

# World Journal of *Gastroenterology*

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## Proton therapy for hepatocellular carcinoma: Current knowledges and future perspectives

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### Abstract

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death, as few patients can be treated with currently available curative local modalities. In patients with HCC where curative modalities are not feasible, radiation therapy (RT) has emerged as an alternative or combination therapy. With the development of various technologies, RT has been increasingly used for the management of HCC. Among these advances, proton beam therapy (PBT) has several unique physical properties that give it a finite range in a distal direction, and thus no exit dose along the beam path. Therefore, PBT has dosimetric advantages compared with X-ray therapy for the treatment of HCC. Indeed, various reports in the literature have described the favorable clinical outcomes and improved safety of PBT for HCC patients compared with X-ray therapy. However, there are some technical issues regarding the use of PBT in HCC, including uncertainty of organ motion and inaccuracy during calculation of tissue density and beam range, all of which may reduce the robustness of a PBT treatment plan. In this review, we discuss the physical properties, current clinical data, technical issues, and future perspectives on PBT for the treatment of HCC.

**Key words:** Radiation therapy; Hepatocellular carcinoma; Proton beam therapy; X-ray therapy

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**Core tip:** Radiation therapy (RT) is being increasingly

utilized for the treatment of hepatocellular carcinoma (HCC). As RT technology develops, proton beam therapy (PBT) has emerged as a method that affords dosimetric advantages compared with X-ray therapy due to its physical properties, including lack of an exit dose along the beam path. Clinical experience with PBT for HCC is accumulating rapidly, and the effectiveness and safety of PBT has been validated. In this review, we discuss the physical properties, current clinical data, technical issues, and future perspectives on PBT for the treatment of HCC.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver, accounting for 90% of all liver cancers<sup>[1]</sup>. HCC is the fifth most common cancer worldwide and the second leading cause of cancer-related death<sup>[2]</sup>. Although there is a relatively high incidence of HCC in South-East Asia, rates have also been increasing in North America and Western Europe<sup>[3]</sup>. HCC has various etiological factors including hepatitis B and C infection, alcohol consumption, liver cirrhosis, non-alcoholic fatty liver disease, obesity, diabetes, aflatoxin exposure, and hereditary disorders such as hemochromatosis and alpha-1-antitrypsin deficiency<sup>[4-6]</sup>.

Although there have been improvements in the management of HCC<sup>[7,8]</sup>, application of curative local modalities such as surgical resection, transplantation, and radiofrequency ablation are often limited due to tumor extent, tumor location, or other patient-related factors<sup>[9-11]</sup>. Therefore, the prognosis of HCC continues to be unsatisfactory, with a five-year survival of less than 20%, despite improvement in overall survival (OS) by non-curative modalities including chemoembolization and sorafenib<sup>[12]</sup>. For this reason, radiation therapy (RT) as a local modality has emerged as an alternative/com-bination treatment approach<sup>[13-15]</sup>. As the prognosis of HCC depends on sustained control of tumor size<sup>[16]</sup>, there has been growing interest in use of external beam RT<sup>[13,14,17,18]</sup>. More specifically, advances in proton beam therapy (PBT) have brought additional innovation to the field of RT for the treatment of HCC<sup>[12,19,20]</sup>.

PBT has a dosimetric advantage compared to X-ray therapy due to the physical properties of the technique<sup>[21,22]</sup>. Therefore, PBT is potentially more beneficial in sparing organs-at risk (OARs), especially for cases where the tumor is proximal to OARs. For liver tumors, the tolerance of surrounding normal liver, biliary tracts, and gastrointestinal (GI) structures is the main limiting factor for dose escalation<sup>[23,24]</sup>. For these reasons, there has been increasing interest in the use of PBT for treating liver

tumors, and clinical experiences and evidences regarding the advantages of PBT continue to accumulate<sup>[12,20,25,26]</sup>. Here, we review the current knowledge and future perspectives on PBT for HCC.

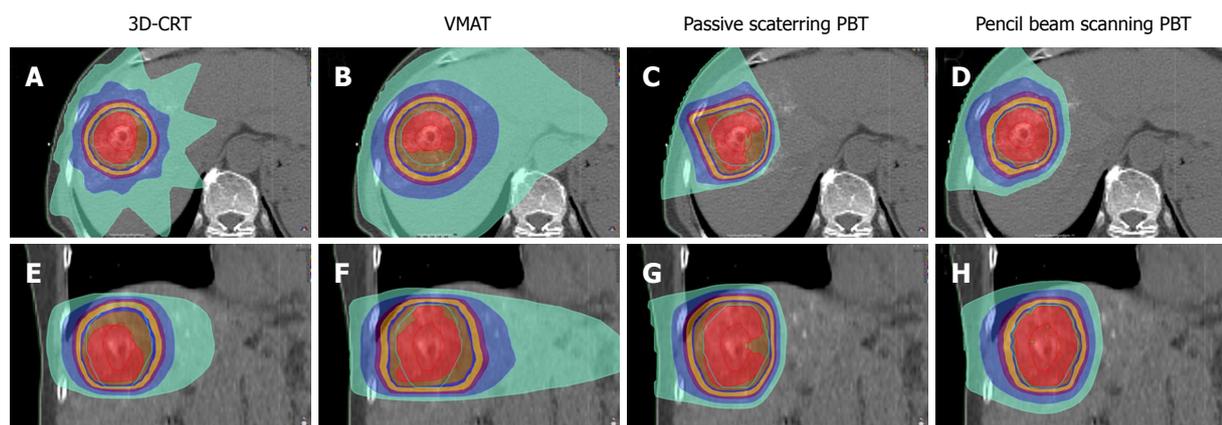
## PHYSICAL CHARACTERISTICS AND DOSIMETRIC ADVANTAGES OF PBT

The deposition of X-ray dose decreases gradually along the beam path with increasing beam depth<sup>[27]</sup>. As a result, an exit dose is inevitably deposited in adjacent normal tissues. Intensity-modulated RT (IMRT) or volumetric-modulated arc therapy (VMAT) techniques can be used to obtain more conformal dose distributions; however, these methods are still unable to avoid low-dose deposition at the distal area of the beam path. Because of these unfavorable characteristics, RT has had a very limited role in the treatment of HCC in patients whose livers are mostly cirrhotic or poorly functioning, as these patients are most vulnerable to radiation-induced liver disease (RILD)<sup>[28,29]</sup>.

Compared to X-ray beams, a 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 (Figure 1). These results in a sharp rise and fall in energy absorption, known as the Bragg peak. Bragg peaks can be superposed to provide wider depth coverage, so-called "spread-out Bragg peak beams (SOBP)"<sup>[27]</sup>. Furthermore, due to the absence of an exit dose, PBT has dosimetric advantages compared with 3-dimensional conformal RT or even IMRT or VMAT<sup>[21,22]</sup>. Therefore, PBT has the potential to both decrease the risk of RILD and allow for safer escalation of radiation dose<sup>[30]</sup>.

## BIOLOGICAL CHARACTERISTICS OF PBT

The proton beams cause deoxyribose-nucleotide acid (DNA) damage and cytotoxicity by direct collisions with DNA molecules and by the generation of radical oxygen specimen (ROS) causing indirect DNA damage<sup>[31]</sup>. The efficiency of DNA damage is better for PBT than X-ray therapy due to relatively high energies of PBT used for RT<sup>[32]</sup>. Therefore, the PBT is more effect for a given prescription dose than X-rays<sup>[33]</sup>. The concept of the relative biological effectiveness (RBE) is useful to consider this issue. The definition of RBE is the ratio of the proton dose to the photon dose for a given level of effect, and proton has higher value of RBE than X-ray. The RBE of the proton beams depends on various parameters such as dose, considered endpoint, linear energy transfer,  $\alpha/\beta$  of the tumor or tissue, and the positions of the SOBP<sup>[34]</sup>. There is trends that the RBE increases as decreasing  $\alpha/\beta$ , decreasing dose, increasing LET, and approaching the distal edge and distal fall-off of the SOBP<sup>[35-37]</sup>. Because these dependencies are considered negligible compared with the uncertainties for tissue density<sup>[33]</sup>, beam ranges, and patients, up to date, fixed value of 1.1 which is



**Figure 1** Radiation dose distribution according to technique of radiation therapy. Axial views of A: 3-dimensional conformal radiation therapy (3D-CRT); B: Volumetric arc therapy (VMAT); C: Passive scattering proton beam therapy (PBT); D: Pencil beam scanning PBT; sagittal views of E: 3D-CRT; F: VMAT; G: PBT with wobbling technique; H: PBT with pencil beam scanning technique. There are low dose distributions in 3D-CRT (A, E) and VMAT (B, F) due to the exit dose.

based on various *in vivo* and *in vitro* data has been commonly used as universal value of RBE for proton beam<sup>[38]</sup>. However, the clinical impact of variability in RBE has been being investigated and with precise modeling variable RBE can be used for further optimization of PBT plan<sup>[33]</sup>.

## CLINICAL OUTCOMES OF PBT FOR HCC

The majority of clinical outcomes regarding PBT for HCC have been reported from Eastern Asia and the United States (US) due to the high incidence of HCC and long-term experience in the clinical use of PBT<sup>[19,20]</sup>. An overview of the published studies of PBT for HCC is summarized in Table 1. The Proton Medical Research Center (PMRC) of the University of Tsukuba, Japan, developed three PBT protocols according to tumor location with respect to the porta hepatis and GI OARs<sup>[30,39-42]</sup>. Specifically, for peripheral tumors > 2 cm from both GI tract and the porta hepatis, a 66-Gy relative biologic equivalent (GyE) in 10 fractions is delivered. Likewise, tumors within 2 cm of the GI tract can be treated with 77.0 GyE in 35 fractions, while those within 2 cm of the porta hepatis are treated with 72.6 GyE in 22 fractions. In those studies, the authors reported local control (LC) in the range of 88% to 95%, which was similar among various dose and fractionations. In addition, the authors reported 3-year OS rates ranging from 45% to 65%<sup>[30,39-42]</sup>. They also found that liver function was a significant prognostic factor associated with OS rates, and that OS was better in patients with a Child-Pugh (CP) A score compared with CP B.

In the US, researchers at Loma Linda University performed a phase II trial of PBT in 76 patients with HCC and liver cirrhosis<sup>[43]</sup>. Patients with extrahepatic metastases, tense ascites, or more than three tumors were excluded. The progression-free survival (PFS) at 3 years for patients meeting the Milan criteria was 60%. Liver transplantation was performed in 18 patients whose eventual 3-year OS rate was 70%; however, the OS rate of patients who did not undergo liver transplantation

was 10%. In these patients, multivariate analysis identified the Milan criteria as the only independent factor associated with OS.

Researchers from Loma Linda University also recently reported a preliminary analysis of a randomized trial of TACE versus PBT<sup>[44]</sup>. In that study, a total of 69 patients who were diagnosed of HCC and met the Milan or San Francisco transplant criteria were enrolled and randomized to either TACE ( $n = 36$ ) or PBT ( $n = 33$ ). The dose fractionation regimen of PBT was 70.2 GyE in 15 fractions. An interim analysis showed a trend toward improved 2-year LC (88% vs 45%) and PFS (48% vs 31%) favoring PBT, although the difference between the two methods was not statistically significant. Another phase II trial of PBT for HCC ( $n = 44$ ) and intrahepatic cholangiocarcinoma ( $n = 37$ ) performed as a multi-center trial in the US<sup>[25]</sup> reported the use of dose fractionation regimens of intention of 67.6 GyE in 15 fractions for tumors > 2 cm from the porta hepatis and 58.05 GyE in 15 fractions for those within 2 cm of porta hepatis. In that study, the median dose actually delivered was 58.05 GyE (range, 15.1 to 67.5 GyE) in 15 fractions. The LC and OS rates at 2 years were 95% and 63%, respectively, supporting ongoing phase III trials of PBT in HCC.

In South Korea, the National Cancer Center performed a phase I dose-escalation study for PBT in HCC comprising 60 GyE in 20 fractions, 66 GyE in 22 fractions, or 72 GyE in 24 fractions<sup>[45]</sup>. The complete response (CR) rates of PBT were 62.5%, 57.1%, and 100% according to increasing dose level, respectively. In addition, the 3-year LC rate was 79.9%, which was significantly higher in patients with CR than in those with non-CR (90% vs 40%,  $P = 0.003$ ). None of the patients experienced liver toxicities greater than grade 2.

## PBT FOR HCC IN SPECIAL SITUATIONS

Although various clinical studies have demonstrated the effectiveness and safety of PBT in the treatment for HCC,

**Table 1** Studies of proton beam therapy for hepatocellular carcinoma

Study	Patients (n)	CTP score	Tumor size (cm)	PVTT	RT regimen (GyE/fractions)	LC	PFS	OS
Tsukuba (2008) <sup>[39]</sup>	53	A: 87% B: 11% C: 2%	≤ 3: 25% > 3 - < 5: 34% ≥ 5 - < 10: 34% ≥ 10: 8%	28%	72.6/22 (80.5 Gy EQD2)	94% at 2 yr 86% at 3 yr	38% at 2 yr 25% at 3 yr	2-yr 57% 3-yr 45%
Tsukuba (2009) <sup>[40]</sup>	51	A: 80% B: 20%	Median 2.8 (range, 0.8 to 9.3) ≤ 5: 88% > 5: 12%	NA	66.0/10 (91.3 Gy EQD2)	95% at 3 yr 88% at 5 yr	NA	3-yr 49% 5-yr 39%
Tsukuba (2009) <sup>[41]</sup>	318	A: 74% B: 24% C: 2%	NA	14%	66.0/10 (91.3 Gy EQD2): 32.7% 72.6/22 (80.5 Gy EQD2): 26.7% 77.0/35 (78.3 Gy EQD2): 20.8%	NA	NA	3-yr 65% 5-yr 45%
Tsukuba (2011) <sup>[42]</sup>	47	A: 75% B: 19% C: 6%	NA	15%	72.6/22 (80.5 Gy EQD2): 34.0% 77.0/35 (78.3 Gy EQD2): 27.7%	88% at 3 yr 88% at 4 yr	IHRFS 1-yr 66% 3-yr 40% 4-yr 17%	3-yr 50% 4-yr 34%
Loma Linda (2011) <sup>[43]</sup>	76	A: 29% B: 47% C: 24%	Mean 5.5 ≤ 2: 7% > 2 - < 5: 45% ≥ 5 - < 10: 43% ≥ 10: 5%	5%	63.0/15 (74.6 Gy EQD2)	70% at 3 yr	80%	Median 36 mo
NCC (2015) <sup>[45]</sup>	27	A: 89% B: 11%	≤ 5: 81% > 5: 19%	NA	60.0/20 (65.0 Gy EQD2): 29.6% 66.0/22 (71.5 Gy EQD2): 25.9% 72.0/24 (78.0 Gy EQD2): 44.4%	80% at 3 yr 64% at 5 yr	3-yr 17% 5-yr 0	3-yr 56% 5-yr 42%
Multiple United States institutions (2016) <sup>[25]</sup>	44	A: 73% B: 20% NA: 7%	Median 5.0 (range, 1.9 to 12.0)	30%	Median 58.05/15 (67.1 Gy EQD2) (range, 15.1-67.5/15)	95% at 2 yr	1-yr 56% 2-yr 40%	1-yr 77% 2-yr 63%

CTP: Child-Turcotte-Pugh; PVTT: Portal vein tumor thrombosis; RT: Radiation therapy; GyE: Gy equivalent; LC: Local control; PFS: Progression free survival; OS: Overall survival; EQD2: Equivalent dose in 2 Gy; NA: Not applicable; NCC: National Cancer Center in South Korea.

the indications for PBT have not yet been determined and continue to evolve. Because of dosimetric advantages, PBT has the potential to be applicable to more complicated cases ineligible for X-ray therapy, such as those with a history of hepatic RT, vascular invasion of the tumor, extremely large tumor burden, and/or poor liver function.

## RE-IRRADIATION WITH PBT FOR HCC

RT has played a role as a salvage treatment for recurrent HCC refractory or ineligible for other modalities<sup>[46-48]</sup>. RT can also be applied to recurrent HCC previously irradiated when there is no appropriate local salvage modality. However, despite the development of modern RT techniques, re-irradiation in HCC remains a challenging issue due to the risk of RILD and GI toxicity<sup>[49-51]</sup>. Therefore, very few studies have evaluated the feasibility and effectiveness of hepatic re-irradiation for HCC<sup>[51]</sup>. Nevertheless, PBT has been investigated as a salvage modality for previously irradiated HCC. Scientists at PMRC reported on the outcomes of repeated PBT for HCC<sup>[52]</sup>. In that study, 27 patients with 68 lesions received 2 or more courses of PBT, and the median interval between the first and second courses was 24.5 mo (range, 3.3 to 79.8 mo). Likewise, the median dose was 72 Gy in 16 fractions and 66 Gy in 16 fractions for the first and subsequent courses, respectively. In the same study, the

LC and OS rates were 87.8% and 55.6%, respectively. Based on these data, the authors concluded that for patients with peripheral tumors and CP A liver function, repeated PBT is safe. More recently, researchers at PMRC reported the results of repeated PBT for 83 patients with HCC, specifically including patients who received 3 ( $n = 12$ ) or 4 ( $n = 3$ ) courses of PBT<sup>[53]</sup>. The median doses for the first, second, third, and fourth courses were 71.0, 70.0, 70.0, and 69.3 GyE, respectively, and the 5-year OS rate was 49.4%. Neither severe acute toxicity nor RILD was observed during the study period.

## PBT FOR HCC WITH PORTAL VEIN TUMOR THROMBOSIS

Portal vein tumor thrombosis (PVTT) at the time of diagnosis is present in 30%-40% of all patients with advanced HCC<sup>[11]</sup>, and PVTT is a poor prognostic factor with a median survival of 2.7 mo to 4.0 mo<sup>[54,55]</sup>. Currently, the Barcelona-Clinic Liver Cancer (BCLC) system recommends sorafenib as the only standard treatment in such patients<sup>[9]</sup>. However, the response rate to sorafenib ranges from 2% to 5%, and the median time to progression is only 2.8 mo<sup>[56]</sup>. Therefore, efficient local modalities leading to improve clinical outcomes are required. Unfortunately, no local modalities have been proven to be efficient for HCC with PVTT. Surgery and TACE alone are

not typically feasible because most cases of HCC with PVTT are unresectable, and the efficacy of TACE is limited due to the aortoportal shunt<sup>[57]</sup>. However, various studies have reported the outcomes of RT with or without TACE, with an objective response rate ranging from 40% to 60%. Furthermore, among responders, the median PFS is reported to be 15 mo to 20 mo<sup>[58-61]</sup>.

The outcomes of PBT for HCC with PVTT have also been evaluated by PMRC. That study analyzed 12 HCC patients with PVTT in which a median dose regimen of 55 GyE in 10-22 fractions was used (range of 50 to 72 GyE in 10-22 fractions). Radiographic CR was achieved in 6 patients, and there was recanalization of the portal vein in 5 patients. Furthermore, the 2- and 5-year OS rates were 88% and 58%, respectively.

Lastly, the National Cancer Center of Korea reported on the outcomes of PBT using a simultaneous integrated boost technique for HCC with PVTT<sup>[62]</sup>. The dose regimens were determined depending on the distance of the tumor from GI OARs, and most tumors were treated with 50-66 GyE in 10 fractions while areas closer to an OAR were treated with 30 GyE in 10 fractions. The LC and OS rates reported in that study at 2 years were 88.1% and 51.1%, respectively. In addition, patients treated with equivalent dose of 2 Gy fractions for  $\alpha/\beta = 10$  Gy (EQD2<sub>10</sub>) of  $\geq 80$  GyE, tended to show better tumor vascular thrombosis response, LC, and OS.

## PBT FOR LARGE HCCs

Tumor size is critical in determining treatment modalities in HCC<sup>[63]</sup>. Patients with large tumors are not candidates for ablation therapies or liver transplantation<sup>[64-66]</sup>. Although surgery seems to have role in the treatment of HCCs larger than 10 cm, few of these tumors are actual candidates for resection<sup>[67-69]</sup>. In such cases, RT represents an alternative modality for large tumors; however, it is not possible to avoid irradiating large volumes of normal liver tissues, which in turn limits sufficient dose escalation<sup>[70,71]</sup>. Importantly, PBT has the potential to overcome this limitation. Researchers at the University of Hokkaido performed dosimetric comparison of spot-scanning PBT vs IMRT for HCC<sup>[72]</sup>. For gross tumors of a nominal diameter more than 6.3 cm, the average risk of RILD according to the Lyman-normal-tissue complication probability model was estimated as 94.5% for IMRT compared to 6.2% for PBT. PMRC also reported the clinical result of PBT for 22 patients with HCC of size  $> 10$  cm<sup>[73]</sup>. In that study, which employed a median dose regimen of 72.6 GyE in 22 fractions (range, 47.3 to 89.1 GyE in 10-35 fractions), the median tumor size was 11 cm (range, 10 cm to 14 cm). The LC and OS at 2 years were 87% and 36%, respectively. RILD occurred in 5 of 22 patients, 3 of whom showed CR.

## PBT FOR HCC PATIENTS WITH POOR LIVER FUNCTION

HCC patients with cirrhotic livers or poor liver function

have a dismal prognosis with a median survival time of 3 to 9 mo<sup>[55]</sup>. Although poor liver function itself is a poor prognostic factor, there are limitations in applying local modalities to those patients because it is difficult to preserve the function of the residual untreated liver<sup>[74]</sup>. Researchers at PMRC reported on the clinical outcomes of PBT for 19 patients with HCC and CP C<sup>[75]</sup>. The median RT dose was 72 GyE in 16 fractions (range, 50 to 84 GyE in 10 to 24 fractions). The crude LC rate was 95% over a median follow-up of 17 mo, and the OS at 2 years was 42%. In addition, there were no therapy-related toxicities of grade  $\geq 3$  or deterioration of CP score. Among the total cohort, 14 patients exhibited an improved CP score. Researchers at PMRC also reported on the feasibility of PBT for HCC patients with uncontrollable ascites<sup>[76]</sup>. Specifically, they used PBT of 24 GyE in a single fraction, and performed precise adjustment of PBT immediately before irradiation. Although their studies only included three patients, objective responses were achieved for all the irradiated tumors, and there were no therapy-related toxicities higher than grade 3.

## HEPATIC TOXICITY

RILD is seldom observed in the era of PBT for HCC, and there is very limited literature on PBT-related RILD. Researchers at PMRC evaluated 60 HCC patients treated with PBT consisting of 76 GyE in 20 fractions<sup>[77]</sup>. Seventy-eight percent of the patients had CP-A liver function, and 82% had liver cirrhosis; prior liver directed therapy had been performed in 60% of the patients. In that study, RILD was defined as anicteric ascites or asterixis. A total of 11 patients exhibited RILD, and seven patients died due to RILD. In addition, they reported that there were no cases of PBT-related RILD for patients with pretreatment indocyanine green retention at 15 min (ICG R15) less than 20%. On the other hand, RILD-related mortality of patients with a pretreatment ICG R15 over 50% was 75%. For patients with pretreatment ICG R15 of 20%-49%,  $V_{30\text{GyE}} < 25\%$  was identified as a predictor for PBT-related RILD. In more recent studies, changes in CP score were reported. Specifically, PMRC evaluated CP scores before and after PBT for 259 HCC patients<sup>[24]</sup>, and found that among the 76% of patients with CP-A, 73% had cirrhosis of the liver and 63% had previously received liver directed treatment. In addition, the rates in the increase in point 1 CP score compared to baseline were 16% and 8% at 1 and 2 years, respectively. Likewise, the rates of point 2 from baseline CP score were 11% and 22% at 1 and 2 years, respectively. On the other hand, literature from the US and South Korea indicate that only 4% of study patients have an increased CP score after PBT<sup>[25,43,78]</sup>.

## GT TRACT TOXICITY

The stomach, duodenum, and bowel are critical OARs because of their proximity to HCC tumors and the vulnerability of patients to radiation toxicity due to portal hypertension-induced gastroduodenopathy<sup>[79,80]</sup>. A group

of researchers from Loma Linda University reported that the incidence of GI toxicities  $\geq$  grade 2 is 7% following RT<sup>[43]</sup>. Similarly, researchers at PMRC reported an incidence of  $\geq$  grade 2 GI toxicities of 1%-2% in various populations<sup>[39,41,81]</sup>. For central tumors abutting the GI tract, however, the incidence of GI toxicities  $\geq$  grade 2 increases to 8.5%, with all of the reported forms of GI toxicity involving hemorrhage<sup>[42]</sup>. Usually, PBT for HCC proximal to GI tract is prone to GI toxicity. Especially, GI tract located near the distal edge of SOBP is potentially vulnerable to severe toxicity because of the uncertainty of the proton beam range and the high RBE value at the distal edge and the fall off of the SOBP. Although there is no specific report regarding the relation between the variation of RBE and the GI toxicities, several literatures reported the distal edge effects of PBT on toxicities of brain stem<sup>[82,83]</sup>. Therefore, special caution is necessary when the location of GI tract is near the distal edge of SOBP. Surgical insertion of tissue expander to displace GI tract away from target is considerable in that situation<sup>[84]</sup>.

## BILIARY AND OTHER GI TRACT TOXICITY

The biliary tract is an OAR that must be protected during liver RT. Indeed, several studies have reported symptomatic biliary inflammation with or without stricture in tumors related to the biliary system<sup>[85,86]</sup>. However, some studies have reported that RT for HCC can be safe with respect to biliary toxicity, even in tumors adjacent to the central biliary system<sup>[87,88]</sup>. For PBT in HCC, data on biliary complications is limited. Researchers at PMRC reviewed 162 patients who underwent PBT for HCC with a median RT dose of 72 GyE in 16 fractions<sup>[81]</sup>. Among the total cohort, three patients exhibited signs of biliary toxicity such as stenosis of the common bile duct ( $n = 1$ ), and biloma with infection adjacent to the irradiated volume ( $n = 2$ ).

## CHEST WALL TOXICITY

As PBT allows for dose escalation in the treatment of HCC, the chest wall is frequently irradiated with increasing high doses. In tumors proximal to the chest wall, there is potential risk of chest wall-related toxicities<sup>[19]</sup>. Although PBT-related chest wall toxicity data are limited, there have been some published studies. Researchers at PMRC reported that the incidence of rib fracture is 16% after PBT of 66 GyE in 10 fractions in 67 HCC patients<sup>[89]</sup>. Specifically, the authors found that V60 at a biologically effective dose with  $\alpha/\beta = 3$  is the most statistically significant parameter for estimating the risk of rib fracture after hypofractionated PBT. In addition, researchers at the MD Anderson Cancer Center reported the chest wall toxicities of 135 patients with lung or hepatobiliary cancer who were treated with  $\geq 52.5$  GyE in 15 fractions of photon therapy or PBT<sup>[90]</sup>. Among the total cohort, 49 patients received PBT. During the median follow-up of 9

mo, 20 patients had grade 1 chest wall pain, while one patient had grade 2 chest wall pain. Furthermore, a chest wall V40  $\geq 150$  cm<sup>3</sup> was identified as an independent predictor for chest wall toxicity. Researchers at the University of Washington and other institutions reported another set of data for chest wall toxicity, comprising 37 patients who underwent PBT with a median dose of 60 GyE (range, 35 to 67.5 GyE) in 15 fractions (range, 13 to 20 fractions)<sup>[91]</sup>. During a median follow-up of 11 mo, chest wall pain of grade  $\geq 2$  occurred in 30% of patients, with none of the patients exhibiting radiographic evidence of rib fracture. For a 15-fraction regimen, a V47 > 20 cm<sup>3</sup>, V50 > 17 cm<sup>3</sup>, and V58 > 8 cm<sup>3</sup> were associated with higher rates of chest wall toxicity. Although there is no consensus regarding dose constraints for chest wall toxicities, efforts should be made to reduce chest wall toxicities based on the reported various dose-volumetric parameters in PBT for HCC.

## TECHNICAL ISSUES

Proton beams have unique physical properties including a finite range in the distal direction. This range is determined by the density of material in the beam path, and any perturbation in the densities can change the dosimetry of PBT more significantly than compared to traditional photon therapy<sup>[92]</sup>. This perturbation can be induced by internal organ motion, daily variation in body shape, uncertainties in machine settings, tissue inhomogeneity, and inaccuracies in dosing, ranges, and density calculations<sup>[93]</sup>. More specifically, the liver is vulnerable to uncertainties of PBT due to organ motion, the interface of air and soft tissue near the diaphragmatic dome, and variations in body shape due to ascites<sup>[76]</sup>.

Various techniques have been investigated to manage the liver-specific problems associated with PBT. In order to overcome uncertainty due to organ motion, the PBT field should ideally encompass the entire range of motion of the tumor; however, this usually results in additional irradiation of normal tissues. Therefore, respiratory gating methods, abdominal compression, or breath hold techniques can be used to reduce the field such that OARs can be protected from unnecessary irradiation<sup>[94,95]</sup>. Because of the requirement for patient cooperation, identifying patients who are eligible for these techniques remains an important issue.

Techniques for motion control require fine image guidance. However, tumor and surrounding normal liver tissue are often undistinguishable on typical imaging studies such as orthogonal KV X-ray images or cone beam computed tomography<sup>[19]</sup>. To set a reference location for setup, radio-opaque fiducial markers are often utilized for more reliable and accurate image guidance<sup>[96]</sup>. Robust optimization is another method for managing imaging uncertainties. One reported algorithm incorporates the uncertainty directly into PBT optimization<sup>[97]</sup>. Using this algorithm, it is possible to quantify the quality of the treatment plan under certain geometric uncertainties, as

well as those from inaccurate calculations of range and tissue density.

## FUTURE PERSPECTIVES

Several studies evaluating the role of PT for HCC are ongoing. These studies are aimed at comparing PBT with radiofrequency ablation, transarterial chemoembolization, or sorafenib, which are the current standard treatments recommended according to BCLC staging. The interim results of a randomized trial comparing PBT with transarterial chemoembolization were reported as discussed above<sup>[44]</sup>. In addition, various single-arm phase II studies of PBT for HCC in specific clinical situations such as PVTT and inoperable disease are ongoing. The results of these studies will provide many answers to ongoing questions and increase the level of evidence in the field of PBT for HCC.

Technologies related to PBT are also under development. Almost all of the clinical data from PBT for HCC have relied on the passive scattering technique<sup>[20]</sup>. However, recently constructed PBT centers are now utilizing pencil beam scanning nozzles, which allow for manipulation of the intensity of proton therapy<sup>[98-100]</sup>. Pencil beam scanning shows better dose optimization and proximal edge conformity compared with passive scattering<sup>[101,102]</sup>. On the other hand, pencil beam scanning takes more time to deliver the proton beam, involves a broader lateral penumbra, and is more sensitive to organ motion<sup>[103-105]</sup>. Therefore, robustness optimization and evaluation tools, respiration management such as repainting, and fine image guidance are required for the use of pencil beam scanning in the treatment of HCC<sup>[106,107]</sup>. Although these issues continue to be investigated and studied, the pencil beam scanning method with simultaneous intensity boost technique is now being tried in HCC<sup>[108]</sup>. Nevertheless, in order to validate the effectiveness and safety of the pencil beam scanning PBT for HCC, large scale prospective trials will be necessary.

Biological issues are another field which can be more advanced in the future. If the RBE variation can be utilized in the optimization of treatment planning, the therapeutic window would be increased<sup>[33]</sup>. The variability of RBE is actively being investigated regarding the relevance of not only dose range but various value of  $\alpha/\beta$ 's from different tissues<sup>[109,110]</sup>. The biology of HCC is diverse according to the various genomic aberrations and the genetic association with radiosensitivity of HCC has been also investigated in *in vitro* and *in vivo*<sup>[111-113]</sup>. Although there is no current data for radio-sensitivity of HCC for PBT specifically, the investigations about the tissue specific radiosensitivity which can be represented with RBE will give the opportunity to provide the optimal strategy of tissue-specific PBT. This is the direction of the approach for PBT to be developed as precision medicine for HCC patients.

## CONCLUSION

PBT has significant dosimetric advantages compared

with X-ray therapy, which has translated to significant differences in clinical outcomes for the treatment for HCC<sup>[20]</sup>. The American Society for Radiation Oncology includes HCC in the "group I" indications for PBT, meaning that PBT is recognized as an effective and safe local modality for the treatment of HCC. Various studies comparing with 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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