Table 2. Tumor Characteristics

Characteristic	No. of Tumors (%)		
	Proton Therapy, n=278	Carbon Ion Therapy, n=108	All Patients, n=386
Tumor size, mm			
<50	196 (71)	81 (75)	277 (72)
50-100	65 (23)	22 (20)	87 (22)
>100	17 (6)	5 (5)	22 (6)
Gross classification			
Single nodular type	153 (55)	54 (50)	207 (53)
Single nodular with extranodular growth type	85 (30)	41 (38)	126 (33)
Confluent multinodular type	13 (5)	6 (6)	19 (5)
Infiltrative type	27 (10)	7 (6)	34 (9)
Macroscopic vascular invasion			
Yes	73 (26)	19 (18)	92 (24)
No	205 (74)	89 (82)	294 (76)
Perivascular location			
Yes	121 (44)	32 (30)	153 (40)
No	157 (56)	76 (70)	233 (60)
Prior treatment history to the target tumor			
Yes	132 (47)	49 (45)	181 (47)
No	146 (53)	59 (55)	205 (53)
Serum AFP, ng/mL			
<100	184 (66)	72 (67)	256 (66)
≥100	94 (34)	36 (33)	130 (34)
Serum PIVKAII, mAU/mL			
<100	129 (46)	58 (54)	187 (48)
≥100	149 (54)	50 (46)	199 (52)

Abbreviations: AFP, α-fetoprotein; PIVKAII, protein induced by vitamin K absence or antagonist II.

HCC was diagnosed on the basis of the results from imaging studies, which usually included a combination of contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) studies. Tumor markers, including serum α-fetoprotein (AFP) and serum protein induced by vitamin K absence or antagonist II (PIVKAII), also were measured before and after treatment. Chest CT scans, bone scintigrams, and positron-emission tomography studies, if necessary, were obtained to exclude the possibility of distant metastasis.

Patient and tumor characteristics are summarized in Tables 1 and 2, respectively, for the proton and carbon ion therapy groups and for all patients. All the patients were staged and categorized as either operable (operable group) or inoperable (inoperable group) according to Barcelona Clinic Liver Cancer (BCLC) classification criteria.[21] Tumors were classified into 3 groups according to tumor size (<50 mm, 50-100 mm, and >100 mm). All tumors were divided grossly into 4 types according to Liver Cancer Study Group of Japan criteria[22]: 1) single nodular type, 2) single nodular type with extranodular growth, 3) confluent multinodular type, and 4) infiltrative type. Studies have indicated that single nodular type tumors have a better prognosis than the other tumor types;[23] therefore, all tumors were categorized further as either single nodular type or nonsingle nodular type. Macroscopic vascular invasion was defined as gross tumor vascular invasion into the portal or hepatic veins identified by pretreatment imaging. Perivascular location was defined as a situation in which the tumor invaded or abutted the main portal trunk and/or inferior vena cava. Among the 181 tumors that had received treatment before particle therapy, 2 tumors were classified as local recurrences after hepatectomy, and 60 tumors were classified as local recurrences after percutaneous local therapy. In addition, 169 target tumors had undergone TACE before particle therapy. All data were analyzed retrospectively for proton and carbon ion therapy, and all patients were considered with regard to local tumor control rates, overall patient survival rates, and treatment-related toxicities.

Table 3. Treatment Protocols

BED_{10}[a]	Protocol (BED_{10})	No. of Patients [%]
Proton therapy		
<100	76 GyE/38 Fr (91.2)	11 [4]
	56 GyE/8 Fr (95.2)	4 [2]
	60 GyE/10 Fr (96.0)	89 [37]
≥100	76 GyE/20 Fr (104.88)	70 [29]
	66 GyE/10 Fr (109.56)	53 [22]
	80 GyE/20 Fr (112)	3 [1]
	84 GyE/20 Fr (119.28)	3 [1]
	52.8 GyE/4 Fr (122.496)	9 [4]
Carbon ion therapy		
<100	52.8 GyE/8 Fr (87.648)	23 [23]
≥100	76 GyE/20 Fr (104.88)	3 [3]
	66 GyE/10 Fr (109.56)	16 [16]
	52.8 GyE/4 Fr (122.496)	59 [58]

Abbreviations: BED_{10}, biologic effective dose for acute-reacting tissues; Fr, fractions; GyE, gray equivalents.
[a] The BED_{10} was calculated by linear-quadratic formalism assuming an α/β ratio of 10 GyE.

Treatment Protocol

The biologic effects of both proton and carbon ion therapy at the HIBMC were evaluated in vitro and in vivo, and the relative biologic effectiveness (RBE) values of these therapies were determined as 1.1 and 2,0 to 3.7, respectively (depending on the depth of the spread-out Bragg peaks).[24] Because we assumed that all tissues had almost the same RBE for protons or carbon ions, doses expressed in gray equivalents (GyE), were directly comparable to photon doses.

Eight protocols for proton therapy (52.8-84 GyE in 4-38 fractions using 150-megaelectron volt [MeV], 190-MeV, 210-MeV, or 230-MeV proton beams) and 4 protocols for carbon ion therapy (52.8-76 GyE in 4-20 fractions using 250-MeV or 320-MeV carbon ion beams) were used during the study period (Table 3). The radiobiologic equivalent dose for acute-reacting tissues (BED_{10}) was calculated for each protocol. The protocols for proton and carbon ion therapy were set first on the basis of earlier experience at the National Cancer Center East (Kashiwa, Japan), the Proton Medical Research Center (Tsukuba, Japan), and the National Institute of Radiological Sciences (Chiba, Japan). Thereafter, we adopted dose-escalation or hypofractionation protocols, depending on patient and tumor factors.

The policy for the selection of beam type was determined by the following: 1) from May to October 2001 and from April 2003 to March 2005, only proton therapy was available (52 patients with 57 tumors); 2) from February to June 2002, only carbon ion therapy was available (6 patients with 6 tumors); and 3) since April 2005, treatment plans for both proton and carbon ion therapy were made for all patients, and a better suited beam was selected on the basis of the treatment plans (285 patients with 323 tumors). Regarding the choice of either proton beam or carbon ion beam therapy, the following factors were considered: 1) the values for the percentage prescription dose received by at least 95% volume (D95) of the gross tumor volume (GTV), 2) D95 of the clinical target volume (CTV), 3) D95 of the planning target volume (PTV), 4) the percentage of the volumes of hepatic noncancerous portions (entire liver volume − GTV) receiving ≥30 GyE (Liver V30), 5) the maximum exposure doses of the adjacent gut (Gut Dmax), 6) the percentage of the volumes of the adjacent gut receiving ≥40 GyE (Gut V40), 7) the maximum exposure doses to the skin, and 8) the maximum exposure doses to the ribs. D95 of the PTV and Liver V30 values have always been high-priority factors. Among these factors, Liver V30 is used as the most important factor for patients whose liver function already has deteriorated, and Gut Dmax and/or Gut V40 values have become secondary major concerning factors in patients who have tumors located close to the gut.

A representative case presentation of treatment plans for both proton therapy and carbon ion therapy is provided in Figure 1. The D95 of PTV was equal for proton and carbon ion therapy. Conversely, Gut Dmax and Gut V40 were significantly higher for the proton treatment plan than for the carbon ion treatment plan. Therefore, carbon ion therapy was selected in this representative case.

Treatment Planning

The radiation treatments were designed to use a CT-based, 3-dimensional treatment planning system (FOCUS-M; CMS, Tokyo, Japan; and Mitsubishi Electric, Kobe, Japan). CT images were obtained at the phase of expiration using a respiratory gating system. A respiratory gating irradiation system that was developed at the National Institute of Radiological Sciences in Chiba[25] was used for irradiation of the beam during the exhalation phase for all patients. The GTV and the organs at a risk of irradiation, such as the liver and intestines, were delineated according to fusion images that were constructed from contrast-enhanced CT and MRI studies. Treatment planning was defined as follows: CTV = GTV + 5 mm, PTV = CTV + 5 mm. In addition, another 5-mm to 10-mm margin was included in the caudal axis to compensate for uncertainty caused by respiration-induced

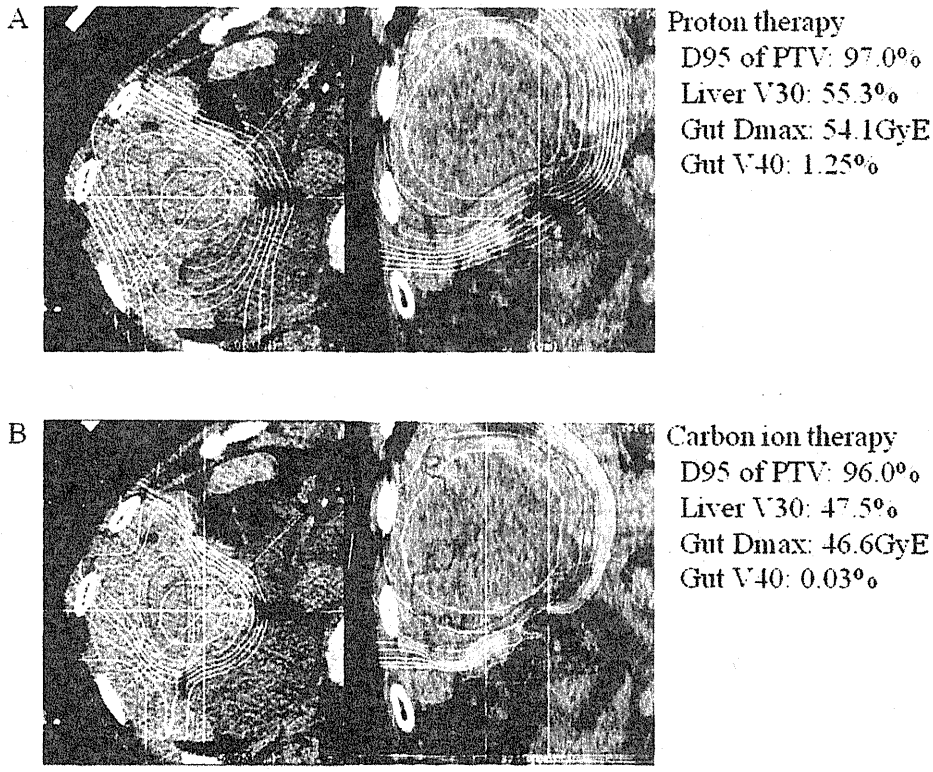

Figure 1. These images are from a representative case presentation of treatment plans for both (A) proton therapy and (B) carbon ion therapy. D95 indicates the dose received by at least 95% volume; PTV, planning target volume; Liver V30, percentage volumes of noncancerous hepatic portions (entire liver volume – gross tumor volume) that received ≥30 gray equivalents (GyE); Gut Dmax, the maximum exposure doses of the adjacent gut; Gut V40, percentage volumes of the adjacent gut that received ≥40 GyE.

hepatic movements. Doses were calculated on the basis of the pencil beam algorithm. Beam parameters, including energy level, the width of the spread-out Bragg peak, and degrader thickness, were selected adequately using FOCUS-M. Dose-volume histograms were calculated for all patients to evaluate the risk of radiation-induced liver disease.

Follow-Up and Evaluation Criteria

Patients underwent a complete blood count, biochemical profile, detection of tumor markers (including serum AFP and PIVKAII), and abdominal imaging studies (CT or MRI) every 3 months for 3 years after treatment and every 6 months thereafter. In general, for patients with HCC, the objective of all effective locoregional therapies is to obtain necrosis of the tumor regardless of the shrinkage of the lesion. Even if extensive tumor necrosis is achieved, this may not be accompanied by a reduction in the greatest dimension of the lesion. Consequently, several studies have indicated that World Health Organization and Response Evaluation Criteria in Solid Tumors criteria have no value in the assessment of tumor response after locoregional therapies in patients with HCC.[26,27] It has been reported that such tumors, even after complete response, tend to persist for a long period after the completion of particle therapy.[19] Therefore, local recurrence was defined either as the growth of an irradiated tumor or as the appearance of new tumors within the PTV based on criteria established in previous reports.[16,17,19,28] Acute and late toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 2.0; National Cancer Institute, Bethesda, Md).

Statistical Analyses

The statistical significance of differences in each classification for both local control and overall survival rates was estimated by the Kaplan-Meier method and was compared using the log-rank test. Univariate and multivariate analyses using Cox proportional hazards regression

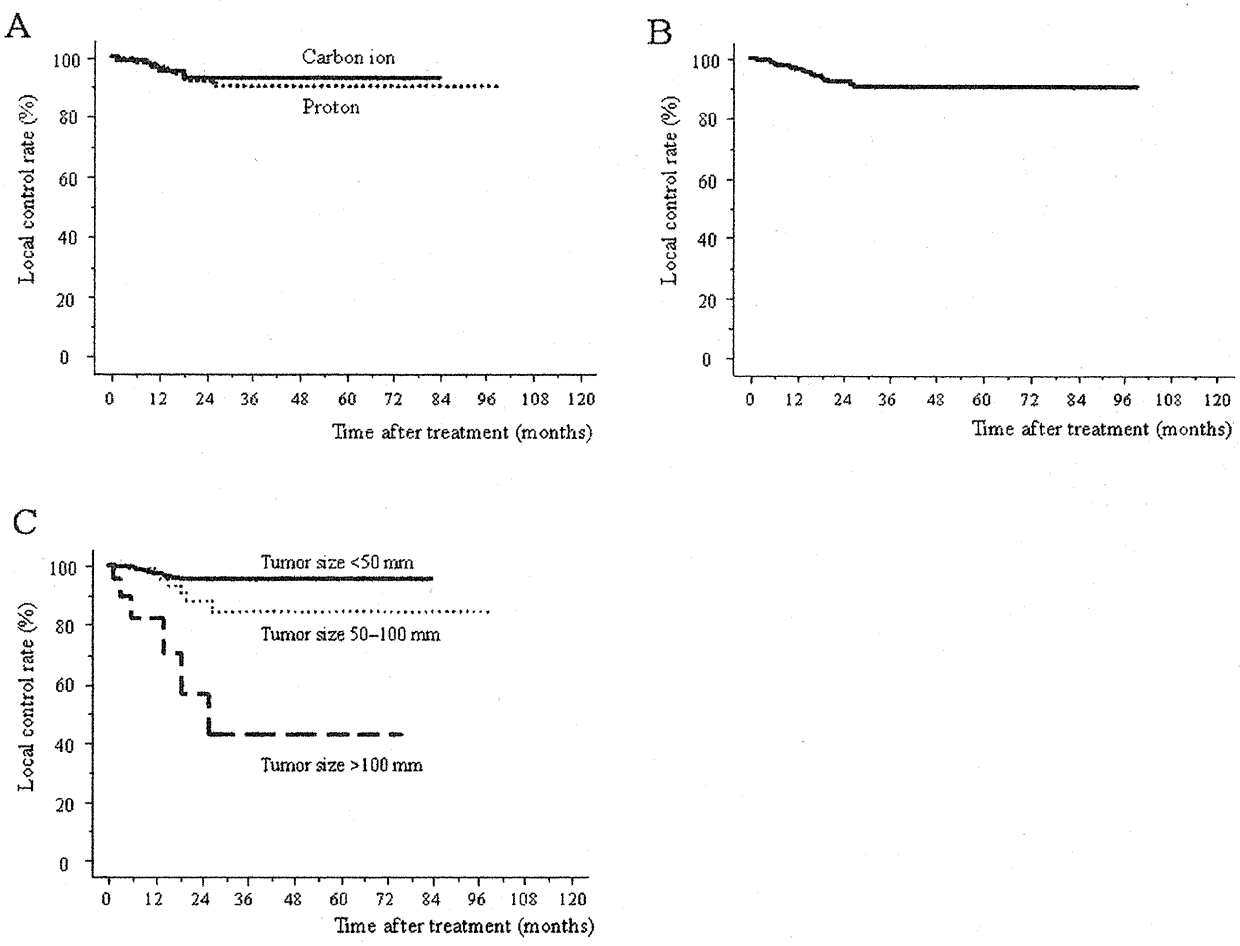

Figure 2. Local control rates after treatment are illustrated for (A) tumors that were treated with proton and carbon ion therapy, (B) all 386 tumors, and (C) all 386 tumors according to tumor size.

models were used to identify independent risk factors that predicted local control and overall survival rates. Differences of $P < .05$ were considered statistically significant, and variables with $P < .10$ were entered into a multivariate analysis using a Cox proportional hazards model. All statistical analyses were performed using SPSS statistical software (version 17.0 for Windows; SPSS, Inc., Chicago, Ill).

RESULTS

Local Control Rates After Proton and Carbon Ion Therapies

Patients were followed either until death or to March 2010 (median follow-up, 31.0 months). Among 343 patients with 386 tumors, 223 patients developed recurrences after treatment. Nineteen patients developed extrahepatic metastasis, and 210 patients developed intrahepatic recurrences, including 23 local recurrences (proton therapy, 18 patients; carbon ion therapy, 5 patients). The longest interval to local recurrence was 27.1 months, and all local recurrences developed within 3 years. The 5-year local control rates for patients who received proton therapy and carbon ion therapy were 90.2% and 93%, respectively (Fig. 2A). The effective 3-year and 5-year local control rates for all 386 tumors were both 90.8% (Fig. 2B). An analysis of the local control rates according to the tumor factors identified above (see Treatment Protocols) is listed in Table 4. Univariate analysis revealed that tumor size was a significant risk factor for local recurrence in the proton therapy group, the carbon ion therapy group, and all patients. In multivariate analysis, tumor size was identified as an independent risk factor for local recurrence in the proton therapy group

Table 4. Univariate Analysis of Prognostic Factors for Local Control Rate

Factor	Proton Therapy, n=278		Carbon Ion Therapy, n=108		All Patients, n=386	
	LC Rate at 5 Years, %	*P*	LC Rate at 5 Years, %	*P*	LC Rate at 5 Years, %	*P*
Tumor size, mm		<.0001		.0062		<.0001
<50	95.5		94.5		95.3	
50-100	84.1		90.9		84.4	
>100	43.4		80		42.2	
Gross classification		.0901		.0943		.0219
Single nodular type	93.3		96		94	
Nonsingle nodular type	86.2		89.4		86.7	
Macroscopic vascular invasion		.2544		.0292		.0535
Yes	83.9		80.4		82.8	
No	92		94.8		92.8	
Perivascular location		.0704		.4267		.0403
Yes	85.5		86.8		85.7	
No	93.5		95.1		93.8	
Prior treatment history		.7332		.9000		.7629
Yes	91.5		95		92	
No	89.2		91.9		89.9	
Serum AFP, ng/mL		.5352		.6111		.4310
<100	90.9		95.1		91.8	
≥100	89		86.8		88.6	
Serum PIVKAII, mAU/mL		.0997		.3468		.2976
<100	94.5		90.1		93.4	
≥100	85.5		97.9		87.8	

Abbreviations: AFP, α-fetoprotein; LC, local control; PIVKAII, protein induced by vitamin K absence or antagonist II.

and in all patients (Table 5). In addition, the local control rates for all 386 tumors that measured <50 mm, 50 to 100 mm, and >100 mm were 95.3%, 84.4%, and 42.2%, respectively (Fig. 2C). In contrast, other tumor factors, including gross classification, macroscopic vascular invasion, perivascular location, treatment history, serum AFP level, and serum PIVKAII level, did not affect the local control rate in any tumor subset in multivariate analysis.

Overall Survival Rates of Proton and Carbon Ion Therapies

The 5-year overall survival rates for patients who received proton therapy and carbon ion therapy were 38% and 36.3%, respectively (Fig. 3A). The overall survival rates for all 343 patients at 3 years and 5 years were 59% and 38.2%, respectively (Fig. 3B). Univariate and multivariate analyses of the overall survival rates according to the 8 relevant tumor factors are provided in Tables 6 and 7, respectively. According to the univariate analysis, Child-Pugh classification, macroscopic vascular invasion, and serum AFP levels were the only factors that significantly affected the overall survival rates in all groups (proton therapy, carbon ion therapy, and all patients) (Table 6). The Child-Pugh classification was the only independent factor for overall survival in proton therapy, carbon ion therapy, and all patients according to the multivariate analysis (Table 7). The 5-year overall survival rates for Child-Pugh classifications A, B, and C were 46.6%, 8.7%, and 0%, respectively (Fig. 3C).

The 5-year overall survival rates for BCLC stages 0, A, B, C, and D were 80.8%, 52.7%, 23.7%, 30.6%, and 0%, respectively (Fig. 4A). According to the BCLC classification, hepatic resection was categorized as stage 0 and part of stage A. In total, 78 patients were categorized into the hepatic resection group. The 5-year overall survival rates for patients classified into groups according to whether they underwent hepatic resection (operable group) or received treatments (inoperable group) were 67.6% and 29.4%, respectively ($P < .0001$) (Fig. 4B).

Local Control and Overall Survival Rates According to the BED_{10}

We also analyzed the local control and overall survival rates after both proton and carbon ion therapies according

Table 5. Independent Risk Factors Related to the Local Control Rate: Multivariate Analysis

Factor	SE	Chi-Square Statistic	RR	95% CI	*P*
Proton therapy					
Tumor size, mm					.0030
50-100 (vs <50)	0.666	1.175	2.058	0.558-7.590	
>100 (vs <50)	0.703	10.463	9.725	2.450-38.596	
Single nodular type (vs nonsingle nodular type)	0.538	0.187	1.262	0.440-3.623	.6652
Perivascular location: Yes (vs no)	0.543	0.147	0.812	0.280-2.354	.7011
Serum PIVKAII ≥100 mAU/mL (vs <100 mAU/mL)	0.530	0.389	1.392	0.492-3.937	.5327
Carbon ion therapy					
Tumor size, mm					.4703
50-100 (vs <50)	1.569	0.069	0.662	0.031-14.322	
>100 (vs <50)	1.905	0.575	4.239	0.101-177.314	
Single nodular type (vs nonsingle nodular type)	1.231	1.110	3.658	0.328-40.853	.2921
Macroscopic vascular invasion: Yes (vs no)	1.585	0.347	2.544	0.114-56.848	.5557
All patients					
Tumor size, mm					.0002
50-100 (vs <50)	0.646	10.527	8.122	2.291-28.789	
>100 (vs <50)	0.562	2.146	0.439	0.146-1.321	
Single nodular type (vs nonsingle nodular type)	0.519	2.544	2.288	0.827-6.327	.1107
Macroscopic vascular invasion: Yes (vs no)	0.651	2.601	2.860	0.798-10.253	.1068
Perivascular location: Yes (vs no)	0.506	0.738	0.647	0.240-1.745	.3902

Abbreviations: CI, confidence interval; PIVKAII, protein induced by vitamin K absence or antagonist II; RR, relative risk; SE, standard error.

to the BED_{10} using a cutoff score of 100 (Fig. 5). The 5-year local control rates for tumors that were treated on the protocols characterized by BED_{10} values <100 and ≥ 100 were 93.3% and 87.4%, respectively, for proton therapy and 80.7% and 95.7%, respectively, for carbon ion therapy. The 5-year overall survival rates for patients who were treated on the protocols characterized by BED_{10} values <100 and ≥ 100 were 31.7% and 43.9%, respectively, for proton therapy and 32.3% and 48.4%, respectively, for carbon ion therapy. There was no significant difference in local control and overall survival rates, irrespective of the BED_{10} score, between proton therapy and carbon ion therapy.

Toxicities

All acute toxicities that occurred during treatment were transient, easily managed, and acceptable. However, grade ≥ 3 late toxicities were observed in 8 patients on proton therapy and in 4 patients on carbon ion therapy, and 4 of 12 patients were diagnosed with radiation-induced liver disease (Table 8). However, all of these patients with hematologic disorders were asymptomatic and required no further treatment. In addition, upper gastrointestinal ulcer, pneumonitis, and subcutaneous panniculitis healed with conservative management. Five patients who received proton therapy developed refractory skin ulcers, and 1 patient required skin transplantation. A salvage drainage operation also was required by 1 patient who developed infectious biloma 10 months after irradiation. No patients died of treatment-related toxicity.

DISCUSSION

We analyzed the safety and efficacy of particle therapy using proton and carbon ion beams for HCC in a single center. The key findings of this study are as follows: 1) particle therapy produced excellent local control and overall survival rates with acceptable adverse events, 2) the treatment results from carbon ion therapy appeared to be equivalent to those from proton therapy, and 3) tumor size was the only risk factor that affected the local control rate.

Local control rates for both proton therapy and carbon ion therapy exceeded 90% in the current study. These data are very similar to those related to particle therapy for HCC, whereas they are superior to data related to conformal radiotherapy.[16,18,29,30] Recent improvements in dose localization techniques, such as intensity-modulated radiotherapy, conformal 3-dimensional planning, and breathing motion management strategies, thus, have made it possible to irradiate smaller, well defined targets in the liver. However, these highly computer-assisted

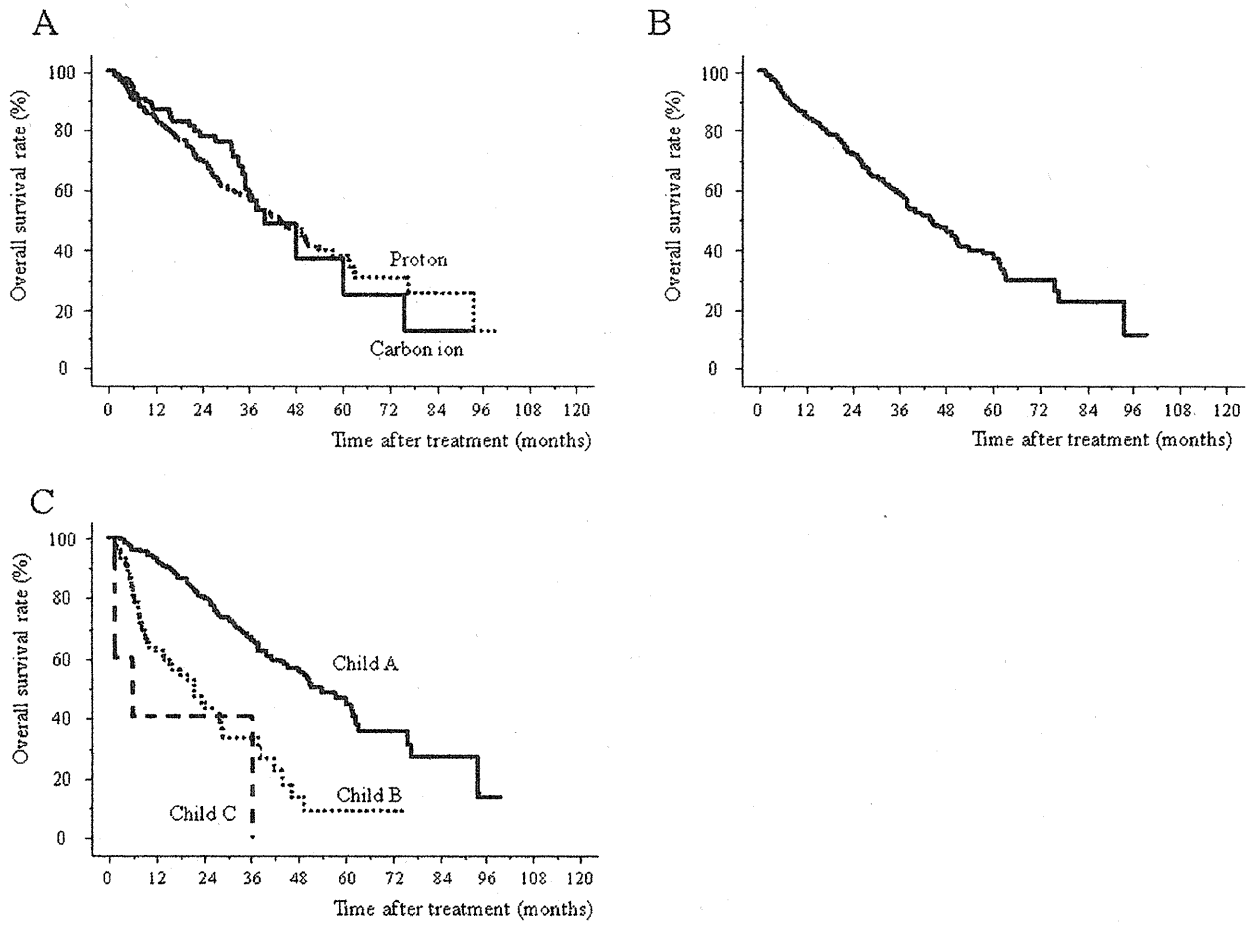

Figure 3. Overall survival rates after treatment are illustrated for (A) patients who received with proton and carbon ion therapy, (B) all 343 patients, and (C) all 343 patients according to Child-Pugh classification.

irradiation techniques using photon beams have achieved limited efficacy in treating patients with HCC. The local control rates produced by these conformal approaches remain in the 40% to 66% range for several reasons.[29,30] Radiation-induced liver disease still is observed frequently with conformal approaches when a sufficient dose is delivered to completely kill the cells of the entire tumor nodule. This is especially the true for large and centrally situated liver tumors.[31] In this regard, particle beams can achieve an excellent dose distribution to these targets. The area of radiation dose deposition can be controlled well by the beam energy, because there is a rapid drop-off in energy deposition beyond the target area. Indeed, such theoretical advantages of particle therapy were proven in part by the impressively high local control rate of approximately 90% in the current study. Therefore, we believe that it is reasonable to say that the tumor-eliminating capability of particle therapy is closely equivalent to that of hepatectomy, an outcome that has not been achieved with other radiation therapies.

Experience in the treatment of HCC by particle therapy has been accumulated mainly in Japanese centers, but there is increasing interest in other countries as well. There were 26 active proton therapy facilities as of February 2009, whereas there were only 3 carbon ion therapy facilities.[32] Until now, several proton treatment centers and 1 carbon ion treatment center have reported HCC treatments results.[16-19] However, except for the HIBMC, no single facility can deliver both proton and carbon ion beams. Therefore, our facility has a distinct advantage over other institutes with regard to comparing the efficacy of the 2 beams. To select proton therapy or carbon ion therapy, we made treatment plans for both proton and carbon ion therapy. When dose distributions were

Table 6. Univariate Analysis of Prognostic Factors for Overall Survival Rate

Factor	Proton Therapy, n=242		Carbon Ion Therapy, n=101		All Patients, n=343	
	OS Rate at 5 Years, %	*P*	OS Rate at 5 Years, %	*P*	OS Rate at 5 Years, %	*P*
Age, y		.7986		.6769		.6448
<70	37.3		43.9		39.4	
≥70	38.2		26.9		36.2	
Positive viral marker		.9754		.1805		.8586
Hepatitis B virus	34.9		44.6		32.4	
Hepatitis C virus	35.8		40.8		36.3	
None	46.7		33.9		46.6	
Performance status		<.0001		.2295		<.0001
0	43.5		43.7		43.6	
1 or 2 or 3	24.8		26.8		24.1	
Child-Pugh classification		<.0001		<.0001		<.0001
A	46.8		41.2		46.6	
B or C	8.2		33.3		8	
Tumor size, mm		.1438		.0003		.0038
<50	37.8		53.5		39.2	
50-100	37.4		17.9		33.8	
>100	41.1		0		39.8	
Macroscopic vascular invasion		.0003		.0055		<.0001
Yes	33.2		22		31.5	
No	40.3		47.8		40.2	
Serum AFP, ng/mL		.0026		.0024		<.0001
<100	42		30.9		42.6	
≥100	29.5		23.1		28.9	
Serum PIVKAII, mAU/mL		.0109		.4041		.0082
<100	40.4		58.4		41.8	
≥100	35.5		16.5		33.8	

Abbreviations: AFP, α-fetoprotein; OS, overall survival; PIVKAII, protein induced by vitamin K absence or antagonist II.

compared, there were many instances in which low-dose areas had spread into the surrounding normal liver during proton therapy planning. This was apparently because of the relatively large penumbra of proton beams. Consequently, dose distribution in a single beam appears to be better in carbon ion therapy than in proton therapy. However, in terms of beam arrangement, carbon ions are emitted from 3 fixed ports, such as vertical, horizontal, or 45-degree oblique; whereas a 360-degree rotating gantry can be used for protons. The high positioning accuracy achieved by irradiating patients in a supine position also was an advantage of proton therapy. Currently, 360-degree rotating gantries for carbon ion beams are under construction in Japan and Germany, and it is expected that these will enable the delivery of highly precise carbon ion beam arrangements and, thus, will improve the effectiveness of carbon ion therapy for HCC.

In addition to dose distribution, there are evident differences in biologic properties between the 2 beams, ie, the RBE. The RBE for proton therapy is comparatively simple. The International Commission on Radiation Units and Measurements has recommended 1.1 as a generic RBE for proton therapy based on an analysis of the published RBE values determined from in vivo systems.[33,34] All proton therapy centers, including the HIBMC, have accepted this recommendation. Conversely, the RBE for carbon ion therapy is complex, because there is no common model for selecting the RBE of carbon ion beams. In addition, it may vary depending on tissue type and the depth of the spread-out Bragg peaks.[32] Because of these differences, planning the physical dose distribution is substantially more complex for carbon ion beams than for proton beams; therefore, a direct comparison of proton therapy and carbon ion therapy is

Table 7. Independent Risk Factors Related to the Overall Survival Rate: Multivariate Analysis

Factor	SE	Chi-Square Statistic	RR	95% CI	*P*
Proton therapy					
Performance status 1-3 (vs 0)	0.200	9.283	0.544	0.368-0.805	.0023
Child-Pugh classification B or C (vs A)	0.204	29.731	0.329	0.220-0.490	<.0001
Macroscopic vascular invasion: Yes (vs no)	0.203	9.410	0.536	0.360-0.799	.0022
Serum AFP ≥100 ng/mL (vs <100 ng/mL)	0.198	2.281	1.349	0.915-1.990	.1310
Serum PIVKAII ≥100 mAU/mL (vs <100 mAU/mL)	0.199	1.231	1.248	0.844-1.844	.2672
Carbon ion therapy					
Child-Pugh classification B or C (vs A)	0.519	17.642	0.113	0.041-0.313	<.0001
Tumor size, mm					.0297
50-100 (vs <50)	0.569	6.795	4.412	1.445-13.468	
>100 (vs <50)	1.040	3.217	6.454	0.841-49.524	
Macroscopic vascular invasion: Yes (vs no)	0.625	0.647	1.654	0.486-5.631	.4211
Serum AFP ≥100 ng/mL (vs <100 ng/mL)	0.396	5.406	2.513	1.156-5.465	.0201
All patients					
Performance status 1-3 (vs 0)	0.180	10.852	0.554	0.389-0.787	.0010
Child-Pugh classification B or C (vs A)	0.182	45.663	0.292	0.204-0.417	<.0001
Tumor size, mm					.5976
50-100 (vs <50)	0.220	0.044	1.047	0.680-1.613	
>100 (vs <50)	0.375	0.656	0.738	0.354-1.539	
Macroscopic vascular invasion: Yes (vs no)	0.216	10.960	0.489	0.320-0.747	.0009
Serum AFP ≥100 ng/mL (vs <100 ng/mL)	0.176	4.848	1.474	1.044-2.083	.0277
Serum PIVKAII ≥100 mAU/mL (vs <100 mAU/mL)	0.186	0.922	1.196	0.830-1.724	.3371

Abbreviations: AFP, α-fetoprotein; CI, confidence interval; PIVKAII, protein induced by vitamin K absence or antagonist II; RR, relative risk; SE, standard error.

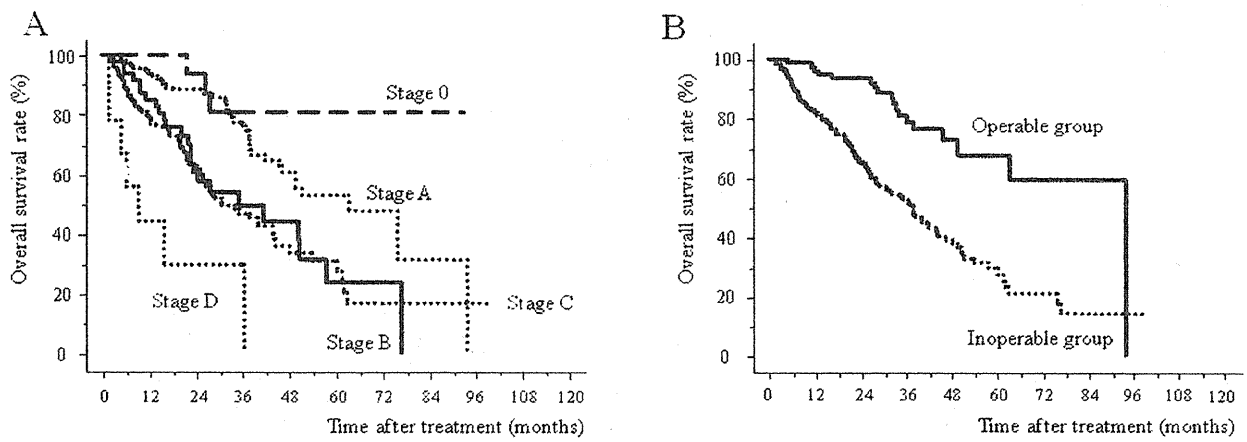

Figure 4. (A) Overall survival rates are illustrated for all 343 patients according to disease stage classified by the Barcelona Clinic Liver Cancer classification. (B) Overall survival rates are illustrated for all 343 patients according to the operative indication based on the Barcelona Clinic Liver Cancer classification.

not feasible. Under these circumstances, we established that the treatment results of carbon ion therapy were equivalent to those of proton therapy at our institute. These results may prove the validity of our treatment planning system for carbon ion therapy by using a variable RBE.

The current study has established the equal effectiveness of proton and carbon ion therapies for HCC. With regard to this result, we speculate that the superior dose distribution compensates for the limitation of carbon ion beam arrangements at HIBMC. With the development of irradiation equipment, compared with proton therapy, carbon ion therapy will play a major role in the treatment of patients with HCC who have tumors adjacent to the gut and/or those whose liver function has deteriorated. However, carbon ion therapy requires huge economic resources, and this issue should be resolved in the future.

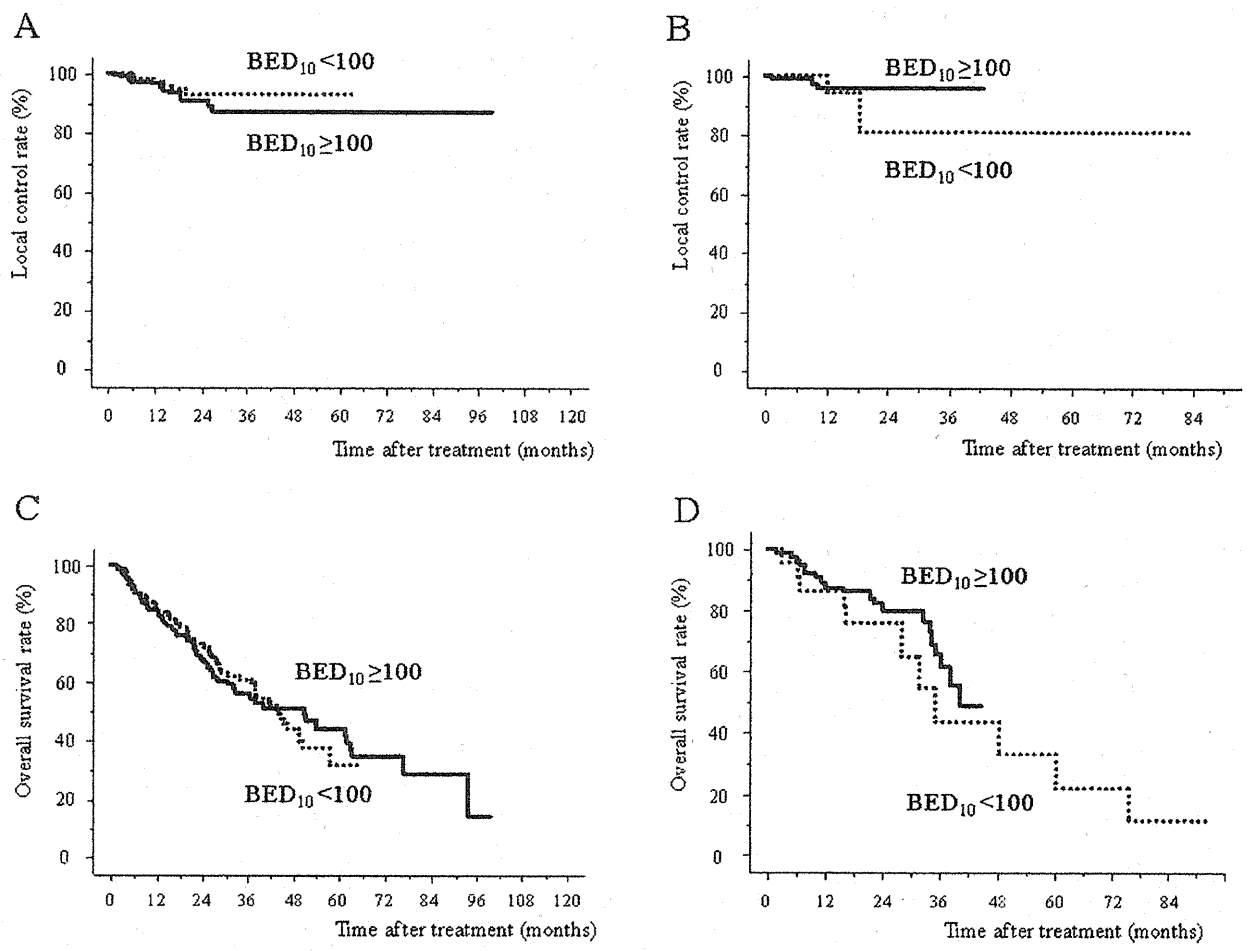

Figure 5. Local control rates are illustrated according to the radiobiologic equivalent dose for acute-reacting tissues (BED_{10}) for (A) proton therapy and (B) carbon ion therapy. Overall survival rates are illustrated according to the BED_{10} for (C) proton therapy and (D) carbon ion therapy.

Tumor size was the only significant risk factor for local recurrence after particle therapy (for proton therapy, carbon ion therapy, and all patients). Conversely, it is noteworthy that the 6 other tumor factors, including gross classification, macroscopic vascular invasion, perivascular location, prior treatment history, serum AFP levels, and serum PIVKAII levels, had no significant influence on the local control rate after either therapy. The application of local ablative therapies is contraindicated in tumors with vascular invasion,[9,35] and it has been reported by several studies that perivascular location significantly increased the local recurrence rate after RFA mainly because of the heat-sink effect.[8,9] In addition, hepatectomy frequently is abandoned to as a treatment for centrally situated tumors adjacent to the inferior vena cava and/or the main portal trunk in patients with cirrhosis, because these tumor locations tend to require major hepatectomy. In the current study, however, neither factor reduced the efficacy of proton therapy or carbon ion therapy in terms of the local control rate.

The local control rates achieved with proton therapy and carbon ion therapy for tumors <50 mm were 95.5%, and 94.5%, respectively. These data are similar or superior to those reported with local ablative therapies.[36] At the same time, the local control rates achieved with proton therapy and carbon ion therapy for tumors that measured from 50 mm to 100 mm in greatest dimension were 84.1% and 90.9%, respectively (Table 4). Because the upper limit of tumor size is 50 mm for local ablative therapies, these results clearly demonstrate the distinct advantage of particle therapy over other local therapies for tumors ≥50 mm. Taken together, in our opinion, particle

Table 8. Late Toxicities After Proton and Carbon Ion Therapy

	No. of Patients (%)								
	Grade 2			Grade 3			Grade 4		
Toxicity	Proton Therapy	Carbon Ion Therapy	All Patients	Proton Therapy	Carbon Ion Therapy	All Patients	Proton Therapy	Carbon Ion Therapy	All Patients
Dermatitis	12 (5)	5 (5)	17 (5)	4 (2)	0	4 (1)	1 (1)	0 (0)	1 (1)
Elevation of transaminase level	5 (2)	3 (3)	8 (2)	1 (1)	3 (3)	4 (1)	0 (0)	0 (0)	0 (0)
Upper gastrointestinal ulcer	3 (1)	1 (1)	4 (1)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Rib fracture	8 (3)	3 (3)	11 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pneumonitis	4 (2)	2 (2)	6 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subcutaneous panniculitis	6 (2)	2 (2)	8 (2)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Biloma	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Low albuminemia	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea/anorexia/pain/ascites	4 (2)	2 (2)	6 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

therapy would be the best therapeutic option for patients who have tumors that preclude currently available local therapies because of tumor size, macroscopic vascular invasion, or deep tumor location.

According to the BCLC classification, the 5-year overall survival rate of patients in the operable group was 67.6%. This survival rate is comparable to reported data associated with hepatic resection.[21] It is noteworthy that the overall survival rate of patients classified with stage C disease at 5 years was 30.6% in the current study; this is far superior to other reported data.[21] Patients in this stage have macroscopic vascular invasion and/or extrahepatic metastasis. According to the BCLC classification, these patients usually are excluded from curative treatments and receive either TACE or sorafenib. In the current study, most of patients with stage C disease had macroscopic vascular invasion without extrahepatic metastasis. They were received proton and carbon ion therapies with curative intent, and the local control rates for these patients exceeded 80% (Table 4). These results suggest that some of patients with BCLC stage C disease may benefit from more aggressive local therapies, such as particle therapy.

Most of the treatment-related toxicities in the current study were transient, easily managed, and acceptable. Rib fracture and dermatitis were observed frequently in patients who were treated during the early period at our center. Most of these patients, including 1 patient with grade 4 dermatitis, were treated with only 1 portal to obtain an adequate spread-out Bragg peak. Thereafter, we used 2 or more portals and rarely observed such complications. Regarding intrahepatic structure-related complications, no studies, including ours, have reported blood vessel-related complications. This is a distinct advantage of particle therapy over other local therapies and supports our proposal that tumors in perivascular locations are appropriate candidates for particle therapy. In contrast, although less common, bile duct complications, including biloma and stenosis, have been reported in several studies.[16] In the current study, biloma formation was observed in 1 patient whose tumor was adjacent to the porta hepatis. The bile duct may stand as the single greatest obstacle of intrahepatic structures after particle therapy. It is almost impossible to predict bile duct complications before treatment; thus, tumors adjacent to the porta hepatis should be treated with caution.

Grade 2 or greater gastrointestinal ulceration was observed in 5 patients whose tumors were adjacent to the gut. To minimize toxicity in these patients, we reduced the fraction size and initiated proton pump inhibitors immediately after treatment; and, ultimately, we were able to prevent the development of severity. The proximity of the gut is an important consideration in selecting particle therapy for patients with HCC. We introduced operative placement of a spacer between the tumor and the gut before particle therapy as a countermeasure for this limitation to ensure safe irradiation.[37,38]

To our knowledge, this is the first study to assess the clinical treatment results from both proton therapy and carbon ion therapy. However, our study has some important limitations: 1) the results of this study were achieved retrospectively and not through randomized or controlled trials; 2) during the study period, we used different treatment protocols for proton therapy and carbon ion therapy; and 3) the RBE of carbon ion beams for HCC

has not been completely clarified. Although further investigation is required, our data can serve as a basis for future refinement of beam selection.

In conclusion, both proton therapy and carbon ion therapy produce favorable results as treatment for HCC. Both therapies have great advantages in treating HCC, a condition that is a contraindication for other local therapies. Randomized clinical trials are required to compare particle therapy with other local therapies and to clarify the roles played by particle therapy in the HCC treatment algorithm.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

The effectiveness of particle radiotherapy for hepatocellular carcinoma associated with inferior vena cava tumor thrombus

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Abstract
Background The prognosis of patients who have hepatocellular carcinoma (HCC) associated with inferior vena cava tumor thrombus (IVCTT) is very poor, and effective treatment modalities are extremely limited. The objective of this study was to determine the therapeutic efficacy of particle radiotherapy for HCC with IVCTT.
Methods Between June 2001 and January 2009, 16 evaluable patients who had HCC with IVCTT were treated with particle radiotherapy. They were divided into 2 groups: 6 were treated with curative intent; 10 with palliative intent. The local tumor control rates, overall survival rates, and toxicities were evaluated.
Results All tumors treated with particle radiotherapy remained controlled without local recurrence at the last follow-up. The overall survival rates for the 16 patients at 1 and 3 years were 61.1 and 36.7%, respectively. We observed a significant difference in the survival rates according to treatment policy. The median survival time was 25.4 months for patients treated with curative intent and 7.7 months for those treated with palliative intent. The one-year survival rates were 100.0 and 33.3%, respectively. No Grade 3 or higher treatment-related toxicities were observed.
Conclusions Particle radiotherapy is thought to be potentially effective and safe for HCC with IVCTT. Considering the current lack of effective and less-invasive local therapy for HCC with IVCTT, particle radiotherapy may therefore be an attractive new therapeutic approach for this type of HCC.

Keywords Hepatocellular carcinoma · Inferior vena cava tumor thrombus · Proton radiotherapy · Carbon ion radiotherapy · Particle radiotherapy

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, with the highest incidence being in Asia and Africa [1]. The prognosis of advanced HCC remains poor, particularly in patients with tumor thrombus in the portal vein or the inferior vena cava (IVC). The incidence of portal vein and IVC tumor thrombus (IVCTT) is high in patients with HCC. Autopsy data report these manifestations in as many as 44–84% of HCC patients [2]; clinical data put the figure at 31–50% [3, 4]. Various treatment modalities for HCC have become available and many patients with the disease can be treated effectively [1, 5]. However, the effectiveness of treatments for HCC with an extensive tumor thrombus in the portal vein or IVC is a point of contention.

Advanced HCC with IVCTT has an extremely poor prognosis, with untreated survival reported to be approximately 3 months [6]. Pulmonary tumor embolism

accounted for 6% of deaths from HCC [7]. Intravenous chemotherapy and transarterial chemoembolization (TACE) have yielded only limited improvements in survival [8, 9], and the application of local ablative therapies, such as radiofrequency ablation (RFA), is contraindicated in tumors with vascular invasion [10, 11]. A liver resection is the only effective treatment for HCC with IVCTT, but few patients are suitable candidates due to advanced tumors or coexisting cirrhosis [12]. Patients with advanced HCC with IVCTT need effective local therapy.

Conventional photon radiotherapy for HCC has so far played a limited role in treatment due to the risk of hepatic toxicity that is known as radiation-induced liver disease (RILD) [13, 14]. RILD is still frequent during attempts to deliver a sufficient dose for complete tumor killing, especially for large and/or centrally situated tumors [15]. In contrast, particle beams, such as proton and carbon ion beams, show increased energy deposition and a penetration depth up to a sharp maximum at the end of their range with the aid of the so-called Bragg peak phenomenon. Due to the fact that particle beams minimize doses to the surrounding normal liver, they are suitable for delivering higher doses to liver tumors [16, 17]. Several recent reports have demonstrated the effectiveness of particle radiotherapy for HCC, and it has become widely accepted as a novel treatment option [18–23]. However, the clinical effectiveness of particle radiotherapy for HCC with IVCTT remains uncertain. The aim of this study was to examine the effectiveness and safety of particle radiotherapy for patients who have HCC with IVCTT.

Methods

Patients

The present study was conducted in accordance with the ethical standards set forth by the Declaration of Helsinki, and all patients provided written informed consent. Between June 2001 and January 2009, 349 consecutive patients with HCC were treated with particle radiotherapy at the Hyogo Ion Beam Medical Center. Patients who met the following conditions were ineligible for the treatment: (1) uncontrolled ascites, (2) tumors larger than 15 cm (the upper limit of the irradiation field).

Of the 349 treated patients, 17 had associated tumor thrombi extending into the IVC (Vv3). IVCTT was diagnosed by the identification of an intraluminal filling defect in the IVC shown in contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). One patient discontinued the treatment, with the discontuance not being attributable to irradiation. Therefore, we retrospectively reviewed 16 patients for local tumor control rates, survival rates, and treatment-related toxicities.

The patient and tumor characteristics are summarized in Table 1. All patients were staged according to criteria in the 6th edition of the American Joint Committee on Cancer *AJCC Cancer Staging Manual* [24]. They were divided into 2 groups according to the treatment policy: 6 patients were treated with curative intent (curative treatment group), and the remaining 10 were treated with palliative intent (palliative treatment group). In the curative treatment group, patients had no extrahepatic metastases and all liver tumors detectable on pretreatment imaging could be treated with particle radiotherapy alone ($n = 5$) or in combination with RFA ($n = 1$). All 10 patients in the palliative treatment group had multiple bilobar metastases in the liver that exceeded the limits of RFA. In addition, 8 of these 10 patients had extrahepatic metastases (Stage IV; lung metastases in 6, bone metastasis in 1, lymph node metastases in 2). Palliative treatment was performed to prevent sudden death due to a pulmonary embolism caused by detached tumor thrombi. Regardless of the treatment policy, the main tumors, including the IVCTT, were equally irradiated in both groups. One patient in the curative treatment group and 2 patients in the palliative treatment group had tumors with IVCTT extending into the right atrium. Ten patients (3 in the curative treatment group and 7 in the palliative treatment group) had tumors with portal vein tumor thrombi.

Protocol and treatment planning of particle radiotherapy

Proton beams of 150–210 MeV and carbon ion beams of 250–320 MeV generated by an accelerator with a synchrotron were used for the irradiation. Five protocols for proton radiotherapy, i.e, 56 Gray equivalent (GyE) in 8 fractions; 60 GyE in 10 fractions; 66 GyE in 10 fractions; 76 GyE in 20 fractions; and 76 GyE in 38 fractions were used for treatment, as were two protocols for carbon ion radiotherapy, i.e., 52.8 GyE in 4 fractions and 52.8 GyE in 8 fractions.

Regarding the choice of either the proton or carbon ion beam, the following factors were considered: (1) the percentage of the prescription dose received by at least 95% (D95) of the gross tumor volume (*GTV*); (2) the D95 of the clinical target volume (*CTV*); (3) the D95 of the planning target volume (*PTV*); (4) the percentage of the volume of the noncancerous hepatic portion (entire liver volume minus gross tumor volume) receiving ≥30 GyE (*Liver V30*); (5) the maximum exposure dose of the adjacent gut (Gut Dmax); (6) the percentage of the volume of the adjacent gut receiving ≥40 GyE (Gut V40); (7) the maximum exposure dose of the skin; and (8) the maximum

Table 1 Clinical details of 16 patients treated with particle radiotherapy

Age (years), Sex	PS	Stage group[a]	AFP (ng/ml)	PIVKA II (mAU/ml)	ICG R15 (%)	Child–Pugh grade (score)	Treatment policy	Targeted tumor size (mm)	Protocol GyE/Fr	*Liver V30* (%)	Status, survival time (months)	Hepatic toxicity
83, M	PS0	Stage IIIA	43	1140	3	A (5)	Curative	32 × 28	Proton, 66/10	20	Alive, 17.0	Acute (Grade 2)
61, M	PS0	Stage IIIA	1079	22	16	A (6)	Curative	43 × 43	Proton, 76/38	11	Alive, 26.2	No
70, M	PS1	Stage IIIA	5	139	22	A (5)	Curative	120 × 120	Proton, 76/20	37	Alive, 36.9	Acute (Grade 1), Late (Grade 2)
81, M	PS0	Stage IIIA	304	1060	9	A (5)	Curative	38 × 28	Proton, 60/10	7	Alive, 42.6	Acute (Grade 1)
78, M	PS1	Stage IIIA	38	67	44	A (6)	Curative	30 × 22	Proton, 76/20	9	Dead, 24.3	No
72, F	PS1	Stage IIIA	1612	772	17	A (5)	Curative	36 × 24	Proton, 76/20	17	Dead, 25.6	Acute (Grade 1)
67, M	PS0	Stage IV	37	1810	27	A (5)	Palliative	105 × 105	Proton, 60/10	15	Alive, 8.2	No
45, F	PS0	Stage IV	7	48	8	A (6)	Palliative	130 × 130	Proton, 66/10	36	Alive, 9.9	No
71, M	PS0	Stage IV	1126	69	10	B (8)	Palliative	90 × 90	Carbon, 66/10	31	Alive, 10.5	No
66, F	PS3	Stage IV	62	1420	26	B (7)	Palliative	130 × 130	Carbon, 52.8/8	27	Alive, 13.5	No
66, M	PS0	Stage IV	2270	175000	38	A (6)	Palliative	130 × 130	Proton, 66/10	31	Dead, 3.1	No
52, M	PS0	Stage IIIA	425	6020	18	A (6)	Palliative	48 × 30	Proton, 66/10	24	Dead, 5.5	No
61, M	PS1	Stage IV	6963	5680	17	A (6)	Palliative	110 × 90	Proton, 56/8	15	Dead, 6.0	No
72, F	PS2	Stage IV	660	90000	35	C (10)	Palliative	112 × 56	Proton, 60/10	25	Dead, 6.2	No
55, M	PS2	Stage IV	8	15	16	B (7)	Palliative	100 × 90	Carbon, 52.8/8	28	Dead, 6.7	No
74, M	PS0	Stage IIIA	170	881	21	A (5)	Palliative	32 × 29	Proton, 60/10	13	Dead, 9.9	No

PS performance status, *AFP* alpha-fetoprotein, *PIVKA II* prothrombin induced by vitamin K absence or antagonist II, *ICG R15* indocyanine green retention rate at 15 min, *GyE* gray equivalent radiation dose, *Liver V30* percentage of the volume of the noncancerous hepatic portion (entire liver volume minus gross tumor volume) receiving ≥30 GyE

[a] According to the American Joint Committee on Cancer *Cancer Staging Manual, 6th edition* [24]

exposure dose of the rib. The D95 of the *PTV* and the *Liver V30* have always been high-priority factors, with the *Liver V30* being employed as the most important factor in patients whose liver function has already deteriorated, while the Gut Dmax and/or Gut V40 have become secondary major factors of concern in patients with tumors located close to the gut.

The patients were immobilized with an individually shaped body cast, and beams were synchronized with respiration according to the respiratory gating system. We used a three-dimensional (3D) treatment planning system (FOCUS-M, CMS Japan, Tokyo; and Mitsubishi Electric, Kobe, Japan) with CT–MRI fusion. MRI scans with a 4 mm thickness and consecutive CT images with a 2 mm thickness were obtained for treatment planning. The *CTV* was defined as the *GTV* plus a 5 mm margin. The *PTV* was defined as the 3D isotropic expansion of the *CTV* plus 10 mm. By including 5 mm around the *PTV* as a penumbra, the initial irradiation fields were customized with 3.75 mm width multileaf collimators on the beam's eye view [25]. Portal vein tumor thrombi were also included in the *PTV*.

The doses were calculated on the basis of the pencil beam algorithm. The beam parameters, including the energy level, width of spread-out Bragg peak, and degraded thickness were adequately selected with FOCUS-M. Dose-volume histograms (DVHs) were calculated for all patients to evaluate the irradiated volume and the doses given to the *CTV* and the *PTV*. The particle beam dose is reported in GyE, which is the physical dose multiplied by the relative biological effectiveness of protons or carbon ions. Because all tissues are judged to have approximately the same relative biological effectiveness for protons or carbon ions, the doses expressed in GyE are therefore directly related to photon doses. The *Liver V30* was also evaluated according to the DVH. Based on the findings of several studies of photon radiotherapy, treatment plans at our center are managed to maintain the *Liver V30* at a level within 40% [26, 27]. In patients with Child–Pugh grade B or C, we strictly adhered to this criterion.

Follow-up and evaluation criteria

The patients underwent physical examinations, CT or MRI imaging, and blood tests every 3 months after the treatments. The definition of local recurrence after particle radiotherapy was based on previously established criteria [19, 21, 28]. Local recurrence was defined as the growth of an irradiated tumor or the appearance of new tumors within the *PTV*. Acute and late toxicities associated with treatment were evaluated based on the Radiation Therapy Oncology Group acute radiation morbidity scoring criteria and the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme, respectively [29].

Statistical analysis

The Kaplan–Meier method was used for the calculations, and the statistical significance of differences for both local tumor control rates and survival rates was examined using the log-rank test for univariate analysis. *P* values of less than 0.05 were considered to be statistically significant. All statistical analyses were performed with the Statview version 5.0 software package (SAS Institute, Cary, NC, USA).

Results

All patients were followed until their death or until September 2009. Their clinical details are shown in Table 1. Four of the 6 patients in the curative treatment group and 4 of the 10 patients in the palliative treatment group were alive at the last follow-up.

Only one patient (in the curative treatment group, with a single intrahepatic metastasis distant from the primary tumor) underwent proton radiotherapy for the primary tumor and subsequent RFA for the metastatic lesion. The other 15 patients received no other treatments during the particle radiotherapy regimen. Five of the 6 patients in the curative treatment group had new recurrences outside the *PTV* after treatment. Two of them had lung metastases, and the remaining 3 had intrahepatic recurrences. One of the 2 patients with lung metastases received conformal radiation therapy against the lung metastases. All 3 patients with intrahepatic recurrences received treatments in combination with RFA and TACE. The mean period to new recurrence in the curative treatment group after particle radiotherapy was 7.4 months, ranging from 3 to 15 months. None of the 10 patients in the palliative treatment group received any additional treatments after the particle radiotherapy because they selected best supportive care.

Local tumor control rate

Complete local tumor control was achieved in all targeted tumors, including IVCTT. The tumors decreased in size with the passage of time after particle radiotherapy, but did not disappear completely. A representative case presentation, with tumor thrombus extending into the IVC to the right atrium, is shown before and after proton radiotherapy in Fig. 1. The irradiated tumor, including the tumor thrombus, totally disappeared, with recanalization of the IVC and marked shrinkage of the liver parenchyma after treatment.

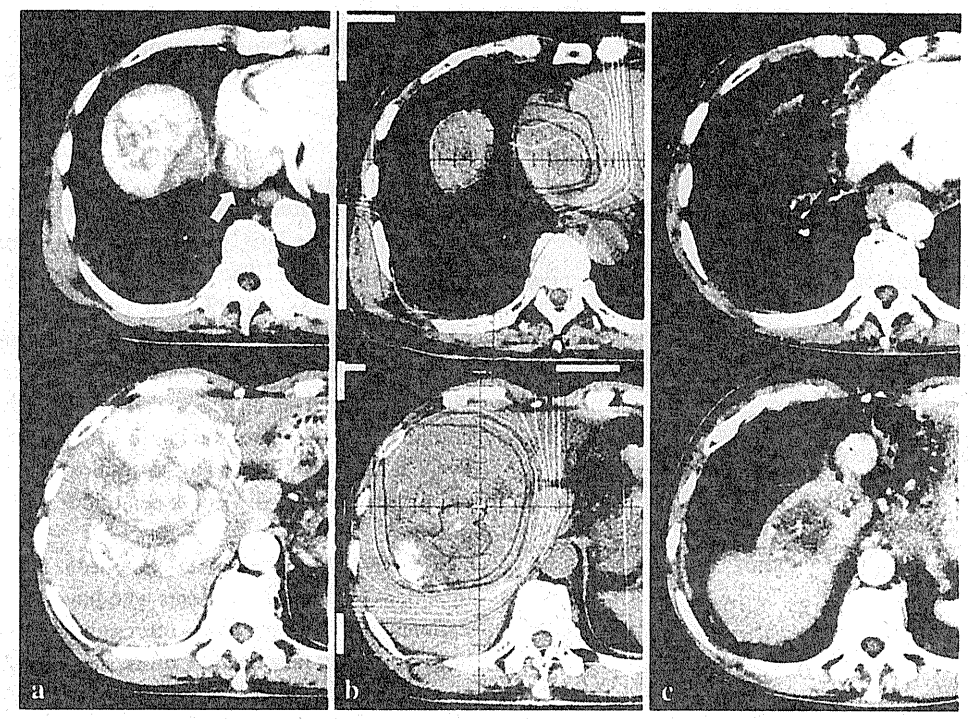

Fig. 1 Findings in a 70-year-old patient demonstrating hepatocellular carcinoma with inferior vena cava tumor thrombus. **a** Contrast-enhanced computed tomography scans before the initiation of proton radiotherapy demonstrated a huge tumor with tumor thrombus extending into the right atrium (*arrow*). **b** Treatment planning of the proton radiotherapy. Isodose curves demonstrate 100% of the prescribed dose at the center and decreasing by 5% of the dose from the inside out. **c** Contrast-enhanced computed tomography scans taken 30 months after completion of proton radiotherapy demonstrated the complete remission of the irradiated tumor including the tumor thrombus, with recanalization of the inferior vena cava and marked shrinkage of the liver parenchyma

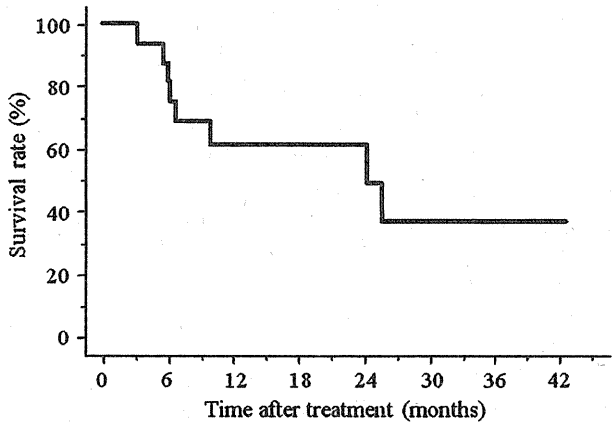

Fig. 2 The overall survival rate of all 16 patients treated with particle radiotherapy is shown

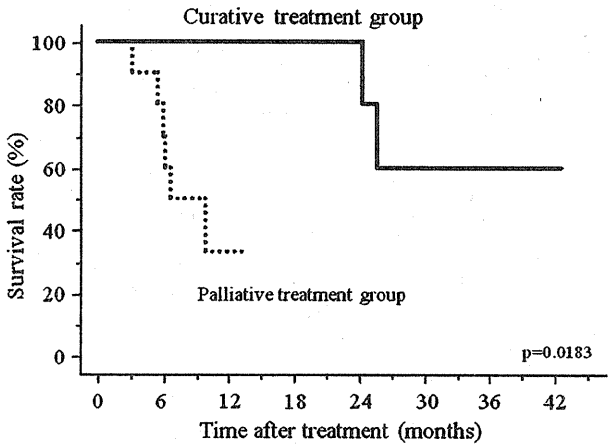

Fig. 3 The overall survival rates according to the treatment policy are shown

Overall survival rates

The overall survival rates for all patients at 1 and 3 years were 61.1 and 36.7%, respectively (Fig. 2). The 1- and 3-year survival rates were 100.0 and 60.0% for patients in the curative treatment group, and 33.3 and 0% for those in the palliative treatment group (Fig. 3). The median survival times in the two groups were 25.4 months and 7.7 months, respectively. A significant difference was observed in overall survival between the two groups ($P = 0.0183$). Five patients in the curative treatment group survived for more than 2 years after treatment, with the longest survival time at 42.6 months. The remaining 1 patient had survived

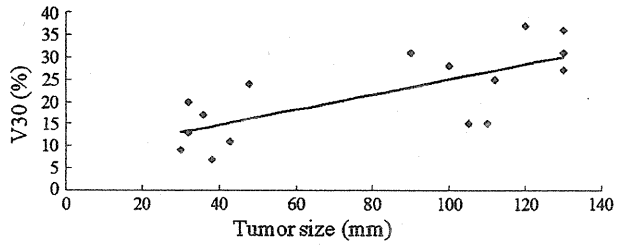

Fig. 4 A scattergram showing the relationship between the tumor size and the *Liver V30* value (percentage of the volume of the noncancerous hepatic portion [entire liver volume minus gross tumor volume] receiving ≥30 gray equivalent radiation dose [GyE])

Table 2 Acute and late toxicities

	Grade 1 No.	Grade 2 No.	Grade 3 No.	Grade 4 No.
Acute toxicities				
Dermatitis	9	2	0	0
Hepatic toxicity	3	1	0	0
Low albuminemia	1	0	0	0
Late toxicities				
Dermatitis	1	0	0	0
Hepatic toxicity	0	1	0	0

for more than 17.0 months after treatment at the last follow-up.

Evaluation of *Liver V30* values

The *Liver V30* values derived from the DVH are shown in Table 1. We plotted the relationship between the tumor size and the *Liver V30* value on a scattergram (Fig. 4). Regardless of tumor size, the *Liver V30* values did not exceed 40%, with an average value of 22% in all cases. The highest *Liver V30* value was 37%, in which the tumor measured 120 mm in greatest dimension. A significant correlation was found between tumor size and *Liver V30* values (the correlation factor was 0.727).

Treatment toxicities

Table 2 shows the treatment-related toxicities in the 16 patients treated with particle radiotherapy. Among the acute toxicities observed, 11 of the 16 patients had dermatitis of grade 2 or less. We observed Grade 2 or less hepatic toxicity in 4 patients, all of whom had no clinically apparent problems. With regard to late toxicities, we observed grade 2 hepatic toxicity in only one patient, whose *Liver V30* value was 37%, the highest among all the patients. However, all acute and late toxicities were transient and tolerable, and they were successfully managed by conservative treatments.

Discussion

This is the first study to demonstrate the efficacy of particle radiotherapy for HCC with IVCTT in a relatively large patient population. The local tumor control rate of HCC with IVCTT was 100.0%, and 1-year survival rates were 61.1% for all patients and 100.0% for patients in the curative treatment group. This result far exceeds any previous data for liver resection, TACE, radiotherapy, and the combination of these modalities for treating HCC with IVCTT [8, 9, 12, 30]; in these studies, the 1-year survival rate of the patients did not exceed 50% with any treatment modality.

To date, liver resection has been the only curative treatment modality for patients who have HCC with IVCTT. Patients for whom liver resection is suitable usually have favorable prognostic factors, such as unifocal lesions, no extrahepatic metastases, and Okuda Stage I [12, 31]. Of the 16 patients in the present study, only 6 patients had these favorable prognostic factors and therefore could be treated with curative intent using particle beams. However, the median survival time of these 6 patients in the present study was 25.4 months, which is much better than that after a liver resection, which has been reported to range from 7 to 8 months [30, 31]. Two possible reasons account for the favorable treatment results of particle radiotherapy in comparison to liver resection for HCC with IVCTT: (1) liver resection for HCC with IVCTT is an invasive procedure that increases the risk of the hematogenous dissemination of tumor cells due to mechanical manipulation during the operation, a factor that accounts for the poor prognosis for a liver resection [32]. In contrast, particle radiotherapy is unrelated to this pattern of tumor development, and (2) surgical stress due to liver resection increases the proliferation of some cytokines, such as vascular endothelial growth factor and hepatocyte growth factor [33, 34], which accelerate tumor growth and invasion [35]. In the absence of surgical stress, particle radiotherapy might minimize the proliferation of these cytokines during and after treatment. Indeed, 4 of the 6 patients in our curative treatment group did not experience extrahepatic metastases after treatment; their median follow-up time was 29.6 months. This result suggests that particle radiotherapy will play a key role in treating HCC with IVCTT. Randomized clinical trials are urgently needed to confirm the best treatment option for these patients.

Historically, the use of external beam radiotherapy for the treatment of HCC has been limited by the poor radiation tolerance of the surrounding liver and subsequent

RILD. Recent improvements of dose localization techniques, including intensity-modulated radiotherapy, conformal 3D planning, and breathing motion management strategies, have made it possible to irradiate smaller, well-defined targets in the liver [36, 37]. However, RILD is still a serious problem in photon radiotherapy. It is especially true with tumors like HCC with IVCTT that are central, deep, and always surrounded by large amounts of normal liver tissues [15]. To compensate for the low antitumor effects of photon beams, a number of radiation fields are needed to deliver a sufficient tumoricidal dose, resulting in increased radiation exposure to the normal liver. Therefore, the application of photon radiotherapy for patients who have HCC with IVCTT has been restricted to small HCCs (<5 cm) or only tumor thrombi [38–41]. Conversely, the highly targeted dose distribution of particle beams exhibited by the Bragg peak enables higher radiation doses to be delivered to tumors, with reduced radiation fields. This significantly lowers the doses to the surrounding normal tissues [16]. Indeed, the *Liver V30* values of all the patients in the present study were less than 40%; nonetheless, most tumors were larger than 5 cm and the tumors, including both the main tumor and the IVCTT were totally irradiated (Fig. 4). In the present study, all treatment-related toxicities developing during or after treatment were transient, easily manageable, and acceptable. The minimal side effects are thought to be associated with the superior dose distribution of the particle beams.

It is obvious that underlying liver disease significantly influences liver damage after radiotherapy. Therefore, treatment targeted to HCC based only on radiation dose-volume analysis should be carefully considered. In this regard, Kawashima et al. [20] proposed that the unirradiated liver volume and pretreatment liver function might be the best indicators for estimating the liver damage after particle radiotherapy. Further studies are required to clarify the upper limit of the radiation dose in combination with liver function in the use of particle radiotherapy to treat HCC.

One of the important clinical questions raised by our data concerns the radiation field of the particle beams in the palliative treatment group. Previous studies of the use of photon radiotherapy on HCC with IVCTT have shown the radiation fields to be focused only on the IVCTT; the main tumors were not included, due to the risk of RILD [38, 39, 41]. However, our data indicate that total irradiation, including the main tumor and the IVCTT, can be safely performed using particle beams. Total irradiation clearly contributed to a longer survival in our curative treatment group in comparison to only a minor survival benefit observed after liver resection. However, the survival benefit of total irradiation in the palliative treatment group remains to be elucidated. The median survival time of the patients in our palliative treatment group was 7.7 months, which was slightly superior to that of untreated patients, which was approximately 3 months [6]. However, it is noteworthy that there were no pulmonary embolic events or sudden deaths after the particle radiotherapy in our study. We hypothesize that the total irradiation may have contributed to reduced growth in the entire tumors, thus leading to a decreased frequency of tumor thrombi dropping into the IVC.

In conclusion, particle radiotherapy appears to be a safe and effective treatment modality for patients who have HCC with IVCTT. Although the number of enrolled patients in the present study was small, our data can serve as a basis for selecting particle radiotherapy as an alternative novel treatment for HCC with IVCTT.

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