Original Paper

Long-Term Prognostic Factors after Hepatic Resection for Hepatitis C Virus-Related Hepatocellular Carcinoma, with a Special Reference to Viral Status

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Keywords

Hepatocellular carcinoma · Hepatitis C · Interferon · Surgery · Sustained virological response

Abstract

Background: Although studies have reported on long-term (10-year) survival after hepatic resection for hepatocellular carcinoma (HCC), they did not focus on patients with hepatitis C virus (HCV)-related HCC, and the contribution of antiviral therapy to long-term survival (especially ≥ 15 years) has not been adequately examined. We investigated the long-term outcome after hepatic resection for HCV-related HCC, including the effects of interferon (IFN) therapy, and the changes in prognostic factors according to postoperative duration. **Methods:** The data of 207 patients who underwent hepatic resection for HCV-related HCC between January 1992 and December 2001 were retrospectively reviewed. We investigated the disease-free and overall survival rates after surgery and analyzed the prognostic factors at 5, 10, and 15 years postoperatively. **Results:** The proportion of patients who survived at 5, 10, and 15 years after hepatic resection was 52% ($n = 107$), 18% ($n = 38$), and 9% ($n = 19$). The overall survival rate was significantly higher in patients who achieved sustained virological response (SVR) with IFN therapy than in those without SVR. Tumor-related factors such as multiple tumor, microscopic vascular invasion, and a high indocyanine green retention rate at 15 min (ICGR15) were unfavorable prognostic factors for 5-year survival. Conversely, a low ICGR15 and SVR were favorable prognostic factors at 10 years, and SVR alone was a favorable prognostic factor at 15 years postoperatively; no tumor-related factors were prognostic factors at 10 and 15 years postoperatively. **Conclusion:** The prognostic factors varied according to the

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duration after hepatic resection for HCV-related HCC. Tumor-related factors were unfavorable prognostic factors in the early postoperative period, whereas SVR and good liver function were favorable prognostic factors at 10 and 15 years postoperatively. Achievement of SVR with IFN therapy is essential for long-term (≥ 15 years) survival after hepatic resection for HCV-related HCC.

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Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide, and its incidence has been increasing [1, 2]. Hepatitis C virus (HCV) infection is a major cause of HCC, accounting for approximately 70% of all cases in Japan [3, 4]. However, a high rate of recurrence after hepatic resection is a major problem, with an overall survival (OS) rate of 40–60% at 5 years after hepatic resection [5–8]. Moreover, the OS rate at 10 years after hepatic resection decreased to 27% and the proportion of actual 10-year survivors was 7.2% (303/4,197), according to a systematic review by Gluer et al. [9]. In that review, good liver function, wide surgical margins, and the presence of a solitary tumor were reported to be favorable factors for 10-year survival after hepatic resection. However, among the 14 studies entered into the systematic review, the era of the cohorts, observation periods, the proportion of patients with hepatitis viral infection (hepatitis B virus infection, HCV infection, and non-B non-C hepatitis), and the proportion of patients with liver cirrhosis were heterogeneous. It is well known that the recurrence pattern and survival after curative treatments differ according to underlying hepatic diseases such as the viral infection status [10–13]. However, the aforementioned 14 studies did not evaluate the effects of antiviral therapies even though controlling viral infections with antiviral therapies decreases postoperative HCC recurrence after hepatic resection [14, 15]. Therefore, it is important to investigate the long-term survival after hepatic resection for HCC according to the viral status, including the effects of antiviral therapy.

In this study, we investigated the disease-free survival (DFS) and OS rates after hepatic resection of HCV-related HCC and the prognostic factors for long-term survival (≥ 15 years) after hepatic resection for HCV-related HCC, with a special reference to viral status and antiviral therapy. We also investigated the changes in the prognostic factors at 5, 10, and 15 years after surgery.

Patients and Methods

Patients

Between January 1992 and December 2001, 240 Asian patients seropositive for HCV antibody and seronegative for hepatitis B virus surface antigen underwent curative hepatic resection for initial HCC at the Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Hospital, Osaka, Japan. Among them, patients with other malignancies in the previous 5 years ($n = 11$), in-hospital death ($n = 7$), and loss of follow-up ($n = 15$) were excluded from the study. The subjects of this study were the remaining 207 patients. Of the 207 patients, 107, 38, and 19 patients were alive at 5, 10, and 15 years after hepatic resection, respectively.

Criteria for Hepatic Resection

In general, the criteria for hepatic resection were in accordance with the criteria of Makuuchi et al. [16] (i.e., based on the presence or absence of ascites, the serum total bilirubin level, and the indocyanine green retention rate at 15 min [ICGR15]). Ascites was either not detected or was controllable with diuretics, and the serum total bilirubin concentration was <2.0 mg/dL. Patients with a serum total bilirubin concentration

between 1.1 and 1.9 mg/mL or those with an ICGR15 $\geq 30\%$ were selected for limited resection or enucleation. In patients with a serum total bilirubin concentration of ≤ 1.0 mg/dL, two-thirds of noncancerous liver parenchyma could be removed if the ICGR15 was $\leq 10\%$, and less than one-third could be resected if this value was 10–19%, whereas those with an ICGR15 of 20–29% underwent Couinaud segmentectomy or less. The hepatic anatomy and type of hepatic resection were classified according to the Brisbane 2000 terminology of liver anatomy and resection [17].

Treatments for Chronic Hepatitis C

The inclusion criteria for interferon (IFN) therapy were as follows [18–21]: persistent elevation of serum alanine aminotransferase (ALT) concentration for at least 6 months, presence of serum antibodies to HCV and serum HCV RNA, absence of hepatitis B virus surface antigen and severe comorbidities, histological features of chronic hepatitis shown by liver biopsy specimens obtained within 6 months after the initiation of therapy, and absence of HCC. Postoperative IFN therapy was performed after confirmation of no recurrence within 3 months after hepatic resection (3–4 months postoperatively) [22]. In this study, 3 patients received IFN therapy after treatments for HCC recurrence. IFN-based therapy was performed according to the standard methods at each time in Japan: (1) IFN- α alone: 6–10 million units once daily for 2 or 4 weeks and then 3 times a week for 22 or 20 weeks [20, 23]; IFN- α was administered for 2 years in some patients in previously reported studies [24, 25]; (2) IFN- β alone: 4–6 million units once daily for 8 weeks [20]; (3) IFN- α plus ribavirin: 6 million units of IFN- α once daily for 2 weeks and then three times a week for 22 or 46 weeks, and daily dose of 600 or 800 mg of ribavirin [19]; and (4) pegylated IFN plus ribavirin: 180 mg/week of pegylated IFN for 48 weeks, and daily dose of 600 mg to 1,000 mg of ribavirin [21]. Of our 207 patients, 46 underwent IFN therapy (IFN- α alone, IFN- β alone, IFN- α plus ribavirin, and pegylated IFN plus ribavirin in 41, 6, 2, and 6, respectively). IFN therapy was repeated in 16 patients because sustained virological response (SVR) could not be achieved by the previous IFN therapy. SVR was defined as undetectable HCV RNA levels for >6 months after cessation of IFN therapy.

For prevention of aggravated liver function, ursodeoxycholic acid was administered in 10 patients and monoammonium glycyrrhizinate/glycine/L-cysteine hydrochloride hydrate was administered in 82 patients because of high serum ALT levels. No patient received direct-acting antivirals.

Data Collection

The clinical data of all patients were retrospectively collected, including the patients' baseline characteristics such as age, sex, number and proportion of patients with SVR, history of alcohol abuse or diabetes mellitus, liver function test findings such as the serum concentration of total bilirubin and albumin, prothrombin activity, ICGR15, patient distribution according to Child-Pugh class, platelet count, serum activities of aspartate aminotransferase (AST) and ALT, and pathological findings of the noncancerous hepatic tissue; surgery-related factors such as the proportion of patients who underwent sectionectomy or more extended resection and blood loss; and tumor-related factors (serum concentration of alpha-fetoprotein, tumor size, tumor number, major vascular invasion, American Joint Committee on Cancer/International Union Against Cancer stage [26], microscopic vascular invasion, microscopic tumor number, postoperative outcomes, and causes of death [HCC, liver failure, and liver-unrelated diseases]). The OS time was defined as the interval from hepatic resection to the date of death or the last follow-up examination. The recurrence time was defined as the duration between the day of hepatic resection and the day when recurrence was diagnosed through imaging assessments. The date of follow-up was censored on April 30, 2017. The observation period ranged from 151 to 8,565 days, and the median observation period was 1,962 days.

Pathology

Liver tissue from biopsy and surgical specimens was cut serially into 5-mm-thick tissue blocks, fixed in 10% formalin, and stained with hematoxylin and eosin. The histological activity index (HAI) with some modifications [27, 28] was used to evaluate the severity of active hepatitis (histological activity score) and degree of hepatic fibrosis (hepatic fibrosis score). The HAI includes four components: (1) periportal necrosis with or without bridging necrosis, (2) intralobular degeneration and focal necrosis, (3) portal inflammation, and (4) fibrosis. The summed HAI for components 1–3 was defined as follows: 0, no activity; 1–3, minimal activity; 4–8, mild activity; 9–12, moderate activity; and >12 , severe activity. These categories were assigned histological activity scores of 0–4, respectively. The hepatic fibrosis score was determined from component 4 of the HAI and defined as follows: 1, portal fibrous expansion; 2, portal-portal septa without architectural distortion; 3, portal-central septa with architectural distortion; and 4, cirrhosis. Steatosis also was investigated.

Follow-Up Methods

All patients were followed up at every 3 months after discharge until 5 years after hepatic resection and every 3–6 months thereafter. The follow-up evaluations included physical examination, liver function tests, chest radiographs to check for pulmonary metastases, and ultrasonography, computed tomography, or magnetic resonance imaging to check for recurrence in the remnant liver or other abdominal organs. Chest computed tomography was performed if the chest radiographs showed any abnormalities. Bone metastasis was diagnosed based on magnetic resonance imaging and/or bone scintigraphy findings. Positron emission tomography was performed if necessary. Patients who developed recurrence were treated with appropriate therapeutic modalities (such as repeat hepatic resection, ablation therapy, transcatheter arterial chemoembolization, sorafenib administration, and best supportive care), and the selection of these treatments depended on the recurrent tumor situation.

Statistical Analysis

Continuous variables are expressed as median values (range) and compared between groups using the Mann-Whitney U test followed by the Tukey method. Differences in categorical variables were analyzed using the χ^2 test or the Fisher exact test followed by the Bonferroni method. Logistic regression was used uni- and multivariately to estimate the relative risk of nonsurvival at 15, 10, and 5 years postoperatively. All of the variables of patients' backgrounds, the results of the liver function tests, tumor-related factors, pathological variables, and types of hepatic resection were investigated univariately. Variables with a p value <0.05 in the univariate analysis were entered into a multivariate analysis. We used the Kaplan-Meier method to calculate the OS and tumor-free survival rates, and differences between the two groups were evaluated using the log-rank test. A p value <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS® v.22.0 software (IBM Corp., Armonk, NY, USA).

Results

Results of IFN Therapy

Of the 46 patients who underwent IFN therapy, SVR was achieved before the detection of HCC in 10 patients and after surgery in 10 patients (SVR group). Among the 10 patients with postoperative SVR, 7 exhibited SVR within 1 year after hepatic resection, whereas 3 exhibited SVR at 4, 6, and 9 years after surgery, respectively. All 3 patients received IFN therapy after treatment for HCC recurrence. No patients had a relapse of chronic hepatitis C after the achievement of SVR. The remaining 26 patients could not gain SVR (no response group). IFN therapy was not performed in another 161 patients (no treatment group). The no response group and the no treatment group were classified into the non-SVR group ($n = 187$).

The clinicopathological findings in the SVR, no response, and no treatment groups are shown in Table 1. Patients were significantly younger in the SVR group than in the other groups. There were no significant differences in sex, proportion of patients with diabetes mellitus, Child-Pugh classification, HCV genotypes, or AST/ALT among the three groups. Histological activity score, histological fibrosis score (liver cirrhosis), and proportion of patients with steatosis were not different among the groups.

Outcomes after Surgery

Among all populations, the OS rate at 5, 10, and 15 years after hepatic resection was 52, 18, and 9%, respectively (Fig. 1).

The DFS rate was calculated in all but 3 patients with SVR after HCC recurrence. The DFS rate was significantly higher in the SVR group than in the no response and no treatment groups ($p < 0.001$; Fig. 2a). There was no significant difference in DFS rate between the no response and no treatment groups ($p = 0.147$). Moreover, the DFS rate was significantly higher in the SVR than in the non-SVR group ($p < 0.001$; Fig. 2b). The initial recurrence site was intrahepatic in 11 patients with HCC recurrence. Among 171 patients with HCC recur-

Fig. 1. OS after hepatic resection for hepatitis C virus-related hepatocellular carcinoma in 207 patients. OS, overall survival; SVR, sustained virological response.

Table 1. Comparison of clinical characteristics among patients with SVR and with no response to IFN therapy (no response group) and those who did not receive IFN therapy (no treatment group)

Variable	SVR (n = 20)	No response (n = 26)	No treatment (n = 161)	p value	
Age, years ¹	60 (49–68)	66 (51–75)	65 (47–77)	0.005	
Sex (male/female)	18/2	19/7	137/24	0.224	
Diabetes mellitus	2 (10%)	6 (23%)	36 (25%)	0.431	
Child-Pugh class A/B/C	20/0/0	26/0/0	152/9/0	0.261	
HCV genotypes				0.081	
1a	0 (0%)	0 (0%)	0 (0%)		
1b	10 (50%)	17 (69%)	104 (71%)		
2a	9 (45%)	6 (23%)	26 (18%)		
2b	1 (5%)	2 (8%)	6 (4%)		
Not detected	0 (0%)	1 (4%)	10 (7%)		
Not measured	0 (0%)	0 (0%)	15 (10%)		
	SVR before surgery (n = 10)	SVR after surgery (n = 10)	No response (n = 26)	No treatment (n = 161)	p value
AST/ALT ¹	0.99 (0.61–1.47)	0.64 (0.50–1.50)	0.86 (0.57–1.55)	0.95 (0.43–3.88)	0.053
HAI activity score					0.948
0	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	
1	4 (40%)	2 (20%)	4 (15%)	40 (27%)	
2	5 (50%)	7 (70%)	17 (65%)	96 (66%)	
3	1 (10%)	1 (10%)	5 (19%)	24 (16%)	
HAI fibrosis score					0.348
0–3	5 (50%)	8 (80%)	14 (54%)	81 (50%)	
4 (cirrhosis)	5 (50%)	2 (20%)	12 (46%)	80 (50%)	
Steatosis	1 (10%)	3 (30%)	9 (35%)	72 (45%)	0.115

Bold indicates statistical significance. Values are expressed as n (%) unless indicated otherwise. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HAI, histological activity index; HCV, hepatitis C virus; IFN, interferon; SVR, sustained virological response. ¹ Dispersion variables are expressed as median values (range).

Fig. 2. a Comparison of DFS rates among patients with SVR, those with no response to IFN therapy, and those who did not undergo IFN therapy. Three patients who exhibited an SVR to treatment for HCC recurrence were excluded. **b** Comparison of DFS rates between patients with SVR and non-SVR. Three patients who exhibited an SVR to treatment for HCC recurrence were excluded. DFS, disease-free survival; HCC, hepatocellular carcinoma; IFN, interferon; SVR, sustained virological response.

rence, the initial recurrence site was intrahepatic in 156 and extrahepatic in 15. Nine patients (82%) with recurrence in the SVR group and 103 (60%) in the non-SVR group met the Milan criteria. There was no significant difference in the initial recurrence site and the proportion of patients with recurrence who met the Milan criteria ($p = 0.603$ and $p = 0.214$, respectively). All patients with HCC recurrence in the SVR group were classified as having Child-Pugh class A disease at the initial recurrence, and 8 of 9 (89%) who underwent curative treatments, including repeat hepatic resection and ablation therapy, for recurrence met the Milan criteria, compared with 58 of 103 (56%) in the non-SVR group ($p = 0.079$).

The OS rates were significantly higher in the SVR group than in the no response and no treatment groups ($p < 0.001$; Fig. 3a) and significantly higher in the no response than in the

Fig. 3. a Comparison of OS rates among patients with SVR, those with no response to IFN therapy, and those who did not undergo IFN therapy. **b** Comparison of OS rates between patients with SVR and non-SVR. IFN, interferon; OS, overall survival; SVR, sustained virological response.

no treatment group ($p = 0.005$). Moreover, the OS rate was significantly higher in the SVR group than in the non-SVR group ($p < 0.001$; Fig. 3b).

The proportion of patients who died of HCC in the SVR group was significantly lower than that in the other groups ($p = 0.007$, Table 2). There was no difference in the proportion of patients who died of HCC between the no response and the no treatment group. Although there was no significant difference in the proportion of patients who died of liver failure among the three groups, no patient in the SVR group died of liver failure (Table 2). All 3 patients with SVR obtained after second hepatic resection for the first HCC recurrence were alive for >15 years after initial hepatic resection without a second HCC recurrence.

Table 2. Diachronic changes in the causes of death of patients after hepatic resection for HCV-related HCC

Group	Cause of death	Patients who died in the postoperative period				Total	p value ¹
		<5 years (n = 100)	5–10 years (n = 69)	10–15 years (n = 19)	≥15 years (n = 2)		
SVR (n = 17)	HCC	3	2	0	1	6 (35%)	0.007
	liver failure	0	0	0	0	0 (0%)	0.565
	liver-unrelated diseases	1	0	2	0	3 (18%)	0.590
No response (n = 26)	HCC	6	8	3	0	17 (65%)	
	liver failure	0	2	0	0	2 (8%)	
	liver-unrelated diseases	1	3	0	0	4 (15%)	
No treatment (n = 161)	HCC	71	42	11	1	125 (78%)	
	liver failure	8	4	2	0	14 (9%)	
	liver-unrelated diseases	10	8	1	0	19 (12%)	

Bold indicates statistical significance. Values are expressed as n. HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virological response. ¹ Difference in the cause of death among the SVR, no response, and no treatment groups (no response: no achievement of SVR for interferon therapy; no treatment: no history of interferon therapy).

Clinicopathological Characteristics and Prognostic Factors of 5-Year Survivors

Two patients who had not achieved SVR by 5 years after surgery were classified into the group of patients with non-SVR at 5 years after surgery. Regarding 5-year survival after surgery, the proportion of patients with SVR was significantly higher (Table 3), and the value of ICGR15 was significantly lower in the 5-year survival group than in the 5-year nonsurvival group. Regarding tumor-related factors, the proportions of patients with multiple tumors, major vascular invasion, advanced-stage disease, microscopic multiple tumors, and microscopic vascular invasion were significantly lower in the 5-year survival group than in the 5-year nonsurvival group. Multivariate analysis indicated that a high ICGR15, microscopic multiple tumors, and microscopic vascular invasion were unfavorable factors for 5-year survival. Of the 100 patients who died within 5 years after surgery (5-year nonsurvival group), 77 (77%) died of HCC, 11 (11%) of liver failure, and the remaining 12 (12%) of liver-unrelated causes.

Clinicopathological Characteristics and Prognostic Factors of 10-Year Survivors

The proportion of patients with SVR was significantly higher and liver function test results, including the serum concentration of albumin and the value of ICGR15, were significantly better in the 10-year survival group than in the 10-year nonsurvival group (Table 4). Regarding tumor-related factors, the proportions of patients with macroscopic and microscopic multiple tumors were significantly lower in the 10-year survival group than in the 10-year nonsurvival group. Multivariate analysis indicated that SVR was an independent favorable factor and an increase in serum concentration of ICGR15 was an unfavorable factor for 10-year survival. Of 69 patients who died between 5 and 10 years after surgery, 51 (74%) died of HCC, 7 (10%) of liver failure, and the remaining 11 (16%) of liver-unrelated causes.

Clinicopathological Characteristics and Prognostic Factors of 15-Year Survivors

The proportion of patients with SVR was much higher in the 15-year survival group than in the 15-year nonsurvival group (Table 5). The proportion of patients with liver cirrhosis was significantly lower and the results of liver function tests were significantly better in the

Table 3. Clinical characteristics of 207 patients with HCC according to 5-year survival after hepatic resection and multivariate analysis-predicted 5-year survival

Variable	5-year survival (n = 107)	5-year nonsurvival (n = 100)	p value	Multivariate analysis		
				p value	OR	95% CI
<i>Background data</i>						
Age, years ¹	64 (49–77)	65 (47–75)	0.179	0.111		
Sex (male/female)	89/18	85/15	0.720			
Sustained virological response	14 (13%)	4 (4%)	0.026			
Alcohol abuse	18 (17%)	19 (19%)	0.683			
Diabetes mellitus	17 (16%)	27 (27%)	0.051			
Liver cirrhosis	46 (43%)	53 (53%)	0.150			
<i>Liver function tests</i>						
Total bilirubin, mg/dL ¹	0.8 (0.4–2.0)	0.8 (0.3–1.6)	0.875	<0.001	1.086	1.040–1.134
Albumin, g/dL ¹	3.6 (2.8–4.5)	3.6 (2.7–4.4)	0.307			
Prothrombin activity, % ¹	91 (56–150)	93 (46–150)	0.902			
ICGR15, % ¹	16.1 (0.8–35.2)	19 (5.7–52.1)	0.001			
Child-Pugh class A/B/C	103/4/0	95/5/0	0.656			
Platelets, ×10 ⁴ /μL ¹	14.3 (4.8–42.0)	13.3 (4.8–32.0)	0.361			
AST, IU/L ¹	61 (25–176)	61 (20–163)	0.617			
ALT, IU/L ¹	74 (17–190)	63 (16–161)	0.243			
<i>Surgery-related factors</i>						
Sectionectomy or more extended	32 (30%)	26 (26%)	0.532			
Blood loss, mL ¹	800 (100–5,100)	995 (40–6,500)	0.188			
<i>Tumor-related factors</i>						
Alpha-fetoprotein, ng/mL ¹	20.3 (2.2–6,078)	30.9 (3.3–1,260,000)	0.289	0.542		
Tumor size, cm ¹	3.1 (1.0–8.0)	3 (1.0–16.0)	0.963			
Tumors, n (solitary/multiple)	74/33	49/51	0.003			
Major vascular invasion	0 (0%)	5 (5%)	0.025			
AJCC/UICC stage			0.002			
I	73 (68%)	47 (47%)				
II	31 (29%)	42 (42%)				
IIIA	3 (3%)	6 (6%)				
IIIB	0 (0%)	5 (5%)				
<i>Pathological findings</i>						
Tumors, n (solitary/multiple)	82/25	52/48	<0.001	0.001	2.831	1.503–5.332
Microscopic vascular invasion	19 (18%)	30 (30%)	0.038	0.046	2.084	1.015–4.282
Postoperative recurrence	74 (74%)	89 (89%)	<0.001			

Bold indicates statistical significance. Values are expressed as n (%) unless indicated otherwise. AJCC/UICC, American Joint Committee on Cancer/International Union Against Cancer; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HCC, hepatocellular carcinoma; ICGR15, indocyanine green retention rate at 15 min; OR, odds ratio. ¹Dispersion variables are expressed as median values (range).

15-year survival group than in the 15-year nonsurvival group. Regarding tumor-related factors, no variables significantly differed between the two groups. Postoperative recurrence was present in 11 (58%) patients in the 15-year survival group and 174 (93%) patients in the 15-year nonsurvival group ($p < 0.001$). Multivariate analysis indicated that SVR alone was an independent favorable factor for 15-year survival. Of the 19 patients who died between 10 and 15 years after surgery, 14 (74%) died of HCC, 2 (11%) of liver failure, and the remaining 3 (16%) of liver-unrelated causes. In the 15-year survival group, 2 patients died of HCC after 15 years.

Table 4. Clinical characteristics of 207 patients with HCC according to 10-year survival after hepatic resection and multivariate analysis-predicted 10-year survival

Variable	10-year survival (n = 38)	10-year nonsurvival (n = 169)	p value	Multivariate analysis		
				p value	OR	95% CI
<i>Background data</i>						
Age, years ¹	64 (51–77)	65 (47–75)	0.255	<0.001	0.073	0.025–0.212
Sex (male/female)	30/8	144/25	0.341			
Sustained virological response	14 (37%)	6 (4%)	<0.001			
Alcohol abuse	8 (21%)	29 (17%)	0.571			
Diabetes mellitus	9 (24%)	35 (21%)	0.686			
Liver cirrhosis	14 (37%)	85 (50%)	0.134			
<i>Liver function tests</i>						
Total bilirubin, mg/dL ¹	0.9 (0.5–1.5)	0.8 (0.3–2.0)	0.111	0.272	1.077	1.013–1.145
Albumin, g/dL ¹	3.8 (3.1–4.5)	3.6 (2.7–4.5)	0.001			
Prothrombin activity, % ¹	95 (61–150)	91 (46–150)	0.084			
ICGR15, % ¹	14.8 (0.8–28.3)	18.4 (4.4–52.1)	0.002			
Child-Pugh class A/B/C	38/0/0	160/9/0	0.216			
Platelets, ×10 ⁴ /μL ¹	16.9 (4.8–23.2)	13 (4.8–42.0)	0.055			
AST, IU/L ¹	57 (25–140)	62 (20–176)	0.169			
ALT, IU/L ¹	64 (17–190)	70 (16–169)	0.791			
<i>Surgery-related factors</i>						
Sectionectomy or more extended	13 (34%)	45 (27%)	0.347			
Blood loss, mL ¹	715 (190–3,480)	950 (40–6,500)	0.528			
<i>Tumor-related factors</i>						
Alpha-fetoprotein, ng/mL ¹	13.3 (2.2–6,078)	29.9 (3.3–1,260,000)	0.147	0.084		
Tumor size, cm ¹	3 (1.5–8.0)	3 (1.0–16.0)	0.848			
Tumors, n (solitary/multiple)	28/10	95/74	0.048			
Major vascular invasion	0 (0%)	5 (3%)	0.587			
AJCC/UICC stage			0.225			
I	27 (71%)	93 (55%)				
II	9 (24%)	64 (38%)				
IIIA	2 (5%)	7 (4%)				
IIIB	0 (0%)	5 (3%)				
<i>Pathological findings</i>						
Tumors, n (solitary/multiple)	30/8	104/65	0.042	0.072		
Microscopic vascular invasion	8 (21%)	41 (24%)	0.674			
Postoperative recurrence	25 (66%)	156 (92%)	<0.001			

Bold indicates statistical significance. Values are expressed as n (%) unless otherwise indicated. AJCC/UICC, American Joint Committee on Cancer/International Union Against Cancer; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HCC, hepatocellular carcinoma; ICGR15, indocyanine green retention rate at 15 min; OR, odds ratio. ¹Dispersion variables are expressed as median values (range).

Diachronic Changes in Prognostic Factors

At 5 years after surgery, tumor-related factors were predominant as prognostic factors compared with background or liver function tests (Table 3). SVR and a low ICGR15 were favorable prognostic factors at 10 years, and SVR alone was a favorable prognostic factor at 15 years after surgery (Tables 4, 5). Thus, the prognostic factors changed according to duration after surgery.

Table 5. Clinical characteristics of 207 patients with HCC according to 15-year survival after hepatic resection and multivariate analysis-predicted 15-year survival

Variable	15-year survival (<i>n</i> = 19)	15-year nonsurvival (<i>n</i> = 188)	<i>p</i> value	Multivariate analysis		
				<i>p</i> value	OR	95% CI
<i>Background data</i>						
Age, years ¹	61 (51–68)	65 (47–77)	0.049	0.896		
Sex (male/female)	18/1	156/32	0.321			
Sustained virological response	12 (63%)	8 (4%)	<0.001	<0.001	0.026	0.008–0.084
Alcohol abuse	5 (26%)	32 (17%)	0.345			
Diabetes mellitus	3 (16%)	41 (22%)	0.770			
Liver cirrhosis	5 (26%)	94 (50%)	0.049	0.113		
<i>Liver function tests</i>						
Total bilirubin, mg/dL ¹	0.9 (0.5–1.5)	0.8 (0.3–2.0)	0.057			
Albumin, g/dL ¹	3.9 (3.2–4.5)	3.6 (2.7–4.5)	0.002	0.311		
Prothrombin activity, % ¹	97 (62–148)	91 (46–150)	0.046	0.386		
ICGR15, % ¹	13 (6.2–28.3)	18.2 (0.8–52.1)	0.011	0.152		
Child-Pugh class A/B/C	19/0/0	179/9/0	0.183			
Platelets, ×10 ⁴ /μL ¹	18.4 (6.0–23.2)	13.2 (4.8–42.0)	0.024	0.256		
AST, IU/L ¹	44 (25–113)	62 (20–176)	0.016	0.863		
ALT, IU/L ¹	65 (17–190)	69 (16–169)	0.344			
<i>Surgery-related factors</i>						
Sectionectomy or more extended	8 (42%)	50 (27%)	0.151			
Blood loss, mL ¹	700 (190–2,660)	933 (40–6,500)	0.389			
<i>Tumor-related factors</i>						
Alpha-fetoprotein, ng/mL ¹	7.2 (2.2–4,077)	29 (3.3–1,260,000)	0.051			
Tumor size, cm ¹	2.6 (1.7–8.0)	3.1 (1.0–16.0)	0.869			
Tumors, <i>n</i> (solitary/multiple)	15/4	108/80	0.087			
Major vascular invasion	0 (0%)	5 (3%)	0.472			
AJCC/UICC stage			0.192			
I	15 (79%)	105 (56%)				
II	3 (16%)	70 (37%)				
IIIA	1 (5%)	8 (4%)				
IIIB	0 (0%)	5 (3%)				
<i>Pathological findings</i>						
Tumors, <i>n</i> (solitary/multiple)	16/3	118/70	0.062			
Microscopic vascular invasion	5 (26%)	44 (23%)	0.776			
Postoperative recurrence	11 (58%)	174 (93%)	<0.001			
<i>Cause of death</i>						
HCC	2 (11%)	142 (76%)				
Liver failure	0 (0%)	20 (11%)				
Liver-unrelated diseases	0 (0%)	26 (14%)				

Bold indicates statistical significance. Values are expressed as n (%) unless indicated otherwise. AJCC/UICC, American Joint Committee on Cancer/International Union Against Cancer; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HCC, hepatocellular carcinoma; ICGR15, indocyanine green retention rate at 15 min; OR, odds ratio. ¹Dispersion variables are expressed as median values (range).

Discussion

In this study, the proportion of actual 5-, 10-, and 15-year survivors was 52, 18, and 9%, respectively, and SVR alone was a favorable factor for 15-year survival after hepatic resection. To our knowledge, five articles have reported on the number of 10-year survivors of HCV-

Table 6. Published articles on 10-year survival of patients with HCV-related HCC after hepatic resection

Reference	Year	Country	All populations			HCV-related HCC patients		
			patients, <i>n</i>	10-year survivors, <i>n</i>	actual survival, %	patients, <i>n</i>	10-year survivors, <i>n</i>	actual survival, %
Shimada et al. [29]	2005	Japan	481	105	21.8	286	54	18.9
Fukuda et al. [30]	2007	Japan	145	29	20.0	68	10	14.7
Hashimoto et al. [31]	2007	Japan	85	19	22.4	64	12	18.8
Franssen et al. [32]	2014	USA	176	28	15.9	68	9	13.2
Zheng et al. [33]	2017	USA	159	50	31.4	50	5	10.0
Total			1,046	231	22.1	536	90	16.8
Our study						207	38	18.4

HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

related HCC after hepatic resection [29–33] (Table 6). The mean actual 10-year survival rate in these reports was 16.8% (range, 10.0–18.9%). Moreover, some patients were reported to exhibit recurrence at >10 years after surgery [33, 34]. However, there was no description regarding the contribution of antiviral therapy to long-term survival after resection. Especially, the clinical characteristics and prognostic factors of 15-year survival after hepatic resection have not been reported. In this study, we investigated and compared the outcomes and prognostic factors diachronically (5, 10, and 15 years of survival among the same populations). Some studies have reported that an advanced tumor stage, patient age, and extent of liver resection predict 5-year survival (Table 7) [35, 36]. Particularly, advanced tumor-related factors have been reported to affect recurrence during early postoperative periods (2–3 years) [37–41], leading to poor OS [32, 33]; this finding corresponds with our results. Regarding 10-year survival after hepatic resection, tumor-related factors [9, 29, 30, 32, 33, 42, 43], surgery-related factors [9, 33, 42, 43], patient backgrounds [29–31, 42, 44], and results of liver function tests [29, 42, 44] have been reported to predict survival (Table 7). In this study, SVR and a low ICGR15 were independent favorable factors at 10 years, and SVR alone was an independent favorable factor at 15 years after surgery. By contrast, multiple tumors were an unfavorable factor for 10-year survival according to the univariate analysis but not the multivariate analysis, and no tumor-related factors were found to be prognostic factors for 15-year survival. Based on these findings, favorable patient backgrounds, such as SVR and good liver function, are essential for long-term (10- and 15-year) survival after hepatic resection. ICGR15 is well correlated with hepatic fibrosis, and a higher ICGR15 has been associated with the appearance rate of HCC in cirrhotic patients [45]. Patients with a low ICGR15 might reflect a decrease in multicentric recurrence, which would lead to long-term survival.

In this study, mean age was significantly lower in the SVR group than in the other groups, and the difference was related to the indication for IFN-based therapy.

The DFS rate was significantly higher in the SVR group than in the no response and no treatment groups. The proportion of patients who died of HCC was significantly lower in the SVR group than in the other groups. The incidence of HCC recurrence after hepatic resection is known to decrease with the pre- or postoperative achievement of SVR with IFN-based therapy [22, 46–50]. In this study, the anticancer effects of IFN therapy without achievement of SVR [51] were not unclear because the DFS rate was not different between the no response and the no treatment group. Thus, achievement of SVR-based therapy suppresses multi-

Table 7. Previously reported prognostic factors for HCC patients after hepatic resection

Prognostic factor	5-year survival	10-year survival
<i>Background data</i>		
Favorable		hepatitis B virus infection [37] female sex [24]
Unfavorable	age ↑ [29]	age ↑ [23, 25] liver cirrhosis [23, 24, 35]
<i>Liver function tests</i>		
Favorable		albumin ↑ [37] ICGR15 ↑ [23, 35, 37]
Unfavorable		Child-Pugh class B [35]
<i>Surgery-related factors</i>		
Favorable		wide surgical margin [8, 27, 35, 36] perioperative transfusion [26]
Unfavorable	resection extent ↑ [29]	presence of postoperative complications [35]
<i>Tumor-related factors</i>		
Favorable		
Unfavorable	AJCC/UICC stage ↑ [29, 30]	vascular invasion [23, 24, 26, 27, 35] tumor number (multiple) [8, 23, 27] tumor size >5 cm [27] tumor without capsule [36]

AJCC/UICC, American Joint Committee on Cancer/International Union Against Cancer; HCC, hepatocellular carcinoma; ICGR15, indocyanine green retention rate at 15 min.

centric recurrence (late recurrence, >2–3 years postoperatively) [37–40] by inducing remission of active hepatitis and improving the degree of hepatic fibrosis in patients with HCV infection [24, 25, 47, 49, 50, 52]. All of our patients with HCC recurrence in the SVR group were classified as having Child-Pugh class A disease at the initial HCC recurrence, and the proportion of patients who underwent curative treatments, including repeated hepatic resection for HCC recurrence, and met the Milan criteria tended to be higher in the SVR than the non-SVR group. None of our patients with SVR died of liver failure during the follow-up period. Many previous studies have shown that achievement of SVR improves liver function. Thus, achievement of SVR increased the likelihood of patients being able to undergo curative treatment for HCC recurrence [14, 25, 50, 53]. As a result, achievement of SVR prolonged OS [14, 22, 25, 48]. Patients who achieved SVR after hepatic resection for HCV-related HCC are expected to be long-term survivors (≥15 years). The recent introduction of new antiviral drugs, direct-acting antivirals, has enabled the achievement of SVR in >90% of treated patients [54, 55]. The effects of direct-acting antivirals on the long-term outcome after liver resection of HCV-related HCC should be clarified.

In conclusion, the prognostic factors varied according to the duration after hepatic resection for HCV-related HCC. Tumor-related factors were unfavorable prognostic factors in the early period (5 years) after surgery, whereas SVR and a low ICGR15 were favorable prognostic factors at 10 years, and SVR alone was a favorable prognostic factor at 15 years after surgery. The achievement of SVR with IFN-based therapy is essential for long-term (≥15 years) survival after hepatic resection for HCV-related HCC.

Statement of Ethics

This study was conducted in accordance with the mandates of the Helsinki Declaration and the guidelines of the ethics committee of Osaka City University (registration No. 1646).

Disclosure Statement

The authors declare no conflicts of interest.

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