the cPD, SSPPD, and PPPD groups (2.9, 5.4, and 6.1%, respectively; $P = 0.704$). No cases with gastric dumping syndrome were observed after the surgery in our series. The hospital stay tended to be shorter in the SSPPD group than in other groups. However, the differences did not reach statistical significance.

Long-Term Nutritional Status

Regarding postoperative weight loss, approximately 12% of the body weight was lost at 6 months after the surgery in all three groups. The body weights in the SSPPD and PPPD groups started to recover by 1 year after the surgery, whereas that in the cPD group continued to decrease (Fig. 2a). The serum total protein and albumin levels were also decreased at 6 months in all three groups. These levels showed better recovery in the SSPPD group than in the cPD and PPPD groups at 1 year, when the difference in the serum albumin levels reached statistical significance ($P = 0.0303$; Fig. 2b, c). The serum cholinesterase, total cholesterol, and hemoglobin levels also tended to be higher in the SSPPD group compared with the cPD and PPPD groups at 1 year after the surgery (Fig. 3a–c). Furthermore, the serum total lymphocyte count was significantly higher in the SSPPD group than in the PPPD group at 1 year after the surgery ($P = 0.0203$; Fig. 3d).

Postoperative Survival

The median disease specific survival times of the patients who underwent cPD, SSPPD, and PPPD were 17.1, 21.3, and 17.7 months, respectively (Fig. 4a). The median disease-free survival times of the patients who underwent cPD, SSPPD, and PPPD were 8.0, 9.1, and 6.9 months, respectively (Fig. 4b). The patients in the SSPPD group showed longer survival times than the patients in the cPD and PPPD groups, but the differences did not reach statistical significance.

Comparison of the Diameter of the Gastric Outlet in PD

The diameter of the gastric outlet of the gastrojejunostomy in the SSPPD group was significantly larger than that in the PPPD group (45 ± 7 and 33 ± 5 mm, respectively; $P < 0.0001$).

DISCUSSION

The postoperative nutritional status has been reported to be greatly associated with antitumor immunity, and malnutrition is well known to affect the prognosis of cancer patients who have undergone surgery.[16] A surgical procedure that can lead to a better nutritional status is more desirable for cancer patients. Surgical procedures for pancreatic cancer, especially PD, often result in remarkable malnourishment.[14,26] Recently, PPPD has been performed as the standard technique for pancreatic head cancer worldwide, in preference to cPD that involves an extensive gastrectomy. In the present study, few metastases to the lymph nodes along the lesser and greater curvatures of the stomach were observed, suggesting that the extensive antrectomy is not necessary from the viewpoint of curativity. However, PPPD failed to dramatically improve the nutritional status in some randomized controlled trials.[6–8] Moreover, DGE is a

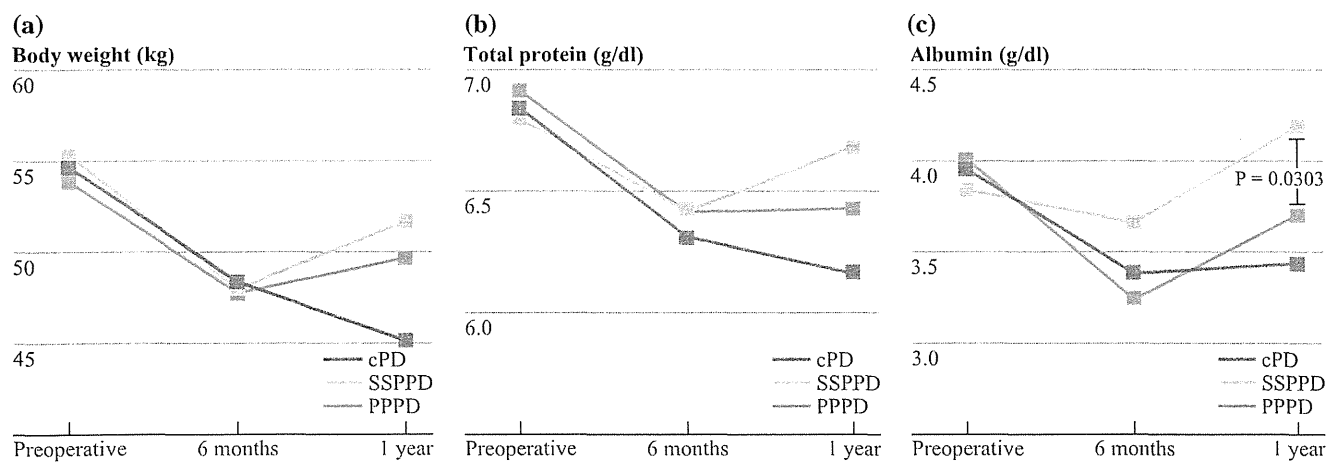
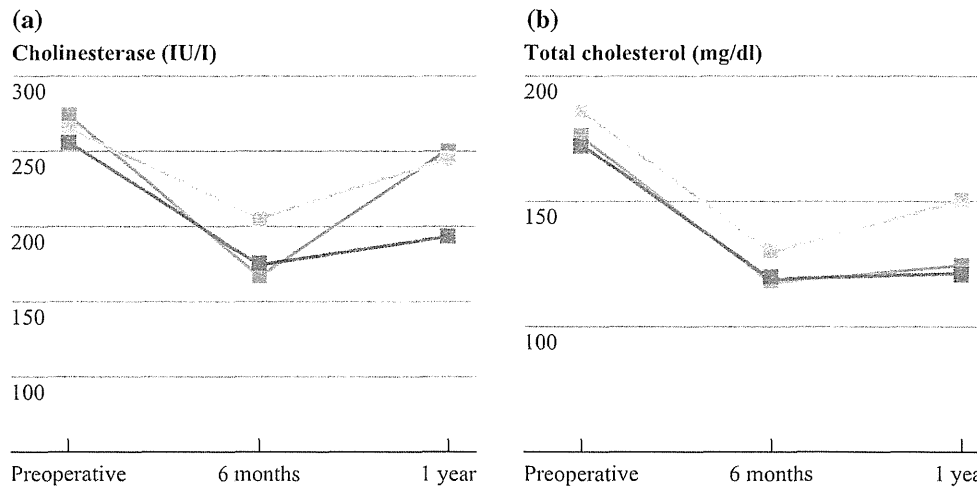


FIG. 2 Changes in the body weight of the patients and the serum total protein and albumin levels. **a** The body weights were decreased at 6 months after the surgery in all three groups. The body weights in the SSPPD and PPPD groups started to recover by 1 year after the surgery, whereas that in the cPD group continued to decrease. The serum total protein (**b**) and albumin (**c**) levels showed better recovery in the SSPPD group than in the cPD and PPPD groups at 1 year after the surgery, and the difference in the serum albumin level reached statistical significance ($P = 0.0303$)



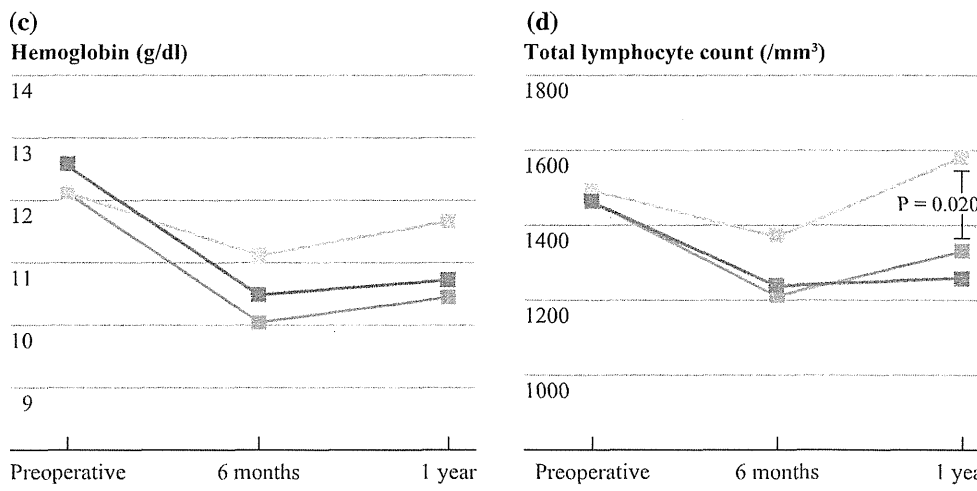


FIG. 3 Changes in the serum cholinesterase (**a**), total cholesterol (**b**), hemoglobin (**c**), and total lymphocyte count (**d**) levels. The levels in the SSPPD group tended to be higher to those in the cPD and PPPD groups at 1 year after the surgery. The serum total lymphocyte count was significantly higher in the SSPPD group than in the PPPD group at 1 year after the surgery ($P = 0.0203$)

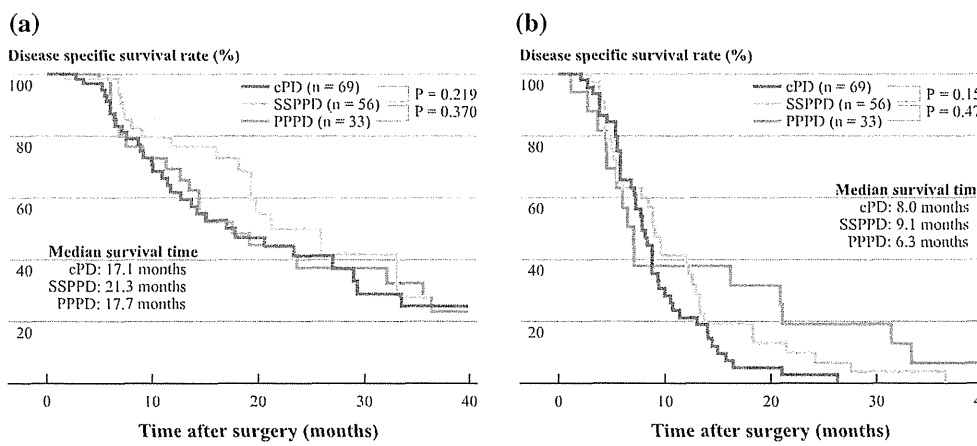


FIG. 4 **a** Disease-specific survival rates of the patients who underwent cPD, SSPPD, and PPPD (with median survival times of 17.1, 21.3, and 17.7 months, respectively). The patients in the SSPPD group showed longer survival times than the patients in the cPD and PPPD groups, although the differences did not reach statistical significance. **b** Disease-free survival rates of the patients who underwent cPD, SSPPD, and PPPD (with median survival times of 8.0, 9.1, and 6.9 months, respectively). The differences did not reach statistical significance

well-known postoperative complication, which occurred more frequently in patients who underwent PPPD compared with cPD.[8]

Recently, Kawai et al.[27] revealed that the frequency of DGE was lower in pylorus-resecting PD than in PPPD in a randomized controlled trial. In surgery for pancreatic head

cancer in particular, the vagal innervation around the pyloric ring is destroyed after the peripyloric lymph node dissection. Their report suggested that preservation of the pyloric ring without vagal innervation resulted in gastric outlet obstruction. Moreover, postoperative adjuvant chemotherapy for pancreatic cancer is pivotal, and a large-scale phase III clinical trial demonstrated that patients who underwent surgery followed by adjuvant chemotherapy had a far better survival than patients who underwent surgery alone.[19,28] Postoperative status could influence the compliance for adjuvant chemotherapy, and poor nutritional condition could eventually result in an adverse prognosis. Thus, a surgical procedure associated with fewer postoperative complications is desirable in surgery for pancreatic cancer. The results of this retrospective study verified the results of Kawai et al. and suggest that there are no benefits in preservation of the pyloric ring, and that SSPPD can be recommended in terms of early postoperative complications when compared with PPPD.

In addition to the short-term postoperative outcomes, the long-term nutritional status is one of the vital aspects of observation. Kawai et al.[27] only reported the short-term outcomes, whereas the nutritional consequences at 1 year after the surgery were also compared in the present study. The postoperative body weight loss and changes in blood examinations after SSPPD were superior to those after PPPD. In particular, there were statistically significant differences in the serum albumin level and total lymphocyte count, which have been noted as immunonutritional indicators.[26] One of the possible reasons for the differences between SSPPD and PPPD was the diameter of the gastric outlet. The gastric outlet diameter, although available only from the recent cases, was larger after SSPPD than after PPPD, and this may have contributed to improved oral intake followed by more favorable nutritional status in the current series. The adjustability of the diameter of the gastric outlet may be one of the possible benefits of SSPPD. An outlet that is too large could cause complications including dumping syndrome, diarrhea, or bile reflux gastritis.[29] However, no cases of gastric dumping syndrome were observed after the surgery in our series. Although the optimal diameter of the gastric outlet after PD is open to discussion, it can be argued, at least, that the pyloric ring without vagal innervation should be removed rather than preserved. In surgery for early gastric cancer, a procedure that preserves the vagal nerve as well as the pyloric ring has been performed.[30–32] However, this procedure is not appropriate for patients with pancreatic cancer, which is well known for its highly aggressive biology, because preservation of the vagal nerve is not compatible with skeletonization of the hepatoduodenal ligament for radical lymph node dissection.

One of the possible postoperative complications after PPPD as well as SSPPD is the development of a peptic ulcer.[33,34] In our institution, H_2-receptor antagonists are usually prescribed prophylactically, and the incidence of peptic ulcer was comparable among the three groups. Further prospective investigations such as randomized controlled trials should be conducted to assess the efficacy of pyloric ring preservation for peptic ulcers.

The long-term survival was reported to be similar between cPD and PPPD.[6–9] In the present study, the median survival time was longer after SSPPD than after cPD and PPPD, although the difference did not reach a statistical significance. Portal vein resection and postoperative adjuvant chemotherapy were more often required in the cPD group, and this could reflect the lower survival. However, a comparison of SSPPD and PPPD revealed that the survival was better in the SSPPD group than in the PPPD group despite the fact that the SSPPD group included more patients with portal vein resection and advanced disease stages than the PPPD group. It can be speculated that preservation of almost the whole stomach without the pyloric ring that led to favorable short-term operative results and long-term nutritional status possibly resulted in the better survival rate in the SSPPD group through improvement in immune status and compliance to adjuvant chemotherapy, although further confirmatory studies are necessary. The limitations of this study are that the patient records were retrospectively analyzed and that the operative procedures were decided according to the surgeon's discretion. Nevertheless, the results of the present study could be a trigger for future prospective trials and reconsideration of the surgical procedures for pancreatic head cancer because PPPD is currently established as the standard procedure.

The findings of the present study offer valuable insights into the perioperative and long-term benefits of SSPPD which is not technically more complicated when compared with the more widely performed PPPD. Our results suggest that preservation of the pyloric ring without vagal innervation offers little benefit, and that the standard procedure for resection of pancreatic head cancer could be reconsidered. Further prospective studies are warranted to clarify this issue.

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Original article

Risk factors for survival and local recurrence after particle radiotherapy for single small hepatocellular carcinoma

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Background: Particle radiotherapy is a novel treatment for malignant tumours. The present study aimed to evaluate risk factors for overall survival and local control after particle radiotherapy of single small hepatocellular carcinoma (HCC), and to identify suitable candidates for this treatment.

Methods: All patients with a single HCC smaller than 5 cm in diameter treated by particle radiotherapy between 2001 and 2008 were identified retrospectively from a prospectively collected database. Clinical outcomes and prognostic factors were analysed.

Results: A total of 150 patients were included. Five-year overall survival and local control rates were 50·9 and 92·3 per cent respectively. Multivariable analysis revealed that several factors, including age and Child–Pugh classification, significantly influenced overall survival. Proximity to the digestive tract and Child–Pugh classification were independent risk factors for local recurrence. Other tumour factors including size, gross classification, previous treatment, macroscopic vascular invasion, and tumour location in relation to the diaphragm and large vessels did not influence local control rate.

Conclusion: Particle radiotherapy seems safe and effective, and may be a novel treatment for small HCC. Recurrences are more frequent when the tumour is located close to the gut.

Paper accepted 19 November 2010

Published online 19 January 2011 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.7397

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide[1]. Hepatectomy and liver transplantation are considered to be the most reliable treatments for HCC, but benefit only approximately 15 per cent of patients[2]. Local ablative therapies, such as radiofrequency ablation (RFA), are commonly used to treat unresectable liver tumours, but may lead to increased local recurrence rates[3–5]. Tumour size and perivascular tumour location are significant risk factors for local recurrence after RFA[4,5]. Patients not eligible for local ablative therapy are usually treated with non-curative modalities, such as transarterial chemoembolization (TACE) or systemic chemotherapy.

Recent improvements in photon radiotherapy, such as conformal three-dimensional planning, intensity-modulated radiotherapy and breathing motion management strategies, have made it possible to irradiate smaller targets in the liver with curative intent. However, these highly computer-assisted irradiation techniques using photon beams have still achieved only limited efficacy in treating large and centrally situated liver tumours[6–8].

Particle beams consisting of protons and carbon ions offer improved dose distribution compared with photons, and therefore enable dose escalation within the tumour while sparing normal tissues. The similar effectiveness of proton and carbon ion radiotherapy has already been proven in several clinical reports[9–13]. Consequently particle radiotherapy has become a realistic treatment option for HCC. However, the best therapeutic targets and the limitations of particle radiotherapy for HCC still remain to be elucidated. The aim of the present study was to identify risk factors for overall survival and local control following particle radiotherapy of a single small HCC.

Methods

An institutional database containing prospectively collected data on patients treated at the Hyogo Ion Beam Medical

Centre was studied retrospectively. Patients who had uncontrolled ascites, multiple tumours and/or tumours larger than 5 cm were not eligible for inclusion. All patients had HCC diagnosed either histologically or clinically based on contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI), and raised levels of α-fetoprotein (AFP) and/or proteins induced by vitamin K absence or antagonist II (PIVKAII). This group included patients ineligible for hepatectomy owing to poor liver function (indocyanine green retention rate at 15 min exceeding 30 per cent) and/or poor performance status, as well as those who deliberately chose to undergo particle radiotherapy as a less invasive curative treatment for HCC. Some of these patients had undergone previous treatments comprising combinations of either surgery, TACE or local ablative therapy. Data were analysed retrospectively with regard to overall survival, local tumour control and treatment-related toxicity. The present study was conducted according to the Helsinki Declaration, and written informed consent was obtained from all patients.

Abdominal CT, MRI, ultrasonography, chest CT and bone scintigraphy were carried out to determine the clinical stage before treatment. All patients had a complete blood count, a biochemical profile including total protein, albumin, total cholesterol, electrolytes, kidney and liver function tests, and serological testing for hepatitis B surface antigen and antihepatitis C antibody. Serum AFP and PIVKAII levels were also measured before and after treatment.

Baseline patient and tumour variables were analysed. Tumour size was classified as either 30 mm or less, or over 30 mm (but less than 50 mm) in largest dimension. Tumours were divided into four gross types according to the rules of the Liver Cancer Study Group of Japan[14]: single nodular type, single nodular type with extranodular growth, confluent multinodular type and infiltrative type. As single nodular tumours have a better prognosis than other types[15], tumours were further categorized as either single nodular or non-single nodular type. Macroscopic vascular invasion was defined as gross tumour invasion into the portal or hepatic veins on pretreatment imaging. Tumour location was also classified based on proximity to the digestive tract (within 10 mm, 10 mm or more), diaphragm (within 10 mm, 10 mm or more), inferior vena cava (IVC) (attached, not attached) and main portal trunk (attached, not attached).

Protocol and treatment planning

The prescribed dose was calculated for the centre of the planning target volume (PTV) and expressed in gray (Gy) equivalents (GyE = proton or carbon physical dose (in Gy) × relative biological effectiveness). Four protocols for proton radiotherapy (52·8–76 GyE in 4–20 fractions using 150-, 190-, 210- or 230-MeV proton beams) and two protocols for carbon ion radiotherapy (52·8 GyE in 4–8 fractions using 250- or 320-MeV carbon ion beams) were employed in the present study. From May to October 2001 and from April 2003 to March 2005, only proton radiotherapy was available. From February to June 2002, only carbon ion radiotherapy was available. After April 2005, treatment plans were made for both proton and carbon ion radiotherapy to allow selection of the better beam[16]. From November 2001 to January 2002, and from July 2002 to March 2003, treatments were not performed because of the licensing procedure. The dose distribution in a single beam appears to be better in carbon ion beams than in proton beams[17]. However, in terms of beam arrangement, carbon ions are emitted from three fixed ports, whereas a 360° rotating gantry can be used for protons. The high positioning accuracy achieved by irradiating patients in a supine position is therefore an advantage of proton radiotherapy.

Radiation treatments were designed with the use of a CT-based three-dimensional treatment planning system (FOCUS-M; CMS Japan, Tokyo, and Mitsubishi Electric, Kobe, Japan). In brief, the patient was immobilized with a custom-made thermoplastic immobilization cast in the supine or prone position, depending on the tumour location. CT slice thickness was 2 mm and MRI slice thickness 5 mm. CT images were obtained at expiration using a respiratory gating system. Target volumes and organs at risk of irradiation, such as the liver and intestine, were delineated on CT–MRI fusion images. Treatment planning was defined in terms of the clinical target volume (CTV). CTV = gross tumour volume + 5 mm (in all directions), PTV = CTV + 5 mm (in all directions). In addition, a further margin of 5–10 mm was included in the caudal axis to compensate for respiration-induced hepatic movements. Dose–volume histograms were made for all patients to evaluate the risk of radiation-induced complications. All treatment plans were established and modified according to the tolerance limits of the exposure doses of each organ.

Doses were calculated based on the pencil beam algorithm. The beam parameters, including energy level, width of the spread-out Bragg peak, and degrader thickness were selected adequately with FOCUS-M.

New symptoms or clinical findings developing within 90 days of the initiation of particle radiotherapy were defined as acute radiation toxicity, and later problems as late toxicity. Acute and late toxicities were graded by severity of

adverse event according to the National Institute Common Terminology Criteria for Adverse Events (version 2.0): grade 1, mild; grade 2, moderate; grade 3, severe; and grade 4, life-threatening or disabling[18].

Follow-up and evaluation criteria

Follow-up consisted of blood tests and monitoring of tumour markers in outpatients; dynamic CT or MRI was performed every 3 months for 3 years after treatment, and every 6 months thereafter.

As HCCs, even after a complete response, tend to persist for a long period after completion of particle radiotherapy[12], local recurrence was defined as either growth of an irradiated tumour or the appearance of new tumours within the PTV, based on previous criteria[9,10,12].

Statistical analysis

Overall survival and local control rates were calculated using Kaplan–Meier methodology. Eight patient variables (age, sex, positive viral marker, performance status, Child–Pugh classification, serum AFP level, PIVKAII level and source of beam) (*Table 1*) and eight tumour features (tumour size, gross classification, previous treatment of target tumour, macroscopic vascular invasion, proximity to the digestive tract, proximity to the diaphragm, proximity to the IVC and proximity to the main portal trunk) (*Table 2*) were investigated as prognostic factors for overall survival and local control. The statistical significance of differences in both overall survival and local control rates was examined using the log rank test in univariable analysis. $P < 0{\cdot}050$ was considered statistically significant, and variables with $P < 0{\cdot}100$ were included in multivariable analysis using Cox proportional hazards model. Statistical analyses were performed using SPSS® version 17.0 software (SPSS, Chicago, Illinois, USA).

Results

Of 339 consecutive patients treated between May 2001 and December 2008, 150 who had a single tumour measuring less than 5 cm in diameter were eligible for inclusion in the study. Eighty-six (57·3 per cent) of the 150 patients had no history of tumour treatment before particle radiotherapy. The remaining 64 had received treatment to the target tumour previously. Two of the 64 patients had local recurrence after hepatectomy and 23 developed local recurrence after local ablative therapy. In addition, 56 of these 64 patients had undergone TACE before particle radiotherapy.

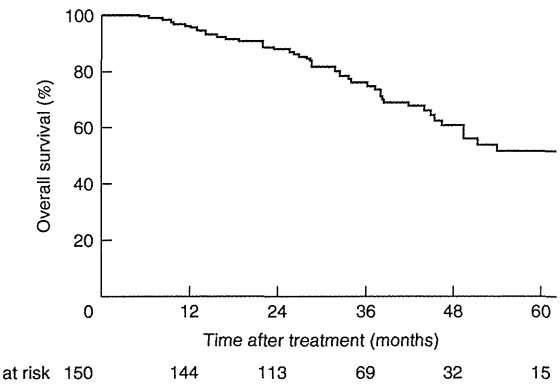

Fig. 1 Overall survival rate among 150 patients treated with particle radiotherapy for a single small hepatocellular carcinoma

Prognostic factors for overall survival

Overall survival rates for all patients at 3 and 5 years were 75·7 and 50·9 per cent respectively (*Fig. 1*). Age, performance status and Child–Pugh classification were identified as significant prognostic factors for overall survival rate in univariable analysis (*Tables 1* and *2*). Multivariable analysis showed that age and Child–Pugh classification were independent factors that significantly affected overall survival (*Table 3*).

Prognostic factors for local control

The cumulative local control rates for all tumours at 3 and 5 years were both 92·3 per cent (*Fig. S1*, supporting information). Univariable analysis showed that sex, performance status, Child–Pugh classification and proximity to the digestive tract significantly affected local control rates (*Tables 1* and *2*). Other tumour factors, including size, gross classification, history of previous treatment, macroscopic vascular invasion and tumour location (proximity to the diaphragm, IVC and main portal trunk) did not affect local control rates. Child–Pugh classification and proximity to the digestive tract were the only independent factors for local recurrence in multivariable analysis (*Table 3; Fig. S2*, supporting information).

Toxicity

All patients tolerated the treatment and completed the planned treatment protocol. A total of 127 patients

Table 1 Univariable analysis of factors related to patient characteristics

	No. of patients	5-year overall survival		5-year local control	
		Rate (%)*	Univariable *P*†	Rate (%)*	Univariable *P*†
Age (years)			0·049		0·696
< 70	69 (46·0)	58·0		93·7	
≥ 70	81 (54·0)	43·2		91·0	
Sex			0·265		0·037
M	115 (76·7)	52·6		95·0	
F	35 (23·3)	45·8		83·9	
Positive viral marker			0·715		0·753
Hepatitis B virus	23 (15·3)	47·9		94·1	
Hepatitis C virus	104 (69·3)	50·0		91·4	
None	23 (15·3)	68·2		95·2	
Performance status			0·036		0·023
0	118 (78·7)	57·0		95·2	
1 or 2	32 (21·3)	29·3		82·1	
Child–Pugh classification			< 0·001		0·007
A	125 (83·3)	59·8		94·6	
B	25 (16·7)	14·6		77·1	
Serum AFP (ng/ml)			0·514		0·934
< 100	118 (78·7)	51·0		92·4	
≥ 100	32 (21·3)	50·3		92·0	
Serum PIVKAII (units/ml)			0·090		0·823
< 100	97 (64·7)	56·2		91·9	
≥ 100	53 (35·3)	38·2		93·4	
Source of beam			0·389		0·972
Proton	105 (70·0)	49·1		92·5	
Carbon	45 (30·0)	68·0		91·9	

Values in parentheses are percentages. AFP, α-fetoprotein; PIVKAII, proteins induced by vitamin K absence or antagonist II. *Kaplan–Meier analysis; †log rank test.

Table 2 Univariable analysis of tumour factors

	No. of patients	5-year overall survival		5-year local control	
		Rate (%)*	Univariable *P*†	Rate (%)*	Univariable *P*†
Tumour size (mm)			0·612		0·924
≤ 30	89 (59·3)	50·0		92·2	
> 30, ≤ 50	61 (40·7)	52·5		92·8	
Gross classification			0·178		0·118
Single nodular type	91 (60·7)	52·7		95·0	
Non-single type	59 (39·3)	48·1		87·9	
Previous treatment of tumour			0·328		0·591
Yes	64 (42·7)	44·5		90·9	
No	86 (57·3)	56·0		93·3	
Macroscopic vascular invasion			0·998		0·729
Yes	10 (6·7)	70·0		88·9	
No	140 (93·3)	49·9		92·7	
Proximity to digestive tract (mm)			0·236		0·009
≤ 10	20 (13·3)	42·2		77·8	
> 10	130 (86·7)	52·5		94·8	
Proximity to diaphragm (mm)			0·941		0·753
≤ 10	50 (33·3)	51·5		93·4	
> 10	100 (66·7)	51·3		91·8	
Proximity to IVC			0·761		0·593
Attached	33 (22·0)	61·8		88·9	
Not attached	117 (78·0)	48·7		93·3	
Proximity to main portal trunk			0·649		0·295
Attached	15 (10·0)	56·7		84·4	
Not attached	135 (90·0)	50·1		93·2	

Values in parentheses are percentages. IVC, inferior vena cava. *Kaplan–Meier analysis; †log rank test.

Table 3 Independent risk factors for overall survival and local control identified by multivariable analysis

	Standard error	χ^2	Hazard ratio	Multivariable *P**
Overall survival				
Age > 70 years	0·322	8·25	2·52 (1·34, 4·74)	0·004
Performance status 1 or 2	0·332	3·68	1·89 (0·99, 3·63)	0·055
Child–Pugh classification B	0·336	31·54	6·59 (3·41, 12·72)	< 0·001
Serum PIVKAII ≥ 100 units/ml	0·316	2·94	1·72 (0·92, 3·19)	0·086
Local control				
Female sex	0·649	1·42	2·17 (0·61, 7·75)	0·232
Performance status 1 or 2	0·637	3·57	3·33 (0·96, 11·63)	0·058
Child–Pugh classification B	0·670	3·85	3·72 (1·00, 13·85)	0·049
Proximity to digestive tract ≤ 10 mm	0·663	5·25	4·57 (1·25, 16·76)	0·021

Values in parentheses are 95 per cent confidence intervals. PIVKAII, proteins induced by vitamin K absence or antagonist II. *Cox proportional hazards regression model.

developed acute toxicity, but this was grade 2 or less in the majority. Grade 3 or higher toxicity was observed in eight patients, but always resolved within 2 weeks and no patient discontinued treatment owing to acute toxicity. With regard to late toxicity, grade 3 dermatitis was noted in one patient; there was no grade 4 toxicity. No patient died from treatment-related toxicity.

Exposure of a portion of non-cancerous liver to particle radiotherapy induced hepatitis and the gradual development of dense fibrosis, resulting in almost complete atrophy.

Discussion

The present study has shown that particle radiotherapy for small HCC is feasible and safe, with overall survival and local control rates similar to those of other local therapies. Proximity to the digestive tract was identified as a significant risk factor for local recurrence after particle radiotherapy. This strongly suggests that marginal parts of tumours close to the digestive tract had received an insufficient dose. Two factors may contribute to this finding. First, a safety margin around the radiation field cannot be ensured for tumours close to the bowel owing to unavoidable respiratory movements. Second, most tumours near the gut are situated on the inferior surface of the liver. As a result, dose centralization of the particle beams is hindered more prominently by the patient's normal respiratory movements in this region than in other areas of the liver. These factors may reduce the safety margin against the dosimetric and geometric uncertainties of particle beams, and could lead to an increase in local recurrence rates. Each local therapy of HCC has inherent limitations regarding the tumour location[4,19]. Tumour location on the inferior surface of the liver, close to the digestive tract, is probably the Achilles heel of particle radiotherapy for HCC. To overcome this limitation, a spacer between the tumour and digestive tract may be inserted before particle radiotherapy[20,21].

Tumour size greater than 3 cm is a significant risk factor for local recurrence after local ablative therapies, such as RFA[5,22]. In contrast, tumour size over 3 cm (but smaller than 5 cm) had no significant effect on the local control rate in the present study. This suggests that, for tumours up to 5 cm in diameter, particle radiotherapy is effective in achieving local control, irrespective of tumour size. This may be a distinct advantage over existing local ablative therapies.

Macroscopic vascular invasion and three other factors related to tumour location (proximity to the diaphragm, IVC and main portal trunk) had no significant influence on the local control rate after particle radiotherapy. This also differs from findings for other local ablative therapies. The application of local ablative therapies is contraindicated for tumours with macroscopic vascular invasion[5]. Furthermore, proximity to major vessels such as the IVC and/or main portal trunk is associated with an increased local recurrence rate after RFA, as a result of the heat-sink effect[4,5]. Others have shown proximity to the diaphragm to be another factor for local recurrence after percutaneous RFA[23,24]. Hepatectomy is felt to be inappropriate in the treatment of centrally situated tumours adjacent to the IVC and/or the main portal trunk in patients with liver cirrhosis[19]. In the present study, however, none of these factors reduced the efficacy of particle radiotherapy in controlling local growth. In particular, particle radiotherapy was equally effective and safe in treating tumours adjacent to the porta hepatis, confirming previous findings[25]. Based on these results, particle radiotherapy would be an attractive therapeutic option for tumours that are not suitable for currently available local therapies owing to size, location and/or vascular invasion.

Child–Pugh classification was the only independent patient factor with a significant influence on overall survival and local control based on both univariable and multivariable analyses. Several other studies have reported that severe fibrosis or cirrhosis has an independent effect on overall survival rates after curative resection[26,27]. Likewise, poor overall survival rates in the present study were strongly associated with pretreatment liver function (Child–Pugh B), regardless of complete remission of the primary tumour. As regards the poor local control rate in patients with Child–Pugh grade B disease, one possible explanation is that liver cirrhosis is associated with *de novo* carcinogenesis and multicentric recurrence may occur adjacent to the target tumour in cirrhotic liver. This type of multicentric recurrence might therefore be considered to represent local recurrence.

Particle beams, such as proton and carbon ion beams, show an increase in energy deposition with penetration depth up to a sharp maximum at the end of their range, to form the so-called Bragg peak. Almost no dose is deposited in normal tissue beyond the Bragg peak. The particle range is determined by the energy of the incoming particles. Favourable dose distributions with a steep dose fall-off at the field borders, and therefore a more precise dose escalation, can be achieved with these beams in comparison with photon beams. Therefore, dose escalation can probably be performed without inducing toxicity in the surrounding normal tissues.

Acute and late toxicities during treatment were all transient, easily manageable and acceptable in the present series. Previous studies have also shown that particle radiotherapy is safe and less invasive than other treatment modalities for HCC[9,11]. However, dense fibrosis developed in non-cancerous liver that had been exposed to particle radiotherapy, resulting in almost complete atrophy. Therefore, particle radiotherapy should be applied judiciously in patients whose liver function has deteriorated.

At present, the candidates best suited for particle radiotherapy are those with tumours situated more than 10 mm from the digestive tract, in whom other local therapies are contraindicated owing to tumour size, location or vascular invasion, and those with recurrence after hepatectomy, local ablative therapy and TACE.

This study has three limitations: different treatment protocols for proton and carbon ion radiotherapy were used during the study interval; the data were analysed retrospectively; and no direct comparison with other local therapies was made. Although further investigation is required, the present data can serve as a basis for selecting particle radiotherapy as a local treatment for HCC. A comparison with other therapies, such as internal radiation with yttrium-90 microspheres, would be interesting and prospective comparison with resection might be justified.

Acknowledgements

The authors thank Dr D. Sugiyama and Dr K. Nishimura for valuable advice regarding the statistical analyses. This study was supported by grants-in-aid for scientific research from the Ministry of Education, Culture, Sports, Science and Technology of Japan to Y.H. (grant category C; no. 21591773) and Y.K. (grant category C; no. 20591611), and by grants from the Global Centre of Excellence Programme for Education and Research on Signal Transduction Medicine in the Coming Generation 'Bringing up clinician-scientists in the alliance between basic and clinical medicine' to Y.K. The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Fig. S1 Local control rate among 150 patients treated with particle radiotherapy for a single small hepatocellular carcinoma (Word document)

Fig. S2 Local control rate among 150 patients treated with particle radiotherapy for a single small hepatocellular carcinoma stratified according **a** Child–Pugh classification and **b** proximity to the digestive tract (Word document)

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Original Article

Clinical Results and Risk Factors of Proton and Carbon Ion Therapy for Hepatocellular Carcinoma

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BACKGROUND: The objective of this study was to evaluate the clinical outcome of proton and carbon ion therapy for hepatocellular carcinoma (HCC). **METHODS:** In total, 343 consecutive patients with 386 tumors, including 242 patients (with 278 tumors) who received proton therapy and 101 patients (with 108 tumors) who received carbon ion therapy, were treated on 8 different protocols of proton therapy (52.8-84.0 gray equivalents [GyE] in 4-38 fractions) and on 4 different protocols of carbon ion therapy (52.8-76.0 GyE in 4-20 fractions). **RESULTS:** The 5-year local control and overall survival rates for all patients were 90.8% and 38.2%, respectively. Regarding proton and carbon ion therapy, the 5-year local control rates were 90.2% and 93%, respectively, and the 5-year overall survival rates were 38% and 36.3%, respectively. These rates did not differ significantly between the 2 therapies. Univariate analysis identified tumor size as an independent risk factor for local recurrence in proton therapy, carbon ion therapy, and in all patients. Multivariate analysis identified tumor size as the only independent risk factor for local recurrence in proton therapy and in all patients. Child-Pugh classification was the only independent risk factor for overall survival in proton therapy, in carbon ion therapy, and in all patients according to both univariate and multivariate analyses. No patients died of treatment-related toxicities. **CONCLUSIONS:** Proton and carbon ion therapies for HCC were comparable in terms of local control and overall survival rates. These therapies may represent innovative alternatives to conventional local therapies for HCC. ***Cancer* 2011;117:4890-904.** © *2011 American Cancer Society.*

KEYWORDS: hepatocellular carcinoma, particle therapy, proton therapy, carbon ion therapy, local recurrence.

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer death worldwide, and the majority of patients with HCC reside in Asian countries.[1,2] HCC is well suited to local therapy, because it has a tendency to stay within the liver, and distant metastasis generally occurs late. This implies that curative local therapy, as represented by hepatectomy and liver transplantation, has a great impact on the disease course and also offers the best chance of long-term survival for patients with HCC.[3,4] However, only 5% to 40% of patients with HCC are amenable to a hepatectomy because of either advanced tumors or coexisting cirrhosis,[5,6] and a shortage of liver grafts limits the applicability of liver transplantation. Although local ablative therapies, such as radiofrequency ablation (RFA), recently have gained widespread clinical acceptance, there is growing evidence of a high local recurrence rate after RFA that reaches up to 36%.[7,8] In addition, local ablative therapies also are unsuitable for patients who have bleeding tendencies, unfavorable anatomic tumor locations, or large tumors.[8,9] Patients who are not eligible for local ablative therapies usually receive noncurative modalities, such as transarterial chemoembolization (TACE) or systemic chemotherapy.

Radiotherapy also is a local therapy but historically has played a limited role in the treatment of HCC, because the hepatic tolerance dose is lower than the tumoricidal dose, especially when liver function is impaired by chronic liver disease.[10-12] Particle beams, such as proton and carbon ion beams, have demonstrated an increase in energy deposition with a penetration depth up to a sharp maximum at the end of their range: the so-called Bragg peak phenomenon.[13] Therefore, higher tumor doses can be delivered without increasing toxicity to the surrounding noncancerous tissues and organs. Particle therapy results for HCC have been reported in several case series, all of which have reported good overall survival and encouraging local control rates.[14-19] However, most of those studies were conducted at proton treatment centers, and few

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DOI: 10.1002/cncr.26134, **Received:** December 12, 2010; **Revised:** February 20, 2011; **Accepted:** February 23, 2011, **Published online** April 14, 2011 in Wiley Online Library (wileyonlinelibrary.com)

Table 1. Patient Characteristics

Characteristic	No. of Patients (%)		
	Proton Therapy, n=242	Carbon Ion Therapy, n=101	All Patients, n=343
Age, y			
<70	115 (48)	55 (54)	170 (50)
≥70	127 (52)	46 (46)	173 (50)
Sex			
Men	182 (75)	73 (72)	255 (74)
Women	60 (25)	28 (28)	88 (26)
Positive viral marker			
Hepatitis B virus	27 (11)	19 (19)	46 (13)
Hepatitis C virus	159 (66)	60 (59)	219 (64)
None	54 (22)	21 (21)	75 (22)
Both	2 (1)	1 (1)	3 (1)
Performance status			
0	172 (71)	73 (72)	245 (71)
1	57 (24)	18 (18)	75 (22)
2	10 (4)	9 (9)	19 (6)
3	3 (1)	1 (1)	4 (1)
Child-Pugh classification			
A	184 (76)	78 (77)	262 (76)
B	55 (23)	20 (20)	75 (22)
C	3 (1)	3 (3)	6 (2)
BCLC stage			
0	9 (4)	9 (9)	18 (5)
A	82 (34)	36 (36)	118 (34)
B	32 (13)	15 (15)	47 (14)
C	113 (47)	37 (36)	150 (44)
D	6 (2)	4 (4)	10 (3)
Recommended treatment according to BCLC stage			
Resection: Operable group	49 (20)	29 (29)	78 (23)
Others: Inoperable group	193 (80)	72 (71)	265 (77)
No. of tumors			
Single	213 (88)	81 (80)	294 (86)
Multiple	29 (12)	20 (20)	49 (14)

Abbreviations: BCLC, Barcelona Clinic Liver Cancer.

studies have reported results of carbon ion therapy for HCC. To our knowledge, no reports have focused on the differences in treatment results between the 2 types of particle beams.

The Hyogo Ion Beam Medical Center (HIBMC) is the only facility in the world that provides both proton and carbon ion therapies.[20] In the current study, we analyzed the efficacy and safety of proton and carbon ion therapy for HCC at the HIBMC.

MATERIALS AND METHODS

Patient and Tumor Characteristics

The current study was conducted according to the Helsinki Declaration, and written informed consent was obtained from all patients. From May 2001 to January 2009, 343 consecutive patients with 400 HCCs were treated at the HIBMC (excluding 6 patients who discontinued treatment). Patients who met the following conditions were ineligible for treatment: 1) uncontrolled ascites and 2) tumors that measured >15 cm in greatest dimension (the upper limit of the irradiation field). No patients were lost to follow-up, although we could not evaluate the post-treatment imaging findings from 12 patients with 14 tumors. Thus, overall survival rates were determined for all 343 patients, and local control rates were determined for 386 tumors. In total, 242 patients with 278 tumors received proton therapy, and 101 patients with 108 tumors received carbon ion therapy. For all patients,

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

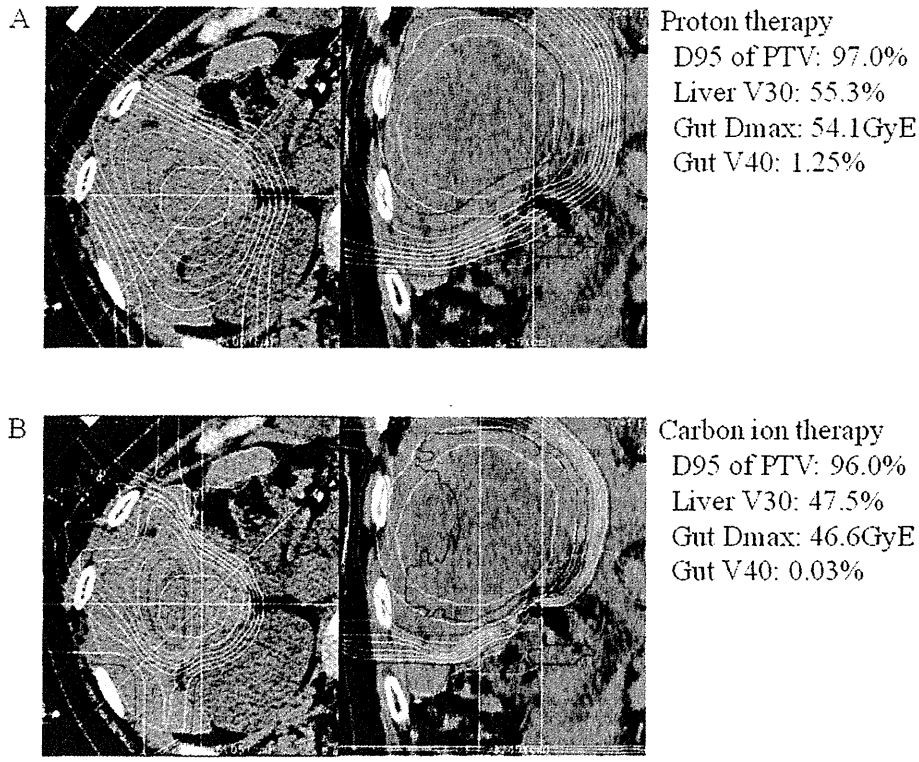

Figure 1. These images are from a representative case presentation of treatment plans for both (A) proton therapy and (B) carbon ion therapy. D95 indicates the dose received by at least 95% volume; PTV, planning target volume; Liver V30, percentage volumes of noncancerous hepatic portions (entire liver 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

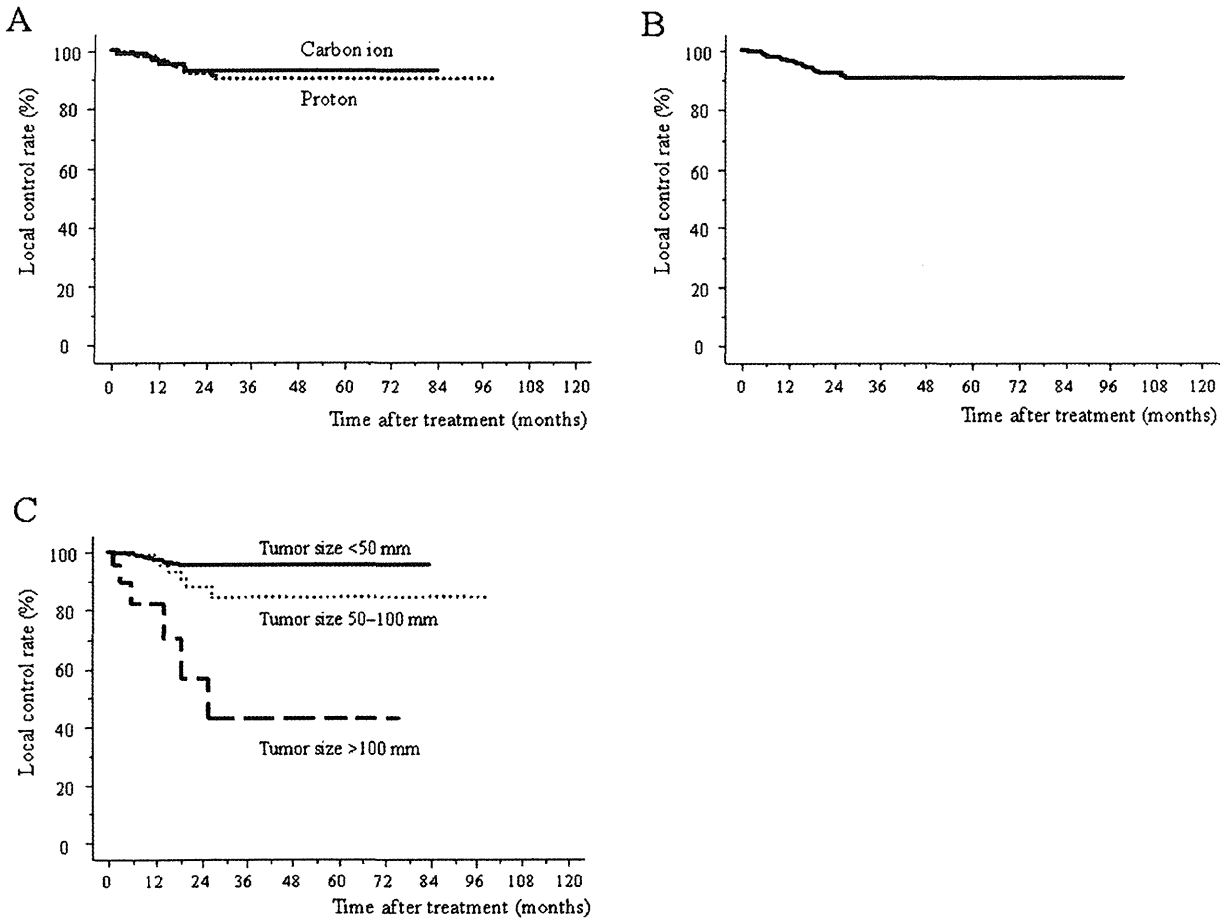

Figure 2. Local control rates after treatment are illustrated for (A) tumors that were treated with proton and carbon ion therapy, (B) all 386 tumors, and (C) all 386 tumors according to tumor size.

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

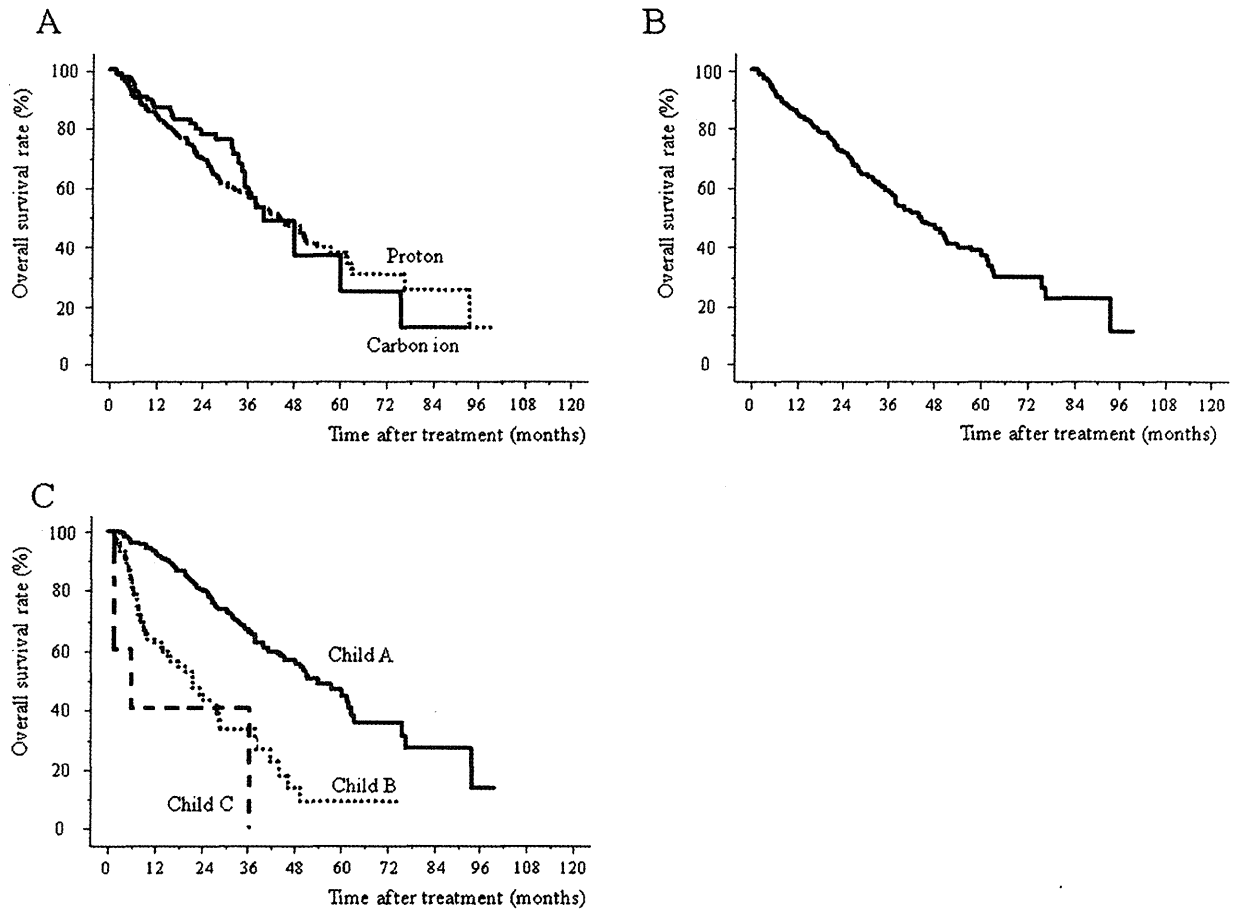

Figure 3. Overall survival rates after treatment are illustrated for (A) patients who received with proton and carbon ion therapy, (B) all 343 patients, and (C) all 343 patients according to Child-Pugh classification.

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