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Liver resection is justified for multinodular hepatocellular carcinoma in selected patients with cirrhosis: A multicenter analysis of 1,066 patients

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A R T I C L E I N F O

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Background: The role of liver resection for multinodular (≥3 nodules) hepatocellular carcinoma (HCC) remains unclear, especially among patients with severe underlying liver disease. We sought to evaluate surgical outcomes among patients with cirrhosis and multinodular HCC undergoing liver resection.
Methods: Using a multicenter database, outcomes among cirrhotic patients who underwent curative-intent resection of HCC were examined stratified according to the presence or absence of multinodular disease. Perioperative mortality and morbidity, as well as overall survival (OS) and recurrence-free survival (RFS) were compared between the two groups.
Results: Among 1066 cirrhotic patients, 906 (85.0%) had single- or double-nodular HCC (the non-multinodular group), while 160 (15.0%) had multinodular HCC (the multinodular group). There were no differences in postoperative 30-day mortality and morbidity among non-multinodular versus multinodular patients (1.8% vs. 1.9%, $P = 0.923$, and 36.0% vs. 39.4%, $P = 0.411$, respectively). In contrast, 5-year OS and RFS of multinodular patients were worse compared with non-multinodular patients (34.6% vs. 58.2%, and 24.7% vs. 44.5%, both $P < 0.001$). On multivariable analyses, tumor numbers ≥5, total tumor diameter ≥8 cm and microvascular invasion were independent risk factors for decreased OS and RFS after resection of multinodular HCC in cirrhotic patients.
Conclusions: Liver resection can be safely performed for multinodular HCC in the setting of cirrhosis with an overall 5-year survival of 34.6%. Tumor number ≥5, total tumor diameter ≥8 cm and microvascular

Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer; TACE, transcatheter arterial chemoembolization; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; CT, contrast-enhanced computed tomography; MRI, magnetic resonance imaging; OS, overall survival; RFS, recurrence-free survival; SD, standard deviation; HR, hazard ratio; CI, confidence interval.

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invasion were independently associated with decreased OS and RFS after resection in cirrhotic patients with multinodular HCC.

Introduction

Hepatocellular carcinoma (HCC) remains one of the most common malignancies worldwide and one of the leading causes of cancer-related death [1,2]. The majority of patients with HCC have underlying liver cirrhosis, as a result of hepatitis B virus (HBV), hepatitis C virus (HCV) infection, or alcoholic hepatitis [3–5]. Liver resection has been established as the mainstay of curative treatments for early-stage hepatocellular carcinoma in patients with well-preserved liver function [6–8]. However, the role of liver resection for multinodular HCC (≥3 nodules, mostly as Barcelona Clinic Liver Cancer (BCLC) intermediate stage) is still controversial as resection can be associated with potentially higher operative risks, as well as increased recurrence and worse long-term survival [9–12].

Several previous studies have suggested that liver resection should be considered for patient with multinodular HCC if the future liver remnant is sufficient [13–17]. In particular, improved survival can be achieved in patients with multinodular HCC undergoing liver resection compared with transcatheter arterial chemoembolization (TACE), although the latter therapy has been recommended as first-line therapy by the European and American Liver Disease Associations [18]. A recent meta-analysis also demonstrated that liver resection had better overall survival versus TACE for patients with multinodular HCC without a significant increase in postoperative complications or 30-day mortality [19]. Whether such data are applicable to patients with underlying cirrhosis has not been examined. In particular, whether the risks and benefits of liver resection for multinodular HCC in cirrhotic patients are justified remain poorly defined.

As such, the objective of the current study was to evaluate short-term and long-term outcomes of cirrhotic patients who underwent curative liver resection for multinodular HCC. In particular, using a multicenter database, we sought to compare the outcomes of HCC patients with versus without multinodular HCC, as well as identify independent risk factors associated with recurrence and survival after liver resection. Such data may offer useful guidance in surgical decision-making, planning recurrence surveillance and adjuvant therapy for patients with multinodular HCC.

Patients and methods

Patients

A multicenter database of patients who underwent curative-intent liver resection for HCC from January 2006 to December 2015 at 8 Chinese hospitals was retrospectively reviewed and analyzed. Inclusion criteria were 1) cirrhosis and HCC, both of which were confirmed by histopathological examination of the resected specimens; 2) curative resection of HCC, defined as complete resection of all microscopic and macroscopic tumors (R0 resection); 3) no extrahepatic metastasis or major portal/hepatic vein invasion; 4) no previous anti-HCC treatment before resection; and 5) complete records on prognostic variables. The exclusion criteria were 1) palliative liver resection, i.e. microscopically positive (R1 resection) or grossly positive (R2 resection) resection margins; 2) recurrent HCC, ruptured HCC or combined HCC-cholangiocarcinoma; and 3) missing data on prognostic variables or follow-up information. Data included in the study were censored on Dec 2017. Informed consent for the data to be used for clinical research was obtained from all enrolled patients. The study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies of all the eight enrolled hospitals.

Clinicopathological and operative variables

Patient demographic characteristics included sex, age, and comorbid illnesses (consists of diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, and renal dysfunction history). The clinicopathological characteristics included etiologies of liver disease, portal hypertension, Child-Pugh grade, preoperative HBV-DNA level, alanine transaminase (ALT), aspartate aminotransferase (AST) and alpha-fetoprotein (AFP) levels within a week before surgery, tumor diameter of every nodule, tumor distribution, satellite nodules, microvascular invasion, and tumor differentiation. Portal hypertension was confirmed as the presence of either esophageal varices or splenomegaly along with a decline in platelet count ($\leq 100 \times 10^9$/L). Satellite nodules were defined as tumors less than 1 cm in diameter and located less than 1 cm from the main tumor. The operative variables consisted of intraoperative blood loss, intraoperative blood transfusion, extent and type of hepatectomy, and resection margin. Major hepatectomy involved three or more Couinaud liver segments, while minor hepatectomy was defined as resection of fewer than three segments. The definition of anatomical resection was based on the Brisbane 2000 Nomenclature of Liver Anatomy and Resections [20] and non-anatomical resection indicated wedge/limited resection.

Follow-up

Patients were followed at each participating institution. The postoperative surveillance strategy for HCC recurrence consisted of a physical examination, serum AFP, ultrasonography or contrast-enhanced computed tomography (CT) scan or magnetic resonance imaging (MRI) of the chest and abdomen at 2-month intervals for the first 6 months, at 3-month intervals thereafter for the next 18 months, and once every 6 months at 2 years or later after resection at each institution. Tumor recurrence was defined as new appearance of intra- or extra-hepatic tumor nodule(s), with or without a rise in serum AFP level and these intrahepatic nodules had the typical imaging features consistent with the characteristics of HCC on contrast-enhanced CT or MRI examinations. Treatment of HCC recurrence was based on the pattern of the recurrent tumor, residual hepatic functional reserve, and general condition of the patient.

Study endpoints

Study endpoints were: 1) postoperative 30-day mortality and morbidity and incidence of various complications; 2) overall survival (OS) and recurrence-free survival (RFS). Perioperative morbidities were classified into 5 grades based on the Clavien-Dindo classification system. Minor morbidities were defined as Clavien-Dindo < 3, while major morbidities were defined as Clavien-Dindo ≥ 3 [21] OS was defined as the time from surgery to death from any cause, while RFS was defined as the time from surgery to tumor recurrence, death, or new HCC occurrence.

Statistical analysis

Baseline patient characteristics and operative variables were summarized using frequencies and percentages for categorical variables and mean ± standard deviation (SD), or median (range) for continuous variables. Categorical variables were compared using the χ^2 test with the Yates correction or Fisher's exact test. Continuous variables were compared using the Student's *t*-test or Mann-Whitney ranked *U* test. The cutoff values of the continuous variables were based on either data in previous studies or the largest Youden index for prognostic prediction [22]. OS and RFS were estimated using Kaplan-Meier curves and compared with the log-rank test. Univariable and Multivariable Cox-regression analyses were performed to identify any independent risk factors which were associated with decreased OS and RFS in cirrhotic patients who underwent liver resection for multinodular HCC. Statistical analyses were performed using the SPSS software version 25.0 (SPSS, Chicago, IL, USA). *P* values were 2-sided and <0.05 were considered statistically significant.

Results

Patient characteristics

Of the 1066 cirrhotic patients undergoing curative-intent liver resection for HCC, 906 (85.0%) had single- or double-nodular HCC (the non-multinodular HCC group), while 160 (15.0%) had multinodular HCC (the multinodular HCC group). Baseline patient characteristics and operative variables among non-multinodular versus multinodular patients were notable for several differences (Table 1). For example, compared with non-multinodular HCC patients, the proportion of patients with preoperative AFP ≥400 μg/L, bilateral tumor distribution, satellite nodules, microvascular invasion, poor differentiation, intraoperative blood transfusion and major hepatectomy were higher among patients with multinodular HCC (all $P < 0.05$).

Comparisons of short-term and long-term outcomes

Short- and long-term outcomes after curative-intent resection of HCC among patients with cirrhotic patients were stratified according to the presence of non-multinodular and multinodular HCC (Table 2). Postoperative 30-day mortality and major morbidity were comparable among patients without and with multinodular disease (1.8% vs. 1.9% and 7.1% vs. 7.5%, $P = 0.923$ and 0.843, respectively); in addition, mean postoperative hospital stay was

Table 1
Comparisons of baseline characteristics and operative variables between the non-multinodular and multinodular groups.

N (%)	Total (n = 1066)	Non-multinodular group (n = 906)	Multinodular group (n = 160)	*P*
Age, years[a]	50.6 ± 10.4	50.9 ± 10.4	49.1 ± 10.3	0.137
Sex				
Male	954 (89.5)	807 (89.1)	147 (91.9)	0.287
Female	112 (10.5)	99 (10.9)	13 (8.1)	
Co-morbid illness	197 (18.5)	163 (18.0)	34 (21.3)	0.328
Etiology of liver disease				
HBV	855 (92.4)	711 (92.9)	144 (90.0)	0.515
HCV	16 (1.7)	12 (1.6)	4 (2.5)	
HBV + HCV	18 (1.9)	13 (1.7)	5 (3.1)	
Others	36 (3.9)	29 (3.8)	7 (4.4)	
Portal hypertension	442 (41.2)	380 (41.9)	62 (38.8)	0.450
Child-Pugh grade				
A	928 (87.1)	784 (86.5)	144 (90.0)	0.229
B	138 (12.9)	122 (13.5)	16 (10.0)	
Preoperative ALT, U/L[a]	45.0 (7.5–1371.7)	44.3 (8.3–1371.7)	47.9 (7.5–334.9)	0.471
Preoperative AST, U/L[a]	43.1 (13.3–528.0)	42.2 (13.3–414.3)	50.2 (15.0–528.0)	0.382
HBV-DNA level ≥ 10^4 copies/mL	460 (43.1)	399 (44.0)	61 (38.1)	0.164
Preoperative AFP, ug/L				
<400	642 (60.2)	575 (63.5)	67 (41.9)	<0.001
≥400	424 (39.8)	331 (36.5)	93 (58.1)	
Tumor diameter of the single or largest nodule, cm[a]	6.1 ± 4.2	5.7 ± 4.1	8.3 ± 4.1	0.056
Tumor distribution				
Unilateral	896 (84.1)	773 (85.3)	123 (76.9)	0.007
Bilateral	170 (15.9)	133 (14.7)	37 (23.1)	
Satellite nodules	308 (28.9)	157 (17.3)	51 (31.9)	<0.001
Microvascular invasion	627 (58.8)	497 (54.9)	130 (81.3)	<0.001
Poor differentiation	886 (83.1)	739 (81.6)	147 (91.9)	0.001
Intraoperative blood loss, ml[a]	350 (0–8000)	300 (0–8000)	550 (50–4000)	0.473
Intraoperative blood transfusion	267 (25.0)	202 (22.3)	65 (40.6)	<0.001
Extent of hepatectomy				
Major	304 (28.5)	208 (23.0)	96 (60.0)	<0.001
Minor	762 (71.5)	698 (77.0)	64 (40.0)	
Type of hepatectomy				
Anatomical	303 (28.4)	217 (27.9)	50 (31.2)	0.390
Non-anatomical	763 (71.6)	653 (72.1)	110 (68.8)	
Resection margin				
<1 cm	383 (35.9)	320 (35.3)	63 (39.4)	0.324
≥1 cm	683 (64.1)	586 (64.7)	97 (60.6)	

AFP, Alpha-fetoprotein; ALT, Alanine transaminase; AST, Aspartate transaminase; HBV, Hepatitis B virus; HCV, Hepatitis C virus.
[a] Values are mean ± standard deviation or median (range) unless otherwise indicated.

Table 2
Comparisons of short-term and long-term outcomes between the non-multinodular and multinodular groups.

N (%)	Total (n = 1066)	Non-multinodular group (n = 906)	Multinodular group (n = 160)	*P*
30-day Mortality	19 (1.8)	16 (1.8)	3 (1.9)	0.923
Overall 30-day morbidity	389 (36.5)	326 (36.0)	63 (39.4)	0.411
Major morbidity	76 (7.1)	64 (7.1)	12 (7.5)	0.843
Minor morbidity	313 (29.4)	262 (28.9)	51 (31.9)	0.449
Complication				
Hepatic dysfunction	78 (7.3)	66 (7.3)	12 (7.5)	0.923
Bile leak	36 (3.4)	30 (3.3)	6 (3.8)	0.777
Surgical site infection	85 (8.0)	72 (7.9)	13 (8.1)	0.939
Abdominal hemorrhage	19 (1.8)	17 (1.9)	2 (1.3)	0.581
Pneumonia	28 (2.6)	24 (2.6)	4 (2.5)	0.913
Pleural effusion	141 (13.2)	119 (13.1)	22 (13.8)	0.832
Ascites	118 (11.1)	97 (10.7)	21 (13.1)	0.371
Others[a]	40 (3.8)	34 (3.8)	6 (3.8)	0.999
Postoperative hospital stay, days[b]	12.5 ± 6.5	12.3 ± 6.3	13.7 ± 7.1	0.396
Patients during follow-up¶	**Total (n = 1047)**	**Non-multinodular group (n = 890)**	**Multinodular group (n = 157)**	***P***
Period of follow-up, months[b]	60.1 ± 44.2	64.8 ± 45.0	51.5 ± 42.5	0.019
Death during the follow-up	676 (64.6)	535 (60.1)	141 (89.8)	<0.001
Recurrence during the follow-up	801 (76.5)	652 (73.3)	143 (91.1)	<0.001
Patterns of Recurrence				
Intrahepatic	567 (54.2)	490 (55.1)	77 (49.0)	0.163
Extrahepatic	64 (6.1)	48 (5.4)	16 (10.2)	0.021
Intrahepatic & extrahepatic	170 (16.2)	114 (12.8)	50 (31.8)	<0.001
Overall survival, months[c]	68.8 ± 8.1	78.4 ± 9.1	29.6 ± 6.7	<0.001
1-year OS rate, %	87.2	90.2	70.1	<0.001
3-year OS rate, %	67.0	71.1	43.5	<0.001
5-year OS rate, %	54.7	58.2	34.6	<0.001
Recurrence-free survival, months[c]	38.2 ± 6.2	46.0 ± 5.3	11.1 ± 2.8	<0.001
1-year RFS rate, %	70.9	74.9	47.1	<0.001
3-year RFS rate, %	51.4	55.4	27.3	<0.001
5-year RFS rate, %	41.7	44.5	24.7	<0.001

Remove the cases of operative death (n = 19).
[a] Others include acute pancreatitis, acute cholangitis and cardiocerebrovascular accident.
[b] Values are mean ± standard deviation.
[c] Values are median ± standard error.

comparable (12.3 vs 13.7 days, $P = 0.396$). During a median follow-up of 60.1 months, 676 of 1047 patients (64.6%) died and 801 (76.5%) developed recurrent HCC. Mortality and recurrence among patients with non-multinodular and multinodular HCC groups were 60.1 and 73.3%, and 89.8 and 91.1%, respectively (both $P < 0.001$). Median OS and RFS among non-multinodular and multinodular HCC patients were 78.4 and 46.0 months and 29.6 and 11.1 months, respectively (both $P < 0.001$).

The 1-, 3- and 5-year OS among patients with non-multinodular and multinodular HCC was 90.2, 71.1 and 58.2%, and 70.1, 43.5 and 34.6% respectively (Fig. 1A and Table 2). Compared with patients who had non-multinodular HCC, patients with multinodular HCC had a decreased OS after curative-intent liver resection (hazard ratio (HR) 2.131, 95% confidence interval (CI) 1.738 to 2.612, $P < 0.001$). The 1-, 3- and 5-year RFS among patients with non-multinodular and multinodular HCC was 74.9, 55.4 and 44.5%, and 47.1, 27.3 and 24.7% respectively (Fig. 1B and Table 2). Compared with patients who had non-multinodular HCC, patients with multinodular HCC had a decreased RFS after curative-intent liver resection (HR 2.044, 95% CI 1.673 to 2.498, $P < 0.001$).

Prognostic analyses for OS and RFS in patients with multinodular HCC

Table 3 describes the prognostic risk factors associated with OS after curative liver resection of multinodular HCC in cirrhotic

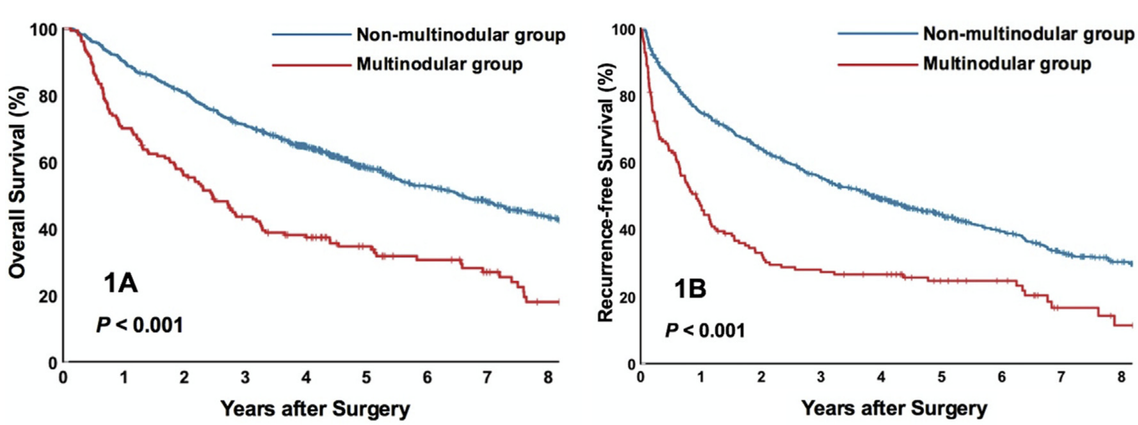

Fig. 1. Cumulative incidence of overall survival (1A) and recurrence-free survival (1B) curves comparisons between cirrhotic patients with non-multinodular and multinodular HCC.

Table 3
Univariablee and multivariable Cox-regression analyses of risk factors for overall survival after curative liver resection of multinodular hepatocellular carcinoma in cirrhotic patients.

Variables	HR comparison	UV HR (95% CI)	UV *P*	MV HR (95% CI)	MV *P*
Age	<60 vs. ≥ 60 years	1.031 (0.649–1.638)	0.898		
Sex	Male vs. Female	0.604 (0.331–1.101)	0.118		
Co-morbid illness	Yes vs. No	1.532 (0.747–3.144)	0.245		
Etiology of liver disease	HBV vs. non-HBV	1.694 (0.789–3.638)	0.177		
Portal hypertension	Yes vs. No	1.796 (1.261–3.580)	<0.001	1.435 (1.015–1.831)	0.040
Child-Pugh grade	A vs. B	1.715 (0.975–3.015)	0.061	NS	0.740
Preoperative AFP	<400 vs. ≥ 400 μg/L	2.375 (1.619–3.484)	<0.001	NS	0.182
Preoperative ALT	<40 vs. ≥ 40 U/L	1.041 (0.716–1.514)	0.833		
Preoperative AST	<40 vs. ≥ 40 U/L	1.450 (0.988–2.127)	0.057	NS	0.741
Preoperative HBV DNA level	$<10^4$ vs. $\geq 10^4$ copies/mL	1.403 (0.852–1.731)	0.121		
Satellite lesions of any tumor	Yes vs. No	2.050 (0.835–5.032)	0.117		
Total tumor diameter	<8.0 vs. ≥ 8.0 cm	1.305 (0.990–1.721)	0.058	1.653 (1.090–2.483)	0.010
Tumor diameter of the largest nodule	<5.0 vs. ≥ 5.0 cm	3.406 (2.091–5.546)	<0.001	NS	0.514
Tumor distribution	Unilateral vs bilateral	1.352 (0.893–1.720)	0.257		
Largest/smallest tumor diameter	<6.0 vs. ≥ 6.0	1.530 (0.918–1.833)	0.183		
Tumor number	<5 vs ≥ 5	1.920 (1.319–2.796)	0.001	1.935 (1.226–3.054)	<0.001
Microvascular invasion of any tumor	Yes vs. No	4.559 (2.528–8.223)	<0.001	1.686 (1.254–2.266)	0.002
Poor differentiation of any tumor	Yes vs. No	5.243 (1.917–14.339)	0.001	NS	0.124
Intraoperative blood loss	<400 vs. ≥ 400 ml	1.818 (1.228–2.692)	0.003	NS	0.287
Intraoperative blood transfusion	Yes vs. No	2.238 (1.554–3.223)	<0.001	1.554 (1.006–1.920)	0.033
Extent of hepatectomy	Major vs. Minor	2.182 (1.486–3.203)	<0.001	NS	0.185
Type of hepatectomy	Anatomical vs. Non-anatomical	0.836 (0.565–1.235)	0.368		
Resection margin	<1.0 vs. ≥ 1.0 cm	2.576 (1.774–3.741)	<0.001	NS	0.152

AFP, Alpha-fetoprotein; ALT, Alanine transaminase; AST, Aspartate transaminase; HBV, Hepatitis B virus; HR, Hazard ratio; CI, Confidence interval; UV, Univariable; MV, Multivariable; NS, Not significant.
*Variables with $P < 0.1$ in univariate analysis were subjected to multivariate Cox-regression model using forward stepwise variable selection.

patients that were identified on univariable and multivariable Cox-regression analyses. There were notable differences in cumulative OS among patients with total tumor diameter <8 cm versus ≥8 cm, tumor numbers <5 versus ≥5, as well as with versus without microvascular invasion among patients with nonmultinodular versus multinodular disease (all $P < 0.001$) (Fig. 2A, C and 2E). Multivariable analyses demonstrated that portal hypertension, total tumor diameter ≥8 cm, tumor number ≥5, microvascular invasion of any tumor and intraoperative blood transfusion were independent risk factors for decreased OS (all $P < 0.05$).

Table 4 depicts the risk factors associated with RFS after curative liver resection of multinodular HCC in cirrhotic patients that were identified on univariable and multivariable Cox-regression analyses. Similar to OS, RFS among patients with total tumor diameter <8 cm versus ≥8 cm, tumor number <5 versus ≥5, as well as with versus without microvascular invasion were different among patients with nonmultinodular versus multinodular disease (all $P < 0.01$) (Fig. 2B, D and 2F). Multivariable analyses demonstrated that total tumor diameter ≥8 cm, largest/smallest tumor diameter ≥6, tumor number ≥5 and microvascular invasion of any tumor were independent risk factors for decreased RFS (all $P < 0.05$).

Discussion

Recent advances in liver surgery and perioperative management have rapidly improved outcomes for patients with HCC, especially in Eastern Asia. However, the role of liver resection for multinodular HCC, especially in patients with cirrhosis is still controversial given concerns with perioperative risks and the uncertain long-term survival benefit [23–27] Data from the current study demonstrated that cirrhotic patients with multinodular HCC had comparable and acceptable 30-day mortality and morbidity compared with patients who had non-multinodular HCC. As such, perioperative safety can be achieved for cirrhotic patients with multinodular HCC. Although patients with multinodular HCC had less favorable OS and RFS than those with non-multinodular HCC, 5-year OS and RFS among patients with multinodular HCC still was 34.6% and 24.7%, respectively. These survival data were far preferable to data reporting non-curative therapies like TACE by the BCLC group's recommendation [28,29]. As such, curative-intent resection should at least be considered for patients with multinodular HCC, even those patients with well-compensated cirrhosis. In addition, the current study identified several independent risk factors associated with OS and RFS among cirrhotic patients following liver resection of multinodular HCC. These data, in turn, may be helpful in surgical decision-making, planning recurrence surveillance and assessing possible adjuvant therapy. To our knowledge, this is the first study to evaluate specifically the surgical safety and postoperative prognosis of cirrhotic patients with multinodular HCC using a large multicenter database. The results from this multicenter cooperative study may lead to a more widely accepted consensus on the role of liver resection in cirrhotic patients with multinodular HCC.

In the current study, total tumor number ≥5, total tumor diameter ≥8 cm, and microvascular invasion were demonstrated as independent risk factors for both OS and RFS after liver resection of multinodular HCC. More tumor nodules, larger tumor volume, and more severe tumor pathological characteristics have previously been demonstrated to be associated with OS and RFS after resection of HCC, whether multinodular or non-multinodular [22,29–33]. In this study, we identified 5 and 8 cm as the optimal cut-off values of total tumor number and total tumor diameter, respectively, which was based on the maximum Youden index, a way of summarizing the diagnostic performance. Additionally, portal hypertension and intraoperative blood transfusion were also identified as independent risk factors for OS. These two risk factors have similarly been associated with the long-term prognosis after resection of HCC. In particular, portal hypertension has been related to potential liver functional reserve [34], while intraoperative blood transfusion may induce immunosuppression and decrease natural-killer cell and/or helper T cell activities [28,35,36]. Therefore, these factors can result in negative oncologic outcomes after resection of multinodular HCC.

Studies on clonal origin suggest that liver resection is a better

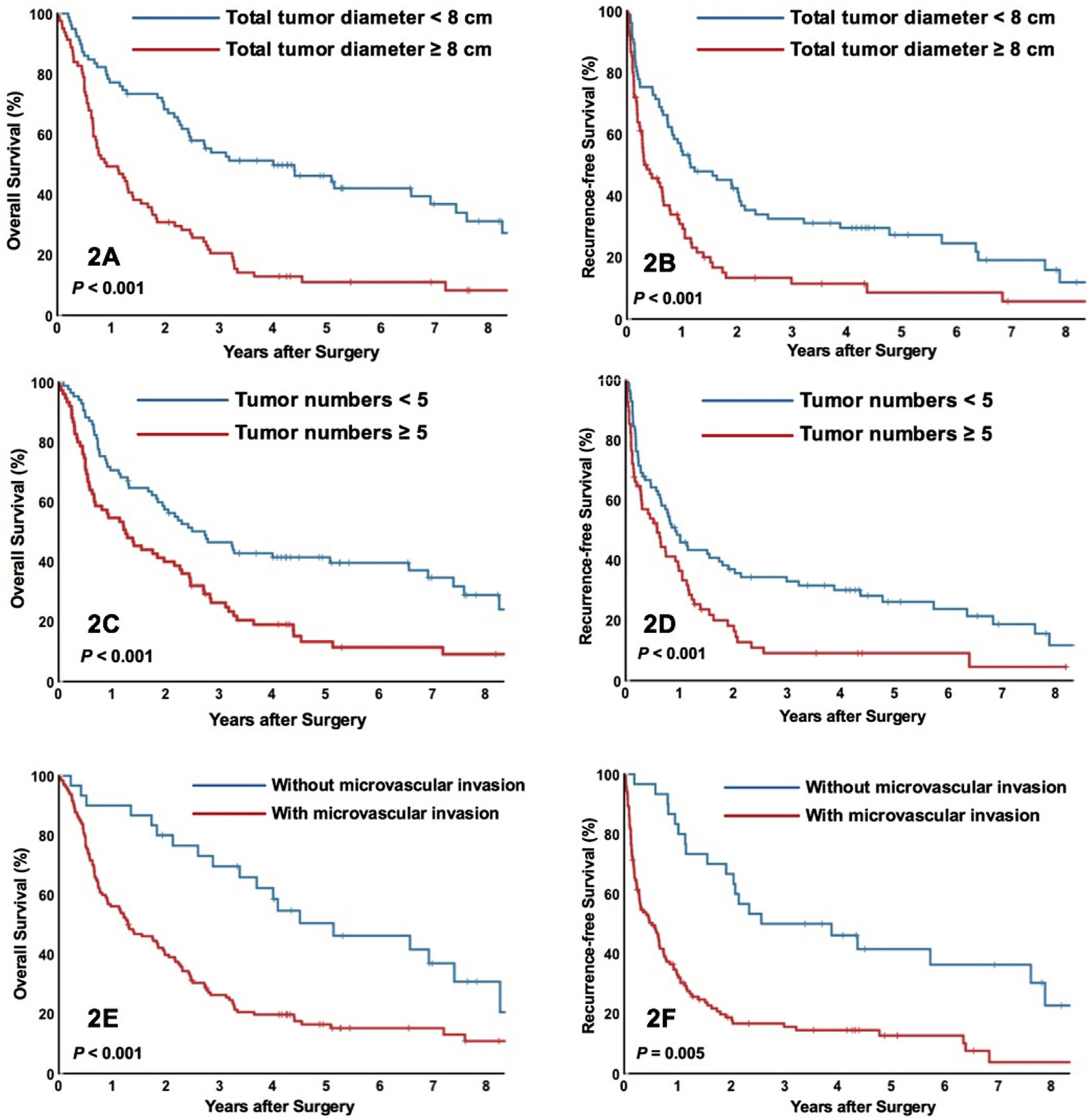

Fig. 2. Comparison curves of overall survival and recurrence-free survival after resection of multinodular HCC between patients with total tumor diameter <8 cm and ≥8 cm (2A and 2B), between patients with tumor number < 5 and ≥5 (2C and 2D), and between patients with and without microvascular invasion (2E and 2F), respectively.

treatment for multiple HCCs from multicentric origin than disease from intrahepatic metastasis [22,37,38]. In this study, the largest/smallest tumor diameter ≥6 was identified as an independent risk factor associated with RFS after curative-intent liver resection of multinodular HCC. A small ratio between the largest and smallest tumors may suggest a small difference in the tumor size among tumors within the liver, thereby suggesting an increased possibility of multicentric origin type of multinodular HCC. In contrast, a large ratio may imply a higher possibility of the origin being intrahepatic metastasis type [37,38]. Because liver resection is a better treatment for the multicentric origin type of multinodular HCC, the ratio between the largest and smallest tumors may have an important prognostic role in multinodular HCC. However, this observation requires further molecular-based validation [39].

The identification of these factors may provide some selection criteria for better stratification of patients with multinodular HCC for surgery or nonsurgical treatment. In addition, data from the current study may also help to select patients with a less favorable prognosis for adjuvant therapy after resection. For instance, patients with operative risk factors such as tumor number ≥5, total tumor diameter ≥8 cm or microvascular invasion may be listed as candidates for adjuvant therapy and rigorous surveillance after liver resection due to the high incidence of recurrence. We demonstrated the surgical safety and postoperative prognosis among cirrhotic patients with multinodular HCC, which can provide practical recommendations and surgical selections for the management of this subset of HCC patients.

The study had several limitations. Firstly, the study design was retrospective and therefore was subject to various inherent bias, which may have affected the reliability of some results. All patients were from China and the majority of patients with HCC had a background of HBV-related cirrhosis. As such, the potential impact of other etiologies of liver disease such as HCV, excessive alcohol and non-alcoholic fatty liver disease may be underestimated. Secondly, some favorable indicators of liver function or cirrhotic severity such as indocyanine green clearance and hepatic venous

Table 4
Univariable and multivariable Cox-regression analyses of risk factors for recurrence-free survival after curative liver resection of multinodular hepatocellular carcinoma in cirrhotic patients.

Variables	HR comparison	UV HR (95% CI)	UV *P*	MV HR (95% CI)	MV *P*
Age	<60 vs. ≥ 60 years	0.997 (0.628–1.583)	0.990		
Sex	Male vs. Female	0.674 (0.361–1.259)	0.216		
Co-morbid illness	Yes vs. No	1.199 (0.585–2.461)	0.620		
Etiology of liver disease	HBV vs. non-HBV	1.285 (0.735–2.478)	0.353		
Portal hypertension	Yes vs. No	1.371 (0.853–1.974)	0.241		
Child-Pugh grade	A vs. B	2.425 (1.351–4.351)	0.003	NS	0.322
Preoperative AFP	<400 μg/L vs. ≥ 400 μg/L	1.717 (1.185–2.487)	0.004	NS	0.163
Preoperative ALT	<40 U/L vs. ≥ 40 U/L	1.172 (0.799–1.717)	0.417		
Preoperative AST	<40 U/L vs. ≥ 40 U/L	1.261 (0.861–1.847)	0.233		
Preoperative HBV DNA level	$< 10^4$ vs. $\geq 10^4$ copies/mL	1.460 (0.903–1.831)	0.195		
Satellite lesions of any tumor	Yes vs. No	1.751 (0.768–3.991)	0.183		
Total tumor diameter	<8.0 vs. ≥ 8.0 cm	1.545 (1.014–1.980)	0.018	1.682 (1.015–2.370)	0.004
Tumor diameter of the largest nodule	<5.0 vs. ≥ 5.0 cm	2.061 (1.342–3.164)	0.001	NS	0.279
Tumor distribution	Unilateral vs bilateral	1.572 (0.883–2.074)	0.215		
Largest/smallest tumor diameter	<6.0 vs. ≥ 6.0	1.415 (1.010–1.785)	0.027	1.389 (1.027–1.743)	0.008
Tumor number	<5 vs ≥ 5	1.856 (1.274–2.704)	0.001	1.810 (1.146–2.861)	0.011
Microscopic vascular invasion of any tumor	Yes vs. No	3.279 (1.955–5.499)	<0.001	2.035 (1.120–3.697)	0.020
Poor differentiation of any tumor	Yes vs. No	1.936 (0.979–3.828)	0.057	NS	0.613
Intraoperative blood loss	<400 vs. ≥ 400 ml	1.314 (0.909–1.900)	0.147		
Intraoperative blood transfusion	Yes vs. No	1.832 (1.071–2.643)	0.043	NS	0.290
Extent of hepatectomy	Major vs. Minor	2.240 (1.516–3.310)	<0.001	NS	0.154
Type of hepatectomy	Anatomical vs. Non-anatomical	0.798 (0.537–1.184)	0.262		
Resection margin	<1 vs. ≥ 1 cm	2.002 (1.389–2.884)	<0.001	NS	0.255

*Variables with $P < 0.1$ in univariate analysis were subjected to multivariate Cox-regression model using forward stepwise variable selection.
AFP, Alpha-fetoprotein; ALT, Alanine transaminase; AST, Aspartate transaminase; HBV, Hepatitis B virus; HR, Hazard ratio; CI, Confidence interval; UV, Univariable; MV, Multivariate; NS, Not significant.

pressure gradient may also be associated with long-term prognosis after liver resection for HCC. However, due to the use of these indicators vary among enrolled centers, and the results of these two indicators were unavailable for most enrolled patients, so we did not put these variables in our analysis. In addition, external validation of the findings will be necessary in a cohort from Western countries. To confirm the role of the liver resection in cirrhotic patients with multinodular HCC, randomized controlled studies are required to compare the outcomes between surgical resection and other treatments, such like TACE.

Conclusion

Liver resection can be safely performed among well-compensated cirrhotic patients with multinodular HCC. Surgical resection was associated with an overall 5-year OS and RFS of 34.6% and 24.7%, respectively. Portal hypertension, tumor numbers ≥5, total tumor diameter ≥8 cm, microvascular invasion and intraoperative blood transfusion were independently associated with worse OS, while tumor number ≥5, total tumor diameter ≥8 cm, largest/smallest tumor diameter ≥6, and microvascular invasion were independent risk factors of worse RFS among cirrhotic patients after liver resection of multinodular HCC. The identification of these factors may provide selection criteria for better stratification of cirrhotic patients with multinodular HCC for resection or nonsurgical treatment. In addition, data from the current study may also help to select patients with a less favorable prognosis for adjuvant or alternative therapies.

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Author's contribution

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