

Long-term outcome after liver resection and clinicopathological features in patients with small hepatocellular carcinoma

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Backgrounds/Aims: Surveillance programs and imaging modality developments have increased the detection rate of small hepatocellular carcinoma (HCC). In particular, liver transplantation produces good results and is now regarded an alternative to liver resection. However, optimal treatment for small HCC is still debated, and thus, the authors designed this study to document clinicopathological characteristics, to identify the prognostic factors of small HCC, and to determine the effectiveness of surgery. **Methods:** A total of 507 patients underwent curative liver resection for HCC between January 1996 and August 2006 in our institution. One hundred and thirty four of these patients with a single HCC of less than 3 cm and no gross vascular invasion were enrolled. **Results:** Major resection was performed in 32 (23.9%) patients; there was no postoperative mortality. Fifty-eight (43.3%) patients experienced recurrence, 53 developed intrahepatic recurrence alone, and 50 (94.3%) of 53 had tumors within the Milan criteria. Five-year disease-free and overall survival rates were 51.0% and 77.3%, respectively. Microscopic vascular invasion, positivity for hepatitis B surface antigen or antibody to hepatitis C, and an indocyanine green retention test at 15 minutes of more than 10% were found to be significantly correlated with disease-free overall survival. A platelet count of less than 100,000/mm³ was the only independent prognostic factors of overall survival identified. **Conclusions:** This study showed favorable outcome comparable to the survival after liver transplantation, thus that liver resection appears to be the primary treatment option for small HCC, even in cases with poor prognostic factors. (*Korean J Hepatobiliary Pancreat Surg 2011;15:199-205*)

Key Words: Small hepatocellular carcinoma; Liver resection

INTRODUCTION

The majority of hepatocellular carcinomas (HCC) arise in the background of chronic hepatitis and cirrhosis, and thus, liver transplantation is the most ideal treatment modality as it corrects the underlying liver disease. However, because of the donor shortage situation, liver resection is the preferred treatment. Furthermore, the use of liver resection in patients with HCC is largely limited by advanced disease and poor liver function.

Recently, a randomized controlled study was performed to determine the merits of HCC screening in China.¹ It was found screening confers survival benefits and that development of imaging modalities and surveillance programs have increased the detection rate of small resectable HCC.^{2,3} Several studies have reported the outcomes of treatment modalities for small HCC,⁴⁻⁸ and despite the

different definitions used for small HCC, liver transplantation has been proposed as an alternative strategy for small HCC instead of liver resection.^{8,9} Nevertheless, the optimal treatment for small HCC remains controversial.^{10,11} Small HCC has a favorable prognosis, but its outcome was different according to the prognostic stratification and prognostic scoring system for patients treated by liver resection.^{6,12}

In the present study, we investigated the clinicopathological characteristics and prognostic factors of small HCC and attempted to determine the effectiveness of surgery with the intention of finding the best approach for its treatment.

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METHODS

Definitions

Curative resection was defined as complete tumor resection with a clear microscopic margin and no residual tumor by imaging at 1 month after surgery. Major liver resection was defined as the resection of ≥ 3 Couinaud segments. Postoperative mortality was defined as death within 1 month after surgery, and recurrence as typical arterial enhancement with delayed washout on computed tomography (CT) images. Causes of patient death were classified as recurred HCC-related death, complications of liver cirrhosis without recurrence, and unrelated causes.

Patients

Five hundred and seven patients underwent curative liver resection for HCC between January 1996 and August 2006 at the Department of Surgery, Yonsei University Health System, Seoul, Korea. Of these 507 patients, 146 had single HCC of ≤ 3 cm in diameter. Twelve of the 146 patients were also excluded because of gross portal or hepatic vein involvement. Finally, 134 patients were enrolled in this study.

Preoperative evaluation and follow-up methods

A preoperative CT scan, biochemistry testing, and an indocyanine green retention test at 15 minutes (ICG R15) were performed on all patients. The decision whether to perform major or minor resection was made preoperatively based on tumor location by CT, liver function, Child-Pugh status, ICG R15, and on the likelihood of achieving an adequate resection margin. Alpha-fetoprotein (AFP) levels were determined and underwent ultrasonography (US) or CT performed on all patients every 3-6 months after surgery.

Outcomes

Prognostic factors for disease-free survival and overall survival were sought from among the following 18 clinicopathologic variables. Nine were patient factors, namely, age, gender, etiology of liver disease, serum albumin level, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, ICG R15, platelet count, and liver cirrhosis grade. Five were surgical factors, that

is, intraoperative bleeding amount, perioperative transfusion, surgical tumor-free resection margin, extent of resection, and type of resection, and four were tumor factors, that is, tumor size, microscopic vascular invasion, Edmondson-Steiner grade, and serum AFP level.

Statistical analysis

Statistical analysis was performed using SPSS v 12.0 software (SPSS Inc., Chicago, IL, USA). Continuous results are presented as medians (ranges) and categorical results are presented as numbers (percentages).

Disease-free and overall survival rates were calculated using the Kaplan-Meier method. Prognostic factors of disease-free and overall survival rates were identified using the log-rank test and univariate analysis. Multivariate analysis was performed using the Cox proportional hazard model; factors significant by univariate analysis were included. Statistical significance was accepted for p -values of < 0.05 .

RESULTS

Clinical characteristics

The clinical characteristics are presented in Table 1. The 134 study subjects had a median age of 53.1 years (range, 24-73 years), and 99 were male. The most common etiology of liver disease was hepatitis B virus ($n=104$, 77.6%). Liver cirrhosis was proved by pathologic examination in 86 patients (64.2%). All patients except one were of Child-Pugh class A. Major resections were performed in 32 patients (23.8%). Forty-five patients (48.9%) received a perioperative transfusion, and there was no postoperative mortality.

Long-term surgical outcomes after resection

During a median follow-up of 43.5 months (4-110 months), 58 (43.3%) patients recurred. Fifty-three patients developed intrahepatic recurrence alone, 4 extrahepatic recurrences alone, and 1 concurrent intrahepatic and extrahepatic recurrence. Fifty (86.2%) of the intrahepatic recurrence patients had tumors within the Milan criteria, and 17 patients (12.7%) expired due to recurrence (Table 2). The 1-year, 3-year, and 5-year disease-free and overall survival rates were 82.0%, 62.4%, and 51.0%, and 97.0%, 89.5%, and 77.3%, respectively (Fig. 1).

Prognostic factors of disease-free and overall survival

Microscopic vascular invasion (Hazard ratio [HR]=1.738; 95% confidence interval [CI], 1.015-2.977; *p*=0.044), positivity for hepatitis B surface antigen or antibody to hepatitis C (HR=3.490; 95% CI, 1.258-9.682; *p*=0.016), and an ICG R15 of >10% (HR=1.737; 95% CI, 1.019-2.960; *p*=0.042) were found to be significantly and negatively correlated with disease-free survival by

both univariate and multivariate analyses (Table 3-5).

A serum albumin of <3.5 g/dl, a serum platelet count of <100,000/mm³ and non-anatomic resection were found to be significantly associated with overall survival by univariate analysis (Table 3, 4). However, only a platelet count of <100,000/mm³ (HR=2.907; 95% CI, 1.341-6.299; *p*=0.007) was found to be independently associated with prognosis by multivariate analysis (Table 5).

DISCUSSION

Mazzaferro et al.¹³ first reported good results for liver transplantation in selected patients, and several studies conducted since have concluded that liver transplantation is the better treatment option.^{9,14-17} Accordingly, liver transplantation is now viewed as the treatment of choice

Table 1. Clinical characteristics

Variables	n (%)
Age (year, range)	53.1 (24-73)
Gender (male/female)	99 (73.9%)/35 (26.1%)
Etiology of liver disease	
Hepatitis B virus	104 (77.6%)
Hepatitis C virus	11 (8.2%)
Others	19 (14.2%)
Child Pugh classification	
A/B	133 (99.3%)/1 (0.7%)
Cirrhosis	86 (64.2%)
Operative procedure	
Major resection	32 (23.9%)
Right hepatectomy	21 (15.7%)
Left hepatectomy	9 (6.7%)
Right or left extended hepatectomy	2 (1.5%)
Minor resection	102 (76.1%)
Lateral sectionectomy	21 (15.7%)
Posterior sectionectomy	6 (4.5%)
Bisegmentectomy	2 (1.5%)
Segmentectomy	53 (39.6%)
Partial hepatectomy	20 (14.9%)
Perioperative transfusion	45 (48.9%)
Postoperative mortality	0 (0.0%)

Table 2. Long-term surgical outcomes after resection

Variables	n (%)
Type of recurrence	58 (43.3%)
IH nodular (≤3 nodules) recurrence	50 (86.2%)
IH multiple (>3 nodules) recurrence	3 (5.2%)
EH recurrence	4 (6.9%)
IH+EH recurrence	1 (1.7%)
Cause of death	27 (20.1%)
HCC recurrence	17 (63.0%)
Complication of liver cirrhosis without recurrence	7 (25.9%)
Unrelated	3 (11.1%)

IH, intrahepatic; EH, extrahepatic; HCC, hepatocellular carcinoma.

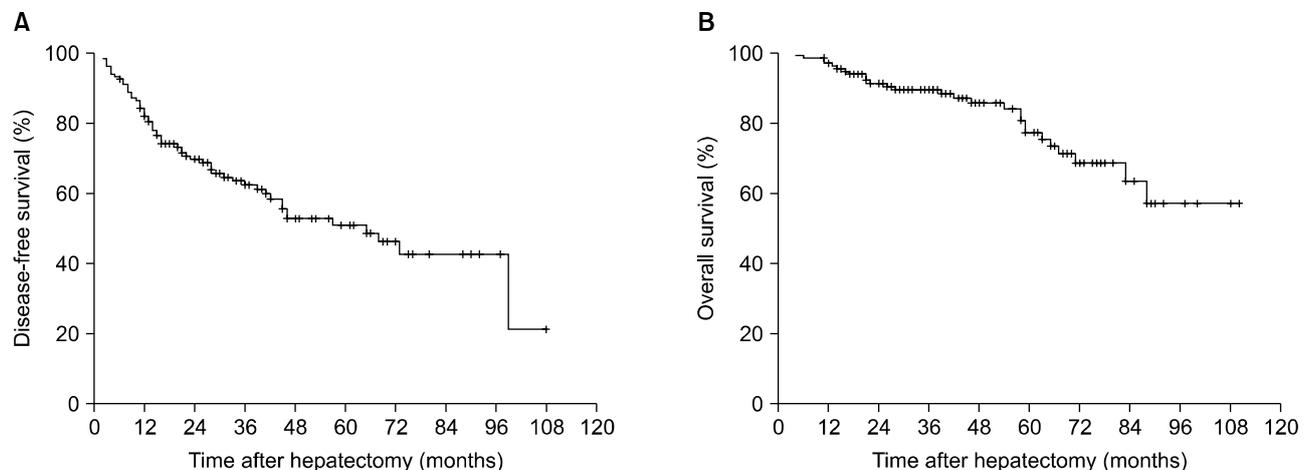


Fig. 1. Survival curves after liver resection for small hepatocellular carcinoma. (A) 1-, 3-, and 5-year disease-free survival rates were 82.0%, 62.4%, and 51.0%, respectively. (B) 1-, 3-, and 5-year overall survival rates were 97.0%, 89.5%, and 77.3%, respectively.

Table 3. Host and treatment related prognostic factors by univariate analysis

Variables	Disease-free survival			Overall survival		
	No. of patients	5-year survival (%)	<i>p</i> -value	No. of patients	5-year survival (%)	<i>p</i> -value
Age (years)			0.469			0.686
≤60	101	51.5		101	75.3	
>60	33	47		33	84	
Gender			0.813			0.598
Male	99	49.6		99	76.8	
Female	35	53.9		35	78.9	
Etiology of liver disease			0.024			0.82
HBV	104	45.8		104	73.3	
HCV	11	63.6		11	85.7	
Others	19	74.6		19	94.1	
Serum albumin (g/dl)			0.108			0.032
≤3.5	14	41.7		14	42.4	
>3.5	120	52.2		120	82	
AST (IU/L)			0.323			0.154
≤50	111	54.1		111	79.6	
>50	23	37.9		23	68	
ALT (IU/L)			0.359			0.598
≤50	94	54.9		94	80.2	
>50	40	41.9		40	70.2	
Liver cirrhosis			0.054			0.222
No	48	56.9		48	81.9	
Yes	86	48		86	74.8	
Intraoperative bleeding (ml)			0.698			0.668
≤1,000	96	50.3		96	74.3	
>1,000	38	52.2		38	85.5	
Platelet count (mm ³)			0.111			0.005
≤100,000	36	46.5		36	68.9	
>100,000	98	52.3		98	81.5	
ICG R15 (%)			0.049			0.075
≤10	85	55		85	78.8	
>10	49	44		49	68.9	
Perioperative transfusion			0.36			0.875
No	89	55.2		89	70.2	
Yes	45	42.9		45	57.1	
Surgical margin (cm)			0.936			0.183
≤1.0	46	56.9		46	62.4	
>1.0	88	47.9		88	65	
Extent of resection			0.875			0.899
Minor	96	52.5		96	76.4	
Major	38	43.4		38	80.9	
Type of resection			0.28			0.013
Anatomic	114	50.6		114	79.9	
Non-anatomic	20	52.6		20	64.5	

ICG R15=indocyanine green retention test at 15 minutes. HBV, hepatitis B virus; HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

for early HCC in Child-Pugh class B or C cirrhosis. However, liver resection has also produced good results in patients with small HCC; in fact, the 5-year overall survival rate in the present study was 77.3%. These results show, although the disease-free survival rate for liver resection is poorer than of liver transplantation, that the

overall survival rates of liver resection and liver transplantation are similar for patients with small HCC, and suggest that liver resection is a good treatment option in patients with small HCC.^{18,19}

The merits and demerits of major versus minor resection and anatomical resection versus non-anatomical resection

Table 4. Tumor related prognostic factors by univariate analysis

Variables	Disease-free survival			Overall survival		
	No. of patients	5-year survival (%)	<i>p</i> -value	No. of patients	5-year survival (%)	<i>p</i> -value
Tumor size			0.521			0.786
≤2 cm	52	49.1		52	75.9	
>2 cm	82	52.2		82	78.4	
Microscopic vascular invasion			0.036			0.256
Absent	92	57.7		92	80.9	
Present	42	39		42	75.2	
Edmondson-Steiner grade			0.801			0.621
I-II	92	49		92	75	
III-IV	23	60.3		23	70.9	
Serum AFP (IU/ml)			0.299			0.201
≤400	107	48.9		107	78.4	
>400	27	60.8		27	72.5	

AFP, alpha-fetoprotein.

Table 5. Independent prognostic factors for disease-free and overall survival by multivariate analysis

Variable	Coefficient	Standard error	<i>p</i> -value	Hazard ratio (95% CI)
Disease-free survival				
Microscopic vascular invasion	0.553	0.275	0.044	1.738 (1.015-2.977)
Etiology of liver disease (HBV vs. others)	1.031	0.524	0.049	2.803 (1.003-7.832)
Overall survival				
Platelet count (≤100,000 vs. >100,000)	1.067	0.395	0.007	2.907 (1.341-6.299)

HBV, hepatitis B virus.

are still debated for small HCC. In the present study, 102 (76.1%) patients underwent minor resection, including non-anatomical resection (n=20, 14.9%), and operation type was not found to be associated with disease-free or overall survival. In a previous report, we reported that non-anatomical resection for small HCC had no adverse effect on disease-free survival,²⁰ and other authors have reported similarly.^{21,22} In fact, these authors also concluded that minor and non-anatomical resection of small HCC (except for deep-seated HCCs or HCCs located alongside a major vessel) is an effective treatment option.

Prognosis after HCC resection has been shown to be affected by tumor invasiveness and underlying liver function.²³⁻²⁵ According to our results, the long-term prognosis of patients with a single small HCC is more associated with underlying liver function than invasiveness. Microscopic vascular invasion and positivity for hepatitis B surface antigen may develop intrahepatic metastasis and de novo carcinogenesis, respectively, after resection, but in the present study, the majority of recurrences (n=53, 91.4%) were confined to the remaining liver. In addition,

50 patients developed nodular recurrence, which was well controlled by multimodality treatments and had a better prognosis than other recurrence patterns. These observations suggest that long-term prognosis is associated with liver function and the extent to which the liver can resist recurrence given aggressive treatment.

However, according to our data, overall survival rate at 5 years after resection decreased, indicating that liver transplantation was eventually required because of the progression of underlying liver disease or HCC recurrence. Salvage liver transplantation provides an alternative in patients with recurrence after liver resection. However, the initial experiences with salvage liver transplantation were relatively poor, in which operative mortality was high (23.5%) and survival was unfavorable, but many of the of patients had a tumor beyond the Milan criteria.²⁶ It has been reported that salvage liver transplantation is feasible in 75-80% of patients after liver resection,²⁷ and in the present study, salvage liver transplantation was found to be feasible in 50 of 53 patients (94.3%). It was recently reported that salvage liver transplantation can be

performed with acceptable morbidity and mortality rates and produce results comparable to those of primary liver transplantation.^{28,29} Furthermore, in one these previous studies, patients that underwent liver resection or liver transplantation showed similar survival rates by intention-to-treat analysis.²⁹ However, salvage rates of only up to 20% have been reported by others.^{29,31} Thus, further studies are needed before salvage liver transplantation can be generally adopted.

Liver resection has been adopted as the primary treatment modality for small HCC because its overall survival rate is comparable to that of liver transplantation. Moreover, because salvage liver transplantation produces attractive results, liver resection, including minor and non-anatomical resection, can be chosen as a primary treatment option for patients with small HCC, even for those with risk factors of a poor prognosis.

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