Clinical and Pathologic Characteristics of Hepatocellular Carcinoma following Resection according to the Tumor Size

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- ABSTRACT -

Clinical and Pathologic Characteristics of Hepatocellular Carcinoma Following Resection According to the Tumor Size

A tumor size of hepatocellular carcinoma (HCC) has been known to be an important prognostic factor after resection and it is considered to be closely correlated with vascular invasion of HCC. We aimed this study to elucidate the outcomes according to some previously studied size criteria and the relationship between the size criteria and clinicopathologic parameters after surgical resection in a single center. Between Apr 2001 and Apr 2008, 307 patients with pure HCC (no combined intrahepatic cholangiocarcinoma) underwent first hepatic resection in a single center without preoperative transcatheter arterial chemoembolization (TACE). The 307 patients' clinicopathologic data were retrospectively investigated. The tumor size criteria (2cm, 5cm and 10cm) were predictive factors for survival in univariate analysis, but not in multivariate analysis. Vascular invasion, tumor necrosis, and absence of tumor capsule were proved to be independent significant factors for overall survival. Among them, vascular invasion and tumor necrosis showed significant correlation with tumor size. On the other hand, tumor capsule did not show any correlation with tumor size. Tumor size should be further subdivided for T-classification of the AJCC/UICC staging system to predict prognosis more accurately. Considering that the AJCC/UICC staging system is a histopathologic staging system and tumor capsule was an independent significant prognostic factor irrespective of tumor size, tumor capsule should be included in T-classification of the AJCC/UICC staging system for more accurate prediction of survival.

Key words: hepatocellular carcinoma, hepatectomy, tumor size, prognostic factor, vascular invasion, spontaneous tumor necrosis, tumor capsule.

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I. INTRODUCTION

Traditionally, a tumor size of hepatocellular carcinoma (HCC) has been known to be an important prognostic factor after resection and it is considered to be closely correlated with vascular invasion of HCC. (Matsuda *et al*., 2007; Sakata *et al*., 2008)

In the fifth AJCC/UICC staging system, T-classification was determined by tumor size (diameter) criterion of 2cm, vascular invasion and multiplicity. (Fleming et al., 1997) However, with the work of Vauthey *et al*., in the sixth AJCC/UICC, T-classification system changed as follows; a single tumor without vascular invasion regardless of size, that is, if the single tumor has no vascular invasion, it is T1. If a single tumor, not more than 5cm, has vascular invasion, it belongs to T2. (Vauthey *et al*., 2002; AJCC, 2002) It means that tumor size itself is not an independent factor; rather it seems related to some important prognostic factors such as vascular invasion or histologic differentiation. However, in the Liver Cancer Study Group of Japan (LCSGJ), still a single tumor not more than 2cm is considered to be T1. (LCSGJ, 2003)

Some authors investigated about HCC greater than 10cm in diameter and called it a 'huge HCC'. Among those investigations, some demonstrated it poses worse prognosis compared with smaller one. (Chen *et al*., 2006; Pandey *et al*., 2007; Shah *et al*., 2007a)

Therefore, the debates about the prognostic significance of tumor size criteria of HCC still exist and to the best of our knowledge, there are few reports considering the clinicopathologic significance of each size criterion (2cm, 5cm and 10cm) of HCC in the same population. We aimed this study to elucidate the outcomes according to aforementioned each size criterion and the relationship between clinicopathologic parameters and the size criteria after surgical resection in a single center.

II. MATERIALS AND METHODS

MATERIALS

We investigated the patients underwent the first hepatic resection at the National Cancer Center of Korea between Apr 2001 and Apr 2008. Among them, 552 patients were proved to have HCC by histopathologic examination of the first hepatic resection specimens. We excluded the patients with multiple tumors (n=33) or with combined hepatocellular-cholangiocellular carcinoma (n = 24) and the patients undergone transcatheter arterial chemoembolization (TACE) before surgery (n = 188) from this study for the validity of histopathologic and clinical analyses. The remaining 307 patients' clinicopathologic data were retrospectively investigated.

The 307 patients were divided into four groups according to the primary tumor size; group A: tumor size ≤ 2cm, group B: 2cm < tumor size ≤ 5cm, group C: 5cm < tumor size ≤ 10cm, group D: tumor size > 10cm. We analyzed the clinicopathologic data to elucidate outcomes and prognostic factors of HCC in patients undergoing hepatic resection. Comparative analyses of clinicopathologic factors and prognosis according to the size criteria and groups were conducted.

METHODS

For those comparative analyses, the following factors were analyzed: age, gender, hepatitis viral markers, tumor marker, blood transfusion, tumor size, vascular invasion, histologic grade, spontaneous tumor necrosis, tumor capsule (absence vs. partial/complete), bile duct invasion, cirrhosis, and resection margin. The cumulative survival rate was calculated by the Kaplan-Meier method. Univariate correlations between factors and cumulative survivals were examined by the log-rank test. Multivariate correlations between factors were made by the Cox-regression model. Comparisons of nominal variables between groups were made using the chi-square test. A *P*-value of less than 0.05 was considered statistically significant.

III. RESULTS

Clinicopathologic profile

In the 307 patients, median age was 54.5 years (range: 26-83) and gender ratio was 251:56 (81.8:18.2%). Viral hepatitis was detected as follows; HBV in 220 (71.7%), HCV in 17 (5.5%), simultaneous HBV and HCV in 2 (0.7%) and no hepatitis virus in 68 (22.1%).

There were 151 (49.2%) major hepatectomies (3 or more Couinaud segments) and 156 (50.8%) minor hepatectomies (less than 3 Couinaud segments) (Table 1). Mean operation time was 279.0 minutes (range: 125-580 minutes) and blood transfusion was done in 18 patients (5.9%) during or immediately after hepatic resection.

Table 1. Modalities of hepatic resection.

Hepatic resection modalities		n	%
Major resection* (n = 151)	Right trisectionectomy	4	1.3
	Left trisectionectomy	0	0
	Extended right hemihepatectomy	10	3.3
	Extended left hemihepatectomy	13	4.2
	Right hemihepatectomy	85	27.7
	Left hemihepatectomy	19	6.2
	Central bisectionectomy	13	4.2
	Other trisegmentectomies	7	2.3
Minor resection† (n = 156)	Right anterior sectionectomy	6	2.0
	Right posterior sectionectomy	47	15.3
	Left lateral sectionectomy	25	8.1
	Other bisegmentectomies	35	11.4
	Monosegmentectomies	43	14.0
Sum		**307**	**100.0**

* Major resection: 3 or more Couinaud segments.

† Minor resection: less than 3 Couinaud segments.

The median tumor size was 4.0cm (range: 1.3-18.5cm). We divided the patients into four groups according to the primary tumor size with 2cm, 5cm and 10cm criteria. Vascular invasion was detected by histopathologic examination in 135 (44.0%) among the 307 patients. As a result, the sixth AJCC/UICC T-classification of the 307 patients with single tumor were as follows; T1 in 172 (56.0%), T2 in 119 (38.8%), T3 in11 (3.6%) and T4 in 5 (1.6%).

Spontaneous tumor necrosis was observed in 143 patients (46.6%) without preoperative TACE; median ratio of estimated necrotic volume was 10% (range: 1-99). Tumor capsule formation was observed in 240 patients (78.2%); complete tumor capsule in 135 (44.0%) and partial tumor capsule in 105 (34.2%).

Overall survival

For the 307 patients, 1-, 3- and 5-year overall survival rates were 92.1%, 78.8% and 69.3%, respectively (Fig. 1 a).

Overall survival was significantly different between the size groups ($P = 0.001$) (Fig. 1 b) and whether vascular invasion was presents or not ($P < 0.001$) (Fig. 1 c). Overall survival according to the sixth AJCC/UICC T-classification system also showed significant difference ($P < 0.001$) (Fig. 1 d). In intergroup analyses for each neighboring paired size groups, none of neighboring groups gained statistical significance (group A vs. B, $P = 0.139$; group B vs. C, $P = 0.061$; group C vs. D, $P = 0.226$) (Fig. 2a). However, all the size criteria of the 307 patients showed significant differences (2cm-criterion, $P = 0.024$; 5cm-criterion, $P < 0.001$; 10cm-criterion, $P = 0.001$) (Fig. 2 b, c and d).

The clinicopathologic factors possibly affecting prognosis following resection of HCC were analyzed. Among them, HCV carrier, tumor size > 2cm, > 5cm and > 10cm, respectively, vascular invasion, high Edmonson-Steiner grade, spontaneous tumor necrosis and absence of tumor capsule were poor prognostic factors for overall survival in univariate analysis (Table 2).

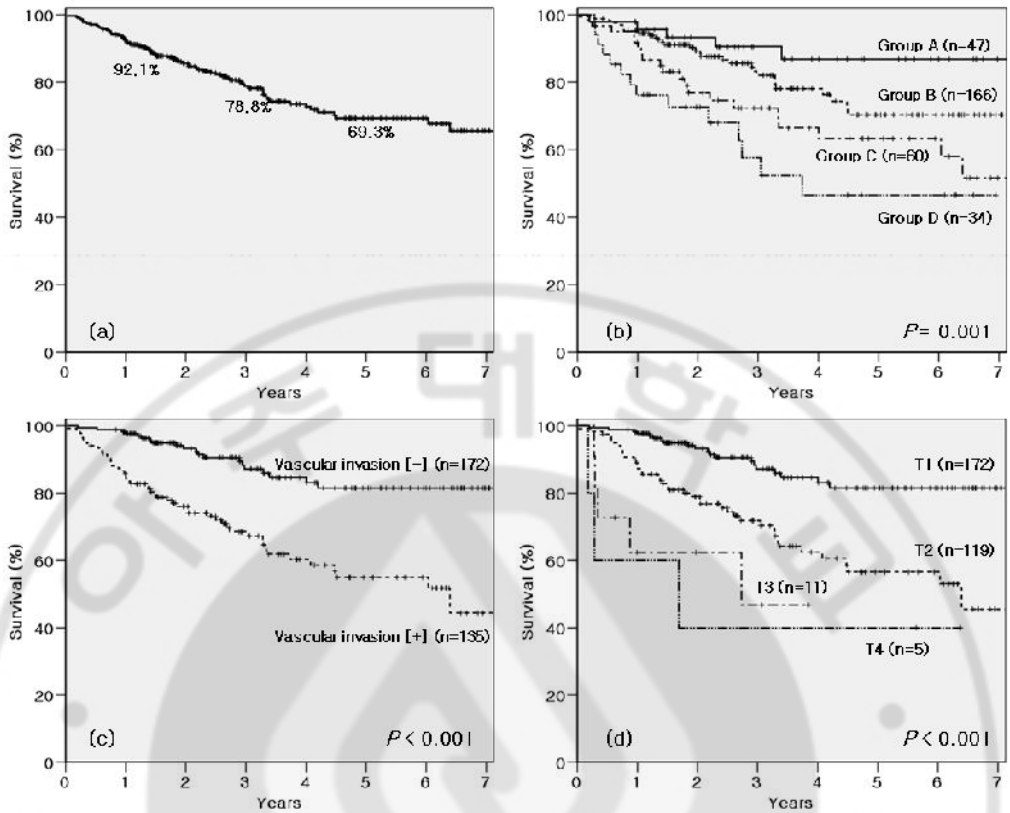

Fig. 1. Overall survival curves according to the factors comprised in the sixth AJCC/UICC T-classification system (Kaplan-Meier method). (a) Overall survival curve of 307 patients. (b) Tumor size groups. (c) Vascular invasion. (d) T-classification. Group A: tumor size ≤ 2cm, Group B: 2cm < tumor size ≤ 5cm, Group C: 5cm < tumor size ≤ 10cm, Group D: tumor size > 10cm.

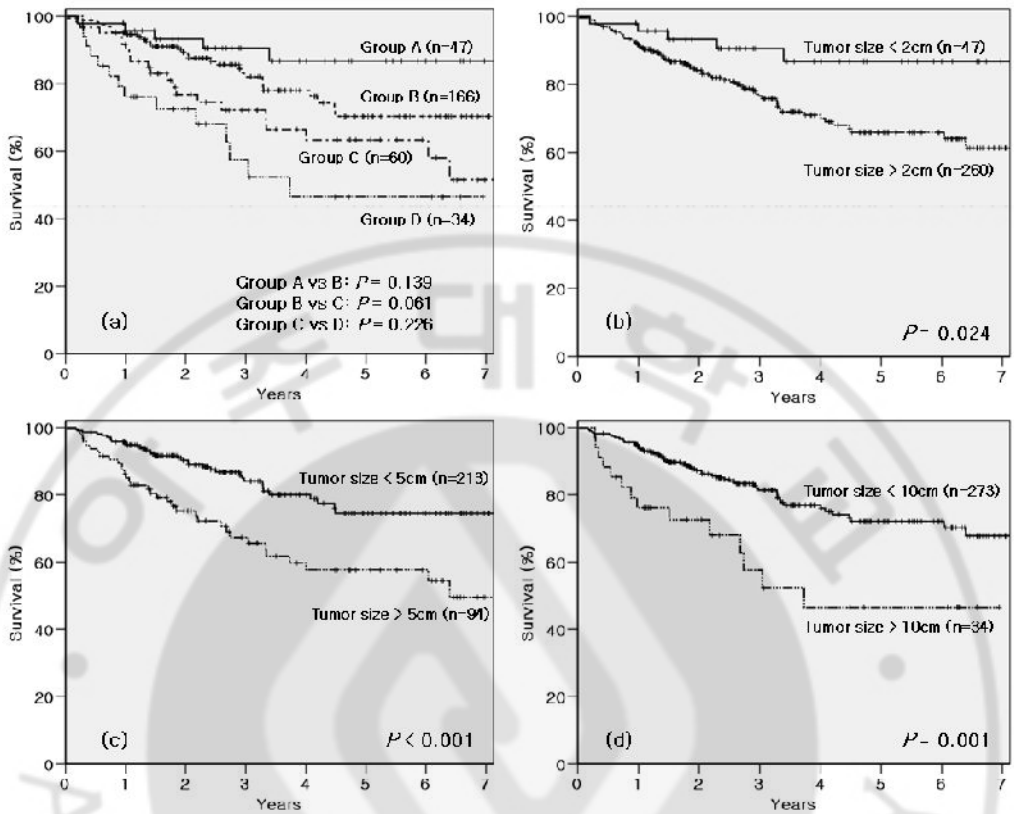

Fig. 2. Overall survival curves according to the tumor size (Kaplan-Meier method). (a) Four tumor size groups with comparison of intergroup differences. (b) Tumor size criterion, 2cm. (c) Tumor size criterion, 5cm. (d) Tumor size criterion, 10cm. Group A: tumor size ≤ 2cm, Group B: 2cm < tumor size ≤ 5cm, Group C: 5cm < tumor size ≤ 10cm, Group D: tumor size > 10cm.

Three size criteria (2cm-, 5cm- and 10cm-borders) were included respectively for the each Cox-regression analysis; however, none of them gained statistical significance in multivariate analyses. By these multivariate analyses vascular invasion ($P < 0.001$), tumor necrosis ($P = 0.021$), and absence of tumor capsule ($P = 0.024$) were proved to be independent significant factors for overall survival (Table 2) (Fig. 3).

Table 2. Clinicopathologic factors for survival (univariate and multivariate analyses).

Factors – Univariate analysis		n	%	5-year survival (%)	*P*-value
Age (years)	≤ 60	202	65.8	71.3	0.994
	> 60	105	34.2	65.3	
Gender	Male	251	81.8	68.7	0.668
	Female	56	18.2	71.6	
Viral hepatitis	NBNC	68	22.1	71.1	**0.001**
	HBV	220	71.7	70.8	
	HCV	17	5.5	49.6	
	HBV+HCV	2	0.7	0.0	
AFP	≤ 200 ng/ml	186	60.6	66.1	0.864
	> 200 ng/ml	121	39.4	72.7	
Blood transfusion	No	18	5.9	52.5	0.213
	Yes	289	94.1	70.2	
Tumor size	size ≤ 2cm	47	15.3	86.7	**0.001**
	2cm < size ≤ 5cm	166	54.1	70.3	
	5cm < size ≤ 10cm	60	19.5	63.3	
	10cm < size	34	11.1	46.5	
Vascular invasion	Absent	172	56.0	81.5	**< 0.001**
	Present	135	44.0	55.0	
E-S grade	I/II	158	51.5	78.6	**0.001**
	III/IV	149	48.5	60.1	
Tumor necrosis*	Absent	164	53.4	80.8	**< 0.001**
	Present	143	46.6	57.8	
Tumor capsule	Present†	240	78.2	72.2	**0.016**
	Absent	67	21.8	58.7	
Bile duct invasion	Negative	290	94.5	69.9	0.608
	Positive	17	5.5	59.7	
Cirrhosis	No	90	29.3	65.6	0.905
	Yes	217	70.7	70.9	
Resection margin	≥ 10 mm	307	60.9	72.4	0.146
	< 10 mm	120	39.1	64.2	

Factors – Multivariate analysis		n	%	HR (95% CI)	*P*-value
Vascular invasion	Absent	172	56.0	2.850	**< 0.001**
	Present	135	44.0	(1.659-4.896)	
Tumor necrosis*	Absent	164	53.4	1.864	**0.021**
	Present	143	46.6	(1.101-3.156)	
Tumor capsule	Present†	240	78.2	1.811	**0.024**
	Absent	67	21.8	(1.082-3.030)	

Abbreviation: NBNC, Non-A and Non-B; AFP, alpha-fetoprotein; E-S grade, Edmonson-Steiner grade; HR, Hazard ratio; CI, Confidence interval.

* Spontaneous tumor necrosis.

† Partial or complete capsule.

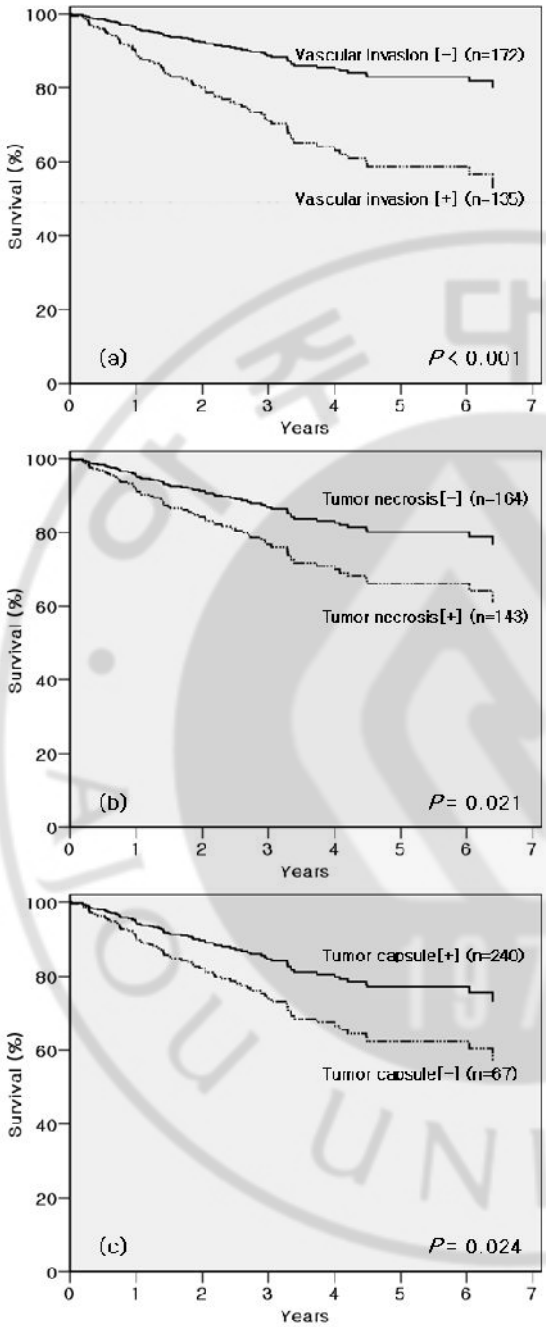

Fig. 3. Adjusted overall survival curves of the independent prognostic factors (Cox model). (a) Vascular invasion. (b) Tumor necrosis. (c) Tumor capsule.

The relationship between tumor size and independent prognostic factors

We analyzed the relationship between the tumor sizes and the three independent prognostic factors (Table 3). Among them, vascular invasion ($P < 0.001$) and tumor necrosis ($P < 0.001$) showed significant correlation with tumor size. On the other hand, tumor capsule did not show any correlation with tumor size ($P = 0.528$).

Table 3. The correlation between tumor size and independent prognostic factors.

Factors / **Group**	**Vascular invasion**		**Tumor necrosis***		**Tumor capsule**	
	Absent	Present	Absent	Present	Present†	Absent
A: tumor size ≤ 2cm	80.9	19.1	83.0	17.0	76.6	23.4
B: 2cm < tumor size ≤ 5cm	64.5	35.5	54.8	45.2	80.7	19.3
C: 5cm < tumor size ≤ 10cm	36.7	63.6	41.7	58.3	71.7	28.3
D: tumor size > 10cm	14.7	85.3	26.5	73.5	79.4	20.6
***P*-value**	**< 0.001**		**< 0.001**		0.528	

* Spontaneous tumor necrosis.

† Partial or complete capsule.

IV. DISCUSSION

HCC is a major cancer in Korea. (Park *et al.*, 2004; Cheon *et al.*, 2004; Korean Liver Cancer Study Group and National Cancer Center of Korea, 2009) HCC is generally known to be a highly malignant tumor with a poor prognosis. Unlike other primary cancers, the prognosis of HCC is not solely determined by cancer itself, since most of HCC occur in the background liver with cirrhosis and/or chronic viral hepatitis. Considerable portion of patients with HCC die of liver failure due to underlying liver disease. As a result, several staging systems which include liver function parameters have been proposed. Recently, liver transplantation has become so-called 'rising sun' for the primary treatment modality of both HCC and underlying liver cirrhosis simultaneously. However, because of organ shortage, it is limited to some lucky patients. As a result, hepatic resection is still the most common and curative measure for HCC.

Despite of all, as for many other cancers, the AJCC/UICC staging system is most commonly used worldwide after surgical resection for HCC. In the sixth AJCC/UICC TNM staging system, T-classification is determined by tumor size, vascular invasion, multiplicity of tumor and direct invasion of adjacent organ.

Multiplicity of HCC is considered to be a poor prognostic factor. (Chen *et al.*, 2003) HCC with multiple tumors is allocated to T2 or more in the sixth AJCC/UICC system. However, in the present study, patients with multiple tumors were observed only in 33 (9.7%) among the 340 patients who underwent first hepatic resection without preoperative TACE and they were excluded from this study.

The tumor size criterion is defined only in 5cm in the sixth AJCC/UICC system. However, other staging system such as LCSGJ, suggests the tumor size criterion as 2cm for T-classification. Besides, HCC larger than 10cm is classified as so-called 'huge HCC' and is considered to possess worse prognosis than smaller one in some previous reports. (Chen *et al.*, 2006; Pandey *et al.*, 2007; Shah *et al.*, 2007b; Lee *et al.*, 2007) In the present study, the patients were divided into four groups according to the aforementioned size criteria (2cm, 5cm and 10cm). Patients with tumor size between 2cm and 5cm were most common (54.1%) among the four size groups, and those with tumor size more than 10cm were 11.1%. The

survival rate comparisons in all the three size criteria showed significant differences. The tumor size proved to be a significant prognostic factor in univariate analysis, but not in multivariate analysis.

Vascular invasion is an established risk factor following surgery as well as a component of the sixth AJCC/UICC T-classification system. (Kaibori *et al.*, 2009; Nathan *et al.*, 2009; Shah *et al.*, 2007) Hematogenous route is considered to be important for both intrahepatic and extrahepatic metastases. (Mitsunobu *et al.*, 1996; Toyosaka *et al.*, 1996; Sawabe *et al.*, 1987) In our study, vascular invasion is proved to be a significant prognostic factor not only in univariate analysis but also in multivariate analysis. Moreover, it is the strongest independent prognostic factor in Cox-regression model of our study.

While some studies suggested bile duct invasion is a poor prognostic factor like the LCSGJ T-classification system, (Ikenaga *et al.*, 2009; Kojiro *et al.*, 1982; Minagawa *et al.*, 2007; Yeh *et al.*, 2004) other studies demonstrated the opposite results. (Lau *et al.*, 1997; Satoh *et al.*, 2000; Shiomi *et al.*, 2001) In our study, bile duct invasion did not attain statistical significance.

In this study, among these factors of T-classification, survival differences were observed in tumor size and vascular invasion by univariate analysis. However, by multivariate analysis, only vascular invasion was proved to be an independent significant factor among these factors. Other independent significant factors were spontaneous tumor necrosis and absence of tumor capsule, in addition to vascular invasion.

We investigated the relationship between the tumor size and three independent prognostic factors, respectively. Among them, tumor size showed statistically significant correlation with spontaneous tumor necrosis and vascular invasion, but not with absence of tumor capsule. Spontaneous tumor regression is rare in HCC. However, generally, a tumor is too large to be fed with enough blood supply to the entire tumor tissue, ischemic necrosis may happen. So, larger tumor tends to accompany spontaneous ischemic necrosis more frequently even without therapeutic embolization, as in our study. Some previous studies demonstrated the correlation between tumor size and vascular invasion. (Esnaola *et al.*, 2002; Pawlik *et al.*, 2005) The authors of these studies suggested that tumor size is regarded as a predictor of microvascular invasion for liver transplantation candidates.

Our study demonstrated that all the respective size criteria (2cm, 5cm and 10cm) were predictive factors for survival in univariate analysis, but not in multivariate analysis. Tumor

size showed significant correlation with some of independent prognostic factors, except for absence of tumor capsule.

V. CONCLUSION

In summary, all the tumor size criteria were valuable predictors for survival in patients with single HCC following resection. Tumor size should be subdivided further for T-classification to predict prognosis more accurately. Though tumor size itself was not an independent prognostic factor, it represents some of independent prognostic factors, but not all of them. Considering that the AJCC/UICC staging system is a histopathologic staging system rather than preoperative parameter such as the Milan criteria and tumor capsule was an independent significant prognostic factor irrespective of tumor size, tumor capsule should be included in T-classification of the AJCC/UICC staging system for more accurate prediction of survival.

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- 국문요약 -

간세포암의 종양 크기에 따른 수술 후 임상적 및 병리학적 특징

아주대학교 대학원의학과

조 성 연

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간세포암의 종양크기는 간절제술 후 중요한 예후인자로 알려져 있으며 간세포암의 혈관침습과 밀접히 관련되어있는 것으로 알려져 있다. 기존에 연구된 종양크기 기준들이 예후에 미치는 영향과 그 기준들과 임상-병리적 인자들의 관계를 알아보고자 본 연구를 시행하였다. 2001 년 4 월부터 2008 년 4 월 까지, 단일기관에서 307 명의 환자들이 순수한 간세포암(간내담관암과 병합되지 않은 간세포암)으로 술 전 경간동맥항암화학색전술 없이 첫 번째 간절제술을 받았다. 그 307 명 환자들의 술 전, 중 그리고 후의 임상-병리적 자료를 후향적으로 분석하였다. 각 종양크기기준들(2cm, 5cm 그리고 10cm)은 각각의 단변량분석에서 생존에 중요한 예후인자로 판명되었으나, 다변량분석에서는 그렇지 않았다. 혈관침습, 종양괴사, 그리고 종양피막의 부재들이 독립적인 예후인자로 판명되었다. 이들 중 혈관침습과 종양괴사는 종양크기와 밀접한 관련을 보였다. 반면에, 종양피막은 종양크기와 관련성을 보이지 않았다. AJCC/UICC 병기체계의 T-분류에서 예후를 보다 정확히 예측하기 위해서 종양크기를 더 세분화 되야 한다. AJCC/UICC 병기체계가 조직병리에 의한 병기체계인 점을 고려한다면, 본 연구의 종양피막 존재여부처럼, 다른 중요한 조직병리인자를 포함시켜야 한다.

핵심어: 간세포암, 간절제술, 종양크기, 예후인자, 혈관침습, 자연종양괴사, 종양피막.