumor, as illustrated in Fig. 1.

![Figure 1](image_url)

**FIGURE 1.** This figure illustrates how a properly shaped proton dose distribution can be formed to deliver a high dose of radiation to the tumor volume while not exceeding the tolerable dose of nearby critical normal tissues. In contrast, the photon depth-dose distribution delivers its maximum dose of radiation at shallow tumor depths, a lower dose at the tumor, and a significant dose to normal tissues distal from the tumor. The optimum dose distribution, indicated by the box over the tumor, delivers the entire dose to the tumor and no dose to normal tissues. The proton beam more nearly approaches the optimum dose distribution than does the photon beam.

One should note that in general, radiation treatments use multiple treatment beams that come from several directions and are focused on the tumor volume. In this approach the tumor dose can be increased without an equivalent increase in normal tissue dose. The advantages shown in Fig. 1 for the proton beam hold true for every beam used, and therefore, when equal numbers of beams are used in equally optimized treatment plans, protons will provide superior dose distributions.

Improved dose localization is the basis for the hypothesis that proton-beam radiation therapy has the potential to improve clinical outcomes in cancer - in
particular, increased local control of tumors and decreased short- and long-term damage to normal tissues and organs.

PRESENT STATUS OF PROTON THERAPY

Currently, 28 facilities worldwide treat cancer patients using charged particle (proton and carbon ion) beams. The distribution of particle therapy facilities is as follows:

- 6 in Japan (4 hospital-based facilities): HIMAC-Chiba, NCC East-Kashiwa, HIBMC-Hyogo, PMRC-Tsukuba, WERC-Wakasa, and Shizuoka Cancer Center
- 6 in the United States (4 hospital-based): Loma Linda University Medical Center, California; Massachusetts General Hospital, Massachusetts; The University of Texas M. D. Anderson Cancer Center, Texas; University of Florida at Jacksonville, Florida; University of Indiana, Indiana; and University of California at Davis, California
- 12 in Europe/Russia
- 4 additional facilities (United Kingdom, China, Korea, South Africa)
- Worldwide, 22 institutions are developing new proton therapy facilities

Approximately 55,000 cancer patients have been treated with proton beams. Three facilities treat cancer patients with carbon ion beams -1 in Germany, and 2 in Japan. A new carbon ion facility is scheduled to open in Heidelberg, Germany, in 2009. Several important changes are occurring in proton therapy that will strongly influence the future development of the field. These changes include:

- Research-based facilities → Hospital-based facilities
- Large facilities → Smaller facilities and, particularly in the United States, single-room installations
- Low-efficiency, low-patient throughput → High-efficiency, high-patient throughput
- Minimal integration → Full integration of medical services and information technology within the particle facility and within the larger medical complex
- Passive-scattering techniques → Beam-scanning techniques
- Conventional accelerators →
  - Superconducting cyclotrons and synchrocyclotrons
  - Laser acceleration
  - Dielectric wall acceleration
  - Fixed-Field Alternating Gradient (FFAG) accelerators
- Implementation of robotic technologies
- More carbon ion facilities
A central theme common to the above trends is the need to reduce the cost of particle therapy to make it more financially competitive with conventional radiation therapy. The most straightforward way to reduce the cost of particle therapy is to reduce the size and complexity of proton therapy technology and to greatly increase the efficiency of operations; that way, more patients can be treated and the high capital costs of proton facilities can be spread among greater numbers of patients.

CURRENT PROTON THERAPY TECHNOLOGIES

Accelerators that are currently used for proton therapy are synchrotrons, isochronous cyclotrons, and synchrocyclotrons that accelerate protons up to energies of 230–250 MeV. Proton therapy cyclotrons and synchrocyclotrons have evolved toward smaller and less-expensive devices, as shown in Fig. 2.

### Commercially Available Cyclotron/Synchrocyclotron Systems

<table>
<thead>
<tr>
<th>System</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBA C230</td>
<td>First commercially available cyclotron for proton therapy</td>
</tr>
<tr>
<td></td>
<td>Isochronous cyclotron; 220 tons</td>
</tr>
<tr>
<td></td>
<td>230 MeV protons</td>
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<tr>
<td>Varian/ACCEL K250</td>
<td>Superconducting isochronous cyclotron</td>
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<td></td>
<td>90 tons; diameter = 3.2 m</td>
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<tr>
<td></td>
<td>250 MeV protons, high extraction efficiency</td>
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<tr>
<td>Still River Systems, Monarch 250</td>
<td>Superconducting synchrocyclotron</td>
</tr>
<tr>
<td></td>
<td>250V Protons 20 tons; diameter = 1.7 m</td>
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</tbody>
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**FIGURE 2.** This figure shows the recent evolution of proton therapy accelerators. The weight of the newest superconducting device is 10% of that for the first commercial proton therapy cyclotron.

Implementation of super-conducting technology has resulted in accelerators that have decreased in weight - from 220 tons in 1995 to 20 tons in 2009 - and in size, accordingly. Importantly, the 20-ton accelerator can be mounted on an isocentric gantry that moves the accelerator around the patient, thus eliminating the need for an accelerator vault external to the treatment room and for expensive beam-transport lines.
The volume of shielding required for the facility, and its cost, will also decrease. Downsizing the accelerator so that it can fit inside the treatment room with the gantry also makes possible a single-room proton therapy system that can be situated more easily in a standard radiation therapy facility. It should be noted, however, that significant challenges are inherent in making such systems less expensive per treatment room than for larger facilities that have one accelerator feeding several treatment rooms. Overall costs of equipment and its maintenance for a facility having multiple treatment rooms may be reduced when one accelerator feeds several treatment rooms rather than having an accelerator for each treatment room.

Superconducting technology also has been applied to the large bending magnets on isocentric gantries, dramatically reducing the weight and size of the overall gantry. For example, the carbon ion gantry at the new particle facility being built in Heidelberg, Germany, weighs 600 tons, whereas a carbon ion gantry with superconducting magnets (developed by Ion Beam Applications in Belgium) has a rotating mass of only 120 tons. Current proton gantries range in weight from about 120 to 190 tons. Superconducting technology has also enabled the design of compact cyclotrons for carbon ion acceleration. Superconducting technology may make it possible to build carbon ion facilities, which also deliver proton beams, similar in size to present-day proton facilities.

To date, almost all proton treatments have used passive-scattering systems, whereby a small pencil beam entering a treatment delivery nozzle is spread out laterally by double-scattering techniques [1]. A range-modulation wheel or ridge filter modulates the energy (beam penetration) and beam weights to uniformly spread the stopping distribution of the beam in the patient. This spreading technique results in a spread-out-Bragg-peak (SOBP), which has a depth dimension determined by the greatest water-equivalent thickness of the tumor target volume. Fig. 3 illustrates this concept.

In the proton treatments described above, a treatment field-specific collimator is used between the nozzle exit and the patient surface to shape the field laterally to conform to the maximum beam’s-eye view extent of the target volume. A range compensator also is used to correct for the patient’s 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 thickness of the target volume in the beam direction. The SOBP size is constant over the entire target volume, and therefore there is generally some pull back of the high-dose region into normal tissues proximal to the target volume (Figure 3). This dose pull back into normal tissues is a primary drawback to passive scattering techniques. The general use of several treatment fields, where the dose pull back for each field does not overlap with that of other fields, reduces the relative-dose impact to normal tissues. Another major disadvantage of this technique is its inefficiency - many protons are lost in the process of scattering and collimating the beam, and these interactions produce neutrons, which have the potential to induce unwanted biological effects in patients, such as secondary tumors, that occur many years after their initial cancer treatment.
The second type of beam delivery utilizes *spot scanning techniques* (often called *pencil beam scanning*) [2]. Fig. 4 illustrates how a target can be scanned by placing Bragg peaks throughout the target volume using 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 these methods plus energy absorbers in the treatment nozzle.

The advantages of beam scanning are: 1) efficient use of protons - except for beam monitors, there are no scattering elements in the nozzle; 2) no neutron production in the nozzle; 3) in general, no requirement of patient-specific appliances (e.g., patient-specific collimators and range compensators); and 4) implementation of intensity-modulated proton treatments (IMPT) that provide optimized-dose distributions. The disadvantages of beam scanning include: 1) increased complexity of treatment planning and delivery; 2) requirement for additional quality assurance methods to ensure accuracy and safety of treatment delivery; and 2) potentially increased treatment errors caused by target motion during treatment. As of this writing, optimized beam scanning for proton-beam treatments is being used at only two facilities: the Paul Scherrer Institute in Switzerland and The University of Texas M. D. Anderson Cancer Center (Houston, Texas, U.S.A.). However, it is anticipated that within the next year, several more facilities will implement optimized-proton treatments utilizing beam-scanning techniques.
NEW TECHNOLOGICAL DEVELOPMENTS

The first hospital-based proton therapy system came on line in 1990 at Loma Linda University Medical Center in the United States [3]. Compared with their photon counterparts, proton-therapy systems are in their relative infancy and are still undergoing significant changes as they develop into mature technologies. Also, with the exception of the DICOM-RT-ION data exchange standards, no standards exist for proton therapy-specific clinical systems. Current development efforts are mainly directed toward implementation of advanced beam scanning systems, robotics (for handling patients, imaging devices, and patient appliances), imaging (cone beam computed tomography [CT], positron emission tomography [PET], and proton imaging), upgrades in control and safety systems, and new accelerator technology. The remainder of this paper will focus mainly on accelerator development.

As noted above, superconducting technology has been applied to magnets in cyclotrons and synchrocyclotrons resulting in reductions in weight and size to the extent that these accelerators can now be mounted on rotating isocentric gantries. Such installations will cut costs for the accelerators, beam transport systems, and shielding.

Currently, there is a great amount of interest in “single-room” proton therapy systems that will make it possible to implement proton therapy in small community hospitals and large private practices. The advantages of single-room systems include the following:

- Reduction of capital costs will make it possible to install more facilities and make proton therapy available to a greater number of cancer patients.
• Single-room systems, where each room has a dedicated accelerator, do not have competition for beam time with other treatment rooms, as do larger systems where a single accelerator feeds beam to several treatment rooms.
• If more than one single-room system is installed, the entire proton treatment capability will not be lost when one accelerator goes down.

The potential disadvantages of single-room systems include the following:

• Neutron shielding around the accelerator may be complex and expensive. Shielding requirements will be stringent because the accelerator and energy selection system will be in the same room as patients undergoing treatment.
• If the demand for proton therapy increases and additional rooms are installed, the single-room cost advantage will be lost.
• Single-room systems may not be cheaper, per room, than current multiple room systems. A preliminary cost analysis indicates that the equipment for a facility having 4 single-room systems will cost approximately the same as a facility having one accelerator that provides a beam for 4 treatment rooms—the primary reason being that for the single-room systems, 4 accelerators would be required instead of 1.
• Operations and maintenance for multiple single-room systems will be more expensive because more accelerators are involved.
• The usability, reliability, and maintainability in clinical environments for the new single-room systems have not been determined.

An alternative to having a single-room system where the accelerator is attached to the gantry is a compact accelerator installed in a separate room adjacent to the treatment room. This concept is attractive for many reasons including the ability to expand to multiple treatment rooms, reduced neutron production in the treatment room, and easier system maintenance. It should be noted that the advantages and disadvantages listed above are generally true for any single-room system, regardless of the accelerator used. A considerable amount of effort is being directed toward the development of new types of proton therapy accelerators, and these developments are discussed below.

**New Accelerator Development**

*Fixed-Field Alternating Gradient Accelerators*

Fixed-field alternating gradient (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 and are 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, non-scaling FFAG accelerators allow strong focusing and therefore smaller aperture requirements, which lead 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.

The FFAG concept was developed in the 1950s in Japan, Russia, and the United States [4]. The first electron FFAG accelerator was 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 non-linear 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 [5] made it possible to overcome these problems, and in 1999, the first proton FFAG was built at KEK in Japan [6]. 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 of 150–250 MeV and others have been proposed.

The non-scaling FFAG accelerator was invented in 1999 [7]. 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 for simplification and cost reduction compared with scaling FFAG accelerators. Keil et al. proposed a hadron cancer therapy system using a non-scaling FFAG accelerator and gantry composed of non-scaling FFAG cells [8]. This accelerator will accelerate carbon ions up to 400 MeV/μ and protons up to 250 MeV.

**Dielectric Wall Accelerators**

Conventional proton 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/meter. In contrast, dielectric wall accelerators
(DWAs) have the potential of producing gradients of approximately 100 MeV/meter. In a DWA, an insulating wall replaces the beam pipe 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 using 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 HGI, fast SiC switching, and new dielectric materials. The DWA technology is being developed at the Lawrence Livermore Laboratory [9], 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 [10], and the first prototype is expected to be installed at the University of California Davis Cancer Center.

**Laser Accelerators**

Laser acceleration will be described briefly in this paper because other papers in these proceedings will address the topic in detail. 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 multi-layer 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 [11]. The short (∼30–80 × 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, and 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 [11-13]; however, because of the technical difficulties, the current development efforts are not expected to be able to achieve the required beams, even for treatment of ocular melanomas (∼70 MeV at a dose rate of approximately 10–12 Gy/min) over the next 5–7 years.

**Primary Requirements for Proton Therapy Accelerators**

Regardless of the type of accelerator, all proton therapy accelerators should meet certain basic requirements [14] that include the following:
• Proton energies in the range of 70 MeV to 230–250 MeV. Energy resolution should be such that changes of penetration of approximately 0.1 g/cm² or less are achievable.
• The goal for energy spread should be approximately 0.1%.
• Intensity of $10^{10}$ protons/sec or about 2 nanoamperes of continuous beam, which will produce a dose rate of approximately 2 Gy/min.
• Rapid energy changes are required. For some intensity modulation techniques (e.g., rapid volumetric repainting) energy changes must occur in time frames less than 150 ms for changes in penetration of 0.5 g/cm².
• Most single-room systems will have the energy selection system near the patient, and therefore adequate neutron shielding will be challenging.
• Accelerators should be capable of either being mounted on an isocentric gantry or feeding the beam directly into a gantry without long beam-transport lines.
• Reliability for clinical operations is very important. Clinical systems are required to have 95-98% of up time, 16 hours/day, 5 days/week, for at least 50 weeks/year.
• All treatment parameters should have very high accuracy and precision. In radiation therapy, the goal is to have <5% error in tumor dose (considering all sources of errors), and this degree of accuracy must be reproducible over relatively long periods of time.
• Control and safety system requirements are very stringent, with triple redundancy required for all critical safety elements.
• All systems must have clearance from federal agencies, such as the U.S. Food and Drug Administration, in the United States.

A pressing need exists for smaller and less-expensive proton therapy systems. Proton therapy has a significant potential to improve clinical outcomes for patients with a broad range of cancers, especially pediatric cancers. Less-expensive systems will enable more particle facilities to be built, which will make proton therapy available to greater numbers of cancer patients. Less-expensive facilities will also make it possible to reduce patient costs for proton therapy. Proton therapy is currently so expensive that most patients who do not have medical insurance, or who live in countries where federally funded health care is not available, cannot afford the cost of treatments. Advancements expected to be made within the next decade should have an appreciable impact on both the quality and cost of proton therapy.

REFERENCES


