J Gastrointest Surg
DOI 10.1007/s11605-011-1538-2

ORIGINAL ARTICLE

Significance of Platelet Count in the Outcomes of Hepatectomized Patients with Hepatocellular Carcinoma Exceeding the Milan Criteria

Hironobu Amano · Hirotaka Tashiro · Akihiko Oshita · Tsuyoshi Kobayashi · Yoshisato Tanimoto · Shintaro Kuroda · Hirofumi Tazawa · Toshiyuki Itamoto · Toshimasa Asahara · Hideki Ohdan

Received: 23 November 2010 / Accepted: 5 April 2011

Abstract

Background The appropriate treatment strategy for advanced hepatocellular carcinoma (HCC) that does not meet the Milan criteria (MC) is unclear. The aim of this study was to determine the significance of surgical treatment for such patients.

Study design From January 1990 to December 2007, 151 patients with HCC exceeding MC who underwent curative surgical treatment were enrolled. Survival and recurrence data and clinicopathological factors were examined. Prognostic factors were analyzed to identify those that contributed to improved surgical outcomes retrospectively.

Results After the initial hepatectomy, the overall 3-, 5-, and 10-year survival rates were 73%, 55%, and 33%, respectively, for the 151 patients in this study; the corresponding disease-free survival rates were 36%, 30%, and 17%, respectively. A platelet count under 10^5/mm^3, multiple tumors, and liver cirrhosis of noncancerous tissue were adverse survival and disease-free survival factors by univariate analysis. Platelet count was an independent prognostic factor by multivariate analysis. The 3-, 5-, and 10-year overall survival rates of HCC exceeding MC in patients whose platelet count was 10^5/mm^3 or greater reached 76%, 65%, and 44%, respectively, and were comparable with those that met MC (86%, 68%, and 37%, respectively).

Conclusions Hepatectomy for patients with advanced HCC exceeding MC improves survival, especially for patients with a sufficiently high platelet count, although recurrence rates after initial hepatectomy are high.

Keywords Hepatocellular carcinoma · Milan criteria · Platelet count · Advanced · Hepatectomy · Prognosis

Abbreviations

HCC	Hepatocellular carcinoma
TACE	Transarterial chemoembolization
OLT	Orthotopic liver transplantation
MC	Milan criteria
ICGR15	Indocianine green retention rate at 15 min
RFA	Radiofrequency ablation
LDLT	Living donor liver transplantation

H. Amano · H. Tashiro (✉) · A. Oshita · T. Kobayashi · Y. Tanimoto · S. Kuroda · H. Tazawa · T. Asahara · H. Ohdan
Department of Gastroenterological Surgery,
Hiroshima University Hospital,
1-2-3 Kasumi,
Hiroshima 734-8551, Japan
e-mail: htashiro@hiroshima-u.ac.jp

T. Itamoto
Department of General Surgery, Hiroshima Prefectural Hospital,
1-5-54 Ujinakanda,
Hiroshima 734-8530, Japan

Published online: 22 April 2011

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. There are various options to treat HCC, including partial hepatectomy, percutaneous ablation therapy, and transarterial chemoembolization (TACE). However, the resulting prognosis of HCC remains inadequate, despite technical refinements in these treatments, due to the high incidence of recurrence of HCC.[1,2]

Orthotopic liver transplantation (OLT) is the preferred treatment for patients with cirrhosis and early HCC per the

Milan criteria (MC: defined as a solitary HCC of a size <5 cm or 2 or 3 tumors <3 cm with no gross vascular invasion).[3] In patients with early HCC, such as within MC, as long as liver function is preserved, liver resection effects an overall 5-year survival rate that is comparable with that of liver transplantation, with minimal morbidity and mortality.[4–6]

The treatment strategy for advanced HCC exceeding MC has not been discussed sufficiently. Due to advanced tumor status, ablation therapy cannot be the first treatment, nor can OLT. Although hepatectomy or TACE is used to treat advanced HCC patients, the 5-year overall survival rate after curative hepatectomy for advanced HCC (tumor size, >5 cm) is 30% to 35%, and its recurrence after hepatectomy is unavoidable.[7,8]

We retrospectively analyzed the impact of hepatectomy on tumor control in patients with HCC exceeding MC. In this study, we examine the rationale for partial hepatectomy as an initial treatment and discuss the development of other strategies for recurrent HCC.

Methods

Patient data began to be collected prospectively by our program in 1986. Between January 1990 and December 2007, 781 consecutive adult patients underwent hepatectomy for HCC at Hiroshima University Hospital. A total of 651 consecutive HCC patients underwent curative intent hepatectomy in our hospital. Curative intent hepatectomy was defined as the removal of all recognizable tumors; patients with macroscopic vascular invasion in the first portal branch, portal vein trunk or hepatic vein trunk, and/or extrahepatic metastasis were excluded due to their poor prognosis.

Data for the remaining 622 HCC patients were included in the analysis. We divided the remaining patients into two groups: transplantable (meeting MC: single lesion with a maximum diameter <5 cm or three lesions with a maximum diameter <3 cm) and advanced (exceeding MC). We focused on the advanced group.

The indications and procedure for hepatectomy have been described.[9,10] Briefly, Child–Pugh class C was regarded as a contraindication for hepatectomy. The decision to perform hepatectomy was made based on liver function and extent of tumor. Liver function was assessed according to Child–Pugh classification and indocianine green retention rate at 15 min (ICGR15). In patients who lacked ascites and had normal bilirubin levels, ICGR15 became the chief determinant of resectability. For example, right hemihepatectomy could be tolerated if ICGR15 was in the normal range. One third of the liver parenchyma could be resected for patients with ICGR15 of 10–19%; segmentectomy was possible for patients with ICGR15 of 20–29%; and limited resection was possible for patients with ICGR15 of ≥30% (9.10).

Hepatectomy was indicated when all tumors could be resected with sufficient hepatic functional reserve, as determined by preoperative imaging. However, when the HCC tumors were hypovascular—suggesting that the tumor was well-differentiated HCC—and ≤2 cm and when the number of tumors ≤3, percutaneous ablation therapies were preferable despite hepatectomy being feasible, depending on the tumor location in the liver. Clinicopathological findings were recorded according to the criteria of the Liver Cancer Study Group in Japan.[11] Liver cirrhosis was confirmed by histological examination of the resected specimen.

A modified Clavien classification was used to grade the severity of postoperative complications.[12] Grade I complications were defined as deviations from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, or radiological intervention. Grade I complications also included wound infections that opened at the bedside.

Grade II complications were defined as those that required pharmacological treatment; blood transfusion and total parenteral nutrition were also included. Grade III complications were those that required surgical, endoscopic, or radiological intervention. Grade IV complications were life-threatening complications that required intermediate care/intensive care unit management. Grade V complications resulted in death. Operative mortality was defined as death within 30 days after surgery. In-hospital mortality was defined as death within the hospitalization period.

Postoperative follow-up evaluations consisted of a clinical physical examination, blood chemistry tests, and measurements of tumor marker levels, including alpha-fetoprotein and des-gamma-carboxy prothrombin, every month for 2 years. After 2 years, patients were assessed every 3 months. Patients were examined by abdominal ultrasonography every 3 months and by computed tomography every 6 months during the follow-up periods.

Our follow-up protocol included an evaluation by hepatologists to monitor cancer recurrence and the progress of chronic hepatitis or liver cirrhosis. When recurrence was noted in any of these examinations, patients underwent hepatic angiography. The patents were followed up regularly until December 31, 2008, and every patient was followed up for at least 6 months. All patients who experienced intrahepatic recurrence were managed with ablative therapy (radiofrequency ablation (RFA) or ethanol injection), TACE, or surgery, including liver transplantation, according to the same criteria as for the initial resection.

Statistical analyses were performed using unpaired Student's t test and chi-square test with Fisher's exact test. Overall survival and disease-free survival rates were calculated using the Kaplan–Meier method and compared using log-rank test. Disease-free survival was calculated, considering any death or recurrence as an event. A P value <0.05 was considered to be statistically significant. Statistical analysis was performed using StatView for Windows (Version 5.0; SAS Institute, Cary, NC, USA).

Results

As shown in Fig. 1, there were 151 patients with initially resectable advanced HCC who did not fulfill MC (i.e., exceeding MC) and 471 patients who met MC.

In the exceeding-MC group, the mean follow-up period for all survivors was 4.1±3.1 years (range, 0.5 to 14.5 years). Table 1 shows the patients' backgrounds. Overall operative mortality and in-hospital mortality rates were the same, i.e., 0.7% (n=1) in both conditions. The incidence of complications that developed after hepatectomy is also shown in Table 1. Thirty of the 151 patients (20%) had postoperative complications (Table 1). Nineteen of the 151 patients (13%) were grade III or more.

Figure 2a shows the survival rates of patients who underwent curative resection of HCC (meeting MC and exceeding MC). The survival rate of the exceeding-MC group was significantly lower than that of the group that met MC (P=0.030). The 3-, 5-, and 10-year survival rates

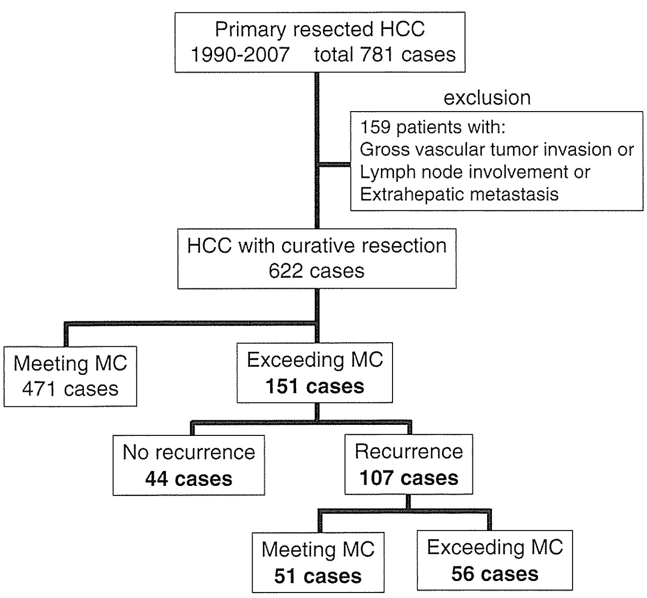

Fig. 1 Overview of outcomes of patients with primary resected hepatocellular carcinoma (HCC). The number of HCC patients who underwent curative resection was 622, subdivided by the Milan criteria (MC)

Table 1 Patients' backgroud

	Number of patients	Percent
Age (year)		
≤60	57	38.4
>60	94	61.6
Gender		
Male	127	84.1
Female	24	15.9
Type of hepatitis virus		
Non-HCV	61	40.4
HCV	90	59.6
Child–Pugh grade		
A	129	85.4
B	22	14.6
Type of hepatectomy		
Limited resection	82	54.3
Segmentectomy or more	69	45.7
Operative mortality: yes	1	0.7
In-hospital mortality: yes	1	0.7
Postoperative complications[a]: yes	30	19.9
Grade I, II	11	7.3
Grade III or more	19	12.6

[a] Postoperative complications was defined as any event satisfying the criteria advocated by Dindo et al.[12]

of the exceeding-MC group were 77%, 55%, and 33% and 86%, 68%, and 37% in those that met MC, respectively. The 3-, 5-, and 10-year disease-free survival rates of the exceeding-MC group were 36%, 30%, and 17% and 47%, 30%, and 13% in those that met MC, respectively (Fig. 2b).

Table 2 summarizes the results of the univariate analysis according to clinicopathological factors. A platelet count $<10^5/mm^3$ (P<0.001), multiple tumors (P=0.012), and cirrhosis of noncancerous tissue (P=0.035) were significant adverse prognostic factors for overall survival. Similarly, a platelet count $<10^5/mm^3$ (P=0.001), multiple tumors (P=0.005), and cirrhosis of noncancerous tissue (P=0.020) were significant adverse prognostic factors for disease-free survival.

By multivariate analysis, a platelet count $<10^5/mm^3$ (P=0.007) was found to be an independent adverse prognostic factor for overall survival (Table 3), and the 3-, 5-, and 10-year overall survival rates of patients with HCC exceeding MC whose platelet count was $\geq 10^5/mm^3$ were 76%, 65%, and 44%, respectively, comparable with the group that met MC (86%, 68%, and 37%, respectively; Fig. 2a). A platelet count $<10^5/mm^3$ (P=0.039) was also an independent adverse factor for disease-free survival (Table 3).

Out of 151, a total of 107 (71%) patients with HCC exceeding MC experienced a recurrence after the initial hepatectomy. Table 4 shows the patterns of cancer recurrence

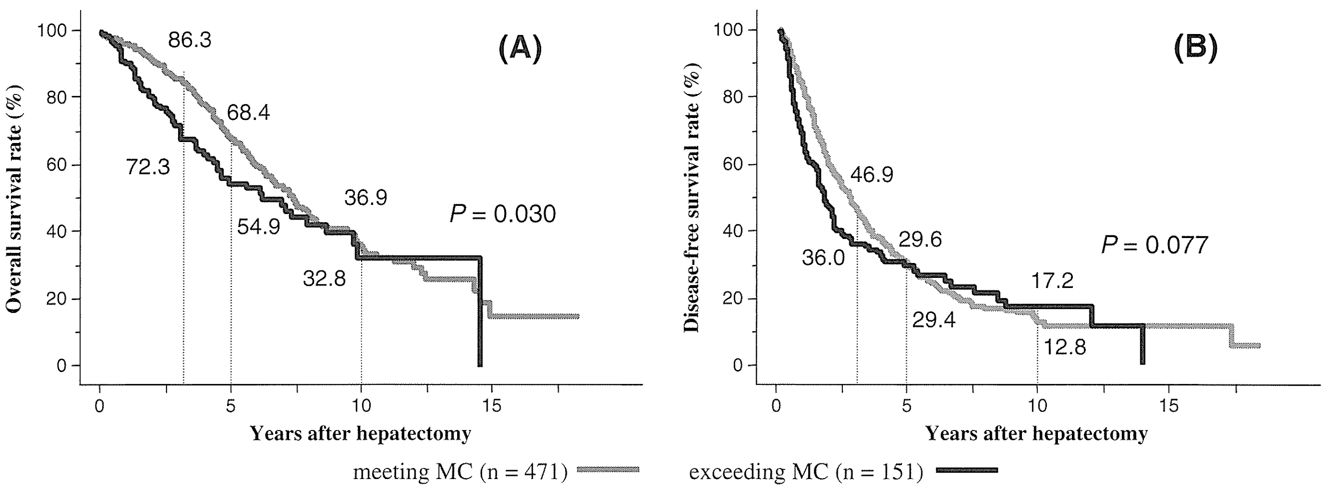

Fig. 2 Survival and disease-free survival curves of patients who received curative resection of HCC that met (471 patients) or were exceeding (151 patients) MC. (A) The 3-, 5-, and 10-y survival rates of patients exceeding MC were 72.3%, 54.9%, and 32.8%, respectively, and 86.3%, 68.4%, and 36.9%, respectively, in those who met MC. (B) The 3-, 5-, and 10-y disease-free survival rates of patients exceeding MC were 36.0%, 29.4%, and 17.2%, respectively, and 46.9%, 29.6%, and 12.8%, respectively, in those who met MC

and compares the consequent treatment details between patients whose platelet counts were $\geq 10^5/mm^3$ and $<10^5/mm^3$. The rate of HCC recurrence was significantly lower in patients whose platelet count was $\geq 10^5/mm^3$; 76 (66%) of such patients experienced a recurrence of HCC after hepatectomy, as compared to 31 (89%) patients whose platelet count was $<10^5/mm^3$ (P=0.009). Further, regarding the pattern of recurrence, the proportion of patients who had a recurrence of HCC that met MC was significantly higher in patients with a platelet count$\geq 10^5/mm^3$ than those with a platelet count of $<10^5/mm^3$ (51% vs. 39%; P<0.001).

The proportion of patients who received curative treatment for the first recurrence, such as repeat hepatectomy and local ablation therapy, had significantly higher platelet counts, i.e., $\geq 10^5/mm^3$ (44% vs. 23%; P=0.047).

Of the 107 patients who experienced a recurrence, 51 (48%) met MC and 56 (52%) were exceeding MC, including extrahepatic recurrence (Fig. 1). The 3- and 5-year survival rates after recurrence were significantly superior in patients with a recurrence that met MC (71% and 40%, respectively) than those exceeding MC (17% and 9%) (P<0.001; Fig. 3).

Table 5 shows the details of the treatments for recurrences after hepatectomy. The proportions of patients who received ablation therapy or repeat hepatectomy after recurrence was higher in patients with a recurrence that met MC than those exceeding MC (P=0.001). Two patients with a recurrence that met MC, who underwent salvage living donor liver transplantation (LDLT), did not have a recurrence after liver transplantation at the 2- and 3-year follow-up, respectively. One patient with a recurrence that was exceeding MC, and who underwent salvage LDLT, experienced a recurrence of HCC within 1.5 years.

Discussion

The ultimate goal of a treatment for HCC is to prolong survival by eradicating malignant legions while preserving hepatic function. Surgical resection, by partial hepatectomy or total hepatectomy followed by OLT, is the standard treatment with a curative intent.[13] The resectability and choice of procedure depend on many factors, including baseline liver function, absence of extrahepatic metastasis, size of residual liver, availability of resources (including liver grafts), and expertise of the surgical team.

Although hepatic resection, ablation therapy, and liver transplantation are accepted, effective treatments for patients with cirrhosis and early HCC, the proper strategy for advanced HCC has not been established. Therefore, we studied HCC patients who were exceeding MC—who are not eligible for OLT as the initial treatment. We investigated the impact of hepatectomy on outcomes of HCC that exceeded MC and examined the rationale of hepatectomy as an initial treatment for HCC exceeding MC.

In our series, the 5- and 10-year survival rates of patients with HCC exceeding MC were 55% and 33%, respectively, comparable with Kamiyama et al.[14] We also identified significant prognostic factors of patients with HCC exceeding MC who underwent hepatectomy: platelet count, tumor number, and cirrhosis. Moreover, our multivariate analysis revealed that platelet count was the sole independent prognostic factor in these HCC patients.

The prognosis of such patients after hepatectomy was clearly stratified by platelet count, which is typically predictable by preoperative laboratory tests. The 3-, 5-, and 10-year overall survival rates of patients with HCC exceeding MC, whose platelet count was $\geq 10^5/mm^3$, were

Table 2 Overall and disease-free survival rates of patients with HCC exceeding MC according to clinicopathological factor

		Overall survival (%)				Disease-free survival (%)			
		3-year	5-year	10-year	*P* value	3-year	5-year	10-year	*P* value
All cases (*n*=151)		73	55	33		36	30	17	
Age (year)	≤60 (*n*=57)	69	58	38	0.873	35	28	17	0.977
	>60 (*n*=94)	74	53	30		37	30	18	
Gender	Male (*n*=127)	75	55	34	0.647	34	27	15	0.247
	Female (*n*=24)	61	56			45	45		
Type of hepatitis virus	Non-HCV (*n*=61)	71	65	36	0.498	46	39	25	0.054
	HCV (*n*=90)	73	50	32		29	22	12	
Total bilirubin (/mm^3)	<1.0 (*n*=125)	71	52	32	0.151	37	32	19	0.515
	≥1.0 (*n*=26)	78	72	36		30	19	9	
Platelet counts (/mm^3)	$<10^5$ (*n*=35)	61	27		< 0.001	16	8		0.001
	$\geq10^5$ (*n*=116)	76	65	44		42	36	21	
ALT (IU/l)	<60 (*n*=106)	71	49	29	0.08	36	30	15	0.707
	≥60 (*n*=45)	77	70	45		36	27	18	
Alb (g/dL)	<3.5 (*n*=37)	73	52	41	0.995	42	31	23	0.55
	≥3.5 (*n*=114)	73	58	32		35	29	15	
ICG-R15 (%)	<20 (*n*=111)	72	57	43	0.303	40	32	20	0.467
	≥20 (*n*=39)	75	52			26	22		
Child–Pugh grade	A (*n*=129)	73	56	30	0.643	35	29	18	0.645
	B (*n*=22)	72	54	46		43	32	17	
AFP (ng/mL)	<400 (*n*=101)	77	56	31	0.905	33	26	16	0.495
	≥400 (*n*=48)	65	55	41		45	39	22	
Number of tumors	Single (*n*=60)	79	71	52	0.012	52	41	28	0.005
	Mutiple (*n*=91)	68	45	23		26	22	12	
Tumor distribution	One section (*n*=77)	81	56	43	0.083	42	33	28	0.091
	more (*n*=74)	61	55	25		32	23	8	
Non-cancer tissue	Cirrhosis (*n*=52)	67	39	29	0.035	23	15	8	0.02
	Others (*n*=99)	75	65	38		42	36	23	
Preoperative TAE	Yes (*n*=102)	72	55	30	0.91	35	28	15	0.366
	No (*n*=45)	73	56	50		40	33	25	
Type of hepatectomy	Limited resection (*n*=82)	73	51	29	0.743	34	27	8	0.472
	Segmentectomy or more (*n*=69)	71	60	39		39	33	33	
Transfusion	Yes (*n*=20)	64	46	0	0.071	25	17	0	0.103
	No (*n*=131)	74	57	37		38	31	21	
Microscopic vascular invasion	Yes (*n*=74)	60	48	30	0.089	30	28	17	0.144
	No (*n*=77)	84	61	35		42	31	18	
Histologic grading	Well or moderate (*n*=122)	71	55	30	0.718	34	28	18	0.777
	poor (*n*=26)	74	52	43		42	31	12	
Diabetes mellitus	Yes (*n*=53)	73	58	34	0.929	39	30	17	0.493
	No (*n*=95)	72	52	31		33	29	17	
SF criteria	Meeting SF (*n*=59)	74	52	23	0.704	30	28	15	0.734
	Exceeding SF (*n*=92)	71	57	38		40	32	19	

HCC hepatocellular carcinoma, *MC* Milan criteria, *ALT* alanine aminotransferase, *ICG-R15* indocianine green retension rate at 15 min, *AFP* alpha-fetoprotein, *SF* San Francisco criteria (1 lesion <6.5 cm, 2–3 lesions each <4.5 cm with total diameter <8 cm)

76%, 65%, and 44%, respectively, comparable with those that met MC (86%, 68%, and 37%, respectively).

Hepatectomy should be the first-line treatment in patients with HCC exceeding MC whose platelet count is $>10^5$/mm^3.

Table 3 Results of Cox's proportional hazards analysis for overall and disease-free survival after hepatectomy

Variables	*P* value	Relative risk	95% CI
Overall survival			
Plt. Count: <10^5/mm^3	0.007	2.155	1.232–3.774
Number of tumors: multiple	0.103	1.65	0.903–3.021
Tumor distribution: more than one section	0.168	1.439	0.858–2.410
Transfusion: Yes	0.13	1.667	0.861–3.228
Microscopic vascular invasion: Yes	0.067	1.596	0.969–2.629
Non-cancer tissue: cirrohsis	0.488	1.207	0.709–2.058
Disease-free survival			
HCV infection: Yes	0.585	1.148	0.699–1.887
Plt. Count: <10^5/mm^3	0.039	1.653	1.025–2.667
Number of tumors: multiple	0.202	1.368	0.845–2.221
Tumor distribution: more than one section	0.098	1.412	0.939–2.123
Non cancer tissue: cirrohsis	0.274	1.277	0.824–1.979

In general, platelet count, which reflects the severity of portal hypertension, is a significant predictor of survival. Several studies have shown that platelet count is a risk factor for carcinogenesis from chronic hepatitis and for survival and recurrence of HCC after treatment, including liver resection.[15–18] In fact, we observed that recurrence of HCC after hepatectomy decreased in patients whose platelet count was ≥10^5/mm^3 and that the proportion of patients who experienced a recurrence of HCC that met MC was significantly higher in patients with a platelet count <10^5/mm^3. Further, the proportion of patients who underwent repeat hepatectomy or RFA as a curative treatment for a recurrence of HCC was significantly higher in patients whose platelet count was ≥10^5/mm^3.

After resection with curative intent, many patients experience a recurrence, which is a significant cause of late death. In this study, the recurrence rate was high: 70.9% of patients with HCC exceeding MC were diagnosed as having had a recurrence (mean follow-up, 4.1 years). Tumor number was an independent factor of disease-free survival, and the 3-, 5-, and 10-year disease-free survival rates were 51%, 41%, and 28%, respectively, even in patients with a single tumor.

The reported cumulative 5-year recurrence rates range from 50% to 100%.[19–22] In our series, 107 (71%) of 151 patients with HCC exceeding MC experienced a recurrence of HCC, 51 (48%) of whom met MC. These results demonstrate that downstaging a recurrence to within MC was achieved by hepatectomy as an initial treatment for HCC exceeding MC. The proportion of patients who underwent repeat hepatectomy or local ablation therapy as a curative treatment for HCC recurrence was significantly higher in patients with a recurrence of HCC within MC versus exceeding MC. The outcomes after recurrence were significantly better in patients whose recurrence was downstaged to within MC compared with those who did

Table 4 Recurrent pattern and treatment of recurrent HCC after hepatectomy (comparison with platelet counts)

	Platelet counts >10^5 (n=116)	Platelet counts <10^5 (n=35)	*P* value
Cancer recurrence[a]: yes	76 (66)	31 (89)	0.009[c]
Recurrent pattern[b]			<0.001[c]
Meeting MC	39 (51)	12 (39)	
Exceeding MC or extrahepatic recurrence	37 (49)	19 (61)	
Treatments for recurrence[b]			0.047[c]
Curative treatment	34 (44)	7 (23)	
Non-curative treatment	41 (55)	22 (70)	
Salvage liver transplantation	1 (1)	2 (6)	

Curative treatment included partial hepatectomy, local ablation therapy; non-curative treatment included transarterial chemoembolization, systemic chemotherapy, radiation therapy and conservative

HCC hepatocellular carcinoma, *MC* Milan criteria

[a] Data are expressed as the number of patients (percentage of total patients)

[b] Data are expressed as the number of patients (percentage of patients who had a recurrence)

[c] Statistically significant difference

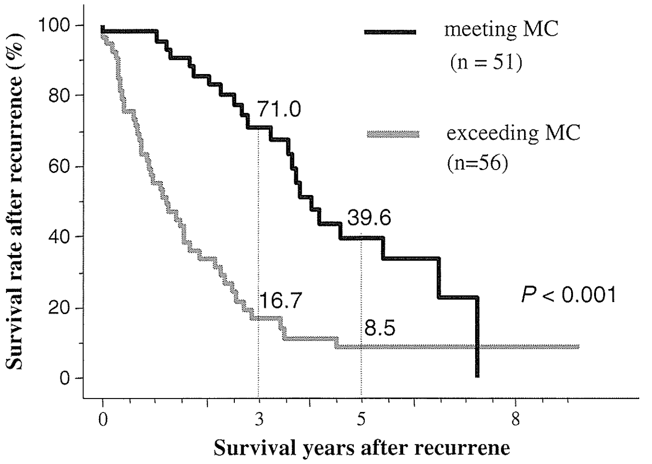

Fig. 3 Comparison of survival curves after recurrence of HCC according to recurrent pattern. The 3-and 5-year survival rates of patients with a recurrence that met MC were 71.0% and 39.6%, respectively, and 16.7% and 8.5%, respectively, in those who exceeding MC including extrahepatic recurrence

not achieve such downstaging. These results indicate that hepatectomy as an initial treatment is an important component of the treatment strategy for HCC exceeding MC.[23]

With regard to the treatment of recurrent HCC patients, we reported that the more hepatectomy was repeated, the shorter the recurrence-free interval became, suggesting a limitation of repeat hepatectomy in curing recurrent HCC.[24] Liver transplantation has been discussed as the next strategy to treat tumor recurrences after initial hepatectomy in patients with advanced HCC. Several studies have reported salvage transplantation for recurrence after hepatectomy,[6,25–27] suggesting that primary hepatectomy and salvage liver transplantation is a feasible and rational strategy for patients with small HCC that preserves liver function. In this series, of the patients who had recurrence after resection for tumors exceeding MC, approximately 48% had recurrent tumors that were within MC. This result also indicates that approximately half of the patients with recurrence would be candidates for salvage liver transplantation after partial hepatectomy performed for downstaging to within MC. Salvage LDLTs were adopted for three patients, two of whom, who had a recurrence that met MC, did not experience a recurrence after salvage LDLT at the 2- and 3-year follow-up, respectively. Yao et al. and Ravaioli et al. reported that locoregional treatments, including RFA, were effective for downstaging prior to liver transplantation.[23,28] In general, RFA was indicated for HCCs with diameters less than 3 cm. Although RFA may be effective for downstaging multiple small HCCs, its effectiveness may be limited in the case of downstaging large HCCs with diameters greater than 3 cm. Further studies are required to clarify the indications for the use of RFA and hepatectomy as downstaging modalities prior to liver transplantation.

A significant proportion of patients with HCC exceeding MC might benefit from liver transplantation. Mazzaferro et al. proposed an expansion of the indications for liver transplantation, using up to seven criteria.[29] Takada et al. demonstrated that LDLT could be safely extended to ≤10 tumors (all ≤5 cm in diameter and PIVA-II≤400 mAU/mL) with acceptable outcomes.[30] Liver transplantation has been proposed as an initial treatment for patients with HCC exceeding MC whose platelet count is $<10^5/mm^3$, although the extension of the indications of liver transplantation is restricted.

Conclusion

Hepatectomy for patients with HCC exceeding MC increases survival rates, especially for patients with sufficiently high platelet counts, although their recurrence rates

Table 5 Treatments for recurrent HCC after initial hepatectomy

Modalities	Recurrent pattern *N* (%)[a]		*P* value
	Meeting MC (*n*=51)	Exceeding MC or extrahepatic (*n*=56)	
Partial hepatectomy	10 (20)	5 (9)	<0.001[b]
Salvage liver transplantation	2 (4)	1 (2)	
Resection of distant metastasis	0	3 (5)	
Percutaneous ablation therapy	18 (35)	8 (14)	
TACE	21 (41)	23 (41)	
Chemotheraphy and/or radiation	0	10 (18)	
Non-treatment	0	6 (11)	

MC Milan criteria, *TACE* transarterial chemoembolization

[a] Data are expressed as the number of patients (percentage of patients who had a recurrence of each group)

[b] Statistically significant difference

after initial hepatectomy are high. Hepatectomy as an initial treatment is an important component of the treatment for HCC exceeding MC to downstage the recurrence to within MC.

References

1. Castells A, Bruix J, Bru C, Fuster J, Vilana R, Navasa M, Ayuso C, Boix L, Visa J, Rodes J. Treatment of small hepatocellular carcinoma in cirrhotic patients: A cohort study comparing surgical resection and percutaneous ethanol injection. Hepatology 1993;18:1121–1126.
2. Arii S, Yamaoka Y, Futagawa S, Inoue K, Kobayashi K, Kojiro M, Makuuchi M, Nakamura Y, Okita K, Yamada R. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinoma: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. Hepatology 2000;32:1224–1229.
3. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinoma in patients with cirrhosis. N Engl J Med 1996;344:693–699.
4. Cha CH, Ruo L, Fong Y, Jarnagin WR, Shia J, Blumgart LH, DeMatteo RP.. Resection of hepatocellular carcinoma in patients otherwise eligible for transplantation. Ann Surg 2003;238:315–323.
5. Margarit C, Escartin A, Castells L, Vargas V, Allende E, Bilbao I. Resection for hepatocellular carcinoma is a good option in Child-Turcotte-Pugh class A patients with cirrhosis who are eligible for liver transplantation. Liver Transpl 2005;11:1242–1251.
6. Sala M, Fuster J, Llovet JM, Navasa M, Sole M, Varela M, Pons F, Rimola A, Garcia-Valdecasas JC, Bru C, Bruix J. High pathological risk of recurrence after surgical resection for hepatocellular carcinoma: an indication for salvage liver transplantation. Liver Transpl 2004;10:1294–1300.
7. Fong Y, Sun RL, Jarnagin W, Blumgart LH. An analysis of 412 cases of hepatocellular carcinoma at a Western center. Ann Surg 1999;229:790–800.
8. Facciuto ME, Koneru B, Rocca JP, Wolf DC, Kim-Schluger L, Visintainer P, Klein KM, Chun H, Marvin M, Rozenblit G, Rodriguez-Davalos M, Sheiner PA. Surgical treatment of hepatocellular carcinoma beyond Milan criteria. Results of liver resection, salvage transplantation, and primary liver transplantation. Ann Surg Oncol 2008;15:1383–1391.
9. Itamoto T, Nakahara H, Tashiro H, Ohdan H, Ochi M, Asahara T. Indication of partial hepatectomy for transplantable hepatocellular carcinoma with compensated cirrhosis. Am J Surg 2005;189:167–172.
10. Nakahara H, Itamoto T, Katayama K, Ohdan H, Hino H, Ochi M, Tashiro H, Asahara T. Indication of hepatectomy for cirrhotic patients with hepatocellular carcinoma classified as Child–Pugh class B. World J Surg 2005;29:734–738.
11. Liver Cancer Study Group of Japan. General rules for the clinical and pathological study of primary liver cancer. Tokyo:Kanehara, 2003.
12. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in cohort of 6336 patients and results of survey. Ann Surg 2004;240:205–213.
13. Song TJ, Ip EW, Fong Y. Hepatocellular carcinoma: current surgical management. Gastroenterology 2004;127:S248-260.
14. Kamiyama T, Nakanishi K, Yokoo H, Kamachi H, Tahara M, Suzuki T, Shimamura T, Furukawa H, Matsushita M, Todo S. Recurrence patterns after hepatectomy of hepatocellular carcinoma: implication of Milan criteria utilization. Ann Surg Oncol 2009;16:1560–1571.
15. Lu SN, Wang JH, Liu SL, Hung CH, Chen CH, Tung HD, Chen TM, Huang WS, Lee CM, Chen CC, Changchien CS. Thrombocytopenia as surrogate for cirrhosis and a marker for the identification of patients at high-risk for hepatocellular carcinoma. Cancer 2006;107:2212–2222.
16. Kubo S, Tanaka H, Shuto T, Takemura S, Yamamoto T, Uenishi T, Tanaka S, Ogawa M, Sakabe K, Yamazaki K, Hirohashi K. Correlation between low platelet count and multicentricity of hepatocellular carcinoma in patients with chronic hepatitis C. Hepatol Res 2004;4:221–225.
17. Lok AS, Seeff LB, Morgan TR, di Bisceglie AM, Sterling RK, Curto TM, Eversion GT, Lindsay KL, Lee WM, Bonkovsky HL, Dienstag JL, Ghany MG, Morishima C, Goodman ZD. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis-C-rerated advanced liver disease. Gastroenterology 2009;136:138–148.
18. Kobayashi M, Ikeda K, Kawamura Y, Yatsuji H, Hosaka T, Sezaki H, Akuta N, Suzuki F, Suzuki Y, Saitoh S, Arase Y, Kumada H. High serum des-gamma-carboxy prothrombin level predicts poor prognosis after radiofrequency ablation of hepatocellular carcinoma. Cancer 2009;115:571–580.
19. Llovet JM, Burroughs A, Bruix J. Hapatocellular carcinoma. Lancet 2003;362:1907–1917.
20. Ercolani G, Grazi GL, Ravaioli M, Del Gaudio M, Gardini A, Cescon M, Varotti G, Cetta F, Cavallari A. Liver resection for hepatocellular carcinoma on cirrhosis: univariate and multivariate analysis of risk factors for intrahepatic recurrence. Ann Surg 2003;237:536–543.
21. Yu AS, Keeffe EB. Management of hepatocellular carcinoma. Rev Gastroenterol Disord 2003;3:8–24.
22. Tung-Ping Poon R, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. Ann Surg 2000;232:10–24.
23. Yao FY, Kerlan RK Jr, Hirose R, Davern TJ 3rd, Bass NM, Feng S, Peters M, Terrault N, Freise CE, Ascher NL, Roberts JP. Excellent out come following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. Hepatology 2008;48:819–827.
24. Itamoto T, Nakahara H, Amano H, Kohashi T, Ohdan H, Tashiro H, Asahara T.. Repeated hepatectomy for recurrent hepatocellular carcinoma. Surgery 2007;141:589–597.
25. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implication for strategy of salvage liver transplantation. Ann Surg 2002;235:373–382.
26. Belghiti J, Cortes A, Abdalla EK, Regimbeau JM, Prakash K, Durand F, Sommacale D, Dondero F, Lesurtel M, Sauvanet A, Farges O, Kianmanesh R. Resection prior to liver transplantation for hepatocellular carcinoma. Ann Surg 2003;238:885–893.
27. Adam R, Azoulay D, Castaing D, Eshkenazy R, Pascal G, Hashizume K, Samuel D, Bismuth H. Liver resection as a bridge to transplantation for hepatocellular carcinoma on cirrhosis: a reasonable strategy? Ann Surg 2003;238:508–519.
28. Ravaioli M, Grazi GL, Piscaglia F, Trevisani F, Cescon M, Ercolani G, Vivarelli M, Golfieri R, Grigioni AD, Panzini I, Morelli C, Bernardi M, Bolondi L, Pinna AD. Liver Transplantation for Hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. Am J Transpl 2008; 8:2547–2557.

29. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T, Roayaie S, Schwartz ME, Grazi GL, Adam R, Neuhaus P, Salizzoni M, Bruix J, Former A, De Carlis L, Cillo U, Burroughs AK, Troisi R, Rossi M, Gerunda GE, Lerut J, Belgiti J, Boin I, Gugenheim J, Rochling F, Van Hoek B, Majino P. Predicting survival after liver transplantation in patients with hepatocelllular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35–43.
30. Ito T, Takada Y, Ueda M, Haga H, Maetani Y, Oike F, Ogawa K, Sakamoto S, Ogura Y, Egawa H, Tanaka K, Uemoto S. Expansion of selection criteria for patients with hepatocellular carcinoma in living donor liver transplantation. Liver Transpl 2007;13:1637–1644.

Ann Surg Oncol (2012) 19:418–425
DOI 10.1245/s10434-011-1866-1

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Impact of Pegylated Interferon Therapy on Outcomes of Patients with Hepatitis C Virus-Related Hepatocellular Carcinoma After Curative Hepatic Resection

Yoshisato Tanimoto, MD[1], Hirotaka Tashiro, MD[1], Hiroshi Aikata, MD[2], Hironobu Amano, MD[1], Akihiko Oshita, MD[1], Tsuyoshi Kobayashi, MD[1], Shintaro Kuroda, MD[1], Hirofumi Tazawa, MD[1], Shoichi Takahashi, MD[2], Toshiyuki Itamoto, MD[3], Kazuaki Chayama, MD[2], and Hideki Ohdan, MD[1]

[1]Department of Gastroenterological Surgery, Hiroshima University Hospital, Hiroshima, Japan; [2]Department of Gastroenterology, Hiroshima University Hospital, Hiroshima, Japan; [3]Department of Surgery, Prefectural Hiroshima Hospital, Hiroshima, Japan

ABSTRACT

Background. Several published reports investigating the effects of interferon (IFN) therapy on survival and tumor recurrence after curative resection of hepatocellular carcinoma (HCC) have been inconclusive. The aim of this study is to investigate the efficacy of pegylated-IFN (peg-IFN) therapy after curative hepatic resection for HCC in patients infected with hepatitis C virus (HCV).

Methods. Data from 175 patients who underwent curative hepatic resection for HCC associated with HCV were retrospectively collected and analyzed; 75 patients received peg-IFN therapy after surgery, whereas 100 patients did not receive IFN therapy. To overcome biases resulting from the different distribution of covariates in the two groups, a one-to-one match was created using propensity score analysis. After matching, patient outcomes were analyzed.

Results. After one-to-one matching, patients ($n = 38$) who received peg-IFN therapy after surgery and patients ($n = 38$) who did not receive IFN therapy had the same preoperative and operative characteristics. The 3- and 5-year overall survival rates of patients who received peg-IFN therapy after hepatic resection were significantly higher than those of patients who did not receive IFN therapy ($P = 0.00135$). The 3- and 5-year overall survival rates were 100 and 91.7% and 76.6 and 50.6% in the peg-IFN group and non-IFN group, respectively. There was no significant difference in disease-free survival between the two matched groups ($P = 0.886$).

Conclusion. Peg-IFN therapy may be effective as an adjuvant chemopreventive agent after hepatic resection in patients with HCV-related HCC.

First Received: 14 February 2011;
Published Online: 28 June 2011

H. Tashiro, MD
e-mail: htashiro@hiroshima-u.ac.jp

Hepatic resection is a well-accepted therapy for hepatocellular carcinoma (HCC), but many patients show cancer recurrence and the cumulative 5-year HCC recurrence rate exceeds 70%.[1–3] This high incidence of tumor recurrence after hepatic resection remains a major drawback. Some benefits of interferon (IFN) therapy on tumor recurrence and survival have been reported.[4–10] IFN suppresses replication of hepatitis C virus (HCV) and exerts a tumoricidal effect on a number of tumors, including HCC.[10,11] However, several randomized controlled trials (RCTs) have revealed inconclusive results regarding the effects of IFN on survival and tumor recurrence after curative resection or ablation of HCC, either because the effects were not statistically significant or because they were considered only with respect to defined subpopulations.[12–15]

Recently, combination therapy consisting of pegylated interferon (peg-IFN) plus ribavirin (RBV) has been developed, and the effect of this combination has been reported to be higher than that of conventional IFN therapy.[16,17] Peg-IFN has an extended serum half-life that provides viral suppression for 7 days, thus allowing weekly administration and enhanced clinical efficacy.[17] Most Japanese patients infected with HCV are infected with HCV genotype Ib and have high viral load. Moreover, treatment with conventional IFN is complicated by a low sustained viral response (SVR) rate of 20–30%.[18–20]

However, peg-IFN plus RBV combination therapy has good tolerability in Japanese patients with HCV and resulted in an SVR rate of approximately 40–50%.[21–23] The impact of adjuvant immunotherapy with IFN after curative resection of HCC is debatable, and few studies have investigated the effects of peg-IFN plus RBV combination therapy on survival and recurrence after curative resection of HCC.

In the present study, we aim to investigate the impact of peg-IFN plus RBV combination therapy on survival and HCC recurrence after curative resection in patients infected with HCV.

PATIENTS AND METHODS

Patients and HCV Diagnosis

From June 2003 to June 2009, 370 HCC patients underwent hepatectomy as initial treatment at the Department of Gastroenterological Surgery, Hiroshima University Hospital, Japan. Of the 370 patients, 175 patients who were HCV RNA-positive/hepatitis B surface antigen-negative underwent curative hepatectomy. Of the 175 patients, 75 patients received IFN therapy after hepatectomy, and 100 patients did not receive any IFN therapy. Of the 75 patients who received IFN, 20 patients who received IFNs such as IFN-α or IFN-β were excluded. Of the 55 patients who received peg-IFN therapy, 43 patients who started peg-IFN within 9 months after curative resection were enrolled in this analysis. Twenty-four patients who had early recurrence of HCC within 9 months after surgery were excluded from the 100 patients who did not receive any IFN therapy, because these patients could lose the opportunity to receive IFN therapy for HCC recurrence if these patients were assigned to the peg-IFN therapy. Consequently, 119 patients were eventually enrolled in this study. Of these 119 patients, 43 received peg-IFN therapy within 9 months after hepatectomy, and 76 did not receive any IFN therapy.

Curative hepatectomy was defined as removal of all recognizable tumors. HCV RNA levels were measured by quantitative reverse-transcription polymerase chain reaction (RT-PCR; Amplicor, Roche Diagnostic Systems, CA, USA). HCV genotype was determined by PCR using a mixed primer set derived from the nucleotide sequences of the NS5 region. HCV negativity was evaluated by quantitative RT-PCR. The lower limit of the assay was 5 kIU/ml (equivalent to 5,000 copies/ml) in the quantitative method and 50 IU/ml (equivalent to 50 copies/ml) in the qualitative method. SVR was defined as undetectable HCV RNA at 24 weeks after completion of IFN therapy. The study was approved by the concerned institutional review boards. Written informed consent was obtained from all patients.

Preoperative Diagnosis and Evaluation of HCC

Hepatocellular carcinoma was diagnosed on the basis of routine imaging modalities such as Doppler ultrasonography (US), computed tomography (CT) during hepatic angiography (CTHA) and CT during arterial portography (CTAP), and magnetic resonance imaging. Tumor stage, liver damage classification, and surgical procedures were defined according to the General Rules for Clinical and Pathologic Study of Primary Liver Cancer, fifth edition, by the Liver Cancer Study Group of Japan.[24]

Hepatectomy

The surgical procedure was determined according to tumor extent and hepatic reserve function. Liver function was assessed by liver damage classification, Child–Pugh classification, and indocyanine green retention rate at 15 min (ICGR 15).[25,26] If permitted by liver function, anatomic resection was performed.[27,28] In patients with insufficient hepatic reserve, limited resection was performed. We divided the liver parenchyma by using an ultrasonic dissector.[29] Postoperative complications were graded according to the method described by Clavien et al.[30]

Follow-Up

Follow-up evaluation after the surgery consisted of monthly blood chemistry tests and measurements of levels of tumor markers, including alpha-fetoprotein and des-gamma-carboxy prothrombin. Patients were examined by US every 3 months and by CT every 6 months. When recurrence was indicated by any of these examinations, patients were examined by CTAP and CTHA.

Patient Selection for IFN Therapy

Patients with HCV genotype 1b in the IFN group received peg-IFNα-2b (Pegintron; Schering-Plough, NJ, USA) at weekly dosage of 1.5 μg/kg subcutaneously for 48 weeks. Daily RBV (Rebetrol, Schering-Plough) was administered orally for 48 weeks, and the dosage was adjusted according to weight (600 mg for patients weighing $\leq$60 kg, 800 mg for those weighing 60–80 kg). Patients with HCV genotype 2 received IFN monotherapy for 24 weeks. Blood samples were obtained every 4 weeks and analyzed for HCV RNA levels. All patients were informed about IFN therapy after hepatectomy, and only consenting patients received IFN therapy. The eligibility criteria for IFN therapy were as follows: (1) detectable serum HCV RNA level, (2) Eastern Cooperative Oncology

Group (ECOG) performance score of 0 or 1, (3) platelet count ≥70,000/μl, (4) patients with no uncompensated cirrhosis (Child class C), and (5) hemoglobin concentration ≥10 g/dl. Peg-IFN therapy was commenced within 24 weeks of surgery or after the eligibility criteria were fulfilled.

Safety Assessments and Dose Modification of Peg-IFN Therapy

Adverse events were graded as mild, moderate, severe, or potentially life-threatening according to a modified World Health Organization grading system. The dose of peg-IFN was decreased by 50% and that of RBV was lowered to half in case of severe adverse events or when laboratory results revealed any of the following: hemoglobin concentration <10 g/dl in patients with no cardiac disease, decrease in hemoglobin concentration >2 g/dl in patients with cardiac disease, white blood cell count <3,000/mm^3, or platelet count <50,000/mm^3. Full dosage could be resumed on resolution of the adverse events. Treatment was permanently discontinued in case of life-threatening events or when laboratory results revealed hemoglobin concentration <7.5 g/dl after 4 weeks of dose reduction, white blood cell count <1,500/mm^3, or platelet count <30,000 mm^3.

Treatment for Recurrence

Patients with intrahepatic HCC recurrence were managed with ablative therapies such as radiofrequency ablation (RFA), percutaneous ethanol injection therapy, transarterial chemoembolization, or surgery including living-donor liver transplantation according to the tumor characteristics (number, size, and location of the tumors) and liver function.

Statistical Analyses

Categorical variables were compared using the chi-square test, and continuous variables were compared using the Mann–Whitney *U*-test. Overall survival and disease-free survival analyses were performed using Kaplan–Meier methods; comparisons between different groups were performed using the log-rank test. *P* value of less than 0.05 was considered significant. Calculations were performed using SPSS software (version 16; SPSS Inc., IL, USA).

Propensity analysis was performed using logistic regression to create a propensity score for the IFN and non-IFN therapy groups.[31,32] Variables entered in the propensity model were age, sex, HCV genotype, liver function test, tumor factors, and operative factors. The model was then used to provide a one-to-one match between the two groups by using the nearest-neighbor matching method.[33,34] Survival and disease-free survival analyses were performed in each matched subgroup to assess the impact of peg-IFN therapy on mortality after adjusting for the confounding factors.

RESULTS

Characteristics and Postoperative Course of the Entire Population

Differences in the characteristics of patients who received peg-IFN therapy after hepatic resection and those who did not receive IFN therapy after hepatic resection are presented in Table 1. Patients who received peg-IFN therapy were younger (65 vs. 71 years; $P = 0.0003$). Regarding tumor characteristics, there was no significant difference between the two groups. Operation times tended to be longer in patients who received peg-IFN therapy than in those who did not receive IFN therapy (260 vs. 242 min; $P = 0.05$). There were no hospital-related deaths in this study. Postoperative complications did not differ between the two groups. In the entire population, the 3- and 5-year overall survival rates of patients who received peg-IFN therapy after hepatic resection were significantly higher than those of patients who did not receive IFN therapy ($P = 0.0024$) (Fig. 1a). However, there was no significant difference in disease-free survival between the two groups ($P = 0.795$) (Fig. 1b).

Results After Propensity Score Matching

Characteristics of the patients after propensity score analysis are presented in Table 1. Thirty-eight of the 43 patients who received peg-IFN therapy after hepatic resection and an equal number of the 76 patients who did not receive IFN therapy were matched after covariate adjustment. The study group of 76 patients was well matched; in particular, all covariates that significantly affected recurrence and postoperative liver failure in the entire study group were equally distributed between the two matched groups. Matched patients who received peg-IFN therapy after hepatic resection had similar total bilirubin and serum albumin levels and similar platelet counts to matched patients who did not receive IFN therapy. Similarly, the tumor characteristics, the surgical procedure, operation times, and blood loss during the operation in matched patients who received peg-IFN therapy were almost similar to those in patients who did not receive IFN therapy. There were no hospital-related deaths in the matched groups. Postoperative complications also did not differ between the two groups. The median follow-up period for patients who received peg-IFN and those who

TABLE 1 Baseline characteristics and operative data on patients who underwent hepatectomy: data are reported for whole study and for the matched study population after propensity score analysis

	Overall series		*P* value	Propensity-matched series		*P* value
	IFN (+) $n = 43$	IFN (−) $n = 76$		Peg-IFN (+) $n = 38$	IFN (−) $n = 38$	
Age (years)	65 (53–78)	71 (48–83)	0.0003	65.5 (53–75)	69 (51–80)	0.2
Sex (male/female)	27/16	47/29	0.918	23/15	25/13	0.634
Preoperative IFN	24 (55.8%)	29 (38.1%)	0.06	20 (52.6%)	14 (36.8%)	0.16
HCV genotype			0.876			0.6
1b	34	61		29	27	
2b	9	15		9	11	
Diabetes mellitus	11 (25.6%)	22 (28.9%)	0.856	11 (28.9%)	13 (34.2%)	0.621
ECOG PS			0.831			0.644
0	39	68		36	35	
1	4	8		2	3	
Platelet (104/mm^3)	10.3 (3.3–26.6)	10.3 (3.8–40.3)	0.381	9.75 (3.3–21.5)	11.2 (3.8–40.3)	0.454
T-Bil (mg/dl)	0.7 (0.3–1.4)	0.8 (0.3–1.7)	0.292	0.7 (0.4–1.4)	0.7 (0.3–1.7)	0.798
AST (IU/l)	42 (18–121)	48 (16–150)	0.152	43.5 (18–127)	41.5 (6–150)	0.567
ALT (IU/l)	38 (13–127)	41.5 (10–196)	0.987	40.5 (11–127)	37.5 (10–196)	0.226
Albumin (g/dl)	3.8 (2.8–5.2)	3.8 (2.5–4.9)	0.215	3.8 (2.8–5.2)	3.8 (2.5–4.5)	0.469
ICGR 15 (%)	17.9 (7.4–77.4)	18.7 (4.6–50.5)	0.734	17.65 (7.4–40.0)	17.55 (4.6–40.0)	0.561
AFP (ng/ml)	11.6 (0.5–3405)	27.6 (0.5–36572)	0.176	13.95 (0.5–3405)	22.9 (0.5–513)	0.635
Child–Pugh grade			0.665			0.556
A	41 (95.3%)	69 (90.8%)		37 (97.4%)	36 (94.7%)	
B	2 (4.7%)	7 (9.2%)		1 (2.6%)	2 (5.3%)	
Hepatic resection			0.322			0.373
Hr0	20 (46.5%)	49 (64.5%)		18 (47.4%)	23 (60.5%)	
HrS	13 (30.2%)	18 (23.7%)		12 (31.6%)	9 (23.7%)	
Hr1	3 (7.0%)	4 (5.3%)		2 (5.3%)	3 (7.9%)	
Hr2	7 (16.3%)	5 (6.6%)		6 (15.8%)	2 (5.3%)	
Hr3	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Operation time (min)	260 (128–623)	242 (90–580)	0.0514	257 (128–623)	247.5 (90–580)	0.18
Blood loss (ml)	200 (20–1900)	225 (10–960)	0.996	210 (20–1900)	210 (10–960)	0.803
Postoperative complications			0.933			0.798
IIIa	4	6		2	2	
IIIb	1	1		1	1	
IVa	1	1		1	0	
Stage			0.315			0.293
I	14 (32.6%)	19 (25.0%)		13 (34.2%)	9 (23.7%)	
II	18 (41.9%)	44 (57.9%)		15 (39.5%)	23 (60.5%)	
III	9 (20.9%)	12 (15.8%)		9 (23.7%)	6 (15.8%)	
IV-A	2 (4.7%)	1 (1.3%)		1 (2.6%)	0 (0.0%)	
Single tumor	28 (65.1%)	57 (75.0%)	0.252	25 (65.8%)	29 (76.3%)	0.312
Tumor size			0.712			0.589
≥3 cm	15 (34.9%)	24 (31.6%)		10 (26.3%)	8 (21.1%)	
<3 cm	28 (65.1%)	52 (68.4%)		28 (73.7%)	30 (78.9%)	
Vascular invasion	4 (9.3%)	3 (3.9%)	0.233	3 (7.9%)	0 (0.0%)	0.239

Continuous variables expressed as median (range)

Hepatic resection and stage were according to General Rules for the Clinical and pathological Study of Primary Liver Cancer, by Liver cancer Study Group of Japan, 5th edition, Kanehara Co., Ltd

Hr0: limited resection, HrS: segmentectomy, Hr1: sectionectomy, Hr2: hemihepatectomy, Hr3: more than hemihepatectomy

T-Bil total bilirubin, *PS* performance status, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ICGR 15* indocyanine green retention rate at 15 min, *AFP* alpha-fetoprotein, did not receive IFN therapy was 3.8 (1.2–6.9) and 3.5 (1.3–6.8) years, respectively. In the matched study groups, the 3- and 5-year overall survival rates of patients who received peg-IFN therapy after hepatic resection were significantly higher than those of patients who did not receive IFN therapy ($P = 0.00135$) (Fig. 1c). However, there was no significant difference in disease-free survival between the two matched groups ($P = 0.886$) (Fig. 1d).

In the matched 38 patients of the peg-IFN group, peg-IFN therapy was initiated at a median of 4.3 (0.9–9.6) months after hepatic resection. Thirty-one of 38 HCC patients began peg-IFN therapy within 6 months after hepatectomy. Seven patients required more than 6 months to commence peg-IFN therapy. Two patients required a longer time to recover platelet counts of more than 70,000/μl. Five patients required a longer time to decide to receive peg-IFN therapy. Sixteen (42.1%) of the matched 38 patients who received peg-IFN therapy after hepatectomy attained SVR. Among 16 patients who attained SVR, 10 patients received full-dose peg-IFN therapy without dose reduction, whereas 6 patients received a reduced dose of peg-IFN and/or RBV until completion of treatment. Nine patients discontinued peg-IFN therapy because of adverse events such as thrombocytopenia and neutropenia ($n = 2$), skin eruption ($n = 1$), depression ($n = 2$), and severe malaise ($n = 4$). Three patients discontinued peg-IFN therapy because of HCC recurrence. Adherence to peg-IFN therapy was 68.4% in this study. No life-threatening adverse events were observed, and none of the total 15 deaths in both sets of matched patients were related to the IFN treatment or to surgical procedures. The 3- and 5-year overall survival rates of patients ($n = 16$) who attained SVR after peg-IFN therapy were 100% and 100%, respectively; those of patients who did not attain SVR ($n = 22$) were 100 and 85.7%, respectively; and those of patients who did not receive IFN therapy were 76.6 and 50.6%, respectively. There was a statistically significant difference in overall survival among the three groups ($P = 0.005$) (Fig. 2a). However, there was no statistically significant difference in disease-free survival among the three groups ($P = 0.90$) (Fig. 2b).

Table 2 presents the patterns of cancer recurrence and the treatment details of the recurrences in both groups. Twenty-one (55.3%) of the patients who received peg-IFN therapy after hepatic resection and 17 (44.7%) of the patients who did not receive IFN therapy had HCC recurrences after hepatic resection. Regarding the pattern of recurrence, the proportion of patients who had multiple

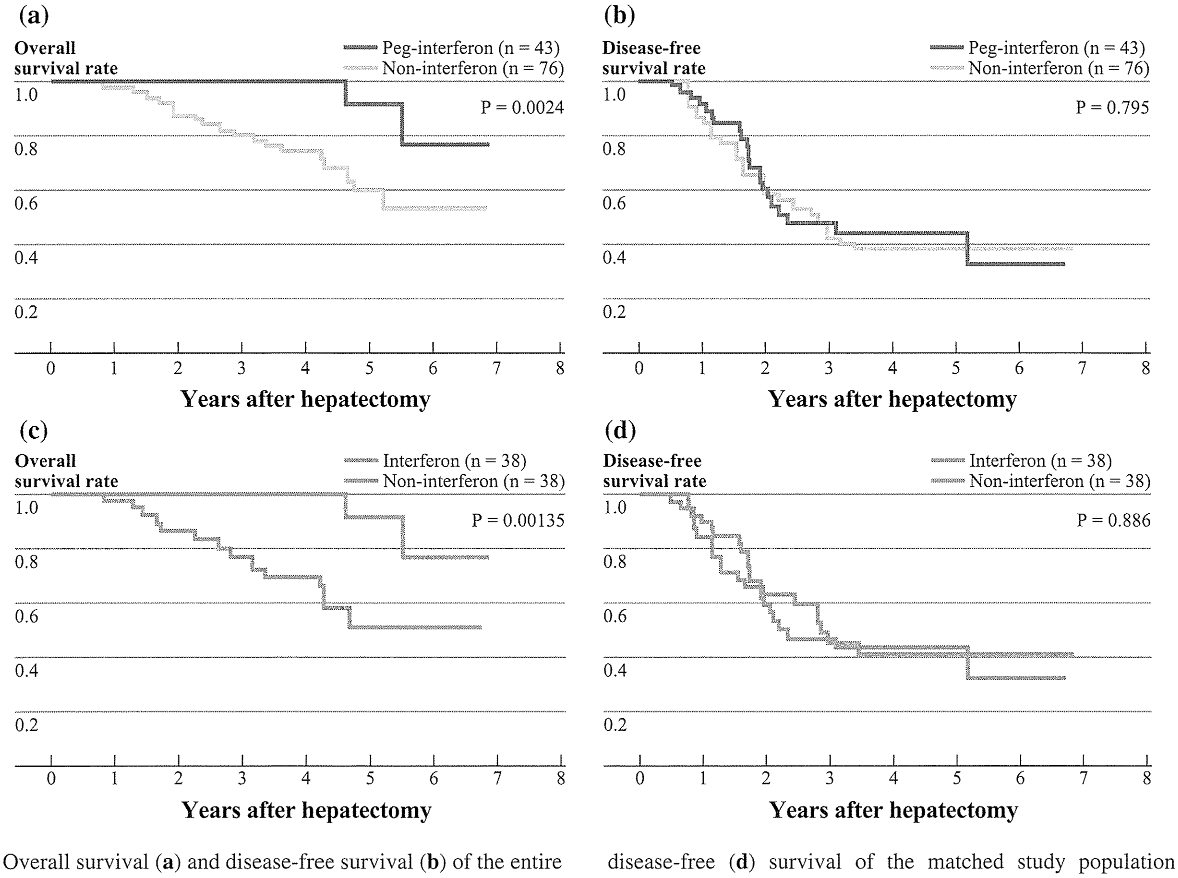

FIG. 1 Overall survival (**a**) and disease-free survival (**b**) of the entire study population of 175 patients with hepatitis C-related HCC with respect to IFN therapy after hepatic resection. Overall survival (**c**) and disease-free (**d**) survival of the matched study population of 76 patients with hepatitis C-related HCC with respect to IFN therapy after hepatic resection

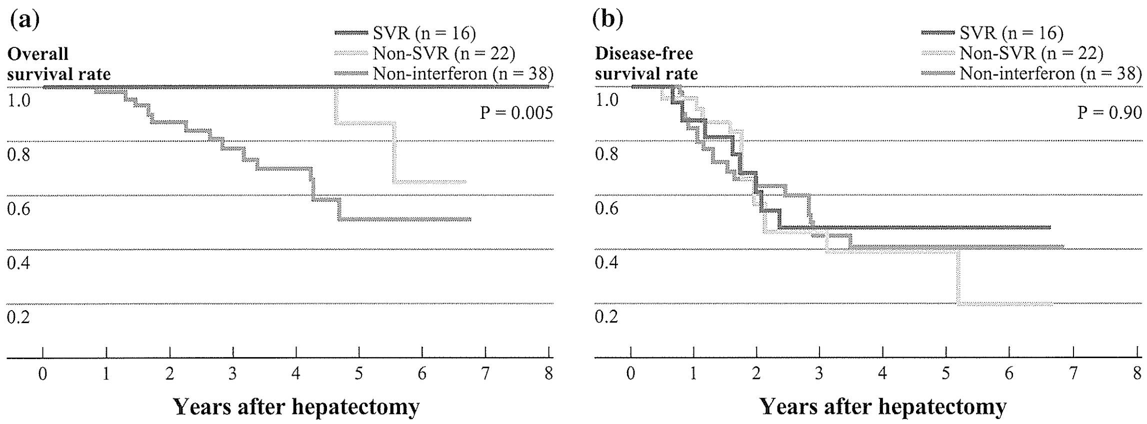

FIG. 2 Overall survival and disease-free survival of patients with hepatitis C-related HCC with respect to SVR after IFN therapy

intrahepatic recurrences (more than four nodules) was significantly lower in the peg-IFN group than in the non-IFN group ($P = 0.0047$). The proportion of patients in whom surgery or RFA was selected for treatment was significantly higher in the peg-IFN group than in the non-IFN group ($P = 0.0346$). Furthermore, regarding re-recurrence of HCC after treatment of the first-recurrent HCC, the 1-year disease-free survival rates of patients after treatment of the first-recurrent HCC was 48.5% in patients ($n = 21$) who received peg-IFN therapy and 12.5% in patients ($n = 17$) who did not receive IFN therapy. There was a statistically significant difference in disease-free survival between the two groups ($P = 0.0012$) (Fig. 3).

A comparison of results of the preoperative liver function test with those of postoperative 1-year liver function tests is presented in Table 3. In patients who received peg-IFN therapy, total bilirubin levels 1 year after surgery were significantly decreased compared with preoperative total bilirubin levels ($P = 0.018$), whereas in patients who did not receive IFN therapy, the total bilirubin level at 1 year after surgery was similar to the total bilirubin level before surgery ($P = 0.107$).

DISCUSSION

Our results revealed that peg-IFN therapy after hepatic resection improved the outcomes of HCV patients, although the interval of disease-free survival was not prolonged. Peg-IFN therapy after hepatectomy improved hepatic reserve function and suppressed multiple HCC recurrences (more than four nodules). Furthermore, re-recurrence after treatment of first-recurrent HCC after hepatic resection was significantly suppressed in the peg-IFN group compared with that in the non-IFN group. IFN has been reported to exert antitumor effects. IFN increases natural killer cell activity and exhibits antiangiogenic properties.[35,36] IFN has also been reported to be effective in eradicating HCV RNA

TABLE 2 Recurrence and treatments for recurrence after hepatic resection

	Peg-IFN (+) ($n = 38$)	IFN (−) ($n = 38$)	*P* value
HCC recurrence[a]: yes	21 (55.3%)	17 (44.7%)	0.359
Pattern of recurrence[b]			0.0047
Intrahepatic (single)	9 (42.9%)	8 (47.1%)	
Intrahepatic (2–3)	10 (47.6%)	1 (5.9%)	
Intrahepatic (multiple)	2 (9.5%)	8 (47.1%)	
Main modalities[b]			0.0346
Repeat hepatectomy	8 (38.1%)	2 (11.8%)	
RFA	8 (38.1%)	4 (23.5%)	
TACE	5 (23.8%)	11 (64.7%)	

peg-IFN pegylated interferon, *RFA* radiofrequency ablation, *TACE* transcatheter arterial chemoembolization

[a] Data expressed as number of patients (percentage of total patients)

[b] Data expressed as number of patients (percentage of patients who had a recurrence)

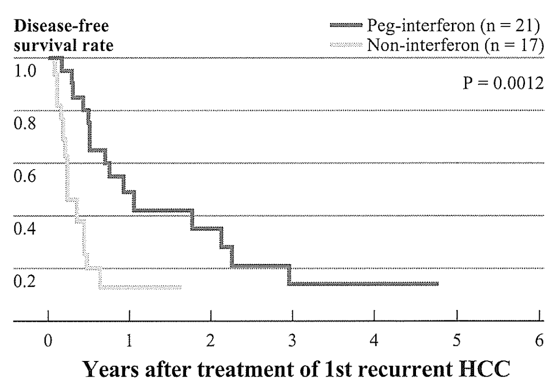

FIG. 3 Comparison of disease-free survival rate after treatment of first-recurrent HCC in patients who received peg-IFN therapy or in those who did not receive IFN therapy

TABLE 3 Comparison of preoperative liver function with 1-year liver function after hepatic resection

	Peg-IFN (+)		*P* value	IFN (−)		*P* value
	Preoperative	1 Year after surgery		Preoperative	1 Year after surgery	
T-Bil (mg/dl)	0.82 ± 0.29	0.71 ± 0.26	0.0189	0.81 ± 0.32	0.92 ± 0.35	0.107
AST (IU/l)	50.1 ± 24.1	45.8 ± 23.5	0.310	42.1 ± 18.9	56.1 ± 26.7	0.0110
ALT (IU/l)	51.3 ± 28.6	36.4 ± 22.8	0.00809	40.3 ± 24.3	49.7 ± 25.8	0.0918
Albumin (g/dl)	3.89 ± 0.80	3.99 ± 0.71	0.251	3.73 ± 0.45	3.75 ± 0.44	0.807

peg-IFN pegylated interferon, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

from serum and hepatic tissue, thereby preventing deterioration of liver function in patients with HCV infection.[37] IFN prevents worsening of compensated cirrhosis.[18,37] Our results are compatible with those reported in those studies. In the peg-IFN group, most patients with HCC recurrence could undergo curative treatments such as repeat hepatectomy or RFA as a recurrence treatment, because the number of recurrent tumors was usually limited to three. IFN therapy appears to increase survival not only by improving residual liver function and increasing the possibility of radical treatment of recurrences but also by suppressing re-recurrence after the first recurrence of HCC.

The current study also revealed that the overall survival of patients with SVR was significantly better than that of patients without SVR. This result suggests that IFN prolongs the outcomes of patients with HCC after hepatic resection by causing remission of active hepatitis and eradication of HCV RNA in patients who attained SVR after hepatic resection.

In this study, to clarify the impact of peg-IFN therapy on outcomes of HCV-related HCC after hepatic resection, patients who received IFNs such as IFN-α or IFN-β were excluded. RCTs investigating adjuvant effects of IFN after resection or ablation of HCC were performed using IFN-α. Few studies have investigated the effects of peg-IFN plus RBV combination therapy on survival and recurrence after curative resection of HCC. Combination therapy with peg-IFN and RBV has recently been developed, and peg-IFN therapy has resulted in significantly higher SVR rates and better tolerability than treatment with IFN-α.[21,23] In our study, incidence of SVR after hepatic resection was 42.1%, which was higher than that in previous studies that reported an SVR rate of 0–10%.[12–14] The compliance of patients to peg-IFN therapy observed in the present study (68.4%) was higher than that reported elsewhere (approximately 40%).[14] This enhanced efficacy of the peg-IFN formulations might contribute to the prolonged survival of HCC patients after hepatic resection.

In this study, HCC patients who received peg-IFN therapy within 9 months after surgery were enrolled, and HCC patients who experienced recurrence of HCC within 9 months after hepatic resection were excluded from the non-IFN group, because these patients could lose the opportunity to receive IFN therapy for HCC recurrence on being assigned to the peg-IFN therapy group.

Before matching by using the propensity score, the clinical characteristics of the entire study population that can strongly influence outcomes differed significantly between the peg-IFN group and non-IFN group. The proportion of older patients was higher in the non-IFN group than in the peg-IFN group, whereas the proportion of patients who had longer operation times tended to be lower in the non-IFN group than in the peg-IFN group. To overcome bias due to the different distribution of the severity of liver function impairment between the two groups, a one-to-one match was created using propensity score analysis. After matching by propensity score, prognostic variables were appropriately handled, and there was no significant difference in prognostic factors between the two matched groups. This study had a limitation related to the small sample size after propensity score matching. To overcome this, further examination with larger sample sizes is necessary, and the potential efficacy of peg-IFN therapy must be validated in larger prospective RCTs.

CONCLUSIONS

Several previous RCTs investigating the effects of IFN on survival and tumor recurrence after hepatic resection were inconclusive. However, in the current study, peg-IFN therapy following hepatic resection improved the survival rates of hepatectomized patients with HCV-related HCC. The results of this study suggest that peg-IFN therapy is effective as an adjuvant chemopreventive agent after hepatic resection in patients with HCV-related HCC.

ACKNOWLEDGMENT The authors thank Prof. Junko Tanaka of the Department of Epidemiology, Infectious Disease Control and Prevention, Hiroshima University, for assistance in performing the propensity score analysis.

CONFLICT OF INTEREST The authors have no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements) that might pose a conflict of interest related to the submitted manuscript.

REFERENCES

1. Poon RTP, Fan ST, Lo CM, Liu CL, Wong J. Intrahepatic recurrence after curative resection of hepatocellular carcinoma: long-term results of treatment and prognostic factors. *Ann Surg*. 1999;229:216–22.
2. Minagawa M, Makuuchi M, Takayama T, Kokudo N. Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. *Ann Surg*. 2003;238:703–10.
3. Itamoto T, Nakahara H, Amano H, et al. Repeat hepatectomy for recurrent hepatocellular carcinoma. *Surgery*. 2007;141:589–97.
4. Ikeda K, Saitoh S, Arase Y, Chayama K, et al. Effects of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. *Hepatology*. 1999;29:1124–30.
5. Imai Y, Kawata S, Tamura S, et al. Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. Osaka Hepatocellular Carcinoma Prevention Study Group. *Ann Intern Med*. 1998;129:94–9.
6. Camma C, Giunta M, Andreone P, Craxì A. Interferon and prevention of hepatocellular carcinoma in viral cirrhosis: an evidence-based approach. *J Hepatol*. 2001;34:593–602.
7. Nishiguchi S, Shiomi S, Nakatani S, et al. Prevention of hepatocellular carcinoma in patients with chronic active hepatitis C and cirrhosis. *Lancet*. 2001;357:196–7.
8. Tomimaru Y, Nagano H, Eguchi H, et al. Effects of preceding interferon therapy on outcome after surgery for hepatitis C virus-related hepatocellular carcinoma. *J Surg Oncol*. 2010;102: 308–14.
9. Jeong SC, Aikata H, Katamura Y, et al. Low-dose intermittent interferon-alpha therapy for HCV-related liver cirrhosis after curative treatment of hepatocellular carcinoma. *World J Gastroenterol*. 2007;13:5188–95.
10. Jeong SC, Aikata H, Kayamura Y, et al. Effects of a 24-week course of interferon-α therapy after curative treatment of hepatitis C virus-associated hepatocellular carcinoma. *World J Gastroenterol*. 2007;13:5343–50.
11. Harada H, Kitagawa M, Tanaka N, et al. Anti-oncogenic and oncogenic potentials of interferon regulatory factors-1 and -2. *Science*. 1993;259:971–4.
12. Liedtke C, Grogner N, Manns MP, Trautwein C. Interferon-alpha enhances TRAIL-mediated apoptosis by up-regulating caspase-8 transcription in human hepatoma cells. *J Hepatol*. 2006;44: 342–9.
13. Kubo S, Nishiguchi S, Hirohashi K, Tanaka H, Shuto T, Kinoshita H. Randomized clinical trial of long-term outcome after resection of hepatitis C virus-related hepatocellular carcinoma by postoperative interferon therapy. *Br J Surg*. 2002;89:418–22.
14. Ikeda K, Arase Y, Saitoh S, et al. Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of primary tumor-a prospective randomized study of hepatitis C virus-related liver cancer. *Hepatology*. 2000;32: 228–32.
15. Mazzaferro V, Romito R, Schiavo M, et al. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. *Hepatology*. 2006;44:1543–54.
16. Lo CM, Liu CL, Chan SC, et al. A randomized, controlled trial of postoperative adjuvant interferon therapy after resection of hepatocellular carcinoma. *Ann Surg*. 2007;245:831–42.
17. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *Lancet*. 2001;358:958–65.
18. Fried MW, Shiffman ML, Rajender Reddy K, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002;347:975–82.
19. Yoshida H, Arakawa Y, Sata M, et al. Interferon therapy prolonged life expectancy among chronic hepatitis C patients. *Gastroenterology*. 2002;123:483–91.
20. Kiyosawa K, Uemura T, Ichijo T, et al. Hepatocellular carcinoma: recent trends in Japan. *Gastroenterology*. 2004;127: S17–26.
21. McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. *N Engl J Med*. 1998;339:1485–92.
22. Muir AJ, Bornstein JD, Killenberg PG. Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites. *N Eng J Med*. 2004;350:2265–71.
23. Shirakawa H, Matsumoto A, Joshita S, et al. Pretreatment prediction of virological response to peginterferon plus ribavirin therapy in chronic hepatitis c patients using viral and host factors. *Hepatology*. 2008;48:1753–60.
24. Kogure T, Ueno Y, Fukushima K, et al. Pegylated interferon plus ribavirin for genotype 1b chronic hepatitis C in Japan. *World J Gastroentrol*. 2008;14:7225–30.
25. Liver Cancer Study Group of Japan. General Rules for the Clinical and Pathological Study of Primary Liver Cancer. 5th ed. Tokyo: Kanehara; 2008.
26. Itamoto T, Nakahara H, Tashiro H, et al. Indications of partial hepatectomy for transplantable hepatocellular carcinoma with compensated cirrhosis. *Am J Surg*. 2005;189:167–72.
27. Oishi K, Itamoto T, Kobayashi T, et al. Hepatectomy for hepatocellular carcinoma in elderly patients aged 75 years or more. *J Gastrointest Surg*. 2009;13:695–701.
28. Makuuchi M, Hasegawa H, Yamazaki S. Ultrasonically guided subsegmentectomy. *Surg Gynecol Obstet*. 1985;161:346–50.
29. Yamamoto M, Takasaki K, Otsubo T, et al. Favorable surgical outcomes in patients with early hepatocellular carcinoma. *Ann Surg*. 2004;239:395–9.
30. Itamoto T, Katayama K, Nakahara H, Tashiro H, Asahara T. Autologous blood storage before hepatectomy for hepatocellular carcinoma with underlying liver disease. *Br J Surg*. 2003;90: 23–8.
31. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien–Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009;250:187–96.
32. Zinsmeister AR, Connor JT. Ten common statistical errors and how to avoid them. *Am J Gastroenterol*. 2008;103:262–6.
33. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41–55.
34. Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med*. 1997;127:757–63.
35. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to non-randomized control group. *Stat Med*. 1998;17:2265–81.
36. Brinkmann V, Geiger T, Alkan S, Heusser CH. Interferon alpha increases the frequency of interferon gamma-producing human CD4+T cells. *J Exp Med*. 1993;178:1655–63.
37. Wang L, Tang ZY, Qin LX, et al. High-dose and long-term therapy with interferon-alfa inhibits tumor growth and recurrence in nude mice bearing human hepatocellular carcinoma xenografts with high metastatic potential. *Hepatology*. 2000;32:43–8.
38. Shiratori Y, Shiina S, Teratani T, et al. Interferon therapy after tumor ablation improves prognosis in patients with hepatocellular carcinoma associated with hepatitis C. *Ann Intern Med*. 2003;138: 299–306.

Journal of Surgical Oncology 2011;104:3–9

Treatment Strategy for Early Hepatocellular Carcinomas: Comparison of Radiofrequency Ablation With or Without Transcatheter Arterial Chemoembolization and Surgical Resection

HIROTAKA TASHIRO, MD,[1]* HIROSHI AIKATA, MD,[2] KOJI WAKI, MD,[2] HIRONOBU AMANO, MD,[1] AKIHIKO OSHITA, MD,[1] TSUYOSHI KOBAYASHI, MD,[1] YOSHISATO TANIMOTO, MD,[1] SHINTARO KURODA, MD,[1] HIROFUMI TAZAWA, MD,[1] KAZUAKI CHAYAMA, MD,[2] TOSHIMASA ASAHARA, MD,[1] AND HIDEKI OHDAN, MD[1]

[1]*Department of Gastroenterological and Transplantation Surgery, Hiroshima University Hospital, Kasumi, Minami-ku, Hiroshima, Japan*
[2]*Department of Gastroenterology and Hepatology, Hiroshima University Hospital, Kasumi, Minami-ku, Hiroshima, Japan*

Background: The preferred choice between surgical treatment and radiofrequency ablation (RFA) for the treatment of small resectable hepatocelluar carcinoma (HCC) has become a subject for debate.
Methods: We compared the results of hepatic resection (n = 199) with those of RFA (n = 87), of which 69 patients were treated with transcatheter arterial chemoembolization followed by RFA, for 286 patients with 3 or fewer nodules, none of which exceeded 3 cm in diameter at Hiroshima University Hospital.
Results: In subgroup analysis of single HCC with tumor size exceeding 2 cm in Child-Pugh class A, the disease-free survival time was significantly longer in the surgical resection group than in the RFA group ($P = 0.048$). In the subgroups of a single and multiple HCC with tumor size $\leq$2 cm in Child-Pugh class A, the overall and disease-free survival rates were almost the same for the surgical resection and RFA groups ($P = 0.46$ and 0.58, respectively, in single HCC, and $P = 0.98$ and 0.98, respectively, in multiple HCC).
Conclusion: Surgical resection may provide better long-term disease-free survival than RFA in the subgroup of a single HCC exceeding 2 cm of Child-Pugh class A.
J. Surg. Oncol. 2011;104:3–9. © 2011 Wiley-Liss, Inc.

KEY WORDS: **early hepatocellular carcinoma; hepatectomy; radiofrequency ablation**

INTRODUCTION

Hepatocelluar carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer death worldwide [1]. Although the majority of cases are still found in Asia and Africa, recent studies have shown that the incidence and mortality rates of HCC are increasing in North America and Europe [2]. Over the past two decades, great progress has been made in the diagnosis of HCC using non-invasive diagnostic modalities, and it is feasible to make early detection of HCC. Current options for the treatment of the early HCC consist of surgical resection, liver transplantation, transcatheter arterial chemoemolization (TACE), and percutaneous tumor ablation. These modalities have all been used for HCC patients according to the clinical characteristics of their tumors and the hepatic functional reserve of the patients. Hepatic resection has been shown to be the most efficacious treatment for HCC [3]; however, hepatic resection is limited to patients with good hepatic functional reserve. Radiofrequency ablation (RFA) is a recently introduced technique that is rapidly being adopted worldwide because of its greater efficacy for local cure compared with ethanol injection [4,5]. RFA is usually indicated for patients with three or fewer nodules, none of which exceed 3 cm in diameter [6]. Livraghi et al. [7] showed that RFA is just as effective as surgery for the treatment of very early HCC (single HCC nodules measuring 2.0 cm or less) in terms of sustained local disease control and survival. They advocated that RFA can be considered as the preferred treatment for patients with single HCC of 2.0 cm or less, even when surgical resection is possible. Recent, studies compared local ablation therapies with surgical resection [8–14]. However, few studies have evaluated the results of RFA in comparison with surgical resection within a subgroup (e.g., nodules $\leq$2.0 cm vs. >2.0 cm, and single vs. multiple HCCs) analysis of patients with early HCC (three or fewer nodules that are $\leq$3 cm in diameter). The aim of this retrospective study is to compare the patients with early HCC who were submitted to surgical resection and RFA from these points of view.

PATIENTS AND METHODS

From 2001 to 2007, 286 patients underwent liver resection, or RFA for single or multiple (less than 3) HCC measuring $\leq$3 cm as an initial treatment at Hiroshima University Hospital.

The diagnosis of HCC was based on routine imaging modalities including ultrasonography (US), computed tomography (CT) during hepatic angiography, and magnetic resonance imaging (MRI). HCC was diagnosed based on the following classic imaging manifestations: hyperattenuation on CT during hepatic arteriography and hypoattenuation on CT during arterial portography [15]. In case of hypovascular lesion, fine-needle biopsy was performed to obtain histological confirmation in patients who underwent RFA. Before treatment, all patients underwent liver function tests including bilirubin, albumin,

*Correspondence to: Hirotaka Tashiro, MD, 1-2-3, Kasumi, Minami-ku, Hiroshima 734-8551, Japan. Fax: +81-82-257-5224.
E-mail: htashiro@hiroshima-u.ac.jp
Received 30 January 2010; Accepted 11 August 2010
DOI 10.1002/jso.21745
Published online in Wiley Online Library
(wileyonlinelibrary.com).

prothrombin time, and indocyanine green retention rate at 15 min (ICGR 15) tests.

Hepatic Resection

In the current study, 199 patients were subjected to surgical resection of early HCC. The surgical procedure was determined according to the extent of the tumor, hepatic reserve function, and the patients' wishes. Liver function was assessed by Child-Pugh classification and ICGR 15. If liver function would allow, anatomic resection (segmentectomy (n = 76), sectionectomy (n = 11), or hemi-hepatectomy (n = 5)) was performed. In patients with insufficient hepatic reserve, limited resection (n = 107) was performed. For example, right hemihepatectomy could be tolerated if ICGR 15 was in the normal range. One-third of the liver parenchyma could be resected for patients with ICGR 15 of 10–19%, segmentectomy was possible with ICGR 15 of 20–29%, and limited resection was possible with ICGR 15 of 30% and more [16]. The procedures of hepatectomy were the same as those described previously [17,18].

RFA

Eighty-seven patients were subjected to RFA. Patients requesting not to undergo hepatectomy underwent RFA. Among the 87 patients, 69 patients were diagnosed as HCC based on CT imaging. The remaining 18 patients were diagnosed as HCC by histopathological methods. Patients were treated with RFA following TACE, if HCC nodules had hypervascularity. TACE was performed an average 3 days before RFA TACE was performed through the femoral artery using the technique of Seldinger under local anesthesia. An angiographic catheter was inserted selectively into the hepatic feeding artery of a segment or subsegments containing the target tumor. We used cisplatinum (Randa; Nippon Kayaku, Tokyo, Japan) as an anticancer drug mixed with iodized oil (Lipiodol; Nihon Schering, Tokyo, Japan) at a concentration of 10 mg/ml and injected at a dose of 10–40 mg/person. The selected dose was based on tumor size. Injection was discontinued upon full accumulation of iodized oil in the tumor vessels. No gelatin sponge or coil embolization was used after TACE in the present study.

RFA was conducted using a commercially available system (Cool-tip RF system; Radionics, Burlington, MA) and electrode that was 17-gauge. Sixty-nine patients whose tumor had hypervascularity were treated with a combination of TACE with RFA. The remaining 18 patients were treated by RFA alone. All patients underwent RFA with a percutaneous approach under real-time ultrasonographic guidance in a ward setting under local anesthesia and conscious sedation [19]. The treatment response was evaluated using CT image. When the diameter of the non-enhancing area was greater than that of the ablated nodule, RFA was considered to have produced a complete effect. HCCs with incomplete response were reevaluated for a new session.

Follow-up

Follow-up evaluation after the surgery or RFA consisted of blood chemistry tests and measurements of tumor markers including α-fetoprotein (AFP) and Des-γ-carboxy prothrombin (DCP), every month. Patients were examined by ultrasound every 3 months and by computed tomographic (CT) scan every 6 months. When recurrence was indicated by any of these examinations, patients underwent CT during arterial portography and arteriography.

Complications were stratified according to the Clavien classification of postoperative surgical complications [20] and imaging-guided tumor ablation: standardization of terminology and reporting [21]. Major complications were defined as those which required treatment or additional hospitalization, or which resulted in permanent adverse sequelae (Clavien classification grade II or higher). This includes any case in which a blood transfusion or interventional drainage procedure is required.

Treatment for Recurrence

All patients with intrahepatic recurrence were managed with ablative therapies (RFA or ethanol injection), TACE, or surgery including liver transplantation according to the same criteria used at the time of initial resection.

Histopathological Examination

The resected specimens were serially sectioned at 10-mm intervals and examined macroscopically. The criteria used to identify intrahepatic micrometastasis were essentially those proposed by the Liver Cancer Study Group of Japan; that is, tumors surrounding the main tumor with multiple other satellite nodules or small solitary tumors located near the main tumor that are histologically similar or less differentiated than the main tumor [22].

Statistical Analyses

Values for continuous variables are presented as means ± SD. Categorical variables were compared using the chi-square test and continuous variables using Student's *t*-test. Overall survival and disease-free survival analyses were carried out using the Kaplan–Meier methods; comparisons between different groups were carried out using the log rank test. The following variables were examined: age (≥70 vs. <70), sex, positivity for hepatitis C virus (HCV) antibody, ICGR 15 (≥15 vs. <15), Child-Pugh class (A vs. B), main tumor size (>20 mm vs. ≤20 mm), tumor number (single vs. multiple), plasma DCP level (≥100 AU/ml vs. <100 AU/ml), and plasma AFP level (≥100 ng/ml vs. <100 ng/ml). Multivariate analyses for survival and disease-free survival were carried out using the Cox's regression model. The regression model was used to evaluate variables found to be associated with infection by univariate analysis ($P < 0.1$). A P-value of less than 0.05 was considered significant. Calculations were performed using SPSS software (version 16; SPSS, Inc., Chicago, IL).

RESULTS

There were no differences in age and gender between the surgical resection and RFA groups. However, the hepatic resection group included more patients with hepatitis B virus (HBV) ($P = 0.049$). With regard to hepatic reserve function, ICGR 15 was significantly better in the surgical resection group than in the RFA group ($P = 0.004$); the ICGR 15 was 19.5 ± 9 in the surgical resection group and 23.7 ± 12 in the RFA group. The surgical resection group included more patients with well-preserved liver function (Child-Pugh class A) without statistical significance ($P = 0.06$). On the other hand, regarding with tumor-related factors, the tumor size and DCP level were significantly greater in the surgical resection group than in the RFA group ($P = 0.001$ and 0.03, respectively), and the tumor number was also greater in the surgical resection group than in the RFA group with statistical significance ($P = 0.023$). The mean follow-up of surgical resection and RFA groups were 35 ± 2.5 and 32 ± 2.5 months, respectively. There was no significant difference in overall survival between two groups ($P = 0.11$); the 3-year overall survival rates were 91% in the surgical resection group and 81% in the RFA group (Fig. 1). There was also no significant difference in disease-free survival between two groups ($P = 0.88$); the 3-year disease-free survival rates were 41% in the surgical resection group and 34% in the RFA group

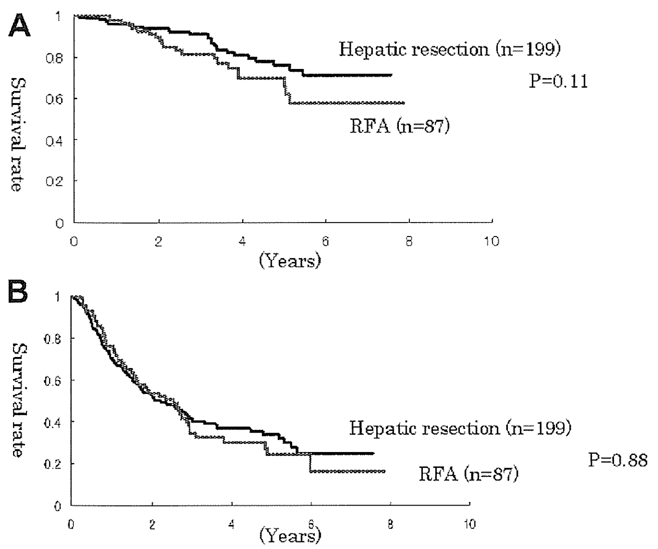

Fig. 1. **A**: Comparison of overall survival rates between patients in the surgical resection and the RFA groups. **B**: Comparison of disease-free survival rates between patients in the surgical resection and RFA groups.

(Fig. 1). Each clinical characteristic including complication was compared between the hepatic resection and RFA groups by univariate analysis, as presented in Table I. There was no mortality during initial hospital stays in both hepatic resection and RFA groups except for one patient who died as a result of suicide within 1 month of hepatic resection. There were no major complications after RFA, whereas major complications occurred in seven patients after hepatectomy. The rate of morbidity after hepatectomy tended to be higher than that after RFA ($P = 0.076$). The hospital stay of hepatectomized patients was significantly longer as compared to that of patients who had underwent RFA ($P = 0.0001$). There was recurrence at the site of the treated tumor in 4 patients who underwent RFA. Complete necrosis was confirmed by imaging in 92% of patients with RFA. Among the four patients who showed recurrence at the site of the treated tumor, three patients had HCC with tumor size exceeding 2 cm (tumor size: 2.0, 2.5, and 3.0 cm), and one patient had HCC with tumor size of 1.5 cm which was located near the liver surface.

Next, subgroup comparisons of overall and disease-free survivals were made between surgical resection and RFA groups (Table II). In subgroup analysis for a single HCC with tumor size exceeding 2 cm in Child-Pugh class A, the disease-free survival was longer in the surgical resection group (n = 72) than in the RFA group (n = 15) with statistical significance ($P = 0.048$); the 3-year disease-free survival rates were 43% in the surgical resection group and 27% in the RFA group (Fig. 2B). In the same subgroup, however, the overall survival was longer in the surgical resection group than in the RFA group without statistical significance ($P = 0.57$); the 3-year overall survival rates were 88% in the surgical resection group and 74% in the RFA group. For multiple HCCs with tumor size exceeding 2 cm in Child-Pugh class A, the overall and disease-free survival rates were longer in the surgical resection (n = 27) than RFA groups (n = 5) without statistical significance. On the other hand, in the subgroup of a single HCC with tumor size $\leq$2 cm in Child-Pugh class A, the overall and disease-free survival rates were almost the same for the surgical resection (n = 53) and RFA (n = 41) groups; the 3-year overall and disease-free survival rates were 95% and 59%, respectively, in the surgical resection group and 94% and 48%, respectively, in the RFA group (Fig. 2A). Moreover, for multiple HCCs with tumor size $\leq$2 cm in Child-Pugh class A, the overall and disease-free survival rates were also almost the same for the surgical resection (n = 30) and RFA groups (n = 11). The subgroup analyses of patients with Child-Pugh class B could not be precisely evaluated due to the small number (less than 4) of cases in each subgroup.

Table III summarizes the results of univariate analyses for all patients according to the clinical characteristics. The Child-Pugh class B ($P = 0.001$) and the tumor number ($P = 0.025$) were significant adverse prognostic factors for overall survival. Similarly, HCV positivity ($P = 0.02$), ICGR 15 $\geq$ 15% ($P = 0.043$), and the tumor number (2 or 3) ($P = 0.0002$) were significant adverse prognostic factors for disease-free survival. In multivariate analyses, Child-Pugh class B ($P = 0.043$) was an independent variable related to adverse overall survival (Table IV). The overall survival rates at 1, 3, and 5 years of 254 patients of Child-Pugh class A were 97%, 91%, and 77%, respectively. The corresponding survival rates of 32 patients of Child-Pugh class B were 94%, 67%, and 56%, respectively.

Table V presents the pathological findings. The incidence of regional cancer spread was significantly lower for HCCs smaller than

TABLE I. Background Characteristics of Patients With Resection or RFA

Variables	Hepatic resection (n = 199)	RFA (n = 87)	*P*-value
Gender (male/female)	137 (68%)/62 (31%)	53 (61%)/34 (39%)	0.19
Age (year)	65.7 ± 9.0	66.3 ± 8.2	0.6
Virus (B/C/others)	38 (19%)/145 (73%)/16 (8%)	9 (10%)/73 (84%)/5 (5%)	0.049
Total bilirubin (mg/dl)	0.86 ± 0.34	0.93 ± 0.36	0.1
Prothrombin time (%)	86.6 ± 14.9	83.7 ± 15.4	0.139
Serum albumin (g/dl)	3.82 ± 0.47	3.78 ± 0.50	0.537
Platelet count ($10^4/mm^3$)	11.8 ± 7.1	10.5 ± 8.6	0.21
ICG R 15 (%)	19.5 ± 9.0	23.7 ± 12	0.004
Child-Pugh classification (A/B)	182 (91%)/17 (9%)	72 (83%)/15 (17%)	0.06
Tumor size (mm)	2.1 ± 0.63	1.8 ± 0.52	0.001
Tumor number (single/multiple)	132 (66%)/67 (34%)	67 (77%)/20 (23%)	0.023
DCP (AU/ml)	197 ± 756	72 ± 223	0.03
AFP (ng/ml)	310 ± 1322	85 ± 166	0.11
Hospital stay (day)	15 ± 8	8 ± 3	0.0001
Major complications			0.076
Ascites or pleural effusion	2 (1%)	0	
Rupture of esophageal varices	2 (1%)	0	
Biliary leakage	3 (2%)	0	

RFA, radiofrequency ablation; B, hepatitis B virus; C, hepatitis C virus; ICGR 15, indocyanine green retention rate at 15 min; DCP, Des-γ-carboxy prothrombin; AFP, alpha-fetoprotein.