

Long-term survival after resection of hepatocellular carcinoma

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Backgrounds/Aims: Although recent advances in surgical techniques and alternative treatment, the long-term survival >5 years after liver resection for hepatocellular carcinoma (HCC) is still unsatisfactory due to the high recurrence rate compared with other solid organ cancers. This study was conducted to analyze long-term survival after HCC resection and to develop an optimal strategy to achieve long-term survival. **Methods:** A retrospective review was performed for HCC patients who underwent liver resection between 1996 and 2006. The survival rates and prognostic factors were assessed. The clinical and pathological factors of patients who survived more than 5 years were compared with those of patients whose survival was less than 5 years. The clinicopathological features characterizing long-term survivors were also reviewed. **Results:** The overall and disease-free 5-year survival rates of 87 cases were 38.5% and 29.4%, respectively. Twenty-seven of 87 patients survived longer than 5 years after liver resection. The univariate analysis revealed that hepatitis C, the serum aspartate aminotransferase (AST) level, liver cirrhosis, Edmondson-Steiner grade, AJCC stage, and vascular invasion were significant factors for overall survival, and serum AST level, liver cirrhosis, Edmondson-Steiner grade, AJCC stage, and vascular invasion were the affecting factors for disease-free survival. In multivariate analysis, serum AST level, hepatitis C and vascular invasion were related with the overall survival, liver cirrhosis and vascular invasion which were associated with disease-free survival. Vascular invasion, AJCC stage, and the Edmondson-Steiner grade were significant factors in long-term survivors. **Conclusions:** Patients without liver cirrhosis, vascular invasion and normal liver function, good differentiation and an early stage may be expected to have a long-term survival. (*Korean J Hepatobiliary Pancreat Surg 2012;16:98-104*)

Key Words: Liver resection; Hepatocellular carcinoma; Prognostic factors

INTRODUCTION

As the initial clinical symptom of hepatocellular carcinoma (HCC) is not apparent, only a periodic examination makes it possible to be detected in the early stage. When it is detected with symptoms, intensive and extensive treatments are not feasible because of the regression of liver function accompanied by chronic liver disease or liver cirrhosis,^{1,2} and even resection is possible, the 5-year survival rate is low owing to recurrence as compared with other solid cancers.^{3,4}

Since the long-term survival rate is the most important index when estimating a treatment strategy for malignant cancer, many studies focused on treatment methods to increase the survival rate after treatments are in progress multilaterally. A single operation, such as a liver transplantation or liver resection which can eliminate all tumor

cells leading to a non-tumorous state, and an operation with non-operative adjuvant therapy such as percutaneous ethanol injection therapy, radiofrequency ablation, and transcatheter arterial chemoembolization have been attempted. But a high recurrence rate resulted in a low long-term survival rate.⁵ Such a high rate of recurrence was related to mortality, so that there was a trial to increase the long-term survival rate by analyzing the factors associated with recurrence, but it has not yet been established.^{6,7}

We had followed up the patients who had undergone liver resection, and evaluated the survival rate and prognostic factors. We tried to figure out the condition to derive the long-term survival rate by analyzing clinical and pathologic characteristics of two groups, the group surviving more than 5 years and the other group with short-term survival.

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METHODS

Of the patients who were diagnosed with HCC and underwent liver resection between January 1996 and August 2006, 87 cases had an elapse of more than 5 years from the first day of September 2011 were studied retrospectively by their medical records.

To evaluate preoperative liver function, liver function tests and indocyanin green 15 minute retention rate (ICG R15) were performed, and abdominal sonography, computed tomography (CT) and angiography were checked. Couinaud's classification was used for resection surgery, and massive liver resection was defined as resection of more than 3 segments and minimal as less than 3 segments. The range of resection was determined by ICG R15. The positive resection margin was defined as when microscopic finding was positive even though it was negative for gross finding.

Prognostic factors were analyzed as followed; sex, age, hepatitis B, hepatitis C, alcohol consumption, aspartate aminotransferase (AST), alanine aminotransferase (ALT), ICG R15, serum alpha-fetoprotein (AFP), a history of preoperative treatment, the range of the resection, blood transfusion, number of tumors, the maximal size of the tumor, differentiation of the tumor (Edmondson-Steiner grade), invasiveness into the resection margin, AJCC TNM stage,⁸ and vascular invasion.

A follow-up study was performed in the out-patient department, which included a routine physical examination, liver function test, AFP, simple chest radiograph, abdominal ultrasonography or CT at an interval of 3 to 4 months. A recurrence was checked out with serum AFP, abdominal ultrasonography or CT, and hepatic artery angiography, and the time of recurrence was determined on the date of the final confirmation for recurrence.

The patients were grouped into two groups as the long-term and short-term survival groups: an L-group who survived 5 or more years after liver resection and an S-group survived less than 5 years. The clinical and pathologic characteristics, treatment methods, and recurrence were analyzed. The SPSS Windows version 15.0 was used for statistical analysis; the continuous variables for a clinical pathologic analysis were analyzed by Student t test, chi-square test and fisher's exact test for categorical variables, the Kaplan-Meier for survival rate,

and log-rank test to compare the survival rate of the two groups were used. To analyze the factors which influenced survival rate, a univariate analysis was performed first and a multivariate analysis using Cox-proportional hazards model method was performed for meaningful factors. A *p*-value < 0.05 was considered significant.

Table 1. The characteristics of 87 patients who received hepatic resections

Variables	Total (n=87)
Age (years)	52.7±10.7 (21-73)
< 53/≥ 53	43/44
Gender	
Male/Female	65/22
HBV	
+/-	63/24
HCV	
+/-	6/81
Alcohol abuse	
+/-	35/52
Liver cirrhosis	
+/-	67/20
ICG R15 (%)	10.2±5.6 (1.1-33.4)
≤ 10/> 10	51/36
AST (U/L)	61.2±98.4 (16.0-928.0)
≤ 50/> 50	50/27
ALT (U/L)	54.8±65.4 (10.0-441.0)
≤ 50/> 50	61/26
Preoperative treatment	
+/-	30/57
α-fetoprotein (IU/ml)	5,156.9±12,209.3 (0.6-60,500.0)
≤ 20/< 20-400 </ ≥ 400	31/21/35
Operative procedure	
Major/Minor	38/49
Perioperative transfusion	
+/-	17/70
Maximal size (cm)	5.4±2.8 (1.2-12.0)
< 5/≥ 5	43/44
Number	
Solitary/Multiple	73/14
Vascular invasion	
+/-	46/31
Resection margin	
+/-	9/78
TNM stage	
I/II/III	34/27/26
Edmondson-Steiner grade	
1 or 2/3 or 4	60/27
Recurrence	
+/-	56/31

HBV, hepatitis B virus; HCV, hepatitis C virus; ICG, indocyanin green; AST, aspartate aminotransferase; ALT, alanine aminotransferase

RESULTS

The clinicopathologic characteristics

The clinical, pathological, and surgical data were summarized at Table 1. There were 65 males (74.7%) in our study, the mean age was 52.7 (range: 21-73) years. Most patients (n=84, 96.6%) were classified as having Child-Pugh class A, and 67 patients (77.1%) were diagnosed with liver cirrhosis in a histological examination. Before surgery, 30 patients (34.5%) were treated with transarterial embolization. Ten percent or less ICG R15

was found in 51 patients (58.6%). The serum AFP, a mean level of 5,156.9 IU/ml, was 400 IU/ml or more in 35 patients (40.2%). The mean size of the tumor was 5.4 cm, the greater diameter was 5 cm or beyond 5 cm in 44 patients (50.6%) of all cases. Seventy-three (83.9%) patients had solitary lesions, and vascular invasion was confirmed in 46 (52.9%) specimens. A radical resection was possible for 78 patients (89.7%), 9 patients were tumor-negative grossly in the resection margin, but tumor cells were detected microscopically. According to the TNM stage classification, 34 patients (39.1%) in stage I,

Table 2. Univariate analysis of prognostic factors, overall survival and disease-free survival after a hepatic resection (n=87)

Factors	Overall survival		Disease-free survival	
	5-years (%)	<i>p</i> -value	5-years (%)	<i>p</i> -value
Age (years)		0.574		0.778
< 53/≥ 53	43.1/33.9		35.3/23.1	
Sex		0.877		0.954
Male/Female	38.4/40.4		28.3/35.1	
Hepatitis B virus		0.428		0.362
+/-	36.6/43.8		25.3/42.5	
Hepatitis C virus		0.034		0.113
+/-	0/41.7		0/32.1	
Alcohol abuse		0.612		0.661
+/-	40.4/38.1		24.6/33.9	
AST (U/L)		0.025		0.012
≤ 50/> 50	48.7/27.0		46.1/12.4	
ALT (U/L)		0.693		0.443
≤ 50/> 50	40.5/34.6		32.5/22.3	
Serum AFP (IU/ml)		0.868		0.700
≤ 20/< 20-400/> 400	37.4/38.1/37.5		30.3/22.2/32.7	
ICG R15 (%)		0.100		0.176
≤ 10/> 10	43.1/31.5		41.5/12.7	
Cirrhosis		0.050		0.023
+/-	32.0/62.2		22.3/53.8	
Preoperative treatment		0.159		0.245
+/-	41.3/37.3		34.5/26.1	
Operative procedure		0.678		0.644
Major/Minor	40.6/36.8		36.8/21.8	
Blood transfusion		0.537		0.396
+/-	26.5/41.2		18.0/31.5	
Number of tumor		0.057		0.051
Multiple/Solitary	21.4/42.0		19.0/31.7	
Max. size of tumor		0.324		0.258
< 5/≥ 5	44.2/32.8		32.3/25.9	
Edmondson-Steiner grade		0.023		0.028
1 or 2/3 or 4	48.7/14.4		36.6/14.1	
Resection margin		0.169		0.115
+/-	22.2/40.6		0/31.2	
AJCC TMN stage		0.007		0.001
I/II/III	63.9/22.9/23.1		46.2/17.0/16.9	
Vascular invasion		0.010		0.001
+/-	22.5/57.9		16.3/42.7	

AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; ICG, indocyanin green

Table 3. Multivariate analysis of the overall and disease-free survival after hepatic resection (n=87)

Variables	Hazards ratio (95% CI)	p-value
Overall survival		
AST (U/L)	0.562 (0.329-0.960)	0.035
Hepatitis C	2.933 (1.226-7.017)	0.016
Vascular invasion	1.950 (1.126-3.377)	0.017
Disease-free survival		
Liver cirrhosis	0.399 (0.188-0.849)	0.017
Vascular invasion	2.570 (1.477-4.472)	0.001

AST, aspartate aminotransferase

27 patients (31.0%) in stage II, and 26 patients (29.9%) in stage III. Also grade I and II in 60 patients (69.0%) by the Edmondson-Steiner grade were more than grade III and IV (Table 1).

Operative treatments

Massive liver resection was performed in 38 patients (43.7%), and blood transfusions were necessary for 17 patients (19.5%). Postoperative morbidity occurred in 32 patients (36.8%), and mortality occurred in one patient (1.1%) as a result of bleeding.

Survival results and prognostic factors

The overall survival rate for all patients was 78.0% in the first year, 53.4% at 3 years, and 38.5% at 5 years, with a median survival of 43 months. Disease-free survival was 60.1% at 1 year, 46.1% at 3 years, and 29.4% at 5 years, with a median disease-free survival of 26 months. Twenty-seven of 87 patients survived longer than 5 years after a liver resection. The univariate analysis revealed those that were hepatitis C negative, serum AST level, of 50 U/L or less without liver cirrhosis, good differentiation (Edmondson-Steiner grade 1 to 2), AJCC early stage (stage 1), and no vascular invasion were the significant factors for overall survival. Also, serum AST level of 50 U/L or less, without liver cirrhosis, good differentiation (Edmondson-Steiner grade 1 to 2), early AJCC stage (stage 1), and no vascular invasion were the affecting factors for disease-free survival (Table 2). After detecting the impact of the abovementioned significant factors on the survival of patients by Cox regression, those that were hepatitis C negative, serum AST level of 50 U/L or less, and no vascular invasion were independent predictors for the overall survival. Meanwhile, liver cirrhosis and vas-

Table 4. Patterns of recurrence

	Total (n=87)	L-group (n=27)	S-group (n=60)
Total recurrence	56	14	42
Recurrence site			
Intrahepatic	36	12	24
Solitary	16	6	10
Multiple	20	6	14
Extrahepatic	13	2	11
Intrahepatic and extrahepatic	7		7

Table 5. Treatments of recurrence

Method	Total (n=56)	L-group (n=14)	S-group (n=42)
TACE	27	8	19
TACE+RFA	5	2	3
RFA	4	2	2
Resection	5	2	3
Systemic chemotherapy	3		3
Radiation	2		2
No treatment	10		10

TACE, transarterial chemoembolization; RFA, radiofrequency ablation

cular invasion independently affected disease-free survival (Table 3).

A total of 56 patients (64.4%) experienced tumor recurrence during the follow-up period, particularly in the liver (36 of 56) (Table 4). Among 56 patients with recurrence, 27 patients (48.2%) were treated mainly with transarterial chemoembolization, 10 patients did not receive any treatment (17.9%) (Table 5).

Comparison of the long-term survival group (L-group) and the short-term survival group (S-group)

The S-group showed more vascular invasion than the L-group ($p=0.014$), and stage I of the TMN classification was overwhelmingly dominant as compared to stage 2 and 3 in L-group, while stage 2 was most dominant, which was similar distribution with stage 2 and 3 in S-group ($p=0.037$). According to Edmondson-Steiner grade, grade 1 and 2 were more than grade 3 and 4 in both of the two groups, which was much more remarkable in the L-group ($p=0.011$) (Table 6). Fourteen recurrences were found in the L-group and 42 in S-group. Intrahepatic tumor recurrence was found in 12 patients and two patients

Table 6. Comparison of the clinicopathologic variables between the long-term (L-group) and short-term (S-group) survivors after surgical resection for hepatocellular carcinoma

Variables	L-group (n=27)	S-group (n=60)	p-value
Age (years)	51.1±9.7 (27-65)	53.4±11.2 (21-73)	
< 53/≥ 53	15/12	28/32	0.443
Gender			
Male/Female	21/6	44/16	0.659
HBV			
+/-	19/8	44/16	0.775
HCV			
+/-	0/27	6/54	0.171
Alcohol abuse			
+/-	13/14	22/38	0.312
Liver cirrhosis			
+/-	19/8	48/12	0.323
ICG R15 (%)	8.7±4.6 (1.1-17.8)	10.8±6.0 (1.6-33.4)	
≤ 10/> 10	18/9	33/27	0.307
AST (U/L)	49.0±26.6 (18.0-112.0)	66.7±117.1 (16.0-928.0)	
≤ 50/> 50	17/10	33/27	0.487
ALT (U/L)	44.0±30.2 (10.0-149.0)	59.7±75.9 (10.0-441.0)	
≤ 50/> 50	18/9	43/17	0.637
α -fetoprotein (IU/ml)	8,095.9±17,476.8 (1.8-60,500.0)	3,834.4±8,772.2 (0.6-35,000.0)	
≤ 20/20-400/≥ 400	8/7/12	23/14/23	0.799
Preoperative treatment			
+/-	11/16	19/41	0.410
Operative procedure			
Major/Minor	13/14	25/35	0.573
Perioperative transfusion			
+/-	4/23	13/47	0.567
Maximal tumor size (cm)	4.9±2.5 (2.0-10.0)	5.6±3.0 (1.2-12.0)	
< 5/≥ 5	14/13	29/31	0.761
Number of tumor			
Solitary/Multiple	25/2	48/12	0.209
Vascular invasion			
+/-	9/18	37/23	0.014
Resection margin			
+/-	1/26	8/52	0.263
TNM stage			
I/II/III	16/5/6	18/22/20	0.037
Edmondson-Steiner grade			
1 or 2/3 or 4	24/3	36/24	0.011
Recurrence			
+/-	14/13	42/18	0.102
Treatment for recurrence			
+/-	14/13	32/28	0.898

HBV, hepatitis B virus; HCV, hepatitis C virus; ICG, indocyanin green; AST, aspartate aminotransferase; ALT, alanine aminotransferase

had extrahepatic recurrences in the L-group. Twenty-four in the intrahepatic, 11 in extrahepatic and 7 in both lobes were seen in the short-term group. Treatment for recurrence was performed in all of the patients of the L-group, while only 10 cases had a treatment in the S-group (Table 5). But treatment for recurrence was not statistically significant ($p=0.898$).

DISCUSSION

It is difficult to perform aggressive treatment of HCC because of the deterioration of liver function caused by chronic hepatitis or liver cirrhosis. It has been generally recognized that HCC is a life-threatening malignancy, because of its high incidence of malignant biological behaviors, such as vascular invasion, infiltrating growth, strong

potential of local recurrence and extrahepatic metastases. However, in the recent 10 years, the prominent improvement of safe surgical procedures are owed to the development of surgical techniques and anesthesia, the improvement of pre- and post-operative care, improved understanding of liver anatomy, and development of the ability to care in an intensive care unit reduces complications and mortality after liver resection.³ Moreover, early detection and treatment are practical owing to the application of computed tomography and ultrasound, and the development of diagnostic tools such as serum AFP. Various non-operative treatment methods, such as percutaneous ethanol injection therapy, radiofrequency ablation, and transarterial chemoembolization have been developed. Also it can be applied to patients who are not indicated to operation. Although this increases the overall survival rate,⁵ yet the survival rate is low as compared to other solitary tumors because of the high recurrence rate which is closely related to long-term survival.^{4,6,7}

Examining previous studies on the factors that influence the recurrent rate showed that there were some agreed upon factors which had shown a significant effect, but some factors were controversial. Hepatitis B and C Infection is known to be directly related to hepatocellular carcinoma,^{4,9,10} but no significant relationship could be found in those studies due to the small number of samples similar to this study.⁶

The size and number of tumors, vascular invasions, existence of satellite nodules, range of resections and ruptures of membrane of tumors, suggested in previous studies^{7,11-13} may influence recurrence. Most studies^{7,12,13} mentioned that vascular invasion was a direct tumor forming factor through circulation. This had significant results for our study as well ($p=0.001$). For the size of tumor, many studies¹²⁻¹⁴ admitted that the significance that a tumor larger than 5 cm had a higher recurrence rate,^{6,12,13} but there was no statistical significance in our study ($p=0.258$). Lee and his colleagues¹⁵ concluded that the tumor size did not have any statistical significance in their multivariate analysis, which was analyzed at every 1 cm of size from 2 cm to 7 cm. Although this study did not investigate the existence and rupture of the membrane, Laurent et al.¹⁶ found in their multivariate study that the recurrence rate was high when the membrane was ruptured. Another study¹⁷ reported the poor survival rate with the rupture of

the tumor itself, on the other hand Han et al.¹⁸ found no difference in the survival rate according to the existence of a membrane, but they reported a difference in survival rate whether or not the tumor cell invaded the membrane. Many studies reported a poor result with multiple tumor masses, but this study found no statistical significance.^{7,11,18}

Bleeding remains a major problem with liver resections. Blood transfusion of any amount, as shown some studies, is related to shortening the overall cumulative and disease-free survival periods.^{17,19-21} But it is considered the reflection of the severity of progressive cirrhosis which causes massive blood loss, not by blood transfusion. To reduce bleeding during mobilization of the tumor, adequate and wide exposure by a generous incision and adequate illumination of the operative field are essential. In our study, transfusion related to the operation had no significance.

Many institutions^{11,13,16} noted that a free margin of parenchyma has been regarded as a prognostic factor in terms of long-term survival and tumor recurrence, but this had no significance in our study. Shah et al.¹³ mentioned that cirrhosis was associated with recurrence, our study also found cirrhosis related to high recurrence rates.

HCC recurred in the intrahepatic region as reported by many institutions.²²⁻²⁴ In our study, there were 64.4% postoperative recurrences, and among these, intrahepatic recurrence was 64.3%. If a recurred hepatocellular carcinoma is detected early in the intrahepatic region, it is not only possible to resect all of lesion, but the non-operative modality, such as transarterial embolization or radiofrequency ablation, also this can be performed when an operation is not possible because of a poor general condition.

To improve the survival rate, it is important to prevent and detect recurrence, yet further study on prevention is needed. Closer follow-up in the out-patient department with more frequent radiologic study (USG or CT) and serologic tumor marker study (AFP) and perhaps with magnetic resonance imaging studies of the liver to detect an early recurrence should be considered. Additionally, patients with an extremely high surgical risk can be treated with other treatment modalities such as transarterial embolization or radiofrequency ablation.

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