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Hypofractionated particle beam therapy for hepatocellular carcinoma—a brief review of clinical effectiveness

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Abstract

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the second leading cause of cancer mortality worldwide. The cornerstone to improving the prognosis of HCC patients has been the control of loco-regional disease progression and the lesser toxicities of local treatment. Although radiotherapy has not been considered a preferred treatment modality for HCC, charged particle therapy (CPT), including proton beam therapy (PBT) and carbon ion radiotherapy (CIRT), possesses advantages (for example, it allows ablative radiation doses to be applied to tumors but simultaneously spares the normal liver parenchyma from radiation) and has emerged as an alternative treatment option for HCC. With the technological advancements in CPT, various radiation dosages of CPT have been used for HCC treatment *via* CPT. However, the efficacy and safety of the evolving dosages remain uncertain. To assess the association between locoregional control of HCC and the dose and regimen of CPT, we provide a brief overview of selected literature on dose regimens from conventional to hypofractionated short-course CPT in the treatment of HCC and the subsequent determinants of clinical outcomes. Overall, CPT provides a better

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local control rate compared with photon beam therapy, ranging from 80% to 96%, and a 3-year overall survival ranging from 50% to 75%, and it results in rare grade 3 toxicities of the late gastrointestinal tract (including radiation-induced liver disease). Regarding CPT for the treatment of locoregional HCC, conventional CPT is preferred to treat central tumors of HCC to avoid late toxicities of the biliary tract. In contrast, the hypo-fractionation regimen of CPT is suggested for treatment of larger-sized tumors of HCC to overcome potential radio-resistance.

Key words: Hepatocellular carcinoma; Proton beam therapy; Carbon ion radiotherapy; Local control; Toxicity; Overall survival

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Core tip: Charged particle therapy (CPT) for hepatocellular carcinoma (HCC), including proton beam therapy and carbon ion radiotherapy, offers physics-related advantages and results in better local control rates and lesser adverse effects. For peripherally large-sized HCC tumors, the hypo-fractionation regimen of CPT provides the benefit of increasing local control rates through overcoming radio-resistance, whereas conventional CPT is preferred for treating central tumors of HCC in terms of avoiding late toxicities of the biliary tract. Prospective data that will add to the accumulated evidence on the dosimetric constraints of hypofractionated CPT for the treatment of HCC are needed.

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INTRODUCTION

Hepatocellular carcinoma (HCC), with a reported 5-year overall survival (OS) of 10% to 15%^[1], is the fifth most common malignancy and the second leading cause of cancer mortality worldwide, with an estimated 782000 new cases and 745000 deaths in the year 2012^[2,3]. The global increase in both the incidence and mortality of HCC is a major concern, and improving the management of HCC is a key challenge.

The cornerstone to improving the prognosis of HCC patients has relied on the control of loco-regional disease progression; loco-regional disease progression is the major cause of HCC-related death^[4]. Surgical interventions, including liver resection and transplantation, are considered the first priority treatment modalities for patients with HCC^[5]. However, only 10%-37% of patients are treated with surgery at the time of diagnosis because of their inability to tolerate the possible surgery-related complications because of underlying comorbidities^[6-9].

Local ablation treatments, including percutaneous ethanol injection (PEI) and radiofrequency thermal ablation (RFA), have been recognized as alternative treatment options for patients with HCC, even though patients with large HCCs (> 5 cm in diameter) are not eligible to receive either PEI or RFA^[10,11]. Transarterial chemoembolization (TACE) provides some benefits of locoregional control and a better prognosis for HCC patients in whom surgery or local ablation treatment is not feasible, although it is regarded as a non-curative treatment^[12,13]. However, HCC patients who present with portal vein tumor thrombus (PVTT) are not advised to receive TACE treatment because of the increased risk of liver failure^[14,15].

Radiotherapy (RT) has not been considered as a preferred treatment modality for HCC; instead, it is a complementary local treatment option for patients who are not candidates for surgery, local ablation, and TACE, mainly because the RT dose required for tumor ablation would be beyond the tolerance dose of the liver parenchyma and may induce liver injury, including classic and non-classic radiation-induced liver disease (RILD)^[16]. In contrast to conventional RT, stereotactic body radiotherapy (SBRT), which combines image guidance technique and radiotherapy planning designation, not only provides highly conformal radiation delivery to allow ablative doses to be applied to tumors, but simultaneously spares the normal liver

parenchyma from radiation^[17-19]. SBRT, which is commonly performed using high radiation dose per fractions, has resulted in excellent local control (LC) for HCC in numerous retrospective and prospective studies^[18-20].

Charged particle therapies (CPT), including proton beam therapy (PBT) and carbon ion radiotherapy (CIRT), possess physics-related advantages, which allow for a better dose distribution than in photon beam therapy, especially for low- and medium-dose dosimetry in the normal liver parenchyma during the treatment of HCC^[21-24]. The physics-related advantages of CPT resulted from the Bragg peak, a property of CPT, which refers to a sharp dose accumulation followed by rapid dose fall-off^[25]. The numerous, stacked Bragg peaks of different energies form the spread-out Bragg peak (SOBP), which possesses dosimetry characteristic of the little exit doses of the clinical tumor target^[21,24,26,27]. In the application of CPT in HCC treatment, the dosimetry benefit derived from SOBP of CPT has been confirmed in several studies^[22,27,28] (Figure 1). In addition, the property of a higher relative biological effectiveness (RBE) for a charged particle beam, which is approximately 1.1 for a proton and 2-5 for a carbon ion^[26,29], indicates higher radiobiological damage, with more DNA double strand breaks and more tumor ablation effects^[26,30]. Moreover, the direct DNA damage effect produced *via* the CPT beam also had another radiobiological advantage in terms of the oxygen enhancement ratio (OER), which is defined as the ratio of radiation dose required to produce the same tumoricidal effect under hypoxic and normoxic conditions. The OER can be reduced to 1 by using the CPT beam, with a linear energy transfer more than 100 keV/ μ m for oxygen concentrations between 0% and 20%^[31]. Consequently, increased application of CPT in HCC patients has been noticed in recent years, especially owing to the improved techniques of CPT and the increased numbers of CPT facilities^[32,33].

With the technological advancements in CPT, it is reasonable that the protocol of the doses schedule shifts from conventional fractionation to hypofractionation, like the evolving process of the photon beam treatment SBRT for HCC. Several studies demonstrated that various radiation dose protocols, which ranged from 77 GyE (1 Gray equivalent protons is equivalent to delivering 1 Gy with photons) in 35 fractions to 66 GyE in 10 fractions for PBT^[34-37] and 76 GyE in 20 fractions to 52.8 GyE in 4 fractions for CIRT^[38,39], provide effective treatment results under different conditions in HCC patients. However, the optimal CPT dose and schedule for effective control of tumors in HCC patients with different comorbidities remain uncertain. The aim of the present systematic review is to evaluate the efficacy and safety of the different CPT dose regimens, leading to a conclusive summary of the adequate dose and fraction for clinical utilization in HCC treatment.

CLINICAL OUTCOMES FOR PARTICLE BEAM THERAPY WITH DOSE REGIMEN OF LESS THAN 5 GY PER FRACTION

The studies on cohorts treated with CPT for HCC are mainly from the United States, Japan, and Korea. We have reviewed 5 prospective and 2 retrospective studies, in which the dose protocols of CPT for treating HCC are less than 5 GyE per fraction. The clinical characteristics and outcomes of CPT for treating HCC using conventional fraction-size doses are summarized in Tables 1 and 2. In addition to the aforementioned characteristics, we summarized the target volume for HCC using CPT, including gross tumor volume (GTV), clinical target volume (CTV) extending from GTV, internal target volume (ITV), and planning target volume (PTV), as well as the toxicities that resulted from CPT (Table 2).

First, two prospective phase II trials were conducted in the US to evaluate the efficacy and safety of PBT for treating HCC. Bush *et al*^[40], in Loma Linda, published their results using the regimen of 63 GyE in 15 fractions of PBT in the treatment of HCC. They recruited a total of 76 HCC patients, of which 58 patients had underlying liver functions characterized by Child-Pugh A or B and mean tumor sizes of 5.5 cm^[40]. The local control (LC) rate was 80%, and the median progression-free survival (PFS) was 36 months; only 5 patients had grade 2 gastrointestinal (GI) adverse effects after PBT treatment^[40]. The 3-year overall survival (OS) was 70% for patients ($n = 18$) who underwent subsequent liver transplantation after PBT, of which 33% ($n = 6$) and 39% of the patients had complete remission (CR) ($n = 7$) and microscopic residues only, respectively^[40]. Hong *et al*^[41] enrolled 44 patients with HCC from the Massachusetts General Hospital, MD Anderson Cancer Center, and University of Pennsylvania who were administered PBT using the regimen of 67.5 GyE in 15 fractions (58.05 GyE in 15 fractions for location of tumors within 2 cm of the porta hepatis), of which 41 patients had liver function of Child-Pugh A or B and median tumor size of 5.0 cm^[41]. The 2-year LC rate and the median PFS for all the patients were 94.8% and 13.9 months,

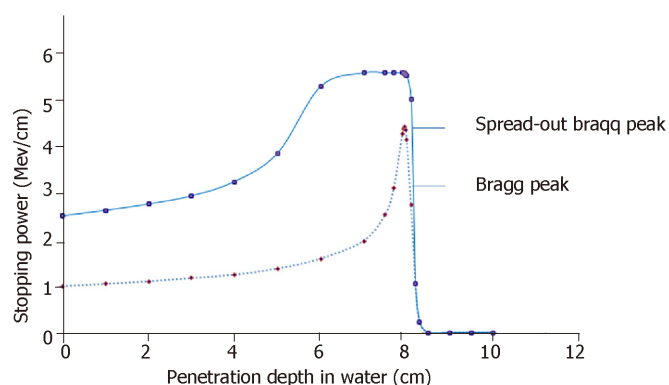


Figure 1 The illustration of Bragg peak and spread-out Bragg peak.

respectively^[41]. In their study, 4 patients experienced grade 3 radiation-related toxicities, including thrombocytopenia, liver failure and ascites, gastric ulcer, and elevated bilirubin. A higher occurrence (29.5%) of vascular thrombosis was reported in patients in their study compared to the 5% occurrence that was reported in Bush *et al*^[40]'s cohort.

Chiba *et al.* reported the clinical experience of PBT for 162 patients with median HCC tumor size of 3.8 cm at the University of Tsukuba using a PBT dose regimen of 50 to 88 GyE in 10-24 fractions with a median fraction dose of 4.5 GyE^[42]. Of these, 88.9% of patients had liver function of Child-Pugh A or B, and 6.1% patients had vascular thrombosis^[42]. The 5-year LC and OS rates were 86.9% and 23.5%, respectively. The 5-year OS rate for patients with a solitary tumor and Child-Pugh class A was 53.5%^[42]. The late toxicities included infected biloma (2 patients), common bile duct stenosis (1 patient), and GI tract bleeding (2 patients)^[42]. Nakayama *et al*^[36] updated the clinical outcomes of the University of Tsukuba, and reported a study of 47 patients, whose HCC tumor locations were within 2 cm of the GI tract. They used the PBT regimen of 72.6 GyE in 22 fractions and 77 GyE in 35 fractions in order to avoid GI tract toxicity. The 3-year LC and OS rates were 88% and 50%, respectively, and 4 patients experienced grade 2 or 3 GI bleeding during follow-up^[36].

Kawashima *et al*^[43] conducted one phase II study, which enrolled 30 HCC patients with Child-Pugh A or B, to evaluate the safety and efficacy of PBT using a dose regimen of 76 GyE in 20 fractions. The median tumor size of the study was 4.5 cm and 40% patients had macroscopic vascular invasion^[43]. The 2-year LC and OS rates were 96% and 66%, respectively; and 8 patients developed hepatic insufficiencies after PBT, of which 4 cases died of hepatic insufficiency-related complications 6 to 9 mo later.

Kim *et al*^[44] reported one phase I dose escalation study of 27 HCC patients, using a PBT dose regimen of 60 GyE in 20 fractions (dose level 1, $n = 8$), 66 GyE in 22 fractions (dose level 2, $n = 7$), and 72 GyE in 24 fractions (dose level 3, $n = 12$). The median tumor size of patients entering into dose level 3 was 2.5 cm. The CR rates of primary tumors after PBT for patients receiving dose levels 1, 2, and 3 were 62.5%, 57.1%, and 100%, respectively ($P = 0.039$)^[44]. The 3-year LC and OS rates for all patients were 79.9% and 56.4%, respectively^[44]. Regarding liver toxicity, 4 cases had a 1-point of decrease in the Child-Pugh score, and 1 case had a 1-point increase in the Child-Pugh score, whereas the other 22 cases showed no change in the Child-Pugh score^[44].

Regarding CIRT, Kato *et al.* conducted the first phase I-II trial with 24 HCC patients with Child-Pugh A or B liver function, a median tumor size of 5.0 cm, and vascular invasion of 12.5%^[45]. Escalated CIRT doses of 49.5 to 79.5 GyE in 15 fractions were used in their study^[45]. The overall tumor response, 3-year LC, and 3-year OS rates were 71%, 81%, and 50%, respectively^[45]. Patients treated with doses ≥ 72.0 Gy (RBE) did not develop recurrence^[45]. No severe liver injury occurred, except in 1 case of grade 2 late lung reaction, 1 case of grade 2 late GI complication, and 2 cases of grade 2 late skin reactions after the completion of CIRT^[45].

Altogether, these findings indicate that conventional fraction-size CPT with varying target volume, including CTV, ITV, and PTV designation, could provide excellent local control for patients with relatively small, isolated tumors and concomitant Child-Pugh class A/B/C liver disease. For central tumors and tumors adjacent to the bowel, conventional fractionation of CPT is a safe approach that not only provides good local tumor control but also lessens the adverse effect (Figure 2).

Table 1 Clinical patient characteristics of the selected studies

Ref.	Study, Patient	Source/ Energy (MeV)	Liver function	Vascular invasion	Tumor size
Bush <i>et al</i> ^[40]	Phase II, 76	Proton	CPC score 5-6 22 7-9 36 10-15 18	4 patients	5.5 cm (mean)
Hong <i>et al</i> ^[41]	Phase II, 44	Proton (230-250)	CPC A 32 B 9 C 3	15 patients	5.0 cm (median,1.9-12.0)
Chiba <i>et al</i> ^[42]	Retro, 162	Proton (250)	CPC A 82 B 62 C 10	10 patients	3.8 cm (median, 1.5–14.5)
Nakayama <i>et al</i> ^[37]	Retro, 47	Proton (155 to 250)	CPC A 35 B 9 C 3	7 patients	N/A
Kawashima <i>et al</i> ^[43]	Phase II, 30	Proton (235)	CPC A 20 B 10	12 patients	45 cm (median,25-82)
Kim <i>et al</i> ^[44]	Phase I, 27	Proton (250)	CPC A 24 B 3	N/A	2.3-3.2 cm (median, 1.3-7)
Kato <i>et al</i> ^[45]	Phase I/II, 24	Carbonion (290-400)	CPC A 16 B 8	3 patients	5.0 cm (median,2.1-8.5)
Mizumoto <i>et al</i> ^[34]	Retro, 266	Proton	CPC A 203 B 60 C 3	N/A	< 3 cm 100 3.0–4.9 cm 96 50–99 cm 62 > 100 cm 8
Komatsu <i>et al</i> ^[39]	Retro, 343	Proton, Carbonion	CPC A 262 B 75 C 6	92 patients	< 50 277 50-100 80 > 100 22
Kim <i>et al</i> ^[46]	Retro, 71	Proton (230)	CPC A 68 B 3	0	1.5 (median,1.0–8.5)
Shibuya <i>et al</i> ^[38]	Retro, 174	Carbonion	CPC A 153 B 20	0	3.0 (median,0.810.3)

CPC: Child-pugh classification; Retro: Retrospective study; N/A: Non-analyses. CPC: Child-pugh classification; Retro: Retrospective study; N/A: Non-analyses.

CLINICAL OUTCOMES FOR PARTICLE BEAM THERAPY WITH DOSE REGIMENS OF MORE THAN 5 GYE PER FRACTION

Regarding dose regimens using fractionation size larger than 5 GyE, we reviewed 4 retrospective studies and summarized the underlying clinicopathological features: patients' number, liver function, and size of the tumor, as well as the treatment characteristics (PBT or CIRT) (Table 1). Table 2 summarizes the dose, fraction size, treatment plan (including GTV, CTV, and PTV), late toxicities, LC, PFS, and OS.

Mizumoto *et al*^[34] reported the LC and OS of a cohort of 266 HCC patients at the Proton Medical Research Center in Tsukuba who were treated with PBT using three

Table 2 Main clinical results of the selected studies

Ref.	Dose fractionation (GyE/fractions)	Treatment planning	Local control	Survival outcome	Late severe adverse events (number or %)
Bush <i>et al</i> ^[40]	63 /15	PTV = GTV + 10-20 mm	80%	median PFS: 36 mo	G2 toxicities: 5/76
Hong <i>et al</i> ^[41]	58.05–67.5 /15	PTV = CTV +5-10 mm	94.8% (2 yr)	Median PFS: 13.9 mo PFS: 39.9% (2 yr) OS: 63.2% (2 yr)	G3 toxicities: 4
Chiba <i>et al</i> ^[42]	72 /16, 78 /20, 84 /28, 50 /10	CTV = GTV + 5–10 mm	86.9% (5 yr)	OS: 23.5% (5 yr)	Infection biloma: 1.1% Biliary duct stenosis: 0.5% GI bleeding: 1.1%
Nakayama <i>et al</i> ^[37]	72.6/22, 77/ 35	PTV1 = CTV + 5-10 mm PTV2 = PTV1 with alimentary tract avoiding	88% (3 yr)	OS: 50% (3 yr)	
Kawashima <i>et al</i> ^[43]	76 /20	CTV= GTV+5 mm, PTV = CTV+3 mm	96% (2 yr)	OS: 62% (3 yr)	Hepatic insufficiencies : 8
Kim <i>et al</i> ^[44]	60/20 –72/24	PTV = ITV + 5-10 mm	71.4%–83.3% (3y)	OS: 42.3% (5 yr)	G2 toxicity: 0
Kato <i>et al</i> ^[45]	49.5–79.5/15	PTV= GTV+10 mm	81% (3 yr)	OS: 25% (5 yr)	No severe liver injury No > 2 points increase in CP score at any time
Mizmoto <i>et al</i> ^[34]	66/10, 72.6/22, 77/35	CTV= GTV+ 5-10 mm	81% (5 yr)	OS: 45 (5 yr)	G 2/3 GI toxicity: 6
Komatsu <i>et al</i> ^[39]	52.8–84.0 /4-38 (proton) 52.8–76.0 /4-20 (carbon ion)	CTV = GTV + 5 mm PTV = CTV + 5 mm	90.8% (5 yr)	OS: 38.2%	G 3: 12 RIHD: 4
Kim <i>et al</i> ^[36]	66/10	PTV = ITV + 0.5-0.7 cm	89.9% (3 yr)	PFS: 26.8% (3 yr) OS: 74.4% (3 yr)	no late GI toxicities or liver failure
Shibuya <i>et al</i> ^[38]	52.8/4, 60.0/4, 48/2,	CTV = GTV + 0.5 cm PTV = CTV+ 515 mm	87.7% (3 yr)	73.3% (3 yr)	G 3-4: 5.7% (10) RIHD: 1.7% (3)

PFS: Progression-free survival; OS: Overall survival; PTV: Planned target volume; GTV: Gross tumor volume; CTV: Clinical target volume; G: Grade; RILD: Radiation-induced hepatic dysfunction; GI: Gastrointestinal.

different treatment protocols according to the tumor location^[35]. The dosage regimen protocols of PBT included 66 GyE in 10 fractions for peripheral tumors (tumor located 2 cm away from hilum), 72.6 GyE in 22 fractions for central tumors (tumor located within 2 cm of the hilum), and 77 GyE in 35 fractions for central tumors which were adjacent to the GI tract^[34,35]. The median tumor size was 3.4 cm, and 99% of patients were characterized by a cirrhosis status of Child-Pugh A or B. The 3-year LC, PFS, and OS rates for all patients were 87%, 21% and 61%, respectively^[34]. Among these three different dosage regimens, there were no significant differences in the LC and PFS of patients. In all, 12 patients experienced symptomatic late toxicity, which included rib fracture (3 patients), dermatitis (grade 1: 2; grade 3:1 patients), and perforation, bleeding, or inflammation of the GI tract (grade 2: 3 patients grade 3: 3 patients)^[34]. For patients whose tumors were located adjacent to the porta hepatis, the PBT (72.6 GyE in 22 fractions or 77 GyE in 35 fractions) resulted in a 3-year LC and OS rates of 86% and 50%, respectively, and no subsequent bile duct stenosis was observed in them^[34].

Komatsu *et al*^[39] reported the clinical outcome of a large cohort of HCC patients who were treated at the Hyogo Ion Beam Medical Center (HIBMC), including 242 and 101 patients (108 tumors) who underwent PBT (278 tumors) and CIRT (108 tumors), respectively, for HCC. The dosage regimens of CPT included 8 and 4 different protocols of PBT (52.8-84.0 GyE in 4-38 fractions) and CIRT (52.8-76.0 GyE in 4-20 fractions), respectively^[39]. The percentage of tumor sizes < 5 cm, within 5-10 cm, and > 10 cm were 37.8%, 37.4% and 41.1%, respectively^[39]. The 5-year LC rate for all patients receiving PBT and CIRT were 90.2% and 93%, respectively^[39]. The 5-year LC rate for patients with tumor < 5 cm, within 5 to 10 cm, and > 10 cm were 95.3%, 84.4%, and 42.2%, respectively^[39]. The PBT and CIRT resulted in equivalent 5-year LC rates of 95.5% and 94.5%, respectively, in the treatment of patients with tumors < 5 cm. For patients whose tumors were within 5 to 10 cm, the PBT and CIRT resulted in equivalent 5-year LC rates of 84.1% and 90.9%, respectively^[39]. In those whose tumors were > 10 cm, CIRT resulted in a better 5-year LC rate of 80% compared to 43.4% for PBT^[39]. Four patients developed RILD after CPT, and no patients died of CPT treatment-related toxicities.

Kim *et al*^[46] designed a study to assess the optimal time of tumor response after PBT

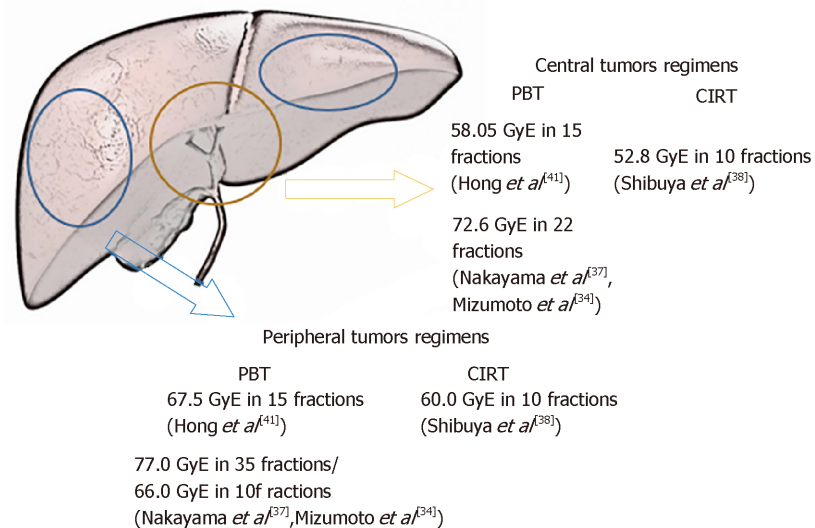


Figure 2 Illustrations of doses and regimens of charged particle therapy in the treatment of different locations of hepatocellular carcinoma. For central tumors and tumors adjacent to the bowel, conventional fractionation of charged particle therapy (CPT) is a safe approach that not only provides good local tumor control but also lessens adverse effects. In contrast to that for central tumors, short-course hypofractionation of CPT might provide better outcomes for larger-sized tumors that are located at peripheral areas of the liver. PBT: Proton beam therapy; CIRT: Carbon ion radiotherapy.

for 71 patients with HCC, which comprised 68 patients with Child-Pugh A, and 3 patients with Child-Pugh B; their median tumor size was 1.5 cm. Use of a PBT regimen of 66 GyE in 10 fractions resulted in the CR rate of 93%, and most patients (93.9%) achieved this within one year after PBT. Overall, the PBT resulted in 3-year local progression-free survival (LPFS), relapse-free survival (RFS), and OS rates of 89.9%, 26.8%, and 74.4%, respectively. Within 3 months after treatment, 3 patients had a 1-point increase in Child-Pugh score, 3 patients experienced grade 1 elevated liver function, and no patients experienced > grade 3 toxicities.

In a multicenter retrospective study conducted by the Japan Carbon Ion Radiation Oncology Study Group (JCROS), Shibuya *et al.*^[38] reported the effectiveness and safety of short-course CIRT for 174 patients with HCC (median tumor size; 3.0 cm). Of these, 153 patients had Child-Pugh A, and 20 patients with Child-Pugh B. The prescription radiation doses of CIRT included 48.0 GyE in 2 fractions ($n = 46$), 52.8 GyE ($n = 108$) in 4 fractions, and 60.0 GyE ($n = 20$) in 4 fractions^[38]. After a median follow-up period of 20.3 (range, 2.9-103.5) months, the 3-year LC and OS rates for all patients were 81.0% and 73.3%, respectively^[38]. Multivariate analysis also disclosed that Eastern Cooperative Oncology Group performance status 1-2, Child-Pugh class B, maximum tumor diameter ≥ 3 cm, multiple tumors, and serum alpha fetoprotein level > 50 ng/mL were significant prognostic factors for a worse OS. Regarding CIPT-related toxicities, 10 patients (5.7%) experienced grade 3 or 4 treatment-related toxicities, and 3 patients (1.7%) experienced RIHD.

Altogether, a larger fraction size of CPT radiation dose possesses similar treatment outcomes to those of CPT with a conventional fraction size, without compromising normal organ toxicities. For larger size tumors, short-course CPT might provide better outcomes (Figure 2). For central tumors, hypofractionation CPT is not preferred according to the protocol proposed by Mizumoto *et al.*^[34] (Figure 2). Further dosimetric constraints for avoiding late toxicities of biliary stenosis are warranted to expand the utilization of hypofractionation CPT.

CONCLUSION

CPT, including PBT and CIRT, could be used to deliver ablative doses to HCC tumors with normal liver sparing. Overall, conventional CPT or hypofractionated CPT (including short-course CPT) could not only provide LC rates > 90% but also result in < 5% grade 3 toxicities. For large-sized HCC tumors, the hypo-fractionation regimen of CPT may provide the benefit of increasing LC through overcoming radio-resistance, whereas conventional CPT is preferred for treating central tumors of HCC

by avoiding late toxicities of the biliary tract. Prospective data are still warranted to accumulate evidence on the dosimetric constraints of hypofractionated or short-course CPT in the treatment of HCC.

REFERENCES

- 1 **De Angelis R**, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, Trama A, Visser O, Brenner H, Ardanaz E, Bielska-Lasota M, Engholm G, Nennecke A, Siesling S, Berrino F, Capocaccia R; EUROCARE-5 Working Group. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5-a population-based study. *Lancet Oncol* 2014; **15**: 23-34 [PMID: [24314615](#) DOI: [10.1016/S1470-2045\(13\)70546-1](#)]
- 2 **Ferlay J**, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin D, Forman D, Bray F. *GLOBOCAN 2012: Estimated Cancer Incidence and Mortality Worldwide v1.0. IARC CancerBase No. 11* [Internet]. Lyon, France: International Agency for Research on Cancer 2013; Available from: <https://publications.iarc.fr/Databases/Iarc-Cancerbases/GLOBOCAN-2012-Estimated-Cancer-Incidence-Mortality-And-Prevalence-Worldwide-In-2012-V1.0-2012>
- 3 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: [25220842](#) DOI: [10.1002/ijc.29210](#)]
- 4 **Trevisani F**, Cantarini MC, Wands JR, Bernardi M. Recent advances in the natural history of hepatocellular carcinoma. *Carcinogenesis* 2008; **29**: 1299-1305 [PMID: [18515282](#) DOI: [10.1093/carcin/bgn113](#)]
- 5 **Benson III A**, D'Angelica M, Abbott D. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hepatobiliary Cancers ver. 1. 2018*. Fort Washington, PA: National Comprehensive Cancer Network 2018; Available from: https://oncolife.com.ua/doc/nccn/Hepatobiliary_Cancers.pdf
- 6 **Fan ST**, Lo CM, Liu CL, Lam CM, Yuen WK, Yeung C, Wong J. Hepatectomy for hepatocellular carcinoma: toward zero hospital deaths. *Ann Surg* 1999; **229**: 322-330 [PMID: [10077043](#) DOI: [10.1097/0000658-199903000-00004](#)]
- 7 **Colella G**, Bottelli R, De Carlis L, Sansalone CV, Rondinara GF, Alberti A, Belli LS, Gelosa F, Iamoni GM, Rampoldi A, De Gasperi A, Corti A, Mazza E, Aseni P, Meroni A, Slim AO, Finzi M, Di Benedetto F, Manocchri F, Follini ML, Ideo G, Forti D. Hepatocellular carcinoma: comparison between liver transplantation, resective surgery, ethanol injection, and chemoembolization. *Transpl Int* 1998; **11** Suppl 1: S193-S196 [PMID: [9664977](#) DOI: [10.1111/j.1432-2277.1998.tb01113.x](#)]
- 8 **Fong Y**, Sun RL, Jarnagin W, Blumgart LH. An analysis of 412 cases of hepatocellular carcinoma at a Western center. *Ann Surg* 1999; **229**: 790-9; discussion 799-800 [PMID: [10363892](#) DOI: [10.1097/0000658-199906000-00005](#)]
- 9 **Pang TC**, Lam VW. Surgical management of hepatocellular carcinoma. *World J Hepatol* 2015; **7**: 245-252 [PMID: [25729479](#) DOI: [10.4254/wjh.v7.i2.245](#)]
- 10 **Weis S**, Franke A, Berg T, Mössner J, Fleig WE, Schoppmeyer K. Percutaneous ethanol injection or percutaneous acetic acid injection for early hepatocellular carcinoma. *Cochrane Database Syst Rev* 2015; **1**: CD006745 [PMID: [25620061](#) DOI: [10.1002/14651858.CD006745](#)]
- 11 **Lau WY**, Lai EC. The current role of radiofrequency ablation in the management of hepatocellular carcinoma: a systematic review. *Ann Surg* 2009; **249**: 20-25 [PMID: [19106671](#) DOI: [10.1097/SLA.0b013e31818e0029](#)]
- 12 **Kaplan DE**, Mehta R, D'Addeo K, Gade TP, Taddei TH. Transarterial Chemoembolization within First 3 Months of Sorafenib Initiation Improves Overall Survival in Hepatocellular Carcinoma: A Retrospective, Multi-Institutional Study with Propensity Matching. *J Vasc Interv Radiol* 2018; **29**: 540-549.e4 [PMID: [29477619](#) DOI: [10.1016/j.jvir.2017.11.033](#)]
- 13 **Lee EW**, Alanis L, Cho SK, Saab S. Yttrium-90 Selective Internal Radiation Therapy with Glass Microspheres for Hepatocellular Carcinoma: Current and Updated Literature Review. *Korean J Radiol* 2016; **17**: 472-488 [PMID: [27390539](#) DOI: [10.3348/kjr.2016.17.4.472](#)]
- 14 **Minagawa M**, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. *World J Gastroenterol* 2006; **12**: 7561-7567 [PMID: [17171782](#) DOI: [10.3748/wjg.v12.i47.7561](#)]
- 15 **Yamada R**, Sato M, Kawabata M, Nakatsuka H, Nakamura K, Takashima S. Hepatic artery embolization in 120 patients with unresectable hepatoma. *Radiology* 1983; **148**: 397-401 [PMID: [6306721](#) DOI: [10.1148/radiology.148.2.6306721](#)]
- 16 **Chapman TR**, Bowen SR, Schaub SK, Yeung RH, Kwan SW, Park JO, Yu L, Harris WP, Johnson GE, Liou IW. Toward consensus reporting of radiation-induced liver toxicity in the treatment of primary liver malignancies: Defining clinically relevant endpoints. *Pract Radiat Oncol* 2018; **8**: 157-166 [PMID: [29426691](#) DOI: [10.1016/j.prro.2017.10.013](#)]
- 17 **Culleton S**, Jiang H, Haddad CR, Kim J, Brierley J, Brade A, Ringash J, Dawson LA. Outcomes following definitive stereotactic body radiotherapy for patients with Child-Pugh B or C hepatocellular carcinoma. *Radiother Oncol* 2014; **111**: 412-417 [PMID: [24906626](#) DOI: [10.1016/j.radonc.2014.05.002](#)]
- 18 **Lasley FD**, Mannina EM, Johnson CS, Perkins SM, Althouse S, Maluccio M, Kwo P, Cárdenas H. Treatment variables related to liver toxicity in patients with hepatocellular carcinoma, Child-Pugh class A and B enrolled in a phase 1-2 trial of stereotactic body radiation therapy. *Pract Radiat Oncol* 2015; **5**: e443-e449 [PMID: [25899219](#) DOI: [10.1016/j.prro.2015.02.007](#)]
- 19 **Bujold A**, Massey CA, Kim JJ, Brierley J, Cho C, Wong RK, Dinniwell RE, Kassam Z, Ringash J, Cummings B, Sykes J, Sherman M, Knox JJ, Dawson LA. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol* 2013; **31**: 1631-1639 [PMID: [23547075](#) DOI: [10.1200/JCO.2012.44.1659](#)]
- 20 **Kang JK**, Kim MS, Cho CK, Yang KM, Yoo HJ, Kim JH, Bae SH, Jung DH, Kim KB, Lee DH, Han CJ, Kim J, Park SC, Kim YH. Stereotactic body radiation therapy for inoperable hepatocellular carcinoma as a local salvage treatment after incomplete transarterial chemoembolization. *Cancer* 2012; **118**: 5424-5431 [PMID: [22570179](#) DOI: [10.1002/cncr.27533](#)]
- 21 **Wang X**, Krishnan S, Zhang X, Dong L, Briere T, Crane CH, Martel M, Gillin M, Mohan R, Beddar S. Proton radiotherapy for liver tumors: dosimetric advantages over photon plans. *Med Dosim* 2008; **33**: 259-

- 267 [PMID: [18973852](#) DOI: [10.1016/j.meddos.2007.04.008](#)]
- 22 **Kim JY**, Lim YK, Kim TH, Cho KH, Choi SH, Jeong H, Kim DW, Park JH, Shin DH, Lee SB, Kim SS, Kim JY, Kim DY, Park JW. Normal liver sparing by proton beam therapy for hepatocellular carcinoma: Comparison with helical intensity modulated radiotherapy and volumetric modulated arc therapy. *Acta Oncol* 2015; **54**: 1827-1832 [PMID: [25765526](#) DOI: [10.3109/0284186X.2015.1009637](#)]
- 23 **Petersen JB**, Lassen Y, Hansen AT, Muren LP, Grau C, Hoyer M. Normal liver tissue sparing by intensity-modulated proton stereotactic body radiotherapy for solitary liver tumours. *Acta Oncol* 2011; **50**: 823-828 [PMID: [21767180](#) DOI: [10.3109/0284186X.2011.590526](#)]
- 24 **Abe T**, Saitoh J, Kobayashi D, Shibuya K, Koyama Y, Shimada H, Shirai K, Ohno T, Nakano T. Dosimetric comparison of carbon ion radiotherapy and stereotactic body radiotherapy with photon beams for the treatment of hepatocellular carcinoma. *Radiat Oncol* 2015; **10**: 187 [PMID: [26377092](#) DOI: [10.1186/s13014-015-0491-8](#)]
- 25 **Levin WP**, Kooy H, Loeffler JS, DeLaney TF. Proton beam therapy. *Br J Cancer* 2005; **93**: 849-854 [PMID: [16189526](#) DOI: [10.1038/sj.bjc.6602754](#)]
- 26 **Fossati P**, Matsufuji N, Kamada T, Karger CP. Radiobiological issues in prospective carbon ion therapy trials. *Med Phys* 2018; **45**: e1096-e1110 [PMID: [30421806](#) DOI: [10.1002/mp.12506](#)]
- 27 **Toramatsu C**, Katoh N, Shimizu S, Nihongi H, Matsuura T, Takao S, Miyamoto N, Suzuki R, Sutherland K, Kinoshita R, Onimaru R, Ishikawa M, Umegaki K, Shirato H. What is the appropriate size criterion for proton radiotherapy for hepatocellular carcinoma? A dosimetric comparison of spot-scanning proton therapy versus intensity-modulated radiation therapy. *Radiat Oncol* 2013; **8**: 48 [PMID: [23497543](#) DOI: [10.1186/1748-717X-8-48](#)]
- 28 **Gandhi SJ**, Liang X, Ding X, Zhu TC, Ben-Josef E, Plastaras JP, Metz JM, Both S, Apisarnthanarax S. Clinical decision tool for optimal delivery of liver stereotactic body radiation therapy: Photons versus protons. *Pract Radiat Oncol* 2015; **5**: 209-218 [PMID: [25703530](#) DOI: [10.1016/j.prro.2015.01.004](#)]
- 29 **Krämer M**, Scholz M. Treatment planning for heavy-ion radiotherapy: calculation and optimization of biologically effective dose. *Phys Med Biol* 2000; **45**: 3319-3330 [PMID: [11098906](#) DOI: [10.1088/0031-9155/45/11/314](#)]
- 30 **Paganetti H**, Blakely E, Carabe-Fernandez A, Carlson DJ, Das IJ, Dong L, Grosshans D, Held KD, Mohan R, Moiseenko V, Niemierko A, Stewart RD, Willers H. Report of the AAPM TG-256 on the relative biological effectiveness of proton beams in radiation therapy. *Med Phys* 2019; **46**: e53-e78 [PMID: [30661238](#) DOI: [10.1002/mp.13390](#)]
- 31 **Tinganelli W**, Durante M, Hirayama R, Krämer M, Maier A, Kraft-Weyrather W, Furusawa Y, Friedrich T, Scifoni E. Kill-painting of hypoxic tumours in charged particle therapy. *Sci Rep* 2015; **5**: 17016 [PMID: [26596243](#) DOI: [10.1038/srep17016](#)]
- 32 **Dionisi F**, Ben-Josef E. The use of proton therapy in the treatment of gastrointestinal cancers: liver. *Cancer J* 2014; **20**: 371-377 [PMID: [25415681](#) DOI: [10.1097/PPO.0000000000000082](#)]
- 33 **Dionisi F**, Widesott L, Lorentini S, Amichetti M. Is there a role for proton therapy in the treatment of hepatocellular carcinoma? A systematic review. *Radiother Oncol* 2014; **111**: 1-10 [PMID: [24560761](#) DOI: [10.1016/j.radonc.2014.02.001](#)]
- 34 **Mizumoto M**, Okumura T, Hashimoto T, Fukuda K, Oshiro Y, Fukumitsu N, Abei M, Kawaguchi A, Hayashi Y, Ookawa A, Hashii H, Kanemoto A, Moritake T, Tohno E, Tsuboi K, Sakae T, Sakurai H. Proton beam therapy for hepatocellular carcinoma: a comparison of three treatment protocols. *Int J Radiat Oncol Biol Phys* 2011; **81**: 1039-1045 [PMID: [20888707](#) DOI: [10.1016/j.ijrobp.2010.07.015](#)]
- 35 **Mizumoto M**, Tokuyue K, Sugahara S, Nakayama H, Fukumitsu N, Ohara K, Abei M, Shoda J, Tohno E, Minami M. Proton beam therapy for hepatocellular carcinoma adjacent to the porta hepatis. *Int J Radiat Oncol Biol Phys* 2008; **71**: 462-467 [PMID: [18243571](#) DOI: [10.1016/j.ijrobp.2007.09.056](#)]
- 36 **Nakayama H**, Sugahara S, Fukuda K, Abei M, Shoda J, Sakurai H, Tsuboi K, Matsuzaki Y, Tokuyue K. Proton beam therapy for hepatocellular carcinoma located adjacent to the alimentary tract. *Int J Radiat Oncol Biol Phys* 2011; **80**: 992-995 [PMID: [21543162](#) DOI: [10.1016/j.ijrobp.2010.03.015](#)]
- 37 **Nakayama H**, Sugahara S, Tokita M, Fukuda K, Mizumoto M, Abei M, Shoda J, Sakurai H, Tsuboi K, Tokuyue K. Proton beam therapy for hepatocellular carcinoma: the University of Tsukuba experience. *Cancer* 2009; **115**: 5499-5506 [PMID: [19645024](#) DOI: [10.1002/cncr.24619](#)]
- 38 **Shibuya K**, Ohno T, Terashima K, Toyama S, Yasuda S, Tsuji H, Okimoto T, Shioyama Y, Nemoto K, Kamada T, Nakano T; Japan Carbon Ion Radiotherapy Study Group. Short-course carbon-ion radiotherapy for hepatocellular carcinoma: A multi-institutional retrospective study. *Liver Int* 2018; **38**: 2239-2247 [PMID: [30240527](#) DOI: [10.1111/liv.13969](#)]
- 39 **Komatsu S**, Fukumoto T, Demizu Y, Miyawaki D, Terashima K, Sasaki R, Hori Y, Hishikawa Y, Ku Y, Murakami M. Clinical results and risk factors of proton and carbon ion therapy for hepatocellular carcinoma. *Cancer* 2011; **117**: 4890-4904 [PMID: [21495022](#) DOI: [10.1002/cncr.26134](#)]
- 40 **Bush DA**, Kayali Z, Grove R, Slater JD. The safety and efficacy of high-dose proton beam radiotherapy for hepatocellular carcinoma: a phase 2 prospective trial. *Cancer* 2011; **117**: 3053-3059 [PMID: [21264826](#) DOI: [10.1002/cncr.25809](#)]
- 41 **Hong TS**, Wo JY, Yeap BY, Ben-Josef E, McDonnell EI, Blaszkowsky LS, Kwak EL, Allen JN, Clark JW, Goyal L, Murphy JE, Javle MM, Wolfgang JA, Drapek LC, Arellano RS, Mamon HJ, Mullen JT, Yoon SS, Tanabe KK, Ferrone CR, Ryan DP, DeLaney TF, Crane CH, Zhu AX. Multi-Institutional Phase II Study of High-Dose Hypofractionated Proton Beam Therapy in Patients With Localized, Unresectable Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma. *J Clin Oncol* 2016; **34**: 460-468 [PMID: [26668346](#) DOI: [10.1200/JCO.2015.64.2710](#)]
- 42 **Chiba T**, Tokuyue K, Matsuzaki Y, Sugahara S, Chuganji Y, Kagei K, Shoda J, Hata M, Abei M, Igaki H, Tanaka N, Akine Y. Proton beam therapy for hepatocellular carcinoma: a retrospective review of 162 patients. *Clin Cancer Res* 2005; **11**: 3799-3805 [PMID: [15897579](#) DOI: [10.1158/1078-0432.CCR-04-1350](#)]
- 43 **Kawashima M**, Furuse J, Nishio T, Konishi M, Ishii H, Kinoshita T, Nagase M, Nihei K, Ogino T. Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma. *J Clin Oncol* 2005; **23**: 1839-1846 [PMID: [15774777](#) DOI: [10.1200/JCO.2005.00.620](#)]
- 44 **Kim TH**, Park JW, Kim YJ, Kim BH, Woo SM, Moon SH, Kim SS, Koh YH, Lee WJ, Park SJ, Kim JY, Kim DY, Kim CM. Phase I dose-escalation study of proton beam therapy for inoperable hepatocellular carcinoma. *Cancer Res Treat* 2015; **47**: 34-45 [PMID: [25381830](#) DOI: [10.4143/crt.2013.218](#)]
- 45 **Kato H**, Tsujii H, Miyamoto T, Mizoe JE, Kamada T, Tsuji H, Yamada S, Kandatsu S, Yoshikawa K, Obata T, Ezawa H, Morita S, Tomizawa M, Morimoto N, Fujita J, Ohto M; Liver Cancer Working Group. Results of the first prospective study of carbon ion radiotherapy for hepatocellular carcinoma with liver

- cirrhosis. *Int J Radiat Oncol Biol Phys* 2004; **59**: 1468-1476 [PMID: [15275734](#) DOI: [10.1016/j.ijrobp.2004.01.032](#)]
- 46 **Kim TH**, Park JW, Kim BH, Kim DY, Moon SH, Kim SS, Lee JH, Woo SM, Koh YH, Lee WJ, Kim CM. Optimal time of tumour response evaluation and effectiveness of hypofractionated proton beam therapy for inoperable or recurrent hepatocellular carcinoma. *Oncotarget* 2017; **9**: 4034-4043 [PMID: [29423102](#) DOI: [10.18632/oncotarget.23428](#)]



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