

## Second Hepatic Resection for Recurrent Hepatocellular Carcinoma in Patients with Chronic Hepatitis C

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### Abstract

**Background** Although a second hepatic resection (SHR) for recurrent hepatocellular carcinoma (HCC) is widely accepted, the indications for SHR have not been established. The risk factors for HCC recurrence after SHR were evaluated to investigate the indications for SHR.

**Methods** Subjects included 51 patients who underwent a second hepatic resection for recurrence of HCV-related HCC. Sixteen patients received interferon therapy before or after the first operation. Six patients attained a sustained viral response (SVR) that was defined as return of the alanine aminotransferase (ALT) activity to within the reference range and no detectable serum HCV RNA for at least 1 year after interferon therapy. A biochemical response (BR), defined as a normalized ALT activity for at least 1 year after interferon therapy with or without the transient disappearance of serum HCV RNA, was attained in three patients. The other seven patients were defined as the nonresponse (NR) group.

**Results** By univariate analysis, NR and lack of interferon therapy, high indocyanine green retention rate at 15 min (ICGR15), high aspartate aminotransferase activity, high ALT activity, large tumor, and multiple tumors were risk factors for HCC recurrence after SHR. By multivariate analysis, NR and lack of interferon therapy, high ICGR15, large tumor, and multiple tumors were independent risk factors.

**Conclusions** Patients in whom active hepatitis has been controlled by interferon therapy are the best candidates for SHR. Interferon therapy should be recommended in patients undergoing resection of an HCV-related HCC because SHR can prolong life in SVR and BR patients.

Despite recent advances in diagnostic and treatment methods, the prognosis for hepatocellular carcinoma (HCC) remains unsatisfactory because the rate of recurrence after treatment is high, especially in patients with chronic hepatitis C [1, 2]. Recurrence after resection of HCC includes metastases from the primary carcinoma and newly developed foci of HCCs (multicentric occurrence) [3–5]. Chronic active hepatitis has been a risk factor for recurrence, especially for multicentric carcinogenesis, after resection of hepatitis C virus (HCV)-related HCC [1, 2, 6] and the recurrence rate at 5 years has been reported to be 70–80%. In addition, the recurrence rate after resection of HCV-related HCC is higher in patients with HCV viremia than in those without viremia [1]. Thus, interferon (IFN) treatment decreases the incidence of HCC and hence the recurrence rate after treatment in patients with chronic hepatitis C [7–16].

A second (repeat) hepatic resection (SHR) for recurrent HCC is now widely accepted as effective treatment [17–20]. However, the disease-free survival rate after SHR is low and the indications for SHR have not been established. Identification of risk factors is essential to improve the selection of patients who might benefit from SHR. This study examines the risk factors for HCC recurrence after SHR to develop objective criteria for SHR.

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## Patients and methods

### Patients

Between October 1992 and May 2006, 53 patients underwent SHR for recurrence of HCV-related HCC. These patients had undergone first hepatic resection between April 1990 and March 2005. During that period, primary hepatic resection was performed for HCV-related HCC in 399 patients. Although the indications for SHR were almost the same as those for the first resection, we performed SHR only when the following two conditions were met [17]. First, the patient must have good liver function, comparable to that at the time of the initial resection. Second, the tumor must be localized so that it can be extirpated completely. For the exceptional patient with multiple recurrent tumors in the remnant liver who have not responded to other available treatments but whose liver function is adequate to tolerate SHR, we perform SHR as part of a multimodality treatment plan. In 2 of the 53 patients with multiple recurrent tumors, SHR was performed only for recurrent tumors for which transcatheter arterial embolization was not effective, as part of a multimodality treatment; the recurrent tumors could not be extirpated completely by SHR in the two patients. SHR was performed according to the standard indications in the remaining 51 patients who the subjects of this study (Table 1). The tumor-free survival rates were compared as a function of clinicopathologic variables. The median follow-up from operation until the detection of HCC recurrence or the study endpoint (31 July 2006) was 415 days (range = 62–4480 days). The median follow-up from operation until death or the study endpoint was 1264 days (range = 62–4480).

This study was conducted in accordance with the Helsinki Declaration and the guidelines of the Ethics Committee of our institution. Informed consent was obtained from each patient.

### Interferon therapy

In 5 of 51 patients, primary HCC was detected after IFN therapy. In 11 patients, IFN therapy was performed after the first operation. IFN $\alpha$  was administered in 12 patients. IFN $\beta$ , IFN $\alpha$ 2a, IFN $\alpha$  and IFN $\beta$ , and IFN $\alpha$  and ribavirin were administered in one patient each.

The response to IFN therapy was classified on the basis of changes in the HCV RNA levels and serum alanine aminotransferase (ALT) activity during and immediately after IFN administration and for at least 1 year after IFN therapy. Six patients attained a sustained viral response (SVR) that was defined as return of ALT activity to within

**Table 1** Subjects' demographics

Age (years)	66.2 $\pm$ 6.3 (56–83)
Gender (male:female)	47:4
Alcohol abuse	12
Interferon therapy	16
Child-Pugh classification (A:B)	49:2
Total bilirubin (mg/dl)	0.9 $\pm$ 0.3 (0.3–1.5)
Albumin (g/dl)	3.8 $\pm$ 0.4 (2.8–4.6)
ICGR15 (%) <sup>a</sup>	16.7 $\pm$ 6.9 (3.8–34.8)
Platelet count ( $\times 10^4/\text{mm}^3$ )	13.8 $\pm$ 6.4 (5.8–43.4)
Aspartate aminotransferase (IU/L)	58 $\pm$ 28 (18–164)
Alaine aminotransferase (IU/L)	65 $\pm$ 36 (13–158)
$\alpha$ -Fetoprotein (>20 ng/ml)	17
Tumor size (cm)	2.6 $\pm$ 1.4 (1.1–9.5)
Differentiation of main tumor (well, moderate: poor)	39:12
Tumor number (single:multiple)	36:15
Portal invasion	15
Grade (0:1:2:3)	2:14:34:1
Stage (0:1:2:3:4)	2:11:8:7:23
Operative methods (anatomic:nonanatomic)	4:47

Age, the results of laboratory tests, and tumor size are shown as mean  $\pm$  SD with range

ICGR15 = indocyanine green retention rate at 15 min

<sup>a</sup> One patient who was intolerant of ICG was excluded

the reference range and no detectable serum HCV RNA for at least 1 year after IFN therapy. A biochemical response (BR), defined as normalized ALT activity for at least 1 year after IFN therapy with or without transient disappearance of serum HCV RNA, was attained in three patients. The other seven patients were defined as the nonresponse (NR) group because they had no decrease in their ALT activity and had persistent serum HCV RNA. The serum samples were tested for anti-HCV antibody using an enzyme-linked immunoadsorbent assay (Ortho Diagnostic Systems, Tokyo, Japan). Serum HCV RNA was assayed by a reverse transcriptase-nested polymerase chain reaction using primers derived from a conserved 5'-untranslated region of the viral genome [7] and by a branched DNA probe method (Quantiplex HCV-RNA, Chiron Corp., Emeryville, CA).

### Detection of recurrence

Serum concentration of  $\alpha$ -fetoprotein and protein induced by vitamin K absence and antagonist II were measured 1 month after surgery and every 3 months thereafter. Ultrasonography, computed tomography, chest radiography, or some combination of these tests was done 1 month after surgery and every 3 months thereafter. When a

recurrence of HCC was strongly suspected on the basis of tumor markers or imaging, selective hepatic angiography, ultrasound-guided biopsy, or both was conducted to establish a definitive diagnosis.

## Histology

The system of the Liver Cancer Study Group of Japan [21] was used to categorize histologic findings. The histologic grade of differentiation (well, moderate, or poor) of HCC was determined according to a modification of Edmondson and Steiner [22]. The grade score (severity of active hepatitis) and stage score (degree of hepatic fibrosis) in noncancerous hepatic tissues were determined by the score of the histologic activity index [23], which was determined by four events, i.e., periportal necrosis with or without bridging necrosis, intralobular degeneration with focal necrosis, portal inflammation, and fibrosis.

## Statistics

The survival rates were calculated by the Kaplan-Meier method and were compared with those from the log-rank test. The tumor-free survival time was measured from the date of resection until the detection of a recurrent tumor or the endpoint of this study (31 July 2006) in patients without recurrence. Cox's proportional hazard model with stepwise variable selection was used for multivariate analysis. A *p* value of less than 0.05 was considered significant. Variables were selected on the basis of previous studies or our own clinical experience. The variables chosen were age ( $\geq 65$  or  $< 65$ ), gender, history of alcohol abuse (intake of at least 86 g of ethanol daily for at least 10 years) [24], history and response to IFN therapy (SVR, BR vs. NR, and no treatment), total bilirubin ( $\geq 1$  or  $< 1$  mg/dl), albumin concentration ( $\geq 3.5$  or  $< 3.5$  g/dl), indocyanine green retention rate at 15 min (ICGR15,  $\geq 20$  or  $< 20\%$ ), platelet count ( $\geq 10 \times 10^4$  or  $< 10 \times 10^4/\mu\text{l}$ ), aspartate aminotransferase (AST) activity ( $> 40$  or  $\leq 40$  IU/L), ALT

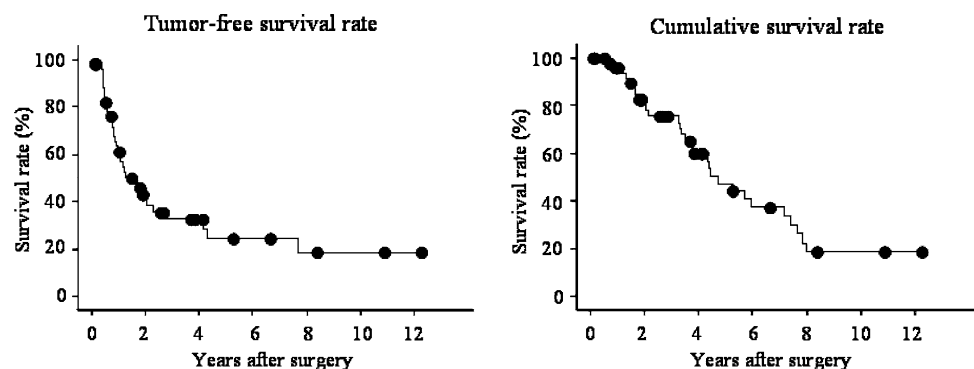
activity ( $> 45$  or  $\leq 45$  IU/L), serum  $\alpha$ -fetoprotein concentration (AFP,  $> 20$  or  $\leq 20$  ng/ml), the largest diameter of the main tumor ( $> 4$  or  $\leq 4$  cm), the degree of differentiation of the main tumor (well-, moderate vs. poorly differentiated HCC), the number of tumors (single or multiple, including intrahepatic metastasis), microscopic portal invasion, the grading score (0, 1, or 2-4), the staging score (0-3 or 4), and operative method.

## Results

There was no operative mortality. Intractable pleural effusion that called for use of diuretics and treatment by thoracentesis developed postoperatively in three patients, intra-abdominal infection in two patients, bile leakage in two patients, and gastric ulcer in two patients. The tumor-free and cumulative survival rates after SHR in the 51 patients are shown in Figure 1.

By univariate analysis, NR and lack of interferon therapy ( $p = 0.0089$ ), high ICGR15 ( $p = 0.0068$ ), high AST ( $p = 0.0607$ ), high ALT ( $p = 0.0930$ ), large tumor ( $> 4$  cm,  $p < 0.0001$ ), and multiple tumors ( $p = 0.0105$ ) were risk factors for HCC recurrence after SHR (Table 2). Multivariate analysis showed that NR and lack of IFN therapy, high ICGR15, large tumor, and multiple tumors were independent risk factors for HCC recurrence after SHR (Table 3). The tumor-free survival rate was higher in SVR and BR patients than in other patients, including NR patients and patients who did not undergo IFN therapy ( $p = 0.0089$ , Fig. 2). The tumor-free survival rate was higher in patients with small tumor ( $\leq 4$  cm) than in patients with large tumor ( $> 4$  cm,  $p < 0.0001$ , Fig. 3). The clinicopathologic findings in patients who were sustained viral responders or biochemical responders and in other patients are shown in Table 4. The mean age and gender distribution were similar in the different groups. Although serum concentrations of total bilirubin, albumin, and ICGR15 were not significantly different between the groups, platelet count was significantly higher in patients who were sustained viral responders or biochemical

**Fig. 1** Tumor-free and cumulative survival rates after second hepatic resection in all patients



**Table 2** Tumor-free survival rates after second hepatic resection for recurrent hepatocellular carcinoma by univariate analysis

Factors (numbers of patients)	Survival rates (%)				
	4 years	8 years	12 years	<i>p</i> value	
Age (years)	≥65 (28)	36	27	27	0.914
	<65 (23)	31	22	–	
Gender	male (47)	36	26	26	0.514
	female (4)	–	–	–	
Alcohol abuse	+ (12)	45	33	33	0.678
	– (39)	31	23	23	
Interferon therapy	SVR + BR (9)	74	74	74	0.0089
	NR + no therapy	42	24	15	
Total bilirubin (mg/dl)	≥1.0 (20)	–	–	–	0.286
	<1.0 (31)	38	28	28	
Albumin (g/dl)	≥3.5 (39)	36	27	27	0.156
	<3.5 (12)	19	–	–	
ICGR15 (%) <sup>a</sup>	≥20 (16)	15	–	–	0.0068
	<20 (34)	42	34	34	
Platelet count ( $\times 10^4/\text{mm}^3$ )	≥10 (35)	32	27	27	0.156
	<10 (16)	37	18	–	
AST (IU/L)	>40 (37)	23	16	16	0.0607
	≤40 (14)	56	44	44	
ALT (IU/L)	>45 (33)	23	16	–	0.0930
	≤45 (18)	52	41	41	
$\alpha$ -Fetoprotein (ng/ml)	>20 (17)	32	32	–	0.866
	≤20 (34)	34	21	21	
Tumor size (cm)	>4.0 (4)	0	0	0	<0.0001
	≤4.0 (47)	36	27	27	
Differentiation of main tumor	Well, moderate (39)	27	21	21	0.469
	Poor (12)	58	39	–	
Tumor number	Single (36)	41	28	28	0.0105
	Multiple (15)	15	–	–	
Portal invasion	+ (15)	47	36	36	0.690
	– (36)	26	18	18	
Grade	0, 1 (16)	42	42	42	0.264
	2–3 (35)	28	19	–	
Stage	0–3 (28)	36	36	36	0.334
	4 (23)	27	13	–	
Operative methods	anatomic (4)	25	–	–	0.649
	nonanatomic (47)	34	26	26	

ICGR15 = indocyanine green retention rate at 15 min; AST = aspartate aminotransferase; ALT = alanine aminotransferase; SVR = sustained viral response; BR = biochemical remission; NR = no response

<sup>a</sup> One patient who was intolerant of ICG was excluded

responders than in other patients. The serum activities of AST and ALT were significantly lower in patients who were sustained viral responders or biochemical responders than in other patients. Thus, active hepatitis was controlled in SVR and BR patients. The proportion of patients with an elevated serum AFP concentration (>20 ng/ml), tumor size, differentiation of the main tumor, prevalences of portal invasion and multiple tumors, grading score, staging

score, and operative methods were similar in the different groups.

## Discussion

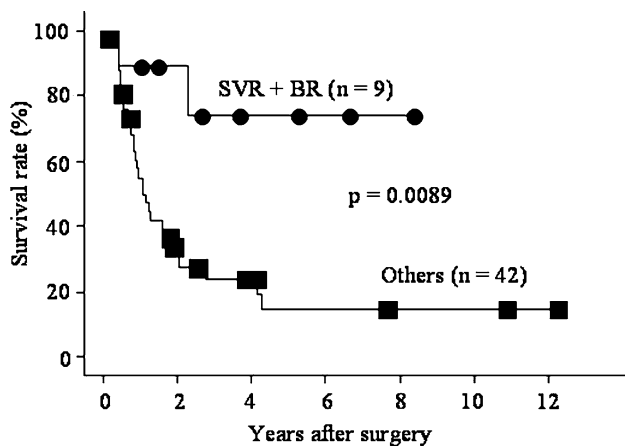
Treatment for recurrent HCCs includes SHR, ablation therapy such as microwave coagulation therapy and

**Table 3** Risk factors for recurrence after second hepatic resection for recurrent hepatocellular carcinoma by multivariate analysis

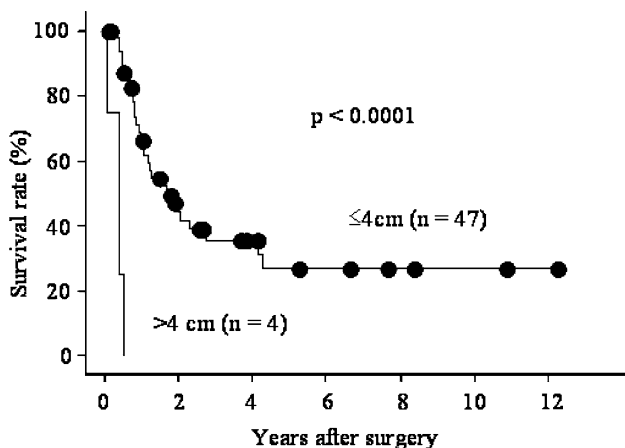
Factors	Risk ratio	95% confidence interval	<i>p</i> value
NR + lack of interferon therapy	17.660	2.252–138.496	0.0063
ICGR15 ( $\geq 20\%$ ) <sup>a</sup>	0.396	0.179–0.878	0.0227
Tumor size ( $>4$ cm)	0.140	0.030–0.643	0.0115
Multiple tumors	0.330	0.143–0.766	0.0098

ICGR15 = indocyanine green retention rate at 15 min

<sup>a</sup> One patient who was intolerant of ICG was excluded



**Fig. 2** Comparison of tumor-free survival rates in patients who were sustained viral responders or biochemical responders with other patients. Circle, 9 patients who were sustained viral responders or biochemical responders; square, other 42 patients



**Fig. 3** Comparison of tumor-free survival rates in patients with large tumor and small tumor. Circle, 47 patients with small tumor ( $\leq 4.0$  cm); another line, 4 patients with large tumor ( $>4.0$  cm)

radiofrequency ablation therapy, and transarterial therapy such as transcatheter arterial embolization. Liver transplantation is another option in selected patients with impaired liver function. Although the value of SHR for recurrence has been demonstrated, indications for SHR are unclear. The tumor-free survival rate in patients with

chronic hepatitis is unsatisfactory because multicentric carcinogenesis persists as long as hepatitis remains active. Recurrence is not uncommon following SHR, even when the resection is considered curative.

Although prognostic factors after first resection for HCC have been evaluated by many investigators, there are a few studies about prognostic factors after SHR. In addition, viral status in patients has not been evaluated in the previous study. In this study univariate analysis showed that NR and lack of IFN therapy, high ICGR15, high AST, high ALT, large tumor, and multiple tumors are risk factors for recurrence. In addition, the tumor-free survival rate was higher in SVR and BR patients than in other patients, nonresponders, and patients who did not undergo IFN therapy. Multivariate analysis showed NR and lack of IFN therapy, high ICGR15, large tumor, and multiple tumors are independent risk factors for HCC recurrence after SHR. Previous studies have indicated that active hepatitis with a sustained increase in the serum aminotransferase activity is a risk factor for recurrence [1, 2, 6, 25]. Other recent studies found that HCC is less likely to develop in patients in whom IFN normalized serum ALT activity, even when HCV RNA remained detectable [11, 12]. IFN therapy also suppresses carcinogenesis after surgery [13, 14, 16, 26, 27]. In this study, active hepatitis had been suppressed in SVR and BR patients, and the tumor-free survival rate after SHR was significantly higher in these patients than in others. Thus, the induction of remission of active hepatitis by IFN therapy suppressed carcinogenesis after SHR. The study of IFN therapy after tumor ablation by Shiratori et al. [16] showed that the rate of second or third recurrence was lower in the IFN group than in the control group, although the incidence of first recurrence of a new foci of HCC was similar in the two groups. It is possible that what is called the first recurrent tumor had already developed by the time of the first operation, and the remission of active hepatitis by IFN therapy suppressed subsequent carcinogenesis. Thus, SHR is likely to be associated with a low incidence of recurrence when IFN therapy has controlled chronic hepatitis C. IFN $\alpha$  was the first therapy for chronic hepatitis C. The combination of IFN and ribavirin increases SVR rates compared with IFN alone. The combination of a

**Table 4** Clinicopathologic findings in patients who were sustained viral responders or biochemical responders and other patients

	SVR + BR ( <i>n</i> = 9)	Others ( <i>n</i> = 42)	<i>p</i> value
Age (mean ± SD)	67.2 ± 6.7	65.9 ± 6.3	0.561
Gender (male:female)	8:1	39:3	>0.999
Total bilirubin (mg/dl)	0.8 (0.7, 1.0)	0.8 (0.5, 1.3)	0.822
Albumin (g/dl)	3.7 (3.6, 4.2)	3.8 (3.3, 4.1)	0.388
ICGR15 (%) <sup>a</sup>	16.4 (10.5, 21.5)	17.1 (6.3, 26.7)	0.695
Platelets (× 10 <sup>4</sup> /mm <sup>3</sup> )	17.7 (15.2, 23.4)	11.1 (6.8, 20.5)	0.0016
AST (IU/L)	34 (25, 53)	56 (29, 104)	0.0091
ALT (IU/L)	25 (18, 64)	67 (23, 119)	0.0165
Tumor size (cm, mean ± SD)	2.4 ± 1.1	2.6 ± 1.5	0.615
Differentiation of main tumor (well:moderate:poor)	0:6:3	4:29:9	0.520
Multiple tumors	4	11	0.421
Portal invasion	3	12	>0.999
Grade (0:1:2:3)	1:3:5:0	1:11:29:1	0.574
Stage (0–1:4)	6:3	22:20	0.488
Operative methods (anatomic:nonanatomic)	0:9	4:38	>0.999

ICGR15 = indocyanine green retention test at 15 min; AST = aspartate aminotransferase; ALT = alanine aminotransferase

<sup>a</sup> One patient who was intolerant of ICG was excluded

pegylated IFN and ribavirin significantly increases SVR rates and is now recognized as the standard therapy [28]. Such IFN therapy is recommended in patients with chronic hepatitis C, even after resection of primary HCC.

The independent risk factors for recurrence after SHR include large tumors and multiple tumors. Thus, a close follow-up after the first operation is important for detecting HCC recurrence at an early stage. When a small recurrent tumor is detected, liver resection or ablation therapy is indicated. We reported that anatomic resection is a favorable prognostic factor in patients in whom IFN was effective [29]. Thus, anatomic resection may be more useful than ablation therapy in such patients. On the other hand, SHR or transarterial therapy is usually used in patients with advanced recurrent tumors such as large tumors and multiple tumors because intrahepatic recurrence was strongly suspected to represent metastasis, in which case IFN therapy is unlikely to be effective. Such lesions require additional treatment such as anticancer chemotherapy.

In conclusion, patients in whom active hepatitis has been controlled by IFN therapy are the best candidates for SHR. IFN therapy should be recommended in patients undergoing resection of an HCV-related HCC because SHR prolongs life if there is a recurrence after liver resection.

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