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Review

Proton therapy in clinical practice

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Abstract

Radiation dose escalation and acceleration improves local control but also increases toxicity. Proton radiation is an emerging therapy for localized cancers that is being sought with increasing frequency by patients. Compared with photon therapy, proton therapy spares more critical structures due to its unique physics. The physical properties of a proton beam make it ideal for clinical applications. By modulating the Bragg peak of protons in energy and time, a conformal radiation dose with or without intensity modulation can be delivered to the target while sparing the surrounding normal tissues. Thus, proton therapy is ideal when organ preservation is a priority. However, protons are more sensitive to organ motion and anatomy changes compared with photons. In this article, we review practical issues of proton therapy, describe its image-guided treatment planning and delivery, discuss clinical outcome for cancer patients, and suggest challenges and the future development of proton therapy.

Key words Proton beam, radiotherapy, spread out Bragg peak

The aim of radiation therapy is to deliver a maximum radiation dose to a tumor, with less impact on healthy tissues and organs. Clinical evidence suggests there is a radiation dose-response relationship in cancers affecting both overall survival (OS) and local control rates, with higher dose associated with better outcome. However, higher radiation dose, particularly with concurrent chemotherapy, is associated with higher levels of toxicity. Therefore, studies predominantly focus on two aspects: developing new treatment planning systems to deliver higher doses of radiotherapy (RT) to properly defined target volumes and searching for a new form of radiation therapy to improve the therapeutic ratio.

Although three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) have potential to reduce toxicity to normal tissues, the relatively high exit dose from photon X-ray therapy limits the possibility of dose escalation or acceleration for tumors. In contrast, a proton beam is composed of charged particles (protons) with a well-defined range of penetration into tissue. As the proton beam penetrates, its particles slow down and deposit a large portion of their energy near the end of their range. The resulting central-axis depth-dose distribution is known as the Bragg peak. Studies estimated proton fields could reduce approximately 50% of the irradiation dose to adjacent normal tissue compared with photon beams[1]. Thus, proton therapy is ideal when organ preservation is a priority.

Employing protons in medical treatment was first suggested in 1946[2]. The first attempts to employ proton radiation to treat patients began in 1954 as reported by Lawrence *et al.*[3] at the University of California Lawrence Berkeley Laboratory. Subsequently, Uppsala University, and collaboration between Harvard University and the Massachusetts General Hospital (MGH) launched clinical proton therapy. Accelerators were not designed for treating patients as their energy was not great enough to penetrate the body for tumor treatment. Applications were limited to a few areas of the body in the treatment of glioblastoma, pituitary adenoma, cerebral arteriovenous aneurysm, sarcoma of the skull base and uveal melanoma[4-7]. In 1990, Loma Linda University Medical Center (LLUMC) applied a dedicated proton medical device, a relatively small facility featured gantry system, indicating the beginning of an official application of proton therapy[8]. The second proton therapy center was opened at MGH in 2001. The University of Texas–MD

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Anderson Cancer Center (UTMDACC) Proton Center was opened in 2006 and the scanning beam system has been employed since 2009. Proton therapy has been gradually accepted, especially with the integration of four-dimensional computed tomography (4D-CT) and image guided radiation therapy (IGRT). However, tumor motion may have significant impact in dose distribution. Additional studies, particularly clinical trials, are needed.

Physical and Biological Features

The main difference between protons and X-rays is the physical properties of the proton beam itself. Protons are large particles with a positive charge, penetrating matter (in this case, tissue) to a limited depth and depositing most of their energy at the end of the beam. The increment of proton dose at a specified area is referred to as the Bragg Peak[9]. This ability allows proton therapy to spare healthy tissue and have a conformal dose distribution (Figure 1)[10,11].

Proton beams are essentially a form of low linear energy transfer (LET) radiation. The effective dose is the computed physical dose in Gray multiplied by a relative biological effectiveness (RBE). Protons have nearly the same RBE as photons; the RBE of photons is 1, whereas prior studies have found that of protons ranged from 1.08 to 1.15, an 1.1 is considered standard in routine clinical practice[12,13]. The RBE can be used to convert photon to proton dose. However, the RBE of a proton beam depends on tissue type, dose, dose rate, energy, and depth of penetration. The increased RBE near the end of the Bragg peak has been estimated to be as high as 2.05[14]. Studies have demonstrated there is no difference in oxygen enhancement ratio (OER) between protons (2.5–3.0) and standard X-rays [15]. Treatment resistance caused by cancer stem cells (CSCs) is a challenging clinical issue. Targeting CSCs may improve the survival rate. The RBE of protons is assumed to be close to that of photons at 1.1 as mentioned above. However, the tissue- and cell-specific RBEs and molecular mechanisms of proton therapy in treatment-resistant cancer cells, such as CSCs, are not well understood. A recent study indicated protons may be more effective than photons in eliminating treatment-resistant CSCs *in vitro* [16]. Additional studies are warranted to validate this finding in the clinical setting.

Equipment for Proton Therapy

Cyclotrons and synchrotrons

The first step in generating a proton beam is to obtain a source of protons which can be accelerated to energies sufficient for treatment. This can be performed using hydrogen as the starting product and separating the hydrogen's electron from its proton by using an electrical field. Once protons have been generated, they must be accelerated such that the proton energy is sufficient to reach the distal edge of a tumor. Presently,

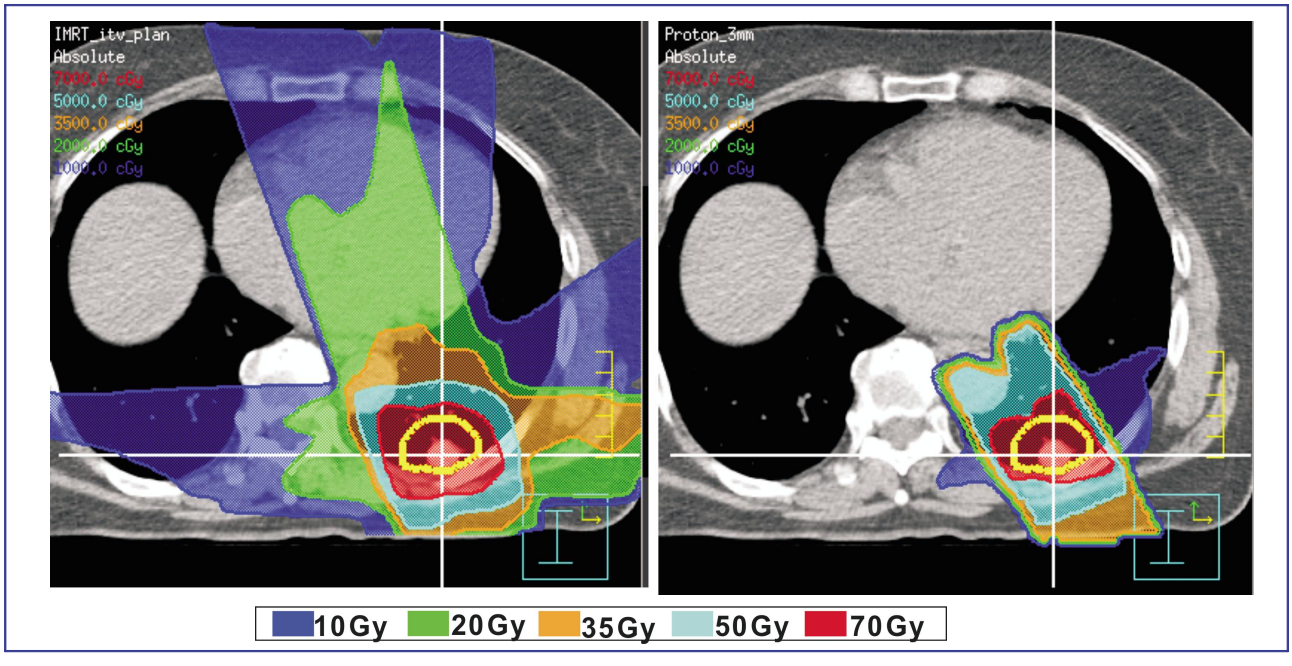

Figure 1. Comparison of photon intensity-modulated radiation therapy (IMRT) plan (left) and proton therapy plan (right).

the two most commonly used devices for proton acceleration are cyclotrons and synchrotrons. The magnetic field helps steer the protons such that they move in a spiral pattern. The magnetic field and voltage differential is kept constant, and as the protons circle, they continue to gain energy and gradually move outward until they can be extracted. Cyclotrons produce a high, continuous current of protons; however, they are only able to produce protons of fixed energy [17]. With synchrotrons, as the protons are accelerated, the magnetic field and the rate of voltage oscillation are both continuously modulated to keep the protons traveling in a fixed loop. Hence, in cyclotrons the protons' path changes as energy increases, whereas in synchrotrons the protons are held in a constant path via changes in the strength of the magnetic field and alteration in the rate of voltage oscillation. Thus, synchrotrons can produce protons of various energies by varying the magnetic and electrical fields[18].

Beam transport, range modulation, and current modulation

Once protons have been accelerated, they must be guided to the gantry for delivery to the patient. In accelerators which are able to produce protons of variable energies, such as synchrotrons, protons can simply be extracted at the appropriate energy. However, in accelerators which produce mono-energetic beams, such as fixed energy cyclotrons, a beam degrader can be used to change the energy of the proton beam. This energy selection system (ESS) degrades the initial beam produced by the cyclotron to produce several different, lower energies. This allows the beam energy to be modulated such that a variety of depths within the tissue can be treated. Once the desired proton beam energy has been produced, it still needs to be "spread out" such that it can cover the entire tumor, as a mono-energetic proton beam would only cover a small portion of the tumor with its Bragg peak. To create a beam with multiple energies that can spread its Bragg peak over multiple depths (spread out Bragg peak, SOBP, Figure 2), a modulator wheel can be used[19].

Gantries and inclined beam systems

After the proton beam has been created and directed to the treatment room using the beam line, there are a variety of ways by which the protons can be precisely directed to treat the tumor. One way is to use a gantry which can rotate in 360 degrees about the patient, allowing the delivery of radiation from any angle within a single plane. However, the gantries need to be quite large (three stories or approximately 10 meters in height) to appropriately guide protons to the patient, and the space at the center of the gantry must be large enough

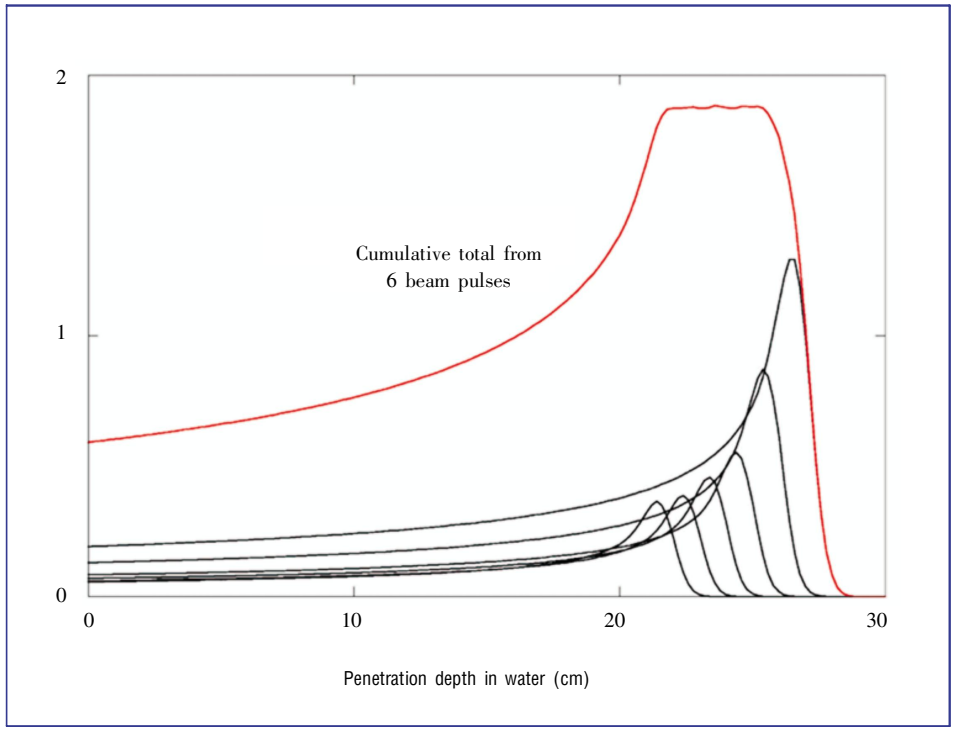

Figure 2. Cumulative total from 6 beam pulses (spread out Bragg peak, SOBP).

to accommodate the patient as well as imaging equipment, which is crucial for the precise delivery of protons. The incline beam system uses two beams, a horizontal beam and a second beam which is angled 30 degrees off vertical. These beams use a common isocenter and can be used together, in conjunction with a robotic patient positioner, to achieve a wide array of angles to treat the patient. There are also fixed beams which can only deliver protons in a single direction. These beams rely on the movement of the treatment table or chair around the beam to allow multiple angles to be treated[20].

Treatment Delivery Systems

Nozzles are used to deliver protons to the patient and are composed of multiple components. There are two main types of proton delivery systems: passive beam scattering and dynamic spot scanning system. Passive systems are relatively simple and achieve adequate conformation of the dose to the planning target volume (PTV). Scanning systems have a greater potential for benefit but are more complicated. Passive systems currently dominate clinical use but the trend is toward scanning.

Passive beam scatting

In a passive scatter system, the nozzle contains the above mentioned components including the scatter foils, ridge filter or modulator wheel, the aperture, and the range compensator (Figure 3). There are two types of scatterings, single or double. The single scatterer is uniform, and the scattered proton intensity has a Gaussian distribution. This trivial system has a low efficiency; the fraction of protons within the useful ±2.5% dose region is only 5% and the transverse dose distribution is not exactly flat even over a small region. The depth-dose distribution is a Bragg peak with a width of approximately 0.6 cm at the 90% level. It is only suitable for targets with very little extent in depth, such as the pituitary gland[21].

Double scattering was developed to reduce energy loss and improve efficiency, making large fields practical. The first scatterer is uniform. It produces a Gaussian beam profile on the second scatterer, which must be non-uniform in some way, modifying the Gaussian distribution so as to produce a flat or nearly flat dose distribution at the patient. The first such scheme used a flat second scatterer partly blocked by a cylindrical plug or occluding ring. The currently preferred method contours the second scatterer so that central protons are more strongly scattered, flattening the field at the patient. A drawback of double scattering is an increased sensitivity to beam steering. If the beam is off center by as little as a millimeter on the second scatterer, the flat dose distribution will tilt [22]. Ridge filters and range modulators are used in proton therapy to modify the beam in order to spread out the Bragg peak, and make it wide enough so that the high dose distribution can cover the treatment targets. The patient aperture is a beam stop with a hole shaped to the outer projection of the target in the beam's eye view. It is impractical to block all protons in this way. A range compensator is a plastic block with material cut away in a complex shape. It is carefully aligned with the aperture and the patient's

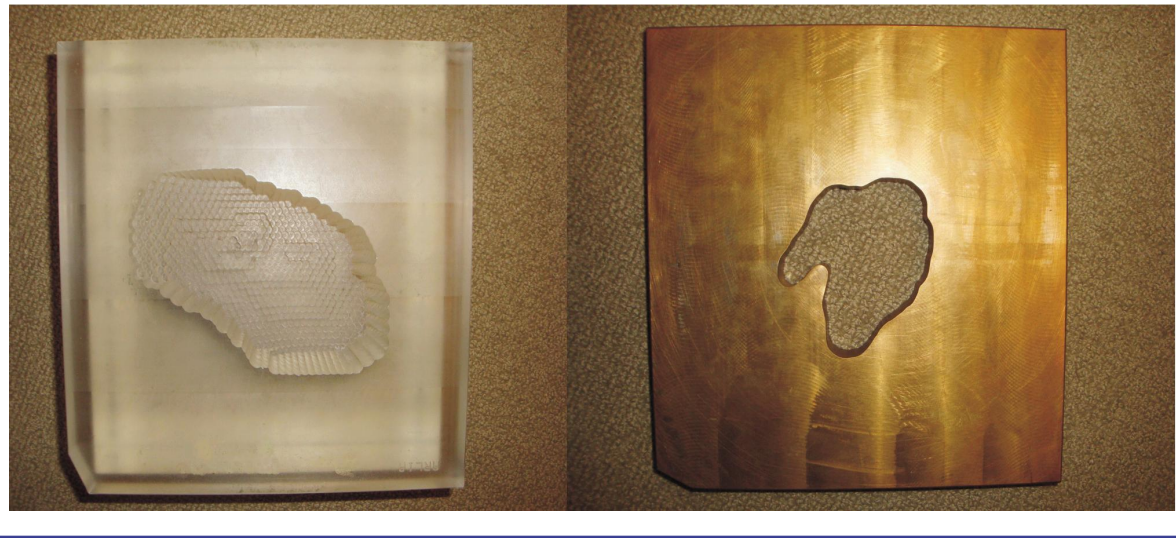

Figure 3. Facilities of passive beam scattering system. Compensator (left) and aperture (right).

PTV, and tailors the dose in depth by shifting greater or lesser proton range depending on what part of the PTV that a particular proton ray is aimed at[23].

The advantages of passive scattering systems include their safety, simplicity, and lower sensitivity to the time structure of the accelerator. Although these systems have well served their intended purpose, passive scattering systems have some disadvantages, the most serious of which being that they are only about 20% to 40% efficient and therefore waste a large number of protons in the scattering system and in the beam-limiting aperture. Passive scattering systems also tend to be sensitive to variations in the beam position. Furthermore, when protons are stopped in the scattering system and aperture, they produce secondary neutrons, many of which can contribute to the whole-body dose to the patient and may increase the incidence of secondary tumors. Another disadvantage of the passive scattering system is that it produces a single SOBP for the entire target volume. Thus, during treatment of large irregular target volumes with notable differences in their thickest and thinnest depths, the high-dose region needs to be pulled back to avoid overdosing distal critical structures while target volume with thicker depth will be underdosing or covers the target volume with thickest depth but overdosing critical structures. Therefore, this system may not be an ideal approach for tumors with a complicated anatomy such as lesions curved around critical structures[21].

Dynamic spot scanning

In dynamic spot scanning, the Bragg peak of a narrow pencil beam entering the treatment nozzle is magnetically scanned across the target cross section and the energy of the protons is adjusted to vary the depth of the spot to achieve the intended dose pattern. Scanning beams use magnets to move the proton beam precisely, so that it can "paint" the area that is to be treated. This technique allows a greater conformity with the shaping of the distal and proximal ends of the proton field. Scanning proton beams also allow the use of IMPT [24]. Fewer neutrons are produced with scanning beams, as a compensator, scatter foil and aperture are not needed. The major disadvantage to the scanning beam is the greater complexity and longer treatment times due to the multiple "layers" which must be "painted". There are also significant challenges to using scanning beams in areas of organ motion, as this technology is more susceptible to problems with motion. Several strategies address the organ motion problem in beam scanning. One strategy is to repaint the dose multiple times over the period of the organ motion to achieve an averaging effect of dose. Other strategies reduce the magnitude of motion, through breathing management, for example, in lung cancer, or by synchronizing the beam delivery with the motion[25]. The sensitivity to organ motion errors is the main reason why only well immobilized tumors, such as those located in the head and neck, spinal cord, lower pelvis, and lung cancer with a movement of less than 5 mm, have been treated using a scanning technique.

Treatment Planning

4D-CT–based simulation

Due to the considerable impact of motion in proton dose distribution, 4D-CT–based simulation is highly recommended for proton planning. 4D-CT images can also be used to delineate internal gross tumor volume (IGTV), which envelops the GTV motion throughout the respiratory cycle. Defining the GTV is to create a maximum intensity projection (MIP) image. In the treatment-planning process, GTV is first created with MIP for the compensator design [26,27]. This GTV MIP approach achieved dose distributions similar to those actually delivered to patients over the course of proton therapy.

Treatment targets

When defining a proton treatment plan, GTV, CTV, PTV, and ITV are also needed. The definition of GTV, CTV and ITV are the same as in the photon treatment plan. However, the concept of the PTV margin typically used in photon therapy is inapplicable to proton therapy. Photons have only lateral edges, and therefore the PTV margin is fixed based on set-up uncertainty and motion. In contrast, proton beams essentially have three edges, and the two lateral penumbras resulting from coulomb multiple scattering and the distal edge. Also, the depth dependence of the lateral penumbras in the proton beam is stronger than that of the photon for depths greater than approximately 17 cm. For shallower depths, the proton lateral penumbra is generally smaller than that of the photon. In general, each proton treatment beam must have its own distal and proximal margins that depend on the distance traveled by the beam in the tissue. Therefore, uniformly expanding the CTV to the PTV is not valid[28].

Image-guided delivery of adaptive proton therapy

Interfractional tumor motion and anatomic changes during radiation therapy are major causes of target miss and/or over-treating normal tissues in lung cancer. A

weekly 4D-CT study was conducted to investigate the magnitude of the changes in tumor volume and mobility in non–small cell lung cancer (NSCLC) during 7 weeks of radiotherapy. Reduction in tumor volume ranged from 20% to 71% and tumor mobility significantly increased. In some cases, an explicit initial determination of the IGTV may not be sufficient to cover the target, owing to variations in tumor motion and anatomy during treatment. Insufficiency of the IGTV coverage was even more severe with significant tumor underdosing in selective cases when proton treatment was used. Protons have been shown to be more sensitive to motion/anatomical change than IMRT over 7 weeks of radiotherapy. Re-planning radiotherapy using repeat 4D-CT images to adapt to changes in patient anatomy and organ motion between treatment fractions may be warranted for selective highly mobile tumors to reduce the potential for missing the target and/or overdosing the normal tissues during proton therapy[29,30].

Clinical Treatment Outcomes of Proton Therapy

Initially, proton therapy was used in limited and selective patients, most of them with advanced disease. Recently, more patients diagnosed with early stage disease have been enrolled. Over 200 articles based on clinical trials using proton radiation therapy have been published. However, most of the trials were single-arm studies and retrospective analyses, with many comparing the use of the technology to itself at different doses of radiation. There was no comparison between groups receiving similar doses of radiation by different methods (Table1) [31]. Clinical trials supported by the National Institute Health (NIH) mainly focus on cancers of the head and neck, prostate, pediatric, lung, and gastrointestinal tract (including liver and pancreas) [http://www.clinicaltrials.gov].

Pediatric tumors

Each year, approximately 10 000 children younger than 14 years are diagnosed with cancer in the United States; roughly 21% of these patients are afflicted with malignancies of the central nervous system (CNS) [32]. Despite the fact that nearly 50% of all patients with CNS tumors are cured, they continue to suffer from acute toxic effects related to treatment as well as devastating long-term effects.

In treating patients with cancers of the CNS, one of the greatest complexities is achieving a balance between morbidity and cure [33]. In a study mentioned above comparing IMRT with 3D-CRT in patients with retinoblastoma, a 5-Gy treatment resulted in integral doses to the orbit bone of 69% using IMRT and 25% using 3D-CRT. However, when comparing the same dose using proton beam therapy, the integral dose to the orbit bone was found to be only 10%[34]. Macdonald *et al.*[34] reported a study in which 22 patients were treated with three-dimensional conformal proton radiotherapy (3D-CPT). At a median follow-up of 28 months, there were no carcinoma recurrences in the CNS; 1 patient had a recurrence outside the CNS. The local control rate, progression-free survival rate, and OS rate were 100%, 95%, and 100%, respectively. IMRT delivered a mean dose of 20.5 Gy to the left temporal lobe, whereas this structure received a mean dose of 13.8 Gy (RBE) with 3D-CPT. IMPT decreased this dose to 12.9 Gy (RBE). The whole-brain dose was substantially decreased with proton therapy. IMRT delivered a mean dose of 15.7 Gy, whereas 3D-CPT decreased the mean dose to the brain to 10.0 Gy (RBE). This was decreased to 9.4 Gy (RBE) with IMPT. Proton therapy, regardless of the delivery technique, provided a substantial benefit in the total volume of temporal lobes and brain receiving radiation. Proton therapy decreased the mean dose to the temporal lobes by one third to nearly one half of the

Table 1. Thirty-six clinical studies of proton therapy

Tumor site	No. of studies[a]	No. of patients
Head and neck tumors	2	62
Prostate cancer	3	1 642
Ocular tumors	9	9 522
Gastrointestinal cancer (liver, pancreas)	5	375
Lung cancer	3	125
CNS tumors	10	753
Sarcomas	1	47
Other sites	3	80
Total	36	12 606

[a] There are at least 20 patients with a follow-up period of at least 2 years in each study. CNS, central nervous system.

mean dose delivered with IMRT, with the greatest sparing achieved with IMPT using fine pencil beams[35].

One of the more common CNS malignancies, standard risk medulloblastoma, carries long-term control rates more than 50%. Regrettably, at diagnosis approximately 20% to 30% of tumors are disseminated throughout the brain and spinal canal. Because of their high risk for spread, these tumors require radiation to the entire neuroaxis, making the greatest challenge in the treatment of these patients a balance between effective treatment and long-term effects[36]. In looking at craniospinal irradiation, major structures affected by the treatment of medulloblastoma were studied. When using 35 Gy radiation, with both 3D therapies 100% of the cochlea was irradiated as compared to 16% with proton therapy. In the hypothalamic-pituitary axis, 40 Gy resulted in 54% irradiation with 3D-CRT electrons, 64% with 3D-CRT photons, and only 3% with the use of proton beams[34]. Studies also indicate proton therapy can deliver high doses to the target while sparing surrounding healthy tissues such as the thyroid, heart, esophagus, liver and gastrointestinal tract, and is able to decrease acute toxicities such as dry cough, dysphagia, nausea and vomiting[37].

Prostate cancer

RT remains one of the principal treatment options in the management of localized prostate cancer. The aim of modern photon RT techniques, including 3D-CRT, IMRT, and brachytherapy, is to increase the RT dose without additional RT toxicity, particularly to the rectum. The 5-year biochemical progression-free survival of low risk patients is approximately 95%[38].

A dosimetric study of pelvic proton radiotherapy compared IMRT, IMRT followed by a prostate 3D-PRT boost (IMRT/3D-PRT), and 3D-PRT plans in high-risk prostate cancer patients was conducted. Compared with the IMRT and IMRT/3D-PRT plans, 3D-PRT plans reduced the mean dose to the rectum, rectal wall, bladder, bladder wall, small bowel, and pelvis. Femoral head doses were higher for the 3D-PRT[39]. Talcott *et al.*[40] performed a post hoc cross-sectional survey of surviving participants in the Proton Radiation Oncology Group (PROG) 9509—a randomized trial comparing 70.2 Gy vs. 79.2 Gy of combined photon and proton radiation for 393 men with clinically localized prostate cancer. At a median of 9.4 years after treatment, the incidence of toxicities such as urinary obstruction/irritation, urinary incontinence, bowel problems, sexual dysfunction and most other outcomes were similar, while the high dose group had a better biochemical control rate[40]. Nihei *et al.*[41] reported a multi-institutional phase II study of proton therapy in which 151 prostate cancer patients were enrolled. PBT was delivered to a total dose of 74 GyE in 37 fractions; median follow-up was 43.4 months. Results showed the incidence of grade 2 acute rectal and bladder toxicity temporarily developed 0.7% and 12%, and that of the 147 patients who had been followed up for > 2 years, the incidence of grade 2 or higher late rectal and bladder toxicity was 2.0% and 4.1% at 2 years, suggesting high dose proton therapy did not increase irradiation-induced toxicity. In addition, it reduced the low irradiation dose (< 40 Gy) to the pelvis[41].

Lung cancer

Proton therapy is the most common ion beam used in lung cancer treatment. UTMDACC conducted a clinical trial in patients with either stage I or stage IIIA/B NSCLC. Compared with standard-dose (60–66 Gy) photon therapy, proton treatment (87.5 and 74 GyE) significantly reduced the dose to normal tissues including the lung, esophagus, spinal cord, and heart, even with dose escalation[28]. One study suggested the local control rate of lung cancer is related to the escalation of irradiation dose, and 1 Gy escalation may increase the local control rate 1%[42]. In another study of proton radiotherapy for stage I NSCLC, Bush *et al.*[43] treated 68 patients with proton therapy [total dose of 60 to 70 Gy (RBE) in 10 fractions]. This regimen resulted in a local control rate of 87% in T1 lesions and 49% in T2 lesions, and the 3-year disease-free survival rate of 72%; no patients developed grade 2 or higher pneumonitis or esophagitis[43]. Hata *et al.*[44] reported preliminary results of a study of hypofractionated proton radiation therapy for 21 patients with stage I NSCLC (tumors < 4.2 cm in diameter), in which a dose of 50 to 60 Gy was given in 10 fractions, and the results showed local progression-free and disease-free rates were 95% and 79% at 2 years, respectively, with no grade 3 or higher toxicities. Nihei *et al.*[45] applied proton therapy to treat 36 patients with stage I NSCLC using a total dose of 70–94 Cobalt gray equivalents (CGE) delivered in 20 fractions and found similarly high rates of local control (92.6%) and OS (81%) at 2 years. No grade 2 or higher acute toxicity was observed, but grade 3 late toxicity was observed in three patients. Among the 19 patients with stage IB disease, two had local progression and eight developed regional lymph node or distant metastasis[45]. In a similar study, Nakayama *et al.*[46] used proton therapy to treat 55 medically inoperable patients with stage I NSCLC using a total dose of 66 GyE in 10 fractions for peripherally located tumors and 72.6 GyE in 22 fractions for centrally located tumors. The overall and progression-free survival and tumor local control rates at 2 years were 97.8%, 88.7%, and 97.0%, respectively. Two patients (3.6%) had deterioration in pulmonary function, and two patients (3.6%) had grade 3 pneumonitis[46].

As proton therapy can reduce the dose to adjacent normal tissues, patients with stage III lung cancer may benefit from this new technique. Nakayama *et al.* [47] analyzed 35 lung cancer cases treated with a median proton dose of 78.3 GyE. Results showed the OS was 81.8% at 1 year and 58.9% at 2 years during a median observation period of 16.9 months, while grade 3 or greater toxicity was not observed. Without concurrent chemotherapy, only 4 patients (11.4%) developed in-field local recurrence [47]. At UTMDACC, Zhang *et al.* [48] analyzed patterns of failure, survival, and toxicity for patients with stage III NSCLC treated with dose-escalated (74 CGE) proton therapy in combination with concurrent chemotherapy in a phase II clinical study. All patients underwent PET/CT staging and 4D-CT simulation-based treatment planning and adaptive proton delivery. With a median follow-up of 16 months, no patients experienced grade 4 or 5 toxicity. The most common non-hematological grade 3 adverse effect was dermatitis (13.3%), followed by esophagitis (6.7%) and pneumonitis (3.3%). The rate of isolated local failure within planned target volume was 13.3%, the rate of regional lymph node failure outside the planned target volume was 13.3%, the rate of distant metastasis was 20%, and the rate of combined distant metastasis and local/regional failure was 16.7%. Compared with our previous clinical outcomes using IMRT in stage IIII NSCLC, proton therapy appears to significantly reduce side effects, particularly for pneumonitis and esophagitis[48]. Dose-escalated concurrent proton therapy and chemotherapy appear to improve local control and reduce toxicity. Additional studies are needed to address the issues of missing targets and treatment uncertainty using proton therapy. Longer follow-up time is also needed. Optimization of proton therapy with the appropriate management of uncertainties is actively being investigated. Image-guided respiratory-gated proton therapy and IMPT will be implemented in the near future.

Head and neck cancer

Impact of organ movements are not significant in head and neck cancers, which allows proton beam therapy to deliver higher doses to the tumor volumes with significantly reduced radiation to normal tissues than do photon beam irradiation.

Chera *et al.* [49] conducted a study comparing the dose-volume data between 3D-CPT and IMRT for a T4N0 maxillary sinus carcinoma. The target volume dose distributions were comparable for 3D-CPT and IMRT. The mean and integral doses for all normal tissues were lower for 3D-CPT. Though the contralateral parotid, lacrimal gland, and lens were avoided with 3D-CPT, the maximum doses for both 3D-CPTand IMRT plans to the ipsilateral optic nerve/retina/lens, temporal lobe, pituitary, and brain exceeded tolerance doses[49]. Another similar study compared tumor and normal tissue dosimetry of proton therapy with IMRT for pediatric parameningeal rhabdomyosarcomas (PM-RMS). The results suggested both proton and IMRT plans provided acceptable and comparable target volume coverage in all cases. Improved dose conformality provided by proton therapy resulted in significant sparing of all examined normal tissues except for ipsilateral cochlea and mastoid [50]. In the modern series of 3D-CRT and photon IMRT for sinonasal tumors at high-volume, experienced centers, the local control rate at 5 years after treatment has been around 60%. In contrast, in the recent PBRT series, the local control rate at 5 years has been 80% to 90%. However, these series included heterogeneous tumor histologic subtypes, ranging from squamous cell carcinoma and sinonasal undifferentiated carcinoma to adenoid cystic carcinoma, esthesioneuroblastoma, and neuroendocrine tumors, making it difficult to draw general conclusions about the relative efficacy of the different techniques[51].

At the MGH, proton therapy has been used to treat locally advanced NPC since 1990. Seventeen patients with newly diagnosed T4N0–3 tumors received combined conformal proton and photon radiation between 1990 and 2002[52]. Of these patients, 12 (71%) had WHO type II or III histology, with a median prescribed dose to the gross target volume of 73.6 GyE (range, 69 to 76.8 GyE); 11 had accelerated hyperfractionated RT; 10 received induction chemotherapy or concurrent chemoradiotherapy, and only one failed to complete the planned concurrent chemotherapy and radiation course. The 3-year OS rate was 74% for all patients. For patients who received chemotherapy, the 3-year OS was 91% compared with 40% for those without chemotherapy. This preliminary evidence suggests proton therapy is effective for locally advanced NPC [52]. Recently, Widesott *et al.* [53] compared IMPT and helical tomotherapy treatment plans for nasopharynx cancer using a simultaneous integrated boost approach. The results suggested excellent target coverage, homogeneity within the PTVs, and sparing of the organs at risk were reached with both modalities. IMPT allows for better sparing of most organs at risk at medium-to-low doses[53].

Hepatocellular carcinoma

Since 85% of hepatocellular carcinoma (HCC) develops in patients with cirrhosis of the liver and its associated liver insufficiency, it is essential the HCC therapy spares uninvolved liver to minimize the risk of further compromise of hepatic function [54]. Apart from surgery, conformal radiation therapy has become

available for patients with HCC. Kawashima *et al.*[55] evaluated the safety and efficacy of radiotherapy using a proton beam (PRT) for unresectable hepatocellular carcinoma. Sixty consecutive patients who underwent PRT between May 1999 and July 2007 were analyzed. Total PRT dose/fractionation was 76 GyE/20 fractions in 46 patients, 65 GyE/26 fractions in 11 patients, and 60 GyE/10 fractions in 3 patients. The risk of developing proton-induced hepatic insufficiency (PHI) was estimated using dose-volume histograms and an indocyanine-green retention rate at 15 min (ICG R15). Local rogression-free and OS rates at 3 years were 90% and 56%, respectively. A gastrointestinal toxicity of grade 2 or above was observed in 3 patients. None of the 20 patients with an ICG R15 of less than 20% developed PHI, whereas 6 of 8 patients with ICG R15 values of 50% or higher developed PHI. Among 32 patients whose ICG R15 ranged from 20% to 49.9%, the PHI was observed only in patients who had received 30 CGE (V30) to more than 25% of the noncancerous parts of the liver (n = 5)[55].

At the University of Tsukuba, Nakayama *et al.*[56] retrospectively reviewed 318 patients with HCC treated with proton beam therapy. The 1-, 3-, and 5-year overall actuarial survival rates were 89.5% [95% confidence interval (95% CI), 85.7%–93.1%], 64.7% (95% CI, 56.6%–72.9%), and 44.6% (95% CI, 29.7%–59.5%), respectively. Child-Pugh liver function [hazards ratio (HR), 2.84; P < 0.01], T stage (HR, 1.94; P < 0.05), performance status (HR, 2.12; P < 0.01), and planning target volume (HR, 2.12; P < 0.05) significantly impacted survival. The authors have shown proton beam therapy to be both safe and effective for the treatment of patients with HCC and strongly recommend the consideration of proton beam therapy in patients for whom other treatment options are risky or contraindicated[56]. Fukumitsu *et al.*[57] reported the results of hypofractionated proton therapy for 51 patients with HCC. The total dose was 66 GyE in 10 fractions. OS rates and local control rates were 38.7% and 87.8% 5 years after treatment. Late treatment sequelae included rib fracture in 3 patients 8, 10, and 27 months after treatment. No patients suffered from liver failure secondary to proton therapy and long-term survival was comparable to surgery. But in this study, the diameters of most of the tumors were less than 5 cm, with a median value of maximal tumor diameter of 2.8 cm, and patients with tumors located < 2 cm from the porta hepatis or digestive tract were excluded in order to ensure safe delivery of treatment[57]. Mizumoto *et al.*[58] summarized 266 HCC patients treated by proton therapy between 2001 and 2007. Three treatment protocols (A, 66 GyE in 10 fractions; B, 72.6 GyE in 22 fractions; and C, 77 GyE in 35 fractions) were used, depending on the tumor location. The 1-, 3-, and 5-year OS rates were 87%, 61%, and 48%, respectively, with a median survival time of 4.2 years[58]. All the above mentioned results showed proton therapy achieved good local control rates for early stage HCC patients. The results of proton therapy in locally advanced HCC patients were even comparable to that of surgery, suggesting the development of proton therapy has made it a new choice of treatment for HCC.

Gynecologic carcinoma

The Tsukuba group reported on the results of combined photon-proton irradiation of 19 patients with uterine cervical carcinoma, including 8 with stage IIB disease and 11 with stage IIIB disease. Whole pelvis irradiation was initially given through parallel opposing 10 MV photons to a dose of 50.4 Gy in 28 fractions. Then the central target volume was irradiated with proton beams through anterior and lateral portals. Proton doses of 46 to 63 Gy (mean, 58 Gy) at 2.6 to 3.8 Gy (mean, 3.3 Gy) were delivered. Local failures occurred in 2 patients (10.5%) with stage IIIB tumors, but no local failures occurred in the patients with stage IIB disease. The actuarial survival rates at 3 years were 87.5% for stage IIB and 75.8% for stage IIIB patients. Two patients developed major radiation related proctitis, but neither required surgical intervention and eventually became symptom-free with conservative measures. Radiation cystitis was described as minimal to moderate[59]. Slater *et al.*[60] performed comparative treatment planning studies comparing photon and proton irradiation for management of carcinoma of the cervix. In the first scenario, patients were treated with 50 Gy of external beam pelvic irradiation, intracavitary brachytherapy, and an external beam parametrial boost. Dose distributions showed the proton beam avoiding more of the bladder, small bowel, and rectum than the photon boost while still covering the lateral parametria. In the second scenario, patients who were not candidates for intracavitary therapy because of tumor bulk or poor geometry were treated with external beam only. In this scenario, the dose to the tumor could be increased within a normal tissue tolerance to 80–90 GyE with protons, whereas the dose with 3D conformal photons was limited to approximately 70 Gy[60].

Similar findings were reported by Smit *et al.*[61] who performed treatment planning studies comparing intracavitary brachytherapies combined with 3D photons or protons. The protons were delivered through a split posterior and two lateral fields. This study suggested the volume of normal tissue irradiated to significant dose could be reduced by up to 60% with protons compared with photons, allowing tumor doses up to 20% higher. Studies also suggested delivery of 2D or 3D conformal

photon doses > 50 Gy to the para-aortic lymph nodes has been associated with an unacceptable risk of small bowel morbidity[61]. Levin *et al*.[62] studied the potential for gain in the use of a proton beam boost to the para-aortic lymph nodes in the management of carcinoma of the cervix. Their study found the use of protons would allow safe dose escalation to the para-aortic lymph nodes to 70 GyE with acceptable doses to bowel and other sensitive structures, estimating this increase in dose may improve disease-free survival by 11% in stage II and as much as 21% in stage III disease[62].

Proton Therapy in the United States

The National Association for Proton Therapy (NAPT) was founded in 1990 and is an independent, non-profit, public benefit corporation. Within the Unites States, there are 7 proton centers in operation with another 3 being under construction. The following 7 proton centers are in operation: (1) James M. Slater, MD Proton Treatment and Research Center at Loma Linda University Medical Center; (2) Francis H. Burr Proton Center at Mass. General Hospital; (3) Midwest Proton Radiotherapy Institute at Indiana University; (4) The University of Florida Proton Therapy Institute; (5) The University of Texas MD Anderson Cancer Center Proton Center; (6) ProCure Proton Therapy Center, Oklahoma City, located at the INTEGRIS Cancer Campus; and (7) The Roberts Proton Therapy Center at University of Pennsylvania Health System. The 3 proton centers under construction are as follows: (1) Northern Illinois University Proton Therapy Center; (2) ProCure Proton Therapy Center in partnership with Princeton Radiation Oncology Group and CentraState Healthcare System; and (3) Hampton University Proton Therapy Institute.

Summary and Future Development

The dose distributions of proton Bragg peaks led to the development of proton therapy that is superior to photon therapy for reducing the radiation dose to normal tissue adjacent to the target. Because of a reduction in the "dose bath" and in the volume of normal tissues irradiated with proton therapy, patient tolerance of radiation and/or chemoradiotherapy was enhanced, allowing a higher dose to be delivered. Delivery of higher proton therapy dose, combined with the increased accuracy obtained from image-guided targeting and greater avoidance of normal tissues, lead to reduced toxicity and better local disease control and survival rates in patients with NSCLC. Reduced tumor motion is required for optimal image-guided proton therapy. 4D-CT planning is recommended for all proton therapy, particularly for IMPT. Respiratory-gated proton treatment further improves normal tissue sparing. More efficient CT imaging that will be performed before each proton therapy treatment is being developed and will facilitate greater accuracy in treatment delivery. Re-simulation during treatment is recommended for selected patients with substantial tumor shrinkage and possible lung expansion.

Compared with photon IMRT or SBRT, proton-based IMPT and SBPT may achieve better target coverage and remarkable normal tissue sparing, particularly in clinically challenging cases. However, before IMPT is used in clinical settings, particularly for hypofractionated stereotactic treatment, more studies are needed to validate the impact of these uncertainties, since small lesions could move more significantly and there is less chance of averaged out uncertainty due to a lower fraction number. In addition, most proton therapy facilities only have on-board kilo-voltage X-ray imaging but lack volumetric imaging such as cone-beam CT or CT–on-rail, which have been widely used in photon SBRT. Implanted fiducial markers to improve clinical set up and target verification, particularly for respiratory gated treatment, may be needed. Alternatively, volumetric verification, either outside or inside the proton treatment room before each fraction of treatment, should be explored.

Although proton therapy is clearly capable of providing superior dose distributions as compared with photons, there are still some questions remain unanswered. What kind of patients can benefit mostly from proton therapy? Can more patients be cured by the proton dose escalation? How does proton therapy decrease treatment toxicities and can it finally improve the life qualities of patients? Can the treatment courses be shortened? How does proton therapy combine with other treatment modalities such as surgery, chemotherapy and photon therapy? Is proton therapy cost effective in cancer treatments?

The use of proton therapy in a clinical setting may translate to better local control, better survival, and less toxicity in cancer patients. Patients with tumors close to critical organs such as lung cancer, esophageal cancer and hepatocellular cancer may benefit from the development of the technique. Also recurrent patients will have a chance of re-irradiation with proton therapy. Actual clinical studies are needed to validate the virtual clinical data.

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