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Long-term outcomes of proton beam therapy in patients with previously untreated hepatocellular carcinoma

Kuniaki Fukuda,[1] Toshiyuki Okumura,[2] Masato Abei,[1] Nobuyoshi Fukumitsu,[2] Kazunori Ishige,[1] Masashi Mizumoto,[2] Naoyuki Hasegawa,[1] Haruko Numajiri,[2] Kayoko Ohnishi,[2] Hitoshi Ishikawa,[2] Koji Tsuboi,[2] Hideyuki Sakurai[2] and Ichinosuke Hyodo[1]

[1]Department of Gastroenterology, Faculty of Medicine; [2]Department of Radiation Oncology and Proton Medical Research Center, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

Key words

Aged patients, Barcelona Clinic Liver Cancer staging, hepatocellular carcinoma, proton beam therapy, vascular tumor thrombi

Correspondence

Hideyuki Sakurai, MD, PhD, Department of Radiation Oncology and Proton Medical Research Center, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan.
Tel: +81-29-853-7100, Fax: +81-29-853-7102;
E-mail: hsakurai@pmrc.tsukuba.ac.jp

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Long-term efficacy of proton beam therapy (PBT) remains unclear for patients with previously untreated hepatocellular carcinoma (HCC). We aimed to study the long-term outcomes of PBT according to Barcelona Clinic Liver Cancer (BCLC) staging classifications in patients with previously untreated HCC. The major eligibility criteria of this observational study were an Eastern Cooperative Oncology Group performance status (PS) 0–2, Child–Pugh grade A or B, previously untreated HCC covered within an irradiation field, and no massive ascites. A total of 66.0–77.0 GyE was administered in 10–35 fractions. Local tumor control (LTC), defined as no progression in the irradiated field, progression-free survival (PFS), and overall survival (OS) were assessed according to BCLC staging. From 2002 to 2009 at our institution, 129 patients were eligible. The 5-year LTC, PFS, and OS rates were 94%, 28%, and 69% for patients with 0/A stage disease (n = 9/21), 87%, 23%, and 66% for patients with B stage disease (n = 34), and 75%, 9%, and 25% for patients with C stage disease (n = 65), respectively. The 5-year LTC and OS rates of 15 patients with tumor thrombi in major vessels were 90% and 34%, respectively. Multivariate analyses revealed that PS (0 versus 1–2) was a significant prognostic factor for OS. No grade 3 or higher adverse effects were observed. PBT showed favorable long-term efficacies with mild adverse effects in BCLC stage 0 to C, and can be an alternative treatment for localized HCC especially when accompanied with tumor thrombi. This study was registered with UMIN Clinical Trials Registry (UMIN000025342).

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide.[1] Many treatment options are currently available, including hepatectomy, liver transplantation, radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE) or radioembolization, and molecular targeted therapy.[2,3] Some new methods of radiation therapy (RT), such as three-dimensional conformal RT, intensity-modulated RT, and stereotactic body RT (SBRT), have been used to treat HCC and demonstrated promising results.[4–6] However, RT has not yet been accepted as a treatment for HCC in the Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy, and is considered a treatment option only for patients who are not eligible for other established local therapies.[7]

Proton beams, unlike conventional X-rays, form a unique Bragg-peak ionization that enables "tumor-targeted radical irradiation".[8,9] Based on this unique property, we first used proton beam therapy (PBT) to treat HCC in 1983 and reported a 5-year local tumor control rate, indicating no progression in the irradiated field, of over 80% and a 5-year survival rate of 24–45% in patients with locoregional HCC, retrospectively.[10–12] Recently, similar good local control of HCC after PBT was reported from other facilities throughout the world.[13–18] However, PBT efficacy and safety in the BCLC staging remains unclear.

Thus, we aimed to study the long-term outcomes of PBT according to BCLC staging classifications in patients with untreated HCC.

Patients and Methods

Patients. Patients with HCC who were treated using PBT were registered at the University of Tsukuba Hospital, Japan, between January 2002 and December 2009. Eligibility criteria for this study were age ≥ 20 years, Eastern Cooperative Oncology Group performance status (PS) 0–2, Child–Pugh grade A or B, no massive ascites, non-irradiated normal liver volume ≥ 500 mL, and previously untreated HCC diagnosed using pathological findings of fine-needle biopsy or typical findings of arterial enhancement and venous washout on dynamic computed tomography (CT) or magnetic resonance imaging (MRI). Solitary HCC and even multiple HCC with or without tumor

thrombi were treated using PBT if all tumors could be covered within the same irradiation field (≤ 135 mm in diameter).

Patient background information and laboratory results were collected before PBT. These data included age, sex, PS, liver disease etiology, comorbidity, blood cell counts, blood biochemistry, tumor markers (alpha-fetoprotein [AFP] and des-gamma-carboxy prothrombin [DCP]), tumor status, and Child–Pugh grade.

This study was approved by the ethics committee of the University of Tsukuba Hospital and conducted in accordance with the ethical standards of the Declaration of Helsinki. All patients were explained about standard therapies and PBT for HCC in detail,[11] and provided written informed consent for this study.

Proton beam irradiation. Before the start of treatment, metallic fiducial markers were implanted percutaneously into the hepatic parenchyma adjacent to the tumors under ultrasound guidance. Custom-made body casts (ESFORM; Engineering System, Matsumoto, Japan) were used to ensure adequate immobilization of each patient during PBT. Treatment planning was performed on respiratory-synchronized CT images taken at 5-mm intervals in the treatment position. The clinical target volume was defined as the gross tumor volume plus 5- to 10-mm margins in all directions. The planning target volume was defined as the clinical target volume plus 8- to 10-mm margins in all directions and an additional 5-mm margin in the caudal direction for respiratory movement. The clinical target volume was homogeneously covered with more than 90% of the prescribed dose using the proton beam spread-out Bragg peaks.[8] The treatment planning system automatically derived the settings required for beam delivery including ridge filters, the range shifter, the collimator, and a bolus. Proton dosimetry was verified using a plastic phantom for each patient prior to treatment initiation.[19]

Proton beams of 155–250 MeV generated by an accelerator with a synchrotron were used for treatment. Beams were delivered using a rotation gantry under respiratory gating through one to three ports with coplanar angles.[20] During each treatment session, the positional relationship between the center of the irradiated field and the implanted fiducial marker was examined using the orthogonal fluoroscopy unit attached to the treatment unit. Reported doses are expressed in gray equivalents (GyE), defined as the proton dose corrected by its relative biological effectiveness. The relative biological effectiveness value of the proton beam was 1.1.

Three irradiation protocols were used for PBT, depending on tumor location. The feasibility of each protocol has been already evaluated and confirmed in our previous report.[21] For the gastrointestinal (GI) protocol, a total dose of 77.0 GyE in 35 fractions was administered for tumors located within 2 cm of a digestive organ. In order to reduce gastrointestinal adverse events, the target field was cut by using multileaf collimators from the middle of treatment.[22] For the hilar protocol, 72.6 GyE in 22 fractions was administered for tumors located within 2 cm of the porta hepatis. For the standard protocol, 66.0 GyE in 10 fractions was administered for peripheral tumors located more than 2 cm from both the GI tract and porta hepatis.[21] All patients received PBT for 5 days each week.

Follow-up and evaluation. Abdominal CT or MRI images and the serum tumor markers AFP and DCP were evaluated every 2–4 months after PBT for patients without disease progression. When progression was suspected based on imaging or tumor marker examinations, patients were followed up at shorter intervals. Disease progression was evaluated according to the Response Criteria in Solid Tumors (RECIST) version 1.0. Local progression was defined as enlargement of the targeted HCC and/or new lesions that occurred in the irradiated field or its boundary. When the disease progression was found, appropriate therapies were given. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 2.0).

Statistical analysis. Overall survival (OS), progression-free survival (PFS), and local tumor control (LTC) were estimated using the Kaplan–Meier method. The survival period was defined as the time between PBT initiation and the event date (any death for OS and any death or disease progression for PFS). The LTC period was defined as the time between PBT initiation and local progression in the irradiated field. Patients without an event were censored at the date of the last event-free confirmation. Differences in survival or LTC times between groups were evaluated using the log-rank test. Factors affecting survival were identified by multivariate analysis using the Cox proportional hazards model. A P-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 21.0 statistical software (IBM, Armonk, NY, USA).

Results

Patients. Between January 2002 and December 2009, 550 patients with HCC were treated using PBT at our hospital. Among them, 135 patients had previously untreated HCC, and 131 met the eligibility criteria. Two patients withdrew consent immediately after PBT. In total, 129 patients were followed and analyzed. The number of patients who received GI protocol, hilar protocol, and standard protocol were 30, 45, and 54, respectively.

Patient and tumor characteristics are shown in Table 1. The median age was 72 years. One-fifth of the patients had severe comorbidities, such as cardiovascular disease, chronic pulmonary disease, cerebrovascular disease, renal failure, active infectious disease, double cancers, and intractable disease, and 12% patients had tumor thrombi that extended to the first branch or main trunk of the portal vein (Vp3/4) or inferior vena cava (IVC). The numbers of patients with very early stage (0), early stage (A), intermediate stage (B), and advanced stage diseases (C) according to BCLC staging were 9, 21, 34, and 65, respectively.

Tumor control and survival. All 129 patients completed PBT without experiencing severe complications. No treatment-related deaths were observed. The median patient observation period was 55 months (95% confidence interval [CI], 43–67 months). Fifty-eight patients died during the study period due to HCC (n = 25), liver failure (n = 9), non-liver-related disease (n = 16), or unknown reasons (n = 8). Local progression was observed in 12 patients. Disease progression at any site was observed in 70 patients. As for subsequent treatments after tumor progression, 16 patients were treated with TACE, 13 patients were treated with PBT, eight patients were treated with RFA, two patients were treated with percutaneous ethanol injection therapy, one patient was treated with RT, one patient was treated with hepatic arterial infusion chemotherapy, and 19 patients were treated with the best supportive care alone. The treatments for the remaining 10 patients were unknown. No patients received hepatectomy or liver transplantation.

The 5-year LTC rates were 94% (95% CI, 82–100%) for 0/A stage, 87% (95% CI, 75–99%) for B stage, and 75% (95%

Table 1. Clinical characteristics of patients and tumors

	Total (*n* = 129)	BCLC 0/A (*n* = 30)	BCLC B (*n* = 34)	BCLC C (*n* = 65)
Age (years)				
Median (range)	72 (39–86)	72 (46–81)	69 (39–82)	74 (57–86)
≧75 years, *n* (%)	50 (38.8)	11 (36.7)	7 (20.6)	32 (49.2)
Gender, *n* (%)				
Male	86 (66.7)	21 (70)	27 (79.4)	38 (58.5)
Female	43 (33.3)	9 (30)	7 (20.6)	27 (41.5)
Etiology, *n* (%)				
HCV infected	95 (73.6)	25 (83.3)	21 (61.8)	49 (75.4)
HBV infected	7 (5.4)	3 (10.0)	2 (5.9)	2 (3.1)
Other	19 (14.7)	0 (0)	9 (26.5)	10 (15.4)
Unknown	8 (6.2)	2 (6.7)	2 (5.9)	4 (6.2)
PS, *n* (%)				
0	70 (54.3)	30 (100)	34 (100)	6 (9.2)
1	50 (38.8)	0 (0)	0 (0)	50 (76.9)
2	9 (7.0)	0 (0)	0 (0)	9 (13.8)
Platelet count ($\times 10^4/mm^3$)				
Median (range)	11.7 (2.6–40.7)	11.0 (3.3–35.0)	13.4 (3.7–40.7)	11.5 (2.6–28.1)
$<10 \times 10^4/mm^3$, *n* (%)	41 (31.8)	13 (43.3)	8 (23.5)	20 (30.8)
$\geqq 10 \times 10^4/mm^3$, *n* (%)	84 (65.1)	15 (50)	26 (76.5)	43 (66.2)
Unknown	4 (3.1)	2 (6.7)	0 (0)	2 (3.1)
Serum AFP (ng/mL)				
Median (range)	27.5 (2–115,591)	25.0 (3–9,535)	34.5 (2–13,055)	29.5 (2–115 591)
<20 ng/mL, *n* (%)	51 (39.7)	13 (43.3)	15 (44.1)	23 (35.4)
≧20 ng/mL, *n* (%)	77 (59.5)	17 (56.7)	19 (55.9)	41 (63.1)
Unknown	1 (0.8)	0 (0)	0 (0.0)	1 (1.5)
Serum DCP (mAU/mL)				
Median (range)	76 (6–206,190)	25 (8–3,676)	146 (6–46,819)	135 (10–206 190)
<100 mAU/mL, *n* (%)	67 (52.7)	25 (83.3)	14 (41.2)	28 (43.1)
≧100 mAU/mL, *n* (%)	59 (45.0)	4 (13.3)	20 (58.8)	35 (53.8)
Unknown	3 (2.3)	1 (3.3)	0 (0)	2 (3.1)
Child–Pugh class, *n* (%)				
A	101 (78.3)	24 (80)	32 (94.1)	45 (69.2)
B	28 (21.7)	6 (20)	2 (5.9)	20 (30.8)
Tumor no., *n* (%)				
1	96 (74.4)	22 (73.3)	23 (67.6)	51 (78.5)
2	23 (17.8)	8 (26.7)	6 (17.6)	9 (13.8)
≧3	10 (7.8)	0 (0)	5 (14.7)	5 (7.7)
Maximum tumor size, *n* (%)				
Median (range)	39 (10–135)	22 (10–30)	42 (32–86)	40 (15–135)
≦3 cm	50 (38.8)	30 (100)	0 (0)	20 (30.8)
>3 cm	79 (61.2)	0 (0)	34 (100)	45 (69.2)
Tumor thrombi, *n* (%)				
Vp 0, 1	112 (86.8)	30 (100)	34 (100)	48 (73.8)
Vp 2	2 (1.6)	0 (0.0)	0 (0.0)	2 (3.1)
Vp 3	6 (4.7)	0 (0.0)	0 (0.0)	6 (9.2)
Vp 4	7 (5.4)	0 (0.0)	0 (0.0)	7 (10.8)
IVC	2 (1.6)	0 (0.0)	0 (0.0)	2 (3.1)
Protocol, *n* (%)				
Standard	54 (41.9)	14 (46.7)	17(50)	23 (35.4)
Hilar	45 (34.9)	9 (30)	14 (41.2)	22 (33.8)
Gastrointestinal	30 (23.3)	7 (23.3)	3 (8.8)	20 (30.8)
Serious non-liver-related diseases, *n* (%)				
Yes	26 (20.2)	2 (6.7)	7 (20.6)	17 (26.2)
No	103 (79.8)	28 (93.3)	27 (79.4)	48 (73.8)

AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; HBV, hepatitis B virus; HCV, hepatitis C virus; PS, Eastern Cooperative Oncology Group performance status.

CI, 58–92%) for C stage ($P = 0.228$) (Fig. 1a). The 5-year PFS rates were 28% (95% CI, 9–46%) for 0/A stage patients, 23% (95% CI, 8–38%) for B stage patients, and 9% (95% CI, 0–18%) for C stage patients ($P = 0.057$) (Fig. 1b). The median PFS times were 23 months (95% CI, 12–34 months) for 0/A stage patients, 22 months (95% CI, 14–31 months) for B stage patients, and 16 months (95% CI, 14–18 months) for C stage patients. The 5-year OS rates were 69% (95% CI, 49–89%) for

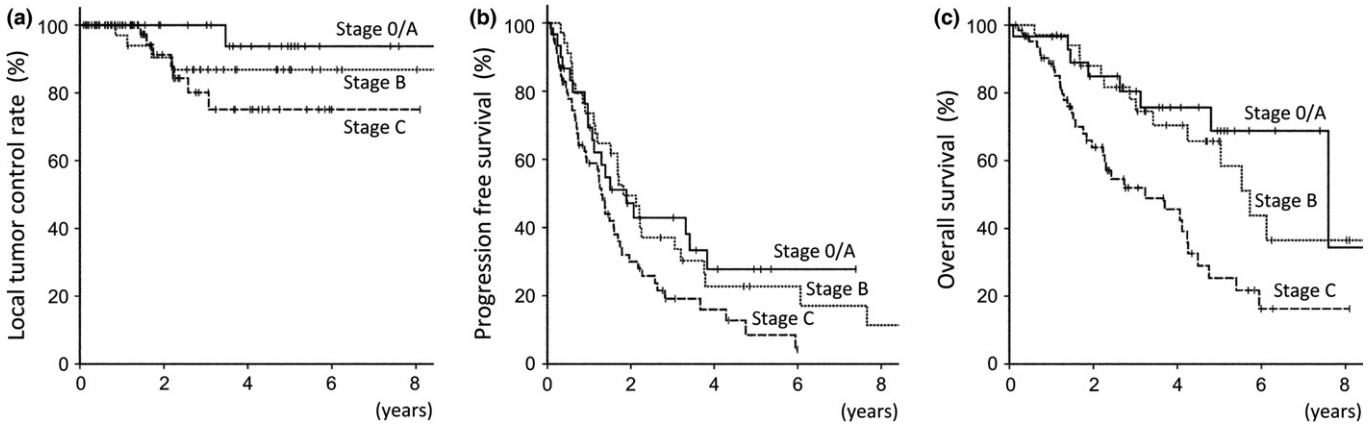

Fig. 1. Kaplan–Meier curves of LTC, PFS, and OS according to BCLC stage in previously untreated HCC patients treated with PBT. Kaplan–Meier curves of the local tumor control (a), progression-free survival (b), and overall survival (c). BCLC staging: stage 0/A stage (solid line; n = 30), B stage (dotted line; n = 34), and C stage (broken line; n = 65). BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; LTC, local tumor control; OS, overall survival; PBT, proton beam therapy; PFS, progression free survival.

0/A stage patients, 66% (95% CI, 48–84%) for B stage patients, and 25% (95% CI, 11–40%) for C stage patients ($P < 0.001$) (Fig. 1c). The median OS times were 92 months (95% CI, 44–141 months) for 0/A stage patients, 70 months (95% CI, 56–83 months) for B stage patients, and 39 months (95% CI, 18–60 months) for C stage patients. There were significant differences in OS between 0/A stage and C stage patients ($P = 0.002$) as well as between B stage and C stage patients ($P = 0.005$). The LTC and OS rates in 15 patients with the extended tumor thrombi (Vp 3/4 or IVC) were 90% (95% CI, 71–100%) and 34% (95% CI, 9–59%) at 5 years, respectively. The median OS for those patients was 50 months (95% CI, 12–88 months).

Factors affecting local tumor control and survival. Multivariate analysis results for LTC and OS are shown in Table 2. There was no significant factor predictive for LTC. On the other hand, PS was the only significant prognostic factor for OS. The median OS times of the patients with PS0, PS1, and PS2 were 74 months (95% CI, 47–100 months), 45 months (95% CI, 23–67 months), and 18 months (95% CI, 14–23 months), respectively (Fig. 2).

Although maximum tumor size and vascular involvement are commonly reported prognostic factors for OS, neither factor was identified in present study (Table 2). LTC rate for HCC <3 cm vs. HCC ≥3 cm was 81% (95% CI 66–96) vs. 86% (95% CI 77–96) at 5 years ($P = 0.85$), and OS was 57% (95% CI 39–75) vs. 43% (95% CI 30–57) at 5 years ($P = 0.16$). The results of multivariate analysis did not change when we used a tumor diameter cutoff of 5 cm.

Figure 3 shows CT images of a successfully treated 81-year-old woman with a large HCC (maximum diameter of 120 mm) in the right hepatic lobe with a hepatic venous tumor thrombus, which reached the right cardiac atrium through the IVC (Fig. 3a). She was treated with PBT targeting the main tumor and tumor thrombus (Fig. 3b). Irradiation of 72.6 GyE in 22 fractions was administered for 30 days. The main tumor and tumor thrombus markedly shrunk, and the IVC tumor thrombus disappeared 2 months after the completion of PBT (Fig. 3c). She did not have remarkable adverse event except for mild and transient radiation pneumonitis 12 month after PBT. She survives for more than 9 years without any progression of HCC.

Table 2. Multivariate analysis using the cox regression model for LTC and OS

	LTC		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years)				
<75 vs. ≧75	0.57 (0.13–2.62)	0.472	1.62 (0.84–3.13)	0.148
Gender				
Female vs. Male	1.43 (0.32–6.46)	0.643	1.22 (0.63–2.34)	0.559
Etiology				
Non-HCV vs. HCV	0.49 (0.07–3.26)	0.460	1.23 (0.54–2.80)	0.619
PS				
0 vs. 1, 2	3.57 (0.75–17.0)	0.111	2.16 (1.08–4.32)	**0.030**
Platelet ($\times 10^4$/mm^3)				
≧10 vs. <10	0.57 (0.09–3.57)	0.544	1.57 (0.83–2.98)	0.168
AFP (ng/mL)				
<20 vs. ≧20	2.36 (0.55–10.0)	0.246	1.36 (0.74–2.51)	0.325
DCP (mAU/mL)				
<100 vs. ≧100	0.15 (0.02–1.09)	0.061	1.47 (0.77–2.80)	0.238
Child–Pugh class				
A vs. B	0.71 (0.10–5.34)	0.743	1.80 (0.78–4.13)	0.168
No. tumors				
Single vs. Multiple	1.31 (0.29–6.05)	0.727	1.07 (0.55–2.09)	0.838
Tumor size (cm)				
≦3 vs. >3	2.33 (0.42–12.8)	0.330	1.32 (0.70–2.49)	0.397
Tumor thrombi				
Vp0/1 vs. Vp2/3/4, IVC	0.85 (0.08–9.25)	0.894	0.85 (0.38–1.89)	0.682
Protocol				
Standard or Hilar vs. GI	2.89 (0.61–13.7)	0.180	0.96 (0.48–1.90)	0.904

Bold text indicates the statistically significant difference with a *P*-value.
AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; GI, gastrointestinal; HCV, hepatitis C virus; IVC, inferior vena cava; LTC, local tumor control; OS, overall survival; PS, Eastern Cooperative Oncology Group-performance status.

Toxicities and complications. No patients had severe complications due to PBT or adverse events higher than grade 2, except for hematologic abnormalities. Hematologic toxicities were difficult to assess the relation to PBT, because cirrhotic

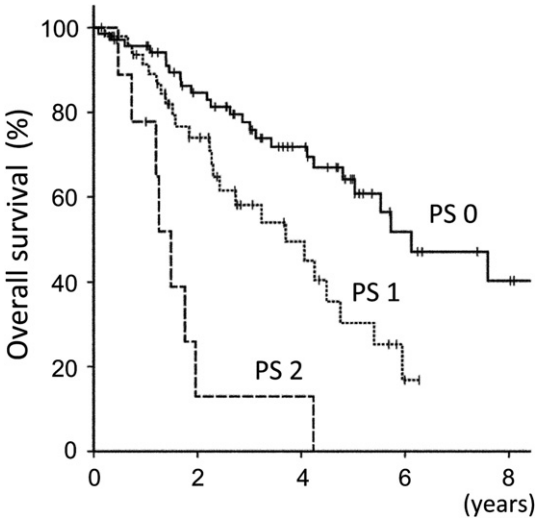

Fig. 2. Kaplan–Meier curves of OS according to PS in previously untreated HCC patients treated with PBT. PS 0 (solid line; *n* = 70), PS 1 (dotted line; *n* = 50) and PS 2 (broken line; *n* = 9). HCC, hepatocellular carcinoma; OS, overall survival; PBT, proton beam therapy; PS, Eastern Cooperative Oncology Group performance status.

patients usually have pancytopenia due to splenomegaly. Indeed, 20% of the patients had grade 2 (<75 000/mm^3) and 5.5% grade 3 (<50 000/mm^3) thrombocytopenia before PBT. However, no patient required a blood transfusion or PBT cessation during treatment. Radiation dermatitis was common, but no patient had grade 3 or higher dermatitis.

Discussion

Proton beam therapy exhibited excellent long-term efficacy and good safety in untreated patients with localized HCC that could be covered within the irradiation field. Our survival results are consistent with those in the BCLC staging report.[23] PBT may be beneficial not only in patients with operable HCC but also in those with operation risks due to comorbidities and with inoperable advanced HCC.

All LTC duration, PFS, and OS showed very similar trends decreasing in accordance with advanced stage of the BCLC. These were compatible with those in previous published reports for the BCLC stage.[23,24] The present study of treatment-naive patients with HCC confirmed that PBT yielded good LTC, as seen in previous reports for PBT.[11,12,18] The 5-year OS (69%) in patients with BCLC 0/A stage disease was comparable to that reported for patients who underwent hepatectomies and local ablative therapies, such as RFA.[23–26] These results indicate that PBT can be considered an additional curative treatment option for patients with HCC. Although our PBT results seem inferior to those of liver transplantation within the Milan criteria,[27] the majority of our patients were not eligible for liver transplantation because of their advanced age (median, 72 years), poor PS (PS ≥ 1; 46%), or severe comorbidities (20%). In fact, there are many HCC patients who refuse surgery or cannot receive it. Advanced age was significantly associated with higher mortality rates following hepatic resection or RFA in a large Japanese national survey of HCC patients.[28] PBT would be a promising treatment for such patients because of its low invasiveness. The subsequent treatments with multimodality for the recurrent lesions contribute on OS prolongation. Taking these together with our present results into consideration, it is suggested that initial PBT could achieve good LTC safely and this would rather favorably influence the subsequent treatment outcome.

Multivariate analysis showed no significant factor affecting LTC rate of PBT for HCC. This is a unique virtue of PBT because tumor diameter is usually the risk factor of local recurrence. The outcomes for patients with large HCCs are generally worse because of the aggressive malignant behavior, which is characterized by potential metastases and vascular

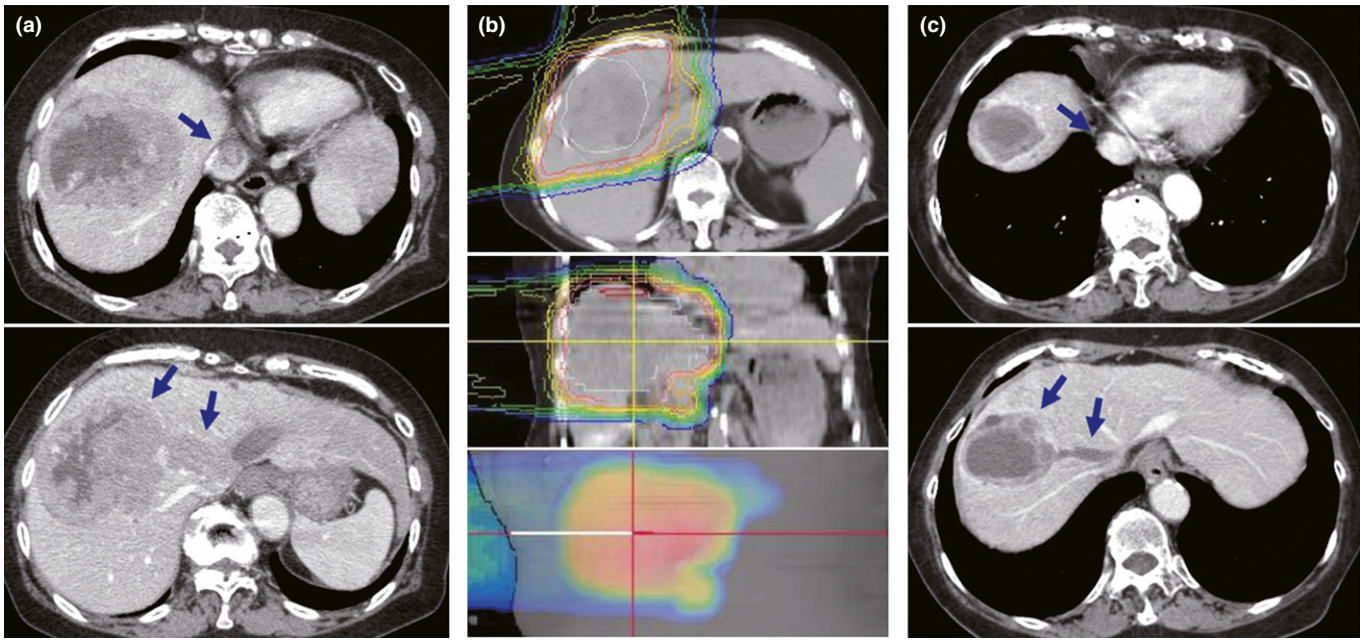

Fig. 3. Computed tomography (CT) images of an 81-year-old woman with advanced HCC involving a massive tumor thrombus in the IVC. Images were obtained before PBT (a), during isodose distribution of PBT (b), and 2 months after the completion of PBT (c). PBT demonstrated marked regression of both the main tumor and tumor thrombus (arrows). Isodose distribution is shown using contour lines (red line, 90% isodose; blue line, 10% isodose). HCC, hepatocellular carcinoma; IVC, inferior vena cava; PBT, proton beam therapy.

invasions. Microsatellite lesions are associated with approximately 50% of HCCs, including the smaller ones (2.5–5.0 cm), and those tumors cannot always be resected during surgery or ablated using RFA for anatomical and technical reasons.[29,30] By contrast, PBT can target tumors, including microsatellite lesions, by securing adequate safety irradiation margins, and this may account for the high LTC rate for patients with large HCCs.

Performance status was the only significant predictor of OS by multivariate analysis, and PS may be a good prognostic indicator in the HCC patients treated with PBT as well as other cancer patients. Although Child–Pugh score is generally reported as a prognostic factor of HCC patients, the score was not selected as a significant prognostic factor in this study. This might be because of confounding with PS, or simply small sample size. Large tumor, which has been commonly identified as a poor prognostic factor for HCC, did not affect OS for patients treated with PBT in the present study. Similar result was reported that tumor size did not affect OS of patients who underwent hepatectomy for solitary HCC.[31] PBT can cover the tumor with adequate margin and provide good LTC, even if a large HCC exists astride both lobes of the liver. For HCC with major vessel invasion, PBT can also treat with adequate margin. Indeed, the patients advanced HCC with major vessel tumor thrombi (Vp 3/4 or IVC) demonstrated favorable survival. These results may be superior to those for any other therapeutic options, including conventional radiotherapy, sorafenib therapy, and hepatic arterial infusion chemotherapy.[32,33] PBT has the potential to prolong survival for some populations of HCC patients who cannot be rescued by other therapies, as in the case shown in Figure 3.

Severe PBT adverse events were infrequent in the present study. This differs greatly from conventional X-ray radiotherapy, even including modern three-dimensional conformal RT or SBRT, which still sometimes induces severe radiation-induced liver disease and worsens liver function.[34,35] We used three types of protocol, which were evaluated for efficacy and safety in a previous report.[21] Although HCC adjacent to alimentary tract are contraindicated for RT generally, PBT with GI protocol could be completed in all patients without severe adverse events. Further studies are required to clarify which patients should be treated with modern RT techniques or particle beam therapies, such as PBT and carbon ion beam therapy.[36]

The major limitation of this study is a study including a selection bias of patients with heterogeneous background. Most subjects were patients introduced to our hospital for PBT, because they refused surgery or conventional interventional radiotherapy. To improve this bias, we analyzed outcomes of patients classified according to BCLC stages, and compared these results with the contemporary large-scale nationwide follow-up study in Japan.[26] The long-term high LTC rates for patients of each HCC stage suggest that PBT has promising therapeutic potential. The downside of PBT is that there are small numbers of facilities where it can be administered because of high construction and maintenance costs, and as such, the treatment is expensive (3 million yen in our hospital). This has made it difficult to generalize PBT into clinical practice and conduct large multicenter comparative studies using this modality. However, the number of PBT facilities has increased gradually in recent years, and its associated costs are decreasing.

In conclusion, PBT achieved long-term tumor control with less toxicity. PBT is a viable treatment option for localized HCC, and we now plan a multicenter controlled study comparing PBT and hepatectomy.

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Disclosure Statement

The authors have no conflict of interest to declare.

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