

Historical Comparison of Overall Survival after Hepatic Resection for Patients With Large and/or Multinodular Hepatocellular Carcinoma

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Abstract: The present study compared the efficacy of hepatic resection (HR) in patients with large hepatocellular carcinoma (HCC) and those with multinodular tumor and examined how that efficacy has changed over time in a large medical center.

The intermediate stage of HCC comprises a highly heterogeneous patient population. Moreover, official guidelines have different views on the suitability of HR to treat such patients.

A consecutive sample of 927 patients with preserved liver function and large and/or multinodular HCC who were treated by initial HR were divided into 3 groups: those with a single tumor ≥ 5 cm in diameter ($n = 588$), 2 to 3 tumors with a maximum diameter > 3 cm ($n = 225$), or > 3 tumors of any diameter ($n = 114$). Hospital mortality and overall survival (OS) in each group were compared for the years 2000 to 2007 and 2008 to 2013.

Patients with > 3 tumors showed the highest incidence of hospital mortality of all groups ($P < 0.05$). Kaplan–Meier survival analysis showed that OS varied across the 3 groups as follows: single tumor > 2 to 3 tumors $> 3+$ tumors (all $P < 0.05$). OS at 5 years ranged from 24% to 41% in all 3 groups for the period 2000 to 2007, and from 35% to 46% for the period 2008 to 2013. OS was significantly higher during the more recent 6-year period in the entire patient population, those with single tumor, and those with $3+$ tumors (all $P < 0.05$). However, in patients with 2 to 3 tumors, OS was only slightly higher during the more recent 6-year period ($P = 0.084$).

Prognosis can vary substantially for these 3 types of HCC. Patients with > 3 tumors show the highest hospital mortality and lowest OS after

HR. OS has been improving for all 3 types of HCC at our medical center as a consequence of improvements in surgical technique and perioperative management.

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Abbreviations: $> 3T$ = more than 3 tumors of any diameter, $2-3T$ = 2–3 tumors with a maximum diameter > 3 cm, HCC = hepatocellular carcinoma, HR = hepatic resection, OS = overall survival, RFA = radiofrequency ablation, SL = single large tumor (≥ 5 cm), TACE = transarterial chemoembolization.

INTRODUCTION

Hepatocellular carcinoma (HCC) is often diagnosed at a late stage, when prognosis is poor. Approximately 75 to 80% of HCC patients are in the Asia-Pacific region,¹ where HCC incidence is driven by the spread of chronic infection with hepatitis B and C virus (HBV/HCV), which leads to liver cirrhosis. In China, the estimated incidence of new cases is 28.71/100,000 and the mortality rate is 26.04/100,000 each year.²

Hepatic resection (HR) offers the best survival benefit for patients in early stages of HCC.³ For patients with intermediate-stage HCC, however, debate continues about whether HR should be used and how extensive it should be in order to balance the benefits of oncological clearance (to reduce risk of postoperative recurrence) against the dangers of inadequate residual liver function (associated with hospital mortality and morbidity).^{4–5} For example, most patients with large multinodular HCC, defined as ≥ 2 tumors of any diameter or at least one lesion ≥ 5 cm in diameter, are treated with major hepatectomy, but this is associated with high hospital mortality.⁶ Therefore, drugs not just surgery might be recommended.^{7–8}

In the most recent reviews written by the authors of the Barcelona Clinic Liver Cancer (BCLC) staging system,^{9–10} patients with single tumors ≥ 5 cm in diameter are classified as having stage A disease and are considered suitable candidates for HR. In contrast, patients with 2 to 3 tumors with a maximum diameter > 3 cm and those with > 3 tumors regardless of size are still classified as having stage B disease. They are not considered suitable for HR but instead should be treated with transarterial chemoembolization (TACE).^{9–10} These BCLC recommendations contrast with those of other professional organizations^{11–12} and with the findings of several large retrospective studies^{13–15} and a 30-year systematic review,⁵ which conclude that tumor multifocality is not an absolute contraindication to HR.

This lack of alignment between treatment guidelines and clinical reality for patients with intermediate HCC means that

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medical centers around the world adopt a broader range of treatment approaches than in the case of patients with early or late disease.^{15–17} To help bring consensus on whether HR is safe and effective for patients with intermediate-stage HCC, we conducted a multicentric study to compare hospital mortality and overall survival (OS) in patients with a single tumor ≥ 5 cm in diameter, 2 to 3 tumors with a maximum diameter >3 cm, or >3 tumors regardless of size. Our goal was to analyze outcomes at a large medical center where HR is routinely applied to such patients and where the incidence of HCC is among the highest in the world.

MATERIAL AND METHODS

Study Population and Design

Retrospective analysis was carried out on medical records of patients diagnosed with HCC by histopathological examination of surgical samples from January 1, 2000, to October 31, 2013, in the Affiliated Tumor Hospital of Guangxi Medical University. Only patients with preserved liver function and large and/or multinodular HCC who underwent initial potential curative HR at our liver center were included in the analysis. Tumor size and number were determined by preoperative imaging and confirmed by postoperative histology.^{17–18} Microvascular invasion was defined as the appearance of tumor thrombus with a microscope. Preoperative tumor rupture, macrovascular invasion, tumor metastasis to the lymph nodes and/or distant metastases were classified as advanced-stage HCC and were excluded.^{18–20} Patients who underwent palliative resection were also excluded. These excluded patients may receive HR plus TACE, TACE monotherapy, sorafenib, or best supportive care. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of Affiliated Tumor Hospital of Guangxi Medical University.

Treatment and Follow-Up

All patients with adequate liver function and radiologically resectable tumor were evaluated initially for HR. Inclusion criteria for deciding whether to use HR to treat large and/or multinodular HCC, as well as the hepatectomy techniques involved, have been described.^{18–20} Adequate remnant liver volume was 30% for HCC patients without cirrhosis, and $>50\%$ for HCC patients with chronic hepatitis, cirrhosis, or severe fatty liver. Patients who satisfied the indications for HR underwent that procedure unless the patient requested another treatment modality. Anatomic HR was the preferred HR procedure, whereas some patients with multiple tumors underwent HR combined with intraoperative radiofrequency ablation (RFA).

Follow-up for all patients began immediately after HR. Patients were followed up with regular clinical examination, blood tests, and computed tomography scanning and/or magnetic resonance imaging. All patients were followed up until death or March 2015.

Recurrence was defined as the appearance of a new lesion with radiological features characteristic of HCC during follow-up. In patients who showed recurrence, HR was repeated if judged feasible on the basis of liver function and remnant liver volume, which were evaluated according to the same criteria as those used at the time of initial HR. If HR could not be performed because of poor liver function or inadequate remnant liver volume, then RFA, TACE, or other palliative therapies were applied.

Outcomes

Outcomes of interest were 30- and 90-day hospital mortality and morbidity, as well as OS. OS was calculated for different time periods, starting from the date of the first diagnosis of HCC to death, last follow-up or March 2015, whichever occurred earliest. These outcomes were compared in 3 patient groups: those with a single tumor ≥ 5 cm in diameter, 2 to 3 tumors with a maximum diameter >3 cm, and those with >3 tumors regardless of size. Outcomes were also compared across 3 patient groups for 2 time periods: January 1, 2000, to December 31, 2007, and January 1, 2008, to October 31, 2013.

Statistical Analysis

All demographic and clinicopathological data for patients were prospectively collected after admission in central database of our hospital. For the purposes of the present retrospective analysis, missing demographic and clinicopathological data were filled in using multiple imputation involving stochastic switching regression and 5 repeated imputations.²¹

Data for continuous variables were expressed as median (range), whereas data for categorical variables were expressed as number (percentage). Intergroup differences in continuous variables were assessed for significance using the Mann–Whitney *U*-test, whereas intergroup differences in categorical data were assessed using the chi-squared or Fisher’s exact tests (2-tailed) where appropriate. Ranked data was compared with Kruskal–Wallis *H* test. Multivariate analysis to identify independent prognostic factors was carried out using the Cox proportional hazards model. Survival curves were estimated

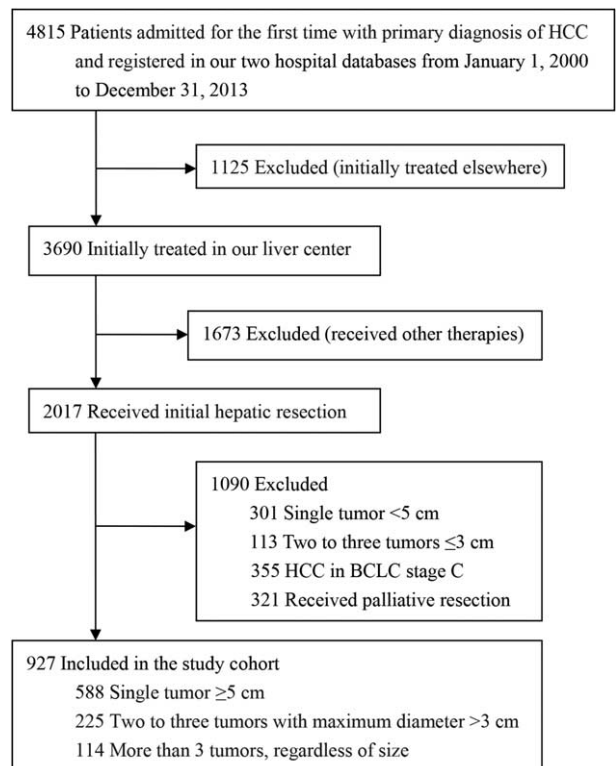


FIGURE 1. Selection of study patients. BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma.

using the Kaplan–Meier method and compared using the log-rank test.

All tests were performed using SPSS 19.0 (IBM) and a 2-tailed *P* value < 0.05 as the threshold of significance. The statistical data were managed by a biostatistician.

RESULTS

Patient Characteristics

We identified 4815 potentially eligible HCC patients admitted for the first time to our hospital and registered in our database between January 1, 2000, and October 31, 2013. We excluded 1125 patients who had initially been treated at other hospitals, and we excluded another 1673 patients who had received other therapies. Lastly, we excluded patients with single tumors < 5 cm in diameter (n = 301), 2 to 3 tumors ≤ 3 cm (n = 113), HCC in BCLC stage C (n = 355), or those received palliative resection (321). In the end, 927 patients were enrolled in the study (Figure 1).

Patient demographic and clinicopathological data at baseline are presented in Table 1. Patients with 2 to 3 tumors with a maximum diameter > 3 cm had a higher level of total bilirubin than the other 2 groups (*P* = 0.042), whereas patients with > 3 tumors had a higher level of alanine aminotransferase (ALT; *P* < 0.001). Patients with > 3 tumors showed significantly higher incidence of Child-Pugh A liver function, incomplete or no tumor capsule, microvascular invasion, and history of major hepatectomy (all *P* < 0.05). In addition, the HR procedure took significantly longer in these patients than in the other 2 groups (*P* < 0.001).

Mortality and Morbidity

Mortality at 30 days was significantly higher in patients with > 3 tumors (3.5%) than in those with a single tumor (0.5%) or those with 2 to 3 tumors (0.9%; *P* = 0.023). Similarly, mortality at 90 days was significantly higher in patients with > 3 tumors (6.1%) than in those with a single tumor (1.7%) or with 2 to 3 tumors (4.4%; *P* = 0.010; Table 1).

TABLE 1. Comparison of Demographic and Clinicopathological Data and Outcomes of Chinese Patients with Large and/or Multinodular HCC after Hepatic Resection

Parameter	SL Group (n = 588)	2–3T Group (n = 225)	>3T Group (n = 114)	<i>P</i>
Age in year, median (range) [§]	48 (19–78)	48 (17–75)	47 (17–73)	0.061
Male, n (%) [†]	535 (91)	209 (93)	105 (92)	0.667
Positive for hepatitis B surface antigen, n (%) [†]	541 (92)	200 (89)	103 (90)	0.365
Median platelet count, × 10 ³ /μL (range) [§]	150 (22–542)	170 (54–390)	172 (39–376)	0.472
Median prothrombin time, s (range) [§]	12.5 (9.4–22.4)	12.8 (8.5–19.7)	12.9 (10.1–16.8)	0.748
Median albumin level, g/L (range) [§]	41 (24–55)	41 (28–65)	41 (32–51)	0.173
Median alanine aminotransferase, U/L (range) [§]	37 (1–410)	39 (7–504)	42 (7–151)	<0.001
Median total bilirubin, μmol/L (range) [§]	13 (3–100)	13 (3–64)	13 (3–34)	0.042
α-fetoprotein, n (%) [†]				
≥400 ng/mL	276 (47)	101 (45)	55 (48)	0.812
<400 ng/mL	312 (53)	124 (55)	59 (52)	
Child–Pugh class, n (%) ^{*†}				
A	488 (83)	194 (86)	104 (91)	0.010
B	100 (17)	31 (14)	10 (9)	
Cirrhosis, n (%) [†]				
Present	459 (78)	182 (81)	96 (84)	0.064
Absent	129 (22)	43 (19)	18 (16)	
Esophagogastric varices, n (%) ^{*†}	112 (19)	50 (22)	27 (24)	0.391
Diabetes mellitus, n (%) [†]	106 (18)	45 (20)	19 (17)	0.717
Tumor capsule, n (%) ^{*†}				
Complete	365 (62)	25 (11)	9 (8)	<0.001
Incomplete/absent	223 (38)	200 (89)	105 (92)	
Microvascular invasion, n (%) ^{*†}				
Present	218 (37)	97 (43)	58 (51)	0.014
Absent	370 (63)	128 (57)	56 (49)	
Major hepatectomy, n (%) ^{*†}	365 (62)	167 (74)	95 (83)	<0.001
Surgical time, min (range) [§]	162 (71–495)	247 (84–581)	264 (83–532)	<0.001
30-day mortality, n (%) [‡]	3 (0.5)	2 (0.9)	4 (3.5)	0.023
90-day mortality, n (%) [‡]	10 (1.7)	10 (4.4)	7 (6.1)	0.010
Postoperative complications, n (%) ^{*†}	166 (28.2)	71 (31.6)	44 (38.6)	0.079
Survival time in mos., median (range) [§]	48.7	40.5	27.8	<0.001

SL = single large tumor (≥ 5 cm), >3T = > 3 tumors of any diameter, 2–3T = 2–3 tumors with a maximum diameter > 3 cm.

* Patient data for this parameter were missing and were imputed as described in Methods.

† chi-squared tests (2-tailed).

‡ Fisher's exact tests (2-tailed).

§ Mann–Whitney *U*-test.

TABLE 2. Historical Comparison of Hospital Mortality Among all Patients and Specific Groups of Patients with Large and/or Multinodular HCC after Hepatic Resection

Group	30-day Mortality (%)			90-day Mortality (%)		
	2000–2007	2008–2013	P	2000–2007	2008–2013	P
Total population (327 vs 600)	1.83	0.5	0.103*	3.06	2.83	0.846*
Single tumor ≥5 cm (207 vs 381)	0.97	0.26	0.591*	1.45	1.84	0.989*
2–3 tumors with maximum diameter >3 cm (79 vs 146)	2.53	0	0.122†	6.33	3.42	0.503*
>3 tumors, regardless of size (41 vs 73)	4.88	2.74	0.948*	4.88	6.85	0.989*

* Chi-squared tests (2-tailed).

† Fisher’s exact tests (2-tailed).

Hospital mortality was compared within each group between the periods 2000 to 2007 and 2008 to 2013. Mortality at neither 30 nor 90 days changed significantly between the 2 time periods both in total population and all the 3 subgroup patients (all $P > 0.05$) (Table 2).

Analysis of postoperative complications based on the Clavien–Dindo classification²² showed a slightly higher incidence among patients with >3 tumors (38.6%) than among those with a single tumor (28.2%) or 2 to 3 tumors (31.6%; $P = 0.079$; Table 1). Most postoperative complications were grade I or II in all 3 groups, with the most frequent complication being liver failure.

Survival Analysis

Among the total study population of 927 patients, OS was 88% at 1 year, 58% at 3 years, and 41% at 5 years. Median survival time was 44.7 months among all patients, 48.7 months among those with a single tumor, 40.5 months among those with 2 to 3 tumors, and 27.8 months among those with >3 tumors. The single-tumor group showed significantly higher OS than the group with 2 to 3 tumors or with >3 tumors; this was true for OS at 1 year (92% vs 86% vs 74%), 3 years (63% vs 53% vs 44%), and 5 years (45% vs 34% vs 31%) ($P < 0.001$; Figure 2).

Among the total study population, OS was significantly better during the period 2008 to 2013 than during the period 2000 to 2007. This was true for OS at 1 year (90% vs 85%), 3 years (64% vs 48%), and 5 years (43% vs 36%) ($P < 0.001$; Figure 3A). Similar results were obtained when the same historical comparison was made for the single-tumor group ($P = 0.017$; Figure 3B) or with >3 tumors group ($P = 0.041$; Figure 3C). However, for the group with 2 to 3 tumors, OS during the recent period was only slightly higher than that during the previous period ($P = 0.084$; Figure 3D).

Tumor Recurrence and Treatment

During follow-up out to March 2015, 614 patients (66.2%) experienced HCC recurrence, of which 539 (87.8%) experienced intrahepatic recurrence. The rate of recurrence was significantly higher in patients with >3 tumors than in the other two groups, whereas it was significantly lower in patients with a single tumor than in the other 2 groups ($P < 0.001$). The rate of intrahepatic recurrence was significantly higher in patients with >3 tumors than in the other 2 groups ($P < 0.001$).

Treatment modality for recurrent HCC included second resection, TACE, RFA, sorafenib, radiotherapy, and systemic chemotherapy (Table 3). TACE was the most frequently used treatment modality; most patients received 2 or more treatment

modalities, such as RFA and TACE, or TACE and sorafenib. Patients treated by HR after 2008 whose serum contained ≥ 2000 IU/mL HBV DNA also received postoperative nucleos(t)ide analog therapy.²³

Predictors of Survival

Multivariate analysis identified 12 factors significantly associated with poor OS (all $P < 0.05$; Table 4): age >60 years, tumor size ≥ 10 cm, tumor number ≥ 3 , preoperative serum albumin < 35 g/L, ALT > 80 U/L, total bilirubin > 1.2 μ mol/L, α -fetoprotein ≥ 400 ng/mL, incomplete tumor capsule, presence of microvascular invasion or esophagogastric varices, major hepatectomy, and diabetes mellitus.

DISCUSSION

A substantial proportion of patients with HCC present with large and/or multinodular tumors at diagnosis because they do

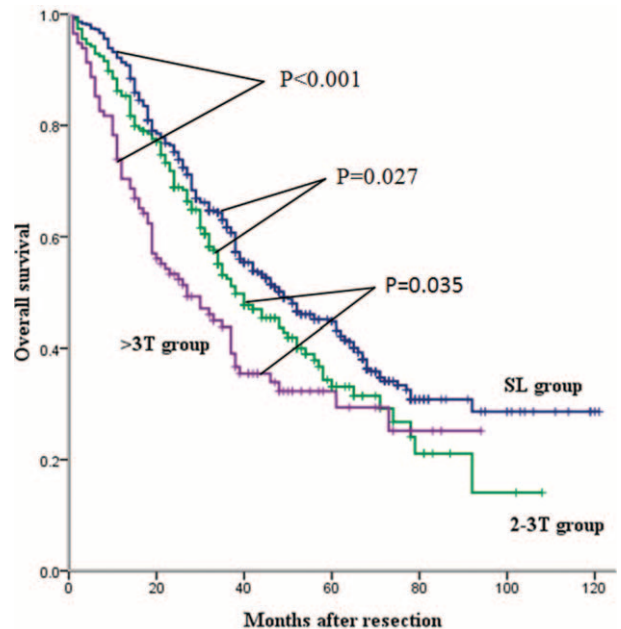


FIGURE 2. Estimated Kaplan–Meier survival curves for patients with large and/or multinodular HCC following hepatic resection. SL, single large tumor (≥ 5 cm); 2–3T, 2–3 tumors with a maximum diameter >3 cm; >3T, >3 tumors of any diameter.

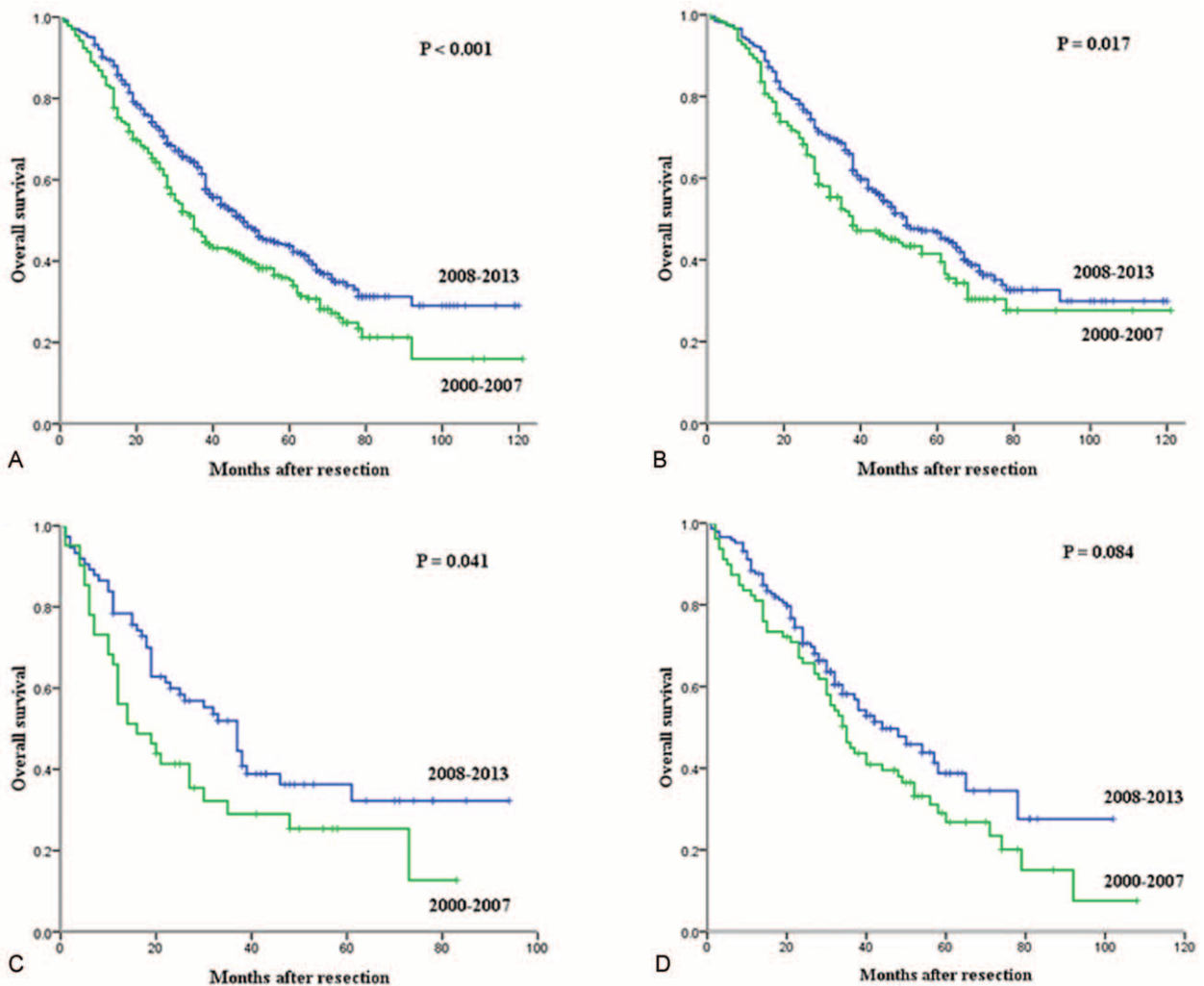


FIGURE 3. Estimated Kaplan–Meier survival curves for patients with large and/or multinodular HCC treated by hepatic resection during the period 2000 to 2007 or 2008 to 2013. A, all study participants (n = 927). B, patients with a single large tumor (n = 588). C, patients with 2 to 3 tumors with a maximum diameter >3 cm (n = 225). D, patients with >3 tumors, regardless of size (n = 114).

not exhibit significant symptoms earlier, and indeed this proportion was >40% in the present cohort (Figure 1). Based on various international treatment guidelines, few of these patients are eligible for percutaneous ethanol injection, RFA, or liver transplantation because of the strict indications for these procedures.^{6,9} TACE does not usually achieve complete tumor necrosis and is often less effective than HR.^{13,16,18} Several large studies and some treatment guidelines argue for expanding the indications of HR to patients with large and/or multinodular tumors, but this remains controversial. Therefore we undertook the present study to gain clear evidence on this question, and our findings suggest that HR can offer such patients good OS and that this OS has significantly improved over the last decade.

Improvements in the surgical technique and perioperative management have rapidly reduced the rate of mortality after HR in patients with HCC, with zero perioperative mortality reported in some larger liver centers.^{24,25} In the present cohort, however, mortality at 30 or 90 days did not differ significantly between the period 2000 to 2007 and 2008 to 2013 when we analyzed the data across total population and all 3 patient groups. It seems

likely that these results at least partly reflect the fact that starting around 2008, the number of patients with HCC undergoing HR at our medical center increased substantially because of expanded indications. These results suggest that although HR can lead to acceptable OS in patients with large and/or multinodular tumors, it still appears to be associated with appreciable mortality, which has not fallen significantly over the last 10 years. In contrast, 5-year OS and disease-free survival were found to have improved over the past 30 years in our recent systematic review involving 14,808 patients with large and/or multinodular HCC.⁵ It remains to be seen whether future improvements in HCC detection and management can reduce mortality; it may also be that these types of HCC carry intrinsically higher risk of mortality.

OS, like mortality, after HR can also vary with surgical experience, willingness to undertake more aggressive therapy and postoperative management practices. Such factors likely help explain why the large systematic review identified a range of 5-year OS from 17% to 66% among Asian patients with large and/or multinodular HCC after HR, and a range from 0% to 56%

TABLE 3. Characteristics of Patients Experiencing HCC Recurrence after Hepatic Resection, and Initial Treatment Modalities Applied

Variable	SL Group (n = 588)	2–3T Group (n = 225)	>3T Group (n = 114)	P
Any recurrence, n (%)	359 (61)	160 (71)	95 (83)	<0.001*
Extrahepatic recurrence, n (%) [†]	97 (27)	18 (11)	8 (8)	<0.001*
Intrahepatic recurrence, n (%)	262 (73)	142 (89)	87 (92)	
Initial treatment after recurrence, n (%)				
Second resection	47 (13)	16 (10)	4 (4)	0.084 [‡]
TACE	212 (59)	102 (64)	67 (70)	
RFA	86 (24)	34 (21)	22 (23)	
Other	14 (4)	8 (5)	3 (3)	

>3T = >3 tumors of any diameter; 2–3T = 2–3 tumors with a maximum diameter >3 cm, RFA = radiofrequency ablation, SL = single large tumor (>5 cm), TACE = transarterial chemoembolization.

* Chi-squared tests (2-tailed).

[†] Including 48 patients with both intrahepatic and extrahepatic recurrence.

[‡] Kruskal–Wallis H test.

among non-Asian patients.⁵ Many Asian medical centers, located in areas with higher HCC incidence, are likely to take a more aggressive approach than Western medical centers in using HR to treat patients in intermediate stages of HCC.

Relatively high recurrence rate is one of the hallmarks of HCC, and aggressive treatment of recurrence using repeat HR, RFA, or TACE can offer satisfactory OS.^{26,27} The recurrence rate in our cohort was significantly higher among patients with >3 tumors (83%) than among patients with 2 to 3 tumors or with a single large tumor. Patients with >3 tumors are also less likely to be eligible for a second resection, which helps explain why they showed the lowest OS in our study. However, those patients with >3 tumors in our cohort benefited from the treatment: OS was 74% at 1 year, 44% at 3 years, and 31% at 5 years, which are higher rates than those reported for patients with similar clinicopathological characteristics who underwent initial TACE.^{13,18,19,28} Therefore, the benefits of HR for these HCC patients may outweigh the risks of hospital mortality and the high rates of tumor recurrence.

At the same time, our data suggest that although HR may offer better OS than TACE for patients with >3 tumors, the

corresponding OS in patients with a single large tumor or in those with 2 to 3 tumors is significantly higher. This highlights the need for careful patient selection for HR. Such selection, particularly in high volume, specialized or tertiary referral centers, should be conducted by multidisciplinary teams. One key factor in patient selection is evaluation of the functional reserve of remnant liver parenchyma, which we performed volumetrically in the present study as per standard procedure at our medical center. Other liver centers have also reported using indocyanine green retention time and/or invasive portal vein pressure.^{14,17}

Based on our clinical experience with the present cohort and more generally, we believe that the ideal candidate for HR is a patient who has well-preserved preoperative liver function and a localized tumor, and who will lose a minimal volume of normal liver parenchyma during the resection procedure. In the present study, we defined resectable disease as a case when all gross tumors could be completely removed while retaining sufficient remnant liver to sustain life. We did not consider tumor size or number per se to be absolute contraindications of HR, consistent with evidence suggesting that HR remains

TABLE 4. Multivariate Analysis of Predictors of Poor Overall Survival in 927 Chinese Patients with Large and/or Multinodular HCC

Variable	Hazard ratio (95% CI)	P
Age > 60 yr	1.183 (1.081–1.467)	0.015
Tumor size ≥ 10 cm	1.134 (1.017–1.231)	0.036
Tumor number ≥ 3	2.416 (1.582–3.693)	<0.001
Albumin <35 g/L	1.617 (1.152–2.491)	0.004
Alanine aminotransferase >80 U/L	1.117 (1.021–1.325)	0.026
Total bilirubin > 1.2 μmol/L	1.263 (1.008–1.542)	0.047
α-Fetoprotein ≥ 400 ng/mL	1.487 (1.266–1.875)	<0.001
Incomplete tumor capsule	1.554 (1.083–2.318)	0.013
Microvascular invasion	1.713 (1.207–3.236)	0.001
Major hepatectomy	2.104 (1.417–3.712)	<0.001
Esophagogastric varices	1.418 (1.127–2.693)	0.009
Diabetes mellitus	1.438 (1.051–2.137)	0.020

CI = confidence interval, HCC = hepatocellular carcinoma.

associated with the best long-term survival.^{4,5,29} Even patients with bilobar HCC may benefit from a combination of HR to remove the predominant tumor and RFA to treat contralateral nodules.^{30,31} Some patients with >3 tumors in our cohort had Child-Pugh A liver function and underwent HR followed by RFA.

Predictors of survival in the present cohort were similar to those identified in other studies involving patients with large and/or multinodular HCC.^{13,14,18,28} These predictors are related to underlying liver disease (albumin, ALT, total bilirubin, α -fetoprotein, esophagogastric varices, diabetes mellitus) and to the tumor(s) (tumor size and number, tumor capsule, microvascular invasion, history of major hepatectomy). Patients in our cohort with >3 tumors showed significantly higher incidence of elevated ALT, and greater incidences of tumor capsule, microvascular invasion, and major hepatectomy than did patients in the other 2 groups (Table 1). This may help explain why the resection procedure took significantly longer in the patients with >3 tumors than in the other 2 groups, which in turn may have contributed to the higher rates of hospital mortality.

Although the present study helps strengthen the case for using HR to treat patients with large and/or multinodular HCC, it does have some substantial limitations. Even though all demographic, clinicopathological, and outcomes data were prospectively entered into our hospital databases, some data (<5%) were missing and had to be imputed. In addition, the observed survival differences among the three groups in our cohort may reflect differences in intraoperative variables that we did not control for, such as blood transfusions, albumin supplements, or surgical margins.

Despite these limitations, the present study strengthens the case for considering HR as a standard therapy for patients with large and/or multinodular HCC who have preserved liver function and sufficient remnant liver to sustain life. Careful patient selection is key, especially in the case of patients with >3 tumors, for whom HR is associated with high risk of hospital mortality.

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