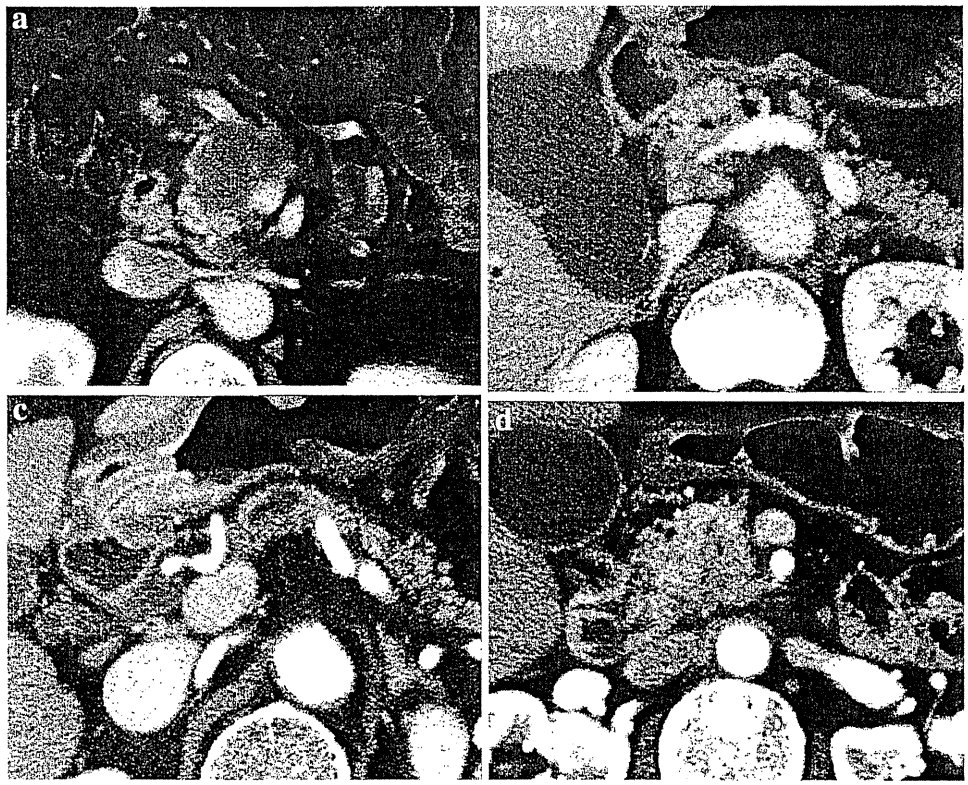

Fig. 1 Axial images from contrast-enhanced MDCT in patients with BRPCs. **a** Bilateral impingement of the SMV by the tumor located in the uncus. **b** Occlusion of a short segment at the confluence of the SMV and splenic vein. **c** Tumor abutment on the CHA. **d** Tumor abutment on the SMA with involvement of the root of the first jejunal artery

Table 1 Clinicopathological characteristics of patients with resectable PC, BRPC, and unresectable PC

Factor	Status of resectability			*P* value
	Resectable PC ($n = 109$)	BRPC ($n = 34$)	Unresectable PC ($n = 175$)	
Age, median (range) (years)	65 (34–85)	64 (40–84)	65 (34–85)	NS
Sex (*n*)				
Male	72	19	84	NS
Female	37	15	91	
Location of tumor (*n*)				
Head	77	17	90	<0.01*
Body or tail	32	17	85	
Histological type of tumor (*n*)				
Well	15	8	24	NS
Moderate/poor or others	94	26	84	
Not classified	0	0	67	
Tumor size, median (range) (cm)	2.8 (1.0–8.0)	3.5 (1.5–10.0)	4.1 (1.8–12.0)	<0.01**
CA 19-9, median (range) (U/ml)	106.0 (0.6–53,820)	191.5 (0.5–35,380.0)	339 (0.1–24,365.0)	NS

* Difference between resectable PC and BRPC

** Difference between resectable PC and BRPC, and between BRPC and unresectable PC

were also resected with pancreatic tumor in 2, 1, 1, and 1 patients, respectively. Positive microscopic surgical margins were more frequently seen in BRPC-s (7 of 24, 29%) than in resectable PC (21 of 109, 19%). However, the difference between the two groups was not significant ($P = 0.41$). There was no mortality. Eight postoperative complications were observed: five cases of pancreatic fistula, two cases of diarrhea, and one case of pleural effusion.

In the BRPC-n group, two patients underwent subtotal stomach-preserving pancreaticoduodenectomy for pancreas head cancer after systemic chemotherapy. One patient was alive with disease 35 months, and the other patient was alive without recurrence 21 months after beginning of the first treatment. Surgical resection was performed significantly more frequently in BRPC-n patients than in unresectable patients ($P < 0.01$).

Survival after resection of BRPC

The 2-year survival rates [estimated median survival time (MST)] of 109 patients with resectable PC, 34 patients with BRPC, and 175 patients with unresectable PC were 50.4% (24.6 months), 33% (15.7 months), and 13.5% (10.3 months), respectively (Fig. 2a). The prognosis of BRPC patients was significantly better than that of unresectable PC patients ($P < 0.01$), but was significantly worse than that of resectable PC patients ($P = 0.04$). In patients who initially underwent surgical resection for PC, survival was significantly shorter after resection of BRPC-s than after resection of resectable PC ($P = 0.03$) (Fig. 2b). On the other hand, in patients who were initially treated with nonsurgical therapy, the prognosis of BRPC-n was significantly better than that of unresectable PC patients ($P = 0.03$) (Fig. 2b).

Correlation between clinicopathological factors and overall survival in 133 PC patients who initially underwent resection

To identify prognostic factors for survival after resection of pancreatic ductal adenocarcinoma, clinicopathological factors and overall survival were analyzed in the 133 patients (Table 2). Maximum size above 3 cm ($P = 0.03$), nerve plexus invasion ($P < 0.01$), N1 ($P = 0.03$), SMV/portal impingement ($P = 0.02$), resectability ($P = 0.03$), and no adjuvant chemotherapy ($P < 0.01$) were significantly correlated with overall survival. The aforementioned factors were entered into multivariate analysis with a Cox proportional hazards model. Resectability was excluded from the analyses because it was strongly correlated with SMV/portal impingement. Nerve plexus invasion ($P < 0.01$), N1 ($P = 0.03$), and no adjuvant chemotherapy ($P = 0.02$) were predictors for decreased overall survival.

Recurrences after resection of BRPC

After surgical resection, 22 patients (92%) in the BRPC-s group and 75 (69%) in the resectable PC group developed recurrences. The locations of the initial recurrences in BRPC-s and resectable PC, respectively, were as follows: liver in 7 (29%) and 34 (31%); local recurrence in 10 (42%) and 23 (21%); lymph node in 4 (17%) and 13 (12%); peritoneum in 9 (38%) and 21 (19%); and other organs in 3 (13%) and 10 (9%). Local recurrence was more frequent in the BRPC-s group than in the resectable PC group ($P = 0.03$).

Postoperative adjuvant chemotherapy

Seven (29%) of 24 BRPC-s patients and 28 (26%) of 109 resectable PC patients received postoperative adjuvant chemotherapy. Gemcitabine was administered to 6 BRPC-s patients and 19 resectable PC patients, while S-1 was administered to 1 BRPC-s patient and 9 resectable PC patients. The median duration from operation to the start of adjuvant chemotherapy was 64 days in the BRPC-s patients and 56 days in the resectable patients (NS). Six (86%) BRPC-s patients and 19 (68%) resectable PC patients completed the 6-month course of adjuvant chemotherapy. Relative dose intensity of adjuvant chemotherapy was 85% in BRPC-s patients and 78% in resectable PC patients (NS).

Survival by postoperative adjuvant chemotherapy

In the resectable PC group, survival in patients with adjuvant chemotherapy (MST: not reached) was significantly better than that in patients without adjuvant chemotherapy (MST: 20.5 months) ($P < 0.01$). However, in

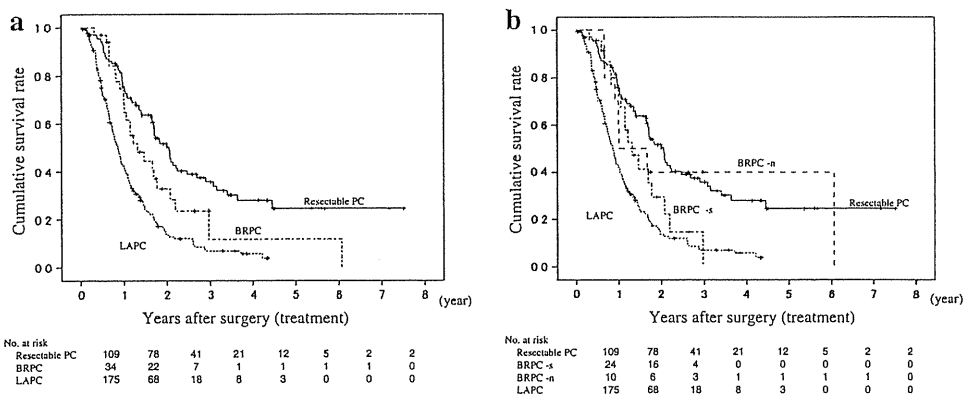

Fig. 2 **a** Comparison of survival in patients with resectable PC, BRPC, and unresectable PC. Both the differences between the resectable PC group and the BRPC group ($P = 0.04$) and between the BRPC group and the unresectable PC group ($P < 0.01$) were significant. **b** Cumulative survival curves according to detailed resectability status. Prognosis of BRPC-s was significantly worse than that of resectable PC ($P = 0.03$). Prognosis of BRPC-n was significantly better than that of unresectable PC ($P = 0.03$). *BRPC-s* BRPC treated with resection initially, *BRPC-n* BRPC treated with nonsurgical therapy initially

Table 2 Associations between overall median survival time (MST) and patient, tumor, and treatment characteristics in PC patients who were initially treated with surgical resection

Factor	MST (months)	Univariate analysis	Multivariate analysis	
		P value	Hazard ratio (95% CI)	*P* value
Age (years)				
<70	22.1	0.97		
≥70	20.8			
Tumor size				
≥3 cm	20.6	0.03	1.31 (0.84–2.05)	0.23
<3 cm	25.5			
CA 19-9				
≥200 U/ml	20.8	0.89		
<200 U/ml	25.0			
Portal vein invasion				
Present	21.6	0.196		
Absent	22.1			
Nerve plexus invasion				
Present	16.4	<0.01	2.33 (1.48–3.67)	<0.01
Absent	30.1			
Nodal status				
N1	20.5	0.03	1.89 (1.08–3.31)	0.03
N0	34.7			
SMV/portal impingement				
Present	12.8	0.02	1.72 (0.83–3.55)	0.15
Absent	25.0			
Tumor abutment on SMA, CE, or CHA				
Present	17.8	0.62		
Absent	22.1			
Status of resectability				
Borderline resectable	16.0	0.03	–	–
Resectable	25.0			
Resection status				
R0	22.4	0.09		
R1	21.6			
Adjuvant chemotherapy				
Yes	–	<0.01	0.49 (0.26–0.91)	0.02
No	20.8			

the BRPC-s group, the difference in survival between patients with adjuvant chemotherapy (MST: 20.3 months) and those without adjuvant chemotherapy (MST: 13.7 months) was not significant ($P = 0.54$).

Discussion

Borderline resectable pancreatic cancer is a newly proposed subset that shows interactions with the PV, SMV, SMA, celiac axis, and hepatic artery, and may have a high possibility of a positive surgical margin and worse prognosis after resection [1–3]. In the report of the AHPBA/SSO/SSAT Consensus Conference, it was recommended that patients with BRPC receive neoadjuvant therapy to increase the possibility of R0 resection in a clinical trial setting specific for BRPC patients [7]. As the rationale for the recommendation, the MD Anderson Cancer Center group demonstrated that neoadjuvant therapy enabled margin-negative resection in 37%, with median survival after resection of 40 months in the 84 patients with anatomical BRPC as defined on CT [2]. Chun et al. [11] also reported significantly better survival (23 vs. 15 months) and a higher R0 resection rate (59 vs. 11%) in 74 BRPC patients with preoperative chemoradiation than in 35 BRPC patients without preoperative therapy. However, little has been reported on the difference in surgical results, including prognosis and positive surgical margin rate,

between resectable PC and BRPC that might support the use of neoadjuvant therapy specific for BRPC patients. Furthermore, prognosis of BRPC patients initially treated with nonsurgical treatment such as chemotherapy or chemoradiotherapy has not been well documented.

In the present study, MDCT findings before initial treatment of all resected PC patients and all patients treated for LAPC were assessed for the possibility of BRPC because BRPC should be diagnosed before initial treatment to determine the treatment plan. BRPC was sub-classified into two types: BRPC-s, which was initially treated with resection, and BRPC-n, which was initially treated with nonsurgical therapy. Prognosis of all 34 BRPC patients was significantly worse than that of resectable PC patients and significantly better than that of unresectable PC patients. Moreover, in patients who initially underwent resection, prognosis of patients with BRPC-s was significantly worse than that of resectable PC patients, and in patients who were initially treated with nonsurgical therapy, prognosis of BRPC-n was significantly better than that of unresectable PC patients.

As possible reasons for the worse prognosis of BRPC-s than that of resectable PC, BRPC-s had a high rate of positive PV invasion and nerve plexus invasion compared to resectable PC ($P < 0.01$). Moreover, BRPC-s tended to show a more advanced stage in nodal status ($P = 0.19$) and tumor size ($P = 0.16$) than resectable PC. Nerve plexus invasion and lymph node metastasis were the independent poor prognostic factors in all 133 resected PC patients. The poor prognosis of BRPC-s patients was primarily attributable to these advanced characteristics. In terms of resection status, patients with BRPC-s had a positive surgical margin rate 10% higher than that of resectable PC patients, but the difference was not significant ($P = 0.41$). Interpretation of the 10% difference in the R0 rate between BRPC-s and resectable PC was difficult when evaluating how much the poor prognosis of BRPC-s patients was due to the difference in the R0 rate, considering both the lesser prognostic value of margin status and the frequent recurrence at locoregional sites in the BRPC-s patients. With respect to the surgical margin, there are no international standardized protocols for processing pancreatic specimens or criteria for positive margins [12, 13], and the relevance of margin status for prognosis is not clear in resected PC patients [6, 14–18]. An international standardized protocol for the histological examination of the surgical margins of pancreatic specimens is needed to prepare comparable data.

Nerve plexus invasion is a distinctive type of tumor spread in pancreatic ductal carcinoma, and it is also known to be a poor prognostic factor after tumor resection [19–21]. The nerve plexus of the pancreatic head runs from the pancreas to the celiac or superior mesenteric plexus along the celiac axis and SMA [22, 23]. Considering the anatomy, it is understandable that BRPC invades the nerve plexus quite frequently. Mochizuki et al. [24] reported that the mass and strand pattern and the coarse reticular pattern continuous with tumor on MDCT images are highly suggestive of nerve plexus invasion. Taking these results into account, tumor abutment on the arteries in BRPC could represent mostly nerve plexus invasion along those arteries. The higher R1 rate and frequent local recurrence in BRPC-s patients could be partly due to nerve plexus invasion.

Curiously, the prognosis of BRPC-n was significantly better than that of unresectable PC in patients who were initially treated with nonsurgical therapy. Less tumor burden as shown in tumor size and CA 19-9 value could mostly account for the better prognosis of patients with BRPC-n than that of patients with unresectable PC. In addition, surgical resection after down-staging by nonsurgical therapy was performed significantly more frequently in the BRPC-n group than in the unresectable PC group. Frequent conversion from nonsurgical therapy to surgical resection might also be one of the possible reasons for better survival of patients with BRPC-n. However, assessment of tumor resectability during nonsurgical treatment was not performed systematically or thoroughly for BRPC-n patients or unresectable PC patients in this study. Thus, the resectability rate of BRPC patients and unresectable PC patients was not definitive in the present study. In order to investigate conversion rate from nonsurgical therapy to surgical resection, systematic assessment for resectability during nonsurgical treatment is required although criteria of resectability after treatment have not been clarified. Owing to the different backgrounds and prognoses between BRPC and unresectable PC, they should be regarded as different categories.

Similar to the AHPBA/SSO/SSAT Consensus Conference recommendation [7], we reached the conclusion that neoadjuvant therapy such as chemoradiation for BRPC should be evaluated separately from those for resectable PC or unresectable PC for several reasons. First, patients with BRPC-s had poorer survival and more frequent recurrence at the local site than patients with resectable PC. Thus, patients with BRPC should be treated with more intensive therapy with strong local effect rather than the existing treatment for resectable PC. Second, neoadjuvant therapy could benefit patients with BRPC by providing early treatment for those with advanced disease at high risk of early systemic and local failure [2, 7]. Several phase II studies showed the possibility of neoadjuvant chemotherapy [25] or chemoradiation [26] for BRPC. Furthermore, adjuvant chemotherapy might not be as effective in BRPC patients as in resectable PC patients according to the results of the present study, although multi-institutional randomized controlled study is needed to clarify the effectiveness of adjuvant treatment for BRPC. Adjuvant chemotherapy

with gemcitabine or S-1 was a favorable prognostic factor for all 133 resected PC patients. However, in BRPC-s, the prognosis of patients with adjuvant chemotherapy was as poor as that of patients without adjuvant chemotherapy, while the duration from surgery to start of adjuvant treatment and relative dose intensity of adjuvant treatment did not differ between BRPC-s patients and resectable PC patients. Third, BRPC should be studied separately from unresectable PC because of the different tumor characteristics and prognoses. BRPC is more often resectable than unresectable PC, thus resectability status should be assessed systematically and thoroughly.

The limitations of our study are its retrospective design and the relatively small number of patients studied.

In conclusion, patients with BRPC showed more advanced tumor characteristics, including frequent nerve plexus invasion, frequent loco-regional recurrence, and poorer prognosis than patients with resectable PC although BRPC had less tumor burden and better prognosis than patients with unresectable PC. Neoadjuvant treatment with intensive local and systemic effect that is specific for BRPC is required. A multi-institutional phase II trial of neoadjuvant chemoradiation for BRPC is now in the planning stage.

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ORIGINAL ARTICLE

Surgical treatment of lymph node metastases from hepatocellular carcinoma

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Abstract
Background No consensus has been reached on the feasibility and efficacy of surgery for lymph node metastases (LNM) from hepatocellular carcinoma (HCC).
Methods Of 2189 patients with HCC treated at our hospital between July 1992 and March 2008, we retrospectively reviewed the medical dossiers of the 18 patients (0.8%) who underwent lymph node resection and were pathologically diagnosed to have LNM from HCC. The surgical procedure for LNM was selective lymphadenectomy of those lymph nodes suspected to harbor metastasis. The feasibility and efficacy of selective lymphadenectomy was examined, and clinicopathological factors were analyzed with the aim of determining which patients would most benefit from surgery.
Results Eighteen patients underwent surgery without mortality or liver failure. Morbidities were found in four patients (22.2%). The median survival time (MST) after surgery was 29 months [95% confidence interval (CI) 21–38 months). The 1-, 3-, and 5-year overall survival rates were 85, 42, 21%. The median progression-free survival (PFS) after surgery was 6 months (95% CI 1–11 months), and the median extrahepatic PFS was 16 months (95% CI 13–18 months). Single LNM was the only favorable prognostic factor after surgery (Hazard ratio 0.082, 95% CI 0.008–0.83).
Conclusion Selective lymphadenectomy of LNM from HCC was a feasible and efficacious procedure. Survival rates can be expected to improve after selective lymphadenectomy of single LNM.

Keywords Hepatocellular carcinoma · Lymph node metastases · Surgery

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Introduction

Lymph node metastases (LNM) are rare and generally associated with poor prognosis in hepatocellular carcinoma (HCC) [1, 2]. No consensus has yet been reached on the treatment strategy for LNM from HCC [3–5]. A few case reports have been published on the surgical treatment of LNM from HCC. Abe et al. [6] described two patients who survived for more than 4 years after the resection of an isolated metastatic lymph node followed by transarterial embolization (TAE). Togo et al. [7] also described a patient who survived for 7 years without recurrence after single node resection and simultaneous hepatectomy. In contrast, Uenishi et al. [8] reported that the resection of multiple LNM led to a poor prognosis, and they questioned the efficacy of regional lymphadenectomy in HCC. Their poor results are partly attributable to the deterioration of cirrhotic liver function due to altered portal or lymphatic drainage caused by extensive LN dissection [9]. Based on these findings, it is possible that selective lymphadenectomy of suspected metastatic lymph nodes instead of regional lymphadenectomy would be an effective treatment for LNM from HCC.

The aims of this study were to present our surgical experiences on LNM from HCC and to discuss the feasibility and efficacy of selective lymphadenectomy. We also

examined prognostic factors to determine who might most benefit from surgical resection.

Patients and methods

From July 1992 to March 2008, 2189 patients with HCC were treated at the National Cancer Center Hospital East in Kashiwa, Japan. Among those 2189 patients with HCC, 75 patients (3.4%) were clinically diagnosed to have LNM from HCC and 21 patients (1.0%) actually underwent surgery. Eighteen patients (0.8%) who underwent lymph node resection and in whom LNM were pathologically diagnosed were included in this and their medical histories retrospectively examined.

The staging and resectability of tumors were assessed by contrast-enhanced computed tomography (CT) scans, magnetic resonance imaging (MRI), hepatic arterial angiography, ultrasounds, and chest X-rays. The clinical diagnosis of LNM was based on the following findings from the contrast-enhanced CT, MRI, or ultrasound scans: (1) the short axis diameter of the lymph node was minimally >1 cm; (2) the lymph node showed hypervascularity in the arterial phase and washout of enhancement in the venous phase; (3) the liver tumor had been pathologically or clinically diagnosed as HCC according to the guidelines issued by American Association for the Study of Liver Diseases [10]. A typical case of LNM from HCC is depicted in Fig. 1. Indications of surgery for LNM from HCC were: (1) isolated LNM; (2) metachronous LNM without any tumor in the liver or synchronous LNM with intrahepatic tumor that was potentially resectable or controllable by non-surgical treatments, such as TAE or radiofrequency ablation (RFA); (3) no extrahepatic metastases except lymph nodes; (4) sufficient liver function (Child–Pugh grade [11]: A or B) and performance status [Eastern Cooperative Oncology Group Performance Status (ECOG PS) [12]: 0 or 1] to undergo surgery. Liver function was assessed by liver biochemistry tests, the Child–Pugh grade, and the indocyanine green retention rate at 15 min [13]. The patients' data were reviewed by hepatic surgeons, medical oncologists, and interventional radiologists during a conference to determine if the patients met the aforementioned criteria.

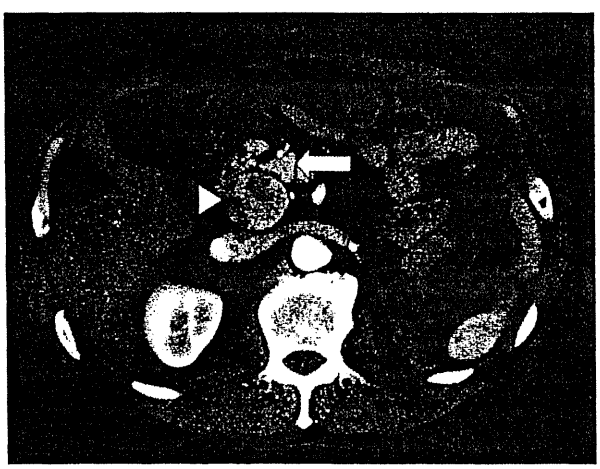

Fig. 1 Computed tomography findings of a solitary lymph node metastasis from hepatocellular carcinoma (HCC). A round-shaped, large lymph node (*arrowhead*) was found on the posterior surface of pancreas head (*arrow*). The lymph node was 6.0 cm in diameter and showed early enhancement in the arterial phase of the dynamic study

The surgical treatment procedure for LNM was, in principle, selective lymphadenectomy in which only lymph nodes suspected of metastasis were resected. With this approach, potential deterioration of liver function caused by altered lymphatic drainage after extensive LN dissection was avoided. Thin vessels around the lymph nodes were ligated whenever possible to prevent lymphatic leakage. Resected lymph nodes were pathologically examined with hematoxylin–eosin (HE) stain. When the results from the HE stain were not definitive, we also performed immunohistochemistry tests to confirm the diagnosis. Patients were followed-up every 3 months after surgery and were assessed for recurrence by CT examination and tumor marker level (alpha fetoprotein and protein induced by vitamin K absence-II).

Survival time was calculated from the date of operation. Clinicopathological findings and survival were compared among the 18 patients who underwent resection for LNM. The correlation between survival and clinicopathological findings was also examined. Survival analyses were performed using the Kaplan–Meier method, and differences between the curves were tested using the log-rank test (SPSS ver. 11.0J for Windows; SPSS, Chicago, IL). Factors related to survival were analyzed with the Cox proportional hazards regression model. p values <0.05 were considered to be statistically significant.

Results

Patient characteristics

Patient characteristics of the 18 patients are listed in Table 1. Sixteen and two patients were Child–Pugh grade A and B, respectively. The LNM was solitary in 13 patients and multiple in five patients. The mean diameter of the metastatic lymph nodes was 5.1 cm. Thirteen patients had received previous treatments that consisted of hepatectomy ($n = 8$), TAE ($n = 3$), percutaneous ethanol injection ($n = 1$), and proton-beam therapy ($n = 1$). Median

Table 1 Patient characteristics

Patient characteristics	Patients ($n = 18$)
Male, *n* (%)	16 (88.9)
Age (years)	65.2 ± 2.1
Performance status (0/1/2/3), *n*[a]	17/1/0/0
HCV Ab (+), *n* (%)	9 (50)
Child–Pugh grade (A/B/C), *n*	16/2/0
Albumin (g/dl)	3.9 ± 0.1
T.Bil (mg/dl)	0.9 ± 0.1
ICG15R (%)	17.3 ± 2.6
PT (% standard)	82.6 ± 3.9
Platelet ($\times 10^4/mm^3$)	15.3 ± 1.1
AFP (ng/ml)	1200 ± 750
PIVKA-II (mAU/ml)	410 ± 270
Previous treatments, *n* (%)	13 (72.2)
Simultaneous intrahepatic lesion, *n* (%)	13 (72.2)
Portal vein invasion, *n* (%)[b]	8 (44.4)
Multiple intrahepatic lesions, *n* (%)[b]	7 (38.9)
T-stage of intrahepatic lesions (T1/T2/T3/T4), *n*[b,c]	3/5/5/5
Size of LNM (cm)	5.1 ± 1.0
Multiple LNM, *n* (%)	5 (27.8)
Extrahepatic metastasis except LNM, *n* (%)	0 (0)
JIS score (3/4/5), *n*[d]	16/2/0

All values are given as the standard error of the mean (SEM) unless otherwise indicated

HCV Ab Hepatitis C virus antibody, *T.Bil* total bilirubin, *ICG15R* indocyanine green retention rate at 15 min, *PT* prothrombin time, *AFP* alpha fetoprotein, *PIVKA-II* protein induced by vitamin K absence-II, *LNM* lymph node metastases, *JIS score* Japan Integrated Staging score

[a] Performance status was evaluated according to the ECOG (Eastern Cooperative Oncology Group) criteria [11]

[b] When LNM was metachronous and the hepatic lesion did not exist simultaneously, the findings were evaluated for the most recently treated hepatic lesions

[c] T-stage was evaluated according to the TNM staging by the Liver Cancer Study Group of Japan [14]

[d] Japan Integrated Staging score can be obtained by combining the TNM stage score by the Liver Cancer Study Group of Japan and the Child–Turcotte-Pugh stage score [18]

duration from the primary treatment for HCC to LN recurrence in these 13 patients was 36 months (range 4–124 months). In 13 patients, LNM were accompanied by simultaneous hepatic lesions, and five of the 13 patients had multiple hepatic lesions. Of the five patients without simultaneous hepatic lesions, two had multiple hepatic lesions previously while three patients had only single lesions. The underlying liver pathology in three patients was normal, while seven patients had chronic hepatitis and eight patients had cirrhosis.

Locations of LNM

The metastatic lymph nodes in the 18 patients were located along the left gastric artery ($n = 4$), on the posterior surface of the pancreas head ($n = 4$), around the abdominal aorta ($n = 3$), above the diaphragm ($n = 3$), in the hepatoduodenal ligament ($n = 3$), and along the common hepatic artery ($n = 1$).

Surgery for LNM

Selective lymphadenectomy was performed in 17 patients, while one patient underwent regional lymphadenectomy along the left-gastric artery, common hepatic artery, and hepatoduodenal ligament. Among the 13 patients with simultaneous hepatic lesions, nine patients underwent simultaneous hepatectomy (3 lobectomies, 3 partial resections, 1 segmentectomy, 1 central bisegmentectomy, and 1 extended lobectomy), three patients received non-operative treatments (2 TAE and 1 RFA), and one patient received careful follow-up without treatment because the lesion became obscure in severely cirrhotic liver and could not undergo TAE. During the same period, one patient underwent surgery for LNM, but the lymph node could not be resected due to involvement of main portal vein. Two other patients underwent surgery for LNM, but the pathological findings revealed that one was benign reactive lymphadenopathy and the other was metastasis from a neuroendocrine tumor. These three cases were not included in the present study. There was no postoperative mortality. Six postoperative complications occurred in four patients: transient pleural effusions ($n = 2$), cholecystitis ($n = 1$), bile leak ($n = 1$), intestinal obstruction ($n = 1$), and wound infection ($n = 1$). No patients developed liver failure or refractory ascites. Transient pleural effusions were treated with single thoracocentesis.

Survival

The median survival time (MST) of 18 patients was 29 months after surgery [95% confidence interval (CI) 21–38 months) and 32 months after clinical diagnosis (95% CI 23–41 months). The 1-, 3-, and 5-year overall survival rates after surgery were 85, 42, 21%, respectively. The median progression-free survival (PFS) after surgery for LNM was 6 months (95% CI 1–11 months), and the median extrahepatic PFS was 16 months (95% CI 13–18 months) (Fig. 2).

Recurrence after resection of LN metastasis from HCC

Among the 12 patients with disease progression after surgery, four patients developed only intrahepatic lesions that were treated by TAE ($n = 2$) or RFA ($n = 2$). The other

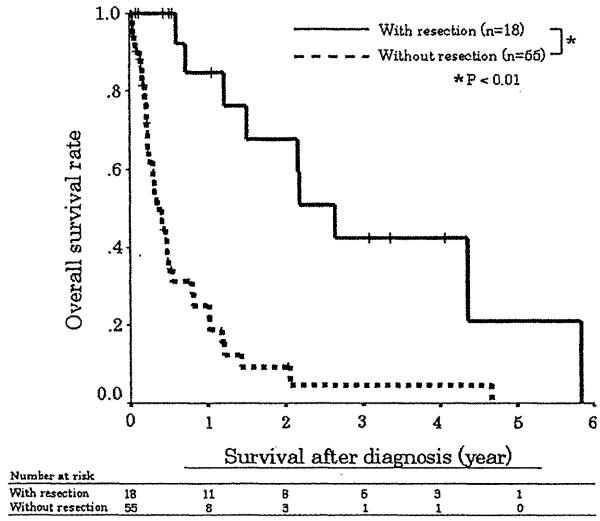

Fig. 2 Cumulative survival curves of patients with or without resection of lymph node metastases (LNM). The median survival time after clinical diagnosis was 32 months with resection (95% CI 23–41 months) and 4 months without resection (95% CI 3–6 months)

eight patients developed both intra- and extrahepatic lesions. The extrahepatic recurrences occurred in LN ($n = 6$), lung and LN ($n = 1$), and peritoneum ($n = 1$). One patient with lung and LN recurrence was treated with repeated selective lymphadenectomy and partial lung resection each time. The remaining seven patients with extrahepatic recurrences received the best supportive care ($n = 4$) or chemotherapy ($n = 3$).

Correlation between clinicopathological factors and overall survival

The correlation between clinicopathological factors and overall survival of the 18 patients is shown in Table 2. The survival rate of the patients with resection of single LNM was statistically higher than that of multiple LNM (MST: 52 vs. 14 months after surgery, $p < 0.01$) (Fig. 3). Liver functions, status of viral hepatitis, history of previous treatments, presence of intrahepatic lesions, curability of simultaneous intrahepatic lesions, regions of metastatic LNs, and other factors were not statistically significant. In order to eliminate the effect of possible confounding factors and small sample size, factors with p values <0.2 by univariate analysis were analyzed with the Cox proportional hazards regression model: the single LNM was found to be the only favorable prognostic factor (hazard ratio 0.082, 95% CI 0.008–0.83).

Non-surgical treatments

During the same period, 55 patients were clinically diagnosed to have LNM, but did not undergo lymphadenectomy due to the following reasons: (1) poor control of intrahepatic lesions ($n = 18$); (2) regional or systemic LNM ($n = 16$); (3) extrahepatic metastasis other than LNM ($n = 9$); (4) poor liver function (Child–Pugh grade C) ($n = 5$); (5) poor performance status (ECOG PS ≥ 2) ($n = 4$); (6) patients' preference ($n = 2$); (7) involvement of main portal vein ($n = 1$). The MST of 55 patients without lymphadenectomy was 4 months after clinical diagnosis (95% CI 3–6 months) and was significantly shorter than that of patients with lymphadenectomy (32 months; 95% CI 23–41 months) ($p < 0.01$) (Fig. 2). Non-operative treatments included the best supportive care ($n = 19$), systemic chemotherapy ($n = 13$), TAE ($n = 8$), external beam radiation therapy ($n = 5$), transarterial infusion chemotherapy ($n = 5$), immunotherapy ($n = 3$), and hepatic arterial continuous infusion chemotherapy ($n = 2$). Four patients developed complications that were directly related to the LNM from HCC, namely, obstructive jaundice ($n = 2$), esophageal obstruction ($n = 1$), and obstruction of inferior vena cava ($n = 1$) (Fig. 4).

Discussion

Lymph node metastases from HCC are rare. The feasibility and efficacy of surgical treatment for LNM from HCC has not been fully evaluated. Several case studies have reported mortality cases and high morbidity rate after surgery [8, 9]. In our study, however, there was no mortality or liver failure associated with surgery for LNM, although eight cases were complicated by liver cirrhosis. These results demonstrate the safety of selective lymphadenectomy for LNM from HCC in selected patients and are in contrast to the high rate of liver failure previously reported following regional lymphadenectomy [8, 9]. The favorable outcomes of selective lymphadenectomy may be attributable to the maximum conservation of the lymphatic and portal flow around the liver. Selective lymphadenectomy of LNM might be a safer and feasible procedure in patients with liver cirrhosis, although the indication for selective lymphadenectomy should still be carefully considered, especially in terms of liver function.

Considering the survival benefit of selective lymphadenectomy for patients with LNM, the MST was 29 months after lymphadenectomy and the 1-, 3-, and 5-year OS were 85, 42, and 21%. Survival more than 3 years was achieved in five patients after surgery, and two of these patients are still alive without a recurrence. These results indicate the survival benefit of selective lymphadenectomy for LNM from HCC in selected patients. The efficacy of lymphadenectomy was recently questioned by Sun et al. [3]. However, the methods and patient backgrounds were different between two studies. In Sun's study, the evaluation

Table 2 Correlation between clinicopathological factors and overall survival after lymph node resection of HCC (the log-rank test)

Patient characteristics	*n*	Univariate analysis				Multivariate analysis		
		3-year OS (%)	5-year OS (%)	MST (months)	*p* value	Hazard ratio	(95% CI)	*p* value
Age (years)								
<70	12	34.3	0	24.5	0.15	0.09	(0.005–1.62)	0.29
≧70	6	66.7	66.7	68.3				
Serology of viral hepatitis								
HBs Ag (−) and HCV Ab (−)	5	100	0	52.3	0.13	0.02	(0.00–1.12)	0.19
HBs Ag (+)/HCV Ab (+)/both (+)	13	22.2	22.2	24.5				
Child–Pugh grade								
A	16	40.9	0	29.4	0.48			
B	2	50	50	24.5				
AFP (ng/ml)								
≥400	5	50	50	14.5	0.97			
<400	13	38.1	19.1	29.4				
PIVKA-II (mAU/ml)								
≥100	9	40	40	29.4	0.77			
<100	9	41.7	41.7	24.5				
Liver cirrhosis								
Yes	8	57.1	57.1	68.3	0.18	0.04	(0.00–5.73)	0.07
No	10	22.2	0	25.6				
Simultaneous hepatic lesions								
Absent	5	75	75	68.3	0.08	0.57	(0.00–88.8)	0.21
Present	13	25.9	0	25.6				
Number of intrahepatic lesions[a]								
Single	12	37.5	37.5	24.5	0.6			
Multiple	6	50	25	25.6				
T-stage of intrahepatic lesions[b]								
T1/2	8	33.3	33.3	24.5	0.67			
T3/4	10	51.4	25.7	52.3				
Portal vein invasion[a]								
Present	8	62.5	0	52.3				
Absent	10	28.6	28.6	25.6	0.77			
Number of LNM								
Single	13	55.6	27.8	52.3	<0.01	0.082	(0.008-0.83)	0.03
Multiple	5	0	0	14.5				
Size of metastatic LN (cm)								
≥4.0	12	33.3	16.7	25.6	0.48			
<4.0	6	66.7	66.7					
Differentiation of metastatic LNs								
Well or moderately differentiated	3	50	50	25.6				
Poorly differentiated	15	40.9	20.5	29.4	0.68			
JIS score[c]								
3	16	40.9	0	29.4	0.48			
4 or 5	2	50	50	24.5				

HCC Hepatocellular carcinoma, *OS* overall survival, *MST* median survival time, *CI* confidence interval, *LN* lymph node, *HBs Ag* hepatitis B surface antigen

[a] Metachronous intrahepatic lesions were evaluated in the absence of simultaneous intrahepatic lesions

[b] T-stage of intrahepatic lesions was evaluated according to the TNM staging by the Liver Cancer Study Group of Japan [14]

[c] Japan Integrated Staging score can be obtained by combination of the TNM stage score by the Liver Cancer Study Group of Japan and the Child-Turcotte-Pugh stage score [18]

of LNM and decision whether lymphadenectomy should be done or not were mostly based on the palpation of surgeons during surgery. The preoperative evaluation of LNM was not performed precisely in most of the patients. In comparison, in our study, the diagnosis of LNM was made by preoperative imaging diagnosis. Selective lymphadenectomy was performed only for lymph nodes which were clinically diagnosed for metastasis. Patients' backgrounds were also different because the present study included many recurrent cases and cirrhotic cases. Based on these aspects, we consider that the efficacy of resection for LNM from HCC was not fully evaluated in Sun's study and that selective lymphadenectomy is a safe and beneficial procedure in selected patients.

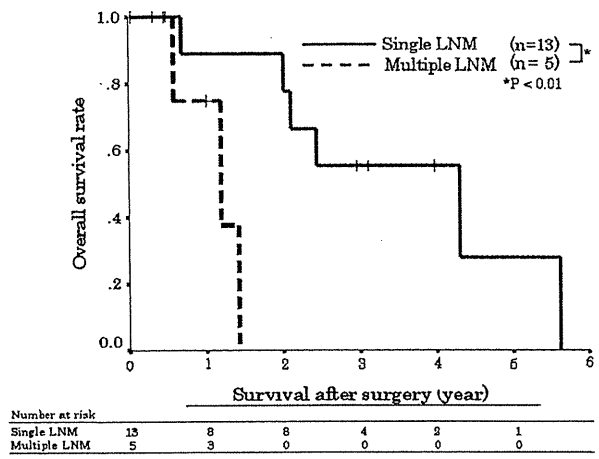

Fig. 3 Cumulative survival curves after surgery according to the number of MLN. The survival rate of the patients with resection of single LNM was statistically higher than that of multiple LNM (mean survival time 52 vs. 14 months; $p < 0.01$)

The possible candidates for selective lymphadenectomy are not many. In the present study, among 2189 patients with HCC who were treated in our institution, 75 patients (3.4%) were clinically diagnosed to have LNM from HCC, and 21 patients (1.0%) actually underwent surgery according to the aforementioned criteria. Among those 21 patients, 19 patients were pathologically diagnosed to have LNM from HCC while benign reactive lymphadenopathy was identified in resected lymph nodes in one case and metastasis from neuroendocrine tumor in the other. The positive predictive value of our diagnostic criteria of LNM from HCC was 90.5%. Among 19 patients with pathologically proven LNM, 18 patients underwent successful lymphadenectomy while it was abandoned due to invasion of the main portal vein in one patient. Thus, selective lymphadenectomy might be indicated in 24.0% (18/75) of cases with clinical diagnosis of LNM from HCC.

A comparison of surgical and non-surgical treatments suggests that external beam radiation therapy can be considered as a possible alternative modality for the treatment of LNM from HCC. However, median survival following this therapy has been found to be only 7–9.4 months, while the incidence of gastrointestinal bleeding was fairly high (9.4–22.0%) [4, 15]. A newer molecular targeting agent, Sorafenib (Nexavar; Bayer HealthCare Pharmaceuticals, Basel, Switzerland/Onyx Pharmaceuticals, Emeryville, CA), has been recently shown to prolong survival in patients with advanced HCC [16, 17]. However, a survival benefit was not demonstrated in the sub-group analysis of patients with extrahepatic metastasis. Long-term survival was rarely seen after those non-surgical treatments. Although candidates for resection are limited, and multimodal treatment might be necessary after resection, surgery for LNM seems to play an important role in achieving

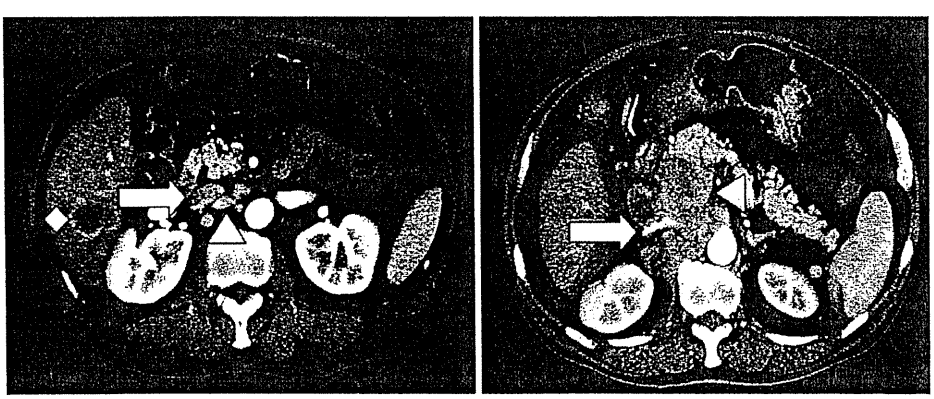

Fig. 4 Computed tomography findings of inferior vena cava obstruction by huge metastatic lymph nodes from hepatocellular carcinoma. *Left* A 57-year-old female underwent proton beam therapy for her solitary HCC (*diamond*). The slightly enlarged lymph nodes (*arrowhead*) around the inferior vena cava (IVC) (*arrow*) were at first judged equivocal as metastases (short axis diameter <1.0 cm). *Right* Only 2 months later, the patient developed IVC obstruction (*arrow*) by the rapidly growing lymph nodes (*arrowhead*)

long-term survival in the treatment strategy for LNM from HCC.

Evaluating the correlation between clinicopathological factors and prognosis after selective lymphadenectomy, single LNM was the only favorable prognostic factor after surgery (hazard ratio 0.082, 95% CI 0.008–0.83). The MST of patients with single and multiple LNM after surgery were 52 and 14 months, respectively ($p < 0.01$). All five patients who survived >3 years had single LNM and four of them did not develop extrahepatic metastasis within 3 years. On the contrary, three of the five patients with multiple LNM developed intra- and extrahepatic recurrences within 6 months after surgery. Therefore, multiple LNM indicated its advanced and systemic nature of the disease, while single LNM might be considered to be a localized disease. The MST of patients with resection of multiple LNM was not significantly longer than that of patients without resection (15 vs. 4 months after diagnosis, respectively; $p = 0.12$). Patients with single LNM appear to be the best candidates for selective lymphadenectomy. On the other hand, efficacy of selective lymphadenectomy for multiple LNM seemed equivocal due to its advanced and systemic nature of the disease.

The LNM from HCC might also cause severe complications, such as obstructive jaundice, pyloric obstruction, and inferior vena cava obstruction [15]. The resection of LNM might prevent these complications. In our institution, there were four complications directly related to LNM during the same period as that covered by our study. One patient developed inferior vena cava obstruction due to rapidly growing lymph nodes while receiving proton beam therapy for her solitary intrahepatic lesion (Fig. 4). Another patient developed esophageal obstruction due to large metastatic lymph nodes in the mediastinum. Two other patients developed obstructive jaundice due to metastatic lymph nodes in the hepatoduodenal ligament, which were treated with percutaneous transhepatic biliary drainage. Although selective lymphadenectomy should be performed with curative intent, it might additionally be beneficial as a preventative and palliative measure against these life-threatening complications.

The present study has several limitations. It is a single institutional study with a small patient population. Also, this study was not performed as a randomized controlled trial (RCT). However, RCTs are very difficult to conduct in this disease group due to the small number of patients scattered over diverse facilities. Our future perspective is to conduct a prospective observational study in a multi-institutional setting focusing on selective lymphadenectomy for patients with single LNM.

Conclusion

Selective lymphadenectomy of LNM from HCC is a feasible and efficacious procedure. Long-term survival can be expected after selective lymphadenectomy, especially in patients with a single LNM.

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CLINICAL INVESTIGATION **Liver**

DOSE–VOLUME HISTOGRAM ANALYSIS OF THE SAFETY OF PROTON BEAM THERAPY FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Purpose: To evaluate the safety and efficacy of radiotherapy using proton beam (PRT) for unresectable hepatocellular carcinoma.

Methods and Materials: Sixty consecutive patients who underwent PRT between May 1999 and July 2007 were analyzed. There were 42 males and 18 females, with a median age of 70 years (48–92 years). All but 1 patient had a single lesion with a median diameter of 45 mm (20–100 mm). Total PRT dose/fractionation was 76–cobalt Gray equivalent (CGE)/20 fractions in 46 patients, 65 CGE/26 fractions in 11 patients, and 60 CGE/10 fractions in 3 patients. The risk of developing proton-induced hepatic insufficiency (PHI) was estimated using dose-volume histograms and an indocyanine-green retention rate at 15 minutes (ICG R15).

Results: None of the 20 patients with ICG R15 of less than 20% developed PHI, whereas 6 of 8 patients with ICG R15 values of 50% or higher developed PHI. Among 32 patients whose ICG R15 ranged from 20% to 49.9%, PHI was observed only in patients who had received 30 CGE (V30) to more than 25% of the noncancerous parts of the liver ($n = 5$) Local progression-free and overall survival rates at 3 years were 90% (95% confidence interval [CI], 80–99%) and 56% (95% CI, 43–69%), respectively. A gastrointestinal toxicity of Grade ≥2 was observed in 3 patients.

Conclusions: ICG R15 and V30 are recommended as useful predictors for the risk of developing PHI, which should be incorporated into multidisciplinary treatment plans for patients with this disease. © **2011 Elsevier Inc.**

Hepatocellular carcinoma, Proton beam radiotherapy, Dose–volume histogram, Radiation tolerance of the liver.

INTRODUCTION

Recent improvements in diagnostic imaging and radiotherapy (RT) techniques have made high-dose radiotherapy a safe and effective treatment for selected patients with unresectable hepatocellular carcinoma (HCC) (1). Charged-particle radiotherapy can potentially deliver considerably larger doses of RT to liver tumors, with greater sparing of normal tissues, and proton beam radiotherapy (PRT) for HCC using aggressively high total and fractional RT doses has been investigated during the last 2 decades. The results have shown local control rates ranging from 75% to 96% and overall survival (OAS) rates exceeding 50% at 2 years in groups of patients that include those who had HCC tumors of ≥5 cm in diameter (2–4). HCC has a high propensity for venous invasion, which is frequently associated with multiple tumors within resected specimens (5–9). In this context, the extent of resection was determined while considering potential tumor spread via portal blood flow and the necessity of preserving a functional liver reserve (5, 7, 10). Even in preselected patients who underwent hepatectomy, more than 50% of tumors with diameters greater than 4 cm demonstrated microscopic vascular invasion (8, 11). Consequently, it will become more crucial to consider the influence of vascular invasion on undetectable tumor dissemination at the periphery of the gross tumor in RT for unresectable HCC.

Given the high probability of obtaining local control by using PRT, an appropriate definition of the clinical target volume (CTV) according to patterns of tumor spread and patients' functional liver reserves is extremely important in order to maximize the therapeutic ratio. Ideally, the entire portal segment that contains HCC nodules should be covered within the CTV when the tumor shows macro- or microscopic vascular invasion. This requires a considerably larger

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irradiated volume even with PRT, partly because of unavoidable uncertainty in treatment planning without using intraoperative ultrasonography (7). Another possible way to eradicate satellite HCC nodules, which are disseminated via portal blood flow, is transarterial chemoembolization (TACE). Currently, the standard treatment for patients with unresectable HCC that is not amenable to local ablation therapy is TACE instead of best supportive care (12). The OAS rate at 3 years after TACE ranges from 32% to 47% in patients with stage III cancer and with liver damage A to B, according to the staging system used in a nationwide cohort study conducted by the Liver Cancer Study Group of Japan (13). Considering that the tumoricidal effect of TACE in HCC with vascular invasion is frequently incomplete (13), a significant benefit of adding PRT to TACE would be expected. However, presently, there has been no robust evidence supporting this concept. Before we examine the validity of targeting the entire anatomical portal segment containing HCC in a multidisciplinary approach that includes PRT, practical methods to estimate the safety of PRT according to the dose–volume histogram (DVH) should be established in patients who have various levels of severity of liver dysfunction. Findings from our previous study consisting of 30 patients suggested that the risk of proton-induced hepatic insufficiency (PHI) could be predicted by the indocyanine green clearance test and the retention rate at 15 minutes (ICG R15) in combination with DVH parameters (14) such as percentages of hepatic noncancerous portions receiving doses of >30 cobalt-Gray-equivalent (CGE) (3). We have subsequently accumulated data from additional patients in clinical practice. The clinical results were evaluated, and we have again used the DVH analysis to examine the relationship between probability of PHI and dose–volume parameters.

METHODS AND MATERIALS

Patients

Patient eligibility was reported previously (3); in brief, they were required to have uni- or bidimensional measurable HCC nodules of ≤10 cm in maximum diameter on computed tomography (CT) and/or magnetic resonance imaging (MRI) without evidence of extrahepatic tumor spread. All patients had a white blood cell count of ≥2,000/mm^3; a hemoglobin level of ≥7.5 g/dl; a platelet count of ≥25,000/ mm^3; and adequate hepatic function (total bilirubin, ≤3.0 mg/dl; alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase of <5.0× normal; no ascites). Patients who had multicentric HCC nodules were not considered as candidates for PRT, except for those who fulfilled the following two conditions: (*1*) multiple nodules could be encompassed within a single clinical target volume; and (2) lesions other than those of the targeted tumor were judged to be controlled with prior surgery and/or local ablation therapy. This retrospective study was approved by the institutional ethics committee, and written informed consent was obtained from all patients.

Treatment Planning

ICG R15 was measured in all patients to quantitatively assess the hepatic functional reserve. Serological testing for hepatitis B surface antigen and anti-hepatitis C antibody was done. All patients were judged to be unresectable by expert hepatobiliary surgeons at our institution, based on the patient's serum bilirubin level, ICG R15, and expected volume of resected liver (10). Percutaneous fine-needle biopsies were performed for all patients unless they had radiologically compatible, postsurgical recurrent HCC (3).

Treatment methods were published previously (3). In brief, gross tumor volume (GTV) was defined using a treatment-planning CT scan, and CTV and planning target volume (PTV) were defined as follows in all but 2 patients: CTV = GTV + 5 mm, and PTV = CTV + 3 mm of lateral, craniocaudal, and anteroposterior margins. CTV encompassed the entire volume of the right lobe in 1 patient who had a tumor of 4 cm in diameter that broadly attached to the bifurcation of the right anterior and posterior portal veins. In this patient, right portal vein embolization was done to facilitate compensatory hypertrophy of the left lobe for expected surgery. However, the patient was finally judged to be unresectable, and PRT was selected. Another patient was treated with a CTV encompassing the entire right anterior portal segment because a tumor of 2 cm in diameter had invaded the bifurcation of the right anterosuperior and anteroinferior portal vein associating with daughter HCC at the right anterosuperior portal segment. The beam energy and spread-out Bragg peak (15) were fine-tuned so that a 90% isodose volume of the prescribed dose encompassed the PTV.

Forty-six patients received PRT to a total dose of 76 CGE in 3.8 CGE once-daily fractions, four to five fractions in a week. Another 3 patients underwent 60 CGE /10 fractions/2 weeks, depending on availability of the proton beam. Eleven patients whose PTV encompassed the gastrointestinal wall received 65 CGE in 2.5 CGE /fraction, five fractions per week. All patients were treated using a 150- to 190-MV proton beam. The relative biological effectiveness of our proton beam was defined as 1.1 (16). No concomitant treatment such as TACE, local ablation, or systemic therapy was allowed during or after the PRT, unless a treatment failure was detected. Both scanning of CT images for treatment planning and irradiation by the proton beam were done during the exhalation phase using the respiration-gated irradiation system and intrahepatic fiducial markers as previously reported (3).

Outcomes

Death from any cause was defined as an event in calculation of OAS, whereas tumor recurrences at any site or patient deaths were defined as events in disease-free survival (DFS). An increase of the tumor diameter within the PTV was defined as local progression, and patients who died without evidence of local progression were censored at the time of last radiographic examination. Adverse events were reviewed weekly during the PRT regimen by means of physical examination, complete blood count, liver function tests, and other biochemical profiles as indicated. The severity of adverse events was assessed using the National Cancer Institute common terminology criteria for adverse events, version 3.0. After completion of PRT, reviews that monitored disease status, including CT and/or MRI examinations and long-term toxicity, were done at a minimum frequency of every 3 months in all 60 patients. The percentages of hepatic noncancerous portions (entire liver volume minus gross tumor volume) receiving CGE doses of >0 (V0), ≥10 (V10), ≥20 (V20), ≥30 (V30), ≥40 (V40), and ≥50 (V50) were calculated using PRT planning software (PT-PLAN/NDOSE System, Sumitomo Heavy Industries Ltd., Tokyo, Japan), and their influence on the outcomes were analyzed (3). Time-to-event analyses were done using Kaplan-Meier estimates from the start of PRT. The differences between time-to-event curves were evaluated with the log-rank test. Multivariate analyses were performed with Cox's proportional hazards model.

RESULTS

Patients

A total of 60 patients with HCC underwent PRT in our institution between May 1999 and July 2007. Approximately 1400 patients with HCC were newly presented to our institution during this study period and about 35%, 30%, 25%, and the remainder primarily treated with hepatectomy, TACE, percutaneous local ablation, and other treatments, respectively. Therefore 60 patients in this study corresponded to approximately 4% of overall, or 7% of patients with unresectable HCC. Patient characteristics at the start of PRT are listed in Table 1. All patients had underlying chronic liver disease. One patient had a history of schistosomiasis, and another patient had autoimmune hepatitis as the cause of liver cirrhosis. Five additional patients were diagnosed with liver cirrhosis caused by non-B, non-C hepatitis. A total of 24 patients received PRT as the first treatment for their HCC. Ten patients had postsurgical recurrences, 22 patients received unsuccessful local ablation and/or TACE to the targeted tumor, and 4 patients underwent successful local ablation to a tumor other than the target prior to PRT. Histological confirmation was not obtained in 1 patient who had a tumor with typical radiographic features compatible with HCC (3). Six patients had HCC nodules of ≤3 cm in diameter; however, they were not considered candidates for local ablation therapy because of the tumor locations, which were in close proximity to the great vessels or the lung.

Adverse events during PRT

All patients completed the treatment plan. Prolongation of the overall treatment time for more than 1 week occurred in 4 patients: treatment of 3 patients was extended due to availability of the proton beam machine, and 1 patient's treatment was extended because of fever associated with grade 3 elevation of total bilirubin that spontaneously resolved within a week. A total of 14 patients experienced transient grade 3 leukopenia and/or thrombocytopenia without infection or bleeding that necessitated treatment. In addition, 8 patients experiencing grade 3 elevation of transaminases without clinical manifestation of hepatic insufficiency maintained good performance status. PRT was not discontinued for these patients; nevertheless, these events spontaneously resolved within 1 to 2 weeks.

Estimation of the risk of PHI by DVH analysis

Development of hepatic insufficiency presented with anicteric ascites and/or asterixis within 6 months after completion of PRT in the absence of disease progression was defined as PHI. Eleven patients, all of whom received a total PRT dose of 76 CGE, developed PHI at 1 to 6 months (median, 2 months) after completion of PRT without elevation of serum bilirubin and transaminases of more than threefold above normal levels. DVHs for hepatic noncancerous portions were drawn according to pretreatment ICG R15 values (Fig. 1A–C). Results showed that all 20 patients with ICG R15 of <20% were free of PHI, regardless of the DVH, for 2 to 94 months (median, 44 months). On the other hand, 6 of 8 patients with pretreatment ICG R15 values of ≥50% died of PHI with (n = 3) or without (n = 3) evidence of HCC recurrence at 2 to 15 months (median, 8 months). There was no obvious relationship between DVH and development of PHI in these 8 patients, as shown in Fig. 1C.

Among 32 patients whose ICG R15 values ranged from 20% to 49.9%, 5 patients developed PHI. The V0 to V50 in these 32 patients are shown in Fig. 2. Differences in distributions of these DVH parameters between patients who did

Table 1. Characteristics of patients

Characteristics	No. of patients (%)
Age (years)	
Median	70
Range	48–92
Gender	
Male	42 (70)
Female	18 (30)
ECOG performance status	
0–1	57 (95)
2	3 (5)
Viral markers	
Hepatitis B surface antigen-positive	3 (5)
Hepatitis C antibody-positive	49 (82)
Both positive	1 (2)
Both negative	7 (12)
Child-Pugh classification	
A	47 (78)
B	13 (22)
C	0
% patients with pretreatment ICG R15 values	
<20	20 (20)
20–40	25 (55)
40–50	7 (12)
≥50	8 (13)
Tumor size (mm)	
Median	45
Range	20–90
20–50	42 (70)
>50	18 (30)
Macroscopic vascular invasion	
Yes	42 (70)
No	18 (30)
Morphology of primary tumor	
Single nodular	45 (75)
Multinodular, aggregating	9 (15)
Diffuse	5 (8)
Portal vein tumor thrombosis	1 (2)
Serum alpha-fetoprotein level (IU/mL)	
<300	41 (68)
≥300	19 (32)
Histology	
Well-differentiated	15 (25)
Moderately-differentiated	28 (47)
Poorly-differentiated	7 (12)
Differentiation not specified	9 (15)
Negative (radiological diagnosis only)	1 (2)
Prior treatment	
None	24 (40)
Surgery	10 (17)
Local ablation/TACE	26 (43)

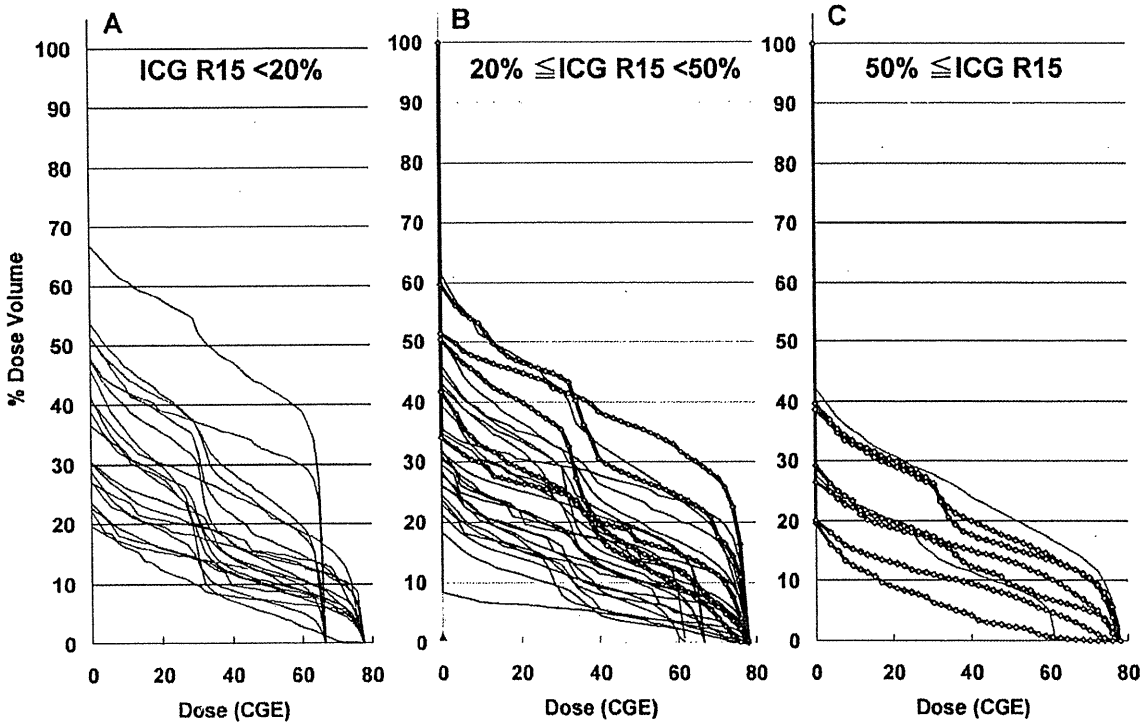

Fig. 1. DVH are shown for all patients according to their pretreatment ICG R15 values, as noted in each panel. Thick lines with rhomboid symbols represent DVHs for patients suffering from hepatic insufficiency within 6 months after completion of PRT.

and did not develop PHI were statistically significant, with p values of 0.012 in V0, 0.009 in V10, 0.012 in V20, 0.006 in V30, 0.016 in V40, and 0.024 in V50 (Mann-Whitney U test). The lowest p value was observed in the difference at V30. Among 32 patients whose ICG R15 values ranged from 20% to 49.9%, none of the 21 patients whose V30 were <25% experienced PHI, whereas 5 of 11 patients (45%) whose V30 was ≥25% developed PHI (p = 0.037, Mann-Whitney U test). The incidence of PHI was 2/25 (8%) in Child-Pugh class A patients, whereas PHI incidence was 3/7 (43%) in class B patients in this group of 32 patients (p = 0.218, Mann-Whitney U test). Of 5 patients who experienced PHI, 1 died at 8 months without evidence of HCC recurrence. PHI spontaneously resolved in 4 patients; 2 patients died of intrahepatic recurrence at 22 and 71 months, respectively; 1 patient died of brain metastasis at 8 months; and 1 patient was alive and disease free at 50 months. In both of the patients who survived for more than 4 years despite development of PHI, the pretreatment functional liver reserve was Child-Pugh class A and ICG R15 was less than 40%. On the other hand, all 3 patients who experienced PHI and died within 2 years had Child-Pugh class B liver functions. Relationships between ICG R15 and V30 according to occurrence of PHI in Child-Pugh class A and B patients are shown in Fig. 3a and b, respectively.

Other serious adverse events

Three patients experienced a gastrointestinal toxicity grade of ≥2. One patient developed hemorrhagic duodenitis associated with anemia at 2 months after completion of 76 CGE/20 fractions/30 days of PRT. The dose administered to the duodenum was estimated to be 50 to 80% of the prescribed dose. Bypass surgery was attempted to alleviate the symptoms; however, this patient died of postoperative hepatic failure at 6 months. Two patients received 65 CGE/26 fractions of PRT, with the entire circumference of the gastrointestinal walls covered within the PTV. One of these 2 patients experienced grade 3 hemorrhagic ulcer at the ascending colon, within the PTV. The patient was managed successfully with right hemicolectomy at 10 months; however, the patient

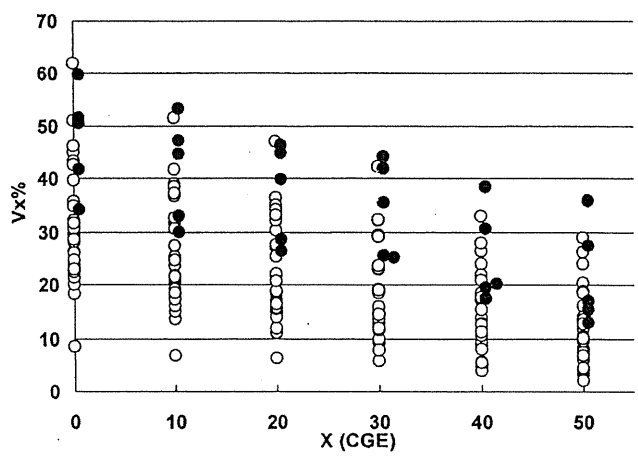

Fig. 2. Distribution of V0 to V50 in DVHs for 32 patients whose pretreatment ICG R15 values ranged from 20% to 49.9%. Open circles represent values for patients who did not experience PHI, whereas closed circles represent those who developed PHI.

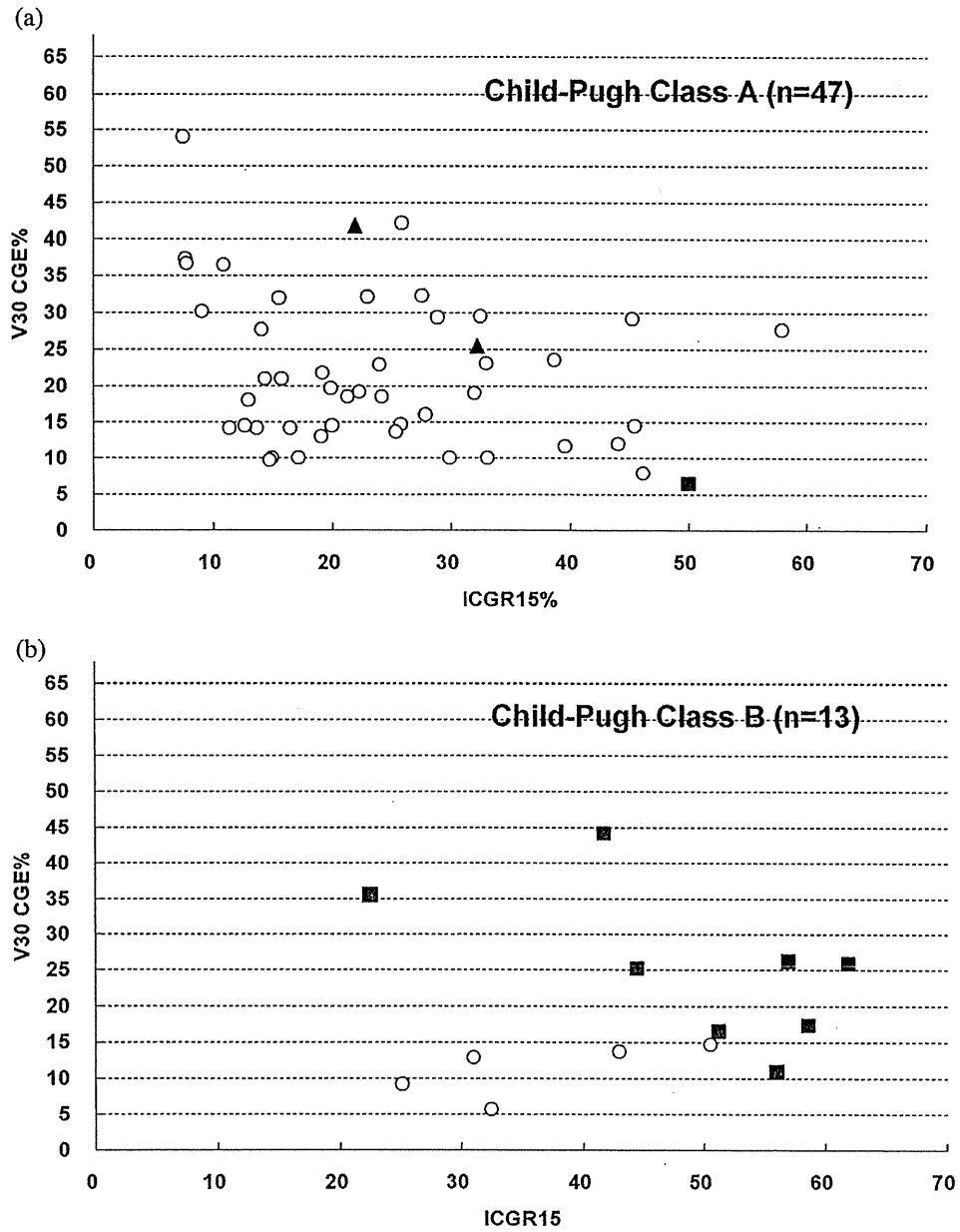

Fig. 3. Scattergram of V30 in each patient who had pretreatment liver functions classified as Child-Pugh class A (a) and class B (b), as shown in each panel, according to the ICG R15 value. Open circles represent values in patients who did not experience PHI. Closed squares represent those who developed PHI and died within 2 years with ($n = 5$) or without ($n = 4$) disease recurrence. Closed triangles represent those who experienced transient PHI and survived for more than 4 years after commencement of PRT.

died of local recurrence and subsequent hepatic failure at 23 months. The other patient developed grade 2 esophagitis within the PTV at 7 months. Repetitive balloon dilatations were required to alleviate the patient's dysphagia; however, the patient was alive without disease and taking a normal diet at 30 months. There were no other observations made of adverse events of Grade ≥3 in any of the patients.

Tumor control and survival

At the time of analysis in August 2009, 42 patients had already died because of intrahepatic recurrence in 27, nodal recurrence in 1, distant metastasis in 3, hepatic insufficiency without recurrence in 9, comorbidity in 1, and senility in 1. Forty of these 42 patients had been free from local progression until death; the durations ranged from 2 to 77 months (median, 20 months). Two patients who experienced local progression died subsequently. A total of 15 patients were alive at 25 to 92 months (median, 43 months) without local progression. Three patients were alive at 49, 53, and 94 months, respectively, after salvage treatment for local progression, using local ablation in 2 and TACE in 1 A total of 37 patients achieved complete disappearance of the primary tumor at 1 to 50 months (median, 10 months) post-PRT. Eighteen patients had residual tumor masses on CT

and/or MRI for 2 to 44 months (median, 21 months) until the time of death or last follow-up visit without local progression. The local progression-free (LPF) rates at 3 and 5 years were 90% (95% confidence interval [CI], 80%–99%) and 86% (95% CI, 74%–98%), respectively.

Of 5 patients who experienced local progression, 3 patients underwent 65 CGE/26 fractions, and 2 patients received 76 CGE/20 fractions of PRT. All 3 patients who received 60 CGE/10 fractions were free from local progression at 6, 30, and 51 months, respectively. LPF rates at 3 and 5 years for 46 patients who received 76 CGE/20 fractions were 97% (95% CI, 92%–100%) and 93% (95% CI, 83%–100%), respectively. LPF rates at 3 years for 11 patients who underwent 65 CGE/26 fractions of PRT were 56% (95% CI, 16%–95%) and was worse than that in patients who received 76 CGE/20 fractions with statistical significance ($p = 0.005$).

A total of 32 patients developed intrahepatic tumor recurrences that were outside of the PTV at 1 to 62 months (median, 20 months). Nine of these tumors occurred within the same segment of the primary tumor. Nodal recurrence at the hepatoduodenal ligament and distant metastasis were observed as the first sites of failure in 2 and 3 patients, respectively. In addition to the above-mentioned five deaths from PHI or postsurgical mortality, 4 patients died of hepatic failure because of underlying liver disease at 17 to 23 months, and 2 patients died from other reasons (comorbidity or senility) without evidence of HCC recurrence. Seven patients remained alive and disease free at 27 to 51 months (median, 30 months). The median survival time for all 60 patients was 41 months, and actuarial OAS rates at 3 and 5 years were 56% (95% CI, 43%–69%) and 25% (12%–39%), respectively. DFS rates at 3 and 5 years were 18% (95% CI, 7%–29%) and 4% (95% CI, 0%–12%), respectively, as shown in Fig. 4. Two Child-Pugh class A patients who underwent PRT with the CTV covering the entire right lobe or right anterior portal segment were alive and disease free at 50 and 26 months, respectively. The former patient had a pre-PRT ICG R15 of 22% and received a V30 of 42% and experienced transient PHI that resolved spontaneously; the latter patient, whose corresponding parameters were 8% and 37%, respectively, did not experience PHI.

Factor analysis

Univariate analyses revealed that factors related to functional liver reserve and occurrence of PHI had significant influence on OAS ($p < 0.05$). Liver function (Child-Pugh class A or B) and prior treatment (none or recurrent) were independent and significant prognostic factors ($p < 0.002$), and occurrence of PHI had marginal significance ($p = 0.011$) by multivariate analysis, as shown in Table 2. The DFS rate at 3 years for 24 patients who had no prior treatment for HCC was 35% (95% CI, 14%–56%), whereas DFS for the remaining 36 patients was 7% (95% CI, 0%–17%) ($p = 0.011$). In Child-Pugh class A patients, OAS at 3 and 5 years for those who had no prior treatment ($n = 17$) was 76% (95% CI, 56%–97%) and 59% (95% CI, 33%–86%), respectively, and 63% (95% CI, 45%–80%) and 25% (95% CI, 7%–42%), respectively, for 30 patients with recurrent tumor ($p = 0.060$). In Child-Pugh class B patients, the 2-year OAS for patients without PHI ($n = 5$) was 80% (95% CI, 45%–100%), while 8 patients who developed PHI died within 2 years with ($n = 5$) or without ($n = 3$) HCC recurrence ($p = 0.009$).

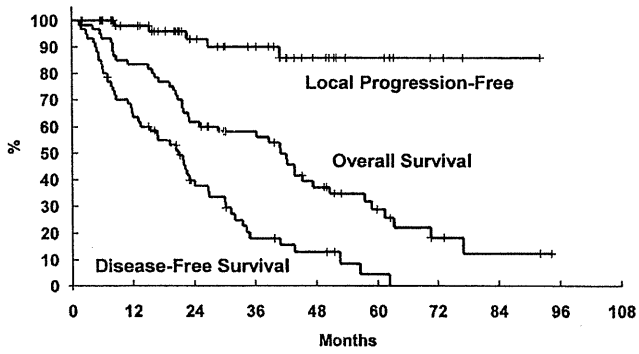

Fig. 4. Kaplan-Meier estimation of local progression-free survival, OAS, and disease-free survival rates for all 60 patients.

DISCUSSION

The promising tumoricidal effect of PRT using aggressive escalation of total and fractional doses, which has been repeatedly reported previously, was reproduced in this study (3, 4). The estimated actuarial local progression-free rate within the PTV in patients receiving 76 CGE/20 fractions exceeded 90% at 3 years. DFS at 3 years for patients who underwent PRT as an initial treatment ($n = 24$) was 35%, and, among them, OAS at 3 years was 76% in Child-Pugh class A patients ($n = 17$). These results are comparable to those observed after surgical treatment (17). Although the number of patients was small, these data indicate that appropriate local control with PRT may provide survival benefit in adequately selected patients with unresectable HCC. The fact that 9 of the 32 intrahepatic HCC recurrences occurred within the same anatomical portal segments showed that it should still be possible to improve the progression-free rate by defining the CTV so it covers undetectable tumor spread via the portal blood flow.

As shown in Fig. 3, no patient who had ICG R15 of less than 20% experienced PHI. In addition, only Child-Pugh class A patients with pre-PRT ICG R15 of less than 40% survived for longer than 4 years despite development of PHI. One of them underwent systematic portal segmental irradiation with the CTV covering the entire right lobe, and the details for this patient will be reported separately. On the other hand, all patients who had pre-PRT liver functions classified as Child-Pugh class B and/or ICG R15 of 40% or higher died within 2 years when they developed PHI. This suggests that the role of systematic portal irradiation requiring a large irradiated volume should be pursued further in Child-Pugh class A patients with favorable ICG R15 values; otherwise, the CTV should be confined to the GTV with adequate margins. Furthermore, in patients who have ICG R15 of 50% or

Table 2. Factors related to overall survival

Factor	No. of patients	% of OAS at 3 years (MST, months)	Univariate *p* value	Multivariate *p* value, hazard ratio (95% CI)
Age				
<70	29	55 (41)	0.660	0.087
≥70	31	61 (42)		0.52 (0.24–1.10)
Gender				
Male	42	62 (41)	0.332	0.194
Female	18	44 (42)		0.62 (0.29–1.30)
Tumor size (mm)				
<50	36	66 (44)	0.178	0.070
≥50	24	46 (23)		0.54 (0.28–1.05)
Pretreatment ICG R15				
<40%	45	67 (44)	0.002	
≥40%	15	33 (15)		
Child-Pugh classification				
A	47	68 (45)	<0.001	<0.001
B	13	23 (15)		0.19 (0.07–0.50)
Serum alfa-fetoprotein level (IU/mL)				
<300	41	61 (42)	0.617	0.618
≥300	19	53 (39)		0.83 (0.39–1.74)
PHI				
No	49	65 (44)	0.001	0.011
Yes	11	18 (9)		0.29 (0.11–0.76)
% of patients receiving V30				
<25%	40	57	0.724	
≥25%	20	60		
Total dose = 65 Gy				
Yes	11	44 (29)	0.646	0.185
No	49	61 (42)		1.88 (0.73–4.76)
Prior treatment				
None	24	67 (47)	0.112	0.002
Recurrence	36	53 (36)		0.32 (0.15–0.66)

Abbreviations: OAS = overall survival; MST = median survival time; CI = confidence interval; PHI = proton-induced hepatic insufficiency.

higher, the indication for PRT should be considered with extreme caution to prevent life-threatening PHI, as shown in Fig. 3.

Results of this retrospective study showed 56% OAS at 3 years in all patients and 68% in 47 Child-Pugh class A patients. All of them were judged strictly as unresectable and not amenable to local ablation. Therefore, a survival benefit of adding PRT to TACE could be expected, which should be tested in randomized trials. Suitable candidates for such a study may be patients who have unresectable HCC of >4 cm in diameter (*i.e.*, a high probability of microscopic vascular invasion) or who show macroscopic vascular invasion, which is amenable to selective segmental TACE as a curative treatment. Nevertheless, before developing that kind of randomized study, data should still be compiled regarding the safety and patterns of failure after PRT combined with TACE while ICG R15 and V30 are taken into account. Preliminary results of hypofractionated stereotactic body radiotherapy for patients with relatively small primary or metastatic liver tumors showed 70% to >90% of objective response rates and 20 or more months of median survival time (1, 18–20). Mature data regarding the relationship between oncological outcomes and tumor characteristics, as well as functional reserve of the liver, are needed to optimize cost-effectiveness of localized, high-dose RT using X-ray or charged particles for treatment of this disease. Nonetheless, RT should have no role in preventing multifocal tumorigenesis, which will be continuously encountered by multidisciplinary approaches (21).

The risk of developing serious gastrointestinal sequela after PRT is another important issue to consider in patients who have HCC located adjacent to the digestive tract. We attempted once-daily fractionation of PRT with 65 CGE/26 fractions. However, 2 of 11 patients who received this treatment developed gastrointestinal toxicity grade of ≥2. Moreover, these 11 patients showed significantly worse LPF rates than those who received 76 CGE/20 fractions of PRT. Three patients who received 60 CGE/10 fractions of PRT were controlled locally. Although our current data are based on a limited number of patients, precluding definitive conclusions, they suggest a low α/β ratio (22) of HCC, and this assumption should be examined further in clinical trials. Based on currently available data, efforts to exclude the gastrointestinal loop from the PTV by using, for example, surgical manipulations, seem to be positively considered in order to expand the role of PRT for HCC.

CONCLUSIONS

In conclusion, PRT achieved excellent local progression-free rates when aggressive, high-dose/fractionation was administered. Child-Pugh class A patients with ICG R15 of less than 40% tolerated PRT of a large irradiated volume well, despite development of transient PHI. However, in Child-Pugh class B patients, it seems reasonable to minimize the irradiated volume to prevent detrimental liver damage induced by PRT and underlying liver diseases. A V30 of less than 25% in the noncancerous portion of the liver is considered an indicator of the safety of PRT in patients who have pre-PRT ICG R15 of 20% to 50%. We believe that there are extremely few indications for PRT in patients who have ICG R15 of 50% or higher. Gastrointestinal toxicity is a major drawback of PRT for tumors adjacent to the gastrointestinal tract, and surgical manipulation to exclude the intestinal loop from the PTV should be positively considered as indicated. If these issues are carefully considered, with special attention to the patterns of tumor spread, when determining the