World J Surg (2014) 38:947–957
DOI 10.1007/s00268-013-2365-2

World Journal of Surgery

Tumor Size Does Not Independently Affect Long-Term Survival after Curative Resection of Solitary Hepatocellular Carcinoma Without Macroscopic Vascular Invasion

Han Zhang · Shou-Xin Yuan · Shu-Yang Dai · Jin-Min Zhang · Xing Huang · Chong-De Lu · Jun-Hua Lu · Fu-Quan Wu · Wan Yee Lau · Meng-Chao Wu · Tian Yang · Feng Shen

Published online: 21 November 2013

Abstract

Objective The aim of this study was to investigate the prognostic value of tumor size alone on long-term survival and recurrence after curative resection for solitary hepatocellular carcinoma (HCC) without macroscopic vascular invasion.

Methods A single-center cohort of 615 patients with solitary HCC (a single tumor, without macroscopic vascular invasion or distant metastasis) undergoing curative hepatic resection from 2002 to 2010 was retrospectively studied. Using 2.0, 3.0, 4.0, 5.0, 8.0, and 10.0 cm as cut-off values of tumor size, the overall survival (OS) and recurrence-free survival (RFS) rates were compared between the groups of patients with tumor size up to a certain cut-off value and the groups of patients with tumor size above that cut-off value. Thus, multiple comparisons were done. The prognostic factors of OS and RFS were evaluated using univariate and multivariate analyses.

Results The median tumor size of all HCCs was 4.0 cm (range 0.9–22.0 cm). The in-hospital mortality rate was 1.0 %, and the overall morbidity rate was 22.3 %. The 1-, 3-, and 5-year OS rates were 96.0, 79.8, and 69.9 %, and the corresponding RFS rates were 83.6, 72.7, and 57.2 %, respectively. On univariate analyses, the 1-, 3-, and 5-year OS and RFS rates were significantly different between the individual two groups of patients as divided by the aforementioned different cut-off values of tumor sizes (all $p < 0.05$). However, when tumor size was put as a continuous variable into multivariate analysis, it was no longer an independent prognostic factor of OS or RFS after curative resection.

Conclusions Tumor size did not independently affect long-term survival and recurrence after curative resection of solitary HCC without macroscopic vascular invasion. Therefore, there is no size limit that precludes hepatic resection for solitary HCC, provided the tumor is resectable.

Han Zhang, Shou-Xin Yuan, Shu-Yang Dai, Jin-Min Zhang, Xing Huang, Chong-De Lu, Jun-Hua Lu and Fu-Quan Wu contributed equally to this work.

H. Zhang · S.-X. Yuan · S.-Y. Dai · J.-M. Zhang · X. Huang · C.-D. Lu · J.-H. Lu · F.-Q. Wu · W. Y. Lau · M.-C. Wu · T. Yang (✉) · F. Shen (✉)
Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, No.225, Changhai Road, Shanghai, China
e-mail: aphpba2013@gmail.com

F. Shen
e-mail: fengshensmmu@gmail.com

S.-Y. Dai · X. Huang
Department of Postgraduate Management Unit, Second Military Medical University, Shanghai, China

W. Y. Lau
Faculty of Medicine, The Chinese University of Hong Kong, Shatin, NT, Hong Kong SAR, China

Introduction

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer and the third most frequent cause of cancer-related death in the world [1]. Although the majority of cases are still found in Asia and Africa, recent studies have shown that the incidences and mortality rates of HCC are increasing in North America and Europe [2].

Hepatic resection provides a potentially curative outcome for HCC patients who are indicated for surgery [3–5]. However, owing to the high recurrence rate, long-term survival after hepatic resection of HCC is far from satisfactory. Patients with large HCC are known to have poorer

long-term outcomes than those with small HCC after curative resection [6–10]. This is often because large HCC has other adverse clinicopathological factors affecting long-term survival and recurrence, such as multiplicity, satellite nodules, macroscopic vascular invasion, or distant metastasis [11–13]. Nevertheless, when HCC is solitary, especially when it is not associated with macroscopic vascular invasion, hepatic resection is still carried out by many surgeons even when the tumor is very large size, provided that the tumor is resectable [4, 14–16]. Until now, the relationship between tumor size and long-term prognosis after curative resection remains unclear for this subset of patients with solitary HCC.

To address this issue, we conducted a single-center retrospective study to evaluate the prognostic value of tumor size on the overall survival (OS) and recurrence-free survival (RFS) after curative resection of solitary HCC without macroscopic vascular invasion, and to appraise the prognostic importance of tumor size on the decision-making of hepatic resection for those patients.

Patients and methods

Patients

From January 2002 to December 2010, all consecutive patients who received R0 curative resections for HCC, which was defined as macroscopically complete removal of tumor with a histopathologically tumor-free surgical margin, from the Fourth Department of Hepatic Surgery at the Eastern Hepatobiliary Surgery Hospital were included into this study. Patients excluded were those with multiple HCC (but not those with microsatellites), macroscopic vascular invasion (defined as a tumor invasion or a tumor thrombus in the vessels visible on radiological imaging prior to surgery or during surgery), and distant metastasis. For this retrospective study, tumor size, cirrhosis, microvascular invasion, tumor encapsulation, and tumor differentiation (evaluated by Edmondson–Steiner grade: I = well, II = moderately, and III–IV = poorly) were obtained by histological examination of resected specimens. The study protocol was approved by the Clinical Research Ethics Committee of the hospital. Written informed consent was obtained from all patients for the patients' data to be used for clinical research before the operation.

Peri-operative procedures

Pre-operative evaluation of the extent of HCC, liver functional status, and general condition of the patient was carried out before any decision for surgery was made. The tumor was assessed by ultrasonography, computed tomography (CT), and/or magnetic resonance imaging (MRI). Liver function was evaluated by biochemistry and Child–Pugh classification. An upper gastrointestinal endoscopy was performed routinely on all HCC patients who were scheduled for operation. Patients older than 60 years and those with significant co-morbid illnesses underwent formal

Table 1 Patient characteristics and operative variables

Variable	*N*	%
Sex		
Male	547	88.9
Female	68	11.1
Age, years[a]	51	5–81
ECOG performance status		
0	404	65.7
1–2	211	34.3
Cirrhosis	421	68.5
Child–Pugh grade		
A	553	89.9
B	62	10.1
Portal hypertension	203	33.0
HBsAg (+)	558	90.7
Anti-HCV (+)	14	2.3
Serum AFP level		
≤400 ng/mL	256	41.6
>400 ng/mL	359	58.4
Prothrombin time (seconds)[a]	13.0	10.0–19.3
Total bilirubin (μmol/L)[a]	14.2	4.8–56.0
Albumin (g/L)[a]	39.8	24.5–52.1
Tumor size (cm)	4.0	0.9–22.0
Microvascular invasion	280	45.5
Microsatellite nodules	105	17.1
Tumor differentiation		
Well or moderately	133	21.6
Poorly	482	78.4
Tumor encapsulation	272	44.2
Resection margin		
≤1 cm	194	31.5
>1 cm	421	68.5
Portal vein embolization before operation	6	1.0
Intra-operative blood loss (mL)[a]	300	30–4,600
Intra-operative transfusion	107	17.4
Operation time (min)	110	45–800
Resection type		
Anatomical	415	67.5
Non-anatomical	200	32.5
Extent of resection		
Major hepatectomy	102	16.6
Minor hepatectomy	513	83.4

AFP alpha-fetoprotein, *ECOG* Eastern Cooperative Oncology Group, *HBsAg* hepatitis B surface antigen, *HCV* hepatitis C virus

[a] Data presented as median with range

cardiopulmonary evaluation. A liver functional status of Child–Pugh C was considered as an absolute contraindication for HCC resection. The resection criteria used were consistent over the study period, and have previously been reported [17, 18]. Portal hypertension was defined to be present when endoscopy revealed esophageal varices, in patients with splenomegaly with a platelet count of $<100 \times 10^9$/L, or when the hepatic venous pressure gradient was >210 mmHg.

The Pringle maneuver was used with cycles of clamping/unclamping times of 15/5 min. Transection of hepatic parenchyma was carried out by the clamp-crushing technique, and hemostasis was achieved on the raw liver surface with an argon beam coagulator. The plane of liver transection was determined by intraoperative ultrasonography. Anatomical resection was the method of choice, but non-anatomical resection was adopted for tumors situated at the junction of several liver segments, or for small and peripherally located tumors, or in patients with a high extent of cirrhosis. Major hepatectomy was defined as resection of three or more Couinaud's liver segments, and minor hepatectomy as resection of fewer than three.

Follow-up

All patients were investigated for postoperative residual tumors using serum alpha-fetoprotein (AFP), ultrasonography or CT, and chest X-ray at 1 month after surgery. The patients were then followed-up for recurrence or distant metastasis at a 2-monthly interval for the first 6 months, and at a 3-monthly interval thereafter. CT, MRI, angiography, bone scan or positron emission tomography were performed when recurrence or distant metastasis was suspected. Further treatment decision was based on the pattern of recurrent tumor, residual hepatic functional reserve, and general condition of the patient. The OS was calculated from the day of the operation to either the day of death or the day of the last follow-up visit. The disease-free survival was calculated from the date of the operation to the date when recurrence/metastasis was diagnosed. This study was censored on 30 June 2012.

Statistical analysis

The clinicopathologic and operative data were collected in a computerized database. Continuous variables were expressed as mean ± standard deviation (SD) or median (range) and compared using the Mann–Whitney *U* test. Categorical variables were compared using the χ^2 test with Yates correction or the Fisher's exact test, as appropriate. Hospital deaths were included in calculating the OS and RFS rates. Cumulative OS and RFS rates and curves were analyzed by the Kaplan–Meier method, and differences were compared by the log-rank test. After univariate analysis, only significant variables with $p < 0.1$ were used in the multivariate analysis, which was performed using a stepwise logistic regression analysis. All statistical analyses in this study were performed with the software package SPSS 18.0 (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was defined as statistically significant.

Results

Patient characteristics and operative variables

Of the 1,324 patients who received an R0 resection for HCC during the study period, 535 patients were excluded from this study because they had multiple HCC. Of the 789 patients with a solitary HCC, 174 patients were excluded

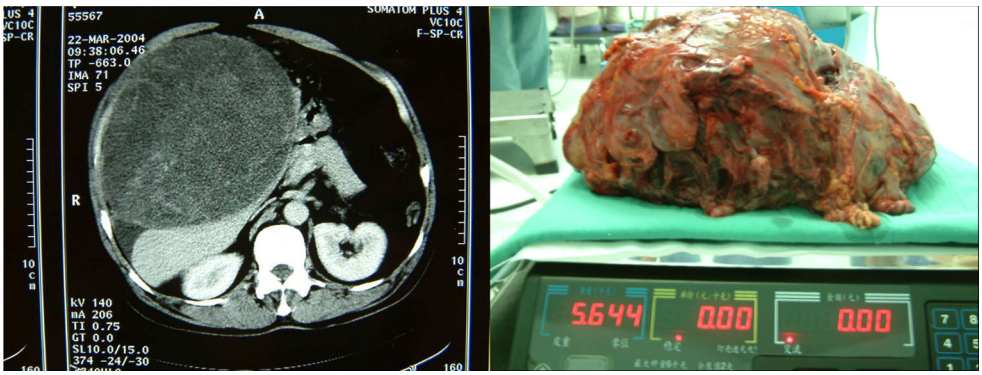


Fig. 1 Male, 54 years old, diagnosed as solitary huge hepatocellular carcinoma in the *right* side of the liver, who had a 22-cm tumor, underwent right hemi-hepatectomy in March 2004. After curative resection, this patient was still alive and disease-free up to June 2012

because of macroscopic vascular invasion. Only 615 patients were shown to have a solitary HCC on pre-operative radiological imaging. There were 547 males and 68 females, and the median age was 51 years (range 5–81 years). The patients' characteristics and operative variables are shown in Table 1. The median tumor size was 4.0 cm (range 0.9–22.0; mean ± SD 5.4 ± 3.6) (Fig. 1). Liver function was relatively good in the majority of all patients at the time of surgery (553 with Child A; 62 with Child B), and 421 (68.5 %) had liver cirrhosis histopathologically. A total of 105 patients were found to have microsatellite nodules on histopathology.

Table 2 Postoperative complications

Variable	Patients (%)
Overall complications according to Clavien–Dindo classification	137 (22.3)
Grade 1	35 (5.7)
Grade 2	51 (8.3)
Grade 3	37 (6.0)
Grade 4	8 (1.3)
Grade 5	6 (1.0)
Type of complications	
Pleural effusion	56 (9.1)
Ascites	44 (7.1)
Subphrenic effusion/infection	31 (5.7)
Wound infection	29 (4.7)
Hepatic insufficiency[a]	21 (3.4)
Intra-abdominal hemorrhage	8 (1.3)
Respiratory infection	7 (1.1)
Bile leakage	6 (1.0)
Cardiovascular accident	1
Upper gastrointestinal bleeding	1
Acute renal failure	1

[a] Hepatic insufficiency is defined as serum total bilirubin >60 mol/l, prothrombin time >18 s, and/or occurrence of encephalopathy

Fig. 2 Comparisons of overall survival and recurrence-free survival between two groups according to various cut-off values of tumor size ▶

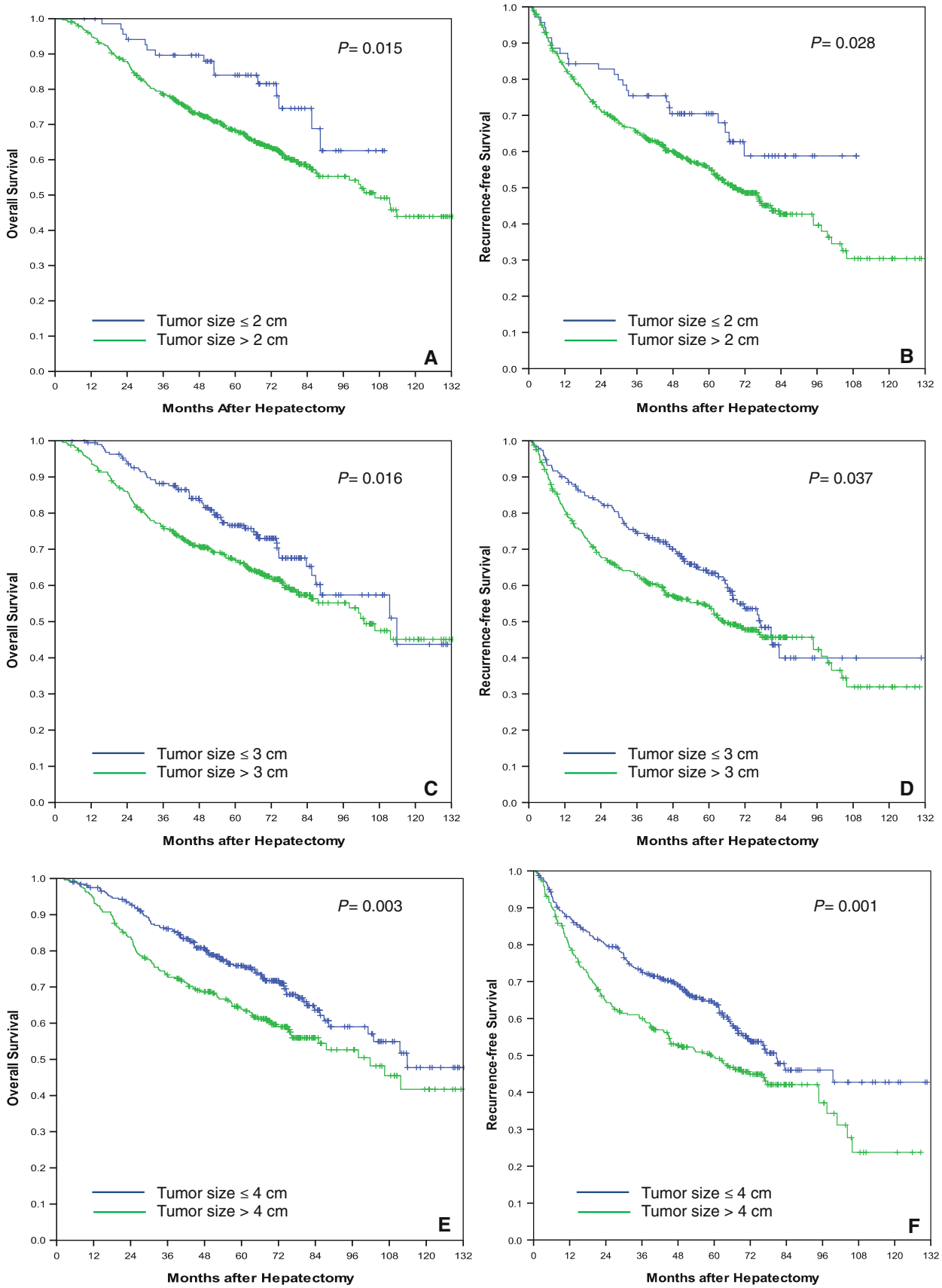
Postoperative outcomes

Of 615 patients, six died within the hospital stay, with an in-hospital mortality of 1.0 %. The primary complications that led to death included hepatic failure ($N = 4$), intra-abdominal hemorrhage ($N = 1$), and pneumonia ($N = 1$). Postoperative complications occurred in 137 patients, with an overall morbidity of 22.3 %. The grades and types of postoperative complications according to the Clavien–Dindo classification [19] are shown in Table 2. A total of 82 (13.3 %) patients developed only one complication, and 55 (8.9 %) patients developed two or more complications. The most common complications were ascites and pleural effusion, which were usually resolved with diuretics or paracentesis.

Table 3 Univariate analysis of various cut-off values of tumor size for overall and recurrence-free survival

	N	1-year OS	3-year OS	5-year OS	OS Median (m)	*p* value for OS	1-year RFS	3-year RFS	5-year RFS	RFS median (m)	*p* value for RFS
Tumor size (1)											
≤2 cm	70	100	89.6	84.0	91.4	0.015	87.1	75.4	70.5	78.0	0.028
>2 cm	539	95.5	78.5	68.2	90.2		83.1	65.3	55.5	70.8	
Tumor size (2)											
≤3 cm	192	99.5	88.2	76.6	96.2	0.016	88.5	74.4	63.4	79.6	0.037
>3 cm	417	94.5	76.0	67.0	89.0		80.6	62.8	54.2	70.1	
Tumor size (3)											
≤4 cm	318	97.5	86.1	75.9	96.1	0.003	87.6	72.8	63.2	79.0	0.001
>4 cm	291	94.5	73.0	63.8	86.0		79.2	59.9	49.6	67.4	
Tumor size (4)											
≤5 cm	380	96.6	83.0	72.4	93.2	0.044	85.7	69.3	61.3	77.8	0.038
>5 cm	229	95.2	74.6	66.2	87.7		81.1	62.2	50.7	66.6	
Tumor size (5)											
≤8 cm	491	96.3	82.1	71.2	92.1	0.039	85.5	69.4	59.8	75.6	0.004
>8 cm	118	94.9	70.3	62.9	84.7		73.3	54.1	46.0	61.9	
Tumor size (6)											
≤10 cm	528	96.2	81.6	71.3	92.4	0.024	85.4	69.0	59.4	75.2	0.001
>10 cm	81	95.1	67.9	60.3	81.8		71.6	51.9	42.9	56.0	

OS overall survival, *RFS* recurrence-free survival


P= 0.015
Overall Survival
Tumor size ≤ 2 cm
Tumor size > 2 cm
A
Months After Hepatectomy
P= 0.028
Recurrence-free Survival
Tumor size ≤ 2 cm
Tumor size > 2 cm
B
Months after Hepatectomy
P= 0.016
Overall Survival
Tumor size ≤ 3 cm
Tumor size > 3 cm
C
Months after Hepatectomy
P= 0.037
Recurrence-free Survival
Tumor size ≤ 3 cm
Tumor size > 3 cm
D
Months after Hepatectomy
P= 0.003
Overall Survival
Tumor size ≤ 4 cm
Tumor size > 4 cm
E
Months after Hepatectomy
P= 0.001
Recurrence-free Survival
Tumor size ≤ 4 cm
Tumor size > 4 cm
F
Months after Hepatectomy

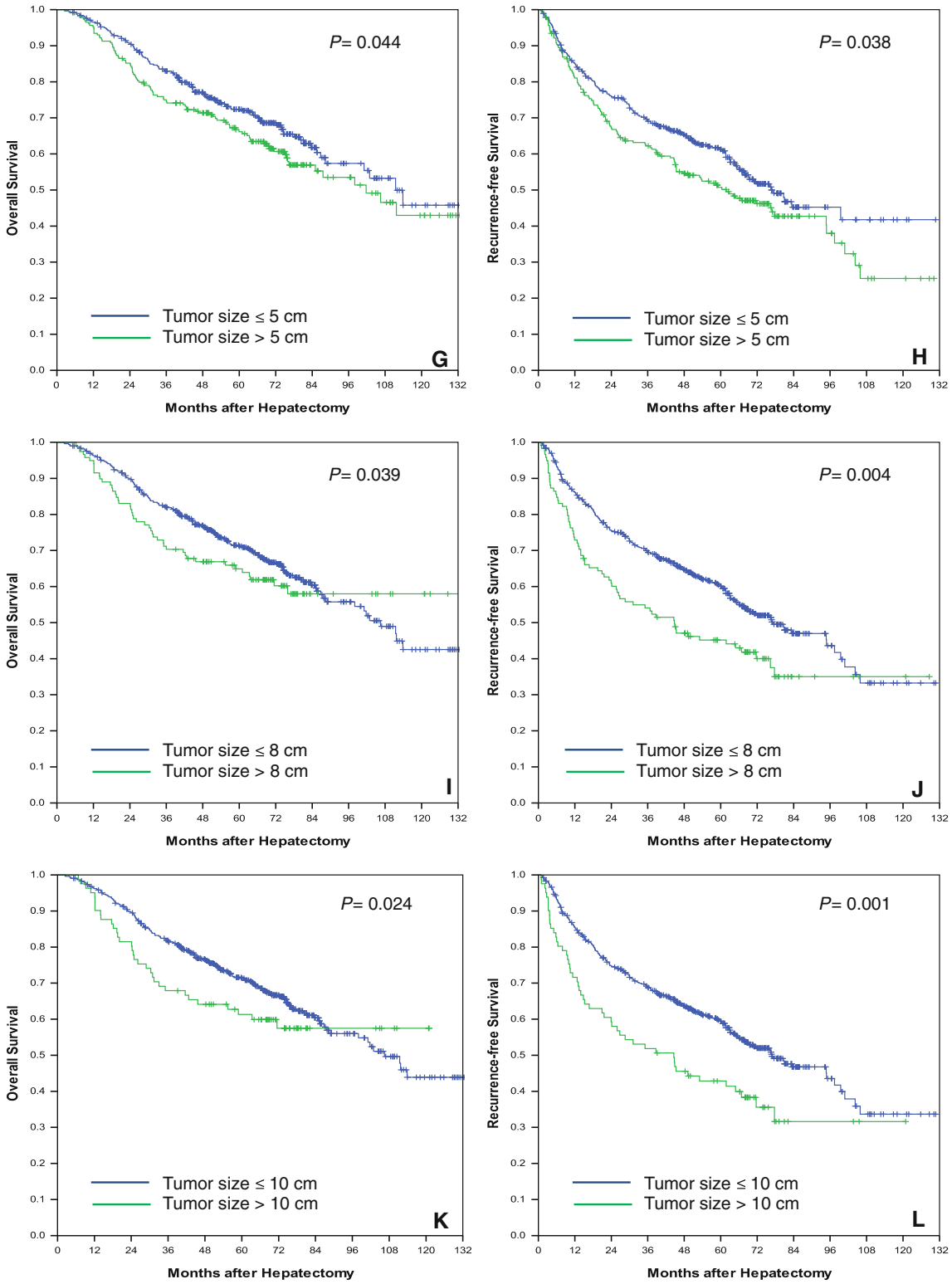


Fig. 2 continued

Long-term OS and RFS

Within a median follow-up of 61.7 months (range 2.4–134.5), recurrences had developed in 287 patients (46.7 %) and deaths in 216 patients (35.1 %). The OS rates of 1-, 3-, and 5-years were 96.0, 79.8, and 69.9 %, and the corresponding RFS rates were 83.6, 72.7, and 57.2 %, respectively.

Comparison of OS and RFS according to different cut-off values of tumor size

Using 2.0, 3.0, 4.0, 5.0, 8.0, and 10.0 cm as cut-off values of tumor size, patients were divided into groups 1–6, the 1-, 3-, and 5-year OS and RFS rates between the different groups of patients with tumor size up to a certain cut-off value were compared with the groups of patients with tumor size above that cut-off value, and are shown in Table 3. The corresponding OS and RFS curves are shown in Fig. 2. There was a significant difference between each of these groups (all $p < 0.05$).

Prognostic factors for OS and RFS

Univariate analyses for the prognostic factors of OS and RFS after curative resection of solitary HCC are shown in Table 4. When putting all the variables with $p < 0.1$ in Table 4, as well as using tumor size as a continuous variable into the multivariate analysis (Table 5), only microvascular invasion, absence of tumor encapsulation, resection margin <1 cm and intra-operative transfusion were independently associated with poorer OS and RFS. In addition, portal hypertension and serum albumin<35 g/L were also independent factors for OS, with poor tumor differentiation for RFS. However, the logistic regression analyses revealed that when putting as a continuous variable into multivariate analyses, tumor size was not an independent prognostic factor of OS, or of RFS after curative resection.

Discussion

In the last few decades, improvements in patient evaluation, surgical techniques, and peri-operative management have significantly reduced the mortality and morbidity rates of hepatic resection. As a result, surgical indications for HCC have extended to resection of tumors even of very large size [20]. Currently, the Barcelona Clinic Liver Cancer (BCLC) staging treatment strategy has become widely accepted, and it is recommended by the American Association for the Study of Liver Diseases [5] and the European Association for the Study of the Liver [21]. In the BCLC staging treatment strategy, hepatic resection is only recommended for BCLC A stage, i.e. early stage HCCs (solitary/single nodule with preserved liver function [Child–Pugh A or B] and asymptomatic [performance status = 0]). For solitary/single HCCs with preserved liver function (Child–Pugh A or B) and without macroscopic vascular invasion, the data from the current study showed that favorable outcomes were achieved after curative hepatic resection, with 5-year OS and RFS rates of 69.9 and 57.2 %, respectively. Thus, the study partly provides support to the BCLC staging treatment strategy on hepatic resection for HCC.

Should symptomatic HCCs (performance status 1–2) be excluded from surgical resection? Many HCCs become symptomatic with increasing size, even though some remain solitary. In the present study, patients with solitary HCC but with performance status 1–2 accounted for more than one-third of all patients. The 5-year OS and RFS rates were 55.7 and 46.3 % after curative resection, which are still quite favorable. Our results cast doubt on the BCLC staging that put these symptomatic HCC patients (performance status 1–2) into an advanced stage (BCLC stage C), and thus deny these patients the chance of a 'curative' hepatic resection. Currently, some other authors also question the BCLC staging on the selection criteria for hepatic resection of HCC [4, 22, 23].

Previous studies identified that there was a negative correlation between HCC tumor size and survival rate, and poor outcomes were observed after hepatic resection for large HCCs [6–10]. Nevertheless, in these studies, although conducted on patients with solitary HCCs, some tumors had macroscopic vascular invasion. The present study identified that tumor size was not an independent predictor of long-term survival and recurrence after curative resection of solitary HCC without macroscopic vascular invasion. Recent studies [14, 24–29] also suggested that patients with large solitary HCCs should be considered for surgical resection. Cho et al. [25] reported that patients with a solitary large HCC without vascular invasion had a 5-year OS and RFS rate of 52.9 and 31.7 %, respectively. Some studies even suggested that solitary large HCC is a specific subtype of HCC that has a good outcome after hepatic resection, as these HCC exhibited specific molecular characteristics [14, 26, 27]. Among all the prognostic clinicopathological factors of long-term survival outcomes, macroscopic vascular invasion is well known to be associated with poor prognosis and a high possibility of tumor recurrence after resection or liver transplantation of HCC [30–32]. In the present study, those solitary HCCs with macroscopic vascular invasion were excluded, thus resulting in relatively better OS and RFS rates than other studies [33–36].

On the other hand, among those solitary HCCs without macroscopic vascular invasion, the occurrence rate of microvascular invasion was 45.5 %. Generally, as the tumors grow in size, progression of their clinicopathological characters usually follows, such as the occurrence of microvascular invasion, multiplicity, satellite nodules, macroscopic vascular invasion, and even distant metastasis. In contrast, it is a sign of ideal clinicopathological characters if a solitary tumor grows only in size without those bad features such as multiplicity, macroscopic vascular invasion, and distant metastasis, which partly

Table 4 Univariate analysis of prognostic factors for overall and recurrence-free survival

	No.	5-year OS (%)	OS median (m)	*p* value for OS	5-year RFS (%)	RFS median (m)	*p* value for RFS
Sex							
Male	541	70.9	92.6	0.253	57.1	73.5	0.761
Female	68	63.0	83.1		57.9	64.5	
Age, years							
≤50	293	73.6	95.6	0.057	56.3	71.0	0.467
>50	316	66.6	87.4		58.1	75.0	
ECOG performance status							
0	401	77.6	100.0	<0.001	62.7	79.4	<0.001
1–2	208	55.7	76.4		46.3	59.9	
Cirrhosis							
Present	415	64.5	85.6	<0.001	53.2	67.3	<0.001
Absent	194	81.6	104.6		65.5	79.2	
Portal hypertension							
Present	198	55.0	74.1	<0.001	58.3	72.2	0.661
Absent	411	77.3	100.1		54.6	75.8	
Serum AFP level, ng/mL							
≤400	253	73.5	93.6	0.151	64.8	79.6	0.006
>400	356	67.6	90.3		51.8	67.6	
Prothrombin time, seconds							
>14	162	62.9	71.6	0.006	54.1	68.2	0.647
≤14	442	72.4	94.9		57.9	73.4	
Total bilirubin, μmol/L							
>17	195	64.1	84.6	0.014	56.4	71.1	0.385
≤17	414	72.8	94.5		59.0	78.4	
Albumin, g/L							
<35	42	41.3	55.7	<0.001	58.0	59.7	0.735
≥35	567	72.2	93.8		57.1	72.7	
HBsAg							
Positive	552	69.5	90.9	0.246	56.9	71.4	0.144
Negative	57	74.9	95.7		59.5	87.9	
Anti-HCV							
Positive	14	64.3	72.2	0.430	43.7	45.3	0.064
Negative	595	70.1	92.2		57.5	73.6	
Microvascular invasion							
Present	278	63.8	82.5	<0.001	46.5	60.8	<0.001
Absent	331	75.3	99.3		66.7	83.8	
Microsatellite nodules							
Present	105	64.0	83.9	0.024	48.0	66.3	0.010
Absent	510	72.9	95.8		60.9	74.7	
Tumor differentiation							
Well or moderately	132	75.0	96.9	0.087	75.4	92.9	<0.001
Poorly	477	68.6	90.0		52.3	66.9	
Tumor encapsulation							
Present	271	79.5	103.0	<0.001	71.8	87.0	<0.001
Absent	338	62.3	83.2		45.3	60.4	
Resection margin, cm							
<1	190	58.1	71.8	<0.001	37.8	48.1	<0.001
≥1	419	75.3	99.7		65.7	82.5	

Table 4 continued

	No.	5-year OS (%)	OS median (m)	*p* value for OS	5-year RFS (%)	RFS median (m)	*p* value for RFS
Intraoperative blood loss, mL							
≥800	150	54.4	75.9	<0.001	47.1	62.8	0.001
<800	459	75.1	97.0		60.4	76.1	
Intraoperative transfusion							
Yes	105	50.2	73.1	<0.001	43.1	57.0	0.001
No	504	74.2	95.7		60.1	75.6	
Operation time, min							
≥120	270	64.2	84.6	0.003	53.7	71.6	0.453
<120	339	74.5	97.0		59.7	73.4	
Resection type							
Anatomical	411	70.5	93.7	0.865	59.0	73.3	0.993
Non-anatomical	198	69.2	90.6		56.4	72.6	
Extent of resection							
Major hepatectomy	100	61.2	85.1	0.088	48.7	64.7	0.025
Minor hepatectomy	509	71.7	93.0		58.8	74.4	

AFP alpha-fetoprotein, *ECOG* Eastern Cooperative Oncology Group, *HBsAg* hepatitis B surface antigen, *HCV* hepatitis C virus, *OS* overall survival, *RFS* recurrence-free survival

Table 5 Multivariate analysis of risk factors for poor overall survival and recurrence-free survival

	Hazard ratio	95 % CI	*p* value
Overall survival			
Portal hypertension	2.340	1.768–3.097	<0.001
Microvascular invasion	1.359	1.021–1.808	0.036
Absence of tumor encapsulation	1.839	1.368–2.472	<0.001
Albumin <35 g/L	0.590	0.376–0.927	0.022
Resection margin <1 cm	0.530	0.399–0.702	<0.001
Intraoperative transfusion	1.501	1.094–2.059	0.012
Recurrence-free survival			
Poor tumor differentiation	1.588	1.129–2.233	0.008
Microvascular invasion	1.503	1.147–1.970	0.003
Absence of tumor encapsulation	1.942	1.502–2.511	<0.001
Resection margin <1 cm	0.529	0.416–0.672	<0.001
Intraoperative transfusion	1.516	1.133–2.029	0.005

CI confidence interval

explains the more satisfying prognosis after curative resection. Therefore, it is easy to understand that microvascular invasion, instead of tumor size alone, is an independent prognostic factor of OS and RFS after curative resection for these patients with solitary HCCs.

In the present study, a resection margin <1 cm was identified as a risk factor of OS and RFS. A previously reported prospective randomized controlled trial revealed that a resection margin aiming grossly at 2 cm efficaciously and safely decreased postoperative recurrence rates and improved survival outcomes when compared with a gross resection margin aiming at 1 cm for solitary HCC [35]. Our study also supported the significance of resection margin status in long-term prognosis of solitary HCC after curative resection. Therefore, attaining a wide enough resection margin is important. On the other hand, the surgeon has to preserve enough volume of the hepatic remnant, which is relatively more difficult for a very large HCC.

Anatomical resection is the preferred procedure in our center, but non-anatomical resection is used for tumors situated at the junction of several liver segments, or for small and peripherally located tumors, or in patients with a high extent of cirrhosis. In the present study, there were no significant differences in OS and RFS between anatomical resection and non-anatomical resection, which have also been reported by Tanaka et al. [37] and Kaibori et al. [38]. However, anatomical resections are more likely to give better outcomes than non-anatomical resections for small solitary HCC [39], T1–T2 HCC [40], and non-cirrhotic patients [41].

There are some limitations to this study. First, this is a retrospective, single-center study; thus, the results may not be generalized. A multi-center prospective study may have to be performed to validate our results. Second, 90 % of HCC patients in the current study had hepatitis B virus infection. This feature is apparently different from the Western countries, where hepatitis C virus infection is the most prevailing etiology. Third, although there are patients

with tumor sizes larger than 10 cm, which bring higher tendencies for recurrence, no further cut-off points were set because the results would not be convincing due to insufficient patient volume.

In conclusion, this study demonstrated that tumor size was not an independent predictor of long-term survival and recurrence after curative resection of solitary HCC, and there was no size limit to preclude hepatic resection for solitary HCC without macroscopic vascular invasion, provided the tumor is resectable.

Acknowledgments Supported by National Natural Science Foundation for Youths of China (No. 81000166); National Natural Science Foundation of China (No. 81172020); Shanghai Guiding Program of Science and Technology Development Commission Foundation (No. 10411963300); Shanghai Program for Excellent Talents in Health System (No. XYQ2011033); Shanghai "Phosphor" Science Foundation (No.12QA1404800); Program for Excellent Young Scholars of SMMU; Municipal Hospital Joint Research Program of Frontier Technology from Shanghai Shen-kang Hospital Developing Center (No. SHDC12010121); and State Key Project on Infectious Diseases of China (2012ZX10002-016).

Conflict of interests None.

References

1. Forner A, Llovet JM, Bruix J (2012) Hepatocellular carcinoma. Lancet 379:1245–1255
2. El-Serag HB (2011) Hepatocellular carcinoma. N Engl J Med 365:1118–1127
3. Song TJ, Ip EW, Fong Y (2004) Hepatocellular carcinoma: current surgical management. Gastroenterology 127:S248–260
4. Jarnagin W, Chapman WC, Curley S, D'Angelica M, Rosen C, Dixon E, Nagorney D (2010) Surgical treatment of hepatocellular carcinoma: expert consensus statement. HPB (Oxford) 12:302–310
5. Bruix J, Sherman M (2011) Management of hepatocellular carcinoma: an update. Hepatology 53:1020–1022
6. Lee NH, Chau GY, Lui WY, King KL, Tsay SH, Wu CW (1998) Surgical treatment and outcome in patients with a hepatocellular carcinoma greater than 10 cm in diameter. Br J Surg 85:1654–1657
7. Lai EC, Ng IO, Ng MM, Lok AS, Tam PC, Fan ST, Choi TK, Wong J (1990) Long-term results of resection for large hepatocellular carcinoma: a multivariate analysis of clinicopathological features. Hepatology 11:815–818
8. Poon RT, Fan ST (2004) Hepatectomy for hepatocellular carcinoma: patient selection and postoperative outcome. Liver Transpl 10:S39–45
9. Tandon P, Garcia-Tsao G (2009) Prognostic indicators in hepatocellular carcinoma: a systematic review of 72 studies. Liver Int 29:502–510
10. Pandey D, Lee KH, Wai CT, Wagholikar G, Tan KC (2007) Long term outcome and prognostic factors for large hepatocellular carcinoma (10 cm or more) after surgical resection. Ann Surg Oncol 14:2817–2823
11. Kim SJ, Lee KK, Kim DG (2010) Tumor size predicts the biological behavior and influence of operative modalities in hepatocellular carcinoma. Hepatogastroenterology 57:121–126
12. Pawlik TM, Delman KA, Vauthey JN, Nagorney DM, Ng IO, Ikai I, Yamaoka Y, Belghiti J, Lauwers GY, Poon RT, Abdalla EK (2005) Tumor size predicts vascular invasion and histologic grade: implications for selection of surgical treatment for hepatocellular carcinoma. Liver Transpl 11:1086–1092
13. el-Assal ON, Yamanoi A, Soda Y, Yamaguchi M, Yu L, Nagasue N (1997) Proposal of invasiveness score to predict recurrence and survival after curative hepatic resection for hepatocellular carcinoma. Surgery 122:571–577
14. Yang LY, Fang F, Ou DP, Wu W, Zeng ZJ, Wu F (2009) Solitary large hepatocellular carcinoma: a specific subtype of hepatocellular carcinoma with good outcome after hepatic resection. Ann Surg 249:118–123
15. Regimbeau JM, Farges O, Shen BY, Sauvanet A, Belghiti J (1999) Is surgery for large hepatocellular carcinoma justified. J Hepatol 31:1062–1068
16. Poon RT, Fan ST, Wong J (2002) Selection criteria for hepatic resection in patients with large hepatocellular carcinoma larger than 10 cm in diameter. J Am Coll Surg 194:592–602
17. Yang T, Zhang J, Lu JH, Yang LQ, Yang GS, Wu MC, Yu WF (2011) A new staging system for resectable hepatocellular carcinoma: comparison with six existing staging systems in a large Chinese cohort. J Cancer Res Clin Oncol 137:739–750
18. Yang T, Zhang J, Lu JH, Yang GS, Wu MC, Yu WF (2011) Risk factors influencing postoperative outcomes of major hepatic resection of hepatocellular carcinoma for patients with underlying liver diseases. World J Surg 35:2073–2082. doi:10.1007/s00268-011-1161-0
19. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibanes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M (2009) The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 250:187–196
20. Zhou YM, Li B, Xu DH, Yang JM (2011) Safety and efficacy of partial hepatectomy for huge (>/=10 cm) hepatocellular carcinoma: a systematic review. Med Sci Monit 17:RA76–83
21. de Lope CR, Tremosini S, Forner A, Reig M, Bruix J (2012) Management of HCC. J Hepatol 56(Suppl 1):S75–87
22. Chow PK (2012) Resection for hepatocellular carcinoma: is it justifiable to restrict this to the American Association for the Study of the Liver/Barcelona Clinic for Liver Cancer criteria. J Gastroenterol Hepatol 27:452–457
23. Capussotti L, Ferrero A, Vigano L, Polastri R, Tabone M (2009) Liver resection for HCC with cirrhosis: surgical perspectives out of EASL/AASLD guidelines. Eur J Surg Oncol 35:11–15
24. Tsoulfas G, Mekras A, Agorastou P, Kiskinis D (2012) Surgical treatment for large hepatocellular carcinoma: does size matter. ANZ J Surg 82:510–517
25. Cho YB, Lee KU, Lee HW, Cho EH, Yang SH, Cho JY, Yi NJ, Suh KS (2007) Outcomes of hepatic resection for a single large hepatocellular carcinoma. World J Surg 31:795–801. doi:10.1007/s00268-006-0359-z
26. Wang W, Yang LY, Huang GW, Lu WQ, Yang ZL, Yang JQ, Liu HL (2004) Genomic analysis reveals RhoC as a potential marker in hepatocellular carcinoma with poor prognosis. Br J Cancer 90:2349–2355
27. Yang LY, Wang W, Peng JX, Yang JQ, Huang GW (2004) Differentially expressed genes between solitary large hepatocellular carcinoma and nodular hepatocellular carcinoma. World J Gastroenterol 10:3569–3573
28. Kobayashi T, Itamoto T, Tashiro H, Amano H, Oshita A, Tanimoto Y, Kuroda S, Tazawa H, Ohdan H (2011) Tumor-related factors do not influence the prognosis of solitary hepatocellular carcinoma after partial hepatectomy. J Hepatobiliary Pancreat Sci 18:689–699

29. Zhou L, Rui JA, Wang SB, Chen SG, Qu Q (2011) Prognostic factors of solitary large hepatocellular carcinoma: the importance of differentiation grade. Eur J Surg Oncol 37:521–525
30. Zavaglia C, De Carlis L, Alberti AB, Minola E, Belli LS, Slim AO, Airoldi A, Giacomoni A, Rondinara G, Tinelli C, Forti D, Pinzello G (2005) Predictors of long-term survival after liver transplantation for hepatocellular carcinoma. Am J Gastroenterol 100:2708–2716
31. Izumi R, Shimizu K, Ii T, Yagi M, Matsui O, Nonomura A, Miyazaki I (1994) Prognostic factors of hepatocellular carcinoma in patients undergoing hepatic resection. Gastroenterology 106:720–727
32. Li B, Yuan Y, Chen G, He L, Zhang Y, Li J, Li G, Lau WY (2010) Application of tumor-node-metastasis staging 2002 version in locally advanced hepatocellular carcinoma: is it predictive of surgical outcome. BMC Cancer 10:535
33. Kondo K, Chijiiwa K, Makino I, Kai M, Maehara N, Ohuchida J, Naganuma S (2005) Risk factors for early death after liver resection in patients with solitary hepatocellular carcinoma. J Hepatobiliary Pancreat Surg 12:399–404
34. Fan ST, Mau LC, Poon RT, Yeung C, Leung LC, Yuen WK, Ming LC, Ng KK, Ching CS (2011) Continuous improvement of survival outcomes of resection of hepatocellular carcinoma: a 20-year experience. Ann Surg 253:745–758
35. Shi M, Guo RP, Lin XJ, Zhang YQ, Chen MS, Zhang CQ, Lau WY, Li JQ (2007) Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. Ann Surg 245:36–43
36. Pawlik TM, Poon RT, Abdalla EK, Zorzi D, Ikai I, Curley SA, Nagorney DM, Belghiti J, Naag IO, Yamaoka Y, Lauwers GY, Vauthey JN (2005) Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. Arch Surg 140:450–457 Discussion 457–458
37. Tanaka K, Shimada H, Matsumoto C, Matsuo K, Nagano Y, Endo I, Togo S (2008) Anatomic versus limited nonanatomic resection for solitary hepatocellular carcinoma. Surgery 143:607–615
38. Kaibori M, Matsui Y, Hijikawa T, Uchida Y, Kwon AH, Kamiyama Y (2006) Comparison of limited and anatomic hepatic resection for hepatocellular carcinoma with hepatitis C. Surgery 139:385–394
39. Cho YB, Lee KU, Lee HW, Cho EH, Yang SH, Cho JY, Yi NJ, Suh KS (2007) Anatomic versus non-anatomic resection for small single hepatocellular carcinomas. Hepatogastroenterology 54:1766–1769
40. Wakai T, Shirai Y, Sakata J, Kaneko K, Cruz PV, Akazawa K, Hatakeyama K (2007) Anatomic resection independently improves long-term survival in patients with T1-T2 hepatocellular carcinoma. Ann Surg Oncol 14:1356–1365
41. Yamashita Y, Taketomi A, Itoh S, Kitagawa D, Kayashima H, Harimoto N, Tsujita E, Kuroda Y, Maehara Y (2007) Longterm favorable results of limited hepatic resections for patients with hepatocellular carcinoma: 20 years of experience. J Am Coll Surg 205:19–26