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Optimizing stage of single large hepatocellular carcinoma

A study with subgroup analysis by tumor diameter

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Abstract

This study aims to refine the designation for single hepatocellular carcinoma (HCC) >5 cm by comparing the postresection prognosis of these patients with those who have a single-tumor ≤5 cm and those with stage B.

Patients with a single-tumor were classified into subgroups based on diameter. Of the 1132 patients analyzed, 426 had a single-tumor >2 and ≤5 cm; 229, a single-tumor >5 and ≤8 cm; 52, a single-tumor >8 and <10 cm; 150, a single-tumor ≥10 cm; and 275, stage B.

Hospital mortality and complications increased with tumor size among the single-tumor subgroups and median survival decreased with increasing of tumor size. Overall survival (OS) among patients with a single-tumor >5 cm was significantly lower than among patients with a single-tumor >2 and ≤5 cm ($P \leq .001$), but significantly higher than among patients with clearly stage B ($P \leq .001$). Patients with a single-tumor >5 and ≤8 cm showed lower OS than patients with a single-tumor >2 and ≤5 cm ($P < .001$). Patients with a single-tumor >8 and <10 cm or a single-tumor ≥10 cm showed lower OS than patients with a single-tumor >5 and ≤8 cm ($P = .033$ and .006), and similar OS to patients with stage B ($P = .323$).

Patients with a single-tumor >5 and ≤8 cm may be assigned to a new stage between early and intermediate. Patients with a single-tumor >8 cm may be assigned to intermediate stage.

Abbreviations: BCLC = Barcelona clinic liver cancer, HCC = hepatocellular carcinoma, HR = hepatic resection, OS = overall survival, RFA = radiofrequency ablation, TACE = transarterial chemoembolization.

Keywords: hepatic resection, hepatocellular carcinoma, overall survival, stage designation, tumor size

1. Introduction

The Barcelona clinic liver cancer (BCLC) staging system, which is considered the most rigorous and comprehensive of hepatocellular carcinoma (HCC) staging systems, assigns multinodular HCCs to stage B.[1,2] Hepatic resection (HR) and ablation are recommended for stage A, and transarterial chemoembolization (TACE) for stage B. The BCLC system provides guidance for staging HCC involving a single-tumor >5 cm without macrovascular invasion as stage A. Although some clinicians assign such disease to stage A,[3–5] others working in the West[6,7] and East[7,8] assigned it to stage B due to a lack of clarity in definition.[9] This means that liver centers around the world apply a broader range of treatments to patients with a single-tumor >5 cm than to patients who fall neatly into BCLC stages. Therefore, evidence-based optimization of BCLC staging is needed for patients with a single-tumor >5 cm.[10] On the other hand, improvements in surgical technique and perioperative care

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at large liver centers worldwide have made HR a successful 1st-line therapy for many patients in BCLC stages A–C.[11–13]

The present study aimed to analyze a large cohort of HCC patients to refine BCLC staging for those with a single-tumor >5 cm. In order to eliminate bias due to different treatment approaches, we examined patients with newly diagnosed HCC who were treated by initial, potentially curative HR. Patients with single tumors were subgrouped according to tumor diameter and compared with patients with 2 to 3 tumors of a maximum diameter >3 cm or >3 tumors of any diameter that fell clearly within BCLC stage B.[1,2]

2. Patients and methods

2.1. Study population and design

This retrospective study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the institutional review board of Guangxi Medical University, who waived the requirement for informed consent. Medical records were analyzed for patients newly diagnosed with HCC between January 2004 and October 2013 at the Affiliated Tumor Hospital of Guangxi Medical University based on pathological examination of surgical samples and diagnostic criteria of the American Association for the Study of Liver Diseases.[2] Patients were included only if they had Child–Pugh grade A or B liver function and if they underwent initial potentially curative HR at our liver center. The inclusion and exclusion criteria were described in Table 1.

Patients with a single-tumor were classified into subgroups based on whether the tumor was >2 and ≤5 cm (BCLC stage A) (group I), >5 and ≤8 cm (group II1), >8 and <10 cm (group II2), or ≥10 cm (group II3).[9] These subgroups, as well as the entire group of single tumor patients, were compared to patients with 2 to 3 tumors of maximum diameter >3 cm or >3 tumors of any diameter (BCLC stage B) (group III).

2.2. Definition

Potentially curative HR was defined as any resection in which all tumors were resected macroscopically and after which no residual tumor was detected by magnetic resonance imaging and/or computed tomography scanning and serum α-fetoprotein returned to normal within 1 month.

Tumor number and size were determined by preoperative imaging and confirmed by pathology after HR.[1,2] If there was a discrepancy between the 2 methods, pathology after resection shall prevail. Patients were excluded if they underwent palliative resection or satisfied the criteria for BCLC stage C, including preoperative tumor rupture, macrovascular invasion, tumor metastasis to the lymph nodes, and/or other adjacent or distant organs.[1,2] Patients were excluded if they had 2 to 3 tumors ≤3 cm, which fits the criteria for BCLC stage A. Patients were also excluded if they had single-tumor ≤2 cm which regarding as very early-stage HCC. In this study, we did not perform molecular diagnosis.

2.3. Treatment

All patients with HCC at our medical center were initially evaluated for the possibility of HR, unless the patient requested another treatment modality. Indications for HR have been described,[14,15] and they took into account patient and tumor characteristics as well as preoperative laboratory data. The resection techniques used for HR have been described[14–17]; anatomic resection was the preferred procedure. No more than 30 days passed from diagnosis to surgery.

2.4. Follow-up

Follow-up for all patients began immediately after HR until death or March 2015. The protocol of follow-up was described as before.[14] Recurrence was defined as the appearance of a new lesion with radiological features similar to those of primary HCC during follow-up. In such cases, HR was repeated if judged feasible based on liver function and remnant liver volume; indications for repeat HR were the same as those for initial HR. If HR could not be performed because of poor liver function or inadequate remnant liver volume, then TACE, radiofrequency ablation (RFA), or other palliative therapies were applied. Postoperative adjuvant TACE was routinely performed on patients with risk factors of recurrence.[18,19] Patients who were diagnosed with HCC at our hospital after 2008 received postoperative nucleos(t)ide analogue therapy if serum levels of hepatitis B virus DNA were ≥2000 IU/mL.[20]

Overall survival (OS) was calculated starting from the date of 1st diagnosis of HCC (date of admission) until death, last follow-up or March 2015, whichever occurred earliest. These outcomes were compared among the 4 subgroups of single-tumor patients and the entire groups of single-tumor patients and patients with stage B.

2.5. Statistical analysis

All patient demographic and clinicopathological data were prospectively collected in the central database of our hospital after admission. Missing data were filled in using multiple imputation involving stochastic switching regression and 5 repeated imputations.[21] All statistical analyses were performed

Table 1

Reasons and patient number of inclusion and exclusion.

Inclusion			Exclusion		
Group	Note	Number of patients	Item	Note	Number of patients
I	Single-tumor ≤5 cm	426	A	Intrahepatic cholangiocarcinoma, hepatic focal nodular hyperplasia, hepatocellular adenoma, or hepatosarcoma	326
II	Single-tumor >5 and ≤8 cm	229	B	BCLC stage C HCC	290
	Single-tumor >8 and <10 cm	52	C	Palliative resection	97
	Single-tumor ≥10 cm	150	D	2–3 tumors ≤3 cm	94
III	2–3 tumors with a maximum diameter >3 cm or >3 tumors of any diameter	275	E	Single-tumor ≤2 cm	58

BCLC = Barcelona clinic liver cancer, HCC = hepatocellular carcinoma.

using SPSS 19.0 (IBM, IL) under the direction of a biostatistician, and a 2-tailed $P < .05$ was defined as the threshold of significance. Data for categorical variables were expressed as absolute number (%). Intergroup differences in categorical data were assessed for significance using the chi-squared or Fisher exact tests (2-tailed) as appropriate. Normally distributed data were expressed as mean ± standard deviation, while skewed data were expressed as median (range). Intergroup differences in continuous variables were assessed for significance using the *t* test or Mann–Whitney *U* test. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariate analysis to identify independent prognostic factors was carried out using a Cox proportional hazards model.

3. Results

3.1. Patient characteristics

Of the 1997 potentially eligible patients with primary liver cancer who were admitted for the 1st time to our hospital and who underwent initial HR during the study period, 326 were excluded because they had intrahepatic cholangiocarcinoma, hepatic focal nodular hyperplasia, hepatocellular adenoma, or hepatosarcoma. Another 387 patients were excluded because they had BCLC stage C HCC or received palliative resection, 94 were excluded because having 2 to 3 tumors ≤3 cm (stage A), and 58 were excluded because they had single-tumor ≤2 cm (BCLC very early stage). Consequently, 1132 patients were enrolled in the present study. The group of single-tumor patients comprised 426 with a tumor >2 and ≤5 cm; 229, >5 and ≤8 cm; 52, >8 and <10 cm; and 150, ≥10 cm. The group of patients with clearly stage B comprised 200 who had 2 to 3 tumors with a maximum diameter >3 cm and 75 who had >3 tumors of any diameter. This content was described in Table 1.

Demographic and clinic-pathological data at baseline are presented in Tables 2 and 3. Patients with single-tumors >5 cm had significantly higher platelet counts than those with single-tumors >2 and ≤5 cm or those with clearly stage B (all $P < .001$). Patients with single-tumors >2 and ≤5 cm had significantly longer prothrombin time than those with single-tumors >5 cm ($P = .004$) or with stage B ($P = .007$), and they had significantly higher albumin levels ($P = .007$) and incidence of cirrhosis ($P = .018$) than those with single-tumors >5 cm. The proportion of patients with a serum level of α-fetoprotein ≥400 ng/mL was significantly higher among those with single-tumors >5 cm or with stage B than among those with single-tumors >2 and ≤5 cm (all $P < .001$). Compared to patients with single-tumors, those with stage B showed a significantly higher incidence of esophagogastric varices ($P = .012$ and .024) and lower incidence of complete tumor capsule (all $P < .001$). Incidence of a serum level of α-fetoprotein ≥400 ng/mL and of major hepatectomy increased with tumor size, as blood volume lost during surgery (Table 3).

3.2. Mortality and morbidity

Mortality at 30 days was similar for patients with single-tumors >2 and ≤5 cm (0%) and for patients with single-tumors >5 cm (.7%; $P = .252$). Mortality among patients with stage B (1.5%) was similar to that among patients with single-tumors >5 cm ($P = .547$), and marginally higher than that among patients with single-tumors ≤5 cm ($P = .047$).

Table 2

Comparison of demographic and clinicopathological data and outcomes of patients with single-tumor or multinodular HCC after initial hepatic resection.

	Single tumor			*P*		
Parameter	Group I (n = 426)	Group II (n = 431)	Group III (n = 275)	I vs II	II vs III	I vs III
Age, y	49.2 ± 10.9	48.8 ± 11.9	48.8 ± 11.4	.599	.979	.614
Male	361 (85)	374 (87)	247 (90)	.394	.226	.053
Positive for hepatitis B surface antigen	393 (92)	384 (89)	253 (92)	.112	.205	.903
Platelet count, $\times 10^9$/L	153 (12–429)	192 (32–668)	172 (54–390)	<.001	.003	<.001
Prothrombin time, sec	13.0 (9.4–22.4)	12.8 (9.8–21.0)	12.8 (8.5–19.7)	.004	.827	.007
Albumin, g/L	41.3 ± 5.0	40.4 ± 4.5	40.8 ± 4.5	.007	.209	.233
Alanine aminotransferase, U/L	35.5 (1.9–399.0)	37.0 (1.0–410.0)	40.0 (7.0–951.0)	.822	.099	.073
Total bilirubin, μmol/L	14.0 ± 7.1	13.5 ± 7.5	13.5 ± 7.0	.315	.987	.365
α-fetoprotein						
≥400 ng/mL	119 (28)	175 (41)	112 (41)	<.001	.974	<.001
<400 ng/mL	307 (72)	256 (59)	163 (59)			
Child–Pugh class						
A	403 (95)	411 (95)	265 (96)	.611	.519	.282
B	23 (5)	20 (5)	10 (4)			
Cirrhosis						
Present	318 (75)	290 (67)	198 (72)	.018	.186	.437
Absent	108 (25)	141 (33)	77 (28)			
Esophagogastric varices	35 (8)	39 (9)	40 (15)	.664	.024	.012
Diabetes mellitus	81 (19)	78 (18)	52 (19)	.730	.786	.972
Tumor capsule						
Complete	276 (65)	233 (54)	99 (36)	.001	<.001	<.001
Incomplete/absent	150 (35)	198 (46)	176 (64)			
Differentiation degree						
Well	64 (15)	56 (13)	27 (10)	.697	.191	.306
Moderately	217 (51)	224 (52)	135 (49)			
Poorly	145 (34)	151 (35)	113 (41)			
Tumor size, cm	3.90 ± 1.3	8.98 ± 3.06	7.42 ± 3.67	<.001	<.001	<.001
Major hepatectomy	12 (3)	82 (19)	66 (24)	<.001	.113	<.001
Blood loss, mL	200 (10–1800)	300 (30–8400)	350 (100–3500)	<.001	.455	<.001
30-day mortality	0 (0)	3 (.7)	4 (1.5)	.252	.547	.047
90-day mortality	2 (.5)	8 (1.9)	13 (4.7)	.116	.029	<.001
Complications	91 (21.4)	143 (33.2)	97 (35.3)	<.001	.567	<.001
Survival time, mo	76 (2–123)	51 (1–121)	42 (1–111)	<.001	.001	<.001

Values shown are mean ± SD, median (range), or n (%). Group I, single-tumor >2 and ≤5 cm; group II, single-tumor >5 cm; group III, ≥2 tumors. HCC = hepatocellular carcinoma, SD = standard deviation.

Table 3

Comparison of demographic and clinicopathological data and outcomes of single-tumor HCC patients after initial resection, stratified by tumor size.

Parameter	Subgroup II1 (n = 229)	Subgroup II2 (n = 52)	Subgroup II3 (n = 150)	*P*		
				II1 vs II2	II2 vs II3	II1 vs II3
Age, y	49.4 ± 12.3	51.0 ± 12.2	47.3 ± 10.9	.380	.039	.083
Male	205 (89.5)	46 (88.46)	123 (82)	.823	.277	.036
Positive for hepatitis B surface antigen	206 (90)	48 (92.3)	130 (86.7)	.796	.139	.331
Platelet count, $\times 10^9$/L	168 (32–542)	207 (44–668)	223 (63–610)	.002	.234	<.001
Prothrombin time, sec	12.9 (9.9–21.0)	12.75 (10.8–17.9)	12.7 (9.8–19.5)	.857	.200	.100
Albumin, g/L	40.6 ± 4.4	40.8 ± 4.7	40.0 ± 4.5	.684	.224	.191
Alanine aminotransferase, U/L	37 (1–283)	38 (12–205)	39 (10–410)	.555	.934	.416
Total bilirubin, μmol/L	13.9 ± 8.6	12.7 ± 6.1	13.1 ± 6.2	.375	.722	.346
α-fetoprotein						
≥400 ng/mL	75 (33)	25 (48)	75 (50)	.016	.926	<.001
<400 ng/mL	154 (67)	27 (52)	75 (50)			
Child–Pugh class						
A	219 (96)	50 (96)	142 (95)	1.000	.670	.665
B	10 (4)	2 (4)	8 (5)			
Cirrhosis						
Present	168 (73)	34 (65)	88 (59)	.248	.416	.003
Absent	61 (27)	18 (35)	62 (41)			
Esophagogastric varices	21 (9)	6 (12)	12 (8)	.601	.625	.693
Diabetes mellitus	41 (18)	11 (21)	26 (17)	.586	.539	.887
Tumor capsule						
Complete	119 (52)	32 (62)	82 (55)	.211	.421	.674
Incomplete/absent	110 (48)	20 (38)	68 (45)			
Differentiation degree						
Well	27 (12)	9 (17)	20 (13)	.303	.582	.842
Moderately	117 (51)	29 (56)	78 (52)			
Poorly	85 (37)	14 (27)	52 (35)			
Tumor size, cm	6.7 ± .8	9.0 ± .3	12.4 ± 2.5	<.001	<.001	<.001
Major hepatectomy	13 (6)	9 (17)	60 (40)	.011	.003	<.001
Blood loss, mL	300 (30–2000)	300 (100–2000)	400 (50–8400)	.024	.207	<.001
30-day mortality	1 (.4)	1 (1.9)	1 (.7)	.336	.450	1.000
90-day mortality	3 (1.3)	1 (1.9)	4 (2.7)	.561	1.000	.569
Complications	65 (28.4)	16 (30.8)	62 (41.3)	.732	.178	.009
Survival time, mo	56 (1–121)	43 (1–104)	45 (1–110)	.033	.920	.006

Values shown are mean ± SD, median (range), or n (%). Subgroup B1, >5 and ≤8 cm; subgroup B2, >8 and <10 cm; subgroup B3, ≥10 cm. HCC = hepatocellular carcinoma, SD = standard deviation.

Mortality at 90 days was similar for patients with single-tumors >2 and ≤5 cm (.5%) and for patients with single-tumors >5 cm (1.9%; $P = .116$). It was significantly higher among patients with stage B (4.7%) than among those with single-tumors >2 and ≤5 cm ($P < .001$) or those with single-tumors >5 cm ($P = .029$; Table 2).

Hospital mortality at 30 and 90 days was compared among the subgroups of single-tumor patients. Although a slight tendency for higher 90-day mortality with increasing tumor size was observed, no significant differences were found (Table 3).

Analysis of postoperative complications based on Clavien–Dindo classification[22] showed a significantly lower incidence of complications among patients with single-tumors >2 and ≤5 cm (21.4%) than among those with single-tumors >5 cm (33.2%) or with stage B (35.3%; all $P < .001$; Table 2). Incidence of complications was similar for patients with single-tumors >5 cm or with stage B. Among the single-tumor subgroups, incidence of postoperative complications increased significantly with tumor size: incidence was significantly higher among patients with single-tumors ≥10 cm (41.3%) than among those with single-tumors >5 and ≤8 cm (28.4%; $P = .009$; Table 3).

Most postoperative complications among single- and multiple-tumor patients were grade I or II, with the most frequent being hydrothorax and liver failure. Most cases of hydrothorax occurred as unusual deviations from the normal postoperative course and resolved without special treatment.

3.3. Survival analysis

Among the total population of 857 patients with single-tumors, OS was 95% at 1 year, 73% at 3 years, and 54% at 5 years; median survival time was 62 months. Median survival time for single-tumor subgroups was: >2 and ≤5 cm, 76 months; >5 and ≤8 cm, 56 months; >8 and <10 cm, 43 months; and ≥10 cm, 45 months. Median survival time across all patients with single-tumors >5 cm was 51 months, and it was 42 months among patients with stage B.

OS at 1, 3, and 5 years was 97%, 81%, and 63% for patients with single-tumors >2 and ≤5 cm, significantly higher than OS for patients with single-tumors >5 cm (92%, 64%, and 45%; $P < .001$; Fig. 1A). These OS values for single-tumors >5 cm were, in turn, significantly higher than those for stage B (81%, 55%, and 32%; $P < .001$). Among the subgroups of single-tumor patients, OS at the 3 follow-up points was significantly higher for patients with single-tumors >5 and ≤8 cm (95%, 72%, and 49%) than for those with single-tumors >8 and <10 cm (85%, 55%, and 39%) or single-tumors ≥10 cm (90%, 56%, and 41%; all $P < .05$). OS at the 3 follow-up points was similar for the latter

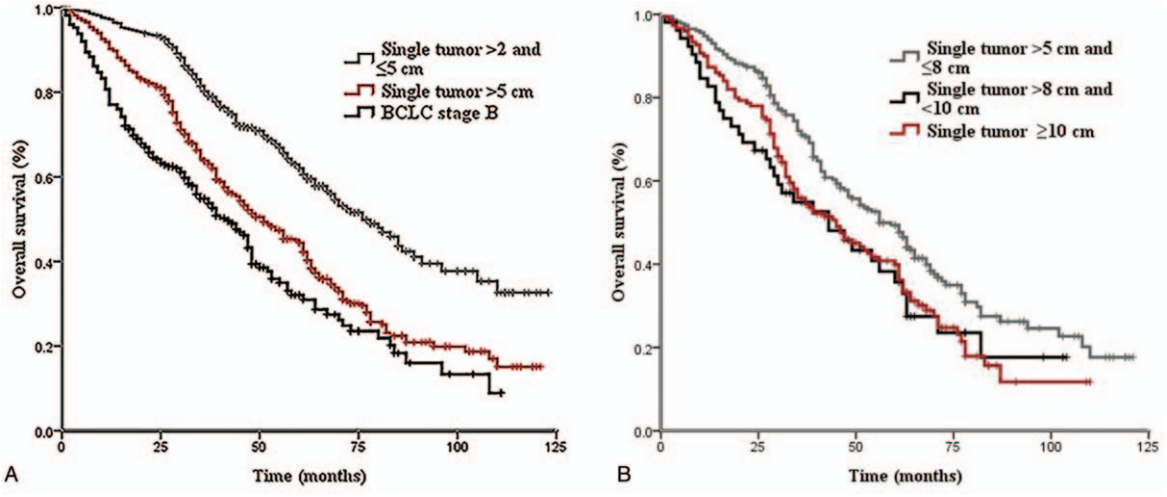

Figure 1. Overall survival curves for patients with single-tumor HCC or BCLC stage B HCC following hepatic resection. (A) Separate curves are shown for patients with a single-tumor >2 and ≤5 cm, a single-tumor >5 cm, or stage B HCC; all curves are significantly different from one another ($P \leq .001$). (B) Overall survival curves of subgroups of patients with single-tumor HCC following hepatic resection; the subgroup >5 and ≤8 cm differed significantly from the subgroup ≥10 cm ($P = .006$) and from the subgroup >8 and <10 cm ($P = .033$); the subgroup >8 and <10 cm was similar to the subgroup ≥10 cm ($P = .920$). BCLC = Barcelona clinic liver cancer, HCC = hepatocellular carcinoma.

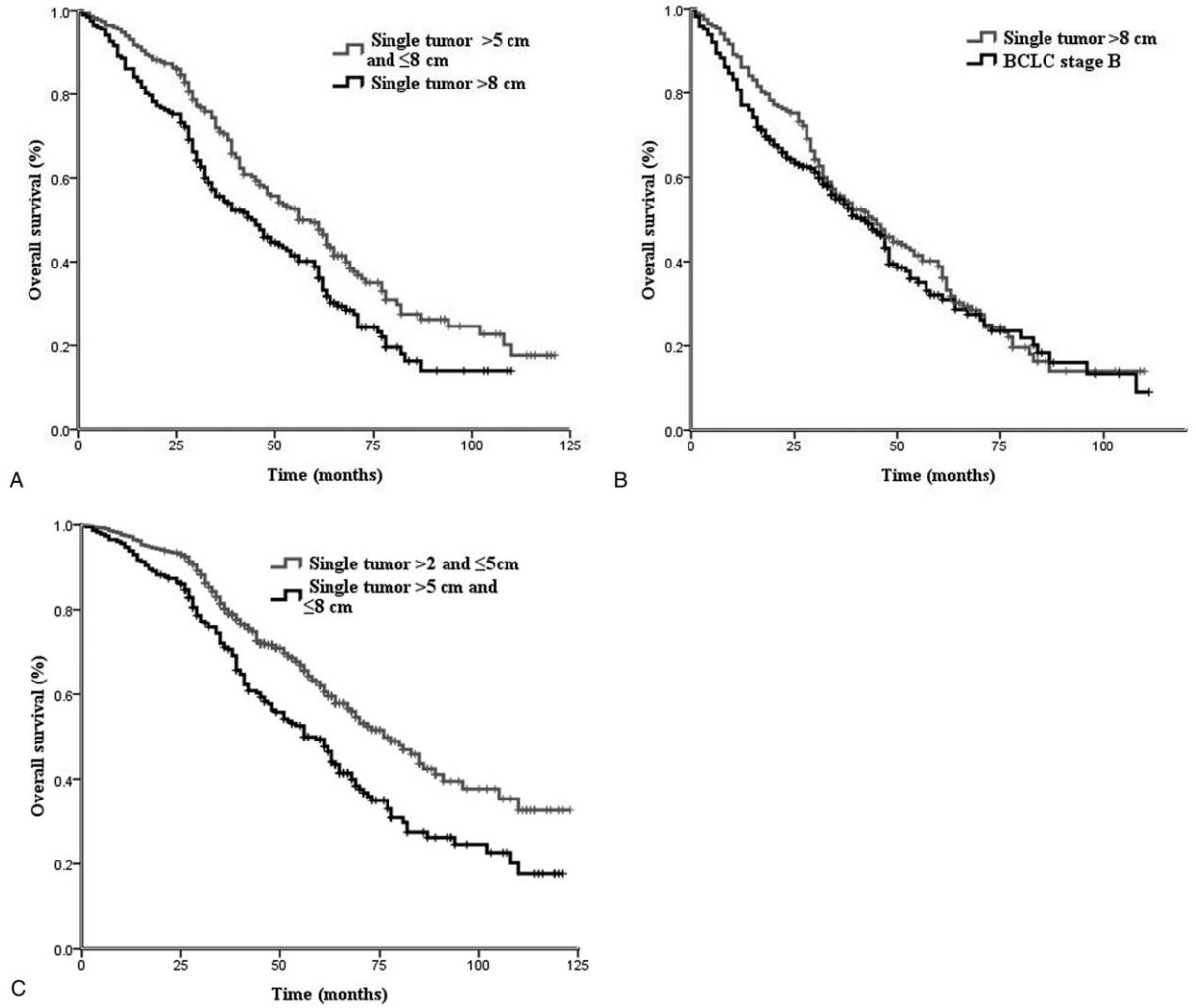

Figure 2. Overall survival compared separately. (A) For patients with a single-tumor >5 and ≤8 cm and patients with a single-tumor >8 cm ($P = .003$). (B) For patients with a single-tumor >8 cm and patients with BCLC stage B HCC ($P = .323$). (C) For patients with a single-tumor >2 and ≤5 cm and patients with a single-tumor >5 and ≤8 cm ($P < .001$). BCLC = Barcelona clinic liver cancer, HCC = hepatocellular carcinoma.

Table 4

Characteristics of patients experiencing hepatocellular carcinoma recurrence after hepatic resection.

Recurrence type	Group I (n = 426)	Group B (n = 431)			Group III (n = 275)	P		
		Subgroup II1 (n = 229)	Subgroup II2 (n = 52)	Subgroup II3 (n = 150)		I vs II	II vs III	I vs III
Intrahepatic + extrahepatic	196 (46)	133 (58)	35 (67)	105 (70)	206 (75)	<.001	.001	<.001
Extrahepatic*	29 (15)	27 (20)	9 (26)	32 (30)	25 (12)	.008	<.001	.434
Intrahepatic	167 (85)	106 (80)	26 (74)	73 (70)	181 (88)			

Values shown are n (%). Groups I to III are defined in Table 1; subgroups II1 to II3, in Table 2.
* Including 31 patients with both intra- and extrahepatic recurrence.

2 subgroups ($P = .920$; Fig. 1B). Patients with single-tumors >5 and ≤8 cm had significantly higher OS at all 3 follow-up points than all patients with single-tumors >8 cm ($P = .003$; Fig. 2A), who had OS similar to that of patients with stage B ($P = .323$; Fig. 2B). Nevertheless, patients with single-tumors >5 and ≤8 cm had significantly lower OS than patients with single-tumors >2 and ≤5 cm ($P < .001$; Fig. 2C).

3.4. Tumor recurrence and treatment

During follow-up until March 2015, 675 patients (59.6%) experienced HCC recurrence, of whom 553 (81.9%) experienced intrahepatic recurrence. The rate of recurrence was significantly lower in patients with single-tumors >2 and ≤5 cm (46.0%) than in those with single-tumors >5 cm (63.3%) or with stage B (74.9%; all $P < .001$). Recurrence occurred significantly less often among patients with single-tumors >5 cm than among those with stage B ($P = .001$). Intrahepatic recurrence was by far the more frequent type of recurrence in all groups and subgroups. The overall recurrence rate and the rate of extrahepatic recurrence increased with tumor size (Table 4).

Treatments for recurrent HCC included repeat resection, TACE, RFA, sorafenib, radiotherapy, and systemic chemotherapy; TACE was used most frequently. Most patients received 2 or more of these treatments, such as RFA followed by TACE, or TACE followed by sorafenib. A total of 302 patients received postoperative nucleos(t)ide analogue therapy for at least 6 months.

Table 5

Multivariate analysis of predictors of poor overall survival in hepatocellular carcinoma (HCC) patients after initial hepatic resection.

Variable	Hazard ratio (95% confidence interval)	P
Patients with single-tumor HCC (n = 857)		
Albumin <35 g/L	1.097 (1.000–1.271)	.049
Alanine aminotransferase >80 U/L	1.104 (1.009–1.310)	.045
α-fetoprotein ≥400 ng/mL	1.557 (1.254–2.475)	.013
Esophagogastric varices	1.317 (1.117–1.795)	.028
Incomplete/absent tumor capsule	1.614 (1.127–2.328)	.011
Tumor size >8 cm	1.727 (1.152–2.796)	.007
Major hepatectomy	2.137 (1.416–3.573)	<.001
Patients with 2–3 tumors with a maximum diameter >3 cm, or >3 tumors of any diameter (n = 275)		
Age >60 y	1.116 (1.004–1.318)	.041
Albumin <35 g/L	1.121 (1.011–1.571)	.038
Alanine aminotransferase >80 U/L	1.182 (1.031–1.517)	.021
Total bilirubin >1.2 μmol/L	1.109 (1.001–1.482)	.048
α-Fetoprotein ≥400 ng/mL	1.579 (1.261–2.734)	.012
Esophagogastric varices	1.426 (1.215–1.815)	.014
Incomplete/absent tumor capsule	1.661 (1.152–2.547)	.008
Tumor size >8 cm	1.817 (1.171–2.915)	.006
Major hepatectomy	2.172 (1.424–3.841)	<.001
Diabetes mellitus	1.142 (1.024–1.624)	.034

3.5. Predictors of survival

Among the 857 single-tumor patients, multivariate analysis identified 7 factors significantly associated with poor OS (Table 5): preoperative serum albumin <35 g/L, alanine aminotransferase >80 U/L, α-fetoprotein ≥400 ng/mL, presence of esophagogastric varices, incomplete/absent tumor capsule, tumor size >8 cm, and major hepatectomy. Among the 275 patients with clearly stage B, the abovementioned predictors were identified, together with 3 additional ones: age >60 years, preoperative serum total bilirubin >1.2 μmol/L, and diabetes mellitus.

4. Discussion

Many HCC patients have single large tumors,[23,24] yet such disease does not fall neatly within BCLC staging and treatment guidelines.[7] Although some medical centers tend to treat such patients with noncurative cares, such as TACE, we have found that treating many of these patients with potentially curative HR leads to significantly better OS than TACE and similar hospital mortality after propensity score analysis.[14,15] Here, we compared the prognosis of patients treated by HR when they had single-tumors >2 and ≤5 cm (BCLC stage A), single-tumors >5 cm, or clearly stage B. We found that patients with a single-tumor >5 cm showed significantly lower OS than those in stage A but significantly higher OS than those in clearly stage B. Patients with a single-tumor >5 cm also showed slightly lower rates of hospital mortality and postoperative complications than patients in clearly stage B. Among subgroups of single-tumor patients stratified by tumor size, increasing tumor size was associated with higher incidence of hospital mortality, postoperative complications, and major hepatectomy as well as greater volumes of blood loss. Conversely, increasing tumor size was associated with lower median survival time and OS.

Our finding that patients with a single-tumor >5 cm showed OS intermediate between BCLC stages A and B suggests that such patients should be assigned to a new BCLC stage between A and B. In contrast to these results, Jung et al[25] reported that patients with single-tumors >5 cm showed similar prognosis as patients in stage B. This discrepancy may reflect the fact that those patients had received heterogeneous initial treatments. When those authors analyzed only patients who underwent HR, OS was similar for patients with a single-tumor >5 cm and for patients in stage A HCC,[25] as reported by other studies[24,26] (Table 6). Although these findings might argue for assigning patients with a single-tumor >5 cm to stage A, the OS of such patients in several

Table 6

Overall survival of patients with single tumors ≤5 cm or single tumors >5 cm after hepatic resection, as reported in recent literature.

Study	Enrollment period	Sample size*	Overall survival, %*			P
			1-y	3-y	5-y	
Yang et al[24]	1992–2002	135/260	93/87	68/56	48/38	.129
Jung et al[25]	2004–2009	134/41	97/93	82/80	77/76	>.05†
Cho et al[26]	1998–2001	169/61	88/85	70/59	59/53	.385
Zhou et al[27]	1995–2002	48/85	96/94	74/56	69/47	.041
Hwang et al[28]	2000–2012	1702/448	97/93	89/81	81/69	<.001
Zhang et al[29]	2002–2010	380/229	97/95	83/75	72/66	.044
This study	2004–2013	426/431	97/92	81/64	63/45	<.001

* Sample size and overall survival are reported as "≤5 cm/>5 cm," except for Jung et al, where these values are reported as "single tumor >2 and ≤5 cm or 2 to 3 nodules ≤3 cm/single tumor >5 cm."
† Overall survival was manually estimated from the published survival curves.

studies, including the present work, was significantly lower than that of stage A patients.[27–29] Therefore, we argue for assigning such patients to a BCLC stage distinct from stage A. In any event, caution should be exercised when comparing the results of the present study with previous work,[24–29] since those studies included many patients with macrovascular invasion, and they did not perform subgroup analyses based on tumor size or compare OS among the subgroups.

Several factors may explain why patients with a single-tumor >5 cm show significantly lower OS than classical stage A patients. We found that increasing tumor size in single-tumor patients was associated with higher preoperative levels of α-fetoprotein, greater blood loss volume, and higher incidence of esophagogastric varices and major hepatectomy. As a result, increasing tumor size was associated with higher incidence of hospital mortality, postoperative complications, and recurrence (Table 4). Tumor recurrence is the main cause of death among patients with HCC.[1,2] In the present cohort, 92% death was due to tumor recurrence.

OS at 1, 3, and 5 years in our cohort was not higher than in previous studies (Table 6).[24–29] This is despite the fact that our enrollment period (2004–2013) is more recent than in those studies, and 5-year OS after HR has gradually increased for patients with single-tumor or multinodular HCC due to improvements in surgical technique and perioperative care.[11,30] In addition, our study did not include patients with macrovascular invasion, while 3 previous studies did.[24,26,27] Our failure to observe higher OS than in previous work may reflect the fact that many of our patients were followed up for fewer than 5 years. We suspect that if we had followed up patients for longer than 5 years, we would have observed higher OS than previous studies. On the other hand, a large number of the included patients were from regions with poor economic condition. They were short of timely reexamination and aggressive treatment after tumor recurrence.

Our results suggest the need for a 2nd modification to BCLC staging.[31] Although our recent studies suggest that tumor size ≥10 cm (originally referred to as "huge HCC")[17] is a risk factor of poor OS after HR,[14,15,23,32,33] earlier work reported the same result for tumors ≥7[34] or ≥8 cm.[35] In the present study, Cox proportional hazard analysis identified a single-tumor >8 cm as a risk factor of poor OS. This is consistent with our observation of similar median survival time and OS at 1, 3, and 5 years for patients with a single-tumor >8 and <10 cm and for patients with a single-tumor ≥10 cm. More importantly for BCLC staging, we found that OS was significantly lower for patients with a single-tumor >8 cm than for those with a single-tumor >5 and ≤8 cm (Fig. 2A); in fact, OS was similar for patients with a single-tumor >8 cm and for patients in clearly stage B (Fig. 2B). Therefore, we suggest that patients with a single-tumor >8 cm should not be assigned to the same BCLC stage as those with a single-tumor >5 cm. Instead they should be assigned to stage B.

Although the issue of optimal treatment is not addressed, the findings of the present study support a substantial body of evidence, based on previous studies[14,15,33] and on large systematic reviews by our group[11] and others[12] that HR is associated with significantly better OS than TACE for patients in stages A–C.[36]

The conclusions from this study are limited by the fact that they are based on retrospective analysis of data from a single liver center, and follow-up of patients enrolled after 2011 was shorter than 5 years. Moreover, the fact that we performed adjuvant TACE on patients with risk factors for recurrence may have confounded our OS analyses. Our findings should be verified and extended in future prospective studies with longer follow-up. On the other hand, only patients with primary HCC after initial HR were included. This could bias the obtained results in terms of insufficient comparison of HR toward liver transplantation or RFA in patients with BCLC A HCC and impaired liver function. Therefore, our results should also be verified among those underwent other therapies, such as liver transplantation, RFA, and TACE. And last, many baseline variables among each group are significantly different, thus conclusions from direct comparisons of complications, survival time, and OS may be confounding. Since the study cohort included patients from China, etiology of HCC was mainly HBV-infection, our results refer mainly to HBV-induced HCC and thus may not be transferable in HCC of other causes with a higher grade of liver function impairment as seen in Europe or in the US.

Despite these limitations, the present work has several strengths. First, the large sample of 1132 patients was recruited consecutively and screened carefully for homogeneity as single-tumor or stage B HCC, without macrovascular invasion or other complications linked to poor prognosis. Second, all patients underwent the same treatment (initial HR), thereby reducing confounding due to heterogeneous HCC treatments that plagues numerous similar studies in the literature. Third, we performed subgroup analysis only for single-tumor size, allowing us to gain more detailed information into effects of tumor size on prognosis while minimizing the risk of false positives due to excessive hypothesis-testing. Based on our analysis, we conclude that patients with a single-tumor >5 and ≤8 cm should constitute a new BCLC stage distinct from stages A and B, and that patients with a single-tumor >8 cm should be assigned to BCLC stage B.

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