

Long-term outcomes of liver resection for multiple hepatocellular carcinomas: Single-institution experience with 187 patients

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Backgrounds/Aims: Surgical resection for the treatment of multiple hepatocellular carcinomas (HCCs) is controversial. This study aimed to evaluate the clinical and oncological outcomes after liver resection in patients with multiple HCCs. **Methods:** Clinicopathological and survival data of 187 patients who underwent curative resection for multiple HCCs between June 2004 and December 2016 at Asan Medical Center, Seoul, South Korea were retrospectively reviewed. The prognostic factors for recurrence and survival were identified using univariate and multivariate analyses. **Results:** Of the 187 patients, 153 (81.8%) had two nodules, 23 (12.3%) had three nodules, and 11 (5.9%) had more than three nodules. Multiple tumors were located in the ipsilateral lobe in 163 (87.2%) patients. Anatomical resection, non-anatomical resection, and both types of resections were performed in 81.3%, 8.0%, and 10.7% patients, respectively. Recurrence occurred in 133 (71.1%) patients, and the mean time to recurrence after surgery was 34.2 months. Independent risk factors for tumor recurrence in multivariate analyses were indocyanine green retention rate at 15 min $\geq 15\%$, preoperative alpha-fetoprotein level ≥ 400 ng/ml, and total tumor diameter ≥ 6 cm. The 1-, 3-, 5-, and 10-year disease-free survival rates were 94.1%, 81.7%, 69.7%, and 39.4%, respectively, and the 1-, 3-, 5-, and 10-year survival rates were 93.5%, 74.2%, 64.9%, and 38.8%, respectively. **Conclusions:** Our experience shows that liver resection can be considered a first-line treatment option for selected patients with multiple HCCs who have well-preserved liver function. (*Ann Hepatobiliary Pancreat Surg* 2020;24:437-444)

Key Words: Carcinoma; Hepatocellular; Hepatectomy; Survival analysis; Multivariate analysis; Retrospective studies

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary neoplasm of the liver and the second leading cause of cancer-related deaths worldwide.¹ Advances in diagnostic imaging and widespread implementation of surveillance programs in the high-risk population enable detection of HCC at early stages,^{2,3} however, some patients with HCC continue to be diagnosed with multiple tumors.⁴ Liver resection has been accepted as the standard treatment modality for patients who have a single lesion with well-preserved liver function.⁵ However, the treatment of multiple HCCs is debatable, with significant variation in the different modalities of treatment across dif-

ferent hepatobiliary institutions.

The choice of treatment for patients with multiple HCCs is based on not only the stage of the tumor but also the degree of liver dysfunction. Although liver transplantation (LT) is considered the optimal treatment for patients with multiple HCCs if the tumors are small and limited in number,⁶ its implementation is limited by the availability of donor organs, tumor progression while on the wait list, and technical demand.

With the advances in surgical techniques and perioperative management in recent times, aggressive surgical resection for multiple HCC has been proposed for patients in whom all the tumors can be completely excised and adequate liver function can be preserved postoperatively.

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Furthermore, several previous studies have suggested that liver resection can provide survival benefits in patients with multiple HCCs either within or beyond the Milan criteria.⁷⁻¹¹ However, the role of liver resection for multiple HCCs is controversial as resection can be associated with potentially higher intraoperative risks, increased recurrence, and worse long-term survival. This study aimed to evaluate the clinical and oncological outcomes and determine the prognostic factors for recurrence and survival after liver resection in patients with multiple HCC.

MATERIALS AND METHODS

The medical records of patients who underwent curative resection for multiple HCCs from June 2004 to December 2016 at the Asan Medical Center, Seoul, South Korea were retrospectively reviewed. Patients who had undergone liver resection for HCC at other hospitals and those who underwent salvage liver transplantation for recurrence after resection for multiple HCCs were excluded. Finally, 187 patients with multiple HCCs were included in this study. Multiple HCCs were diagnosed when there were two or more tumors. The diagnosis of HCC and the number of HCCs were confirmed by histopathological examination of the surgical specimens.

Preoperative evaluation

Preoperative diagnosis of multiple HCCs was based on preoperative imaging studies including dynamic computed tomography (CT) and magnetic resonance image (MRI) or a combination of imaging findings and elevated serum alpha-fetoprotein (AFP) and prothrombin induced by vitamin K absence II (PIVKA-II) levels. Liver function was assessed in detail using liver biochemistry test results, coagulation profile, indocyanine green retention rate at 15 min (ICGR15), and Child-Pugh classification. The presence of portal hypertension (esophageal varix, noticeable collaterals, and splenomegaly with thrombocytopenia) was also assessed. Based on these laboratory and radiologic examinations, the extent of resection was determined.

Postoperative follow-up

Patients were followed up using abdominal contrast-enhanced CT or MRI and chest X-ray every 2-3 months during the first year after resection, every 4

months during the second year, and every 6 months subsequently. Serum AFP levels were measured at the same intervals.

The diagnosis of intrahepatic recurrence was established on imaging if the tumor showed the typical enhancement characteristics. The line of treatment followed for recurrent HCC was essentially the same as that for primary HCC. Patients with extrahepatic recurrence were managed with all available locoregional treatment modalities. Patients with unsatisfactory responses to locoregional treatments were finally treated with systemic chemotherapy.

Ethical considerations

This study protocol was reviewed and approved by the institutional review board of the Asan Medical Center (approval number 2020-1502) at the University of Ulsan College of Medicine in Seoul, Korea. The requirement for informed consent was waived because of the retrospective nature of the study.

Statistical analysis

Data are expressed as mean±standard deviation. Discrete variables are presented as totals and percentages. The recurrence-free survival (RFS) and overall survival (OS) were calculated using the Kaplan-Meier method. Variables that showed statistical significance ($p < 0.05$) in the univariate analysis were subsequently included in a multivariate analysis using Cox proportional hazards regression models. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) for Windows.

RESULTS

Clinicopathological features of all patients

The clinical characteristics of the 187 patients with multiple HCCs are shown in Table 1. Of the 187 patients, 158 (84.5%) were male. Of all patients, 158 (84.5%) and 15 (8.0%) patients had associated hepatitis B and C virus infection, respectively. Further, 97.9% patients had relatively good liver function with Child-Pugh class A. Liver cirrhosis was present in 147 (75.9%) patients, confirmed on histological examination after surgery. The preoperative mean serum AFP and PIVKA-II levels were 4692.6±

Table 1. Demographics characteristics of the patients

Variables	Total (n=187)
Sex, M:F	158:29
Age, mean (\pm SD, year)	58.8 (\pm 9.71)
Liver disease, n (%)	
HBV	158 (84.5)
HCV	15 (8.0)
HBV and HCV	1 (0.5)
Others	5 (2.7)
Comorbid disease, n (%)	
Cardiac disease	58 (31.0)
Pulmonary disease	1 (0.5)
Renal disease	1 (0.5)
Diabetes mellitus	42 (22.5)
Others	1 (0.5)
ASA score I/II/III	3/180/4
CTP score A/B	183/4
Preoperative blood tests, mean (\pm SD)	
Hemoglobin (g/dl)	13.5 (\pm 1.53)
Total bilirubin (μ mol/L)	0.7 (\pm 0.27)
AST (IU/L)	41.3 (\pm 28.29)
ALT (IU/L)	37.8 (\pm 27.25)
PT (INR)	1.1 (\pm 0.08)
Creatinine (mg/dl)	0.9 (\pm 0.85)
Albumin (g/dl)	3.6 (\pm 0.39)
Platelet count ($\times 10^3/\mu$ l)	156.8 (\pm 63.26)
AFP (ng/ml)	4692.6 (\pm 29256.36)
PIVKA-II (mAU/ml)	633.1 (\pm 2735.05)
ICG-r15 (%)	13.9 (\pm 6.66)
History of HCC treatment	
TACE	65 (34.8)
RFA	19 (10.2)
Preoperative portal vein embolization	29 (15.5)
BCLC stage A/B/C	20/162/5

SD, standard deviation; HBV, hepatitis B virus; HCV, hepatitis C virus; ASA, American society of anesthesiologists; CTP, child-turcotte-pugh; AST, aspartate transaminase; ALT, alanine transaminase; PT, prothrombin time; AFP, alpha-feto-protein; PIVKA-II, prothrombin induced by vitamin K absence II; ICG, indocyanine green; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; BCLC, Barcelona Clinic Liver Cancer

29256.36 ng/ml and 633.1 \pm 2735.05 mAU/ml, respectively. Of the 187 patients, 84 (45.0%) received preoperative treatment—65 were treated with transarterial chemoembolization (TACE) and 19 were treated with radiofrequency ablation (RFA).

The characteristics of HCC are summarized in Table 2. Of the 187 patients, 153 (81.8%) had two nodules, 23 (12.3%) had three nodules, and 11 (5.9%) had more than three nodules. Multiple tumors were located in the ipsilateral lobe in 163 (87.2%) patients. On histopathological

Table 2. Tumor characteristics

Characteristics	Total (n=187)
Tumor distribution, n (%)	
Ipsilateral lobe 163 (87.2)	
Right lobe	161 (86.1)
Left lobe	50 (26.7)
Bilateral lobe	24 (12.8)
Pathological characteristics	
Liver cirrhosis, n (%)	142 (75.9)
Number of tumors, n (%) 2/3/more	153/23/11 (81.8/12.3)
Size of the largest tumor, cm (\pm SD)	4.1 (\pm 3.11)
Total tumor diameter, cm (\pm SD)	6.1 (\pm 3.82)
Tumor-free margin, mm (\pm SD)	13.1 (\pm 15.16)
Lymphovascular invasion, n (%)	42 (22.5)
Satellite nodule, n (%)	16 (8.5)
Bile duct invasion, n (%)	9 (0.5)
Portal vein invasion, n (%)	19 (10.2)
Glisson capsule invasion, n (%)	20 (10.7)
Edmondson-Steiner grade, n (%) I, II/III, IV	58/114 (30.9/61.0)

SD, standard deviation

examination, the mean largest tumor size was 4.1 cm, and the total tumor diameter was 6.1 \pm 3.82 cm. The rates of microvascular and macrovascular invasion were 22.5% and 10.2%, respectively. Further, 114 (61.0%) patients had Edmondson-Steiner grade III or IV cancer.

The extent of resection in all patients is summarized in Table 3. Anatomical resection, non-anatomical resection, and both types of resections were performed in 81.3%, 8.0%, and 10.7% patients, respectively. Tumor-free resection margin was obtained in all patients. Tumor thrombectomy from the portal vein and combined resection of the adjacent organs was performed in 4 patients (2.1%) and 9 patients (4.8%), respectively.

Tumor recurrence

Recurrence was seen in 133 (71.1%) patients during the follow-up, and the mean time to recurrence after surgery was 34.2 months. Of these, 109 patients had only intrahepatic recurrence, 14 had only extrahepatic recurrence, and 10 had both intrahepatic and extrahepatic recurrence. The most common treatment modalities for the recurrence of HCC were TACE (n=96, 72.2%) and RFA (n=18, 13.5%) (Table 4).

Overall, the 1-, 3-, 5-, and 10-year disease-free survival (DFS) rates were 94.1%, 81.7%, 69.7%, and 39.4%, re-

Table 3. Type of resection

Types	Total (n=187)
Open/laparoscopic approach, n (%)	185/2 (98.9/1.1)
Anatomical/non anatomical resection/Both, n (%)	152/15/20 (81.3/8.0/10.7)
Type of resection, n (%)	
Right hepatectomy	53 (27.9)
Right hepatectomy+wedge resection	5 (2.7)
Right anterior sectionectomy	27 (14.4)
Right anterior sectionectomy+wedge	2 (1.1)
Resection	
Right posterior sectionectomy	28 (15.0)
Right posterior sectionectomy+wedge	5 (2.7)
Resection	
Right trisectionectomy	1 (0.5)
Right trisectionectomy+wedge resection	1 (0.5)
Central bisectionectomy	3 (1.6)
Left medial sectionectomy	1 (0.5)
Left medial segmentectomy+S3	1 (0.5)
Segmentectomy	
Left medial segmentectomy+wedge	1 (0.5)
Resection	
Extended left hepatectomy	1 (0.5)
Left hepatectomy	11 (5.8)
Left hepatectomy+wedge resection	4 (2.1)
Left lateral sectionectomy	11 (5.8)
Left lateral sectionectomy+wedge resection	2 (1.1)
Monosectionectomy	14 (7.5)
S5, 6 segmentectomy	1 (0.5)
Wedge resection	15 (8.0)
Tumor thrombectomy, portal vein, n (%)	4 (2.1)
Combined resection of adjacent organs	9 (4.8)

Table 4. Recurrence pattern and the treatment for recurrence

Pattern and treatment	Number of recurrences (n=133)
Time to recurrence after surgery, (mean, months)	34.2
Site of recurrences:	109/14/10
Intrahepatic/extrahepatic, n (%)	(82.0/10.5/7.5)
Number of intrahepatic recurrences:	70/49
Single/multiple, n (%)	(37.4/26.2)
Treatment for recurrence	
TACE	96 (72.2)
RFA	18 (13.5)
RT	9 (6.8)
Re-resection	10 (7.5)
Chemotherapy	10 (7.5)

TACE, transarterial chemoembolization; RFA, radiofrequency ablation; RT, radiative therapy

spectively (Fig. 1A). Univariate analysis showed that ICGR15 \geq 15%, preoperative AFP level \geq 400 ng/ml, number of tumors \geq 3, size of the largest tumor \geq 3 cm,

total tumor diameter \geq 6 cm, and presence of lymphovascular invasion were predictors of recurrence. Multivariate analysis showed that ICGR15 \geq 15%, preoperative alpha-fetoprotein level \geq 400 ng/ml, and total tumor diameter \geq 6 cm were predictors of recurrence (Table 5).

Overall survival

The cumulative OS rates for all patients at 1-, 3-, 5-, and 10-years were 93.5%, 74.2%, 64.9%, and 38.8%, respectively (Fig. 1B).

Univariate analysis revealed that size of the largest tumor \geq 3 cm) and total tumor diameter \geq 6 cm were predictors of survival. On multivariate analysis, total tumor diameter \geq 6 cm was the only significant predictor of survival (Table 6).

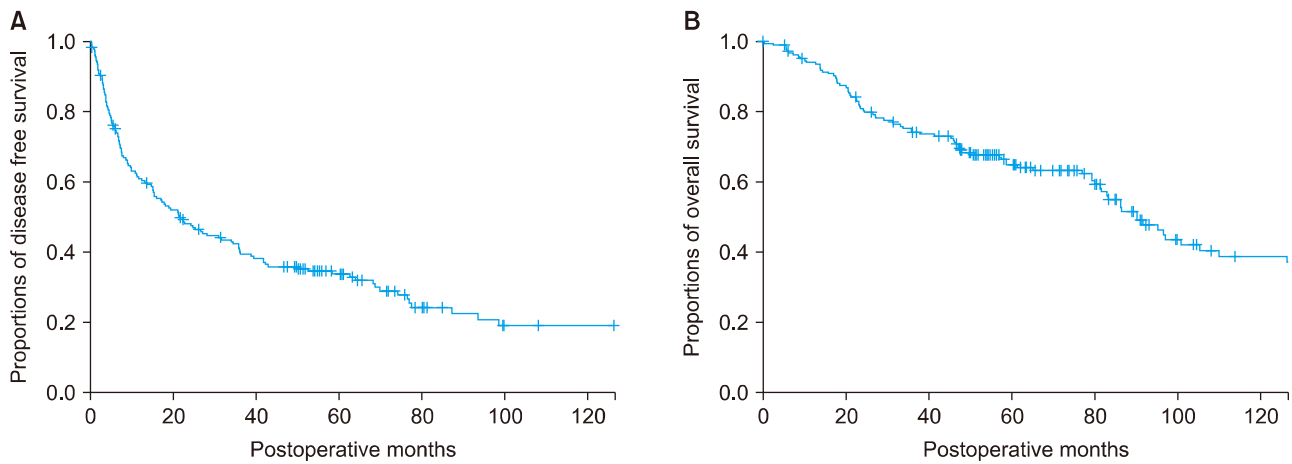


Fig. 1. (A) Disease-free survival rates and (B) overall survival rates and in patients who underwent liver resection for multiple HCC.

Table 5. Univariate and multivariate analysis of risk factors for recurrence

Variables	Univariate			Multivariate				
	Hazard ratio	95% CI	<i>p</i>	Hazard ratio	95% CI	<i>p</i>		
Age ≥ 70 years	0.822	0.480	1.408	0.475				
Sex, male	0.942	0.596	1.490	0.798				
Cirrhosis, (P)*	1.263	0.827	1.930	0.280				
Serum albumin < 4 g/dl	1.229	0.737	2.049	0.429				
Serum total bilirubin ≥ 1 mg/dl	1.243	0.821	1.880	0.304				
ICGR15 [†] $\geq 15\%$	1.510	1.067	2.138	0.020	1.549	1.087	2.207	0.015
Prothrombin activity $\geq 85\%$	1.027	0.701	1.504	0.891				
Platelet count $\geq 15 \times 10^4/\text{mm}^3$	0.935	0.662	1.319	0.701				
Preoperative AFP ≥ 400 ng/ml	1.618	1.029	2.544	0.037	1.685	1.061	2.675	0.027
Number of tumors ≥ 3 (P)*	1.672	1.099	2.542	0.016				
Satellite nodule	1.602	0.902	2.844	0.108				
Tumor distribution, bilateral lobe	1.245	0.765	2.025	0.378				
Size of the largest tumor ≥ 3 cm (P)*	2.008	1.400	2.880	0.000				
Total tumor diameter ≥ 6 cm (P)*	2.292	1.619	3.246	0.000	1.803	1.130	2.879	0.013
Lymphovascular invasion (P)*	1.626	1.094	2.419	0.016				
Non anatomical resection	1.458	0.963	2.208	0.075				

*Identified after postoperative pathological examination; [†]Indocyanine green retention rate at 15 min
CI, confidence interval; AFP, alpha-fetoprotein

DISCUSSION

Our study showed that surgical resection can provide acceptable OS for patients with multiple HCCs. In the present study, the 1-, 3-, 5-, and 10-year DFS rates were 94.1%, 81.7%, 69.7%, and 39.4%, respectively, and the 1-, 3-, 5-, and 10-year OS rates were 93.5%, 74.2%, 64.9%, and 38.8%, respectively. Both the survival rates were promising. This was owing to early detection of recurrence and aggressive treatment for both intrahepatic

and extrahepatic recurrences with close follow-up and surveillance imaging examination.

The management of HCC is complicated because of its heterogenous biological behavior and association with chronic liver disease.¹² In South Korea, HCC is the second leading cause of cancer mortality and it is the fifth most common newly diagnosed cancer.¹³ The choice of treatment in patients with HCC depends on not only tumor staging but also careful evaluation of liver function and physical status. For the treatment of multiple HCCs, surgi-

Table 6. Univariate and multivariate analysis of overall survival in patients with multiple hepatocellular carcinomas

Variables	Univariate				Multivariate		
	Hazard ratio	95% CI		<i>p</i>	Hazard ratio	95% CI	<i>p</i>
Age \geq 70 years	0.493	0.117	2.076	0.335			
Sex, male	0.838	0.341	2.060	0.700			
Cirrhosis, (P)*	1.191	0.484	2.926	0.704			
Serum albumin $<$ 4 g/dl	0.712	0.289	1.752	0.459			
Serum total bilirubin \geq 1 mg/dl	0.700	0.243	2.015	0.509			
ICGR15 [†] \geq 15%	2.095	0.993	4.420	0.052			
Prothrombin activity \geq 85%	0.532	0.253	1.116	0.095			
Platelet count \geq $15 \times 10^4/\text{mm}^3$	1.052	0.507	2.184	0.891			
Preoperative AFP \geq 400	1.236	0.471	3.242	0.667			
Number of tumors \geq 3 (P)*	1.199	0.488	2.948	0.692			
Satellite nodule	2.091	0.727	6.018	0.171			
Tumor distribution, bilateral lobe	0.771	0.233	2.549	0.670			
Size of the largest tumor \geq 3 cm (P)*	2.278	1.009	5.145	0.048			
Total tumor diameter \geq 6 cm (\pm SD) (P)*	2.431	1.168	5.058	0.017	2.476	1.172	5.231
Lymphovascular invasion (P)*	1.411	0.602	3.309	0.428			
Non anatomical resection	1.216	0.519	2.851	0.653			

*Identified after postoperative pathological examination; [†]Indocyanine green retention rate at 15 min
CI, confidence interval; AFP, alpha-fetoprotein

cal and nonsurgical modalities have been used, but the treatment strategies are controversial.¹⁴ LT has been generally considered the treatment of choice for small and limited multiple HCCs as it can resolve the corresponding underlying liver cirrhosis and HCC.^{6,15} Even in patients with HCC beyond the Milan criteria, LT has been performed alone or in combination with a nonsurgical modality, such as TACE, RFA, and percutaneous ethanol injection, to control the tumor as much as possible. However, there are many controversies regarding LT in patients with HCC, such as selection of patients considering the organ shortage, tumor progression while on the wait list, use of living donors, and choice of immunosuppression or adjuvant therapies.¹⁶

In addition to transplantation, surgical resection and TACE are the two most widely used treatments for multiple HCCs. TACE is the most commonly used and is considered the standard palliative treatment for patients with multiple HCCs.⁵ TACE can induce extensive necrosis in $>$ 50% patients¹⁷ and improve their survival.^{18,19} However, several studies have suggested that palliative TACE results in a high incidence of viable residual tumor, even after repeated TACE,^{20,21} and that the poor response in avascular and/or large tumors restricts its use for treating HCCs. Moreover, in recent retrospective cohort studies,

resection provided better survival than TACE, even in patients with multiple HCCs in various stages.^{4,9,10,22} Therefore, liver resection should be included as a treatment option for multiple HCCs in patients who have well-preserved hepatic function.

The indications for surgery in patients with multiple HCC have not been established thus far. The predictors of survival for multiple HCCs found in our study were similar to those reported for HCCs in previous studies.^{4,23} In our study, multivariate analysis identified that total tumor diameter \geq 6 cm was an independent prognostic factor for both DFS and OS. These results on the prognostic factor in patients with multiple HCCs can help in patient selection for liver resection.

There are a few limitations in our study. First, this study was retrospective in nature, and there might be some selection bias in the choice of treatment. Second, comparison with alternative treatment modalities was not performed. To confirm the efficacy of resection for multiple HCCs, its superiority over non-surgical treatment should be proven. Third, our results are mainly based on the data of patients with two HCCs. Further randomized, prospective studies including comparison with alternative treatment modalities and with a large number of patients are necessary to confirm the therapeutic role of liver re-

section in the treatment of patients with multiple HCCs.

In conclusion, on the basis of our experience of liver resection for multiple HCCs, we suggest that surgical resection could be an important strategy to improve long-term outcomes. However, careful selection of candidates for surgery, meticulous surgical techniques, and early detection and aggressive treatment for recurrence is necessary. In addition, given the complexity of HCC and the availability of several potentially useful treatment modalities, the treatment of patients with multiple HCCs associated with chronic liver disease should be discussed with a multidisciplinary team, including hepatologists, surgeons, radiologists, and oncologists.

CONFLICT OF INTEREST

There is no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: CSA. Data curation: SYL, YIY, SGL, SH, KHK, DBM, TYH, GWS, DHJ, GCP. Formal analysis: SYL, CSA, YIY, TYH, GWS, DHJ, KHK, DBM, GCP. Methodology: SYL, YIY. Writing - original draft: SYL, CSA. Writing - review & editing: SYL, CSA, YIY.

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