INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
www.redjournal.org

CLINICAL INVESTIGATION

Proton Beam Therapy for Hepatocellular Carcinoma: Multicenter Prospective Registry Study in Japan

Masashi Mizumoto, MD, PhD,[*] Hiroyuki Ogino, MD, PhD,[†] Toshiyuki Okumura, MD, PhD,[*] Kazuki Terashima, MD, PhD,[‡] Masao Murakami, MD, PhD,[§] Takashi Ogino, MD, PhD,[‖] Hiroyasu Tamamura, MD, PhD,[¶] Tetsuo Akimoto, MD, PhD,[#] Takahiro Waki, MD, PhD,[**] Norio Katoh, MD, PhD,[††] Masayuki Araya, MD, PhD,[‡‡] Tsuyoshi Onoe, MD, PhD,[§§] Masaru Takagi, MD, PhD,[‖‖] Hiromitsu Iwata, MD, PhD,[†] Haruko Numajiri, MD, PhD,[*] Tomoaki Okimoto, MD, PhD,[‡] Yusuke Uchinami, MD, PhD,[††] Kazushi Maruo, PhD,[¶¶] Kei Shibuya, MD, PhD,[##] and Hideyuki Sakurai, MD, PhD[*]

[*]*Department of Radiation Oncology, University of Tsukuba, Tsukuba, Ibaraki, 305-8576, Japan;* [†]*Department of Radiation Oncology, Nagoya Proton Therapy Center, Nagoya City University West Medical Center, Nagoya, 462-8508, Japan;* [‡]*Department of Radiology, Hyogo Ion Beam Medical Center, Tatsuno, Hyogo, 679-5165, Japan;* [§]*Department of Radiation Oncology, Southern Tohoku Proton Therapy Center, Koriyama, Fukushima, 963-8052, Japan;* [‖]*Medipolis Proton Therapy and Research Center, 4423 Higashikata, Ibusuki, Kagoshima, 891-0304, Japan;* [¶]*Proton Therapy Center, Fukui Prefectural Hospital, Fukui, Fukui, 910-8526, Japan;* [#]*Department of Radiation Oncology, National Cancer Center Hospital East, Chiba, 277-8577, Japan;* [**]*Department of Radiology, Tsuyama Chuo Hospital, Tsuyama, Okayama, 708-0841, Japan;* [††]*Department of Radiation Oncology, Hokkaido University Institute of Medicine, Hokkaido, 060-8648, Japan;* [‡‡]*Proton Therapy Center, Aizawa Hospital, Matsumoto, Nagano, 390-8510, Japan;* [§§]*Radiation and Proton Therapy Center, Shizuoka Cancer Center, Nagaizumi, Suntou-gun, Shizuoka, 411-8777, Japan;* [‖‖]*Department of Radiation Oncology, Sapporo Teishinkai Hospital, Sapporo, Hokkaido, 065-0033, Japan;* [¶¶]*Department of Biostatistics, Institute of Medicine, University of Tsukuba, Tsukuba, Ibaraki, 305-8575, Japan; and* [##]*Department of Radiation Oncology, Gunma University Graduate School of Medicine, Maebashi, 371-8511, Japan*

Received Jan 10, 2023; Accepted for publication Sep 21, 2023

Purpose: A prospective multicenter registry study was started May 2016 in Japan to evaluate the efficacy and safety of proton beam therapy (PBT) for hepatocellular carcinoma (HCC).

Methods and Materials: Patients who received PBT for HCC from May 2016 to June 2018 were registered in the database of the Particle Beam Therapy Committee and Subcommittee of the Japanese Society for Radiation Oncology. Overall survival (OS), progression-free survival (PFS), and local recurrence were evaluated.

Results: Of the 755 registered patients, 576 with initial PBT and no duplicate cancer were evaluated. At final follow-up, 322 patients were alive and 254 had died. The median follow-up period for survivors was 39 months (0-58 months). The median OS time of the 576 patients was 48.8 months (95% CI, 42.0-55.6 months) and the 1-, 2-, 3-, and 4-year OS rates were 83.8% (95% CI, 80.5%-86.6%), 68.5% (64.5%-72.2%), 58.2% (53.9%-62.2%), and 50.1% (44.9%-55.0%), respectively. Recurrence was observed in 332 patients, including local recurrence in 45 patients. The median PFS time was 14.7 months (95% CI, 12.4-17.0 months) and the 1-, 2-, 3-, and 4-year PFS rates were 55.2% (95% CI, 51.0%-59.2%), 37.5% (33.5%-41.5%), 30.2% (26.3%-

Corresponding author: Masashi Mizumoto, MD, PhD; E-mail: mizumoto@pmrc.tsukuba.ac.jp

Disclosures: This work was supported by Hokkaido University (Functional Enhancement Promotion funding from the Ministry of Education, Culture, Sports, Science, and Technology) and AMED under grant no. JP16lm0103004. The sponsors had no role in the preparation of data, the decision to publish the manuscript, or the writing of the manuscript.

Data Sharing Statement: All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ijrobp.2023.09.047.

https://doi.org/10.1016/j.ijrobp.2023.09.047

34.2%), and 22.8% (18.5%-27.4%), respectively. The 1-, 2-, 3-, and 4-year OS rates were significantly higher for tumor size <5 versus 5 to 10 cm ($P < .001$) and <5 versus ≥10 cm ($P < .001$); Child-Pugh score A/B versus C ($P < .001$); and distance of the tumor from the gastrointestinal tract <1 versus 1 to 2 cm ($P < .008$) and <1 versus >2 cm ($P < .001$). At final follow-up, 27 patients (4.7%) had late adverse events of grade 3 or higher, with liver failure (n = 7), and dermatitis (n = 7) being most common.

Conclusions: This multicenter prospective data registry indicated that PBT for HCC gives good therapeutic effects (3-year local control rate of 90%) with a low risk of severe late adverse events.

Introduction

The annual number of cases of hepatocellular carcinoma (HCC) worldwide is 750,000, which is the sixth largest among all carcinomas.[1] Surgical resection, radiofrequency ablation (RFA) and liver transplantation are standard curative treatments for HCC[2-5] and are selected according to liver function and tumor size and number. Good local control is likely for a lesion with a maximum tumor diameter ≤3 cm, whereas surgery is mainly selected for tumors with a large maximum diameter.[6] In a case with a large number of lesions or poor liver function, transcatheter arterial embolization (TACE), or systemic therapy is used next to surgery or RFA.[7]

Stereotactic body radiation therapy (SBRT) for HCC permits administration of a curative dose due to advances in irradiation technology, and results in a high local control rate, especially for small lesions.[8,9] Proton beam therapy (PBT) has excellent dose concentration that allows safe administration of high doses to tumors, even for large lesions that are difficult to cure with SBRT, and also gives good local control.[10,11] PBT is also effective for HCC with portal vein tumor thrombosis (PVTT) or inferior vena cava tumor thrombosis, which is difficult to treat with surgery or RFA.[12,13]

These findings indicate that the indication for PBT as curative treatment for HCC is likely to expand. However, most studies of PBT for HCC have been retrospective, and higher quality data are needed to clarify the role of PBT.[10,11] Thus, a prospective multicenter registry study was started in May 2016 in Japan to evaluate the efficacy and safety of PBT for malignant carcinoma. Here, we evaluate the preliminary results of this study for use of PBT for HCC.

Methods and Materials

Patients who received PBT from May 2016 to June 2018 were registered in a database managed by the Hepatocellular Cancer Working Group of the Particle Beam Therapy Committee and Subcommittee of the Japanese Society for Radiation Oncology (JASTRO). Twelve centers participated in the study, after obtaining prior approval from ethics committees and written informed consent from all patients. The study protocol was reviewed and approved by the Ethical Review Board for Life Science and Medical Research at Hokkaido University Hospital (approval no. 016-0106).

Eligibility for the study was defined as unresectable HCC, including patients who refused surgery or RFA, and all active tumors amenable to PBT. Irradiation was performed using a respiratory-gated system or a motion tracking system.

The initial registration items were name of the center, sex, age, PBT (initial treatment, second or more), localized (localized, with metastasis), surgical indication (operable, inoperable), initial treatment (initial, recurrence), diagnostic method (histologic diagnosis, clinical diagnosis), duplicate cancer (yes or no), radiation treatment history (yes or no), performance status (PS), treatment policy (radical, nonradical), tumor location (peripheral, hepatic portal, gastrointestinal [GI tract] proximity), PBT method (broad beam, spot scanning), PBT start/end date, total dose, number of fractions, treatment period, irradiation completion status (complete, complete with break ≥8 days, discontinuation at ≥50% of schedule, discontinuation at ≤50% of schedule), Child-Pugh class (A, B, C), hepatitis (none, alcohol, type B, type C, autoimmune), maximum tumor diameter (cm), indocyanine green 15 minute value, PVTT (VP0-2 or 3-4), hepatic vein tumor thrombosis (Vv0-1 vs 2-3), and clinical stage (TNM, Union for International Cancer Control, Japan Pancreas Society) at the starting date of PBT. Surgical indication (operable or inoperable) was determined by the cancer board at each facility, with participation of radiation oncologists, gastroenterologists, and GI surgeons.

The registration items were late adverse events (yes or no), date of confirmation of late adverse events, Classification of Late Adverse Events, Grade of Late Adverse Events, version 4 (Common Terminology Criteria for Adverse Events ver. 4, grade 3 or higher), status (death from HCC, survival with recurrence, survival without recurrence, unknown), date of confirmation of survival status, recurrence (yes or no), date of confirmation of recurrence, site of recurrence (inside irradiated field, outside irradiated field and inside liver, affiliated lymph nodes, distant metastasis, unknown), secondary cancer (yes or no), date of confirmation of secondary cancer, and registered at least once a year.

Individual patient information was Secure Socket Layer encrypted and anonymized. If patients were followed at a center that differed from the center at which PBT was performed, data were entered based on the rules of the follow-up hospital or with ethical approval. Overall survival (OS) and progression-free survival (PFS) were estimated with the Kaplan-Meier method. The cumulative incidence for local

recurrence with the competing risk of death without local recurrence was estimated with the ordinary nonparametric method. OS, local control, and PFS were calculated starting from the first day of PBT. Multivariate Cox regression models were applied for OS and PFS and a multivariable Fine-Gray regression model[14] was used for local recurrence. The candidate covariates in these models were age, tumor size, sex, surgical indication, prior treatment, prior radiation therapy, PS, tumor location, Child-Pugh class, history of hepatitis, PVTT, tumor size, and clinical stage. Variable selection for multivariate models was conducted using the stepwise method with AIC. The significance level for statistical tests was set at .05 and 95% confidence level. Analyses were conducted using the survival, prodlim, cmprsk, and crrstep packages in R software v.4.2.0.[15-19]

Results

A total of 755 cases that received PBT for HCC were registered between May 2016 and June 2018. Of these cases, 576 with initial PBT and no duplicate cancer were included in this analysis. The 576 cases (Table 1) had a male:female ratio of 437:139, and a median age of 71 years old (21-93 years old). The background data for the patients are summarized in Table 1.

The treatment protocol was selected using the unified treatment policy stipulated by JASTRO. In this policy, 66.0 Gy (RBE) in 10 fractions (fr) was mainly selected for peripheral HCC, 72.6-76 Gy (RBE) in 20 to 22 fr for HCC adjacent to the porta hepatis and 74.0-76.0 Gy (RBE) for HCC adjacent to the alimentary tract.[20] This protocol was selected from past reports in Japan and adopted after consultation with an expert team. Only the irradiation dose is specified in this policy and setting of the irradiation range and margin depended on the standard approach at each facility. An irradiation dose outside this protocol is acceptable when the treatment period must be adjusted due to the patient's circumstances or adjustment is necessary based on the tolerable dose of organs at risk. The acceptable dose to such organs is not specified in the policy.

At final follow-up, 322 patients were alive and 254 had died. The median follow-up period for survivors was 39.0 months (0.4-58.3 months). The causes of death were tumor progression (n = 162), another illness (n = 57), and an unknown reason (n = 35). The median survival time of the 576 patients was 48.8 months (95% CI, 42.0-55.6 months) and the 1-, 2-, 3-, and 4-year OS rates (Fig. 1) were 83.8% (95% CI, 80.5%-86.6%), 68.5% (64.5%-72.2%), 58.2% (53.9%-62.2%), and 50.1% (44.9%-55.0%), respectively.

Recurrence was observed in 332 cases, including in the liver outside the irradiated area (n = 247), lymph node metastasis in (n = 14), distant metastasis (n = 44), and local recurrence (n = 45) (with more than one type of recurrence in some cases). The median PFS time was 14.7 months (95% CI, 12.4-17.0 months) and the 1-, 2-, 3-, and 4-year PFS rates (Fig. 1) were 55.2% (95% CI, 51.0%-59.2%), 37.5%

Table 1 Characteristics of patients and tumors

Characteristic	No.	%
Age (y)	21-93	71 (median)
Sex		
Male	437	75.9
Female	139	24.1
Surgical indication		
Operable	134	23.3
Inoperable	442	76.7
ECOG performance status		
0	460	79.9
1	90	15.6
2	17	3.0
3	9	1.6
History of hepatitis		
Yes	473	82.1
No	103	17.9
Child-Pugh class		
A	459	79.7
B	110	19.1
C	6	1.0
Tumor location		
Peripheral	222	38.5
Hepatic portal	294	51.0
Gastrointestinal proximity	60	10.4
Tumor size (mm)		
All cases	5-200	35 (median)
<30	224	38.9
30-49	163	28.3
50-99	126	21.9
≥100	63	10.9
Portal vein tumor thrombus		
Vp 0-2	502	87.2
Vp 3-4	74	12.8
Prior treatment		
Yes	224	38.9
No	352	61.1
Prior radiation therapy		
Yes	58	10.1
No	518	89.9
Clinical stage		
I	236	41.0
II	156	27.1
III	168	29.2
IV	15	2.6

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

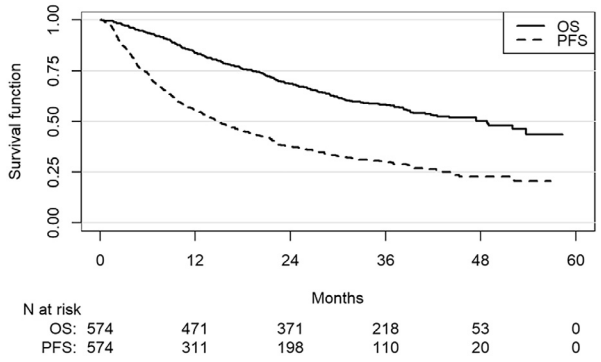

Fig. 1. Overall survival and progression-free survival rates for all patients. *Abbreviations*: OS = overall survival; PFS = progression-free survival.

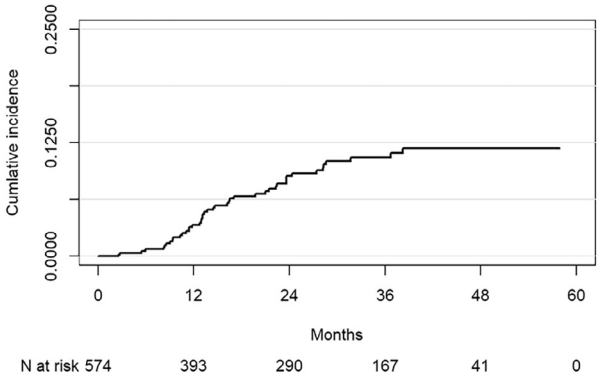

Fig. 2. Local recurrence rate for all patients.

(33.5%-41.5%), 30.2% (26.3%-34.2%), and 22.8% (18.5%-27.4%), respectively. The 1-, 2-, 3-, and 4-year local recurrence rates (Fig. 2) were 3.5% (1.8%-5.1%), 8.8% (6.1%-11.6%), 10.8% (7.7%-14.0%), and 11.9% (8.5%-15.3%), respectively.

Multivariate analyses (Table 2) were performed to evaluate factors with a possible relationship with OS, PFS, and local recurrence. Age, tumor size, sex, surgical indication, prior treatment, prior radiation therapy, PS, tumor location, Child-Pugh class, history of hepatitis, PVTT, tumor size, and clinical stage were evaluated as prognostic factors. The analyses showed significant associations of surgical indication, PS, Child-Pugh class, PVTT, and clinical stage with OS; surgical indication, prior treatment, tumor location (adjacent to porta hepatis), tumor size and clinical stage with PFS; and tumor location (adjacent to alimentary tract) and tumor size with local recurrence.

The 1-, 2-, 3-, and 4-year OS rates based on tumor size (Fig. 3), Child-Pugh score (Fig. 4), and distance from the GI tract (Supplemental Materials E3) are shown in Supplemental Materials E1. These rates were significantly higher for tumor size <5 versus 5 to 10 cm ($P < .001$) and <5 versus ≥10 cm ($P < .001$); Child-Pugh score A/B versus C ($P < .001$); and distance from the GI tract <1 versus 1 to 2 cm ($P < .008$) and <1 versus >2 cm ($P < .001$).

Similar data for the 1-, 2-, 3-, and 4-year local recurrence rates (Figs. 5 and 6; Supplemental Materials E4) are also shown in Supplemental Materials E1. These rates did not differ significantly for tumor size <5 versus 5 to 10 cm ($P = .160$) but were significantly lower for tumor size <5 versus ≥10 cm ($P = .006$). The local recurrence rates did not differ significantly for Child-Pugh score A/B versus C ($P = .24$) or for distance from the GI tract <1 versus 1 to 2 cm ($P = .630$) but were significantly lower for distance from the GI tract >2 versus <1 cm ($P = .002$).

At final follow-up, 27 patients (4.7%) had late adverse events of grade 3 or higher for which a relationship with PBT could not be excluded (Supplemental Materials E2). The median time to an adverse event in the 27 patients was 4.4 months (1.7-16.6), and 23 adverse events developed within 1 year. The details of the adverse events are shown in Supplemental Materials E2. The 7 patients with hepatic failure all had hepatitis, and it was difficult to determine whether the hepatic failure was due to hepatitis or PBT. Three patients who died due to liver failure had hepatitis B (n = 2) and hepatitis C (n = 1). Of the 4 patients with GI tract disorders of grade 3 or higher, the distance of the tumor from the GI tract was <1 cm (n = 2), 1 to 2 cm (n = 1), and >2 cm (n = 1).

Discussion

This is the first multicenter prospective data registry study of PBT for HCC in Japan. The 3-year OS and local recurrence rates of 58.1% and 10.8% are consistent with previous findings.[10,11,21-26] The PBT protocol for HCC in Japan is stipulated by JASTRO based on tumor location.[20] The biological effective dose (BED_{10}) in this protocol is about 91.2 Gy (76 Gy [RBE] in 38 fr, adjacent to alimentary tract), 96.6 Gy (72.6 Gy [RBE] in 22 fr, adjacent to porta hepatis) and 109.6 Gy (66.0 Gy [RBE] in 10 fr, peripheral). This indicates that PBT of at least 90 Gy (BED_{10}) within a safe range of the GI tract, blood vessels, or bile duct is likely to be effective for HCC. However, the local recurrence rate in this study was significantly higher in cases with tumors adjacent to the GI tract. This may be due to the insufficiency of 90 Gy (BED_{10}) and a decreased dose in areas close to the GI tract. The correlation between tumor location and PBT protocol and the various protocol patterns make it difficult to determine whether the lower BED_{10} affected OS and local recurrence. A detailed analysis of the recurrence site may show if recurrence is due to a reduced dose caused by proximity to the GI tract, or if 90 Gy (BED_{10}) is simply an insufficient dose; however, this issue is difficult to examine in a registry study.

Child-Pugh class, PS, and tumor progression have all been suggested as prognostic factors for OS after PBT for HCC.[21-26] Similarly, in the present study, PS, Child-Pugh class, PVTT, and clinical stage were prognostic factors for OS. The surgical indication judged from liver function and lesion progression[2-4,27] was also related to OS, as might be

Table 2 Multivariate analysis of potential predictive factors for overall survival, progression-free survival, and local recurrence

Factor	No.	3-year (%)	HR	HR range	z-value	*P* value
Overall survival						
Surgical indication						
Yes	134	87.6				
No	442	49.1	3.045	1.946-4.765	4.874	.000
Performance status						
0	460	62.7				
1-3	116	40.0	1.507	1.138-1.996	2.862	.004
Child-Pugh class						
A	459	61.8				
B/C	116	43.4	1.533	1.152-2.040	2.928	.003
Portal vein tumor thrombus						
vp0-2	502	63.4				
vp3-4	74	21.7	1.469	1.037-2.082	2.162	.031
Clinical stage						
1/2	392	71.9				
3/4	183	28.0	2.359	1.681-3.310	4.967	.000
Progression-free survival						
Surgical indication						
Yes	134	48.6				
No	442	24.5	1.683	1.286-2.201	3.794	.000
Prior treatment						
No	352	34.5				
Yes	224	23.4	1.468	1.194-1.804	3.648	.000
Tumor location						
Peripheral	222	41.0				
Porta hepatis	294	23.5	1.276	1.015-1.603	2.090	.037
Alimentary tract	60	23.0	1.089	0.766-1.548	0.474	.635
Tumor size (cm)						
≤3.5	301	38.2				
>3.5	275	21.5	1.337	1.038-1.723	2.246	.025
Clinical stage						
1/2	392	37.1				
3/4	183	15.1	1.678	1.302-2.162	4.004	.000
Local recurrence						
Tumor location						
Peripheral	222	5.8				
Porta hepatis	294	13.7	1.825	0.860-3.873	1.567	.120
Alimentary tract	60	22.0	3.527	1.348-9.232	2.568	.010
Tumor size (cm)						
≤3.5	301	6.9				
>3.5	275	17.0	2.424	1.251-4.695	2.624	.009

Abbreviation: HR = hazard ratio.

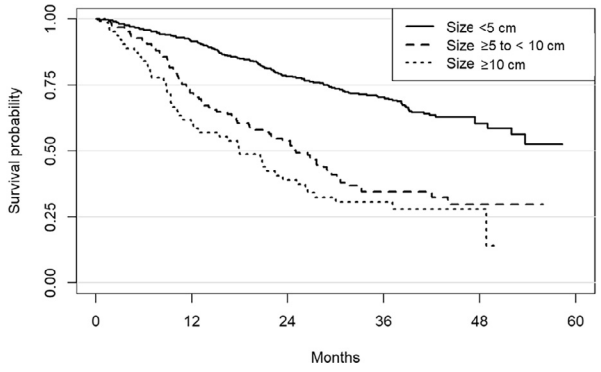

Fig. 3. Overall survival rates by tumor size (<5, 5-10, or ≥10 cm).

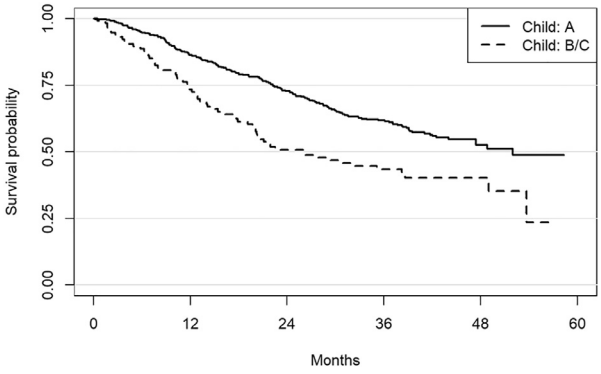

Fig. 4. Overall survival rates by Child-Pugh score (A/B or C).

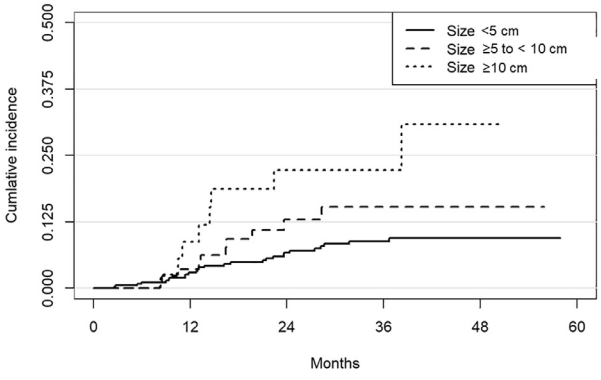

Fig. 5. Local recurrence rates by tumor size (<5, 5-10, or ≥10 cm).

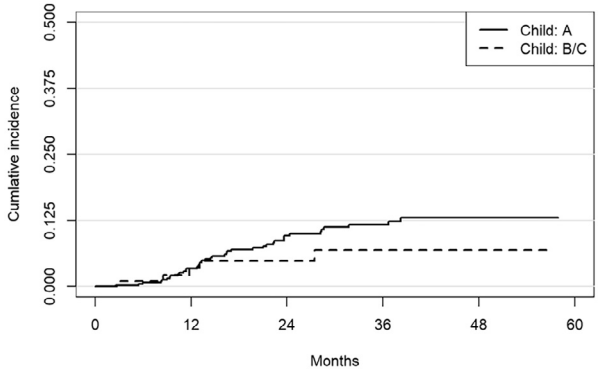

Fig. 6. Local recurrence rates by Child-Pugh score (A/B or C).

expected. PVTT was a poor prognostic factor, but all cases with PVTT were inoperable, and those that also could not undergo PBT had a particularly poor prognosis. Therefore, PBT is an option in these cases.[12,13] The prognostic factors for PFS were surgical indication, treatment history, tumor location (porta hepatis), and tumor size. These findings are also reasonable because surgical indication and tumor size are related to tumor progression, and a more advanced tumor has a generally higher risk of recurrence and metastasis. Tumor size and GI tract proximity were also identified as risk factors for local recurrence. A larger tumor generally has a higher local recurrence rate if the treatment intensity is similar.[24,28] The high recurrence rate in cases with GI tract proximity may be due to use of insufficient doses to avoid the GI tract and initial use of a lower total dose.[20] There have been recent attempts to place spacers between the tumor and GI tract to allow sufficient irradiation of tumors in such cases.[29]

PBT for HCC has rates of late toxicity of grade 3 or higher of 3.2% to 8.1%.[10,11,21-26,30-32] These late toxicities include liver failure, GI tract disorders, rib fractures, and pneumonitis. In the current study, this rate was 4.7% and the main late toxicities were hepatic failure, GI tract disorders, and pneumonitis. The 7 cases of liver failure were all complicated by hepatitis, and 4 of the patients also had recurrence. Thus, it was difficult to determine whether liver failure was due to PBT, recurrence or exacerbation of hepatitis. We note that Mizumoto et al found a low risk of liver failure with PBT.[33] High reproducibility of PBT outcomes and adverse event rates are possible with selection of appropriate irradiation based on the position of the risk organ.[20]

SBRT can give good local control for small HCC,[8,34] but comparisons of SBRT and PBT have shown better prognosis, less liver damage, and a significantly better prognosis for large tumors using PBT.[35-37] In this study, liver failure of grade 3 and higher was found in 7 (1.2%) subjects and GI tract disorder in 4 (0.7%) subjects, both of which are low rates. This is probably due to lower-dose irradiation of PBT to the normal liver than with SBRT and slow treatment with a low dose in patients with lesions near the intestine. In particular, in patients with poor liver function at dosing points, even low-dose irradiation is likely to cause liver failure. Therefore, PBT appears to be more effective than SBRT. However, DHV analysis of risk organs was not conducted, and it is difficult to evaluate how PBT contributed to reduction of adverse events in the liver and GI tract.

The 1- and 2-year OS rates for PBT for HCC with a maximum tumor diameter of 5 to 10 cm were 72.0% (63.2%-79.0%) and 53.8% (44.6%-62.2%), respectively, in this study. Recent studies using SBRT have reported 1- and 2-year OS of 62% (35%-73%) and 43% (36%-70%), respectively.[38-44] Among studies of SBRT and particle therapy for PVTT, the mean survival time with particle therapy is 13.2 to 22 months and 1-year OS is 56% to 61%, and those with SBRT are 9 to 12 months and 9% to 49%.[45-48] The mean survival time with particle therapy for cases with poor liver function (Child-Pugh B/C)

is 13 to 23 months and 1-year OS is 80%, and those for SBRT are 8 to 20 months and 32% to 71%.[49-53] All these data are from nonrandomized studies, but particle therapy appears to have similar or better outcomes than SBRT, even for larger tumors. It is difficult to conduct a randomized control trial in patients with poor general conditions, and a systematic comparative analysis is needed to determine whether particle therapy and SBRT have better treatment outcomes than three-dimensional conformal radiation therapy. However, it seems that particle therapy and SBRT can both be selected for small HCC tumors that are suitable for SBRT, whereas particle therapy is useful for large HCC tumors that are difficult to treat with SBRT, and for HCC with impaired liver function because particle beam irradiation has minimal effects on normal liver function.

Treatment of HCC in Japan is performed in accordance with Japan Hepatology of Society guidelines.[54] Surgery and RFA are the preferred local treatment options. In cases in which this treatment is difficult, TACE and molecular targeted drugs are selected. Whether particle therapy should be a first-choice treatment similarly to surgery and RFA is difficult to determine because there are only a few comparative trials of PBT with other treatments. In 69 cases without a surgical or RFA indication that were randomly chosen for treatment with TACE or PBT of 70.2 Gy (RBE) in 15 fr, Bush et al[55,56] found improved PFS and local control with PBT, and similar 2-year OS for PBT and TACE of 68% and 65%, respectively. In a randomized comparative study of PBT and percutaneous RFA for 144 cases of recurrent HCC of 2 lesions or less and ≤3 cm, Kim et al[57] found no significant difference in 4-year local recurrence-free survival (83.0% with PBT vs 78.3% with RFA), 4-year PFS (18.7% vs 12.6%), or 4-year OS (75.4% vs 77.0%). These results at least suggest noninferiority of PBT compared with other treatments.

Based on the results of this study, we suggest 2 main types of cases that may be suitable for PBT: those in which surgery or RFA is difficult due to complications, tumor condition, or patient refusal; and those requiring additional treatment for a residual tumor after surgery, RFA, or TACE. This proposal requires validation in prospective studies and meta-analyses comparing PBT with other treatments. Ongoing clinical trials include the JCOG (Japan Clinical Oncology Group) 1315c phase 3 trial comparing surgery and PBT for resectable HCC, and the NRG-GI003 randomized trial comparing PBT with x-ray therapy. Meta-analyses and matched-pair analyses have found almost equivalent treatment effects for PBT and SBRT compared with RFA.[58,59] These results and a future prospective study will assist in guiding treatment recommendations across modalities.

There are 2 limitations in the study. First, the patient selection criteria were not strict, and cases with various backgrounds were included. Second, only dose fractionation was stipulated in the protocol, and the irradiation margin and dose constraints for normal tissue and the follow-up methods were determined at each facility. Within these limitations, we conclude that PBT has a good therapeutic effect (3-year local control rate of 90%) for HCC with an irradiation schedule selected based on the risk organ. The results suggest that cases in which surgery or RFA is difficult due to tumor size or complications are a good indication for PBT. However, there are few comparisons of PBT with other treatment, and high-level evidence randomized control trials are needed to clarify the role of PBT for HCC.

Conclusion

The results suggest that cases in which surgery or RFA is difficult due to tumor size or complications are a good indication for PBT. However, there are few comparisons of PBT with other treatment, and high-level evidence RCTs are needed to clarify the role of PBT for HCC.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394-424.
2. Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg* 2006;243:321-328.
3. Huang J, Yan L, Cheng Z, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann Surg* 2010;252:903-912.
4. Ng KKC, Chok KSH, Chan ACY, et al. Randomized clinical trial of hepatic resection versus radiofrequency ablation for early-stage hepatocellular carcinoma. *Br J Surg* 2017;104:1775-1784.
5. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693-699.
6. Liau KH, Ruo L, Shia J, et al. Outcome of partial hepatectomy for large (>10 cm) hepatocellular carcinoma. *Cancer* 2005;104:1948-1955.
7. Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial. *Lancet* 2002;359:1734-1739.
8. Takeda A, Sanuki N, Tsurugai Y, et al. Phase 2 study of stereotactic body radiotherapy and optional transarterial chemoembolization for solitary hepatocellular carcinoma not amenable to resection and radiofrequency ablation. *Cancer* 2016;122:2041-2049.
9. Wahl DR, Stenmark MH, Tao Y, et al. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. *J Clin Oncol* 2016;34:452-459.
10. Igaki H, Mizumoto M, Okumura T, Hasegawa K, Kokudo N, Sakurai H. hepatocellular carcinoma. *Int J Clin Oncol* 2018;23:423-433.
11. Spychalski P, Kobiela J, Antoszewska M, et al. Patient specific outcomes of charged particle therapy for hepatocellular carcinoma: A systematic review and quantitative analysis. *Radiother Oncol* 2019;132:127-134.
12. Sugahara S, Nakayama H, Fukuda K, Mizumoto M, Tokita M, Abei M, et al. Proton-beam therapy for hepatocellular carcinoma associated with portal vein tumor thrombosis. *Strahlenther Onkol* 2009;185:782-788.
13. Sekino Y, Okumura T, Fukumitsu N, Iizumi T, Numajiri H, Mizumoto M, et al. Proton beam therapy for hepatocellular carcinoma associated

with inferior vena cava tumor thrombus. *J Cancer Res Clin Oncol* 2020;146:711-720.
14. Fine JP, Robert JG. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509.
15. Therneau T. A package for survival analysis in R. R package version 3.3-1, 2022. Available from: https://CRAN.R-project.org/package=survival. Accessed October 23, 2023.
16. Gerds TA. prodlim: Product-limit estimation for censored event history analysis. R package version 2019.11.13, 2019. Available from: https://CRAN.R-project.org/package=prodlim. Accessed October 23, 2023.
17. Gray B. cmprsk: Subdistribution analysis of competing risks. R package version 2.2-11, 2022. Available from: https://CRAN.R-project.org/package=cmprsk. Accessed October 23, 2023.
18. Varadhan R, Kuk D. crrstep: Stepwise covariate selection for the Fine & Gray competing risks regression model. R package version 2015-2.1, 2015. Available from: https://CRAN.R-project.org/package=crrstep. Accessed October 23, 2023.
19. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2022. Available from: https://www.R-project.org/. Accessed October 23, 2023.
20. Proton Guideline JASTRO 7_13_2017-2.xlsx. Available from: https://www.jastro.or.jp/en/news/proton_guideline_jastro_7_13_2017-2_cmarkandwatermark.pdf. Accessed October 23, 2023.
21. 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.
22. Fukumitsu N, Sugahara S, Nakayama H, Fukuda K, Mizumoto M, Abei M, et al. A prospective study of hypofractionated proton beam therapy for patients with hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2009;74:831-836.
23. Kawashima M, Furuse J, Nishio T, et al. Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma. *J Clin Oncol* 2005;23:1839-1846.
24. Komatsu S, Fukumoto T, Demizu Y, et al. Clinical results and risk factors of proton and carbon ion therapy for hepatocellular carcinoma. *Cancer* 2011;117:4890-4904.
25. Mizumoto M, Okumura T, Hashimoto T, Fukuda K, Oshiro Y, Fukumitsu N, et al. Proton beam therapy for hepatocellular carcinoma: a comparison of three treatment protocols. *Int J Radiat Oncol Biol Phys* 2011;81:1039-1045.
26. Mizumoto M, Oshiro Y, Okumura T, Fukuda K, Fukumitsu N, Abei M, et al. Association between pretreatment retention rate of indocyanine green 15 min after administration and life prognosis in patients with HCC treated by proton beam therapy. *Radiother Oncol* 2014;113:54-59.
27. Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: An update. *Hepatology* 2011;53:1020-1022.
28. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: Clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer* 2004;101:1623-1631.
29. Komatsu S, Demizu Y, Sulaiman NS, et al. Space-making particle therapy for sarcomas derived from the abdominopelvic region. *Radiother Oncol* 2020;146:194-199.
30. Chadha AS, Gunther JR, Hsieh CE, et al. Proton beam therapy outcomes for localized unresectable hepatocellular carcinoma. *Radiother Oncol* 2019;133:54-61.
31. Oshiro Y, Mizumoto M, Okumura T, Fukuda K, Fukumitsu N, Abei M, et al. Analysis of repeated proton beam therapy for patients with hepatocellular carcinoma. *Radiother Oncol* 2017;123:240-245.
32. Sugahara S, Oshiro Y, Nakayama H, Fukuda K, Mizumoto M, Abei M, et al. Proton beam therapy for large hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2010;76:460-466.
33. Mizumoto M, Okumura T, Hashimoto T, Fukuda K, Oshiro Y, Fukumitsu N, et al. Evaluation of liver function after proton beam therapy for hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2012;82:e529-e535.
34. Jang WI, Bae SH, Kim MS, et al. A phase 2 multicenter study of stereotactic body radiotherapy for hepatocellular carcinoma: Safety and efficacy. *Cancer* 2020;126:363-372.
35. Qi WX, Fu S, Zhang Q, Guo XM. Charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: A systematic review and meta-analysis. *Radiother Oncol* 2015;114:289-295.
36. Sanford NN, Pursley J, Noe B, et al. Protons versus photons for unresectable hepatocellular carcinoma: Liver decompensation and overall survival. *Int J Radiat Oncol Biol Phys* 2019;105:64-72.
37. Hasan S, Abel S, Verma V, et al. Proton beam therapy versus stereotactic body radiotherapy for hepatocellular carcinoma: Practice patterns, outcomes, and the effect of biologically effective dose escalation. *J Gastrointest Oncol* 2019;10:999-1009.
38. Beaton L, Dunne EM, Yeung R, et al. Stereotactic body radiotherapy for large unresectable hepatocellular carcinomas: A single institution phase II study. *Clin Oncol (R Coll Radiol)* 2020;32:423-432.
39. Shen PC, Chang WC, Lo CH, et al. Comparison of stereotactic body radiation therapy and transarterial chemoembolization for unresectable medium-sized hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2019;105:307-318.
40. Wong TC, Chiang CL, Lee AS, et al. Better survival after stereotactic body radiation therapy following transarterial chemoembolization in nonresectable hepatocellular carcinoma: A propensity score matched analysis. *Surg Oncol* 2019;28:228-235.
41. Bettinger D, Pinato DJ, Schultheiss M, et al. Stereotactic body radiation therapy as an alternative treatment for patients with hepatocellular carcinoma compared to sorafenib: A propensity score analysis. *Liver Cancer* 2019;8:281-294.
42. Bettinger D, Gkika E, Schultheiss M, et al. Comparison of local tumor control in patients with HCC treated with SBRT or TACE: A propensity score analysis. *BMC Cancer* 2018;18:807.
43. Su T-S, Lu H-Z, Cheng T, et al. Long-term survival analysis in combined transarterial embolization and stereotactic body radiation therapy versus stereotactic body radiation monotherapy for unresectable hepatocellular carcinoma >5 cm. *BMC Cancer* 2016;16:834.
44. Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol* 2013;31:1631-1639.
45. Lee SU, Park J-W, Kim TH, et al. Effectiveness and safety of proton beam therapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. *Strahlenther Onkol* 2014;190:806-814.
46. Shui Y, Yu W, Ren X, et al. Stereotactic body radiotherapy based treatment for hepatocellular carcinoma with extensive portal vein tumor thrombosis. *Radiat Oncol* 2018;13:188.
47. Matsuo Y, Yoshida K, Nishimura H, et al. Efficacy of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein tumor thrombosis/inferior vena cava tumor thrombosis: Evaluation by comparison with conventional three-dimensional conformal radiotherapy. *J Radiat Res* 2016;57:512-523.
48. Xi M, Zhang L, Zhao L, et al. Effectiveness of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombosis. *PLoS One* 2013;8:e63864.
49. Hiroshima Y, Wakatsuki M, Kaneko T, et al. Clinical impact of carbon-ion radiotherapy on hepatocellular carcinoma with Child-Pugh B cirrhosis. *Cancer Med* 2023;12:14004-14014.
50. Su TS, Liang P, Lu HZ, et al. Stereotactic body radiation therapy for small primary or recurrent hepatocellular carcinoma in 132 Chinese patients. *J Surg Oncol* 2016;113:181-187.
51. Yamashita H, Onishi H, Murakami N, et al. Japanese Radiological Society multi-institutional SBRT study group (JRS-SBRTSG). Survival outcomes after stereotactic body radiotherapy for 79 Japanese patients with hepatocellular carcinoma. *J Radiat Res* 2015;56:561-567.
52. Culleton S, Jiang H, Haddad CR, et al. Outcomes following definitive stereotactic body radiotherapy for patients with Child-Pugh B or C hepatocellular carcinoma. *Radiother Oncol* 2014;111:412-417.

53. Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2011;81:e447-e453.
54. The Japan Society of Hepatology. Clinical practice guidelines for hepatocellular carcinoma 2017. https://www.jsh.or.jp/English/examination_en/guidelines_hepatocellular_carcinoma_2017.html. Accessed October 23, 2023.
55. Bush DA, Smith JC, Slater JD, et al. Randomized clinical trial comparing proton beam radiation therapy with transarterial chemoembolization for hepatocellular carcinoma: results of an interim analysis. *Int J Radiat Oncol Biol Phys* 2016;95:477-482.
56. Bush DA, Volk M, Smith JC, Reeves ME, Sanghvi S, Slater JD, deVera M. Proton beam radiotherapy versus transarterial chemoembolization for hepatocellular carcinoma: Results of a randomized clinical trial. *Cancer* 2023;129:3554-3563.
57. Kim TH, Koh YH, Kim BH, et al. Proton beam radiotherapy versus radiofrequency ablation for recurrent hepatocellular carcinoma: A randomized phase III trial. *J Hepatol* 2021;74:603-612.
58. Sekino Y, Tateishi R, Fukumitsu N, et al. Proton beam therapy versus radiofrequency ablation for patients with treatment-naïve single hepatocellular carcinoma: A prospective score analysis. *Liver Cancer* 2022;1-12.
59. Rim CH, Lee JS, Kim SY, Seong J. Comparison of radiofrequency ablation and ablative external radiotherapy for the treatment of intrahepatic malignancies: A hybrid meta-analysis. *JHEP Rep* 2022; 5 100594.