REVIEW ARTICLE

Precision and Future Medicine 2019;3(3):91-102
https://doi.org/10.23838/pfm.2019.00058
pISSN: 2508-7940 · eISSN: 2508-7959

PRECISION AND FUTURE MEDICINE

Proton therapy: the current status of the clinical evidences

Dongryul Oh

Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Received: May 8, 2019
Revised: June 10, 2019
Accepted: July 12, 2019

Corresponding author:
Dongryul Oh
Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82-2-3410-2612
E-mail: dongryul.oh@samsung.com

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

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

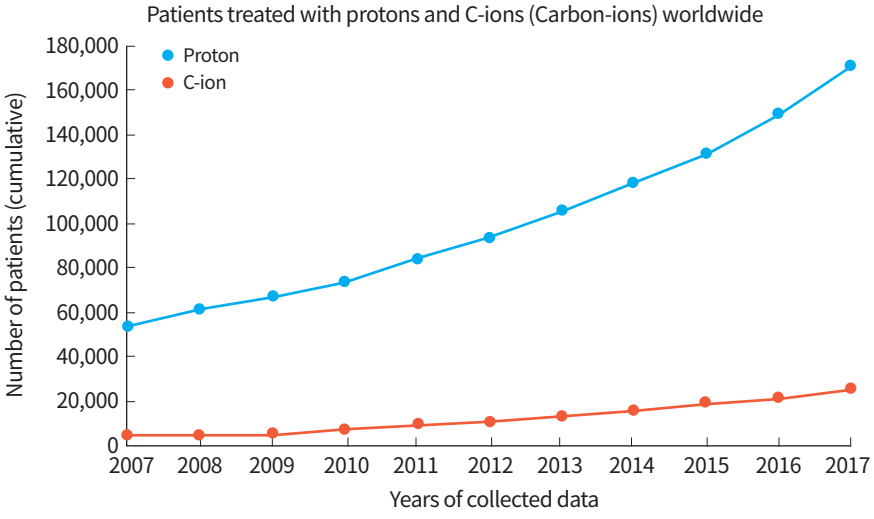

Fig. 1. **Patients treated with particle therapy. Adapted from Particle Therapy Co-Operative Group [9], with permission from PTCOG.**

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

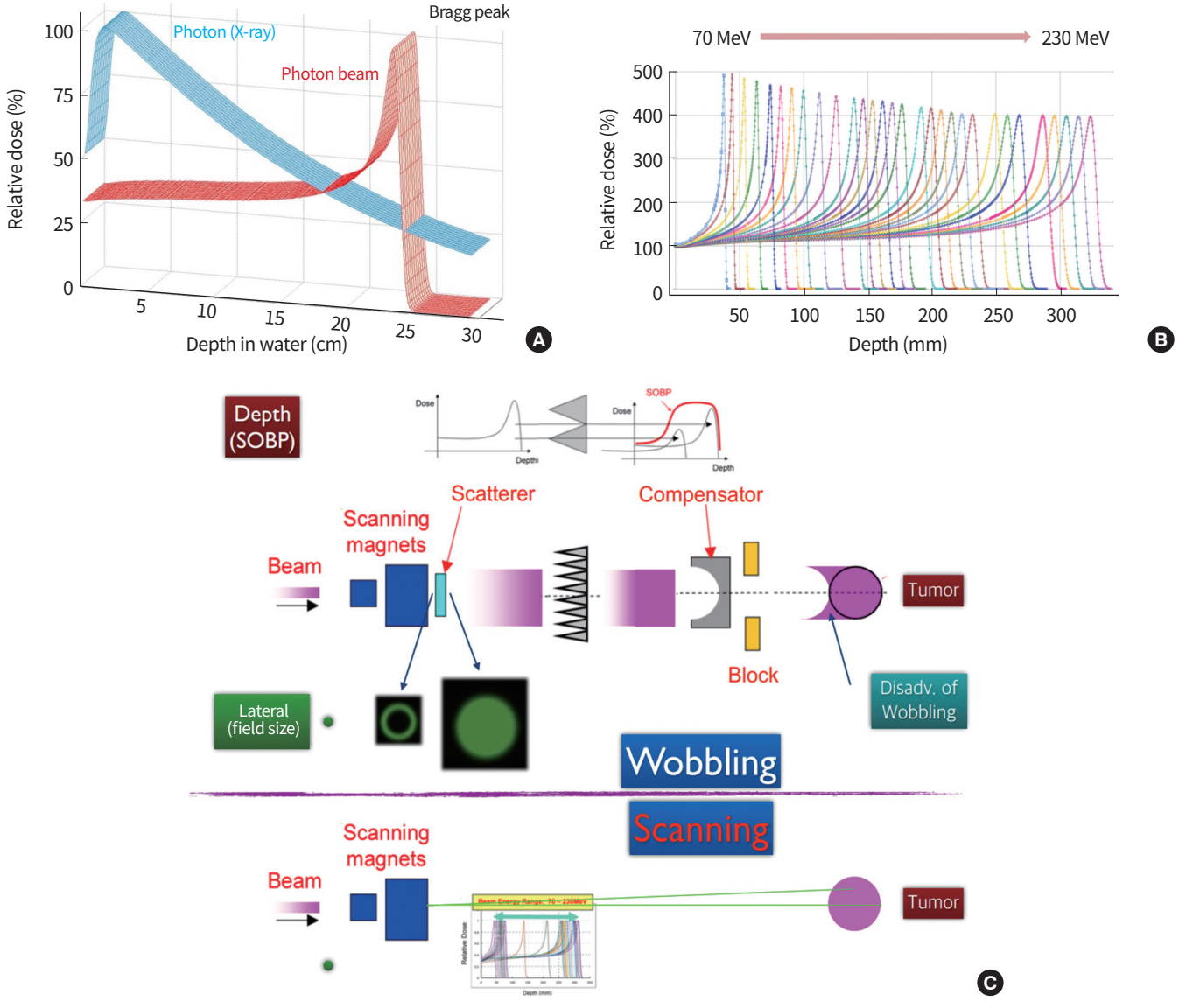

Fig. 2. Physical properties of proton therapy: (A) Bragg peak, (B) Bragg peak according to the energy of particle, and (C) scattering (wobbling) versus scanning technique. SOBP, spread-out Bragg peak.

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 underdose 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 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%

confidence interval (CI), 0.19 to 1.0; P=0.05] at 3 months after treatment; and OR, 0.23 [95% CI, 0.07 to 0.73; P=0.01] at 1 year after treatment), while significant differences were not observed in OS (P=0.44) or in PFS (P=0.96) [31].

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].

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 in treating low-grade gliomas. At the University of Pennsylvania (Philadelphia, PA, USA), 21 patients with low-grade glioma or meningioma were treated with 54.0 Gy (RBE) of proton therapy. The most acute toxicities were grade 1 or 2 headache or fatigue [39]. At the MGH, 20 patients with grade 2 glioma were treated with 54.0 Gy (RBE) of proton therapy. There was no decline in cognitive function or quality of life over time. At 5 years' follow-up, the results of long-term complications with proton therapy were promising compared with those with photon therapy [40].

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 hepatis [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

LC with particle therapy than with photon therapy [45].

In esophageal cancer, RT is an essential modality in multidisciplinary management. Because the esophagus is a centrally located organ between the heart and lung, cardiopulmonary toxicity is a major concern when irradiating esophageal cancer. In many dosimetric comparison studies, proton therapy significantly reduced the irradiated dose and volume to the heart and lung compared with 3D-CRT or IMRT [46]. In some retrospective studies, a clinically significant reduction in treatment-related toxicities was shown. Investigators at the MDACC reported that in patients treated with neoadjuvant chemoradiation followed by surgery, there was a significant increase in pulmonary complications for 3D-CRT (OR, 9.13; 95% CI, 1.83 to 45.42) and a trend for IMRT (OR, 2.23; 95% CI, 0.86 to 5.76) compared with that for proton therapy [47]. In a recent study, the treatment outcomes of proton therapy for locally advanced esophageal cancer were better than those of IMRT. A total of 343 patients who received definitive chemoradiation with either proton therapy (n=132) or IMRT (n=211) were analyzed retrospectively. Proton therapy resulted in significantly better OS (P=0.01), PFS (P=0.0001), and locoregional failure-free survival (P=0.041) in multivariate 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 $\geq$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

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 Lma 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.

ORCID

Dongryul Oh https://orcid.org/0000-0002-5643-5519

REFERENCES

1. Veldeman L, Madani I, Hulstaert F, De Meerleer G, Mareel M, De Neve W. Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies. Lancet Oncol 2008;9:367-75.
2. Otto K. Volumetric modulated arc therapy: IMRT in a single gantry arc. Med Phys 2008;35:310-7.
3. Rong Y, Welsh J. Basics of particle therapy II biologic and dosimetric aspects of clinical hadron therapy. Am J Clin Oncol 2010;33:646-9.
4. Hu M, Jiang L, Cui X, Zhang J, Yu J. Proton beam therapy for cancer in the era of precision medicine. J Hematol Oncol 2018;11:136.
5. Wilson RR. Radiological use of fast protons. Radiology 1946;47:487-91.
6. Lawrence JH, Tobias CA, Born JL, Mccombs RK, Roberts JE, Anger HO, et al. Pituitary irradiation with high-energy proton beams: a preliminary report. Cancer Res 1958;18:121-34.
7. Kjellberg RN, Koehler AM, Preston WM, Sweet WH. Stereotaxic instrument for use with the Bragg peak of a proton beam. Confin Neurol 1962;22:183-9.
8. Coutrakon G, Hubbard J, Johanning J, Maudsley G, Slaton T, Morton P. A performance study of the Loma Linda proton medical accelerator. Med Phys 1994;21:1691-701.
9. Particle Therapy Co-Operative Group. Statistics of patients treated in particle therapy facilities worldwide [Internet]. Villigen (CH): PTCOG; c2019 [cited 2019 July 23]. Available from: https://ptcog.ch/index.php/patient-statistics.
10. Palm A, Johansson KA. A review of the impact of photon and proton external beam radiotherapy treatment modalities on the dose distribution in field and out-of-field; implications for the long-term morbidity of cancer survivors. Acta Oncol 2007;46:462-73.
11. Unkelbach J, Paganetti H. Robust proton treatment planning: physical and biological optimization. Semin Radiat Oncol 2018;28:88-96.
12. McGowan SE, Burnet NG, Lomax AJ. Treatment planning optimisation in proton therapy. Br J Radiol 2013;86:20120288.
13. Paganetti H. Range uncertainties in proton therapy and the role of Monte Carlo simulations. Phys Med Biol 2012;57:R99-117.
14. Paganetti H, Niemierko A, Ancukiewicz M, Gerweck LE, Goitein M, Loeffler JS, et al. Relative biological effectiveness (RBE) values for proton beam therapy. Int J Radiat Oncol Biol Phys 2002;53:407-21.

15. Saager M, Peschke P, Brons S, Debus J, Karger CP. Determination of the proton RBE in the rat spinal cord: Is there an increase towards the end of the spread-out Bragg peak? Radiother Oncol 2018;128:115-20.
16. Guan F, Geng C, Ma D, Bronk L, Kerr M, Li Y, et al. RBE model-based biological dose optimization for proton radiobiology studies. Int J Part Ther 2018;5:160-71.
17. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006; 355:1572-82.
18. Journy N, Indelicato DJ, Withrow DR, Akimoto T, Alapetite C, Araya M, et al. Patterns of proton therapy use in pediatric cancer management in 2016: an international survey. Radiother Oncol 2019;132:155-61.
19. Gondi V, Yock TI, Mehta MP. Proton therapy for paediatric CNS tumours: improving treatment-related outcomes. Nat Rev Neurol 2016;12:334-45.
20. Yock TI, Yeap BY, Ebb DH, Weyman E, Eaton BR, Sherry NA, et al. Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study. Lancet Oncol 2016;17:287-98.
21. Kahalley LS, Ris MD, Grosshans DR, Okcu MF, Paulino AC, Chintagumpala M, et al. Comparing intelligence quotient change after treatment with proton versus photon radiation therapy for pediatric brain tumors. J Clin Oncol 2016; 34:1043-9.
22. Chung CS, Yock TI, Nelson K, Xu Y, Keating NL, Tarbell NJ. Incidence of second malignancies among patients treated with proton versus photon radiation. Int J Radiat Oncol Biol Phys 2013;87:46-52.
23. Ursino S, D'Angelo E, Mazzola R, Merlotti A, Morganti R, Cristaudo A, et al. A comparison of swallowing dysfunction after three-dimensional conformal and intensity-modulated radiotherapy: a systematic review by the Italian Head and Neck Radiotherapy Study Group. Strahlenther Onkol 2017;193:877-89.
24. Marta GN, Silva V, de Andrade Carvalho H, de Arruda FF, Hanna SA, Gadia R, et al. Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. Radiother Oncol 2014;110:9-15.
25. Zhang B, Mo Z, Du W, Wang Y, Liu L, Wei Y. Intensity-modulated radiation therapy versus 2D-RT or 3D-CRT for the treatment of nasopharyngeal carcinoma: a systematic review and meta-analysis. Oral Oncol 2015;51:1041-6.
26. Leeman JE, Romesser PB, Zhou Y, McBride S, Riaz N, Sherman E, et al. Proton therapy for head and neck cancer: expanding the therapeutic window. Lancet Oncol 2017;18:e254-65.
27. Munzenrider JE, Liebsch NJ. Proton therapy for tumors of the skull base. Strahlenther Onkol 1999;175 Suppl 2:57-63.
28. Weber DC, Rutz HP, Pedroni ES, Bolsi A, Timmermann B, Verwey J, et al. Results of spot-scanning proton radiation therapy for chordoma and chondrosarcoma of the skull base: the Paul Scherrer Institut experience. Int J Radiat Oncol Biol Phys 2005;63:401-9.
29. Patel SH, Wang Z, Wong WW, Murad MH, Buckey CR, Mohammed K, et al. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. Lancet Oncol 2014;15:1027-38.
30. Sio TT, Lin HK, Shi Q, Gunn GB, Cleeland CS, Lee JJ, et al. Intensity modulated proton therapy versus intensity modulated photon radiation therapy for oropharyngeal cancer: first comparative results of patient-reported outcomes. Int J Radiat Oncol Biol Phys 2016;95:1107-14.
31. Blanchard P, Garden AS, Gunn GB, Rosenthal DI, Morrison WH, Hernandez M, et al. Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer: a case matched analysis. Radiother Oncol 2016;120:48-55.
32. Romesser PB, Cahlon O, Scher E, Zhou Y, Berry SL, Rybkin A, et al. Proton beam radiation therapy results in significantly reduced toxicity compared with intensity-modulated radiation therapy for head and neck tumors that require ipsilateral radiation. Radiother Oncol 2016;118:286-92.
33. Klein M, Heimans JJ, Aaronson NK, van der Ploeg HM, Grit J, Muller M, et al. Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study. Lancet 2002;360:1361-8.
34. Matsuda M, Yamamoto T, Ishikawa E, Nakai K, Zaboronok A, Takano S, et al. Prognostic factors in glioblastoma multiforme patients receiving high-dose particle radiotherapy or conventional radiotherapy. Br J Radiol 2011;84 Spec No 1:S54-60.
35. Mizumoto M, Yamamoto T, Ishikawa E, Matsuda M, Takano S, Ishikawa H, et al. Proton beam therapy with concurrent chemotherapy for glioblastoma multiforme: comparison of nimustine hydrochloride and temozolomide. J Neurooncol 2016;130:165-70.
36. Wenkel E, Thornton AF, Finkelstein D, Adams J, Lyons S, De La Monte S, et al. Benign meningioma: partially re-

sected, biopsied, and recurrent intracranial tumors treated with combined proton and photon radiotherapy. Int J Radiat Oncol Biol Phys 2000;48:1363-70.
37. McDonald MW, Plankenhorn DA, McMullen KP, Henderson MA, Dropcho EJ, Shah MV, et al. Proton therapy for atypical meningiomas. J Neurooncol 2015;123:123-8.
38. Weber DC, Schneider R, Goitein G, Koch T, Ares C, Geismar JH, et al. Spot scanning-based proton therapy for intracranial meningioma: long-term results from the Paul Scherrer Institute. Int J Radiat Oncol Biol Phys 2012;83:865-71.
39. Maquilan G, Grover S, Alonso-Basanta M, Lustig RA. Acute toxicity profile of patients with low-grade gliomas and meningiomas receiving proton therapy. Am J Clin Oncol 2014;37:438-43.
40. Shih HA, Sherman JC, Nachtigall LB, Colvin MK, Fullerton BC, Daartz J, et al. Proton therapy for low-grade gliomas: results from a prospective trial. Cancer 2015;121:1712-9.
41. Mizumoto M, Tokuuye K, Sugahara S, Nakayama H, Fukumitsu N, Ohara K, et al. Proton beam therapy for hepatocellular carcinoma adjacent to the porta hepatis. Int J Radiat Oncol Biol Phys 2008;71:462-7.
42. Nakayama H, Sugahara S, Fukuda K, Abei M, Shoda J, Sakurai H, et al. Proton beam therapy for hepatocellular carcinoma located adjacent to the alimentary tract. Int J Radiat Oncol Biol Phys 2011;80:992-5.
43. Fukumitsu N, Sugahara S, Nakayama H, Fukuda K, Mizumoto M, Abei M, et al. A prospective study of hypofractionated proton beam therapy for patients with hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2009;74:831-6.
44. Kim TH, Park JW, Kim YJ, Kim BH, Woo SM, Moon SH, et al. Phase I dose-escalation study of proton beam therapy for inoperable hepatocellular carcinoma. Cancer Res Treat 2015;47:34-45.
45. Qi WX, Fu S, Zhang Q, Guo XM. Charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: a systematic review and meta-analysis. Radiother Oncol 2015;114:289-95.
46. Chuong MD, Hallemeier CL, Jabbour SK, Yu J, Badiyan S, Merrell KW, et al. Improving outcomes for esophageal cancer using proton beam therapy. Int J Radiat Oncol Biol Phys 2016;95:488-97.
47. Wang J, Wei C, Tucker SL, Myles B, Palmer M, Hofstetter WL, et al. Predictors of postoperative complications after trimodality therapy for esophageal cancer. Int J Radiat Oncol Biol Phys 2013;86:885-91.
48. Xi M, Xu C, Liao Z, Chang JY, Gomez DR, Jeter M, et al. Comparative outcomes after definitive chemoradiotherapy using proton beam therapy versus intensity modulated radiation therapy for esophageal cancer: a retrospective, single-institutional analysis. Int J Radiat Oncol Biol Phys 2017;99:667-76.
49. Dorr W, Gabrys D. The principles and practice of re-irradiation in clinical oncology: an overview. Clin Oncol (R Coll Radiol) 2018;30:67-72.
50. Nieder C, Langendijk JA, Guckenberger M, Grosu AL. Prospective randomized clinical studies involving reirradiation: lessons learned. Strahlenther Onkol 2016;192:679-86.
51. Verma V, Rwigema JM, Malyapa RS, Regine WF, Simone CB 2nd. Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation. Radiother Oncol 2017;125:21-30.
52. Wu CT, Motegi A, Motegi K, Hotta K, Kohno R, Tachibana H, et al. Dosimetric comparison between proton beam therapy and photon radiation therapy for locally advanced non-small cell lung cancer. Jpn J Clin Oncol 2016;46:1008-14.
53. Ohno T, Oshiro Y, Mizumoto M, Numajiri H, Ishikawa H, Okumura T, et al. Comparison of dose-volume histograms between proton beam and X-ray conformal radiotherapy for locally advanced non-small-cell lung cancer. J Radiat Res 2015;56:128-33.
54. Chang JY, Zhang X, Wang X, Kang Y, Riley B, Bilton S, et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in Stage I or Stage III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2006;65:1087-96.
55. Mesko S, Gomez D. Proton therapy in non-small cell lung cancer. Curr Treat Options Oncol 2018;19:76.
56. Chang JY, Komaki R, Wen HY, De Gracia B, Bluett JB, McAleer MF, et al. Toxicity and patterns of failure of adaptive/ablative proton therapy for early-stage, medically inoperable non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2011;80:1350-7.
57. Chang JY, Zhang W, Komaki R, Choi NC, Chan S, Gomez D, et al. Long-term outcome of phase I/II prospective study of dose-escalated proton therapy for early-stage non-small cell lung cancer. Radiother Oncol 2017;122:274-80.
58. Chi A, Chen H, Wen S, Yan H, Liao Z. Comparison of particle beam therapy and stereotactic body radiotherapy for early stage non-small cell lung cancer: a systematic review and hypothesis-generating meta-analysis. Radiother Oncol 2017;123:346-54.
59. Chang JY, Jabbour SK, De Ruysscher D, Schild SE, Simone CB 2nd, Rengan R, et al. Consensus statement on proton

therapy in early-stage and locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2016;95:505-16.
60. Liao Z, Lee JJ, Komaki R, Gomez DR, O'Reilly MS, Fossella FV, et al. Bayesian adaptive randomization trial of passive scattering proton therapy and intensity-modulated photon radiotherapy for locally advanced non-small-cell lung cancer. J Clin Oncol 2018;36:1813-22.
61. Dutz A, Troost EGC, Lock S. Proton therapy not superior to IMRT in locally advanced NSCLC. Strahlenther Onkol 2018;194:790-3.
62. Cushman TR, Verma V, Rwigema JM. Comparison of proton therapy and intensity modulated photon radiotherapy for locally advanced non-small cell lung cancer: considerations for optimal trial design. J Thorac Dis 2018; 10(Suppl 9):S988-90.
63. Fellin F, Azzeroni R, Maggio A, Lorentini S, Cozzarini C, Di Muzio N, et al. Helical tomotherapy and intensity modulated proton therapy in the treatment of dominant intraprostatic lesion: a treament planning comparison. Radiother Oncol 2013;107:207-12.
64. Vargas C, Fryer A, Mahajan C, Indelicato D, Horne D, Chellini A, et al. Dose-volume comparison of proton therapy and intensity-modulated radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:744-51.
65. Nihei K, Ogino T, Onozawa M, Murayama S, Fuji H, Murakami M, et al. Multi-institutional phase II study of proton beam therapy for organ-confined prostate cancer focusing on the incidence of late rectal toxicities. Int J Radiat Oncol Biol Phys 2011;81:390-6.
66. Coen JJ, Zietman AL, Rossi CJ, Grocela JA, Efstathiou JA, Yan Y, et al. Comparison of high-dose proton radiotherapy and brachytherapy in localized prostate cancer: a case-matched analysis. Int J Radiat Oncol Biol Phys 2012; 82:e25-31.
67. Fang P, Mick R, Deville C, Both S, Bekelman JE, Christodouleas JP, et al. A case-matched study of toxicity outcomes after proton therapy and intensity-modulated radiation therapy for prostate cancer. Cancer 2015;121:1118-27.
68. Sheets NC, Goldin GH, Meyer AM, Wu Y, Chang Y, Sturmer T, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. JAMA 2012; 307:1611-20.
69. Pan HY, Jiang J, Hoffman KE, Tang C, Choi SL, Nguyen QN, et al. Comparative toxicities and cost of intensity-modulated radiotherapy, proton radiation, and stereotactic body radiotherapy among younger men with prostate cancer. J Clin Oncol 2018;36:1823-30.