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# Prognostic factors after hepatic resection for the single hepatocellular carcinoma larger than 5 cm

**Ji Hyun Noh, Tae-Seok Kim, Keun Soo Ahn, Yong Hoon Kim, Koo Jeong Kang**

*Department of Surgery, Dongsan Medical Center, Keimyung Univsersity School of Medicine, Daegu, Korea*

**Purpose:** This study aimed to determine which factors affect the prognosis of hepatectomy for hepatocellular carcinoma (HCC) larger than 5 cm, including the prognostic difference between tumor sizes from 5–10 cm and larger than 10 cm.
**Methods:** The medical records of 114 patients who underwent hepatectomy for single HCC larger than 5 cm were reviewed and analyzed retrospectively.
**Results:** In the analysis of the entire cohort of 114 patients, the 5-year overall and diseases-free survival rates were 50% and 29%, respectively. In a comparison of survival rates between groups, tumor sizes of 5 to 10 cm and larger than 10 cm, the overall and disease-free survival rates were not significantly different, respectively (54% *vs*. 41%, P = 0.433 and 33% *vs*. 23%, P = 0.083). On multivariate analysis, positive hepatitis B, high prothrombin induced by vitamin K absence or antagonist-II levels over 200 mIU/mL, and vascular invasion (micro- and macrovascular invasion) were independent prognostic factors for recurrence after hepatic resection. However, tumor size larger than 10 cm was not significant for recurrence after resection.
**Conclusion:** This study shows that surgical resection of solitary HCC larger than 5 cm showed favorable overall survival. And there is no survival difference with tumors between 5–10 cm and larger than 10 cm.
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**Key Words:** Hepatocellular carcinoma, Hepatectomy, Prognosis

## INTRODUCTION

Liver resection has been accepted as the best treatment modality to achieve curative goals of hepatocellular carcinoma (HCC), particularly in patients with a single tumor, although nonsurgical treatments such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA), percutaneous ethanol injection (PEIT), and radiation treatment have been performed widely for treatment of HCC in cases of small tumors, multiple bilateral tumors, and anatomically or functionally unresectable tumors. Single HCC has generally manifested good prognosis after resection and accepted as a good candidate. However, tumor size has been considered as an important prognostic factor and adopted in the recent staging system, the 7th edition of American joint Committee on Cancer (AJCC) cancer staging with a cutoff value 5 cm in size [1,2].

Despite recent advances in diagnostic imaging, HCC frequently presents in large size and advanced stage as a result of the absence of early symptoms and poorly performed screening. Consequently tumor sizes were over 10 cm in 7% to 14% of the patients with HCC who underwent surgical resection [3-6]. Because of increased risk of morbidity and mortality after resection, nonsurgical treatments such as TACE and radiation treatment have been often performed for huge HCC [3]. However, surgical indications in liver surgery have been expanded to include advanced cases in response to technical advances [6], and the feasibility of hepatic resection for a large HCC has been established already with statistically similar peri-

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**Corresponding Author: Koo Jeong Kang**
Division of Hepatobiliary & Pancreatic Surgery, Department of Surgery, Dongsan Medical Center, Keimyung University School of Medicine, 56 Dalseong-ro, Jung-gu, Daegu 41931, Korea
**Tel:** +82-53-250-7655, **Fax:** +82-53-250-7322
**E-mail:** kjkang@dsmc.or.kr

operative morbidity and mortality rates [3,5].

Tumor size has been considered a significant factor for intrahepatic and extrahepatic recurrence. However, many studies reported favorable survival with 5-year survival rates exceeding 30% after resection, even in tumor sizes larger than 10 cm; and tumor size is not a significant prognostic factor after resection in cases of tumor size larger than 5 cm [2,3,5-8].

On the other hand, another study reported better survival outcome after resection in patients with tumor sizes below 10 cm than over 10 cm [3]. Therefore, it is still necessary to validate the influence of tumor size on prognosis after resection in large HCC using a larger volume of patients or different settings.

Regarding the prognosis after curative resection of HCC, various pathologic factors such as vascular invasion [5,9], multiplicity [9,10], Edmonson-Steiner grade and tumor markers [9,11] are known to predict the outcome after resection. In addition to pathologic factors, other factors including tumor size, viral status, margin status, and underlying liver disease should be elucidated in large HCC. Therefore, the aim of this study is to report long-term outcomes and to identify prognostic factors after surgical resection in patients with single HCC larger than 5 cm in diameter and to assess the influence of tumor size on prognosis after resection in large HCC.

## METHODS

A total of 421 patients underwent hepatic resection for HCC at Keimyung Univsersity Dongsan Medical Center in Daegu between January 2001 and November 2013. Among these patients, 114 patients (27.1%) had single HCC larger than 5 cm and were included in this study. In this study, single HCC was defined based on the preoperative imaging studies regardless of postoperative pathologic results including satellite nodules and/or vascular invasion. The medical records of these patients were reviewed retrospectively and the following data were collected for each patient: demographics; laboratory data including tumor marker and hepatitis serologic test; tumor pathology; operative outcomes; date of last follow-up, recurrence, and death. Hepatic reserve was assessed using Child-Pugh classification and preoperative Indocyanine green retention at 15 minutes (ICG R-15) was routinely performed to assess liver function. Tumor size was defined as the largest diameter of the tumor in the specimen. Anatomical resection was defined as the systematic resection of hepatic segment according to the segmental and sectional anatomy described at the International Hepato-Pancreato Biliary Association Brisbane meeting in 2000.

Vascular invasion is classified as macrovascular invasion, which is grossly recognizable mostly in large to medium vessels, and microvascular invasion, which can be defined as the presence of tumor emboli mainly in small vessels such as portal vein branches in portal tracts, central veins in noncancerous liver tissue and venous vessels in the tumor capsule [2,12]. Tumor grade was assessed using the nuclear grading scheme outlined by Edmondson and Steiner. Grades 1 and 2 were considered low-grade HCC, and grades 3 and 4 were considered high grade.

The routine follow-up program consisted of physical examination, CT and laboratory tests including α-FP and prothrombin induced by vitamin K absence or antagonist-II (PIVKA-II) level every 3 month for the first year, and then every 6 month for next 5 years, thereafter annually for patients who have neither recurrence nor metastasis. Recurrence was defined as the appearance of a new lesion compatible with HCC in radiologic examination during follow-up period.

Statistical analysis was performed with IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA). Cumulative survival curves were analyzed by using the Kaplan-Meier method, and significance was determined by log-rank test. To investigate the prognostic factors predicting tumor recurrence, univariate and stepwise multivariate regression analysis was performed using a Cox proportional hazard model with $P < 0.05$ considered statistically significant.

## RESULTS

### Demography and clinicopathologic features

The demographics and clinical features of the 114 patients are summarized in Table 1. Among these patients 89 patients were male (78.1%) and 25 patients were female (21.9%). The mean age of the patients was 56.2 years. All of these patients were classified as Child-Pugh A in preoperative liver function assessment. The median preoperative α-FP and PIVKA-II were 69.1 ng/mL and 61.8 mIU/mL, and the mean preoperative ICG R-15 level was 11.2%. The mean tumor size was 9.1 cm. Among these patients, 73 patients (64%) had tumors measuring between 5 and 10 cm and 41 patients (36%) had tumors larger than 10 cm. The location of tumor was dominant in right liver (57%) and HBsAg was detected in 86 patients (75.4%). Anatomical resection was performed in 91 patients (79.8 %) and nonanatomical tumorectomy was performed in 23 patients (20.2%).

Pathological features of the patients in this study are summarized in Table 2. Portal vein gross invasion was identified in 22 patients (19.3%) and microscopic vascular invasion in 63 patients (55.3%), and satellite nodule was detected in 16 patients (14%). Underlying liver cirrhosis was identified in 58 patients (50.9%). Resection margin was grossly free from tumor in all patients. However, microscopic margin status of 10 patients (8.8%) was positive.

### Clinicopathologic features and survival according to tumor size

In comparison of the clinicopathologic characteristics bet-

**Table 1.** Clinical features of 114 patients who underwent resection for single hepatocellular carcinoma larger than 5 cm

| Variable | Value |
|---|---|
| Age (yr) | 56.2 ± 10.40 |
| Sex | |
| Male:female | 89 (78.1):25 (21.9) |
| Etiology of liver disease | |
| Hepatitis B | 86 (75.4) |
| Hepatitis C | 9 (7.9) |
| Hepatitis B & C | 3 (2.6) |
| Alcoholics | 46 (40.4) |
| Nonviral, nonalcoholic | 10 (8.8) |
| Preoperative ICG R-15 | 11.2 ± 6.17 |
| α-FP (ng/mL) | 69.05 (1–200,000) |
| PIVKA-II (mAU/m) | 61.82 (3–589,500) |
| Tumor size (cm) | 9.1 ± 3.58 |
| 5–10 | 73 (64.0) |
| >10 | 41(36.0) |
| Tumor location | |
| Right | 65 (57.0) |
| Left | 35 (30.7) |
| Central | 12 (10.5) |
| Caudate | 2 (1.8) |
| Surgical resection | |
| Anatomical | 91 (79.8) |
| Nonanatomical | 23 (20.2) |
| In-hospital mortality | 1 (0.9) |
| Recurrence time (mo) | |
| Mean | 29.0 ± 37.48 |
| Median (range) | 11.2 (0.3–150.9) |
| Follow-up period (mo) | |
| Mean | 42.3 ± 39.86 |
| Median (range) | 26.4 (0.3–159.7) |

Values are presented as mean ± standard deviation, number (%), or median (range).
ICG R-15, Indocyanine green retention at 15 minutes; PIVKA-II, prothrombin induced by vitamin K absence or antagonist-II.

**Table 2.** Pathologic features of 114 patients who underwent resection for single hepatocellular carcinoma larger than 5 cm

| Pathologic feature | No. (%) |
|---|---|
| Edmonson grade | |
| I | 7 (6.1) |
| II | 46 (40.4) |
| III | 54 (47.4) |
| IV | 7 (6.1) |
| Underlying cirrhosis | |
| Negative/positive | 56 (49.1)/58 (50.9) |
| Microscopic margin | |
| Negative/positive | 104 (91.2)/10 (8.8) |
| Serosa invasion | |
| Negative/positive | 93 (81.6)/21 (18.4) |
| Portal vein gross invasion | |
| Negative/positive | 92 (80.7)/22 (19.3) |
| Microvascular invasion | |
| Negative/positive | 51 (44.7)/63 (55.3) |
| Satellite nodule | |
| Negative/positive | 98 (86.0)/16 (14.0) |

ween groups stratified on the basis of tumor size (5–10 cm and over 10 cm), there were significant differences in preoperative α-FP level (P = 0.01) and microvascular invasion of the tumor (P = 0.02). However, other demographics and pathologic findings were not significantly different between groups and anatomical resection was performed similarly in both groups (Table 3). The 1-, 3- and 5-year overall survival rates were 84%, 62%, and 54% in patients with tumors 5–10 cm, and 72%, 46%, and 41% in patients with tumors over 10 cm, respectively (Fig. 1A). The 1-, 3- and 5-year recurrence-free survival rates were 63%, 41%, and 33% in patients with tumors 5–10 cm, and 35%, 26%, and 23% in patients with tumors over 10 cm, respectively (Fig. 1B). Although there were significant differences in preoperative α-FP and the rate of microvascular invasion that are known as prognostic factors after resection, there was no significant difference in overall and recurrence-free survival between patients with tumors 5–10 cm and those with tumors over 10 cm (P = 0.433 and P = 0.083. respectively).

## Survival & recurrence of the entire cohort

The median follow-up period was 26.4 months (range, 0.8–159.7 months). During a follow-up period, tumor recurrence occurred in 85 patients (74.6%) and median time to recurrence was 11.2 months after surgery, respectively. At the time of last follow-up, 59 patients (51.8%) had died of recurrent disease progression. In-hospital mortality occurred in only 1 patient (0.9%). For the entire cohort of 114 patients, 1-, 3- and 5-year overall survival rates were 79%, 57%, and 50%, (Fig. 2A) and recurrence-free survival rates were 53%, 36%, and 29%, respectively (Fig. 2B).

## Prognostic factor analysis for tumor recurrence

The outcome of univariate and multivariate analysis of risk factors for tumor recurrence is summarized in Table 4. In univariate analysis, positive HBsAg, high level of α-FP (≥2,000 ng/mL), high level of PIVKA-II (≥200 mIU/mL), Edmonson-Steiner grade III/IV, the presence of portal vein gross invasion and microvascular invasion, and the presence of satellite nodule were significant factors to predict tumor recurrence after resection. However, tumor size over 10 cm, positive surgical margin, and anatomical resection were not associated with tumor recurrence. Multivariate analysis revealed that positive HBsAg (hazard ratio [HR], 1.94; P = 0.043), PIVKA ≥200 mIU/mL (HR, 3.07; P < 0.001), portal vein gross invasion (HR, 2.30; P = 0.011) and microvascular invasion (HR, 2.15; P = 0.004) were

**Table 3.** Comparison of clinicopathologic features of patients underwent resection for single hepatocellular carcinoma larger than 5 cm

| Variable | 5–10 cm (n = 73) | >10 cm (n = 41) | P-value |
|---|---|---|---|
| Age (yr) | 56.85 ± 10.17 | 55.1 ± 10.82 | 0.390 |
| Sex | | | 0.814 |
| Male | 56 (77) | 33 (80) | |
| Female | 17 (33) | 8 (20) | |
| Preoperative α-FP (ng/mL) | 4,669.46 ± 23,688.20 | 25,673.41 ± 48,549.53 | 0.012 |
| Preoperative PIVKA-II (mAU/m) | 12,797.70 ± 74,056.60 | 6,511.26 ± 15,608.60 | 0.637 |
| ICG R-15 (%) | 11.59 ± 6.83 | 10.52 ± 4.78 | 0.328 |
| Safety margin (cm) | 1.13 ± 0.80 | 1.06 ± 1.29 | 0.731 |
| Anatomical resection | 58 (79) | 33 (80) | 0.985 |
| Underlying liver disease | | | |
| HBV (+) | 52 (71) | 34 (79) | 0.182 |
| HCV (+) | 8 (11) | 1 (2) | 0.153 |
| Alcoholics | 31 (42) | 15 (35) | 0.558 |
| Underlying cirrhosis | 42 (58) | 16 (39) | 0.079 |
| α-FP ≥ 2,000 ng/mL | 15 (21) | 20 (49) | 0.003 |
| PIVKA-II ≥ 200 mAU/m | 26 (36) | 19 (46) | 0.089 |
| Microscopic margin positive | 4 (5) | 6 (14) | 0.164 |
| Edmonson grade | | | 0.865 |
| I | 4 (5) | 3 (7) | |
| II | 31 (42) | 15 (37) | |
| III | 33 (45) | 21 (51) | |
| IV | 5 (7) | 2 (5) | |
| Serosa invasion | 13 (18) | 8 (20) | 0.807 |
| Portal vein gross invasion | 11 (15) | 11 (27) | 0.144 |
| Microvascular invasion | 34 (47) | 29 (71) | 0.018 |
| Satellite nodule | 9 (12) | 7 (17) | 0.577 |

Values are presented as mean±standard deviation or number (%).
PIVKA-II, prothrombin induced by vitamin K absence or antagonist-II; ICG R-15, Indocyanine green retention at 15 minutes.

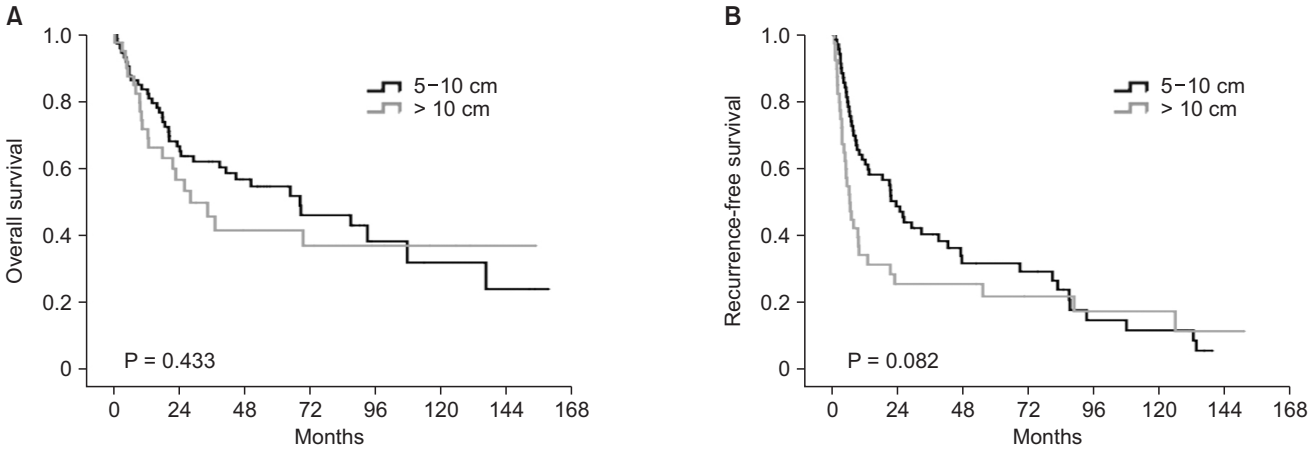


**Fig. 1.** Overall survival curve (A) and recurrence-free survival curve (B) according to tumor size, between 5–10 cm and over 10 cm.

independent risk factors for HCC recurrence after resection in patients with single HCC larger than 5 cm. The differences of recurrent-free survival according to independent prognostic factors revealed in this study were shown in Fig. 3.

## DISCUSSION

In patients with large HCC, long-term prognosis is generally considered to be poor [13,14]. In previous studies, the size of

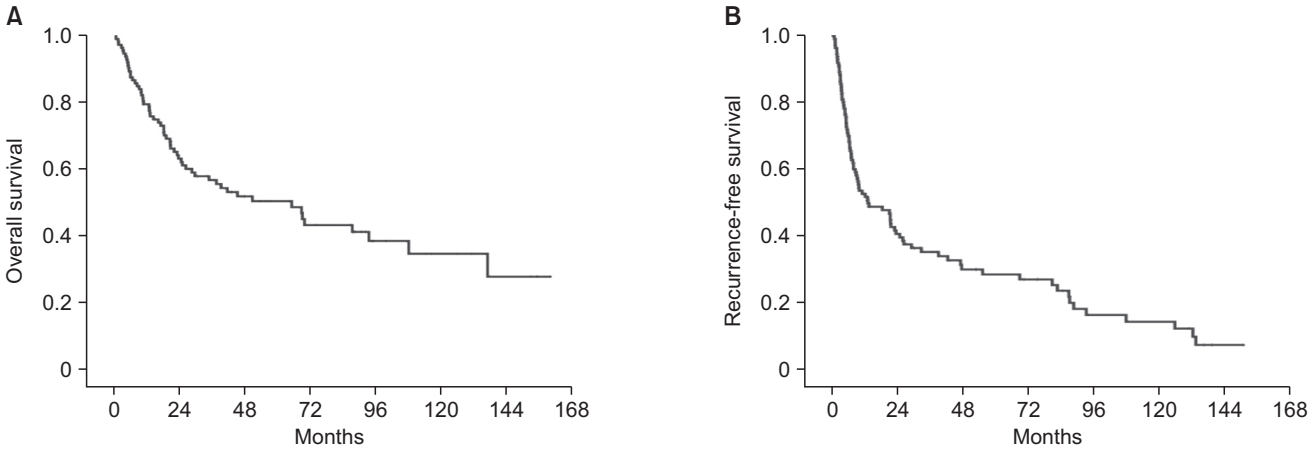


**Fig. 2.** Overall survival curve (A) and recurrence-free survival curve (B) for entire cohort after surgical resection for single hepatocellular carcinoma larger than 5 cm. The 1-, 3-, and 5-year overall survival rates were 79%, 57%, and 50%. The 1-, 3-, and 5-year recurrence-free survival rates were 53%, 36%, and 29%, respectively.

**Table 4.** Prognostic factors associated with hepatocellular carcinoma recurrence

| Variable | Univariate | | Multivariate | |
|---|---|---|---|---|
| | P-value | HR (95% CI) | P-value | HR (95% CI) |
| HBV (+) | 0.03 | 1.77 (1.06–2.97) | 0.043 | 1.94 (1.02–3.69) |
| HCV (+) | 0.21 | 1.60 (0.76–3.36) | - | - |
| Alcoholics | 0.296 | 0.79 (0.51–1.22) | - | - |
| α-FP > 2,000 ng/mL | 0.031 | 1.64 (1.04–2.59) | - | - |
| PIVKA-II > 200 mAU/m | 0.001 | 2.26 (1.39–3.67) | <0.001 | 3.07 (1.80–5.23) |
| Underlying cirrhosis (+) | 0.233 | 1.30 (0.84–2.00) | - | - |
| Tumor size > 10 cm | 0.084 | 1.47 (0.94–2.29) | - | - |
| Non-anatomic resection | 0.884 | 1.04 (0.68–1.75) | - | - |
| Edmonson grade III/IV | 0.008 | 1.81 (1.17–2.79) | - | - |
| Margin < 0.5 | 0.79 | 1.06 (0.67–1.70) | - | - |
| Microscopic margin positive | 0.087 | 1.78 (0.92–3.46) | - | - |
| Serosa invasion (+) | 0.281 | 1.34 (0.78–2.29) | - | - |
| Portal vein gross invasion | 0.004 | 2.09 (1.26–3.47) | 0.011 | 2.30 (1.21–4.38) |
| Microvascular invasion | 0.002 | 1.98 (1.28–3.06) | 0.004 | 2.15 (1.28–3.61) |
| Satellite nodule positive | 0.016 | 2.06 (1.14–3.70) | - | - |

HR, hazard ratio; CI, confidence interval; PIVKA-II, prothrombin induced by vitamin K absence or antagonist-II.

HCC has been considered an independent risk factor for patient survival and tumor recurrence. It may be related with higher incidence of occult vascular invasion, satellite nodules, and more advanced histologic grade in large HCC than small HCC [9].

The cutoff value that has an influence on the survival after resection for HCC was defined as 5 cm in the 7th edition of AJCC cancer staging system. In the AJCC 7th cancer staging system, T stage of HCC is classified based on vascular invasion, tumor multiplicity, and tumor size (5 cm). This is based on a report that identified independent prognostic factors after surgical resection by survival analysis of 557 patients collected from 4 centers [2]. In this report, tumor size had no effect on patient survival in patients with a single tumor without vascular invasion, while large tumor size over 5 cm had an effect on patient survival in cases of multiple tumors or presence of vascular invasion. However, tumor size was not a prognostic factor after resection even if tumor size was larger than 10 cm in patients with HCC over 5 cm in size [2]. In addition to this study, another study by a Tokyo group reported comparable survival between patients with HCC 5–10 cm and over 5 cm, regardless of significant differences in prognostic factors such as underlying liver status including cirrhosis, tumor markers, histologic grade, microvascular invasion and satellite nodules [6]. Moreover, excellent long-term survival rates after resection in patients with single large HCC have been reported in several studies [15-17].

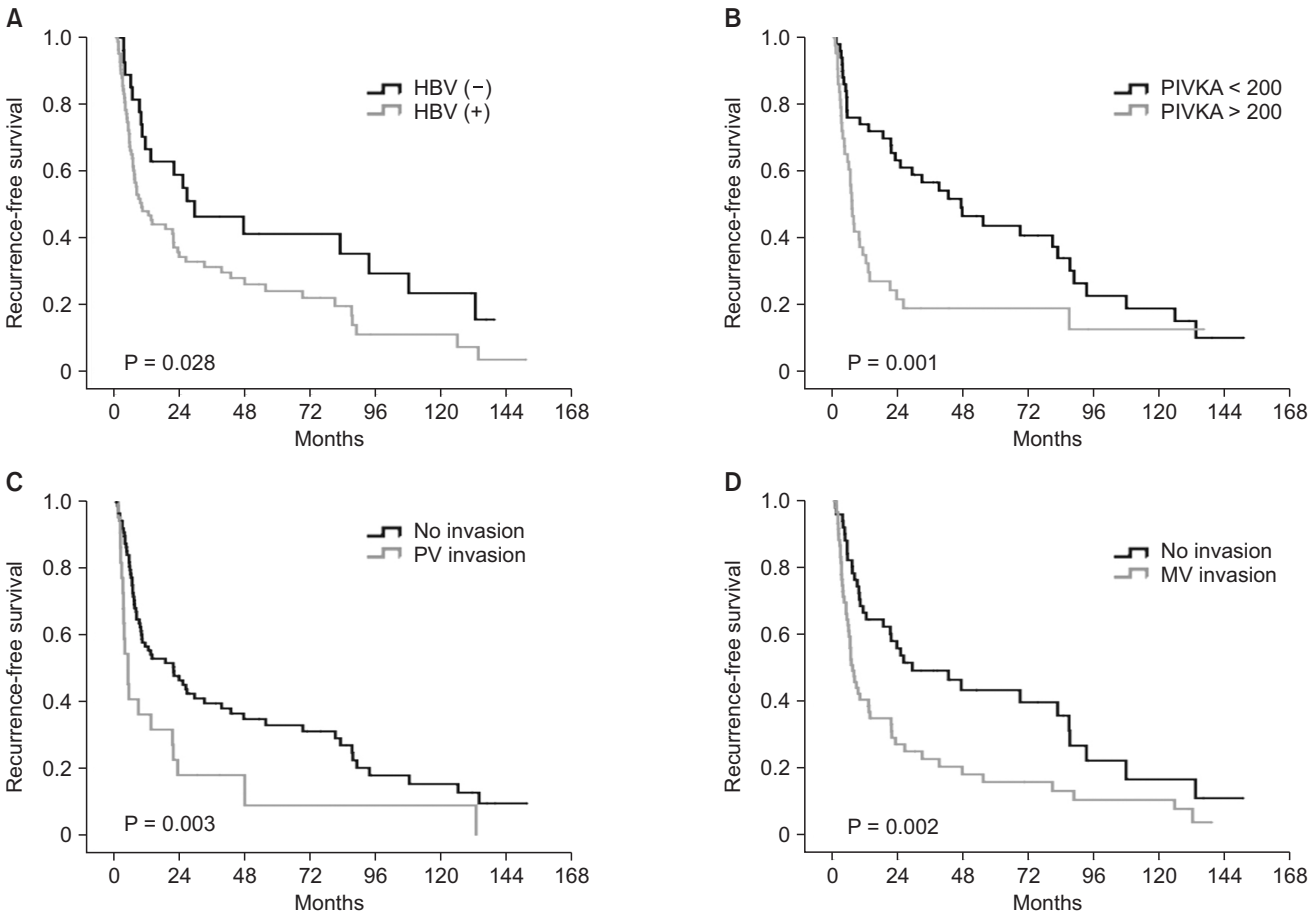


**Fig. 3.** Recurrence-free survival curves according to HBV (A), prothrombin induced by vitamin K absence or antagonist-II (B), the presence of portal vein gross invasion (C), and the presence of microvascular invasion (D).

In our study, our group analyzed the survival rate after resection in patients with HCC larger than 5 cm, and the 3-, 5-year overall and recurrent-free survival rates were 57%, 50% and 36%, 29%, respectively. The overall and recurrent-free survival rates after surgical resection in patients with HCC over 10 cm were not significantly different from those in patients with HCC 5–10 cm even though there were significant differences in α-FP level and microvascular invasion, and these results are comparable with the data from other reports [3,5-7]. Therefore, our data suggest that surgical resection of large single HCC is feasible and should be considered in patients with resectable HCC regardless of tumor size.

Recent studies showed that macrovascular invasion [5,9], microvascular invasion [9,10], elevated α-FP level [10,11], presence of liver cirrhosis [9,10], presence of satellite nodules [6] and multiple tumor nodules [9-11] influence prognosis after hepatic resection in patients with single large HCC. In our study, 4 prognostic factors predicting tumor recurrence after resection for single large HCC were identified; hepatitis B, PIVKA-II level over 200 mIU/mL, portal vein gross invasion and microvascular invasion. However, α-FP, presence of satellite nodule, presence of liver cirrhosis, and histologic grade, which have been known as poor prognostic factors, were not associated with tumor recurrence in our study. The presence of satellite nodules was significantly associated with tumor recurrence in univariate analysis; however, not significant in multivariate analysis. This may have been caused by the small number of patients in whom satellite nodules were identified.

One of the interesting results in our study is that microscopic positive resection margin status shows no adverse effect on recurrence and survival. This result is consistent with other reports [6,18]. In our study, capsule exposure on resection margin was interpreted as microscopic positive margin. However, tumor capsule was preserved intact in most cases. It is likely that tumor capsule exposure on resection margin would have less impact on prognosis after resection in encapsulated large HCC. Therefore, if tumor capsule is grossly intact and has no evidence of tumor invasion, capsule exposure on resection margin could be considered as negative margin. Practically, in cases where the tumor is very close to major vessels, parenchymal dissection near vessels should be performed using careful techniques, which can preserve capsule and prevent

cancer spread, such as Kelly clamping technique rather than using Cavitron Ultrasonic Surgical Aspirator technique.

Our study showed high recurrence rate (74.6%, 11.2 median recurrence months) after resection of single HCC larger than 5 cm. Because of the high recurrence rate, postoperative restrictive surveillance by checking tumor markers and imaging studies every 3–6 months are needed and appropriate treatments by multimodal approach such as repeat resection, TACE, RFA, and PEIT should be performed if recurrence is detected.

There are some limitations in this study. This study is a retrospective, single-center study and thus the results cannot be generalized. Therefore, a high-powered multicenter study with large cohort should be performed to validate our results. And the presence of comorbidity such as diabetes, cardiopulmonary disease, and cerebrovascular disease, which can have influence on the survival, was not assessed exactly in this study due to the limitations of a retrospective study. Another limitation of this study is that the different types and strengths of treatment after HCC recurrence in each patient were not assessed in this study. However, the survival status of all patients was completely identified through the assistance of the Korean National Health Insurance Service, and the most important variables for predicting prognosis are included in this study.

In conclusion, this study showed that tumor recurrence after surgical resection for single HCC larger than 5 cm is significantly influenced by the presence of portal vein gross invasion and microscopic vascular invasion, HBV, and elevated PIVKA-II. Hepatic resection for single HCC larger than 5 cm showed favorable survival outcome and there was no significant difference in survival after hepatic resection for single HCC larger than 10 cm compared to tumor sizes of 5–10 cm. Therefore, tumor size alone is not a poor prognostic factor after resection and surgical resection could be considered in patients with resectable single large HCC regardless of size.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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