



A comparison of the outcomes between surgical resection and proton beam therapy for single primary hepatocellular carcinoma

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Abstract

Purpose There are many treatment choices for hepatocellular carcinoma (HCC), one of which is proton beam therapy (PBT). The purpose of this study was to compare surgical resection (SR) and PBT to clarify the prognostic factors for operable HCC based on a single institution's database.

Methods Patients with single primary nodular HCC ≤ 100 mm without vessel invasion on pretreatment imaging were divided into the SR group and PBT group. In the PBT group, the patients with unresectable HCC due to their liver function and/or performance status were excluded.

Results There were 314 and 31 patients who underwent SR and PBT, respectively. The median survival time in the SR group was significantly better than in the PBT group (104.1 vs. 64.6 months, $p=0.008$). Regarding the relapse-free survival (RFS), there was no significant difference between the SR and PBT groups (33.8 vs. 14.0 months, $p=0.099$).

Conclusion The RFS was comparable between the PBT and SR groups. However, the PBT group had a significantly worse overall survival than the SR group. SR may therefore be favorable as an initial treatment for HCC compared to PBT.

Keywords Hepatocellular carcinoma · Proton beam therapy · Surgical resection

Abbreviations

HCC	Hepatocellular carcinoma
PBT	Proton beam therapy
SR	Surgical resection
PS	Performance status
RFS	Relapse-free survival
RFA	Radiofrequency ablation
TACE	Transarterial chemoembolization
CTCAE	Common Terminology Criteria for Adverse Events
CD	Clavien–Dindo
ICG R15	Indocyanine green retention rate at 15 min

OS	Overall survival
HR	Hazard ratio
CI	Confidence interval
AFP	Alpha-fetoprotein
PSM	Propensity score matching

Introduction

Hepatocellular carcinoma (HCC) is one of the most common and deadly cancers as the fifth-most common cause of cancer-related death worldwide [1, 2]. There are many treatment choices for HCC, including surgical resection (SR), liver transplantation, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), molecular-targeted drugs [3], radiation therapy, and proton beam therapy (PBT). PBT has a Bragg peak peculiar to a charged particle beam that enables the delivery of a conformal high dose to a localized target volume, which improves the local control rate and reduces the rate of normal tissue impairment [4]. Some reports have shown a 5-year local tumor control rate of over 80% and a 5-year survival rate of 24–45% in patients with locoregional HCC [5–7]. The

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efficacy and safety of PBT for HCC are being increasingly recognized, and PBT may be considered a curative treatment similar to SR and RFA in selected patients [7, 8]. However, most previous reports suggesting the efficacy of PBT targeted cases of HCC that were unresectable due to a poor liver function and/or performance status (PS) [9]. No report has compared the long-term outcomes between PBT and SR for HCC.

The present study compared PBT and SR to clarify the prognostic factors for operable HCC based on a single institution's database.

Methods

The clinical records of patients who received primary treatment for HCC between August 2003 and November 2017 were reviewed. Patients who received SR or PBT for single nodular HCC ≤ 100 mm without vessel invasion on pretreatment imaging (potential candidates for PBT) were extracted, and those who were eligible for both SR and PBT were identified. Indications for therapies of HCC were determined at a weekly cancer board meeting. HCC was diagnosed before treatment by typical findings of computed tomography or magnetic resonance imaging or pathological findings of a fine-needle biopsy in cases for which a pretreatment diagnosis was difficult to determine by imaging. The patients had the details of HCC treatment, including the therapeutic benefits, risks, and outcomes of different treatment modalities, explained to them. Shared decisions were made between patients and clinicians after the delivery of this detailed explanation.

The patients' background information and laboratory results were collected and analyzed retrospectively. The variables used in this study were as follows: age, sex, viral infection, blood cell counts, blood biochemistry, tumor markers, tumor status, and Child–Pugh grade. PBT-related toxicities and complications of SR were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5 (National Cancer Institute, Bethesda, MD, USA), and Clavien–Dindo (CD) Classification, respectively [10].

This study was retrospective, and we obtained approval (No. 1856) from the Institutional Review Board of Shizuoka Cancer Center for the exception of patients' consent. In addition, the content of this study was presented in the ethical disclosure section of our institution's website (<https://www.scchr.jp/clinicaltrial/wp-content/uploads/sites/13/2016/11/keizi30-8-12.pdf>), and all patients had opportunity to opt out of the study. This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. All patients were informed of the details of the standard therapies and PBT for HCC.

SR procedure

The suitability of SR was determined according to Makuuchi's criteria [11]. The hepatic reserve was assessed using the Child–Pugh classification [12] and liver damage criteria [13], including the indocyanine green retention rate at 15 min (ICG R15). The details of the SR strategy and procedure have been previously reported [14]. The types of hepatectomies were defined according to the Brisbane 2000 terminology as minor (two liver segments or fewer) or major (three liver segments or more) [15].

Proton beam irradiation

In this study, patients selected PBT therapy after being informed that they were eligible for both SR and PBT therapies. Patients were deemed eligible for PBT if they had a single nodular HCC ≤ 100 mm without vessel invasion on pretreatment imaging. Before treatment planning, metallic fiducial markers were implanted in the vicinity of the target tumor as landmarks. The clinical target volume involved the tumor volume with a 5–10-mm margin in all directions. The schedule of fractionated PBT was selected from among three options depending on the tumor location according to the proposal of the Japanese Society for Radiation Oncology. A total dose of 66.0 GyE in 10 fractions was selected for peripheral liver tumors, 72.6–76.0 GyE in 20–22 fractions was selected for hepatic hilar tumors, and 74.0–76.0 GyE in 37–38 fractions was selected for tumors that were adjacent to the gastrointestinal tract [16, 17].

Statistical analyses

Continuous variables are presented as the median and range and were compared using the Mann–Whitney *U* test. The categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. The overall survival (OS) and relapse-free survival (RFS) were estimated using the Kaplan–Meier method. The survival period was defined as the time between the day of SR or PBT conclusion and the event date (any death for the OS and recurrence for the RFS). Differences in the survival and relapse-free time between the two groups were evaluated using the log-rank test. Factors affecting the survival and recurrence were identified by a multivariate analysis using the Cox proportional hazards model. A *p* value < 0.05 was considered statistically significant. To minimize the influence of potential confounders on the selection bias, propensity scores were generated using binary logistic regression. Independent variables entered into the propensity model included the performance status, platelet count and viral infection. One-to-one

matching between the groups was accomplished using the nearest-neighbor matching method. All statistical analyses were performed using the EZR software program (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Patients

During the study period, 799 patients underwent primary treatment for HCC. We extracted 540 patients with single nodular HCC ≤ 100 mm without vessel invasion. We excluded 120 patients receiving radiofrequency ablation. Among the 106 patients in the PBT group, we extracted 31 who were eligible for both SR and PBT but refused SR and ultimately elected to undergo PBT. The present study ultimately included 314 patients as the SR group and 31 as the PBT group (Fig. 1).

Patient characteristics

The patient and tumor characteristics are shown in Table 1. This study included 269 men and 76 women with a median age of 71 years (range 39–87 years). The median tumor size was 35 mm (7–100 mm). The SR group included significantly fewer patients with a poor PS than the PBT group. The platelet count in the SR group was significantly higher than in the PBT group. In the PBT group, all of the patients completed PBT with a total median dose of 73.5 GyE (range 47.6–78.4 GyE). The prescribed dose was administered at the discretion of the treating physician.

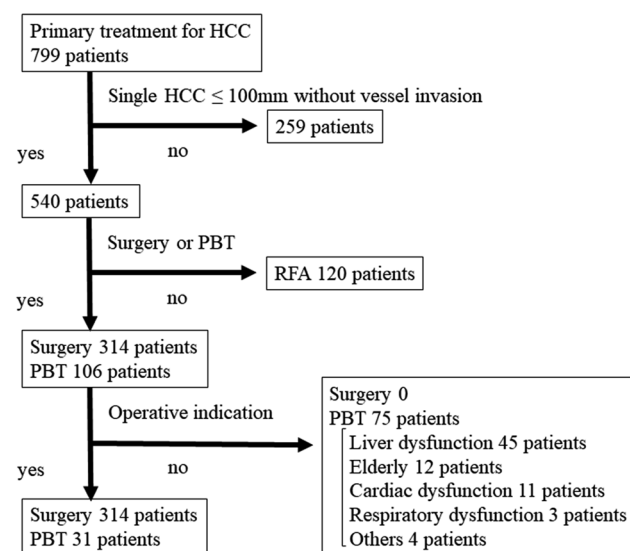


Fig. 1 Study cohort selection flowchart

Results of univariate and multivariate analyses to identify the prognostic factors and predictors of recurrence

In the SR group and PBT group, the median length of follow-up was 64.2 months (95% CI 56.1–71.8) and 56.3 months (95% CI 22.2–82.3), respectively (Kaplan–Meier estimate), with no significant differences between periods ($p=0.070$). The 3- and 5-year survival rates and median survival time were significantly better in the SR group than in the PBT group (84.5% vs. 69.2%, 75.8% vs. 51.1% and 104.1 vs. 64.6 months, respectively: $p=0.008$) (Fig. 2a). A univariate analysis of the OS is shown in Table 2. A multivariate analysis showed that PBT for HCC (hazard ratio [HR] 2.188, 95% confidence interval [CI] 1.185–4.038, $p=0.008$), alpha-fetoprotein (AFP) (HR 2.054, 95% CI 1.372–3.076, $p=0.003$), the PS (HR 2.039, 95% CI 1.261–3.297, $p=0.004$) and age (HR 1.787, 95% CI 1.187–2.691, $p=0.027$) were independent prognostic factors (Table 2).

Conversely, the 3- and 5-year RFS rates of the SR vs. PBT groups were 47.9% vs. 38.9% and 37.3% vs. 31.1%, respectively, and the median RFS was 33.8 vs. 14.0 months with no significant difference between the groups ($p=0.099$) (Fig. 2b). Furthermore, a multivariate analysis showed that higher AFP (HR 1.606, 95% CI 1.205–2.141, $p<0.001$) and aspartate aminotransferase levels (HR 1.466, 95% CI 1.092–1.967, $p=0.011$) were independent prognostic factors (Table 2).

A comparison of complications after treatment

In the SR group, complications of CD [10] Grade \geq IIIa were confirmed in 34 patients (10.8%). One patient (3.2%) experienced grade 3 toxicity (CTCAE) of gastric ulcer in the PBT group, and the rates of toxicities or complications were not significantly different between the SR and PBT groups ($p=0.343$). The median postoperative hospital stay in the SR group was 10 days (range 3–103 days), whereas, in principle, PBT was conducted at the outpatient clinic, so hospitalization was not necessary. The Grade \geq IIIa complications in the SR group were bile leakage (20 cases), postoperative bleeding (4 cases), refractory ascites (4 cases), aspiration pneumonia (3 cases), arrhythmia (2 cases), pleural effusion (2 cases), wound dehiscence (1 case), intraabdominal abscess (1 case) and stomach ulcer (1 case).

A comparison of recurrence sites, therapy for recurrence and causes of death

There was no significant difference in the recurrence rate between the SR and PBT groups (52.9% vs. 51.6%, $p=1.000$). However, the PBT group had local recurrence significantly more frequently than the SR group (19.4% vs. 2.2%, $p<0.001$)

Table 1 Patient and tumor characteristics in the surgical resection and proton beam therapy groups

	Surgery group (n = 314)	PBT group (n = 31)	p
Age (years) ^a	70 (39–87)	72 (51–84)	0.174
Gender			
Male	249 (79.3)	20 (64.5)	0.069
Female	65 (20.7)	11 (35.5)	
Viral infection			
HCV	128 (40.8)	18 (58.1)	0.292
HBV	55 (17.5)	4 (12.9)	
HCV + HBV	1 (0.3)	0 (0)	
Non-HBV and non-HCV	130 (41.4)	9 (29.0)	
Performance status			
0	269 (85.6)	20 (64.5)	0.012
1	42 (13.4)	10 (32.3)	
2	3 (1.0)	1 (3.2)	
Platelet count ($\times 10^4/\text{mm}^3$) ^a	15.6 (4.8–37.1)	13.2 (5.0–22.6)	0.002
Aspartate aminotransferase (U/L) ^a	33 (16–128)	34 (14–103)	0.869
Alanine aminotransferase (U/L) [†]	33 (5–191)	27 (7–85)	0.151
Albumin (g/dL) ^a	4.2 (2.3–5.6)	4.0 (3.3–4.9)	0.104
α -Fetoprotein (ng/mL) ^a	8.4 (1.2–199,133)	11.3 (1.6–40,735)	0.941
PIVKA-II (mAU/mL) ^a	111.5 (1–446,000)	149.0 (14–5,370)	0.588
Child–Pugh grade			
A	309 (98.4)	29 (93.5)	0.124
B	5 (1.6)	2 (6.5)	
Tumor size (mm) ^a	35.0 (7–100)	35.0 (10–90)	0.670
Type of hepatectomies			
Minor	310 (98.7)		
Major	4 (1.3)		
Methods of irradiation			
66 GyE/10 Fr		8 (25.8)	
72.6–76 GyE/20–22 Fr		22 (71.0)	
74–76 GyE/37–38 Fr		1 (3.2)	
Treatment-related complications of grade ≥ 3	34 (10.8) (CD)	1 (3.2) (CTCAE)	0.343

Percentages are shown in parentheses unless otherwise indicated

HCV hepatitis C virus, HBV hepatitis B virus, PIVKA-II protein induced by vitamin K absence-II, CD Clavien–Dindo, CTCAE common terminology criteria for adverse events

^aValues are the median (range)

(Table 3). In addition, there was a significant difference among the kinds of therapy for recurrence (SR, PBT and RFA vs. others), as one SR, one PBT and no RFA therapies tended to be selected for recurrence lesions in the PBT group ($p=0.031$). Furthermore, the PBT group had significantly larger proportion of patients who died of pneumonia than the SR group (25.0% vs. 3.3%, $p=0.020$) (Table 3).

Results of univariate and multivariate analyses to identify the prognostic factors after therapy for recurrence

The median survival after recurrence in the SR and PBT groups was 63.0 and 40.2 months, respectively ($p=0.196$).

In a multivariate analysis of the OS after recurrence, the PS (≥ 1) (HR 3.508, 95% CI 2.207–6.069, $p < 0.001$) and therapy for recurrent tumors (others vs. SR, PBT and RFA) (HR 2.016, 95% CI 1.261–3.224, $p=0.003$) were prognostic factors (Table 1, supplementary material).

Results of univariate and multivariate analyses to identify the prognostic factors and predictors of recurrence limited to patients with a PS of 0

A multivariate analysis of the OS showed PBT as the therapy for HCC (HR 2.493, 95% CI 1.182–5.257, $p=0.016$) and elevated AFP levels (HR 1.956, 95% CI 1.243–3.076, $p=0.004$) were independent prognostic factors for the

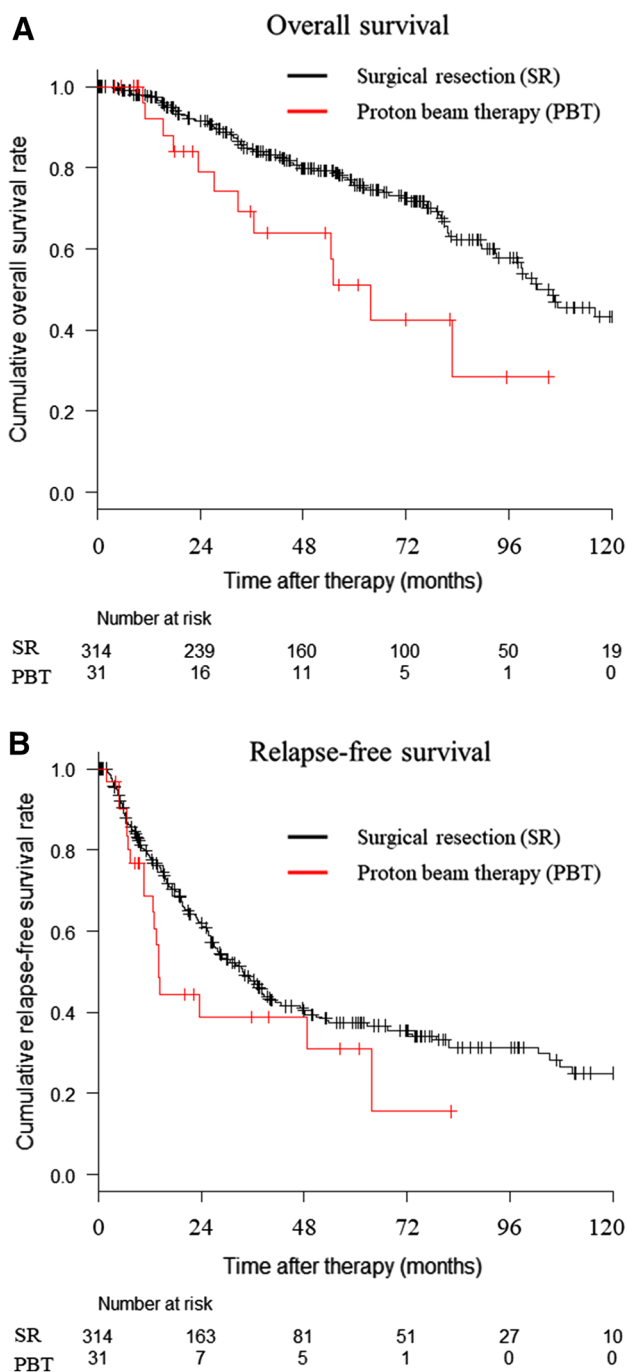


Fig. 2 **a** Kaplan–Meier curve of the overall survival after surgical resection and proton beam therapy of hepatocellular carcinoma. **b** The cumulative relapse-free survival of the surgical resection group and proton beam therapy group

patients with a PS of 0 (Table 4). Regarding the RFS, elevated AFP levels (HR 1.713, 95% CI 1.260–2.330, $p < 0.001$) were the only independent prognostic factor for the patients with a PS of 0 (Table 4).

A comparison of the patient characteristics, OS and RFS after propensity score matching

The pretreatment factors became balanced between the two groups after propensity score matching (PSM) (Table 5). The 3- and 5-year survival rates of the SR vs. PBT groups were 81.0% vs. 69.2% and 61.8% vs. 51.1%, respectively, and median survival was 63.5 vs. 64.6 months, with no significant difference between the groups ($p = 0.481$). The median RFS was 25.7 and 14.0 months in the SR and PBT groups, respectively, which did not reach statistical significance ($p = 0.643$).

Discussion

The present study showed that PBT had an RFS comparable to that of SR, although PBT was an independent poor prognostic factor for the survival in patients with primary HCC. However, it remains difficult to draw definitive conclusions regarding the superiority of SR or PBT, as the backgrounds of the two groups in the present study differed markedly. SR may be favorable as an initial treatment for HCC compared to PBT in patients with a good liver function and PS. In contrast, PBT should be considered in patients with a poor PS based on our post-PSM analysis, as the advantage of SR disappeared when there was no significant difference in the PS.

Previous reports showed that PBT was associated with excellent local control rates for HCC [7, 8]. One reason for this excellent local control is that PBT can target HCCs, including microsatellite lesions, by securing adequate safety irradiation margins despite the presence of microsatellite lesions that can cause recurrence in approximately 50% of HCC cases. However, the present study showed that SR was better than PBT with respect to achieving local control. Although some studies have reported that the survival rates of patients undergoing PBT for HCC may be comparable to those of SR and RFA [7, 8], there have been no reports directly comparing the long-term outcomes between PBT and SR for HCC.

In the present study, the RFS rate did not differ significantly between the SR and PBT groups; however, the OS rate in the SR group was significantly better than in the PBT group. We propose two hypotheses for why SR achieved a better survival time than PBT. First, the therapy for recurrent lesions differed significantly between the SR group and the PBT group. A previous study comparing SR and RFA for HCC reported that SR achieves a significantly better RFS rate, whereas the rate of OS after recurrence is not significantly different between SR and RFA [18]. These results imply that tumor recurrence may not crucially determine the prognosis after SR and RFA. The kind of treatment for recurrent lesions may affect the survival time after

Table 2 Univariate and multivariate analyses of prognostic factors associated with the overall survival and relapse-free survival in patients who underwent surgical resection or proton beam therapy for hepatocellular carcinoma

	<i>n</i>	Overall survival			Relapse-free survival				
		Median (month)	<i>p</i>	Multivariate analysis		Median (month)	<i>P</i>	Multivariate analysis	
				Hazard ratio (95% CI)	<i>p</i>			Hazard ratio (95% CI)	<i>p</i>
Age (years)									
≤ 70	173	107.2	0.027			34.8	0.252		
> 70	172	89.6		1.787 (1.187–2.691)	0.031	28.7			
Sex									
Female	76	107.2	0.829			40.2	0.205		
Male	269	99.9				32.0			
Viral infection									
NBNC	139	106.1	0.773			40.2	0.121		
HCV HBV	206	99.9				27.8			
Performance status									
0	289	107.2	<0.001			33.5	0.417		
1 or 2	56	59.8		2.039 (1.261–3.297)	0.004	28.6			
Child–Pugh grade									
A	338	102.6	0.721			32.9	0.694		
B	7	99.9				36.4			
AST (U/L)									
≤ 40	235	132.6	0.076			38.7	<0.001		
> 40	110	82.0				26.3	1.466 (1.092–1.967)	0.011	
ALT (U/L)									
≤ 40	218	106.1	0.908			36.4	0.056		
> 40	127	99.1				28.9			
Albumin (mg/dL)									
≥ 3.8	286	102.6	0.678			33.8	0.444		
< 3.8	59	99.1				27.0			
Platelet (×10⁴/μL)									
≥ 13	242	106.1	0.518			35.5	0.185		
< 13	103	99.9				26.3			
AFP (ng/mL)									
≤ 10	187	116.1	0.003			42.5	<0.001		
> 10	158	89.3		2.054 (1.372–3.076)	0.003	25.6	1.606 (1.205–2.141)	0.001	
PIVKA-II (mAU/mL)									
< 40	119	102.6	0.028			38.2	0.068		
≥ 40	224	97.9		1.550 (0.996–2.410)	0.130	27.8			
Tumor size (mm)									
≥ 20	293	102.3	0.328			33.5	0.991		
< 20	52	102.6				29.8			
Therapy									
SR	314	102.6	0.008			33.8	0.099		
PBT	31	63.7		2.188 (1.185–4.038)	0.026	14.0			

HBV hepatitis B virus, HCV hepatitis C virus, NBNC non-HBV and non-HCV, AST aspartate aminotransferase, ALT alanine aminotransferase, AFP α-fetoprotein, PIVKA-II protein induced by vitamin K absence-II, SR surgical resection, PBT proton beam therapy

Table 3 Recurrence site of hepatocellular carcinoma, therapy for recurrence tumor and causes of death

	Site of recurrence		<i>p</i>
	Surgery (%) (<i>n</i> = 314)	PBT (%) (<i>n</i> = 31)	
All recurrence	166 (52.9)	16 (51.6)	1.000
Liver solitary	75 (23.9)	6 (19.4)	0.662
Liver multiple	72 (22.9)	7 (22.6)	1.000
Local recurrence ^a	7 (2.2)	6 (19.4)	<0.001
Distant	19 (6.1)	3 (9.7)	0.433
Therapy for recurrence			
No. of recurrence	166	16	1.000
SR, PBT and RFA	67 (40.4)	2 (12.5)	0.048
TACE	67 (40.4)	8 (50.0)	
Others	32 (19.2)	6 (37.5)	
Best supportive care	16 (9.6)	6 (37.5)	
Radiation therapy	9 (5.4)	0	
Molecular-targeted drugs	5 (3.0)	0	
Chemotherapy	1 (0.6)	0	
Transhepatic arterial infusion	1 (0.6)	0	
Causes of death			
Number of deaths	91	12	
Hepatocellular carcinoma	64 (70.3)	8 (66.7)	0.750
Pneumonia	3 (3.3)	3 (25.0)	0.020
Another cancer	12 (13.2)	0 (0)	0.351
Others	12 (13.2)	1 (8.3)	

RFA radiofrequency ablation, TACE transcatheter arterial chemoembolization, PBT proton beam therapy

^aAmong the six local recurrent tumors in the PBT group, five showed an increasing size over time and exhibited enhancement in the arterial phase and washout in the portal phase on contrast-enhanced CT. One case showed an increasing tendency of tumor marker values, and the tumor showed no reduction in size after PBT

recurrence. In the present study, the multivariate analysis of the OS after recurrence showed that the type of therapy for recurrent tumors (SR, PBT and RFA vs. others) and the PS were independent prognostic factors. The patients in the PBT group underwent SR and PBT in one case each and no RFA for recurrent tumors because recurrent tumors cannot be detected by ultrasonography, have vascular invasion and are located under the diaphragm. Second, a poor PS has been reported as a prognostic factor for the survival in HCC patients [8, 19]. In the present study, the PS was again confirmed to be an independent prognostic factor for the survival. Based on the patients' background characteristics in the present study, the rate of a poor PS in the PBT group was higher than in the SR group. We also found that the PBT group had a significantly greater proportion of patients who died of pneumonia than the SR group. A previous study showed a poor PS was associated with the severity and mortality of pneumonia [20]. The high rate of a poor PS in the PBT group may therefore have influenced the survival duration being worse than in the SR group.

After PSM, there were no significant differences in the OS or RFS between the SR and PBT groups. The rate of a poor PS was much higher in the SR group after PSM (35.5%) than before PSM (14.4%). A poor PS may have resulted in the OS and RFS rates being comparable between the SR and PBT groups. The present study suggested that the PS of patients was a very important factor to consider when deciding on the treatment strategy for HCC.

In addition to the treatment outcomes, the quality of life of patients who undergo treatment for HCC is important. Dermatitis, gastrointestinal toxicities (bleeding or ulceration) and hepatic insufficiencies were reported as major possible adverse events after PBT for HCC [9, 21–23]. Hong et al. reported that 4.8% patients of PBT experienced grade 3 radiation-induced toxicity of the hepatic function or gastrointestinal ulcers. Kimura et al. [23] reported that PBT achieved high response rates for HCC over 5 cm without accompanying severe toxicity. In the present study, the rates of toxicities or complications were not significantly different between the SR and PBT groups; however, the SR group

Table 4 Univariate and multivariate analyses of prognostic factors associated with the overall survival and relapse-free survival in PS 0 patients

	n	Overall survival				Relapse-free survival					
		Median (month)		p	Multivariate analysis		Median (month)		p	Multivariate analysis	
					hazard ratio (95% CI)	p				hazard ratio (95% CI)	p
Age (years)											
≤ 70	157	132.6		0.169			33.5		0.602		
> 70	132	98.7					33.8				
Sex											
Female	59	NA		0.453			36.4		0.269		
Male	230	102.6					33.5				
Viral infection											
NBNC	108	107.2		0.845			42.5		0.155		
HCV HBV	181	106.4					28.9				
Child–Pugh grade											
A	283	107.2		0.403			33.6		0.992		
B	6	99.9					35.0				
AST (U/L)											
≤ 40	197	132.6		0.167			38.3		0.009		
> 40	92	97.9					27.7		1.363 (0.987–1.883)	0.060	
ALT (U/L)											
≤ 40	180	132.6		0.836			36.4		0.065		
> 40	109	99.9					30.7				
Albumin (mg/dL)											
≥ 3.8	239	107.2		0.722			34.0		0.492		
< 3.8	50	99.9					27.7				
Platelet (×10 ⁴ /μL)											
≥ 13	198	116.1		0.284			36.4		0.24		
< 13	91	102.3					26.3				
AFP (ng/mL)											
≤ 10	161	132.6		0.006			42.5		< 0.001		
> 10	128	99.1			1.956 (1.243–3.076)	0.004	23.9		1.713 (1.260–2.330)	< 0.001	
PIVKA-II (mAU/mL)											
< 40	107	106.4		0.089			41.4		0.083		
≥ 40	180	107.2					26.9				
Tumor size (mm)											
≥ 20	240	116.1		0.582			33.5		0.984		
< 20	49	102.6					38.2				
Therapy											
SR	269	107.2		0.034			34.0		0.053		
PBT	20	82.8			2.493 (1.182–5.257)	0.016	14.1				

HCV hepatitis C virus, HBV hepatitis B virus, NBNC non-HBV and non-HCV, AST aspartate aminotransferase, ALT alanine aminotransferase, AFP α-fetoprotein, PIVKA-II protein induced by vitamin K absence-II, SR surgical resection, PBT proton beam therapy

had more cases of complications than the PBT group. The patients with a poor PS may be better suited to PBT, as PBT is minimally invasive with an RFS comparable to that of SR.

Finally, several limitations associated with the present study should be mentioned. First, there were significant differences in the patient background characteristics.

However, the authors believe that the results of the present study reflect the actual clinical situation, which is also an important finding. Furthermore, to avoid such biases, PSM was performed to match the background characteristics between the groups. Another limitation is the small number of subjects due to the retrospective nature of the

Table 5 Patient and tumor characteristics in the surgical resection and proton beam therapy groups after propensity score matching

	Surgery group (n = 31)	PBT group (n = 31)	p
Age (years) ^a	75 (53–83)	72 (51–84)	0.434
Gender			
Male	26 (83.9)	20 (64.5)	0.146
Female	5 (16.1)	11 (35.5)	
Viral infection			
HCV	19 (61.3)	18 (58.1)	0.860
HBV	2 (6.5)	4 (12.9)	
Non-HBV and non-HCV	10 (32.2)	9 (29.0)	
Performance status			
0	20 (64.5)	20 (64.5)	1.000
1	9 (29.0)	10 (32.3)	
2	2 (6.5)	1 (3.2)	
Platelet count ($\times 10^4/\text{mm}^3$) ^a	14.0 (4.8–23.7)	13.2 (5.0–22.6)	0.554
Aspartate aminotransferase (U/L) ^a	43 (18–90)	34 (14–103)	0.234
Alanine aminotransferase (U/L) ^a	38 (5–117)	27 (7–85)	0.101
Albumin (g/dL) ^a	4.0 (3.3–5.1)	4.0 (3.3–4.9)	0.876
α -Fetoprotein (ng/mL) ^a	8.8 (2.0–24,982)	11.3 (1.6–40,735)	0.989
PIVKA-II (mAU/mL) ^a	91.0 (15–345,000)	149.0 (14–5,370)	0.989
Child–Pugh grade			
A	31 (100.0)	29 (93.5)	0.492
B	0 (0)	2 (6.5)	
Tumor size (mm) ^a	33.0 (13–93)	35.0 (10–90)	0.746

Percentages shown in parentheses unless otherwise indicated

PBT proton beam therapy, HCV hepatitis C virus, HBV hepatitis B virus, PIVKA-II protein induced by vitamin K absence-II

^aValues are the median (range)

study and single-institution setting, so further studies in a large population will be needed to verify our findings in the future. A direct comparison between PBT and surgery for HCC is difficult for several reasons, none of which have been reported. However, the Japanese Clinical Oncology Group is now planning a non-randomized prospective concurrent control study between surgery and PBT for HCC [9].

In conclusion, the present findings suggest that patients with a single primary nodular HCC ≤ 100 mm without vessel invasion should undergo SR if they have a good liver function and PS, whereas PBT may be considered in patients with a poor PS. To our knowledge, the present study, while not a prospective one, is the first to compare SR and PBT for HCC.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

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