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Above 5 cm, Size Does Not Matter Anymore in Patients with Hepatocellular Carcinoma

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Abstract

Background Solitary hepatocellular carcinoma (HCC) is a good candidate for surgical resection. However, the significance of the size of the tumor in solitary HCC remains unclear.

Objective The aim of this study was to evaluate the impact of tumor size on overall and recurrence-free survival of patients with solitary HCC.

Materials We retrospectively reviewed 616 patients with histologically confirmed solitary HCC who underwent curative surgical resection between 1994 and 2010. The characteristics and prognosis of patients with HCC were analyzed stratified by tumor size.

Results A total of 403 patients (65 %) had tumors <5 cm, 172 (28 %) had tumors between 5 and 10 cm, and 41 (7 %) had tumors >10 cm. The incidence of microvascular invasion, satellite nodules, and advanced tumor grade significantly increased with tumor size. The 5-year overall and recurrence-free survival rates of HCC <5 cm were 69.6 % and 32 %, respectively, which were significantly better than those of HCC between 5 and 10 cm (58 % and 26 %, respectively) and HCC >10 cm (53 % and 24 %, respectively). On multivariate analysis, cirrhosis ($p = 0.0307$), Child–Pugh B ($p = 0.0159$), indocyanine green retention rate at 15 min >10 % ($p = 0.0071$), microvascular invasion ($p < 0.0001$), and satellite nodules ($p = 0.0009$) were independent predictors of poor survival, whereas tumor size >5 cm was not.

Conclusion Although recurrence rates are high, surgical resection for solitary HCC offers good overall survival. Tumor size was not a prognostic factor. Solitary large HCC >10 cm would be a good candidate for hepatectomy as well as solitary HCC between 5 and 10 cm.

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Introduction

Liver resection represents the mainstay of curative treatment for hepatocellular carcinoma (HCC) and provides the only consistent long-term survival [1]. Technical advances in liver surgery have expanded surgical indications towards advanced cases [2]. Solitary HCC is generally thought to have a good prognosis after resection. It might be generally believed that patients with large tumors have a worse prognosis than those with small tumors. As there are several pathologic factors, such as vascular invasion, satellite nodules, high differentiation grade, or underlying liver disease, that may predict poor outcome after hepatic resection for HCC [3–6], tumor size would also be an important prognostic factor, and has been adopted in recent staging systems [7, 8]. One of the cut-off values for HCC is defined as 2 cm in diameter [9].

Despite the known correlation between tumor size and vascular invasion, excellent long-term survival rates in patients with solitary large HCC have been reported in several studies [6, 10–12]. However, the significance of other pathologic risk factors, such as satellite nodules, histologic grade, or underlying liver disease, in solitary HCC, in combination with the tumor size, remains ill defined. Therefore, the aims of the present study were to report long-term outcomes and to identify predictors of survival and recurrence after liver resection in a single-center-based Eastern cohort of patients with solitary HCC, and to assess the relationship between tumor size and the other prognostic factors.

Methods

All patients who underwent curative hepatic resection for primary and solitary HCC at Tokyo University Hospital, Tokyo, Japan, between November 1994 and December 2010 were retrospectively studied. In this study, solitary HCC was defined as any single HCC of any size, with no satellite nodules and/or vascular invasion at the time of treatment indication, and corresponding to Barcelona Clinic Liver Cancer (BCLC) 'A', according to the BCLC guidelines and the European Association for the Study of the Liver–American Association for the Study of Liver Diseases (EASL–AASLD) recommendations [13, 14]. Patients with multiple lesions and/or vascular invasion on imaging or patients who underwent repeat hepatectomy for single lesion were excluded.

Surgical strategy

The indications and extent of hepatectomy were based on an algorithm including the presence of ascites, the serum bilirubin level, and the indocyanine green retention rate at 15 min (ICG-R15), as previously described [15]. The operative procedure was chosen according to the location of the tumor and evaluation of functional hepatic reserve. Our policy was to perform anatomical resection whenever possible, irrespective of tumor size. Anatomical resection was defined as any type of systematic resection of the portal area based on Couinaud liver segmentation. Technically, the procedure for anatomical resection included the following four steps: (1) confirmation and marking of the border of segments and sectors to be resected, using a combination of external anatomic landmarks, segmental staining method, and selective devascularization using clamping of the segmental inflow; [16, 17] (2) parenchymal transection from the segmental border to the landmark veins under ultrasonography guidance; [16] (3) full exposure of the landmark veins on the cut surface of the liver; and (4) ligation of the segmental or sectoral portal pedicle near the root of the segment or sector. Otherwise, wedge resection or enucleation was defined as non-anatomic resection. When a major right-sided hepatectomy (resection of four or more Couinaud's segments [18]) was required for the treatment of such large tumors, the indication for portal vein embolization (PVE) was determined based on the ICG-R15 and the volume of the remnant left liver [19].

When performing a right hepatectomy, we routinely used the conventional approach [20]. Briefly, a thoracophrenolaparotomy was performed to provide a good view around the vena cava. The right adrenal gland was carefully dissected from the liver, and dissection of the inferior vena cava ligament allowed the vena cava to protrude to the right, making it possible to control the right hepatic vein extrahepatically.

Indications for transcatheter arterial chemoembolization (TACE) before hepatectomy were as follows: (1) in case of ruptured HCC; [21] and (2) in some cases, before a right hepatectomy in association with PVE in order to improve the rate of hypertrophy of the left remnant liver [22].

Histopathology

The size of the tumor and width of the surgical margin were recorded before the specimen was fixed. Background liver status, grade of tumor cell differentiation, presence/absence of microvascular invasion, and satellite nodules were detected on microscopic evaluation. Microvascular invasion was defined as gross or microscopic invasion of the portal vein, hepatic vein, and inferior vena cava. Satellite nodules were defined as the presence of intrahepatic metastases to the segment in which the principal tumor was located.

Follow-up

All patients were regularly followed-up at an outpatient clinic and monitored for recurrence by serum alfa-fetoprotein (AFP) and des-carboxy prothrombin (DCP) every 1–2 months, ultrasonography every 2 months, and dynamic computed tomography every 4 months, as previously reported [22]. Recurrence was defined as the appearance of a new lesion with radiological features compatible with HCC, as confirmed using at least two imaging modalities. When a recurrence was detected, the patient received further treatment by repeat hepatectomy, locoregional ablation treatments, including radiofrequency ablation, TACE, administration of sorafenib, or other treatment options. The disease-free survival period was defined as the interval between the operation and the date of the diagnosis of the first recurrence (either intrahepatic or extrahepatic). The remaining cases were censored at the date of the last follow-up assessment.

Statistical analysis

Continuous data were presented as median with range and were compared using the Student's *t* test or Mann–Whitney Wilcoxon test. Categorical data were analyzed by Pearson's χ^2 or Fischer's exact test. Time-to-endpoint analyses were performed using the Kaplan–Meier method. Overall survival was measured from date of resection to last living visit or loss to follow-up. Recurrence-free survival was measured from date of resection to recurrence or death. All variables were evaluated by the univariate log-rank test. Variables achieving a p value <0.1 were entered into a multivariate cox regression analysis. A p value of <0.05 was considered significant. Analyses were carried out using Statview software (version 5, 1992–1998, SAS Institute Inc., Cary, NC, USA).

Results

Clinical and histopathological characteristics

Our selection criteria identified 616 patients with resected solitary HCC. Overall, these patients had a median age of 66 years (range 13–85) (Table 1). The majority of patients were male (77 %). Among them, 292 (47 %) patients had cirrhosis, 530 patients (86 %) were classified as Child–Pugh A, and 86 (14 %) were Child–Pugh B. Of the 616 patients, 360 (58 %) patients were positive for hepatitis C and 138 (22 %) were positive for hepatitis B. The median tumor size was 35 mm (range 8–230).

In this study, four patients underwent TACE followed by liver resection for tumor rupture, and one patient underwent preoperative PVE following selective TACE for planned major hepatic resections.

When stratified according to tumor size, 403 (65 %) patients had tumors smaller than 5 cm, 172 (28 %) had tumors measuring between 5 and 10 cm, and 41 (7 %) had tumors larger than 10 cm (Table 2). Patients with larger tumors were less likely to be associated with hepatitis C

Table 1 Patient, operative, and pathologic characteristics

Characteristics	Overall ($n = 616$)
Patient	
Age (years)	66 (13–85)
Sex ratio (M/F)	476 (77)/140 (23)
Underlying liver disease	
HBV	138 (22)
HCV	360 (58)
Non-B non-C	130 (21)
Child-pugh grade	
A	530 (86)
B	86 (14)
Background liver	
Normal	38 (6)
Chronic hepatitis or fibrosis	286 (46)
Cirrhosis	292 (47)
HCC rupture	4 (0.6)
Portal vein embolization	21 (3.4)
ICG-R15	8.7 (2.2–72.30)
ICG-R15 >10	419 (68)
AFP (ng/ml)	19.20 (0–436,000)
AFP >200	169 (27)
DCP (mAu/ml)	62.5 (0–200,135)
DCP >100	265 (43)
Operative	
Major hepatectomy ≥4 segments	86 (14)
Anatomic resection	426 (69)
Pathologic	
Tumor size (mm)	35 (8–230)
Grade	
Well differentiated	97 (16)
Moderately differentiated	427 (69)
Poorly differentiated	71 (11.5)
Combined	6 (1)
Necrosis	15 (2)
Microvascular invasion	191 (31)
Bile duct invasion	27 (4)
Satellite nodules	80 (13)
Positive surgical margins	20 (3)

Data are presented as n (%) or median (range)

AFP alfa-fetoprotein, *DCP* des-γ-carboxyprothrombin, *F* female, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *ICG-R15* indocyanine green retention rate at 15 min, *M* male

Table 2 Clinicopathologic characteristics and operative details according to tumor size

	<5 cm $n = 403$ (65 %)	5–10 cm $n = 172$ (28 %)	>10 cm $n = 41$ (7 %)	p value
Clinical factors				
Age (years)	66 (13–85)	67 (22–85)	62 (21–81)	0.0251
Sex ratio (M/F)	306/97	136/36	34 (83)	0.4781
Underlying liver disease				
HBV	83 (21)	43 (25)	12 (29)	0.2814
HCV	260 (65)	87 (51)	13 (32)	<0.0001
Non-B non-C	67 (17)	47 (27)	16 (39)	0.0002
Child-pugh grade				0.1146
A	352 (87)	147 (85)	31 (76)	
B	51 (13)	25 (14.5)	10 (24)	
Background liver				<0.0001
Normal	15 (4)	16 (9)	7 (17)	
Chronic hepatitis or fibrosis	169 (42)	90 (52)	27 (66)	
Cirrhosis	219 (54)	66 (38)	7 (17)	
HCC rupture	0	2 (1)	2 (5)	0.0006
Portal vein embolization	5 (1)	9 (5)	7 (17)	<0.0001
ICG-R15	14.2 (2.5–72.3)	12.80 (2.5–48.9)	10.10 (2.2–34)	0.0042
ICG-R15 >10	282 (70)	115 (67)	22 (54)	0.0953
AFP (ng/ml)	16 (0–49,124)	25 (2–69,000)	1,314 (2–436,000)	<0.0001
AFP >200	86 (21)	59 (34)	24 (59)	<0.0001
DCP (mAu/ml)	51 (0–37,545)	243.5 (0–77,520)	14,730 (38–200,135)	<0.0001
DCP >100	124 (31)	104 (60)	37 (90)	<0.0001
Operative factors				
Major hepatectomy ≥4 segments	27 (7)	33 (19)	26 (63)	<0.0001
Anatomic resection	268 (66.5)	121 (70)	37 (90)	0.0068
Pathological factors				
Tumor size (mm)	28 (8–49)	65 (50–100)	130 (105–230)	<0.0001
Grade				0.0003
Well differentiated	82 (20)	14 (8)	1 (2)	
Moderately differentiated	273 (68)	125 (73)	29 (71)	
Poorly differentiated	36 (9)	25 (14.5)	10 (24)	
Combined	3 (1)	2 (1)	1 (2)	
Necrosis	9 (2)	6 (3.5)	0	
Microvascular invasion	83 (21)	80 (47)	28 (68)	<0.0001
Bile duct invasion	14 (3)	10 (6)	3 (7)	0.2898
Satellite nodules	30 (7)	39 (23)	11 (27)	<0.0001
Positive surgical margins	10 (2.5)	6 (3.5)	4 (10)	0.0426

Data are presented as n (%) or median (range)

AFP alfa-fetoprotein, *DCP* des-γ-carboxyprothrombin, *F* female, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *ICG-R15* indocyanine green retention rate at 15 min, *M* male

virus; more likely to be associated with non-B non-C hepatitis; more likely to have normal underlying liver parenchyma (17 % in the group with tumors >10 cm, 9 % in tumors measuring 5–10 cm, and 4 % in the group with tumors <5 cm; $p < 0.0001$), elevated tumor markers, including AFP ($p < 0.0001$) and DCP ($p < 0.0001$), and a better ICG-R15 value ($p = 0.0042$). Histopathologically, microvascular invasion (68 % in tumors >10 cm, 47 % in tumors 5–10 cm, and 21 % in tumors <5 cm; $p < 0.0001$), satellite nodules, and a less differentiated tumor were more prevalent in patients with larger tumors. The rate of macroscopic vascular invasion was 4.7 % (29 patients, including 16 patients with macroscopic portal vein invasion, 12 patients with hepatic vein invasion and one patient with both macroscopic portal and hepatic vein invasion). Of these 29 patients, three had tumors <5 cm, 16 had

tumors measuring 5–10 cm, and ten patients had tumors >10 cm.

Survival and recurrence of the entire cohort

The median follow-up period was 53.4 months (range 1.2–193.2). Seven (1 %) patients were lost to follow-up during the study period. In-hospital or 90-day mortality occurred in two patients (0.3 %). At the time of last follow-up, 274 (44 %) patients had died of recurrent disease progression, and 335 (54 %) patients were alive, 154 (25 %) of whom were disease free. For the entire cohort of 616 patients, overall median survival was 86 months, and 5- and 10-year overall survival rates were 65 and 42 %, respectively (Fig. 1). The median time to recurrence was 28 months, and disease-free survival rates after 3 and 5 years were 42 and 30 %, respectively.

Survival and recurrence according to tumor size

Patients with larger tumors were more likely to have a worse overall and disease-free survival (Fig. 2). The 5-year overall survival was better in patients with tumors <5 cm than in those with tumors 5–10 cm (69.6 % for tumors <5 cm vs. 58 % for tumors 5–10 cm; $p = 0.009$) and those with tumors >10 cm (69.6 % for tumors <5 cm vs. 53 %; $p = 0.0136$; Fig. 2a). The 5-year recurrence-free survival was also significantly better for patients with tumors <5 cm (32 %) than for those with tumors 5–10 cm (26 %, $p = 0.0092$) and tumors >10 cm (24 %, $p = 0.0090$; Fig. 2b). However, there was no significant difference in overall and recurrence-free survival between patients with tumors 5–10 cm and those with tumors >10 cm ($p = 0.6804$ and 0.4037, respectively).

Long-term survival according to current staging systems

Disease was stratified on the basis of HCC size and presence of macro- and microvascular invasion according to the current tumor/node/metastasis (TNM) staging systems: the fifth edition of the Liver Cancer Study Group of Japan (LCSGJ) classification [7] and American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) classification [8]. Within each staging system, the overall survival rates of patients with different stages of diseases were compared. The patients were well stratified by both staging systems (Fig. 3).

Prognostic factors of survival and recurrence of solitary HCC

We assessed the prognostic significance of tumor size in HCC by evaluating different cut-off points (1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 cm). We adopted the cut-off value that was defined by the minimum p value to predict overall survival after surgical resection. The p value was lowest at 5 cm ($p = 0.0063$).

Univariate and multivariate analysis of potential prognostic factors within the total patient cohort identified five variables associated with worse overall survival: cirrhosis (hazard ratio (HR) 1.35; $p = 0.0307$), Child–Pugh B (HR 1.46; $p = 0.0159$), ICG-R15 > 10 (HR 1.6; $p = 0.0071$), microvascular invasion (HR 1.94; $p < 0.0001$), and satellite nodules (HR 1.7; $p = 0.0009$) (Table 3). Tumor size >5 cm was not an independent variable on multivariate analysis. In the 389 (63 %) solitary HCC patients without microvascular invasion and satellite nodules, tumor size had no impact on 5-year overall survival (74 %; $p = 0.61$).

As for recurrence-free survival, five variables were identified on univariate and multivariate analysis: cirrhosis (HR 1.4; $p = 0.0013$), ICG-R15 >10 (HR 1.286; $p = 0.0385$), microvascular invasion (HR 1.442; $p < 0.001$), and satellite nodules (HR 1.997; $p < 0.0001$). On the other hand, anatomic resection was associated with good recurrence-free survival (HR 0.795; $p = 0.0364$).

Prognostic factors of survival by tumor size

Among patients with tumors <5 cm, four factors were significant predictors of worse overall survival in both univariate and multivariate analysis: Child–Pugh B (HR 1.703, $p = 0.0120$), ICG-R15 >10 (HR 1.579; $p = 0.0486$), presence of microvascular invasion (HR 1.928; $p = 0.0006$), and satellite nodules (HR 1.911; $p = 00054$).

Among patients with tumors 5–10 cm, both microvascular invasion (HR 1.772; $p = 0.0113$) and satellite nodules (HR 1.930; $p = 0.0054$) were identified as significant predictors of worse overall survival. Among patients with tumors >10 cm, none of the studied factors were predictors of overall survival.

Discussion

In the present study, we retrospectively analyzed data on a cohort of patients from a single center with histologically confirmed solitary HCC. We found that the median survival in this entire cohort was 86 months, and overall 5-year survival rate was 65 %. The prognosis of patients with HCC <5 cm was significantly better than those with HCC >5 cm. Despite this, 5-year survival rates in patients with large tumors of diameter >10 cm were 58 % and comparable to that of patients with tumors 5–10 cm (53 %), which was acceptable. The frequency of microvascular invasion, satellite nodules, and advanced tumor

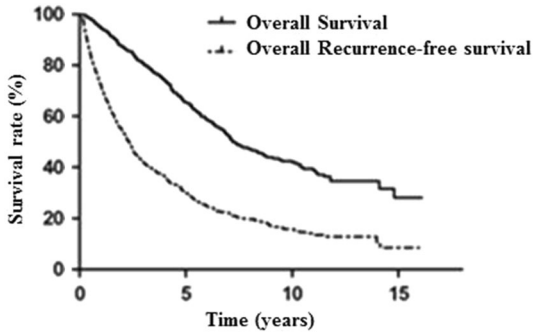

Fig. 1 Overall and recurrence-free survival curves

grade increases with tumor size; however, the influence of tumor size on the survival of patients decreased proportionally with the increase in size. This paradoxical phenomenon might be because, first, tumor size itself would not independently influence the survival of patients with solitary HCC, but size is associated with microvascular invasion and tumor aggressiveness. As previously reported, 2 cm [9] or 5 cm would be the threshold for microvascular invasion and satellite lesions that would rapidly increase with tumor size. Size and other important factors should be confounding factors. Second, most cirrhotic patients with large tumors or patients with multiple and/or bilateral tumors were not included in this study. Cirrhosis has been shown to influence survival and recurrence after resection of HCC [23]. In the current study, cirrhosis was present in more than half (54 %) of patients with tumors <5 cm, but in only 17 % of those with tumors >10 cm. This may be expected, as most patients with larger tumors require major hepatectomy, which was not possible in the presence of cirrhosis.

The present study revealed interesting data on the prevalence of various pathologic risk factors in solitary

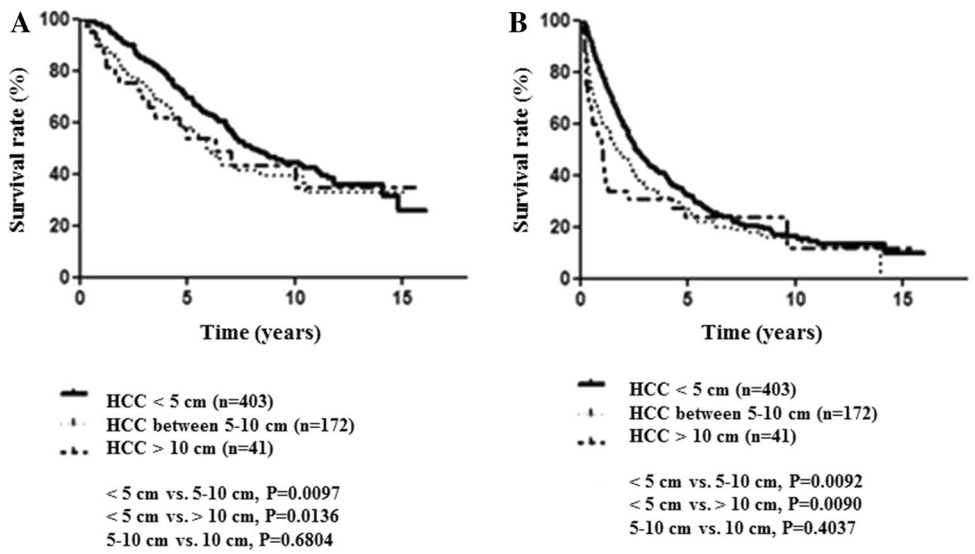

Fig. 2 Overall (**a**) and recurrence-free (**b**) survival curves stratified according to tumor size

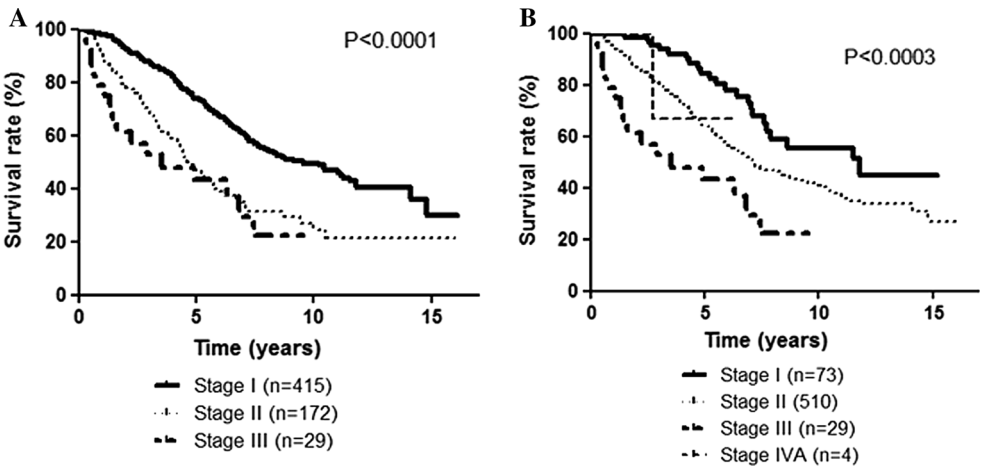

Fig. 3 Survival of patients with solitary hepatocellular carcinoma according to current staging systems.**a** American Joint Committee on Cancer, 7th edition. **b** Liver Cancer Study Group of Japan, 5th edition

Table 3 Prognostic factors of overall survival and recurrence-free survival in the entire population cohort with solitary hepatocellular carcinoma ($n = 616$)

Variable		Overall survival				Recurrence-free survival			
		Univariate	Multivariate analysis			Univariate	Multivariate analysis		
		p value	*p* value	HR	95 % CI	*p* value	*p* value	HR	95 % CI
Age ≥65 (years)	Yes	0.0171	NS			0.8448			
	No								
Male (vs. female)	Yes	0.1953				0.5474			
	No								
HBV	Yes	<0.0001	NS			0.1202			
	No								
HCV	Yes	<0.0001	NS			0.0039	NS		
	No								
Non-B non-C	Yes	0.2213				0.1283			
	No								
Child-Pugh B	Yes	0.0001	0.0159	1.464	1.074–1.995	0.0003	NS		
	No								
HCC rupture	Yes	0.9733				0.8990			
	No								
Portal vein embolization	Yes	0.4943				0.3483			
	No								
ICG-R15	<10	<0.0001	0.0071	1.602	1.137–2.256	<0.0001	0.0385	1.286	1.013–1.631
	≥10								
AFP (ng/ml)	<200	0.7214				0.1467			
	≥200								
DCP	<100	0.1058				0.0140	NS		
	≥100								
Anatomic resection	Yes	0.0203	NS			0.0009	0.0364	0.795	0.642–986
	No								
Tumor >5 cm	Yes	0.0063	NS			0.0019	NS		
	No								
Microvascular invasion	Yes	<0.0001	<0.0001	1.940	1.467–2.564	<0.0001	0.001	1.442	1.159–1.795
	No								
Bile duct invasion	Yes	0.0490	NS			0.2988			
	No								
Poorly differentiated	Yes	0.3658				0.9419			
	No								
Satellite nodules	Present	<0.0001	0.0009	1.706	1.246–2.2336	<0.0001	<0.0001	1.997	1.527–2.612
	Absent								
Cirrhosis	Present	0.0025	0.0307	1.351	1.028–1.775	<0.0001	0.0013	1.404	1.141–1.727
	Absent								
Major hepatectomy	Yes	0.5851				0.4433			
	No								
Surgical margins	Positive	0.1982				0.0910	NS		
	Negative								

AFP alfa-fetoprotein, *CI* confidence interval, *DCP* des-γ-carboxyprothrombin, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *HR* hazard ratio, *ICG-R15* indocyanine green retention rate at 15 min, *NS* non significant

HCC. Specifically, first, up to 80–90 % of all HCC in this series appeared in patients with underlying liver disease and chronic viral hepatitis. Second, most tumors (65 %) were smaller than 5 cm (vs. 7 % for tumors >10 cm), which suggests that a large proportion of HCC is being detected with increasing frequency due to routine screening

of patients with the hepatitis virus in the Japanese screening system. Third, we found that the incidence of microvascular invasion, satellite nodules, and advanced differentiation grade is associated with increased tumor size. In this series, microvascular invasion, which was found in 31 % of the entire cohort, significantly increased with tumor size (21 % in tumors <5 cm, 47 % in tumors 5–10 cm, and 68 % in tumors >10 cm, $p < 0.0001$). Similarly, 9 % of tumors <5 cm were high-grade differentiated, compared with 14.5 % of tumors 5–10 cm and 24 % of tumors >10 cm ($p = 0.003$). Further, 7 % of tumors <5 cm were high-grade differentiated, compared with 23 % of tumors 5–10 cm and 27 % of tumors >10 cm ($p < 0.0001$). These findings are consistent with previous results from one multicenter study that showed that 36 % of tumors <5 cm were high grade compared with 54 % of tumors sized 5.1–6.5 cm [24], and 55 % of tumors sized 5.1–6.5 cm were associated with microvascular invasion compared with 31 % of tumors sized <5 cm.

The reported 5-year survival rates for surgical resection of large HCC >10 cm varies widely in the literature, ranging from 19 to 54 % [10, 11, 25–32]. Heterogeneity in patients (cirrhosis) and tumor characteristics (vascular invasion vs. no vascular invasion, single vs. multiple lesions) may be one of the reasons for different outcomes following resection of large HCC. In our series, the 5-year overall and recurrence-free survival rates after resection of solitary HCC were comparable between tumors sized 5–10 cm and large tumors >10 cm. Therefore, patients with large solitary HCC >10 cm should always be considered for liver resection, as this treatment offers acceptable overall survival exceeding 50 %. Even in cases of recurrence, surgical resection should always be considered as long as R0 resection can be achieved, and clinical and pathological factors should not be used to exclude these patients from repeat hepatectomies because they do not reliably predict outcomes.

In our study, we identified five adverse predictors of survival: cirrhosis, Child–Pugh class B, ICG-R15 >10, microvascular invasion, and satellite nodules on histology. Only factors related to liver function were available at the time of surgery. Assessment of the other factors was based on the examination of the resected tumors, and this is information that is not available at the time of treatment indication. Thus, the results of our study show that patients with a single HCC of any size (including patients with a solitary HCC >10 cm), with evidence of portal hypertension or poor liver function at the time of treatment indication, should not be offered an operation. An interesting result of this study was the absence of the negative impact of R1 resection for overall and recurrence-free survival in the entire series, even in patients with tumors <5 cm. This is line with our previous report, which showed no correlation between tumor exposure and risks of tumor recurrence in patients with HCC <5 cm [33]. It is likely that the tumor exposure would impact less on prognosis in huge tumors because the frequency of micrometastases and vascular invasion increases with tumor size.

This study has several limitations. A strong selection bias exists in this work, as in any retrospective study. One limitation of this study might be the relatively few preoperative variables collected and analyzed, such as diabetes or quality of underlying liver disease. However, we included the most important variables in this study. Another limitation includes that the results of combination therapies, such as TACE and/or PVE plus liver resection, in instances of tumor rupture or for planned major hepatic resection, could not be assessed in this present series. The heterogeneity of both tumor and patient characteristics, combined with the sample size, preclude any relevant comment on this topic.

Conclusion

The present study showed that surgical resection for solitary HCC is associated with a good prognosis. Solitary large HCC >10 cm would be a good candidate for hepatectomy, as would solitary HCC between 5 and 10 cm. Size alone is not a contra-indication, but the presence of adverse predictors in some patients preclude good outcome.

Conflict of interest None.

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