Outcome after curative resection for a huge (≥10cm) hepatocellular carcinoma

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Outcome after curative resection for a huge (≥10cm) hepatocellular carcinoma

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<ABSTRACT>

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Introduction: Despite recent advances in imaging modalities and widespread application of screening programs, occurrence of huge hepatocellular carcinomas **(**HCCs) with a diameter of 10 cm or more remains common. Recent studies have reported improved perioperative and long-term outcomes over initial postoperative results of huge HCC. The purpose of this study was to investigate the surgical outcomes in patients with huge HCC and to identify any subgroups that would be likely to benefit from hepatic resection.

Methods: From January 1996 to August 2006, 497 patients who underwent curative resection were divided into groups with huge (≥ 10 cm) HCC (n=50, group A) and patients with smaller tumors (n=447, group B). Clinicopathological features, operative procedures, morbidity, initial recurrence pattern, and long-term outcomes were compared between the two groups. In addition, we investigated prognostic factors for survival after resection in group A. All tumors in group A were classified as either nodular type or non-nodular type.

Results: Group A patients had a higher incidence of α-fetoprotein at more than 1000 IU/mL, microscopic vascular invasion, and advanced AJCC stage tumors. The mean indocyanine green retention rate at 15 minutes was higher in

Group B patients. The proportion of patients with cirrhosis was higher in group B. Although group A patients received more major resections and had more intraoperative blood loss and a subsequently greater requirement for transfusion, the rate of morbidity and mortality were similar between both groups. The 1-, 3- and 5-year disease-free survival rates of group A were 49.0%, 38.6% and 38.6%, respectively, significantly lower than those of group B (72.7%, 53.1%, and 45.4%) ($p=0.028$). As for the initial recurrence pattern, the rates of extrahepatic recurrence and early recurrence ($\leq$ 12 months after resection) were higher in group A. The overall survival of group A (70.0%, 50.2%, and 40.2% at 1, 3, and 5 years, respectively) was significantly worse than that of group B (91.3%, 77.2%, and 65.9%)($p<0.001$). In group A, multivariate analysis revealed that the presence of nodular type tumors was the only good prognostic factor for overall survival after resection ($p=0.030$, Hazard ratio=2.653).

Conclusions: Huge HCCs exhibit a more aggressive clinical behavior and worse survival after resection compared with smaller tumors. However, because the outcome of surgical treatment is far better than that of non-surgical treatment, resection should be actively considered for patients with huge HCC. In addition, patients with a single nodular type tumor are the best candidates for surgical resection.

Key words : Hepatocellular carcinoma, huge, surgical resection, prognosis, gross type of tumor

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I. INTRODUCTION

Despite recent advances in imaging modalities and widespread application of screening programs in high risk populations, huge HCC with a diameter of 10 cm or larger is still frequently encountered in clinical practice[1, 2]. Initial results of surgical resection of huge HCCs suggest a high operative mortality rate of up to 14.3% and a generally dismal prognosis compared to smaller tumors[3-5]. Moreover, hepatic resection is not recommended in patients with large HCC (≥5 cm in diameter) according to the 2001 guidelines for HCC provided by the European Association for the Study of Liver[6]. However, more recent studies have demonstrated that hepatic resection of huge HCC has similar perioperative outcomes compared with those of smaller tumors, and has a 5-year survival rate of 20% -35%[1, 7-10]. This survival outcome is still worse than that of smaller tumors, but is far superior to that of non-surgical treatment, as the 5–year survival rate of huge HCC following transarterial chemoembolization is reported to be less than 10%[11].

According to the 6th American Joint Committee on Cancer (AJCC) tumor staging system, a single large HCC without vascular invasion is no longer considered an unfavorable tumor[12]. Furthermore, the American Association for

the Study of Liver Diseases in 2005 suggested that the size of the tumor alone is not a limiting factor for surgical resection[13]. Huge HCC seems to exhibit aggressive clinical behavior and has a poor prognosis, but some cases do indeed have good prognosis and are comparable to smaller tumors. Because huge HCC is not a homogenous group, it is necessary to further stratify this disease into better-defined subgroups on the basis of similar clinical behavior and prognosis.

In this study, we compared the clinicopathological features and the perioperative and longterm outcomes between patients with huge HCC and smaller tumors. In addition, prognostic factors for disease-free and overall survival after resection in patients with huge HCC were investigated to identify subgroups that would be the most likely to benefit from surgical resection.

II. MATERIALS AND METHODS

1. Patients and follow-up

From January 1996 to August 2006, 497 patients underwent curative resection for HCC in Yonsei University Health System, Seoul, Korea. Curative resection was defined as grossly complete removal of the tumor with a clear microscopic margin and no residual tumors detected on imaging studies 1 month following hepatectomy. All patients were divided into groups according to the maximum diameter of the tumor: huge (≥ 10 cm) HCC (n=50, group A) and patients with smaller tumors (n=447, group B).

To evaluate liver function, all patients underwent preoperative liver biochemistry tests, Child-Push grading, and measurement of the 15 minute retention rate for indocyanine green (ICR R 15). In our hospital, surgical treatment was performed mainly in Child-Pugh A patients; of the 497 total patients, only six patients were Child-Pugh B. The extent of resection was determined according to the ICG R15 and gross findings of the liver during the laparotomy. ICG R15<10% was regarded as having no impaired liver function.

According to the proposal by Makuuchi M et al.[14], patients with normal ICR R15 can tolerate major resection more than right hepatectomy. At ours hopstital, in terms of the tumor, it was considered resectable if there was no extrahepatic metastasis on preoperative imaging studies, no evidence of tumor thrombosis in major vessels such as the main portal vein and inferior vena cava, and if adequate tumor-free margins and sufficient remnant volumes were secured. Perioperative mortality was defined as death in the hospital after hepatectomy during the first admission for liver resection. Regarding morbidity, any complication requiring medication or interventional procedure was considered to be perioperative morbidity.

All patients were screened for the tumor marker alpha-fetoprotein [aFP] and protein induced by vitamin K absence or antagonist-II (PIVKA II), and underwent ultrasonography (US) or dynamic computed tomography (CT) 1 month post-surgery and every 3 months thereafter. When intrahepatic recurrence was suspected, the majority of patients were readmitted and received hepatic angiography for either diagnostic or therapeutic purposes. The median follow-up time after resection was 36 months (range 2 - 128 months).

To compare the recurrence pattern and time to recurrence between the two groups, recurrent HCC was classified as extrahepatic and intrahepatic recurrence, as well as early (≤ 12 months after hepatectomy) and late recurrence. Intrahepatic recurrent HCCs were further divided into three types (nodular recurrence [≤3 nodules], multinodular-diffuse recurrence [≥4 nodules], and infiltrative recurrence) on the basis of imaging studies such as dynamic CT, magnetic resonance imaging (MRI), and hepatic angiography.

2. Analysis of prognostic factors for disease-free and overall survival in patients with huge HCC

Prognostic factors for disease-free and overall survival were investigated using 18 clinicopathologic variables. The eight host factors were age, sex,

serum albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), indocyanine green retention at 15 minutes (ICG R15), liver cirrhosis, and preoperative treatment. Twenty five patients preoperatively received repeated courses of transarterial chemoembolization (TACE) or hepatic arterial infusion chemotherapy. The four surgical factors were perioperative transfusion, amount of intraoperative bleeding, surgical free margin, and extent of resection. Major resections were defined as a resection of three or more segments, while minor resections were defined as a resection of two or fewer segments according to the Couinaud classification. The six tumor factors were gross classification, satellite nodules, macroscopic vascular invasion, microscopic vascular invasion, Edmondson-Steiner grade, and serum a-FP level.

All tumors were grossly divided into four types according to the classification scheme developed by The Liver Cancer Study Group of Japan: single nodular type (a roughly round tumor with a clear demarcation), single nodular type with extranodular growth (resembling type I but exhibiting extranodular growth), confluent multinodular type (a tumor formed by a cluster of small and contiguous nodules), and infiltrative type (a tumor not clearly defined, with an indistinct boundary) [15, 16]. Previous studies have demonstrated that single nodular type tumors have better prognosis than other types [17-20]; therefore, all tumors were further categorized as being single nodular type or non-single nodular type.

3. Statistical Analysis

All continuous data are presented as a mean with standard deviation and were compared using the Student t test. Categorical variables were compared using the chi-square test or Fisher's Exact test, where appropriate. Survival curves were obtained by the Kaplan-Meier method and differences in survival between the groups were compared by the log-rank test. Clinicopathologic variables of previously reported prognostic values were dichotomized and analyzed on the

basis of their effect on eliminating disease and overall survival after resection. Perioperative mortalities were included in the overall survival analysis but were excluded from disease-free survival analysis. Following univariate analysis of the factors affecting survival, only the significant variables were used in the multivariate analysis according to the Cox-proportional hazards model. Statistical analyses were carried out using SPSS 12 for Windows (SPSS Inc., Chicago, IL, USA). A value of $P<0.05$ was considered statistically significant.

III. RESULTS

1. Comparison of clinicopathologic features, operative procedures, and perioperative outcomes

Clinicopatholgic characteristics between group A and group B are shown in Table 1. The two groups had similar mean ages and gender ratios. The hepatitis B virus was the most common etiology of liver disease in both groups. The mean level of 15 minute indocyanine green retention and the proportion of patients with cirrhosis was lower in group A than in group B. Group A had a higher incidence of patients with AFP >1000 IU/mL, microscopic vascular invasion, and advanced AJCC TNM stage tumors. The incidence of satellite nodules tended to be higher in group A, but this result did not reach statistical significance ($p=0.063$). There were no differences between the two groups with respect to Child-Pugh classifications, gross classification of tumors, macroscopic vascular invasion, Edmondson-Steiner grade, or margin of resection.

Operative procedures and perioperative outcomes between the two groups are shown in Table 2. Major resections were performed more frequently in Group A. Similarly, group A patients had more intraoperative blood loss and a greater transfusion requirement; however, there were no differences in perioperative morbidity and mortality between the two groups.

Table 1. Comparison of clinicopathologic features between patients with huge hepatocellular carcinomas (group A) and patients with smaller tumors (group B).

Variable	Group A (n=50)	Group B (n=447)	P value
Age (years)	50.8±12.5	53.3±9.7	0.175
Gender (male/female)	34/16	344/103	0.159
Etiology of liver disease			0.199
HBV	33 (66.0%)	331 (74.0%)	
HCV	1 (2.0%)	26 (5.8%)	
HBV+HCV	1 (2.0%)	6 (1.3%)	
Alcohol	3 (6.0%)	7 (1.6%)	
Occult HBV	6 (12.0%)	37 (8.3%)	
Cryptogenic	6 (12.0%)	40 (8.9%)	
Child-Pugh classification			0.114
A	48 (96.0%)	443 (99.1%)	
B	2 (4.0%)	4 (0.9%)	
ICG-R 15 (%)	7.46±4.86	10.73±8.66	0.011
AFP >1000 IU/mL	18 (36.0%)	82 (18.3%)	0.003
Gross classification			0.193
Single nodular type	22 (44.0%)	193 (45.8%)	
Confluent multinodular type	12 (24.0%)	126 (29.9%)	
Single nodular with extranodular growth type	7 (14.0%)	67 (15.9%)	
Infiltrative type	9 (18.0%)	33 (7.8%)	
Vaguely nodular type	0	2 (0.5%)	
Satellite nodules	13 (26.0%)	70 (15.7%)	0.063
Cirrhosis	13 (26.0%)	244 (54.6%)	<0.001
Macroscopic vascular invasion	5 (10.0%)	35 (7.8%)	0.583

Microscopic vascular invasion	34 (68.0%)	209 (46.8%)	0.004
Edmondson-Steiner grade			0.224
I-II	26 (59.1%)	255 (68.2%)	
III-IV	18 (40.9%)	119 (31.8%)	
Margin of resection ≤1.0 cm	26 (52.0%)	187 (41.8%)	0.168
Sixth AJCC TNM stage			<0.001
I	14 (28.0%)	212 (47.4%)	
II	24 (48.0%)	215 (48.1%)	
IIIA	6 (12.0%)	17 (3.8%)	
IIIB	4 (8.0%)	3 (0.7%)	
IIIC	2 (4.0%)	0	

ICG R 15: indocyanine green retention at 15 minutes; AFP: alpha-fetoprotein; AJCC: American Joint Committee on Cancer; TNM: Tumor Node Metastasis

Table 2. Comparison of operative procedures and perioperative outcomes between groups A and B.

Variable	Group A (n=50)	Group B (n=447)	P value
Operative procedure			<0.001
Major resection	37 (74.0%)	201 (45.0%)	
Minor resection	13 (26.0%)	246 (55.0%)	
Intraoperative blood loss (mL)	1390±1711	941±1289	0.030
Perioperative blood transfusion	35 (70.0%)	200 (44.7%)	0.001
Operative time (min)	284±80	270±100	0.315
Complications	12 (24.0%)	130 (29.1%)	0.451
Postoperative bleeding	0	4	
Liver dysfunction	0	10	
Ascites	3	42	
Intraabdominal abscess	0	3	

Bile leakage or biloma	3	17	
Pleural effusion	0	27	
Wound infection	4	9	
Others	2	18	
Perioperative mortality	0	9 (2.0%)	0.608

2. Comparison of long-term outcomes between groups A and B

The 1-, 3- and 5-year disease-free survival rates of group A were 49.0%, 38.6%, and 38.6%, respectively; these were significantly lower than those of group B (72.7%, 53.1%, and 45.4%) (p=0.028) (Figure 1). During the median follow-up period of 36 months post-resection, 29 patients (58%) in group A and 215 patients (48%) in group B experienced recurrence. Table 3 shows the comparison of recurrence pattern and time to recurrence between the two groups. Although the intrahepatic recurrence patterns were not different between the two groups, the incidence of extrahepatic recurrence and early recurrence ≤12 months after resection were significantly higher in group A than group B. Because aggressive recurrence patterns occurred more frequently in group A, survival after recurrence of the 29 recurrent patients in group A was significantly worse than that of the 215 recurrent patients in group B (median survival 9 months vs. 35 months, p<0.001). Figure 2 shows the overall survival after resection between the two groups. The overall survival of group A (70.0%, 50.2%, and 40.2% at 1, 3, and 5 years) was significantly worse than that of group B (91.3%, 77.2%, and 65.9%) (p<0.001) (Figure 2).

3. Prognostic factors for disease-free and overall survival in 50 patients with huge HCC

Univariate analysis revealed that minor resection, non-single nodular type tumor, microscopic vascular invasion, and serum AFP>1000 IU/mL were adverse prognostic factors for disease-free survival following resection. As for

overall survival after resection, surgical margins of ≤ 1.0 cm and non-single nodular gross type were found to be poor prognostic factors (Tables 4 and 5).

Multivariate analysis indicated that the gross classification of tumor type (single nodular vs. non-single nodular) was the only independent prognostic factor for both disease-free and overall survival after resection (Table 6). The overall 1-, 3-, and 5-year survival rates of 22 patients with single nodular type tumor were 77.3%, 67.6%, and 67.6%, respectively; these rates were significantly higher than those of the 28 patients with non-single nodular type tumors (64.3%, 35.6%, and 28.5%) (p=0.022) (Figure 3).

Figure 1. Disease-free survival curves of patients with huge (≥ 10 cm) hepatocellular carcinomas and patients with smaller tumors.

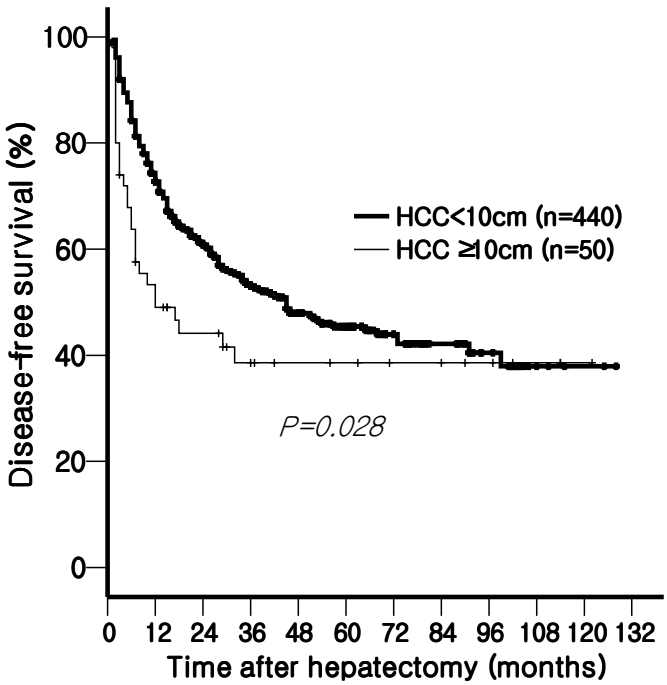


Table 3. Comparison of recurrence patterns and time to recurrence between the two groups.

Variable	Group A (n=29)	Group B (n=215)	P value
Intrahepatic recurrence	16	169	0.569
Nodular recurrence	10 (62.5%)	120 (71.0%)	
Multiple-diffuse recurrence	5 (31.3%)	34 (20.1%)	
Infiltrative recurrence	1 (6.3%)	15 (8.9%)	
Extrahepatic recurrence	13 (44.8%)	46 (21.4%)	0.006
Time to recurrence ≤ 12months	25 (86.2%)	119 (55.3%)	0.002

Figure 2. Overall survival curves of patients with huge (≥ 10 cm) hepatocellular carcinomas and patients with smaller tumors.

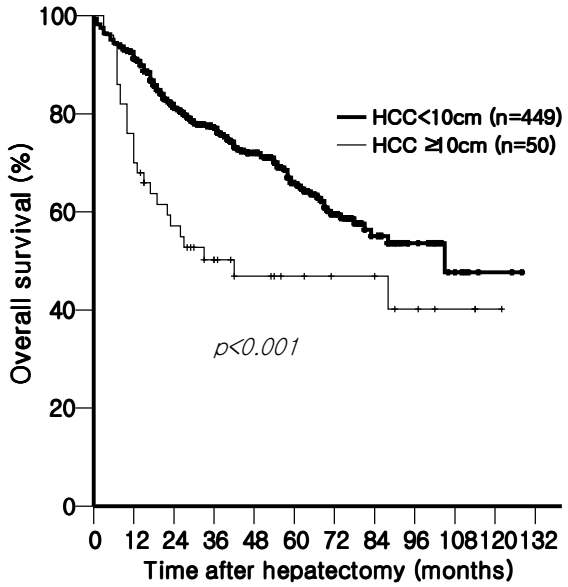


Table 4. Host and treatment-related prognostic factors for disease-free and overall survival of 50 patients with huge hepatocellular carcinoma as assessed by univariate analysis.

Variable	No. of patients (n=50)	1-year disease-free survival (%)	P value	3-year overall survival (%)	P value
Age (yrs)			0.546		0.241
≤60	39	50.2		46.7	
>60	11	45.5		63.6	
Gender			0.805		0.264
Male	34	43.6		42.7	
Female	16	60.6		68.2	
Serum albumin (g/dL)			0.407		0.173
≤3.5	18	37.0		32.4	
>3.5	32	55.4		61.5	
ALT (IU/L)			0.125		0.260
≤50	39	55.4		54.1	
>50	11	27.3		36.4	
AST (IU/L)			0.541		0.756
≤50	35	50.3		50.1	
>50	15	46.7		50.8	
ICG R 15 (%)			0.910		0.976
≤10	38	48.9		51.1	
>10	12	50.0		46.9	
Liver cirrhosis			0.628		0.281
No	37	47.3		46.9	
Yes	13	53.9		59.8	
Preoperative Treatment			0.538		0.538

No	25	44.0		54.2	
Yes	25	54.7		46.9	
Intraoperative bleeding			0.234		0.102
≤1000mL	19	57.9		68.0	
>1000mL	31	43.4		39.7	
Perioperative transfusion			0.273		0.109
No	15	65.5		73.3	
Yes	35	42.4		40.0	
Surgical margin (cm)			0.268		0.046
≤1.0	25	37.9		33.4	
>1.0	25	60.0		66.5	
Extent of resection			0.017		0.117
Minor	13	23.1		23.1	
Major	37	58.5		61.1	

HBsAg: hepatitis B surface antigen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ICG R 15: indocyanine green retention rate at 15 minutes

Table 5. Tumor-related prognostic factors for disease-free and overall survival of 50 patients with huge hepatocellular carcinoma as assessed by univariate analysis.

Variable	No. of patients (n=50)	1-year disease-free survival (%)	P value	3-year overall survival (%)	P value
Gross type			0.006		0.022
Single nodular	22	63.6		67.6	
Non-single nodular	28	18.8		35.6	
Satellite nodules			0.250		0.132
Absent	37	55.7		55.3	
Presence	13	30.8		35.2	
Macroscopic vascular invasion			0.135		0.160
Absent	45	52.3		54.4	
Present	5	20.0		0	
Microscopic vascular invasion			0.049		0.253
Absent	16	67.3		61.4	
Present	34	40.6		45.2	
Edmondson-Steiner grade*			0.055		0.078
I-II	26	53.9		59.8	
III-IV	18	31.6		32.4	
Serum AFP (IU/mL)			0.044		0.500
≤1000	32	56.1		51.6	
>1000	18	35.9		48.1	

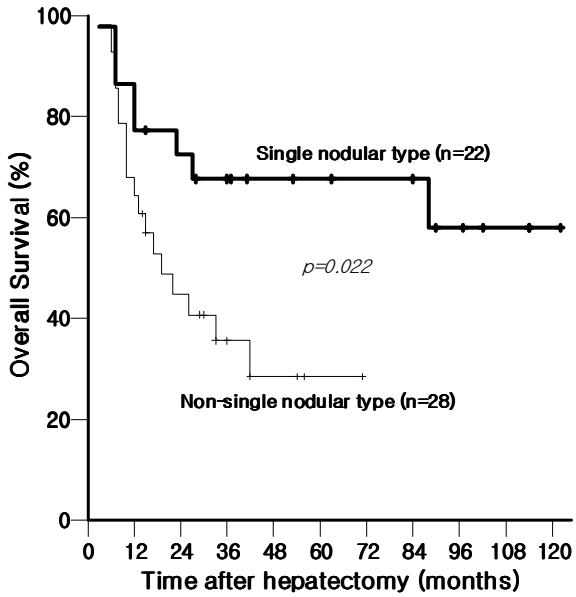
*: Not available in six patients due to total tumor necrosis following preoperative treatment

AJCC: American Joint Committee on Cancer; TNM: Tumor Node Metastasis; AFP: alpha-fetoprotein

Table 6. Independent prognostic factors for disease-free and overall survival of 50 patients with huge hepatocellular carcinoma according to multivariate analysis.

Variable	Coefficient	Standard error	P value	Relative risk (95% CI)
Disease-free survival				
Gross type (Non-single nodular vs. Single nodular type)	1.064	0.419	0.011	2.899 (1.275-6.591)
Overall survival				
Gross type (Non-single nodular vs. Single nodular type)	0.976	0.449	0.030	2.653 (1.101-6.396)

Figure 3. Overall survival curves according to the gross type of huge hepatocellular carcinoma.



IV. DISCUSSION

Several previous studies have indicated that tumor size is an independent predictor for recurrence and survival following resection in patients with HCC[21-23]. Specifically, as the size of tumor becomes larger, the incidence of vascular invasion and intrahepatic metastasis also increases[24, 25]. Similarly, in this study, huge HCC had a higher incidence of microscopic vascular invasion, AFP >1000 IU/mL, and more advanced stage tumors. In agreement with previous reports[9, 10, 26-28], disease-free and overall survival of patients with huge HCC were worse that those of patients with smaller tumors. Regarding the recurrence pattern, patients with huge HCC developed both extrahepatic recurrence and early recurrence $\leq$ 12 months after resection more frequently. In addition, the disease-free survival rate 3 years after resection in patients with

huge HCC remained consistent. Together, these findings suggest that recurrence of huge HCC originates largely from dissemination of the primary tumor. Because of the unfavorable recurrent patterns of huge HCC, the difference in overall survival after resection between the two groups was more prominent than that of the disease free survival group in this study.

In this study, extrahepatic metastasis and early recurrence (≤ 12 months) after resection were more common in patients with huge HCC. Similar results have been reported in previous studies[7, 9]. Although this finding is likely due to the more aggressive clinical behavior of huge HCC cases, it may be partly associated with the spillage of cancer cells into the systemic circulation during manipulation and mobilization of the tumor-located liver. Mok et al. demonstrated that patients who received surgical treatment for huge HCC had higher rates of both early recurrence and extrahepatic recurrence than patients who only received non-surgical treatment[7]. As for large right liver HCC, the anterior approach was shown to have better operative and survival outcomes compared with the conventional approach in a prospective randomized controlled study[29]. The survival benefit of this approach appeared more obvious in patients with high risk for tumor dissemination (stage II tumors and lymphovascular permeation of the tumor). Therefore, an anterior approach with minimal manipulation of the tumor should be the standard surgical technique in patients with huge HCC.

In our studies, few events occurred within 3 years of the introduction of both disease-free and overall survival curves of huge HCC, indicating that some of patients with huge HCC can be effectively treated by surgical resection. Indeed, 9 (18%) of 50 patients with huge HCC maintained disease-free status at least 5 years after resection. This finding is supported by the sixth AJCC tumor staging system, in which huge HCC without vascular invasion is no longer considered an advanced stage tumor. In a multicenter study of 300 patients with huge HCC by Pawlik et al., one third of the patients did not exhibit any evidence of either

macro or microscopic vascular invasion and the 5-year actuarial survival rate following surgical resection was 27%[1]. Therefore, huge HCC is not a homogenous group and should be classified into subgroups based on similar biologic behavior and prognosis.

Identification of the prognostic factors for long-term survival after resection of huge HCC is important in helping to clarify the heterogeneity of huge HCC. Macroscopic vascular invasion[8, 9], vascular invasion including macro and microscopic findings[1, 10, 30, 31], multiple tumors[1, 9, 28, 30], a high value of AFP[1, 28], and cirrhosis[1, 30] have all been demonstrated to be independent prognostic factors for survival after resection of huge HCC in several studies. Vascular invasion, especially macroscopic invasion, seems to be the most powerful prognostic factor for survival after resection. In this study, patients with macroscopic vascular invasion did not survive after 27 months following resection; however, macroscopic vascular invasion did not affect overall survival after resection according to univariate analysis because of the small numbers of patients with macroscopic vascular invasion (Table 5).

HCC has various morphological growth patterns. Although Eggel's gross classification of HCC (nodular, massive, or diffuse) was introduced in 1901 and has been commonly used since, the classifications of Kanai and the Liver Cancer Study Group of Japan have been shown to have more clinical value in patients with surgically resectable HCC [15, 17-20]. In these studies, single nodular type tumors were reported to have a lower incidence of vascular invasion and intrahepatic metastasis and had a better survival following resection compared with the other types. However, most of these studies were based on resected small HCC specimens. In our study, Kanai's gross classification was first applied only to huge HCCs. In accordance with previous studies, the single nodular type was the most common huge HCC type. In addition, the distributions of gross classifications between huge HCCs and smaller (< 10 cm) HCC tumors were not different (Table 1).

The invasiveness and metastatic potential of HCC appears to be associated with the gross tumor appearance. Genda et al. demonstrated that highly metastatic HCC cell lines formed tumors capable of infiltrative growth, and that non-metastatic cell lines formed tumors with expansive growth when implanted into the livers of immunodeficient mice[32]. The aggressive clinical behavior of confluent multinodular HCC and single nodular HCC with extranodular growth has been reported to be associated with loss of normal expression of E-cadherin, which acts as a suppressor of cancer cell invasion[19, 33]. In this study, single nodular type HCC was the only good independent prognostic factor for both disease-free and overall survival after curative resection. This result suggests that single nodular type HCC maintains its favorable biologic behavior and prognosis even when it grows beyond a diameter of 10 cm. Such gross classification of a tumor can be predicted preoperatively as a result of recent advances in diagnostic imaging techniques[18]. Therefore, gross classification of tumors may help to select the best candidates for surgical resection in patients with huge HCC.

A few studies have addressed the results of non-surgical treatments for huge HCC. TACE for huge HCC resulted in a 5-year survival rate of less than 10%[11]. In addition, the 5-year survival rate in 38 patients who had undergone 3 or more sessions of treatment, among a total of 75 patients who received non-surgical multidisciplinary therapy, was 16.3%[7]. In this study, patients who received curative resection for huge HCC had a 5-year survival rate of 40.2%, while patients with non-single nodular type HCC had a 5-year survival rate of 28.5%, which is far better than the results of non-surgical treatment discussed above. Therefore, in patients with a less favorable gross type of huge HCC, surgical resection should be considered if reserved liver function is sufficient and curative resection can be expected.

V. CONCLUSION

In conclusion, huge HCC exhibits a more aggressive clinical behavior and poor prognosis after resection than smaller tumors. To reduce the incidence of aggressive recurrence patterns, including extrahepatic recurrence and early recurrence, the anterior approach and minimal manipulation of the tumor should be the standard surgical techniques in patients with huge HCC. However, because the outcome of surgical resection is far better than that of non-surgical treatments, resection should be actively considered in these patients. In addition, patients with single nodular tumor type are the best candidates for surgical treatment.

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< ABSTRACT(IN KOREAN)>

거대 간세포암의 근치적 절제 후 성적

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도입: 최근 방사학적 진단기술의 발전과 고 위험 군을 대상으로 광범위한 검진으로 초기 간세포암의 발견이 증가하고 있지만, 아직도 진행된 상태에서 진단되는 간세포암을 흔히 경험하게 된다. 유럽과 미국의 간연구회는 5cm 이상의 간세포암의 경우 절제 후 높은 재발률과 불량한 예후로 인해 수술적 절제보다는 내과적 치료를 권고하고 있다. 그렇지만 최근 보고에서는 10cm 이상의 간세포암의 절제 후 5년 생존율이 20-35%로 다른 치료보다는 월등한 결과를 보고하고 있다. 이에 저자들은 10cm이상의 거대 간세포암환자들의 수술 후 성적 및 예후인자를 분석하였다.

방법: 1996년 1월부터 2006년 8월까지 세브란스병원에서 간세포암으로 진단받고 근치적 절제술을 시행 받은 497명의 환자를 수술 전 영상 검사 및 절제된 조직 병리검사에서 종양의 크기가 10cm 이상이었던 환자군 (group A)과 10cm 미만이었던 환자군 (group B)으로 분류하였다. 두 군간 임상 병리학적 특징, 수술방법 및 합병증, 일차 재발 형태 그리고 무병 및 전체생존율을 비교하였고, 또한 10cm 이상 환자 (group A)에서 근치적 절제 후 무병 및 전체생존율에 관여하는 예후인자를 분석하였다. 종양의 육안적 형태는 대한간암연구회의 분류를 이용하여 팽창결절형과 팽창결절형이 아닌 형태(다결절융합형, 결절주위파급형, 침습형) 즉, 두개의 이분형 변수로 분류하였다.

결과: Group A는 50명 group B는 447명의 환자가 해당되었다. ICG

R15%의 평균값이 group A에서 더 낮았고, AFP이 1000IU/mL이상인 경우, 간경변이 동반되지 않은 경우, 현미경적 혈관침범이 있는 경우가 group A에서 통계학적으로 의미 있게 더 많았다. Group A에서 대량간절제가 더 많이 시행되었고, 수술 중 평균 출혈량과 수혈의 빈도 또한 Group A에서 더 많았지만 수술 후 합병증 및 사망률은 두 그룹간 차이가 없었다. 두 그룹간 초기 재발 형태를 비교해 보았을 때 간내 재발형태 (결절형 재발, 다발성 재발, 침윤성재발)의 빈도 분포는 차이가 없었으나 간외재발 및 12개월 이내 초기 재발은 group A에서 많이 발생하였다. Group A의 1년, 3년 및 5년 무병생존율은 49.0%, 38.6% 및 38.6%로 group B의 72.7%, 53.1% 및 45.4%에 비해 통계학적으로 의미 있게 낮았다 (p=0.028). 1년, 3년 및 5년 전체생존율 또한 group A에서 70.0%, 50.2% 및 40.2%로 group B의 91.3%, 77.2% 및 65.9%에 비해 의미 있게 낮았다 (p<0.001). 간세포암이 10cm 이상인 group A에서 절제 후 전체 생존율에 관여하는 인자를 분석해 보았을 때 다변량 분석에서 종양의 육안적 분류형태(p=0.030, Hazard ratio=2.653 [95% Cl, 1.101-6.396])가 유일한 예후 인자로 나왔다.

결론: 10cm 이상 거대 간세포암은 10cm 미만 간세포암보다 공격적인 임상 양상 및 수술 후불량한 예후를 보였다. 그렇지만 5년 전체 생존율이 38.6%로 기존의 다른 치료 보다 월등한 결과를 보여 이런 환자에서 적극적인 수술적 절제가 필요하며 팽창결결형 간세포암인 경우 절제 후 가장 양호한 결과를 기대할 수 있을 것이다.

핵심되는 말 : 거대 간세포암, 수술적 절제, 예후, 종양의 육안적 분류