Proton therapy: the current status of the clinical evidences

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ABSTRACT

Proton therapy has the potential advantages of better conformal planning and higher biological effect than photon therapy (X-ray) for targeting tumor tissues. While the energy of a photon passes through the target, the energy of a proton is deposited at a certain depth, which in turn is negligible beyond this stopping point (i.e., the “Bragg peak”). In addition, the proton beam has a 10% higher biological effect in the same dose than the photon beam. Recent technological advances have led to wide use of proton therapy in clinical practice. To date, more than 170,000 patients have received proton therapy. Although clinical experience with proton therapy is increasing now, only approximately 1% of all radiation therapy recipients receive proton therapy and prospective randomized studies involving large sample populations remain very limited yet. The aim of this review is to describe the physical and biological properties of proton therapy and discusses the clinical evidence supporting proton therapy in various disease sites.

Keywords: Evidence-based practice; Proton therapy; Radiotherapy

INTRODUCTION

In recent years, technological advances in radiation therapy (RT) have led to improvements in precision with an increasing therapeutic ratio. In the aspect of photon (i.e., X-ray) therapy, the development of multi-leaf collimators with widths < 5 mm has improved the physical properties of photon therapy and the dose distribution between tumor and normal tissues. Intensity-modulated radiation therapy (IMRT) is widely used in cancer patients and resulted in better treatment outcomes with lower toxicities than three-dimensional conformal radiation therapy (3D-CRT) [1]. In addition, IMRT can be used more efficiently because it can shorten treatment time by developing volumetric modulation therapy, a type of arc therapy using IMRT [2].

With advances in photon therapy, the use of particle therapy with protons or carbon ions in clinical practice has increased dramatically. Particle therapy has the potential advantages of better conformal planning for high-dose regions and biological effect than photon therapy [3]. Despite these advantages, however, the cost of constructing a particle facility is significantly higher than that for a photon-based facility and, as such, particle therapy is available in only a
The current status of proton therapy

limited number of institutions. However, since the cost and scale of construction have decreased with advances in technology, many centers have been built around the world and, as a result, clinical experience is also increasing. Most of these institutional and clinical experiences involve proton therapy, and the number of carbon ion centers is still limited. To date, numerous planning studies comparing proton therapy with photon therapy and early clinical results have demonstrated the clinical efficacy and safety of proton therapy [4]. However, up to now, prospective randomized studies involving large sample populations remain very limited. The present review describes the physical and biological properties of proton therapy and discusses the clinical evidence supporting proton therapy in the current status.

HISTORY

In 1946, Wilson [5] first demonstrated the potential use of the Bragg peak for the treatment of deeply localized tumors. In 1954, at the University of California, Berkeley (Berkeley, CA, USA), the first patient was treated with proton therapy [6]. Thereafter, some physics laboratories, including the Harvard Cyclotron Laboratory (HCL; Cambridge, MA, USA), treated patients [7]. In 1990, the Loma Linda University Medical Center (Loma Linda, CA, USA) built the first hospital-based proton facility [8]. The second was opened at the Massachusetts General Hospital (MGH)-Harvard University. Over several decades, many centers worldwide have built proton therapy facilities. Currently, 97 facilities are in operation, and 44 facilities are under construction worldwide (http://www.ptcog.ch). Proton therapy in the clinic was initially used for ocular, skull base, and paraspinal tumors. Over time, however, indications for proton therapy have expanded, and the technology is being used to treat a variety of solid tumors. To date, more than 170,000 patients have received proton therapy (Fig. 1) [9]. According to the Particle Therapy Co-Operative Group (PTCOG) website (http://www.ptcog.ch), although experience with proton therapy is increasing, only approximately 1% of all RT recipients receive proton therapy, which still requires significant research to assess efficacy and cost-effectiveness compared with photon therapy.

PHYSICAL PROPERTIES OF PROTON THERAPY

Proton therapy has unique physical properties compared with photon therapy [3]. While the energy of a photon passes through the target, the energy of a proton is deposited at a certain depth, which depends on the initial energy of the particle, which in turn is negligible beyond this stopping point (i.e., the “Bragg peak”) (Fig. 2A). Because of this physical property, particle therapy has the innate advantage of sparing the normal tissues in distal of the peak when irradiating a specific target. The depth of the Bragg peak depends on the energy of proton beam, which can be controlled by varying the energy of the generated proton beam (Fig. 2B). The width of the Bragg peak is narrow; thus, it needs to be spread out to cover the tumor volume longitudinally, which is otherwise known as “spread-out Bragg peak.” In addition, the beam should be broaden to cover the tumor volume laterally. Wobbling or double scattering technique is used to broaden thin Gaussian shaped pencil beam. In the scattering technique

Fig. 1. Patients treated with particle therapy. Adapted from Particle Therapy Co-Operative Group [9], with permission from PTCOG.
which uses lateral and longitudinal spreading of the beam, dose conformity of the tumor volume is made by the block in the lateral beam margin and by the compensator in the distal end of the beam. Consequently, the dose conformity of the high-dose area in the proximal margin of the tumor volume can be decreased in the scattering techniques. However, the scanning technique directly steers each proton beam using dipole magnets to achieve dose conformity. This conformal dose distribution is produced by “dose painting” each layer of the tumor volume—voxel by voxel—so there is no extra dose delivered to the proximal edge of the tumor, as with scattering techniques (Fig. 2C).

In clinical practice, photon therapy produces high dose conformity in the tumor volume using multi-beam or arc therapy. IMRT can achieve better conformity by modulating the intensity of a beamlet than 3D-CRT. However, low to moderate levels of RT dose should be delivered to the surrounding normal tissues to achieve conformity in the high-dose region. In contrast, proton therapy can achieve comparable conformity using only a few beams, which significantly reduces low to moderate radiation doses to the surrounding tissues [10].

Despite the advantages inherent in its physical properties, uncertainties with proton therapy should be considered in treatment planning [11,12]. The range of the Bragg peak depends on the energy of the beam, as well as the density of
the tissue in the beam passage. If all tissues are composed of water-equivalent material and are unchanged during treatment, the proton beam always delivers the exactly calculated dose to a certain depth. However, in real-world practice, soft tissue volume in the path of the beam can be decreased owing to tumor shrinkage and/or weight loss, and the amount of air cavity (e.g., paranasal sinus or stomach gas), thus altering beam passage. These changes shift the Bragg peak to a different position from that calculated during treatment planning. Therefore, an overdose to critical normal organs or undertreatment to the tumor volume can occur during treatment. Thus, additional margin and/or robust optimization methods which makes the distal falloff of the target dose less stiff are necessary to compensate for the dose uncertainty in treatment planning. In addition, image-guided treatment, such as cone-beam computed tomography (CT) with adaptive planning, is now incorporated into proton therapy. When the changes mentioned above occur during the course of treatment, adaptive re-planning should be required to irradiate adequate dose to target volume or to avoid the overdose to critical normal tissues. In certain cases, several times of adaptive re-planning should be conducted. An additional uncertainty is in dose calculation algorithm. The calculation of delivered dose via interaction between proton energy and matter is based on the stopping power in each voxel of CT images acquired in simulation. However, the CT image does not provide the atomic number of each type of tissues; thus, the density information has to be converted into a stopping power employing calibration data which has inherent uncertainty. In addition, pencil beam algorithm which is widely used in proton therapy has limited accuracy in describing the scattering effects of protons. The most advanced algorithm, Monte-Carlo algorithm account for the complicate interaction mechanism of protons in tissues, but it is a time-consuming to calculate [13]. Now, it can be applied in clinical practice due to advances in computer systems. However, in cases of dental or surgical implants in the treatment volume, the calculation remains still uncertain and the use of proton therapy is currently not recommended.

BIOLOGICAL PROPERTIES OF PROTON THERAPY

Proton therapy has the advantage of greater biological effectiveness than photon therapy. The relative biological effectiveness (RBE) is defined as the ratio of a dose required to produce the same biological effects. In the clinic, the RBE of a proton beam is generally assumed to be 1.1 compared with that of a photon beam, which means the proton beam has a 10% higher biological effect in the same dose than the photon beam (cf., the RBE of the carbon ion is approximately 2 to 3) [14]. Thus, in clinical practice, the dose of a proton beam is calculated by multiplying the physical dose by 1.1. However, the use of this fixed RBE value is controversial because it is determined based on an average of data, which have exhibited wide error bars in many in vitro and in vivo studies using a limited number of cell lines and tissues. In addition, recent studies have shown that the RBE is variable according to depth. The RBE increases with depth, and is highest particularly near the distal edge due to the increased linear energy transferred to the tissue per unit length [15]. This finding has not been applied to optimizing treatment plans in real-world practice yet. Instead, placing critical organs (e.g., spinal cord, brainstem) at the distal edge of the proton beam should be careful when treatment planning. Recent studies have shown that models used to predict actual dose distribution consider the RBE variable; however, they have not been used in clinical practice due to limited data [16].

CLINICAL EVIDENCE

Pediatric tumors
RT has an important role in treating pediatric tumors including central nervous system (CNS) tumors, extra-cranial sarcomas, neuroblastoma, and hematopoietic tumors. Long-term toxicities, including secondary malignancies, neurocognitive dysfunctions, growth and musculoskeletal problems, and cardiac problems, are major concerns in pediatric patients who undergo RT [17]. There have been many efforts to reduce the RT dose and volume to avoid these RT-related toxicities. Proton therapy is one of the best options to reduce unnecessary irradiation dose and volume in pediatric patients. Many institutions with a proton therapy facility primarily use proton therapy to treat pediatric patients. The worldwide survey in 2016 reported that a total of 1,860 patients were treated; 1,205 in North America, 432 in Europe, and 223 in Asia. More than 30 pediatric tumor types were treated, mainly with curative intent: 48% were CNS, 25% extra-cranial sarcomas, 7% neuroblastoma, and 5% hematopoietic tumors [18]. In the United States, one survey study reported that the number of children with CNS tumors who were treated with proton therapy increased by 36% between 2010 and 2013 [19]. Because of the relatively low incidence of pediatric tumors and the ethical challenges related to randomly assign-
ing children to receive unwanted radiation to healthy growing normal tissues, performing randomized studies of proton therapy are impossible in real practice. As a result, non-randomized trials have been conducted, despite the inherent limitations and potential bias, to demonstrate that proton therapy can alleviate or prevent radiation-related sequelae affecting the quality of life of pediatric cancer patients. Most data published so far are the treatment outcomes for pediatric CNS tumors.

The long-term complications after proton therapy in pediatric medulloblastoma were assessed in an open-label, single-center, phase II trial conducted at the MGH. The patients received a median craniospinal irradiation dose of 23.4 Gy (RBE) delivered at 1.8 Gy (RBE) per fraction, followed by a boost to 54 Gy (RBE). A total of 59 patients were followed up for a median of 7.0 years. The cumulative incidence of grade 3 to 4 ototoxicity was 12% at 3 years. The Full Scale Intelligence Quotient (FSIQ) decreased by 1.5 points per year after a median follow-up of 5.2 years. The processing speed and verbal comprehension indexes were mainly decreased, while the perceptual reasoning index and working memory did not change significantly. The average loss of FSIQ per year was lower than that of several patient cohorts who were treated with photon therapy despite the limitations in direct comparison between cohorts. The cumulative incidence of any neuroendocrine deficit was 55% at 5 years, with growth hormone deficiency being the most common. There were no late cardiac, pulmonary, or gastrointestinal toxicities [20].

Investigators at the MD Andersen Cancer Center (MDACC, Houston, TX, USA) compared changes in intelligence quotient (IQ) over time among 150 patients who were treated with photon therapy versus proton therapy. In the proton group, no change in IQ over time was detected (P=0.130), whereas in the photon group, IQ declined by 1.1 points per year (P=0.004), while IQ slopes did not differ between the groups (P=0.509). IQ was lower in the photon group by 8.7 points (P=0.011). It appears that proton therapy was not associated with IQ decline in pediatric patients with brain tumor(s); nevertheless, additional long-term follow-up is needed to determine whether proton therapy resulted in clinically meaningful benefits to cognitive function [21].

There are no data to compare the risk for secondary malignancies between proton and photon therapy in pediatric patients. In one retrospective study, 558 patients treated with proton therapy, including 44 pediatric patients <18 years of age. They were matched with 558 patients treated with photon therapy. Second malignancies occurred in 29 proton patients (5.2%) and 42 photon patients (7.5%), with a median follow-up of 6.7 years. The adjusted hazard ratio for a secondary malignancy developing in a patient treated with proton therapy was 0.52 compared with photon therapy (P=0.009) [22].

**Head and neck cancer**

RT is used as a definitive or as an adjuvant treatment for head and neck (H&N) cancer patients. When delivering RT to H&N cancer, many critical structures such as optic apparatus, brainstem, spinal cord, parotid glands, oral mucosa, and pharyngeal muscles can be included in the irradiated volume. The irradiated dose and volume to these critical organs is a major determinant for RT toxicity as well as for irradiating adequate dose to target volume. Compared to 3D-CRT, the use of IMRT not only increased treatment outcomes but also reduced toxicity significantly [23-25]. Many expect further benefit from the use of proton therapy [26].

Historically, proton therapy has been used to treat skull base tumors due to the proximity of the brainstem and optic nerves. Retrospective data have demonstrated better local control (LC) and overall survival (OS) with proton therapy than with photon therapy including IMRT and stereotactic body radiation therapy (SBRT). Studies from the MGH reported that the 5-year local relapse-free survival rates were 73% for chordoma and 98% for chondrosarcoma in 519 patients [27]. The Paul Scherrer Institut (PSI) assessed the treatment outcomes of spot scanning proton therapy. They reported that 3-year LC rates were 87.5% and 100% for chordoma and chondrosarcoma, respectively [28].

Proton therapy has also demonstrated better survival rates in nasal cavity and paranasal sinus tumors. In a meta-analysis including many retrospective studies, proton therapy demonstrated a higher 5-year OS (P=0.038) and progression-free survival (PFS) (P=0.003) than photon therapy [29].

In oropharyngeal cancers, proton therapy can reduce toxicity to normal tissues. The MDACC analyzed patient-reported outcomes from 35 patients treated with intensity-modulated proton therapy (IMPT) and from 46 treated with IMRT. The symptoms of altered taste and appetite during the subacute and chronic phases favored IMPT (P<0.048). During the subacute phase, the symptom score of the MD Anderson Symptom Inventory for Head and Neck Cancer (MDASI-HN) was better in the IMPT group (P=0.013) [30]. In a case-matched analysis of 50 IMPT and 100 IMRT patients, IMPT was associated with reduced rates of feeding tube dependency and severe weight loss (odds ratio [OR], 0.44 [95%
Many studies have evaluated the toxicities of proton therapy. Proton therapy only, and the 5-year LC and OS rates were reported. At PSI, 39 patients with skull base benign meningioma were treated with a combination of photon and proton therapy. The recurrence-free survival rate was 88% at 10 years [36]. At Indiana University (Bloomington, IN, USA), 22 patients were analyzed after proton therapy with a median 63.0 Gy (RBE) in atypical meningioma. The 5-year LC rate was 71.1% [37]. At PSI, 39 patients with atypical and malignant meningioma were treated with proton therapy only, and the 5-year LC and OS rates were 84.8% and 81.8%, respectively [38].

Several investigators have reported treatment outcomes of proton therapy for meningioma. At the MGH, 46 patients with skull base benign meningioma were treated with a combination of photon and proton therapy. The recurrence-free survival rate was 88% at 10 years [36]. At Indiana University (Bloomington, IN, USA), 22 patients were analyzed after proton therapy with a median 63.0 Gy (RBE) in atypical meningioma. The 5-year LC rate was 71.1% [37]. At PSI, 39 patients with atypical and malignant meningioma were treated with proton therapy only, and the 5-year LC and OS rates were 84.8% and 81.8%, respectively [38].

Many studies have evaluated the toxicities of proton therapy. Proton therapy can also reduce toxicities in unilateral irradiation, such as in cases involving major salivary gland tumor and oral cavity cancers, because the exit dose of the proton beam is essentially negligible. Romesser et al. [32] reported that proton therapy decreased acute toxicities, except for radiation dermatitis, compared with IMRT in 41 salivary gland tumors or cutaneous squamous cell carcinoma. Acute grade 2 or higher toxicities were lower in terms of oral mucositis (16.7% vs. 52.2%, P=0.019), dysgeusia (5.6% vs. 65.2%, P<0.001), and nausea/vomiting (11.1% vs. 56.5%, P=0.003) in proton therapy [32]. Proton therapy does not have the skin sparing effect of a photon beam and, as such, skin toxicity can be increased compared with photon therapy.

CNS tumors
Cognitive impairment has been one of major concerns following RT for CNS tumors [33]. Proton therapy has a potential benefit to reduce the irradiated dose to normal brain tissue to prevent cognitive dysfunction. In addition, a dose escalation could be possible in radioresistant brain tumors such as high-grade gliomas.

Several retrospective and prospective studies investigating high-grade gliomas have been reported. At Tsukuba University (Tsukuba, Japan), proton therapy resulted in a median OS of 24.4 months following 50.4 Gy (RBE), followed by a 23.1 Gy (RBE) boost, which was better than the 14.2-month OS for photon therapy in 67 patients with newly diagnosed glioblastoma [34]. Tsukuba University recently reported a prospective study involving 46 patients with glioblastoma. Using the same proton therapy regimen, the median OS was 21.1 months and the 2-year OS was 47.6% [35].

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Gastrointestinal tumors
Proton therapy can spare the surrounding normal tissues when it is used to treat gastrointestinal tumors. In the management of hepatocellular carcinoma (HCC), it is very important to spare liver function. Because the liver is an organ with parallel functional subunit in the model of radiation response of normal tissues, liver toxicity is more sensitive to irradiated volume. Proton therapy has a major advantage in reducing the irradiated volume of remnant liver when irradiating the tumor. In many retrospective trials, proton therapy resulted in favorable outcomes.

At the University of Tsukuba, investigators serially reported treatment outcomes of proton therapy for HCC [41-43]. Proton therapy was delivered with 72.6 Gy (RBE) in 22 fractions or 77 Gy in 35 fractions for HCC located within 2 cm of the main portal vein [41,42], a 66 Gy (RBE), and in 10 fractions for HCC 2 cm apart from both gastrointestinal tract and the porta hepatitis [43]. In those studies, favorable outcomes with LC of 88% to 95% and 3-year OS rates of 45% to 65% were reported. At the National Cancer Center of South Korea, a dose-escalation study was performed for HCC. An RT dose of 60 Gy (RBE) in 20 fractions, 66 Gy (RBE) in 22 fractions, and 72 Gy (RBE) in 24 fractions was tested. Complete response (CR) rates were increased with dose escalation, resulting in CR rates of 62.5%, 57.1%, and 100%, respectively. The 3-year LC rate was significantly higher in patients who achieved CR than in those who did not (90% vs. 40%, P=0.003) [44]. The study also reported treatment outcomes for tumor thrombosis of HCC using a simultaneous integrated boost-proton beam therapy technique. The different dose level was used according to the distance between the gross tumor target volume and the gastrointestinal tract. A RT dose of 50 Gy (RBE), 60 Gy (RBE), and 66 Gy (RBE) in 10 fractions was delivered. Higher doses >60 Gy tended to result in better tumor venous thrombosis response (92.8% vs. 55.5%, P=0.002). One meta-analysis reported better outcomes in OS, PFS, and
showed appropriate loco-regional control (LRC) and favored dose of 33 to 59.4 Gy (RBE). Proton re-RT for H&N cancers complications. For adult CNS tumors (mostly high-grade gliomas), patients with recurrent uveal melanoma at Harvard University, focus and relevance, were included in the analysis. In 31 patients, which were found to have sufficient data analysis. In stage III disease, 5-year OS (34.6% vs. 25.0%, P=0.038) and PFS (33.5% vs. 13.2%, P=0.005) rates were higher in the proton therapy group, while there were no significant differences in survival for Stage I/II patients [48].

Re-irradiation
Re-irradiation may be a viable option for recurrent tumors to increase LC and to provide cure in a substantial portion of localized disease, although it often results in severe radiation toxicity [49,50]. Proton therapy has the advantage of irradiating the target while reducing the dose to the surrounding normal tissues; thus, it has a potential benefit in re-irradiation. Many retrospective studies investigating re-irradiation in various tumor sites have been reported.

One systematic review evaluated clinical outcomes and toxicities of proton re-RT [51]. Among 315 published articles, 16 original investigations, which were found to have sufficient focus and relevance, were included in the analysis. In 31 patients with recurrent uveal melanoma at Harvard University, proton re-RT showed that the rate of LC was 31%, with a 5-year eye retention rate of 55%. There were no major ocular complications. For adult CNS tumors (mostly high-grade gliomas), there were no grade ≥ 3 adverse events with median dose of 33 to 59.4 Gy (RBE). Proton re-RT for H&N cancers showed appropriate loco-regional control (LRC) and favorable toxicity profiles compared to historical data with photon therapy, including low (9% to 10%) rates of feeding tube placement. One multi-institutional analysis reported clinical outcomes of proton re-RT with scanning technique for 92 recurrent H&N cancer patients. The median initial and reRT doses were 61.4 Gy and 60.6 Gy, respectively. Despite of relatively short-term follow-up (median, 10 months), the 1-year LRC and OS were 75% and 65%, respectively. There were 5 patients (5.4%) suffered grade 4 skin toxicities, and 2 (2.2%) died from pharyngeal bleeding and carotid rupture. For lung cancer, MDACC showed 1-year LRC of 54% and OS of 47% following proton re-RT of median 66 Gy (RBE). Re-RT was tolerated, with a 9% rate of grade 3 esophagitis and 21% with grade 3 pneumonitis. Three cases of fistula and tracheal necrosis were developed. Like MDACC report, a multi-center prospective study of 57 patients showed that central regions, as well as composite RT doses, correlated with higher rates of adverse events. Proton re-RT for recurrent gastrointestinal tumors (esophageal, rectal, pancreatic, and liver cancer) showed very few high-grade complications, although most studies have analyzed a small number of patients. In summary, proton therapy can be a safe and effective re-RT modality for salvage treatment of recurrent disease. However, data are still limited to date, and further studies to report clinical outcomes and toxicities should be needed.

NON-SMALL CELL LUNG CANCER

Low-dose shower is a major risk for radiation pneumonitis (RP) when treating non-small cell lung cancer (NSCLC) with photon therapy. If the lateral beam placement is avoided to reduce the lung dose, the irradiated dose to heart is consequently increased and results in increased cardiac death in long-term follow-up. In many dosimetric studies, proton therapy demonstrated advantages in lung and heart dose compared with photon therapy [52-54]. Several clinical studies have reported treatment outcomes and toxicities of proton therapy in early-stage disease, locally advanced disease, re-irradiation, and in postoperative settings [55]. Most studies have used scattering techniques. In early stage NSCLC, proton therapy resulted in favorable LC and toxicity, particularly in centrally located tumors [56,57]. In one meta-analysis, 72 SBRT and 9 proton therapy with hypofractionated regimens were analyzed. In multivariate analysis, OS and PFS were not statistically different, while LC favored proton therapy (P=0.03) [58]. The International Particle Therapy Cooperative Group recommends considering proton therapy for

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larger or multiple or central tumors, and not for peripheral tumors [59]. Recently, one interesting study compared proton therapy with IMRT in patients with locally advanced NSCLC. The patients were randomly assigned to proton therapy or IMRT with concurrent chemotherapy if treatment plans satisfied the same prespecified dose-volume constraints for at-risk organs at the same tumor dose of 66 to 74 Gy (RBE). In designing the study, the investigators assumed a 15% RP rate in the IMRT group and a 5% RP rate in the proton therapy group, with same local failure rate of 25% in both groups. Unexpectedly, grade 3 or higher RP developed in 6.5% for IMRT and 10.5% for proton therapy. Local failure rates were 10.9% for IMRT and 10.5% for proton therapy. There was no benefit in RP and local failure after proton therapy [60,61]. Some criticism has been raised for inadequate planning of proton therapy due to the learning curve, the use of passive scattering techniques, non-standard RT doses of 66 to 74 Gy (RBE), and selection bias due to insurance coverage issues [62]. Nevertheless, this study concluded that there was no clear benefit of proton therapy in locally advanced NSCLC.

PROSTATE CANCER

Although proton therapy has been widely used to treat prostate cancer, consensus regarding its role in this particular disease remains controversial. Many dosimetric studies showed better outcomes in reducing RT dose to rectum and bladder with equivalent coverage of the prostate [63,64]. However, there is no clinical data to show the superior disease control of proton therapy compared to photon therapy or brachytherapy.

In Japan, early results of a multi-institutional prospective study of proton therapy for localized prostate cancer were reported. A total of 151 patients were treated with 74 Gy (RBE) in 2 Gy (RBE) per fraction and followed-up with median 43.4 months. Acute grade ≥ 2 rectal and bladder toxicity developed in 0.7% and 12%, respectively. The incidence of late grade ≥ 2 or rectal and bladder toxicity was 2.0% (95% CI, 0% to 4.3%) and 4.1% (95% CI, 0.9% to 7.3%) at 2 years, respectively. The biochemical free survival (BFS) rate was 94% at 3 years (95% CI, 90% to 98%) [65]. A case-matched analysis comparing a combination of photon and proton therapy with brachytherapy was reported. At MGH and Loma Linda University, 196 patients enrolled to high dose arm of 79.2 Gy (RBE) were matched with 203 similar patients treated with brachytherapy. At 8 years, there were no significant differences in OS (93% vs. 96% for proton therapy and brachytherapy, respectively; P=0.45) and in BFS (7.7% [95% CI, 2.8% to 12.6%] and 16.1% [95% CI, 9.0% to 23.1%], P=0.42) [66].

There are several studies to compare toxicity profile of proton therapy to that of photon therapy. At University of Pennsylvania, a case-matched analysis was performed in 394 patients who treated with proton therapy or IMRT. There were no statistically significant differences between IMRT and proton therapy in the risk of grade ≥ 2 acute gastrointestinal toxicity (P=0.09), grade ≥ 2 acute genitourinary toxicity (P=0.36), grade ≥ 2 late genitourinary toxicity (P=0.22), and grade ≥ 2 late gastrointestinal toxicity (P=0.62) [67]. A large population-based study with 12,976 patients using Surveillance, Epidemiology, and End Results-Medicare-linked data compared morbidity and disease control of IMRT, proton therapy, and conformal RT for primary prostate cancer treatment. In a propensity score-matched comparison between IMRT and proton therapy (n=1,368), IMRT patients had a lower rate of gastrointestinal morbidity (absolute risk, 12.2 per 100 person-years vs. 17.8 per 100 person-years; relative risk, 0.66; 95% CI, 0.55 to 0.79). There were no significant differences in other morbidities between IMRT and proton therapy [68]. At MDACC, the toxicities of proton therapy were compared to those of IMRT among the patients younger than 65 years of age. Using the MarketScan Commercial Claims and Encounters database, a total of 693 proton therapy patients were matched to 3,465 IMRT patients. Proton therapy showed a lower risk of urinary toxicity (33% vs. 42% at 2 years, P<0.001) and erectile dysfunction (21% vs. 28% at 2 years, P<0.001), but a higher risk of bowel toxicity (20% vs. 15% at 2 years, P=0.02) [69].

It remains unclear whether the effectiveness of proton therapy is better than IMRT or brachytherapy; thus, further well-designed studies are needed. Currently, American Society for Radiation Oncology (ASTRO) has recommended insurance coverage only for patients enrolled in an Institutional Review Board-approved clinical trial or registry.

INDICATIONS FOR PROTON THERAPY

Consensus regarding adequate indications for proton therapy is necessary because it is available in only a limited number of facilities and has relatively higher costs than photon therapy. For example, ASTRO has updated the recommendations for insurance coverage. The ASTRO recommendation is based on four selection criteria: the target volume is in close proximity to ≥ 1 critical structure(s), and a steep dose gradient outside the target must be achieved to avoid exceeding
the tolerance dose to the critical structure(s); a decrease in dose inhomogeneity in a large treatment volume is required to avoid an excessive dose “hotspot” within the treated volume to lessen the risk for excessive early or late normal tissue toxicity; a photon-based technique would increase the probability of clinically meaningful normal tissue toxicity by exceeding an integral dose-based metric associated with toxicity; and, finally, the same or an immediately adjacent area has been previously irradiated, and the dose distribution in the patient must be carefully modelled to avoid exceeding the cumulative tolerance dose to nearby normal tissues. Based on the above medical necessity requirements and published clinical data, group 1, which is recommended coverage is listed as follows: ocular tumors, including intraocular melanomas; skull base tumors, primary or metastatic tumors of the spine, where spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated; hepatocellular cancer; pediatric tumors; patients with genetic syndromes making total volume of radiation minimization crucial; malignant and benign primary CNS tumors; advanced and/or unresectable H&N cancers; the paranasal sinuses and other accessory sinuses cancers; non-metastatic retroperitoneal sarcomas; and cases requiring re-irradiation. All other indications are recommended only for clinical trials or prospective registries.

**CONCLUSION**

The dosimetric advantages of proton therapy—compared with photon therapy—have been clearly defined in many comparison studies involving various tumor sites. There are now accumulating clinical data demonstrating that this dosimetric advantage can lead to better outcomes such as reduced RT toxicity and improved treatment outcomes. Ongoing prospective or randomized clinical studies may provide higher levels of clinical evidence supporting indications for proton therapy in the future.

**CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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