두경부암의 양성자치료: 현재의 임상 적용 및 발전 방향

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Proton Therapy for Head and Neck Cancer: Current Clinical Applications and Future Direction

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= Abstract =

Intensity-modulated radiation therapy (IMRT) using X-rays is a standard technique implemented for treating head and neck cancer (HNC). Compared to 3D conformal RT, IMRT can significantly reduce the radiation dose to surrounding normal tissues by using a highly conformal dose to the tumor. Proton therapy is a type of RT that uses positively charged particles named protons. Proton therapy has a unique energy deposit (i.e., Bragg peak) and greater biological effectiveness than that of therapy using X-rays. These inherent properties of proton therapy make the technique advantageous for HNC treatment. Recently, advanced techniques such as intensity-modulated proton therapy have further decreased the dose to normal organs with a higher conformal dose to the tumor. The usage of proton therapy for HNC is becoming widespread as the number of operational proton therapy centers has increased worldwide. This paper aims to present the current clinical evidence of proton therapy utility to HNC clinicians through a literature review. It also discusses the challenges associated with proton therapy and prospective development of the technique.

Key Words : Proton therapy · Intensity-modulated proton therapy · Radiation therapy · Head and neck cancer

Introduction

Radiation therapy (RT) is an integral part of a multi-disciplinary approach for the management of head and neck cancer (HNC). It is used as a definitive treatment with or without chemotherapy or adjuvant therapy following surgery or palliative treatment for HNC. Due to the rapid technological development over the last two decades, in-tensity-modulated RT (IMRT) using X-rays has been widely adopted as a standard technique for the treatment of HNC. Compared to 3D conformal RT (3D-CRT), IMRT can reduce the radiation dose to normal organs surrounding the tumor and deliver a highly conformal dose distribution.[1] Many studies have shown that IMRT in HNC reduces acute and late RT-toxicity and improves treatment outcomes.[2-5]

Proton therapy is a type of RT that uses the positively charged nuclei of a hydrogen atom called proton, and not X-rays. Proton therapy has the advantage of reducing the radiation dose to the surrounding normal tissue more effectively than therapy with X-rays due to a unique physical property of proton beams called the Bragg peak.[6,7] In recent years, with an increase in the number of operational proton therapy centers worldwide, more than 220,000 patients have

undergone proton therapy.[8] The growing usage of proton therapy is generating a significant level of clinical evidence regarding the effectiveness of this technique. In particular, proton therapy has shown relatively favorable treatment outcomes and toxicity profiles compared to those of the current standard IMRT technique, and it has been widely used in various clinical settings for the treatment of HNC.[9-12] Furthermore, as proton therapy techniques have evolved, intensity-modulated proton therapy (IMPT), which provides a more conformal radiation dose distribution than standard proton therapy does, has become available.[10] Currently, many prospective cohort or randomized controlled trials of proton therapy are ongoing worldwide. These studies address the issues of clinical efficacy, toxicity, and cost-effectiveness.[13]

This review aims to introduce the basic characteristics of proton therapy to HNC clinicians and to present the current clinical evidence of proton therapy through a literature review. It also discusses current challenges of proton therapy and future directions for this technique.

Physical and biological properties of proton therapy: the Bragg peak and RBE 1.1

Proton beams have a unique energy deposit compared to that of X-rays.[6] X-rays deposit most of the energy near the surface of the body, and the absorbed dose is gradually decreased; however, it continues to deliver the energy until it leaves the patient's body. In contrast, proton beams deposit a small dose when entering the patient's body, and the absorbed dose suddenly increases at a certain depth (i.e., the "Bragg peak"). Beyond this peak, the energy of the proton beam is negligible (the no-exit dose) (Fig. 1). The initial
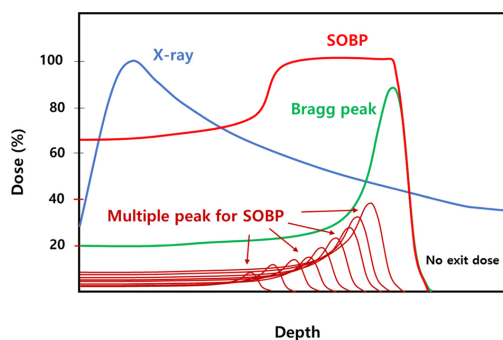
energy of the proton beam generated by a cyclotron determines the depth of the peak, which can precisely control the Bragg peak and localize it at the tumor site (target volume). The Bragg peak is an inherent advantage of proton therapy. Consequently, this technique can spare the surrounding normal tissue to a better degree during a target volume irradiation compared to that with therapy using X-rays.

Proton therapy is characterized by a greater biological effectiveness than that of X-ray therapy.[14] Relative biological effectiveness (RBE) is the ratio of the doses required by two different radiation types to cause the same level of a biological effect. When planning proton therapy, an RBE of 1.1 is generally assumed.[15] This means that X-rays require a 10% higher dose than proton beams do to produce the same biological effect. This RBE of 1.1 is mainly based on experimental in vitro data. However, limited data exist on the RBE of various human cancers and normal tissues. The use of a fixed RBE value of 1.1 for proton therapy imposes the limitation of not representing considerable tumor heterogeneity and different normal tissues.[16,17]

What is IMPT?

As mentioned above, the Bragg peak is a narrow peak of the dose deposit; therefore, different methods are required to cover the whole tumor volume using this narrow peak. Passively scattered proton therapy (PSPT), analogous to 3D-CRT using X-rays, uses a uniform spread-out Bragg peak (SOBP) to cover the tumor volume.[18] For dose conformity, the lateral edge of the beam is blocked, and the distal edge of the beam is modified by a compensator as the tumor shape (Fig. 2). In contrast to PSPT, IMPT, similar
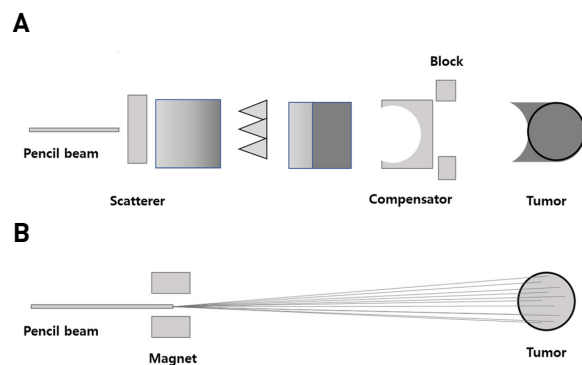

Fig. 1. Physical properties of a proton beam. SOBP, Spread-out Bragg Peak.

Fig. 2. Scattering and scanning techniques of proton therapy. (A) Scattering. (B) Scanning.

to IMRT with X-rays, uses a "pencil beam technique" or "scanning technique."[10] It directly uses a pencil beam from a cyclotron without scattering the beam. It covers the tumor volume by using the electromagnetic control of a pencil beam. Similar to the 3D-printing technique, the irradiated dose can be deposited to each layer of the tumor volume voxel by voxel. The dose distribution can be modulated by the number of protons, beam energy, and off-axis position control of the electromagnetic deflection.

Clinical evidence of proton therapy in HNC

Skull base tumors

Skull base tumors, including chordoma and chondrosarcoma, have been treated with proton therapy for many decades.[19] These tumors require high doses of radiation for effective tumor control, but their location is close to the brain, brainstem, and optic apparatus, limiting the possibility of dose escalation. Many retrospective studies have shown excellent local control (LC) and survival outcomes with proton therapy in the treatment of skull base tumors. A large clinical series of 519 skull base tumor cases was included in a report from the Massachusetts General Hospital in 1999.[20] The 5-year local relapse-free survival rate was 73% for chordoma and 98% for chondrosarcoma. The 5-year overall survival (OS) rates were 80% and 91%, respectively. Similarly, the Paul Scherrer Institute reported the treatment outcomes of a scanning technique in proton therapy.[21] Initially, they reported that the 3-year LC rates were 87.5% and 100% for chordoma (n=28) and chondrosarcoma (n=11), respectively. The long-term follow-up results for chondrosarcoma showed that the actuarial 8-year LC and OS rates were 89.7% and 93.5%, respectively.[22] Grade 3 or higher radiation-induced toxicity was reported in only 7.8% of patients. Recently, the risk of radiation-induced optic neuropathy was analyzed in 216 patients with skull base tumors, including chordoma and chondrosarcoma, who were treated with scanning proton therapy.[23] Radiation-induced optic neuropathy of any grade was observed in only 6.5% of patients with a median follow-up of 5.3 years when the median maximum dose was 59.5 Gy to the optic nerve and 58.8 Gy to the optic chiasm. Although proton therapy has shown better results than those of X-ray therapy historically, recent IMRT or stereotactic body radiation therapy (SBRT) techniques also enable the delivery of high-dose irradiation to skull base tumors and sparing of adjacent critical normal organs. Further studies are required to determine whether IMRT or SBRT results are comparable to those of proton therapy.

Paranasal sinus and nasal cavity cancers

Sinonasal cancers are a rare and heterogeneous group of tumors of various histological types, including squamous cell carcinoma, adenocarcinoma, adenoid cystic carcinoma, neuroendocrine carcinoma, and melanoma. Surgery with or without adjuvant RT is the mainstay of treatment for a resectable tumor, while definitive RT with or without chemotherapy is used for unresectable tumors.[24] Delivering a high dose of RT to the sinonasal site is challenging because of the surrounding normal tissues (both lenses and the retina, optic nerve, optic chiasm, brain, and brainstem). Proton therapy has a dosimetric advantage over X-ray therapy in sparing the surrounding normal organs. A meta-analysis by Patel et al. reported that proton therapy demonstrated higher 5-year OS (relative risk [RR] 1.51, 95% confidence interval [CI] 1.14-1.99; P=0.038) and disease-free survival (DFS) (RR 1.93, 95% CI 1.36 - 2.75; P=0.003) rates than did X-ray therapy.[25] Additionally, a subgroup analysis showed that proton therapy showed significantly higher 5-year DFS (RR, 1.44, 95% CI 1.01-2.05; P=0.045) and locoregional control (LRC) (RR 1.26, 95% CI 1.05-1.51; P=0.011) rates compared to those of IMRT. Although this study demonstrated better treatment outcomes of proton therapy compared to that of X-ray therapy, the meta-analysis included only 43 cohorts from 41 non-comparative observational studies. The Proton Collaborative Group analyzed 69 sinonasal cancer patients who underwent curative proton therapy.[26] This study included 27 patients who underwent re-irradiation. For de novo proton therapy, the 3-year OS, freedom from disease progression (FFDP), and freedom from locoregional recurrence (FFLR) rates were 100%, 77.3%, and 92.9%, respectively. For re-irradiation, the 3-year OS, FFDP, and FFLR rates were 76.2%, 32.1%, and 33.8%, respectively. There were no grade 3 or higher late toxicities. This registry data showed that proton therapy might be an effective and safe treatment for sinonasal cancers. One prospective cohort study reported physician-assessed toxicities (PATs) and pa-

tient-reported outcomes (PROs) of 64 patients with sino-nasal cancer treated with proton therapy.[27] There was only one acute grade 3 neurologic PAT and no grade 3 or higher late PAT reported in the study. Significant worsening of PRO was notable in the acute and subacute periods, but no significant changes from baseline to the chronic period were noted. The 3-year LC, DFS, and OS rates were 88%, 76%, and 82%, respectively. Owing to the rarity of sino-nasal tumors, a randomized controlled trial for proton therapy compared with IMRT may be difficult. However, multiple retrospective and prospective registry studies are currently being conducted.

Re-irradiation in HNC

Recurrent or secondary HNCs often require re-irradiation of tissues that had previously received a substantial radiation dose for salvage or adjuvant treatment. A significant cumulative dose to normal tissue can result in severe or fatal toxicity, including soft tissue or bone necrosis. Thus, radiation oncologists strive to minimize dose overlap with the previously irradiated target volume when planning a re-irradiation.[28-30] Here, proton therapy has an inherent advantage.[31] The MD Anderson Cancer Center (MDACC) reported the results of an initial study on 60 patients who were re-irradiated with proton therapy for HNC.[32] The 1-year LR failure-free survival and OS rates were 68.4% and 83.8%, respectively. Acute grade 3 toxicity occurred in 30% of patients, and the late grade 3 toxicity rate was 16.7% at the 1-year follow-up. Three patients died due to re-irradiation-related side effects. McDonald et al. also reported the clinical outcomes of re-irradiation with proton therapy in HNC cases.[33] Sixty-one patients received a median dose of 66 Gy for microscopic control and 70.2 Gy for gross tumors. The 2-year OS rate was 32.7%, and the 2-year local failure rate was 19.7%. Grade 3 or higher toxicities occurred in 14.7% of patients in the acute period and 24.6% in the late period, and these included three deaths. A systematic review, including four studies of HNC re-irradiation, showed appropriate local/locoregional control and favorable toxicity profiles, including low feeding tube placement rates of 9-10%, of proton therapy versus historical X-ray-based methods.[34] The usage of proton re-irradiation for HNC is still limited, and long-term follow-up studies on large populations will be needed. Therefore, the

MDACC has started a phase II randomized trial to compare the 2-year rate of grade 3 or higher toxicity between SBRT and IMRT/IMPT (NCT03164460).

Oropharyngeal cancer

Several single-institution retrospective studies have demonstrated favorable efficacy and low toxicity of proton therapy for oropharyngeal cancer.[35-37] Lower toxicity compared to that of IMRT suggests that IMPT could be an optimal option for de-intensified treatment of HPV-associated oropharyngeal cancer. The MDACC has reported a series of data on the toxicities of IMPT. The authors compared PRO between the IMPT (n=35) and IMRT groups (n=46).[38] The IMPT group showed better symptom scores for altered taste and appetite during the subacute and chronic phases than did the IMRT group (P<0.048). The MD Anderson Symptom Inventory for Head and Neck Cancer (MDASI-HN) score was better in the IMPT group than in the IMRT group (P =0.013) during the subacute phase. In a case-matched analysis of IMPT (n=50) and IMRT (n=100), IMPT reduced the rates of feeding tube dependency and severe weight loss (odds ratio [OR], 0.44; 95% CI 0.19-1.0; P=0.05 at 3 months after treatment and 0.23; 95% CI 0.07-0.73; P = 0.01 at 1 year after treatment).[39] Recently, the MDACC reported that IMPT decreased xerostomia compared to IMRT in oropharyngeal cancer.[40] The authors compared xerostomia questionnaire scores between the IMRT (n=429) and IMPT groups (n=103), and IMPT resulted in lower rates of moderate to severe xerostomia at 18-24 months (IMPT vs IMRT, 6% vs. 20%; P=0.025) and 24-36 months (IMPT vs IMRT, 6% vs. 20%; P=0.01) than did IMRT. Moreover, it was demonstrated that a decreased irradiated dose and volume to the oral cavity in IMPT was related to less common late xerostomia. Our institution reported the early clinical outcomes of a combination of IMRT and IMPT (n=67) and compared it with those of IMRT alone (n=81) for oropharyngeal cancer.[41] There were no significant differences in OS and PFS between the groups after propensity score matching (PSM) analysis. After matching, the 2-year OS rates were 92.4% and 100%, and the PFS rates were 78.8% and 82.4% for IMRT alone and IMRT/IMPT, respectively. Grade 3 or higher mucositis was less common in the IMRT/IMPT group than in the IMRT alone group (15.8% and 39.5%, respectively; P=0.021).

Although these retrospective results of similar oncologic outcomes and lower toxicity compared to those of IMRT favor the use of IMPT for treating oropharyngeal cancer, no level 1 evidence supporting the use of IMPT exists to date. A randomized phase II/III study is ongoing to clarify the clinical superiority of IMPT to IMRT in the US (NCT01893307). This study initially aimed to compare 70 Gy of IMRT with the same dose of IMPT. The primary endpoint was the rate of late grade 3-5 toxicities within two years. Later, the study design was changed to non-inferiority of IMPT to IMRT with regard to PFS. Two other randomized trials, including the TORPEdO (Toxicity Reduction using Proton beam therapy for Oropharyngeal cancer) trial in the UK and the ARTSCAN V trial at the Lund University Hospital in Sweden (NCT03829033), are also underway.

Uni-lateral irradiation

Well-lateralized HNCs, including salivary gland tumors and some oral cavity or tonsil cancers, have a low risk of contralateral metastasis. In these cases, uni-lateral (or ipsilateral) irradiation is indicated. In such a clinical scenario, proton therapy has dosimetric advantages related to the exit dose nearing zero. Stromberger et al. showed that IMPT delivered significantly lower mean doses to contralateral salivary glands (<0.001-1.1 Gy) than did rotational IMRT techniques such as tomotherapy or volumetric intensity-modulated arc (parotid gland: 6-10 Gy; submandibular gland: 15-20 Gy) when using a total dose of 70.4 Gy to the high-risk clinical target volume.[42] Romesser et al. reported the outcomes of patients with salivary gland tumors and cutaneous squamous cell carcinomas.[43] In 41 patients, proton therapy had a lower rate of acute toxicities, except for radiation dermatitis, than that with IMRT. Compared to IMRT, proton therapy resulted in lower rate of acute grade 2 or higher toxicities in oral mucositis (Proton therapy vs IMRT, 16.7% vs. 52.2%; P=0.019), dysgeusia (Proton therapy vs IMRT, 5.6% vs. 65.2%; P<0.001), and nausea/vomiting (Proton therapy vs IMRT, 11.1% vs. 56.5%; P=0.003), but it showed higher rate of dermatitis (Proton therapy vs IMRT, 100% vs. 73.9%; P<0.032), suggesting a loss of skin-sparing effect in proton therapy. Recently, the MSKCC reported clinical outcomes of proton therapy for major salivary gland tumors.[44] Fifty-one patients with parotid gland tumors and 17 patients with submandibular tumors were analyzed retrospectively. Positive surgical margins were identified in 52.9% of the patients. A median dose of 66.07 cGy was delivered. The 3-year LRC, PFS, and OS rates were 95.1%, 80.7%, and 96.1%, respectively. Grade 2 or higher oral mucositis and dysgeusia occurred in only 5.9% and 2.9% of patients with parotid gland tumors and submandibular tumors, respectively. Grade 2 or higher dermatitis was observed in 69.1% of patients. Therefore, proton therapy resulted in excellent LRC with low toxicity in cases of salivary gland tumor, despite limitations in the retrospective analysis of the heterogeneous group. Currently, a phase II randomized trial is ongoing to compare grade 2 or higher toxicity rate of IMRT to that of proton therapy when 60-66 Gy of unilateral irradiation is delivered for salivary gland cancer, skin cancer, and melanoma (NCT02923570).

Nasopharyngeal cancer

IMRT is the current standard RT technique for nasopharyngeal cancer as it decreases RT-related toxicities and improves therapeutic outcomes compared to 3D-CRT.[45] Several dosimetric comparison studies have shown that proton therapy reduces the irradiated dose to critical normal organs.[46-48] However, this should be further validated in a clinical setting. Holliday et al. performed a matched case-control study to determine if IMPT reduced toxicity compared to IMRT for nasopharyngeal cancer.[49] In a matched cohort of 10 IMPT and 20 IMRT patients, tube feeding was less frequent (IMPT vs. IMRT, 20% vs. 65%; P=0.02) in the IMPT group than in the IMRT group. This effect may have been attributed to a lower mean dose to the oral cavity. Alterio et al. compared the outcomes of IMRT followed by IMPT (a mixed beam, MB) to those of IMRT alone for nasopharyngeal cancer.[50] Twenty-seven patients underwent MB therapy with 54-60 Gy of IMRT followed by a proton boost up to 70-74 Gy. The IMRT alone group received 69.96 Gy. While therapeutic outcomes were comparable between the two groups, acute grade 3 mucositis (MB vs. IMRT, 11% vs. 76%; P=0.002) and grade 2 xerostomia (MB vs. IMRT, 7% vs. 35%; P=0.02) were less frequent in the MB group than in the IMRT alone group. There was no statistically significant difference in late toxicity. Our institution reported early clinical outcomes of tomotherapy/IMPT combination therapy for nasopharyngeal cancer.[51]

Ninety-eight patients underwent definitive CCRT. Among them, 63 patients were treated with tomotherapy alone, while the others were treated with tomotherapy/IMPT combination therapy. Before PSM, grade ≥2 mucositis (tomotherapy vs. tomotherapy/IMPT, 69.8% vs. 45.7%; P=0.019) was found to be less frequent in the tomotherapy/IMPT group than in the tomotherapy group. After PSM, it was still less frequent in the tomotherapy/IMPT group (tomotherapy vs. tomotherapy/IMPT, 62.9% vs. 45.7%; P=0.150), but the difference was not statistically significant. In the whole cohort, LR and distant failures occurred in 9 (9.2%) and 12 (12.2%) patients in the tomotherapy and tomotherapy/IMPT groups, respectively, with no difference between the groups. Our preliminary results showed comparable early therapeutic outcomes with more favorable acute toxicity profiles in the tomotherapy/IMPT combination group than in the tomotherapy group.

Pitfalls of proton therapy for HNC

During proton therapy planning, the exact location of the Bragg peak is crucial for precise delivery of the radiation dose. However, many factors affect the precise position of the Bragg peak. The range of the Bragg peak depends on the energy of the beam, as well as the density of the tissue that the beam passes. In HN sites, the path of the beam usually contains soft tissue, bone, air, and other materials, such as dental prostheses. Furthermore, changes in aeration (e.g., in nasal cavity and paranasal sinus), tumor volume, and body shape due to weight loss during the treatment occur in the majority of patients. These changes can shift the Bragg peak to a different position, which is calculated during the treatment-planning phase in a simulation. As a result, an overdose or underdose to the tumor and/or critical normal tissues can occur during treatment. To compensate for this uncertainty, additional margins and/or robust optimization methods are essential for optimal treatment planning. In addition, adaptive planning, i.e., re-planning to compensate for changes during the course of RT, should be implemented if concerns for under- or overdosing arise.

Uncertainty is also related to the dose calculation method. The treatment planning system (TPS) calculates the dose distribution in the body based on the interaction between the proton energy and matter (body) using the stopping power acquired in simulation computed tomography (CT) scan. If dental or surgical implants are present in the treatment volume, artifacts in the CT scan can cause significant errors in the proton stopping powers used for dose calculation.[52,53] (Fig. 3) In addition, a metal implant such as titanium within the beam path of proton therapy should be calibrated during CT density correction, which may result in a significant dose difference. In such cases, the use of proton therapy is currently not recommended. The Monte Carlo calculation method is known to be a more accurate algorithm for dose calculation; however, it is a time-consuming method. Currently, commercial TPSs used in the clinic facilitate Monte Carlo calculations.

Recent studies have shown an increase in RBE at the distal edge of the SOBP.[54] This means that the biological effect of the proton beam can be enhanced at the distal edge of the beam. Thus, placing critical organs (e.g., the spinal cord and brainstem) at the distal edge of the proton beam should be avoided during treatment planning. Currently, dose calculation is performed based on a fixed RBE of 1.1. Several investigators have reported unexpected brainstem necrosis in pediatric brain tumor patients treated with proton therapy, which may be associated with different RBE issues. Currently, RBE-based dose optimization is under investigation.[55,56]

Proton therapy generally induces more severe radio-dermatitis than X-ray therapy does, especially when the
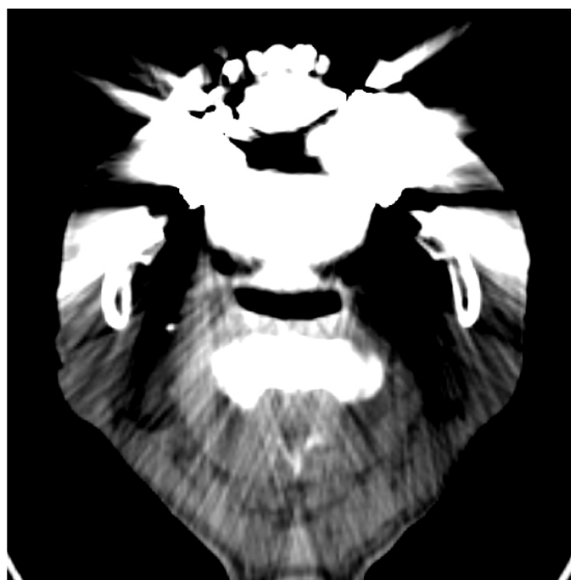

Fig. 3. Computed tomography (CT) artifact due to a dental prosthesis: artifacts in a CT scan can cause significant errors in proton therapy dose calculation.

scattering technique is used. Multiple Bragg peaks of different energies are summed to create the SOBP. In addition, proton therapy uses a limited number of beams compared to X-ray therapy. This can lead to a substantial increase in the entrance dose to the skin. Several studies have demonstrated a higher risk of radiodermatitis in patients treated with proton therapy compared with that of patients treated with X-rays.[36,43,57] Therefore, physicians should carefully monitor any skin reactions that occur during and after proton therapy.

Future directions

Although many retrospective and case-matching analyses have shown that proton therapy is less toxic than IMRT, the use of proton therapy is still limited because of the high cost of construction and management of proton therapy facilities. In Korea, only two institutions use proton therapy. Under these circumstances, clinicians should carefully select patients for whom proton therapy would be most beneficial. A systematic review of cost-effective analyses showed that proton therapy is cost-effective for cases of pediatric brain tumors, well-selected breast cancers, locoregionally advanced non-small cel lung cancer (NSCLC), and high-risk HNCs. However, this is not true for patients with prostate cancer and early stage NSCLC. The results and conclusions of such an economic analysis could be different in countries with other health systems. Future studies should investigate the utility of proton therapy in Korea. Many studies suggest that normal tissue complication probability (NTCP) modeling could help select patients who are most suitable for proton therapy.[58-60] This modeling technique allows estimation of the expected toxicity difference between modalities based on large validated data of irradiated dose and volume of normal tissue and clinical outcomes. For robust results of NTCP modeling, large datasets of dosimetric results of normal tissue and toxicity outcomes are essential. In addition, data showing better efficacy of proton therapy compared to that of IMRT are scarce. Thus, large prospective studies, including randomized controlled studies, should be conducted to validate the clinical outcomes of proton therapy by providing confirmative level 1 evidence.

As mentioned above, there is a controversy around the use of a fixed RBE value of 1.1 during proton therapy planning. RBE can vary depending on the fractionation, depth of protons, and properties of normal tissues or tumors.[16,17] A recent study suggested that the brain-specific RBE is 1.18, based on the temporal lobe changes of 60 NPC cases treated with the scattering technique of proton therapy.[61] An increase in application of proton therapy will help optimize normal tissue and tumor-specific RBE in the future. Furthermore, RBE-optimized planning is currently under investigation.

Proton therapy for HNC is generally delivered with two or three beams at fixed angles. Determining the optimal beam angle is a crucial component for obtaining the best dose distribution. In selected cases, arc therapy, which delivers beams over 360 degrees, may achieve a significant reduction in high and moderate doses to normal tissues, even though arc beams inevitably increase the low dose area of normal tissues.[62] The optimal beam arrangement, including use of arc therapy, requires further investigation. FLASH RT is a new cutting-edge technology. FLASH RT is an ultra-high dose rate RT with a mean dose rate of >40 Gy/s (c.f., the conventional usual dose rate of $\geq$0.01 Gy/s). Many cell- and animal-based studies have shown that FLASH RT using X-ray results in a significant decrease in normal tissue toxicity, making it an interesting treatment modality. Certainly, more research is needed to evaluate this technique in the clinical setting.

Conclusion

The current evidence of proton therapy utility is relatively weak; however, the technique is associated with lower toxicity compared to those of standard treatments. The efficacy of proton therapy should be investigated in well-designed multi-center studies. The issues of cost-effectiveness and uncertainty will be solved with proper patient selection and rapid evolution of technology in the near future.

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