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ORIGINAL ARTICLE

The Impact of Tumor Size on Long-Term Survival Outcomes After Resection of Solitary Hepatocellular Carcinoma: Single-Institution Experience with 2558 Patients

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Abstract

Background According to the 7th AJCC TNM staging system, solitary hepatocellular carcinoma (HCC) is classified as T1 or T2 based on microvascular invasion (MVI) regardless of tumor size. This study intended to evaluate the prognostic impact of tumor size on survival outcomes after macroscopic curative resection of solitary HCC.

Methods Patients who underwent R0 resection of solitary HCC <10 cm (n=2558) were selected for study. Follow-up lasted ≥24 months or until death.

Results HCC was detected during regular health screening or routine follow-up in 2054 cases (80.3 %). Hepatitis B virus (HBV) infection was associated in 2127 (83.2 %). Mean patient age was 54.4±9.9 years. Anatomical resection was performed in 1786 (69.8 %). MVI was identified in 407 (16.0 %) which therefore became stage T2; the other 2150 became stage T1. Tumor recurrence and patient survival rates were 24.9 and 95.0 % after 1 year, 49.6 and 84.1 % after 3 years, 57.7 and 75.0 % after 5 years, and 67.3 and 56.6 % after 10 years, respectively. Multivariate analysis showed that non-anatomical resection, MVI, and tumor size >5 cm were independent risk factors for both tumor recurrence and overall patient survival. Long-term survival correlated negatively with tumor size and MVI. Subgroup analysis with MVI and size cutoff of 5 cm revealed a significant survival difference (p=0.000). Tumor size >5 cm was not a significant prognostic factor in non-HBV patients.

Conclusions These results suggest that the prognostic impact of tumor size may be underestimated in the current version of the AJCC staging system and that solitary HCC staging could be improved with inclusion of tumor size cutoff of 5 cm in HBV-associated patients. Further validation is necessary with multicenter studies.

Keywords Hepatocellular carcinoma · Resection · Recurrence · Microvascular invasion

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and one of the leading causes of cancer-related death.[1] Hepatic resection is regarded as the treatment of choice if hepatic functional reserve permits it, but tumor recurrence is common, even after curative resection.[2,3] The overall prognosis after surgical treatment is determined by curability of the primary hepatic resection and additional treatment for recurrence in addition to the functional status of the remnant liver.[4]

Features of HCC are diverse in size at the time of diagnosis. Generally, the prognosis of large HCC after curative resection is inferior to that of small HCC because large HCC is more frequently associated with adverse prognostic factors.[5] Therefore, the size of tumors has been traditionally considered one of the most important risk factors for tumor recurrence and patient survival.[6]

However, this tumor size-oriented concept was changed based on high-volume studies that showed that survival outcomes were independent of tumor size in patients who underwent resection of solitary HCCs without vascular invasion.[7,8] These results were reflected in the 6th and 7th

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versions of the American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) staging system. It is generally suggested that there is no size limit that precludes hepatic resection of solitary HCC if the tumor is resectable.

Although the prognoses following surgical resection of large solitary HCC versus small solitary HCC are reported to be comparable statistically, we have encountered unfavorable long-term outcomes more frequently in patients with large solitary HCC. Our observation conforms to the traditional concept that HCC size is a significant prognostic factor, which is reflected in the majority of HCC staging systems[9–12]; thus at this time, whether the prognosis of post-resection solitary HCC is independent of tumor size is controversial. This study was therefore intended to evaluate the prognostic impact of tumor size on long-term patient survival after curative resection of solitary HCC.

Patients and Methods

Patients

The HCC database at our institution was searched to identify patients who underwent primary hepatic resection for HCC from January 2000 to April 2012 and 4148 patients were initially identified. To evaluate the prognostic value of tumor size objectively, the patients were primarily screened according to the following inclusion criteria: solitary HCC <10 cm, curative resection with tumor-free surgical margin, usual HCC pathology with exclusion of HCC-cholangiocarcinoma mixed tumor, no macroscopic vascular invasion, no extrahepatic metastasis including lymph node metastasis, no additional resection of adjacent organs, no later salvage liver transplantation, and Korean citizenship and registration with the National Health Insurance Service. The prognosis of patients with HCC ≥10 cm was separately analyzed in our previous study[4]; thus such cases were excluded from this study. Finally, 2558 patients were selected as the study population.

Medical records were reviewed retrospectively after approval by the Institutional Review Board of our institution. Patients were followed until March 2014 with medical record review and through the assistance of National Health Insurance Service, therefore making the patient follow-up period ≥24 months or until death. All patients were completely followed for identification of patient survival status.

Preoperative Evaluation and Surgical Procedures

Korean general population with chronic liver disease has been regularly followed up for detection of HCC according to the guideline of Korean Association for the Study of the Liver.[13–15]

Routine preoperative evaluation for HCC included abdomen and chest computed tomography (CT), magnetic resonance imaging (MRI), 2-^{18}F-fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET), and upper gastrointestinal endoscopy. Liver function was assessed with indocyanine green retention rate at 15 min (ICG-R_{15}) and presence of portal hypertension (esophageal varix, noticeable collaterals, and splenomegaly with thrombocytopenia). The extent of hepatic resection was primarily determined by the future liver remnant volume with consideration for tumor-free resection margins and hepatic functional reserve. If future liver remnant appeared too small, right portal vein embolization was performed 2–4 weeks before surgery.

Hepatic resection was classified as anatomical or non-anatomical hepatectomy. Anatomical hepatectomy included resection of one or more adjacent hepatic segments along the hepatic vasculature. Major hepatectomy was defined as resection of two hepatic sections/three segments or more and minor hepatectomy as resection of one section or less.

Perioperative mortality was defined as death of any cause within 30 days of surgery.

Tumor Size Assessment and HCC Staging

A small proportion of patients underwent various anti-HCC treatments before surgery, therefore resulting in variable degrees of tumor necrosis. To avoid bias from down-staging, the largest tumor diameter with inclusion of the necrotic portion was measured at the last preoperative CT. Patients were stratified into ten groups with 1-cm intervals (1 to 10 cm) and five groups with 2-cm intervals (2 to 10 cm). The latter groups were further divided into ten subgroups based on the status of microscopic vascular invasion (MVI).

HCCs were staged primarily based on the 7th edition of the AJCC TNM staging system and thus all patients were simply divided into T1N0M0 (stage I) and T2N0M0 (stage II) according to MVI. According to Barcelona Clinic Liver Cancer (BCLC) staging, our patients were widely distributed from very early stage (0) to intermediate stage (B).[9] In the Hong Kong Liver Cancer staging system,[12] which was developed in the Asian population, our patients were also widely distributed from early tumor (stage I) to locally advanced tumor (stage IIIb).

Postoperative Surveillance and Treatment for HCC Recurrence

Patients were followed up every 1 to 3 months during the first year after surgery, and thereafter every 3 months in principle.

The serum hepatitis B virus (HBV) concentration was monitored before and after surgery. More than 90 % of HBV-positive patients became HBV DNA-negative during postoperative follow-up due to vigorous antiviral treatment.[16]

The general principles of treatment for recurrent HCC lesions were applied to the study population, but patients having undergone salvage liver transplantation were excluded due to different survival outcomes.[17] Every locoregional treatment was performed including transarterial chemoembolization (TACE), radiofrequency ablation (RFA), percutaneous ethanol injection therapy (PEIT), external beam radiotherapy (EBRT), and surgical resection. Patients showing unsatisfactory responses to various locoregional treatments were finally treated with systemic chemotherapy, including sorafenib.[18]

Statistical Analysis

The primary and secondary endpoints of this study were the overall patient survival and the tumor recurrence after curative resection, respectively. Numeric data are reported as mean with standard deviation or as median with range. Survival curves were estimated by the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazard regression was used for multivariate survival analysis. A p value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 20, IBM, USA) and Statistica (version 6.0, StatSoft, OK, USA).

Results

Patient Demographics and Tumor Volume Characteristics

The clinical features of the 2558 patients are summarized in Table 1. Of these, HCC was detected in 2054 asymptomatic patients (714 during regular health screening, 1220 during routine follow-up for liver diseases, and 122 during work-up for other diseases), and 502 patients had symptoms or signs that led to specific HCC work-up. HBV infection was detected in 2127 patients (83.2 %) and antiviral agents were administered to 1846 patients (86.8 %), starting before or after surgery. The mean tumor diameter was 4.1 cm and the median tumor diameter was 3.8 cm.

Of the 2558 study patients, 513 patients (20.1 %) received preoperative locoregional treatments, including 360 patients treated with TACE, 35 with RFA, 49 with TACE and RFA, 15 with EBRT, and 54 with other treatments. Seventy-three patients (2.9 %) underwent preoperative right portal vein embolization for right liver resection.

Extents of Resection and Pathology

The extent of resection is summarized in Table 2. Anatomical resection was performed in 1786 patients (69.8 %). Pathological findings are summarized in Table 3. Most of the patients showed gross features of liver cirrhosis or chronic hepatitis, but 118 patients (4.6 %) showed grossly normal-appearing background liver. MVI was identified in 408 patients (16.0 %) who were therefore assigned to stage T2; the other 2150 patients were assigned to stage T1.

The incidence of MVI increased incrementally with tumor size as follows: 4.1 % (20 of 487) among patients with tumor size ≤2 cm, 13.1 % (143 of 1092) among patients with tumor

Table 1 Clinical features of 2558 patients with solitary hepatocellular carcinoma

Age (mean±SD)	54.4±9.9 years (range, 20–90)
Sex (*n*)	
Male	2200 (79.0 %)
Female	538 (21.0 %)
Background liver disease (*n*)	
Hepatitis B virus infection	2117 (82.8 %)
Hepatitis C virus infection	167 (6.5 %)
Hepatitis B and C virus infection	10 (0.4 %)
Alcoholic liver disease	145 (5.7 %)
Others	119 (4.7 %)
Blood laboratory profiles (mean±SD)[a]	
Albumin	3.7±0.8 g/dL (range, 1.6–5.8)
Aspartate aminotransferase	40.2±28.5 IU/L (range, 4–489)
Alanine aminotransferase	39.1±31.2 IU/L (range, 3–431)
Total bilirubin	0.93±0.38 mg/dL (range, 0.2–4.3)
Platelet count	156.7±61×10^3/μL (range, 23–580×10^3)
Prothrombin time (INR)	1.06±0.09 (range, 0.86–1.98)
Serum AFP (*n*=2521)	
<200 ng/mL (*n*)	1,753 (69.5 %)
≥200 ng/mL (*n*)	768 (30.5 %)
Mean±SD	2,151.1±11,072.9 ng/mL
Median	23 ng/mL (range, 0.4–262,000)
Serum PIVKA-II (*n*=1389)	
<200 mAU/mL (*n*)	977 (70.3 %)
≥200 mAU/mL (*n*)	412 (29.7 %)
Mean±SD	833.3±2788.1 mAU/mL
Median	53.0 mAU/mL (range, 1–>20,000)
FDG-PET (*n*=1241)	
Hypermetabolic (*n*)	702 (56.6 %)
Not hypermetabolic (*n*)	539 (43.4 %)
ICG-R_{15} (mean±SD, *n*=2491)	12.2±5.4 % (range, 0.1–36.1)
Child-Pugh classification (*n*)	
Class A	2443 (95.5 %)
Class B	125 (4.5 %)
MELD score (mean±SD)	7.6±1.3 (range, 5–16)
Preoperative locoregional treatment (*n*)	513 (20.1 %)

AFP alpha-fetoprotein, *PIVKA-II* proteins induced by vitamin K antagonist or absence-II, *ICG-R_{15}* indocyanine green retention test at 15 min, *MELD* model for end-stage liver disease

[a] One day before surgery

Table 2 Extent of liver resection for solitary hepatocellular carcinoma

Anatomical resection (*n*)	1786 (69.8 %)
Right hepatectomy±caudate resection	292
Left hepatectomy±caudate resection	187
Right anterior sectionectomy	377
Right posterior sectionectomy	425
Left lateral sectionectomy	216
Left medial sectionectomy	92
Central bisectionectomy	65
Monosegmentectomy	126
Right trisectionectomy	2
Left trisectionectomy	4
Non-anatomical resection (*n*)	772 (30.2 %)
Partial hepatectomy[a]	772

[a] Including subsegmentectomy and non-anatomical partial hepatectomy

size 2.1–4.0 cm, 20.6 % (118 of 572) among patients with tumor size 4.1–5.9 cm, 31.5 % (84 of 267) among patients with tumor size 6.1–7.9 cm, and 30.7 % (43 of 140) among patients with tumor size 8.1–9.9 cm. In addition, MVI was detected in 12.8 % (236 of 1938) of the patients with tumor size ≤5 cm and 27.7 % (172 of 620) of the patients with tumor size 5.1–9.9 cm (p=0.000).

Table 3 Summary of pathological findings and tumor staging in patients with solitary hepatocellular carcinoma

Background liver findings	
Liver parenchymal status (*n*)	
Normal	118 (4.6 %)
Chronic hepatitis	1312 (51.3 %)
Liver cirrhosis	1128 (44.1 %)
Fatty change (n)	502 of 2045 (24.5 %)
Tumor findings	
Simple nodular growth(n)	1477 (57.7 %)
Microvascular invasion (n)	408 (16.0 %)
Satellite nodules (n)	36 (1.4 %)
Tumor necrosis (n)	806 (31.5 %)
Tumor capsule invasion (*n*=1995)	443 (22.2 %)
Glisson capsule invasion (*n*=2357)	168 (7.1 %)
Tumor differentiation (*n*=2532)	
Most common	Well, 1451; moderate, 692; poor, 389
Worst	Well, 909; moderate, 1277; poor, 346
Tumor diameter (*n*)	
≤2 cm	487 (19.0 %)
2.1–4.0 cm	1092 (42.7 %)
4.1–5.9 cm	572 (22.4 %)
6.1–7.9 cm	267 (10.4 %)
8.1–9.9 cm	140 (5.5 %)
Mean±SD	4.1±2.1 cm
Median	3.8 cm (range, 0.2–9.9)

Tumor Recurrence and Overall Survival Outcomes

During a mean follow-up period of 58.1±36.7 months (median, 53.5; range, 1–172), death occurred in 743 (29.1 %) patients. Seven patients (0.3 %) died during the first 30 days after resection due to postoperative complications (hepatic failure in four and sepsis in three).

The 1-, 3-, 5-, and 10-year tumor recurrence rates were 24.9, 49.6, 57.7, and 67.3 %, respectively (Fig. 1a). The tumor recurrence curves of the patients with and without MVI (stage T2 versus T1) showed a statistical difference (p=0.000) and are presented in Fig. 1b.

The 1-, 3-, 5-, and 10-year overall patient survival rates were 95.0, 84.1, 75.0, and 56.6 %, respectively (Fig. 1c). The survival curves of the patients with and without MVI (stage T2 versus T1) showed a statistical difference (p=0.000) and are presented in Fig. 1d.

Prognosis Analysis According to Stratification by Tumor Size

The tumor recurrence rates after stratification into ten groups with 1-cm-size intervals and show a statistical difference (p=0.000). Patients were also divided into five groups with 2-cm-size intervals, which also showed a statistical difference (p=0.000). The 2-cm-interval groups were further divided by MVI status, in which the subgroups with and without MVI showed statistical differences (all p=0.000).

The overall survival curves are collectively presented after stratification into ten groups with 1-cm intervals (Fig. 2a) and show a statistical difference (p=0.000). Patients were also divided into five groups with 2-cm intervals (Fig. 2b), which also showed a statistical difference (p=0.000). The 2 cm-interval groups were further divided by MVI status (Fig. 2c, d), which showed a statistical difference (p=0.000 and p=0.004, respectively). When confining to the patients with solitary HCC ≤2 cm (n=487), MVI status was closely associated with overall survival rates (p=0.005), but not for HCC recurrence (p=0.207).

Prognosis Analysis According to Stratification by Tumor Size and MVI

Patients were divided into two groups based on a size cutoff of 5 cm and then further stratified by MVI status; thus patients were classified into four subgroups.

The 5-year tumor recurrence rates were 52.9 % in patients with HCC ≤5 cm and no MVI (n=1702), 69.1 % in patients

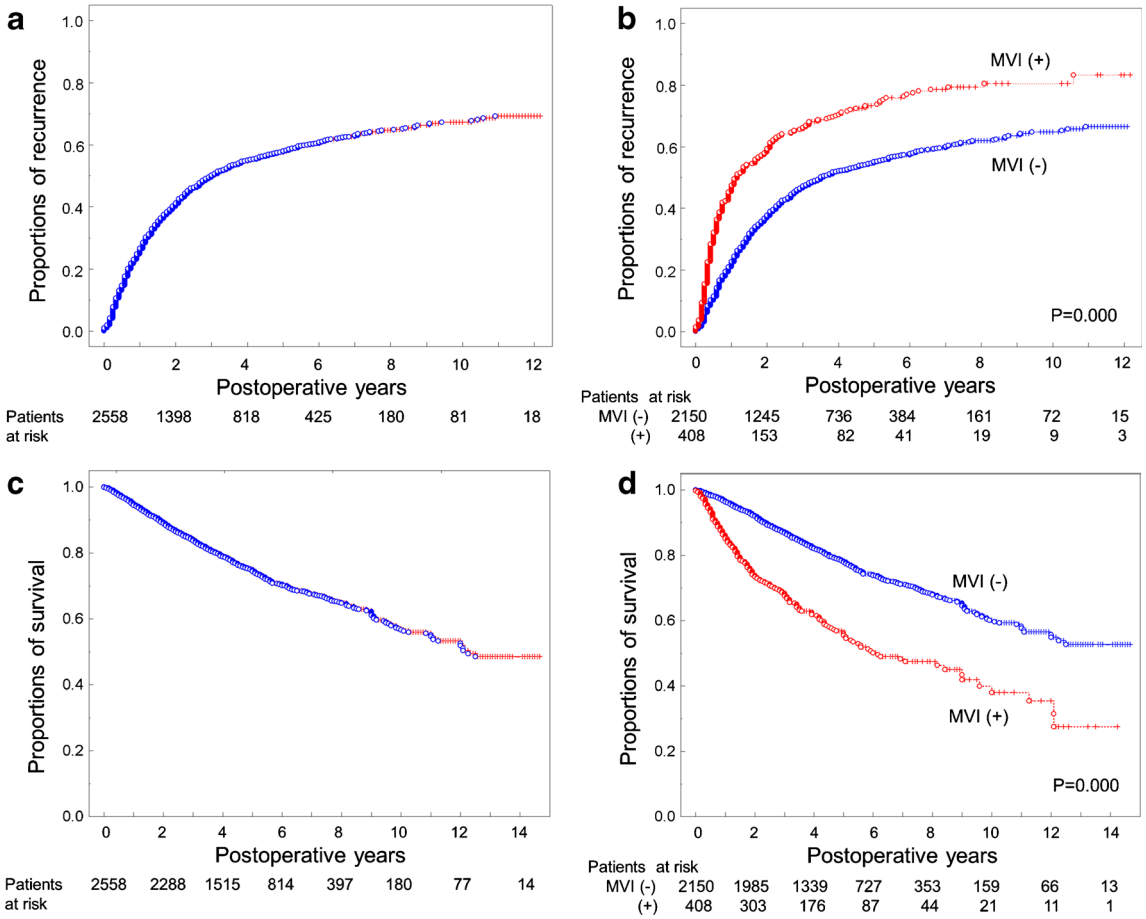

Fig. 1 Tumor recurrence and patient survival curves. Tumor recurrence was presented with cumulative tumor recurrence curve (**a**) and its stratification according to microvascular invasion (*MVI*) (**b**). Patient survival was presented with overall patient survival curve (**c**) and its stratification according to MVI status (**d**)

with HCC ≤5 cm and MVI (n=236), 62.2 % in patients with HCC of 5.1–9.9 cm and no MVI (n=448), and 79.3 % in patients with HCC of 5.1–9.9 cm and MVI (n=172). The comparison of tumor recurrence rates between any two subgroups showed a statistical difference (all p=0.000 except 0.019 between (HCC >5 cm without MVI) and (HCC ≤5 cm with MVI)) (Fig. 3a).

The overall 5-year survival rates were 80.9 % in patients with HCC ≤5 cm and no MVI (n=1702), 61.2 % in patients with HCC ≤5 cm and MVI (n=236), 69.2 % in patients with HCC of 5.1–9.9 cm and no MVI (n=448), and 50.2 % in patients with HCC of 5.1–9.9 cm and MVI (n=172). Comparison of the overall survival rates between any two subgroups showed a statistical difference (all p=0.000) (Fig. 3b).

Risk Factor Analysis for Tumor Recurrence and Overall Survival

The results of univariate analysis of tumor recurrence and overall survival are summarized in Table 4. Multivariate analysis revealed that independent risk factors were non-anatomical resection, tumor size >5 cm and MVI for tumor recurrence, and hypermetabolic uptake on FDG-PET, non-anatomical resection, tumor size >5 cm and MVI for overall patient survival (Table 5).

To evaluate the prognostic impact of anatomical and non-anatomical resection, the patients were divided into four groups based on MVI and size cutoff of 5 cm. Non-anatomical resection showed shortened disease-free survival in all subgroups (p<0.048) except in a subgroup with tumor size >5 cm and MVI presence (p=0.576) as well as deteriorated overall survival in all subgroups (p<0.045) except in a subgroup with tumor size >5 cm and MVI presence (p=0.534).

Risk Factor Analysis According to the Background Liver

We divided the patients into HBV group (n=2117) and non-HBV group (n=441) depending on the status of HBV serology and then multivariate analysis of tumor recurrence and overall survival was performed with only two factors of MVI and tumor size >5 cm.

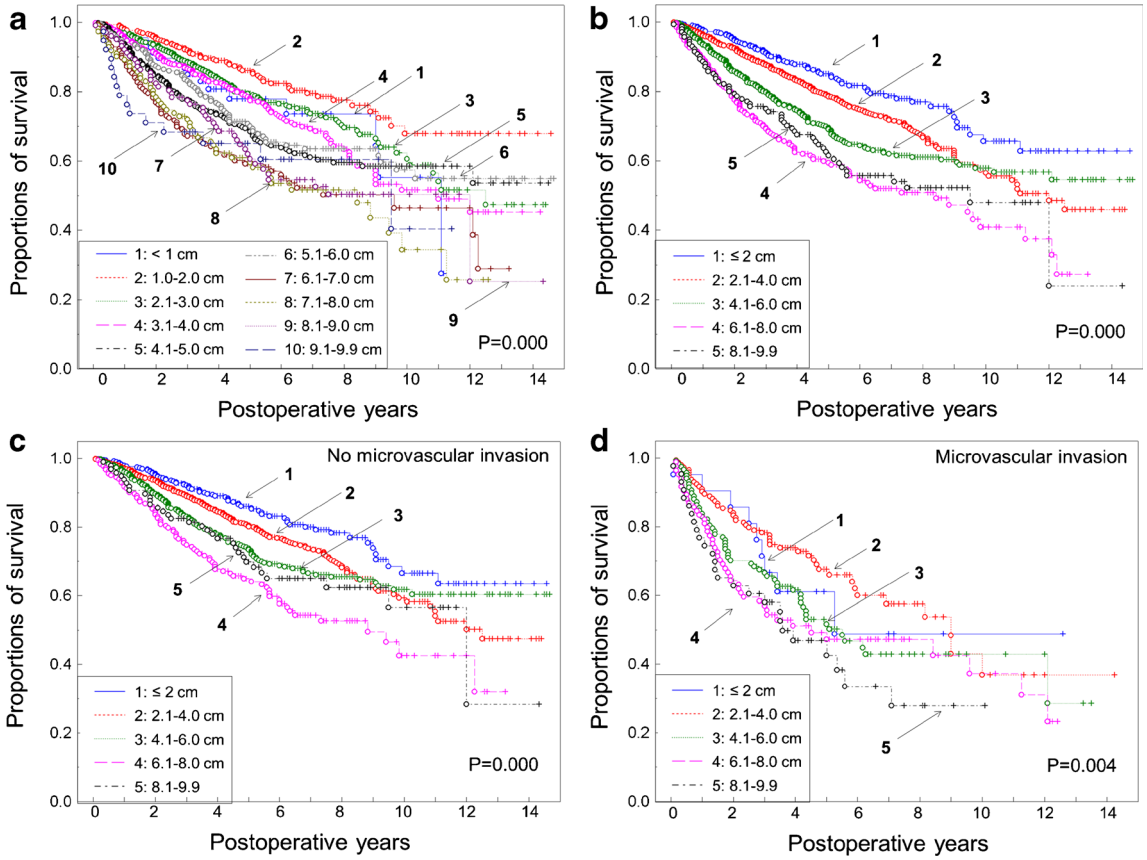

Fig. 2 Overall patient survival curves according to tumor size with stratifications in 1-cm intervals (**a**), 2-cm intervals (**b**), 2-cm intervals without microvascular invasion (*MVI*) (**c**), and 2-cm intervals with MVI (**d**)

In the HBV group, both MVI and tumor size >5 cm were independent prognostic factors. After confining to the non-HBV group, we found that MVI was statistically significant, but the prognostic impact of tumor size >5 cm was no longer statistically significant in both tumor recurrence and overall survival (Table 6).

Discussion

It is generally accepted that there is no size limit that precludes hepatic resection, especially for solitary HCCs if these tumors are resectable. Although large solitary HCCs≥10 cm were not included in the present study to avoid overlap with our previous study,[4] resection was performed for HCC when possible, regardless of tumor size. In practice, such surgery-oriented treatment policy is not well matched with the guidelines of the BCLC and Hong Kong Liver Cancer staging systems because of different sociomedical environment regarding HCC treatment.[9,12]

The size of HCC tumors has been traditionally considered one of the most important risk factors for tumor recurrence and overall survival, but this concept was modified after a noticeable multicenter study showed that survival outcomes were independent of tumor size in patients who underwent resection of solitary HCC without MVI.[7] These results were reflected in the 6th and 7th versions of the AJCC TNM staging system for HCC.[19] Other high-volume studies also supported that tumor size did not independently affect the long-term patient survival or tumor recurrence after curative resection of solitary HCC without vascular invasion.[8,20,21] Although there is no size cutoff for solitary HCC in the current AJCC TNM staging system, other HCC staging systems include tumor size. The BCLC system had size cutoffs at 2 and 5 cm,[9] but the cutoff at 5 cm was omitted at the BCLC/American Association for the Study of Liver Diseases (AASLD) guideline update in 2014[22]; the Hong Kong Liver Cancer staging system has a cutoff at 5 cm[12]; and the Japan Integrated Staging (JIS) Score includes a cutoff at 2 cm.[10,11] A high-volume multicenter study revealed that small HCCs ≤2 cm is associated with an excellent prognosis regardless of the status of MVI.[23] In a meta-analysis of prognostic indicators in HCC, tumor size was one of the most significant risk factors in 57 % of good-quality studies.[6]

There are several well-known risk factors for HCC prognosis after resection. In order to analyze the prognostic effects from tumor size without bias in this study, we intentionally selected the study patients without definite risk factors such as

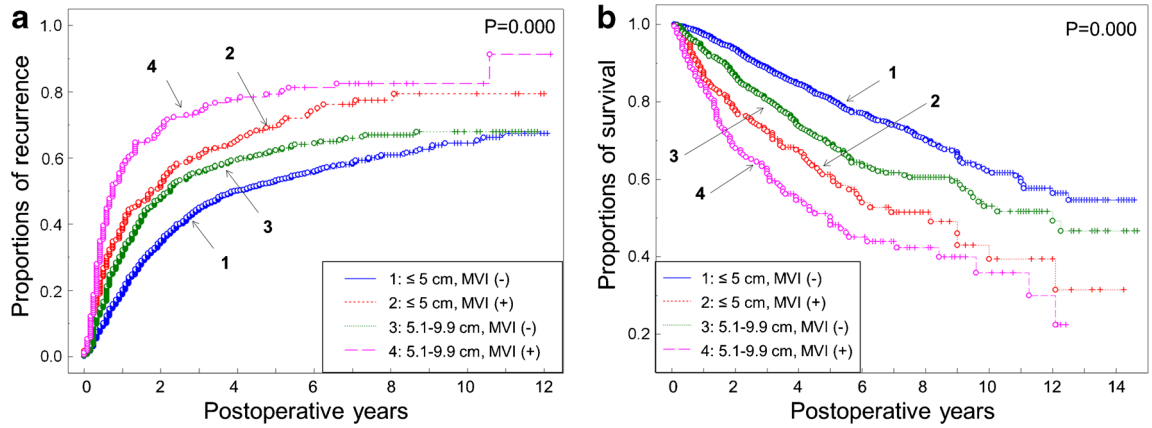

Fig. 3 Tumor recurrence (**a**) and overall patient survival (**b**) curves according to microvascular invasion (*MVI*) status and a tumor size cutoff of 5 cm

huge HCC, non-curative resection, unusual pathology, macroscopic vascular invasion, and lymph node metastasis. The results of this study demonstrated a stepwise incremental deterioration in tumor recurrence and overall survival outcomes with increased tumor size. After stratifying tumor size in 1-cm intervals, we confirmed that increased tumor size correlates with shorter overall and disease-free survival periods. Thereafter, stratification in 2-cm intervals made the prognostic differences more evident, especially in tumors <6 cm. With a combination of tumor size and MVI status, the prognostic impact of tumor size was demonstrated most clearly since larger tumors with MVI showed the worst survival outcome. The 7th version of AJCC TNM staging system for HCC divides solitary HCCs into T1 and T2 stages because MVI is the only determinant; however, we demonstrated that each stage T1 and T2 could be stratified into two subgroups with a cutoff of 5 cm in tumor size. Since the prognostic impact of a tumor size >5 cm did not overcome that of MVI, T stage cannot be

Table 4 Univariate analyses of factors associated with hepatocellular carcinoma recurrence and overall patient survival

Variables	Patient number	Tumor recurrence rate					Overall patient survival rate				
		1 year	3 years	5 years	10 years	*p* value	1 year	3 years	5 years	10 years	*p* value
Background liver											
HBV	2117	24.7 %	49.4 %	57.1 %	67.2 %	0.37	95.2 %	83.7 %	74.6 %	58.0 %	0.59
Non-HBV	441	25.7 %	50.37 %	60.3 %	66.4 %		93.8 %	85.6 %	75.1 %	65.6 %	
Serum AFP											
<200 ng/mL	1753	23.1 %	49.2 %	58.3 %	68.1 %	0.29	95.2 %	85.6 %	75.9 %	55.1 %	0.21
≥200 ng/mL	768	29.4 %	50.9 %	57.4 %	67.2 %		92.8 %	78.8 %	71.1 %	28.8 %	
Serum PIVKA-II											
<200 mAU/mL	977	21.5 %	44.8 %	50.9 %	57.4 %	0.000	96.0 %	88.0 %	79.3 %	73.4 %	0.000
≥200 mAU/mL	412	29.3 %	55.1 %	63.5 %	–		94.4 %	80.7 %	71.3 %	57.7 %	
FDG-PET											
Not hypermetabolic	539	18.4 %	43.8 %	51.8 %	–	0.000	97.2 %	91.8 %	83.1 %	76.1 %	0.000
Hypermetabolic	702	28.3 %	51.4 %	58.5 %	–		92.7 %	81.5 %	71.9 %	56.0 %	
Type of resection											
Anatomical	1786	24.1 %	47.8 %	55.9 %	64.6 %	0.003	95.5 %	84.7 %	76.2 %	59.8 %	0.002
Non-anatomical	772	26.3 %	52.9 %	60.8 %	71.9 %		94.4 %	81.9 %	71.9 %	51.9 %	
Tumor size											
≤5 cm	1938	21.0 %	46.1 %	54.8 %	66.3 %	0.000	97.0 %	88.6 %	80.7 %	59.6 %	0.000
5.1–9.9 cm	620	37.0 %	60.4 %	67.0 %	72.0 %		92.7 %	75.9 %	65.3 %	50.9 %	
Microvascular invasion											
Absent	2150	21.0 %	46.6 %	54.8 %	64.8 %	0.000	96.7 %	87.2 %	78.4 %	60.2 %	0.000
Present	408	45.5 %	65.9 %	73.3 %	80.5 %		86.3 %	68.5 %	56.5 %	38.1 %	

AFP alpha-fetoprotein, *HBV* hepatitis B virus, *PIVKA-II* proteins induced by vitamin K antagonist or absence-II, *FDG-PET* 2-^{18}F-fluoro-2-deoxy-d-glucose positron emission tomography

Table 5 Multivariate analyses of factors independently associated with hepatocellular carcinoma recurrence and overall patient survival

Variables	Tumor recurrence			Overall patient survival		
	Hazard ratio	95 % CI	*p* value	Hazard ratio	95 % CI	*p* value
PIVKA						
≥200 mAU/mL vs. <200 mAU/mL	1.22	0.99–1.49	0.056	1.26	0.92–1.72	0.144
FDG-PET						
Hypermetabolic vs. not hypermetabolic	1.12	0.94–1.32	0.194	1.19	1.04–1.36	0.012
Type of resection						
Non-anatomical vs. anatomical	1.12	1.03–1.23	0.007	1.22	1.08–1.39	0.002
Tumor size						
>5 cm vs. ≤5 cm	1.42	1.18–1.71	0.000	1.39	1.06–1.82	0.004
Microvascular invasion						
Present vs. absent	1.72	1.45–2.08	0.000	2.04	1.55–2.68	0.000

CI confidence interval, *PIVKA-II* proteins induced by vitamin K antagonist or absence-II, *FDG-PET* 2-^{18}F-fluoro-2-deoxy-d-glucose positron emission tomography

changed. According to the results of present study, MVI showed higher hazard ratios than tumor size >5 cm on both tumor recurrence and overall survival, which suggests that MVI carries a more negative prognostic impact than tumor size >5 cm. Therefore we suggest a minor modification of the T stage of solitary HCC as follows: for example, T1a for tumors ≤5 cm and T1b for tumors >5 cm in the absence of MVI, and T2a for tumors ≤5 cm and T2b for tumors >5 cm in the presence of MVI, since these four subgroups showed statistically different survival outcomes. Interestingly, unlike solitary HCCs, the 7th AJCC TNM system has a size component for multiple tumors, by which multiple tumors are currently classified as stage T2 and T3a with a cutoff of 5 cm.[19]

In a study of 1,109 patients with solitary HCC from six major international hepatobiliary centers, small HCCs ≤2 cm reported to be associated with an excellent prognosis that is not affected by the presence of MVI.[23] However, the results of the present study revealed that MVI in small HCCs ≤2 cm did not increased the tumor recurrence rate but deteriorated the overall survival rates significantly. Thus, it is necessary to perform further validation studies regarding on the prognostic impact of MVI in patients with small HCCs ≤2 cm.

Independent risk factors for both tumor recurrence and overall survival in the present study included non-anatomical resection, MVI, and tumor size >5 cm. There are debates in the role of anatomical resection for solitary HCCs,[24–28] but we found that anatomical resection is an independent favorable factor for overall and disease-free survival except in patients with HCC >5 cm with MVI. These results indicate that oncological aggressiveness of MVI-present large tumors may not be effectively overcome through systematic macroscopic curative resection. We observed that hypermetabolic uptake on FDG-PET was a significant risk factor only for overall patient survival. The degree of tumor aggressiveness is partially

Table 6 Multivariate analyses of risk factors according to the background livers

Variables	Tumor recurrence				Overall patient survival			
	HBV group		Non-HBV group		HBV group		Non-HBV group	
	Hazard ratio	*p* value	Hazard ratio	*p* value	Hazard ratio	*p* value	Hazard ratio	*p* value
Tumor size								
>5 cm vs. ≤5 cm	1.34	0.000	1.19	0.198	1.72	0.000	1.06	0.762
Microvascular invasion								
Present vs. absent	1.79	0.000	1.65	0.004	2.19	0.000	2.09	0.001

HBV hepatitis B virus

determined by the nature of tumor biology, and FDG-PET uptake is known to be associated with tumor biology. FDG metabolism is nearly normal in highly differentiated HCC, but notably increased in undifferentiated HCC. FDG accumulates similarly in highly differentiated HCC and normal liver, with the signal strength of FDG being relatively weak, making FDG uptake a predictor of the grade of HCC differentiation.[29,30] By contrast, considering its relatively lower statistical impact, FDG-PET finding might not have been an independent risk factor if the study population had been smaller.

There is a close association between HCC size and MVI. In solitary HCCs, the incidence of MVI was reported to be 31 % in HCCs ≤5 cm, 41 % in HCCs of 5.1–6.5 cm, and 58 % in HCCs >6.5 cm.[5] These results are comparable with our results, with a progressive increase from 4.1 to 30.7 % as tumor size increased from <2 to 8.1–9.9 cm, as well as 12.8 % in tumor size ≤5 cm and 27.7 % in tumor size of 5.1–9.9 cm. Although HCC size and incidence of MVI are crudely correlated, both are strong independent prognostic factors of overall patient survival, therefore warranting their inclusion in HCC staging guidelines.

MVI encompasses a heterogenous population of patients with a wide range of potential outcomes. A risk score system based on histologic features of MVI that includes invasion of the vessel with muscular wall and invasion of vessels ≥1 cm from the tumor capsule was reported to be able to stratify patients into three distinct groups with significantly different risks of recurrence and death. Interestingly, the patients with MVI and no risk factors had outcomes similar to patients with no MVI, whereas patients with MVI and both risk factors behaved like patients with macroscopic vascular invasion in terms of both tumor recurrence and patient survival.[31] Although this proposed MVI classification system was not fully validated externally, thorough pathological investigation of MVI seems to be mandatory for accurate tumor staging.

The prognostic impact of tumor size >5 cm was one of the main concerns of this study. In a high-volume ten-center study on the basis of the network of HCC East-West Study Group,[32] HBV-associated patients were 364 of 2046 (17.8 %) and tumor size >5 cm was an independent risk factor of overall patient survival. In the present study, tumor size >5 cm was an independent prognostic factor in HBV-associated patients. However, after confining to the 441 non-HBV patients, we found that the prognostic impact of tumor size >5 cm was no longer statistically significant in both tumor recurrence and overall survival. Considering that the sample number of our non-HBV patients was not small, such inconsistency should be verified by further validation through multicenter high-volume studies. In a Western center study with 314 HCC patients, tumor size was not an independent predictor of overall or recurrence-free survival on multivariate analyses, thus suggesting that tumor size alone is a limited prognostic factor and tumor biology and condition of the underlying liver are better prognosticators.[33] In a Japanese study with 219 HCC patients, the prognostic factors were different according to the background liver diseases.[34]

The condition of the underlying liver in HCC patients is one of the most important factors to decide treatment modality as well as to alter the survival outcomes. Although HCC most commonly occurs in the cirrhotic liver, approximately 10 to 40 % of cases develop against non-fibrotic to moderately fibrotic parenchyma.[35,36] In the present study, about 4.6 % of patients were regarded as definitely non-fibrotic and an additional considerable proportion of patients might have less advanced fibrosis. HBV-associated tumors seem to have a better prognosis in the non-fibrotic or minimally fibrotic population.[35] Most of our HBV patients were vigorously treated with antiviral agents, which might have beneficial effects regarding on slow or delayed progression of liver cirrhosis. We presume that preserved liver function in HBV patients might play non-negligible influence on modification of the prognostic factors.

There are some limitations to this study. This is a retrospective, single-center study and thus the results may not be generalizable although the study population is large enough. Multicenter prospective studies may have to be performed to validate our results. A uniquely strong point of this study is that the survival status of all patients was completely followed up through the assistance of Korean National Health Insurance Service.

In conclusion, this study suggested that the prognostic impact of tumor size was rather underestimated in the 7th version of AJCC TNM staging system for HCC. Therefore, we suggest including the concept of tumor size with a cutoff at 5 cm in solitary HCC, especially in HBV-associated patients. Further validation is necessary with multicenter studies.

Conflict of Interest None of the authors has any conflict of interest.

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Author Contribution Hwang S, Lee YJ, and Lee SG designed the study; Kim KH, Ahn CS, Moon DB, Ha TY, Jung DH, and Song GW contributed to the acquisition and analysis of data; and Hwang S drafted and revised the article.

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