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Review Article

Current role of proton beam therapy in patients with hepatocellular carcinoma

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A B S T R A C T

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, the sixth most common cancer, and the fourth leading cause of cancer-related deaths worldwide. There are curative local treatment options for HCC, including liver transplantation, surgical resection, and radiofrequency ablation, all of which are applicable for a few patients. For advanced HCC, systemic treatments, such as target agents or immunotherapies, are recommended, however, with unsatisfactory efficacy. Therefore, radiation therapy (RT) has been used as an alternative or combination therapy. With the advances of RT technique in image guidance and accurate beam delivery, its applications have increased for the management of HCC. Proton beam therapy (PBT) is a highly advanced RT technique. Since proton beams have unique physical properties with a finite range in the distal direction, PBT has the potential to escalate the radiation dose without a significant increase in the risk of complications compared with X-ray therapy in the treatment of HCC. Various studies have reported favorable oncological outcomes and toxicity risks of PBT for HCC patients. In this review, we discuss the physical and biological properties, technical issues, current clinical data, and future perspectives on PBT for the treatment of HCC patients.

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Keywords: Hepatocellular carcinoma; Proton beam therapy; Radiation therapy

Introduction

Liver cancer is the sixth most common cancer and the fourth leading cause of cancer-related deaths worldwide.¹ Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver, accounting for 75%–85% of primary liver cancers.² It is reported that 72% of HCC cases occurs in Asia, especially in East Asia, which is the highest, followed by 10% in Europe, 7.8% in Africa, and 5.1% in North America.¹ The heterogeneity in the incidence of HCC is a result of the variable prevalences in the etiological factors, including hepatitis viral infection, alcohol, liver cirrhosis, non-alcoholic fatty liver disease, obesity, diabetes, aflatoxin exposure, and hereditary disorders such as hemochromatosis and alpha-1-antitrypsin deficiency.^{3–5}

Surgical resection, liver transplantation, and radiofrequency ablation (RFA) are recommended as liver-directed local modalities for the curation of HCC in the early stages. However, these treatments are often limited due to tumor extent, tumor location, or other patient-related factors.^{6–8} For the treatment of advanced HCC, transarterial chemoembolization (TACE), systemic target

agents, such as sorafenib and regorafenib, or a combination of bevacizumab and atezolizumab are recommended.^{9–11} However, the tumor response rates remain low, and the prognosis of HCC remains unsatisfactory.¹² Therefore, there is the need for a complementary modality for the curation or palliation of HCC. In this trend, radiation therapy (RT) has emerged as alternative or combination treatment approach.^{13–15} In particular, since the durable local control (LC) of primary HCC has been recognized as important for long-term survival, the application of RT for primary HCC has increased, and the relevant clinical evidence has also accumulated.^{13,14,16,17}

While liver-directed irradiation has been very limited due to concerns about radiation-induced liver disease (RILD) in the past, advances in RT techniques have enabled safe liver-directed RT. Among the advances in RT techniques for primary HCC, the introduction of proton beam therapy (PBT) has provided additional innovation in the field of local therapy for primary HCC.^{12,18,19}

Owing to the unique physical properties of PBT which can avoid the unnecessary exposure of radiation in broad area, the PBT is advantageous comparing with X-ray RT in terms of pro-

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tecting the normal liver parenchyma, biliary tract, or the gastrointestinal tract close to the target HCC.^{20,21} For these reasons, the application of PBT for the treatment of primary HCC is increasing, and relevant clinical evidence is enriching.^{12,19} Herein, we review the current status of PBT for HCC and discuss future perspectives.

Physical and Biological Properties of Proton Beam Therapy

X-rays deposit their energy gradually along the beam pathway.²² Therefore, there is inevitable energy deposition on the normal organ located distal to the target lesion in the direction of the beam path; this can potentially induce radiation damage in normal organs. To overcome these unfavorable characteristics in X-ray RT, intensity-modulated RT or volumetric-modulated arc therapy techniques can be introduced to obtain more conformal dose distributions by distributing the beams in various directions. However, these methods can result in low-dose irradiation in a broad area owing to which the normal liver parenchyma may be

affected.^{23–25} However, a proton beam path in the body shows a Bragg peak, which is a peak-like rise and drop in energy deposition. Therefore, the proton beam has a finite range of energy deposition and loses most of its energy within a very short distance at the end of the beam range. This range is determined by the energy of the proton and the density of the material in the beam path.²⁶ The Bragg peaks can be spread to lead to a wider dosimetric coverage, which is called “spread-out Bragg peak (SOBP).”²² Fig. 1 shows the comparison of the energy deposition as the beam passes through the body between X-ray and proton beams. Due to the absence of an exit dose, PBT shows no proton beam exposure in the normal liver parenchyma or gastrointestinal tract located distal to the target lesion in the direction of the proton beam pathway, thereby, leading to superior dosimetry compared with X-ray RT.^{27,28} The dosimetric distributions according to the technique of RT were shown in Fig. 2. Owing to this physical property, PBT can potentially reduce the risk of RILD and increase the radiation dose safely.²⁹

The biological effect of RT starts with double strand deoxyribose-nucleotide acid (DNA) breakage by a chemical reaction triggered by radiation. The radiation used in RT has the potential for atomic ionization, which causes the generation of radical oxygen species, causing indirect or direct DNA damage.³⁰ Between PBT and X-ray RT, the efficiency of DNA damage is higher in PBT because PBT induces a more direct attack on DNA, leading to clustered DNA damage. Therefore, PBT is more biologically effective at a given prescription dose than X-rays³¹ with a relative biological effectiveness (RBE) of 1.1, which is defined as the ratio of the photon dose to the proton dose for a given level of effect.³²

Technical Issues of Proton Beam Therapy for Hepatocellular Carcinoma

PBT adopts two types of beam techniques: passive scattering (PS) and pencil-beam scanning (PBS) methods.³³ The former is a technique of broadening the mono-energetic proton beams laterally, adequate to cover the target lesions using a ridge filter, while the latter is used for the delivery of narrow proton beams using

Fig. 1. Comparison of the energy deposition as the beam passes through the body between X-ray and proton beam. SOBP, spread-out Bragg peak.

Fig. 2. Radiation dose distribution according to radiation therapy (RT) techniques. Axial views of (A) 3-dimensional conformal RT; (B) volumetric arc therapy; (C) proton beam therapy (PBT) with passive scattering; (D) PBT with pencil-beam scanning technique. X-ray RT (A, B) results in low dose spread in wide area outside the target lesion which are not shown in the PBT plans (C, D).

the magnetic system, deflecting each beam to encompass a cross-sectional area of the target.³³ The PS system is an earlier form of PBT; however, nozzles for PBS are widely equipped in recently constructed PBT centers.³⁴ The PBS technique enables intensity modulation, which can facilitate more conformal dosimetry, especially in the treatment of complicated-shaped tumors compared with PS.³⁵ The clinical data of PBT for primary HCC are mostly focused on the PS beam module.

Another technical issue is the motion control of primary HCC during PBT. Proton beams have unique physical properties, including a finite range in the distal direction, which can be affected by the spatial and temporal variations in the material densities.²⁶ There are many factors that induce variations in material densities, including internal organ motion, body shape change, tissue inhomogeneity, and uncertainty in calculations of density and dosimetry.³⁶ In particular, the liver is prone to uncertainties in PBT resulting from organ motion because the interface of air and soft tissue near the diaphragmatic dome can critically affect the dosimetry.³⁷ Therefore, it is important to control the uncertainty from organ motion, mainly by the patients' breath. One of the methods is the breath-hold technique, which can minimize the effect of temporal motion of the liver. However, breath-holding is

feasible only for a limited number of patients. Instead, the method of PBT covering the entire trajectory of the target motion under the condition of regular breathing is usually chosen. While this method can provide robust proton beam delivery to the target lesion, it can potentially result in unnecessary irradiation of normal tissues due to the large field size. To overcome these limitations, respiratory gating or abdominal compression is adopted to reduce the PBT fields leading to normal organs near the target lesion, such as normal liver parenchyma or gastrointestinal tract.^{38,39}

Since these methodologies require patient cooperation, appropriate patient selection is required. Furthermore, image-guidance techniques for monitoring the location of tumors or normal organs during PBT sessions are also needed. For image-guidance PBT, orthogonal kilovoltage (kV) X-ray images or cone beam computed tomography (CBCT) are utilized in the treatment room.¹⁸ However, primary HCC and the surrounding normal liver parenchyma or other soft tissues are hardly distinguished by these modalities. To improve the performance of image guidance, radio-opaque fiducial markers, which can be detected in orthogonal kV X-ray images or CBCTs, are often used for more reliable and accurate image guidance.⁴⁰

Table 1 Selected Studies of Proton Beam Therapy for Hepatocellular Carcinoma

Study (published year)	Patients (n)	Tumor size (cm)	MVI (%)	RT regimen (GyRBE/fractions)	LC	PFS	OS
PMRC (2008) ⁴¹	53	≤ 3: 25% > 3 to < 5: 34% ≥ 5 to < 10: 34% ≥ 10: 8%	28	72.6/22	94% at 2 yr 86% at 3 yr	38% at 2 yr 25% at 3 yr	57% at 2 yr 45% at 3 yr
PMRC (2009) ⁴²	51	Median 2.8 (range, 0.8–9.3) ≤ 5: 88% > 5: 12%	NA	66.0/10	95% at 3 yr 88% at 5 yr	NA	49% at 3 yr 39% at 5 yr
PMRC (2009) ⁴³	318	NA	14	66.0/10: 32.7% 72.6/22: 26.7% 77.0/35: 20.8%	NA	NA	65% at 3 yr 45% at 5 yr
PMRC (2011) ⁴⁴	47	NA	15	72.6/22: 34.0% 77.0/35: 27.7%	88% at 3 yr 88% at 4 yr	IHRFS 66% at 1 yr 40% at 1 yr 17% at 4 yr	50% at 3 yr 34% at 4 yr
Loma Linda (2011) ⁴⁵	76	Mean 5.5 ≤ 2: 7% > 2 to < 5: 45% ≥ 5 to < 10: 43% ≥ 10: 5%	5	63.0/15	70% at 3 yr	80%	Median 36 mo
NCC (2015) ⁴⁸	27	≤ 5: 81% > 5: 19%	NA	60.0/20: 29.6% 66.0/22: 25.9% 72.0/24: 44.4%	80% at 3 yr 64% at 5 yr	17% at 3 yr 0% at 5 yr	56% at 3 yr 42% at 5 yr
Mul-institutions in US (2016) ⁴⁷	44	Median 5.0 (range, 1.9–12.0)	30	Median 58.05/15 (range, 15.1–67.5/15)	95% at 2 yr	56% at 1 yr 40% at 2 yr	77% at 1 yr 63% at 2 yr
NCC (2019) ⁷³	243	≤ 2: 47.3% > 2: 52.7%	82.5	50.0/10: 16.5% 62.5/10: 24.7% 66/10: 58.8%	54.6% at 5 yr 94.7% at 5 yr 92.4% at 5 yr	NA	48.1% at 5 yr
SMC (2020) ³⁵	172	≤ 2: 43.0% > 2: 57.0%	31.4	50/10: 19.2% 60–66/10: 67.4% 50–60/5: 4.7% Others: 8.7%	85.5% at 2 yr	NA	86.4% at 2 yr
NCC (2021) ⁴⁹	80	< 2: 43.0% ≥ 2: 57.0%	0	66.0/10	85.8% at 4 yr	15.6% at 4 yr	74.0% at 4 yr

MVI, macrovascular invasion; RT, radiation therapy; GyRBE, Gy relative biological effectiveness; LC, local control; PFS, progression-free survival; OS, overall survival; PMRC, Proton Medical Research Center; NA, not applicable; IHRFS, intrahepatic recurrence-free survival; NCC, National Cancer Center in South Korea; US, United States; SMC, Samsung Medical Center.

Clinical Outcomes of Proton Beam Therapy for Hepatocellular Carcinoma

The clinical outcomes of PBT for primary HCC have been reported mainly in eastern Asia and the United States (US), where the incidence of HCC is high or PBT is relatively widely used.^{18,19} Previous clinical results of PBT for primary HCC are summarized in Table 1. Early data, particularly retrospective data, were mainly published by the Proton Medical Research Center (PMRC) of the University of Tsukuba, Japan. The group adopted three different dose schemes according to tumor location with consideration of the porta hepatis and gastrointestinal tract.^{29,41–44} A 66 Gy relative biological effectiveness (GyRBE) in 10 fractions was prescribed for peripheral tumors greater than 2 cm from both the porta hepatis and the gastrointestinal tract. For tumors within 2 cm of the gastrointestinal tract, 77 GyRBE in 35 fractions was prescribed. Those within 2 cm of the porta hepatis were treated with 72.6 GyRBE in 22 fractions. The LC rates were reported to be 88%–95% with an overall survival (OS) of 45%–65%.^{29,41–44}

In the US, clinical data from Loma Linda University regarding a prospective phase II study on PBT for HCC patients with liver cirrhosis was reported.⁴⁵ This study revealed that patients who met the Milan criteria showed better OS and progression-free survival (PFS) of 70% and 60% at 3 years, respectively. In addition, researchers at Loma Linda University have also reported the results of a randomized trial of TACE versus PBT.⁴⁶ In this study, HCC patients who met the Milan or University of California San Francisco transplant criteria were enrolled and randomized to either TACE ($n = 36$) or PBT ($n = 33$) with a dose scheme of 70.2 GyRBE in 15 fractions. Although the data were preliminary, the results favored PBT in terms of 2-year LC (88% vs 45%) and PFS (48% vs 31%). Another multi-institutional phase II trial of PBT for primary liver cancer, including HCC ($n = 44$) and cholangiocarcinoma ($n = 37$), was performed in the US.⁴⁷ While the researchers intended to prescribe 67.6 GyRBE in 15 fractions for tumors more than 2 cm from the porta hepatis and 58.05 GyRBE in 15 fractions for those within 2 cm of the porta hepatis, the actual median dose delivered was 58.05 GyRBE (range, 15.1–67.5 GyRBE) in 15 fractions. For the HCC subgroup, the 2-year LC and OS rates were 95% and 63%, respectively.

In South Korea, although there are only two institutes that perform PBT for primary HCC, relevant clinical studies have been actively performed. The National Cancer Center (NCC) has conducted a phase I dose-escalation study on 60 GyRBE in 20 fractions, 66 GyRBE in 22 fractions, and 72 GyRBE in 24 fractions.⁴⁸ The complete response (CR) rates of PBT were 62.5%, 57.1%, and 100%, respectively, with increasing doses. In addition, the 3-year LC rate was 79.9%, which was significantly higher in patients with CR than in those without CR (90% vs 40%, $P = 0.003$). None of the patients experienced liver toxicity greater than grade 2. Recently, the NCC conducted the first phase III randomized controlled trial evaluating the clinical outcomes of PBT vs RFA and reported that PBT was non-inferior to RFA in terms of LC (92.8% in PBT vs 83.2% in RFA with $P < 0.001$ for intention-to-treatment population) and safety.⁴⁹ Furthermore, the rate of switching the modality between PBT and RFA was higher in patients who were initially allocated to be treated with RFA but their treatment was changed to PBT, compared to the opposite cases. Another institute in South Korea, Samsung Medical Center (SMC), also reported the outcomes of PBT for primary HCC.³⁵ Researchers from SMC compared PS and PBS PBT for primary HCC with propensity score matching and reported a comparable 2-year LC (83.3% in the PS group vs 81.4% in the PBS group; $P = 0.471$) and OS (87.1% vs

83.2%; $P = 0.766$). This result implies that PBS PBT, which has the potential to reduce the oncologic outcome because of the interplay effect resulting from the movement of the target during proton beam scanning, can also show excellent outcome. This is the first study reporting the feasibility of PBS PBT for primary HCC and its clinical importance, considering that nozzles for PBS are increasingly being equipped in newly constructed PBT centers.

Fig. 3. An example of radiation dose distribution of 6,600 cGy or cGyRBE in 10 fractions for the patient with centrally located hepatocellular carcinoma invading the inferior vena cava according to radiation therapy techniques. (A) Volumetric modulated arc therapy (VMAT); (B) proton beam therapy (PBT) with pencil-beam technique; (C) comparison of dose-volume histograms (DVHs) for VMAT (dot lines) and PBT (solid lines). The orange and sky-blue lines represent the DVHs for gross tumor volume, and clinical target volume, respectively. The yellow and red lines represent the DVHs for esophagogastric junction and liver, respectively. The irradiated area in the liver parenchyma is significantly smaller in the PBT plan (B) comparing with VMAT plan (A). The DVH shows that the irradiation in the liver and esophagogastric junction is higher in the VMAT plan comparing with PBT (C).

Proton Beam Therapy for Hepatocellular Carcinoma in Special Clinical Situations

Despite the various reports showing the excellent outcomes of PBT for primary HCC, the indications for PBT have not yet been determined. Considering the dosimetric advantages compared with X-ray RT, PBT can potentially be applied to more complicated cases ineligible for other liver-directed local modalities.

PBT can be used in selected HCC patients with declined liver function, which limits other liver-directed local modalities, to spare untreated normal liver parenchyma.⁵⁰ The PMRC at Tsukuba University has reported on the clinical outcomes of PBT for HCC patients with Child-Pugh class C.⁵¹ The researchers prescribed a median PBT dose of 72 GyRBE in 16 fractions (range, 50–84 GyRBE in 10–24 fractions) and achieved a crude LC rate of 95% over a median follow-up of 17 months, with a 2-year OS of 42% and without any therapy-related toxicities of grade ≥ 3 or deterioration of the Child-Pugh score. Of the 19 patients, 14 exhibited an improved Child-Pugh score. Researchers from the PMRC also argue that PBT is feasible even in selected patients with uncontrollable ascites with 24 GyRBE in a single fraction.³⁷ Although the relevant data regarding PBT for HCC patients with poor liver function are very limited and the sample size is very small, PBT is an option when liver-directed local therapy is required while other local modalities are not feasible.

In the same context, PBT can be a salvage modality for HCC patients who have a history of liver-directed local treatment. While repetitive liver-directed local treatments tend to be very frequent in HCC patients, previous local treatments can reduce the reserve of liver function, and the additional applications of liver-directed local treatment are sometimes limited. Due to the power of PBT in sparing the residual normal liver parenchyma, PBT can be a good option. In particular, for HCC patients who have experienced hepatic irradiation and are at risk of RILD, PBT can provide an opportunity for effective and safe treatments. Relevant data were also published from the PMRC, showing the effectiveness and safety of re-irradiation of PBT, especially for HCC patients with peripheral tumors and Child-Pugh class A.⁵²

The strength of PBT can be observed in patients with HCC located in the central or periportal areas. Local treatment of centrally located HCCs is challenging because of the difficulty in the approach or inefficiency of the treatment, such as RFA, which is affected by the heat sink effect of the blood flow inside the portal vein. Furthermore, the application of RT for centrally located or periportal HCCs is challenging due to the concern of intrahepatic irradiation or the toxicity of adjacent gastrointestinal tract.⁵³ How-

ever, the PBT can provide dosimetric advantage in the treatment of the central HCC comparing with X-ray RT (Fig. 3). Researchers from SMC have reported the treatment outcomes of high-dose hypofractionated PBT for perihilar HCC with a 2-year LC higher than 85% and a low rate of PBT-related biliary complication of only 3.8%.⁵³

Finally, PBT shows good oncological outcomes for the treatment of large HCCs. Patients with large HCCs are frequently excluded from ablation therapies or liver transplantation.^{54–56} Although surgery can be a treatment option for large HCCs, the recurrence rates are reportedly high.^{57–59} For X-ray RT, as the tumor size increases, the irradiated volume in the normal liver also increases; consequently, sufficient dose escalation is limited.^{60,61} In contrast, PBT can cover a large volume of HCC without a significant increase in the risk of hepatic toxicity. Regarding the PBT for large HCC, the PMRC reported the clinical results from 22 patients with HCC of sizes more than 10 cm.⁶² The median tumor size was 11 cm (range, 10–14 cm) and median dose was 72.6 GyRBE in 22 fractions (range, 47.3–89.1 GyRBE in 10–35 fractions). The LC and OS at 2 years were 87% and 36%, respectively, with an RILD rate of 22.7%, although, the rate of RILD was high in selected cases with large HCC PBT.

Toxicity after Proton Beam Therapy

As mentioned above, the rates of hepatic toxicities after PBT for primary HCC, including RILD or biliary complications, have been reported to be very low. However, because proton beam exposure in the beam pathway is inevitable, there may be some complications in the normal tissue at the proximal edge of the proton beam. Furthermore, although the RBE of PBT is regarded as a fixed value of 1.1, the actual biological effectiveness may vary through the beam path and increase at the distal edge of the Bragg peak.⁶³ Therefore, caution should be exercised to spare the normal organ near the distal edge of the beam.

One of the toxicities after PBT requiring concern is chest wall toxicity.^{64,65} As the prescribed dose is escalated in the treatment of HCC by PBT, the irradiation dose delivered to the chest wall is also frequently increased, especially when the HCC proximal to the chest wall is treated by PBT.¹⁸ Toxicities in the chest wall present as chest wall pain due to radiation-induced myositis or rib fractures. The radiation-induced myositis can be detected on T2-weighted magnetic resonance imaging scan showing high signal intensity at the site of myositis which is included in the previous irradiated area.^{64,66} The example of radiologic finding for the PBT-induced myositis at chest wall is shown in Fig. 4. Researchers

Fig. 4. An example of myositis in the chest wall after the proton beam therapy (PBT) for primary hepatocellular carcinoma (HCC). A 62-year-old male patient with HCC in right lobe (A) received pencil-beam scanning PBT with 6,000 cGyRBE in 10 fractions (B). He performed magnetic resonance imaging (MRI) scan due to the right anterior chest wall pain, about 8 months after the completion of the PBT. In the T2-weighted MRI, there was high signal intensity at the right anterior chest wall (white arrows) which had been irradiated during the PBT (C). After administration of oral steroid, the symptom was subsided.

Table 2 Currently Ongoing Clinical Trials of Proton Beam Therapy for Hepatocellular Carcinoma

National clinical trial number	Country	Design	Condition	Intervention
NCT02640924	Taiwan	Phase III	Tumor size > 3 cm, ≤ 7 cm	Arm 1: Proton beam therapy Arm 2: Radiofrequency ablation
NCT03186898	United States	Phase III	Tumor size ≥ 1 cm, ≤ 15 cm	Arm 1: Proton beam therapy Arm 2: Radiofrequency ablation
NCT04805788	United States	Phase II	Tumor size ≥ 1 cm, ≤ 15 cm	Single arm: Stereotactic proton beam therapy

at the MD Anderson Cancer Center investigated the chest wall toxicities of 135 patients with lung or liver cancer after X-ray RT or PBT.⁶⁷ Of the total cohort, 20 patients had grade 1 chest wall pain, and one patient had grade 2 chest wall pain. The dosimetric factor of $V_{40\text{ Gy}} \geq 150\text{ cm}^3$ on the chest wall was identified as a predictor of chest wall toxicity. There were other reports from the University of Washington and other institutions regarding chest wall toxicity after PBT.⁶⁵ In the report, chest wall pain of grade ≥ 2 occurred in 30% of patients, without any radiographic evidence of rib fracture. The researchers also identified the dosimetric factors, $V_{47\text{ Gy}} > 20\text{ cm}^3$, $V_{50\text{ Gy}} > 17\text{ cm}^3$, and $V_{58\text{ Gy}} > 8\text{ cm}^3$, associated with higher rates of chest wall toxicity. In addition, the PMRC reported the incidence of rib fracture to be 16% after PBT of 66 GyRBE in 10 fractions.⁶⁸ In this study, $V_{60\text{ Gy}}$ was identified as a predictor of the risk of rib fracture after hypofractionated PBT. These data are heterogeneous, and the dosimetric parameters are extremely diverse for clinicians to establish a consensus for dose constraints on the chest wall. However, care to mitigate chest wall toxicity is necessary in PBT for primary HCC.

In addition to chest wall toxicity, toxicity in the gastrointestinal tract is an important issue. Owing to the high rates of portal hypertensive gastroduodenopathy in HCC patients, the vulnerability to irradiation of the gastrointestinal tract is potentially higher than that in patients with other malignancies.^{69,70} Although the reported rates for toxicities of the gastrointestinal tract were low (less than 7%–10%), the toxicity can be severe. In particular, the gastrointestinal tract located near the distal edge of the SOBP is potentially at risk because of the uncertainty of the proton beam range, the potentially high RBE at the distal edge, and the fall off of the SOBP. There is no specific report regarding the relationship between high RBE at the distal SOBP and gastrointestinal toxicities. However, this issue has been critically reported in the field of PBT for brain tumors, showing that the risk of brain necrosis increased at the distal edge effects of PBT, especially the brain stem.^{71,72} Therefore, special caution is necessary when the location of the gastrointestinal tract is near the distal edge of the SOBP. To reduce the risk of gastrointestinal toxicity, it is necessary to establish a risk-adapted PBT protocol based on the proximity to the gastrointestinal organs.⁷³

Future Perspectives

As a recently reported randomized controlled trial of PBT vs. RFA for recurrent HCC,⁴⁹ other prospective trials comparing PBT with RFA, TACE, or sorafenib are ongoing as shown in Table 2. Furthermore, single-arm phase II studies of PBT for HCC in various disease statuses, such as HCC with portal vein tumor thrombosis or unresectable HCC, are ongoing. From the results, it is expected that appropriate indications for PBT in primary HCC should be established.

The role of RT as an immune modulator is currently receiving increasing interest.⁷⁴ As regards the effect of radiation on immune modulation, the role of radiation in enhancing immunotherapy

is actively being investigated in various solid tumors. For HCC, immune checkpoint inhibitors have also been introduced, and the role of radiation has also been studied.^{75,76} Since PBT has no exit beam, PBT is potentially effective in protecting lymphocytes, which are important in immune reactions but vulnerable to radiation due to their high sensitivity to radiation.^{77,78} Therefore, for the combination therapy of RT and immunotherapy, PBT can be a good option to maximize efficacy. However, further clinical studies are necessary.

As the concept of oligometastases or oligoprogression is becoming more emphasized, PBT can be an excellent option for the LC of oligometastatic lesions in HCC patients.⁷⁹ Although metastatic diseases are systemic and palliative systemic treatments are usually the mainstay of treatment for metastatic diseases, oligometastatic diseases are considered curable by definitive local treatment.⁷⁹ Owing to its physical properties, PBT can deliver an ablative dose with minimal increase in risk of complications in many cases, PBT can provide opportunities for curation in oligometastatic HCC patients.⁸⁰ Further investigation to evaluate the efficacy of PBT would be worthwhile.

Conclusion

PBT has significant dosimetric advantages compared with X-ray therapy, and these advantages lead to a high level of efficacy and safety. Furthermore, compared with other local modalities, the oncologic outcomes of PBT seem to be comparable in HCC patients, and PBT can cover some cases in which other local modalities are not applicable due to tumor location or patient status. With the immune modulation effect, various studies comparing other local modalities are ongoing, and we expect that PBT will become a mainstay of local treatment of HCC in the near future.

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Conflicts of Interest

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

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