Proton therapy advancement

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Abstract

The benefit of proton therapy over conventional photon and electron therapies has been recognized in the past few decades. The physical characteristics of proton beams are exploited to enhance the dose to the target and to reduce the dose to healthy tissues. It has been shown that there is a great advantage in using proton therapy for treatment of medulloblastoma, lung, head and neck, gastrointestinal, and other sites. The innovation in proton therapy equipment has and will help to reduce the cost of acquiring this modality and will enable many cancer centers to employ this technique to their current practice for cancer patients’ treatment. It is foreseen that this methodology will be a common practice in almost all the cancer centers in the US and abroad as intensity modulated radiotherapy is currently.

Keywords: Proton Therapy; New Modality; Radiotherapy; IMPT

Mini-Review

1. Introduction

The use of proton beams for treating cancers has increased in the past few decades even though the cost of installing a proton therapy center still far outweighs the expense of a traditional photon therapy installation. In spite of the large cost associated with this modality, the physical dose delivery characteristics of proton beams make this modality attractive for treating cancer patients. At the time of publishing this report, there are 14 proton therapy centers that are actively treating patients in the US and another 11 centers are under construction. The most distinctive difference between photon and proton therapy is the finite range of proton beams in tissue. In addition, there is a large dose enhancement near the end of the range (under the Bragg peak) and a nominal dose at the tissue entrance.

The history of particle accelerators evolved in 1929 when Ernest Lawrence invented the first cyclotron for applications in physics and chemistry. It took almost 15 years until Robert R. Wilson proposed that proton beams might be an applicable method to treat cancer. In 1946, while Wilson worked at the Harvard Cyclotron Laboratory (HCL), he published his first paper in this regard. The first patients were treated with proton beams at Berkeley Radiation Laboratory in 1954 and in Uppsala in Sweden in 1957. In 1961, a collaborative effort between HCL and Massachusetts General Hospital (MGH) was established to pursue proton radiotherapy. This effort resulted in the first study to compare proton and photon radiotherapy for treatment of prostate cancer in the 1970s. The first dedicated hospital based proton therapy facility was built in the 1980s at Loma Linda University Medical Center (LLUMC) in California. By the 1990s, over 25,000 patients had been treated with proton therapy worldwide.

In recent years, there has been an increase in the number of manufacturers that build proton radiotherapy machines. The different types of proton accelerators, along with their associated technical characteristics are utilized to produce clinical beams. Since the treatment of the first patient with a cyclotron accelerator in 1954, the technology and the beam delivery of proton therapy machines have changed rapidly. The newer type of cyclotron using superconducting magnets as well as smaller synchrotrons, and a single gantry mounted synchrocyclotron accelerator are a just few examples of progression of this technology as the demand to acquire this modality of treatment increases.
2. Physical characteristics of proton therapy

All charged particles (electrons, protons, carbon ions, etc.) interact with tissue and other material by either coulomb (electromagnetic) forces or nuclear reaction. The three basic interactions between charged particles and matter include 1) a loss of energy (slowing down) due to interactions with atomic electrons, 2) scattering by atomic nuclei, and 3) in some instances a head-on collision with a nucleus, leading to a nuclear reaction that results in the production of other particles such as charged particles, gamma, and neutrons.

The benefit of using proton beams rather than photons or electrons in radiotherapy is threefold (Figure 1). The physical characteristics of proton beams are: 1) a finite range, which reduces dose to healthy tissue beyond the distal edge of the target tumor, 2) it has a lower entrance dose, which reduces the proximal dose to healthy tissue, and 3) provides a higher linear energy transfer (LET) about 1.1 compared to photon beams, which results in better therapeutic ratios.

Proton beams have very low ionization density (energy loss per unit path length) at the entrance region. The increase in ionization density occurs gradually to the point of maximum range where a narrow region with high ionization density, called the Bragg peak, arises. The shape and the position of the Bragg peak can be calculated using the Bethe Block equation. As protons traverse the media and interact with atomic electrons in the material, they produce delta ray electrons that have a typical range of a few microns and deposit their energy close to the path of the proton’s track. At the vicinity of maximum range, where the Bragg peak occurs, proton energies are reduced to about 8-20 MeV. Only a few protons travel beyond their practical range (R10), which is the distance where dose drops to 10% of its maximum dose. The typical ratio of ionization at the Bragg peak to ionization at the entrance region is about 3:1. There are small amounts of dose deposited beyond the practical range from neutrons that are generated by nuclear reactions. Depending on the proton energy, this dose is a small percentage compared to the dose at the Bragg peak. The higher the energy of the proton and the higher the Z value of interacting media, the larger the neutron-generated dose beyond the practical range.

3. Delivery techniques

There are different techniques employed in delivering useful clinical beams. The proton beams generated by accelerators have Gaussian profiles. To produce beams that are useful for patient treatment, delivery systems may use single or double scattering techniques to produce flat and uniform dose distributions laterally. To produce a uniform dose distribution longitudinally, a scattering system uses range modulation wheel to modulate the distal depth of Bragg peak in order to produce spread-out-depth dose that is commonly called “spread-out Bragg peak” or simply SOBP. The new proton therapy machines use pencil beams that are deflected magnetically in one or two dimensions to scan and paint the target. The beam scanning itself can be implemented either by moving the beam spots discretely from one position to the next or by moving the spot continuously to paint the target. In a discrete delivery system, the beam is switched off between each spot to allow for adjustment of the magnet parameters. In uniform scanning, a single scatterer is used to expand the Gaussian beam profile to approximately 5 cm (two standard deviations of the profile). The scanning magnets move the proton beam in two-dimensional directions in circular, raster, triangle, Lissajous, or spiral forms to produce the desirable uniform dose at a specific depth. The process is repeated until the desired dose is delivered to a single layer. Afterward, the beam energy entering the nozzle is changed to repeat the process for the next depth layer, a process called “energy stacking.” The depth of penetration is varied either by introducing a wedged degrader (in the case of a cyclotron) or by an acceleration and deceleration sequence (in the case of a synchrotron) to deliver pencil beams of specific energies.

The advantage of utilizing a scanning dose delivery is an increase in range, a reduction in proximal dose, and a reduction in the number of neutrons that are produced when proton beams impinge on the modulation wheels, compensators, and field blocks. In general, passive scattering systems produce the highest neutron dose, while pencil-beam scanning systems produce the lowest number of neutrons. The neutron dose from uniform scanning systems falls somewhere between the other two, as they lack the modulation wheel, but generally still employ apertures and compensators. Dynamic scanning is a disadvantage when organ motion is a concern.
4. Intensity-modulated proton therapy

In intensity-modulated proton therapy (IMPT), the beam delivery is optimized and dose conformity is enhanced in three dimensions by three criteria: 1) assigning and optimizing the arrangement of the “spots,” which are the individual point targets in the target volume that will receive the planned dose from a given field; 2) adjustment of each individual spot intensity for each field; and 3) variation of the range in order to deliver the correct dose at different depths. In this technique, multiple beam directions may be employed to deliver a conformal dose distribution to the target. The selection of beam spots and their intensities are determined for each beam angle based on the optimization criteria and presence of organs at risk, either along the beam path or in the vicinity of the target. Figure 2 illustrates the order in which the dose is deposition by pencil-beam spots in different layers of a tumor using a single field. The spots are deposited at the deepest layer first, and then the second layer proximal to the first layer, and so on until the target is covered with the desired dose.

5. Comparison of proton to photon radiotherapy

Proton therapy has gained popularity as a brilliant modality in radiation therapy. However, in the past there have been some debates regarding the advantage and effectiveness of proton therapy versus photon therapy. There is no argument that the higher dose delivered to the tumors while sparing healthy tissue can have a rewarding outcome for the longevity of patients. The physical characteristics of proton beams’ depth doses are fundamental to providing a high dose to the tumor while reducing the integral dose to healthy tissue. Figure 1 shows a comparison of dose distributions for a pencil beam and a proton spread-out depth dose curve and photon and electron depth doses. This illustrates that for the same amount of dose, the sparing of healthy tissue at shallow depths and distally, relative to SOBP region where the target is located, is considerably higher for proton beams than for other modalities. In practice, multiple beams are used when a tumor is treated to spread and reduce the integral dose to the surrounding healthy tissue. Figure 3 shows a comparison of the dose distribution for a prostate treatment using two proton fields versus Rapid Arc photon radiotherapy, which delivers dose continuously while the gantry rotates around the patient.

The superiority of proton therapy is manifested in craniospinal treatments for medulloblastoma, where dose is restricted to the treatment area and several regions at risk—such as bone marrow in the sternum and circulating hematopoietic stem cells—are spared because of proton range limitation.

Figure 2: The order in which the dose is deposited in a target by a pencil-beam scanning system. First, the deepest layer is irradiated, and then the second layer proximal to the first layer, and so on. The accelerator energy stacking varies the pencil-beam energies to deposit the dose in each specific layer inside the tumor. (Courtesy of PSI website: http://p-therapie.web.psi.ch/e/spot-scanning.html)

Figure 3: Color wash dose distribution comparison of Rapid Arc therapy on the left and two-field intensity-modulated proton therapy (IMPT) on right. The IMPT provides a conformal dose distribution to the target with less integral dose to healthy
tissue.

Figure 4: Comparison of the predicted dose distribution for (a) proton and (b) photon craniospinal therapy in a pediatric patient.

This benefit is demonstrated in Figure 4, where the predicted dose distribution from photon and proton craniospinal therapies are compared for a pediatric patient, showing the relatively greater sparing of internal organs by protons. Proton therapy potentially is beneficial for the treatment of lung, gastrointestinal, gynecological, head and neck, base of skull, eye, and other tumor sites. Proton therapy offers reduced overall integral dose to healthy tissue, better sparing of organs at risk, and, therefore, the prospect of dose escalation beyond what is achievable via conventional photon radiotherapy. The most challenging aspect of proton therapy treatment involves moving targets. Since the proton beam depth dose is very sensitive to changes in tissue density, any motion involving either the target or surrounding structures that fall in the beam path is likely to adversely impact the dose distribution and reduce target coverage or increase the dose to critical organs.

6. Summary

As the advantages offered by heavy ion radiation therapy increase in popularity, more institutions will likely acquire heavy ion therapy systems to treat their cancer patients. However, the cost of these facilities is substantially higher than conventional photon radiation therapy. As new technologies are employed and new compact particle therapy machines become available, the cost of these machines and their housing facilities will decrease. The new generation of machines will become more affordable to many radiation oncology centers. In the past few years, less expensive compact machines with highly advanced technologies have been introduced, some of which are currently being installed in the United States. Examples of the new generation of compact proton therapy systems include:

- The Radiance 330 by ProTom (ProTom International, Inc., Flower Mound, TX), a compact synchrotron dedicated to proton therapy that only delivers pencil beams; and
- The Mevion S250 (Mevion Medical System,
Littleton, MA), which uses a gantry-mounted superconducting synchrocyclotron that produces broad passive-scattered proton beams for a single treatment room.

There has recently been experimental investigation into the use of lasers to accelerate protons for radiotherapy. At the present time, limitations in laser technology (an intensity >1022 W/cm² is required to accelerate protons to >200 MeV) have constrained the maximum energy obtained with this method to 78 MeV,76 which is not sufficient for radiotherapy purposes. Fixed-field, alternating-gradient (FFAG) accelerators use both cyclotron and synchrotron technology to accelerate protons. This approach relies upon time-independent magnetic fields (fixed fields, similar to a cyclotron) and strong focusing (alternating gradient, similar to a synchrotron) to produce proton beams in the range of 150–200 MeV. A new type of induction linear accelerator uses a dielectric wall accelerator (DWA) to produce a uniform accelerating field along the length of a single-gantry pencil-beam accelerator, yielding protons with energies up to 250 MeV.77 With the continued development of new and more affordable types of heavy ion accelerators, it appears quite likely that the cost-to-benefit ratio of particle therapy will continue to decrease, spurring an increase in the development of new heavy ion therapy centers in the United States and throughout the world. Although particle therapy, especially with protons, has been performed on a small scale for many decades now, many potential benefits still remain somewhat unproven and will likely be clarified by the results of upcoming clinical trials, fueled by the ongoing growth of the field.

Conflict of Interest
Dr. Arjomandy is an Editorial Board Member of the Journal of Proton Therapy. The author declares that he has no other conflict of interest. The author alone is responsible for the content and writing of the paper.

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