Hepatic Resection Associated With Good Survival for Selected Patients With Intermediate and Advanced-Stage Hepatocellular Carcinoma

Jian-hong Zhong, MD, Yang Ke, MD,* Wen-feng Gong, MD,* Bang-de Xiang, MD, PhD,* Liang Ma, MD,* Xin-ping Ye, MD, PhD,† Tao Peng, MD, PhD,† Gui-sheng Xie, MD,‡ and Le-qun Li, MD, PhD**

Objective: The efficacy and safety of hepatic resection (HR) to treat patients with Barcelona Clinic Liver Cancer (BCLC) stage B and C hepatocellular carcinoma (HCC) was retrospectively assessed.

Background: Although guidelines from the European Association for the Study of Liver Disease and the American Association for the Study of Liver Disease do not recommend HR for treating BCLC stage B/C HCC, several Asian and European studies have come to the opposite conclusions.

Methods: A consecutive sample of 1259 patients with BCLC stage B/C HCC who underwent HR ($n = 908$) or transarterial chemoembolization (TACE, $n = 351$) were included. Moreover, propensity score-matched patients were analyzed to adjust for any baseline differences. In parallel with this retrospective clinical study, the MEDLINE database was searched for studies evaluating the efficacy and safety of HR for BCLC stage B/C HCC.

Results: Among our patient sample, the 90-day mortality rate in the HR group was 3.1%. HR provided a survival benefit over TACE at 1, 3, and 5 years (88% vs 81%, 62% vs 33%, and 39% vs 16%, respectively; all $P < 0.001$). Propensity scoring and subgroup analyses based on tumor size, tumor number, presence or absence of macrovascular invasion, and portal hypertension (PHT) also showed that HR was associated with better long-term survival than TACE. All 36 studies identified in our literature search reported that HR is associated with good long-term survival and low morbidity. Multivariate analyses revealed that alpha-fetoprotein more than or equal to 400 ng/mL, diabetes mellitus, macrovascular invasion, and PHT are independent predictors of poor prognosis in patients with BCLC stage B/C HCC.

Conclusions: Our clinical and literature analyses suggest that in patients with HCC with preserved liver function, the presence of large, solitary tumors, multinodular tumors, macrovascular invasion, or PHT are not contraindications for HR.

Keywords: hepatic resection, hepatocellular carcinoma, overall survival, transarterial chemoembolization

(*Ann Surg* 2013;00:1–12)

Hepatocellular carcinoma (HCC) is associated with poor prognosis, and its incidence is increasing in many countries.[1] As a result of remarkable advances in diagnostic methods, surgical techniques, and perioperative care, hepatic resection (HR) remains a popular curative treatment for patients who have HCC satisfying the Milan criteria (up to 3 lesions <3 cm, <5 cm for any single lesion, no extrahepatic manifestations, no vascular invasion)[2] and who have well-preserved liver function. In such patients, the 5-year survival rate after HR exceeds 50%.[3–6]

Treatment outcomes for HCC patients are affected by multiple variables, including tumor burden, the Child-Pugh score of liver function reserve, and the performance status of the patient.[7] The Barcelona Clinic Liver Cancer (BCLC) classification staging system takes into account these 3 variables.[8] It links staging with treatment indications and prognostic information, such as estimated life expectancy. Studies have validated and proposed the clinical usefulness of this staging system, making it one of the most reliable for HCC.[9,10]

The BCLC staging system recommends different treatment options for each stage of the disease. According to this staging system,[8] transarterial chemoembolization (TACE) should be considered in patients with intermediate (BCLC-B) HCC and in certain patients with advanced (BCLC-C) HCC. Curative HR, in contrast, is indicated only in some patients with early-stage HCC and satisfactory liver function. The efficacy and safety of HR for treating BCLC stage B/C HCC are therefore poorly understood. Some studies[11–13] have reported that major HR for large or multinodular HCC may increase the risk of intraoperative blood loss and postoperative liver failure, leading them to advise against HR as a first-line treatment for HCC outside the Milan criteria.[11–13] Nevertheless, many hepatobiliary institutions, including our own,[14] advocate HR to treat HCC outside the Milan criteria. Given these conflicting recommendations, the efficacy and safety of HR for treating these HCC patients needs to be clarified.

In this multicenter retrospective study, we assessed the therapeutic value of HR and compared it with TACE for treating BCLC stage B/C HCC patients in the Guangxi province of China, where the population shows the highest HCC incidence rates in the world.[15,16] To complement this clinical study, we comprehensively searched MEDLINE for studies evaluating the efficacy of HR for BCLC stage B/C HCC.

PATIENTS AND METHODS

This study was approved by the institutional review board of Guangxi Medical University, and it was conducted in accordance with the Declaration of Helsinki and current ethical guidelines.

Patients

Retrospective analysis was carried out on medical records of patients diagnosed with HCC who had been included, between January 2000 and December 2007, in prospective databases at the Tumor Hospital, First Affiliated Hospital, and Third Affiliated Hospital of Guangxi Medical University, Nanning, China. During the study period, 4535 consecutive HCC patients from Guangxi province of China were enrolled in the databases. Only Child-Pugh A patients with BCLC stage B/C HCC were included in the retrospective analysis. Similar inclusion criteria were used when deciding whether to use HR to treat BCLC stage B/C HCC.[14] Patients with metastasis to

From the *Hepatobiliary Surgery Department, Tumor Hospital of Guangxi Medical University; †Hepatobiliary Surgery Department, The First Affiliated Hospital of Guangxi Medical University; and ‡General Surgery Department, The Third Affiliated Hospital of Guangxi Medical University, Nanning 530021, PR China.

Disclosure: Specific funding was not used to perform this study. All authors declare no conflicts of interests.

Reprints: Jian-hong Zhong, MD, and Le-qun Li, MD, PhD, Hepatobiliary Surgery Department, Tumor Hospital of Guangxi Medical University, He Di Rd No. 71, Nanning 530021, PR China. E-mail: zhongjianhong66@163.com (J.H.Z.); xitongpingjia@163.com (L.Q.L.).

ISSN: 0003-4932/13/00000-0001
DOI: 10.1097/SLA.0000000000000236

the lymph nodes and/or distant metastases were excluded on the basis of preoperative imaging results and perioperative findings.

In the HR group, HCC diagnosis was confirmed by histopathological examination of surgical samples. In the TACE group, in contrast, HCC diagnosis was confirmed by needle biopsy or by 2 types of clinical imaging (ultrasonography, computed tomography, or magnetic resonance imaging), together with a serum level of α-fetoprotein (AFP) higher than 400 ng/mL. If diagnosis based on imaging and AFP level was uncertain, needle biopsy was performed. Tumor status was assessed by ultrasonography, computed tomographic scanning, magnetic resonance imaging, and/or hepatic angiography. Vascular invasion was defined by the presence of thrombus adjacent to the tumor in the portal and hepatic vein with vague boundaries confirmed using at least 2 imaging modalities.[17] Since our centers adopted ICG-15 in 2010, ICG-15 was not applied to the patients in this study.

Definitions

In this study, clinically relevant portal hypertension (PHT) was defined as the presence of esophageal varices and/or a platelet count of less than 100 000 per μL in association with splenomegaly. BCLC stage B and stage C HCC were defined as follows.[8,18]

BCLC Stage B

One lesion more than 5 cm in diameter; or 2 to 3 lesions, of which at least 1 is more than 3 cm in diameter; or more than 3 lesions of any diameter.

BCLC Stage C

Any tumor with radiologically evident and/or histologically proven macrovascular invasion (segmental branches, right/left and main portal vein, hepatic vein, superior mesenteric vein, inferior vena cava).

Recurrence during follow-up was defined as the appearance of a new lesion with radiologic features characteristic of HCC.

Treatment and Follow-up

Indications for HR were the presence of appropriate residual liver volume determined by volumetric computed tomography and lack of hepatic encephalopathy. For HCC patients without cirrhosis, 30% remnant liver volume after HR was considered adequate, whereas for those with chronic hepatitis, cirrhosis, and severe fatty liver, the remnant volume should be more than 50%. If the patient has intermediate or advanced cirrhosis and with Child-Pugh B or C liver function, HR should not be carried out. The indication for TACE was a lack of main portal vein tumor thrombus. Patients who satisfied the indications for both HR and TACE were treated by HR unless the patient requested TACE. Both techniques were performed as described.[14]

Serum AFP assay, ultrasonography, and chest radiography were performed every 3 months in the first postoperative year and every 6 months in subsequent years. Postoperative enhanced computed tomography was performed every 6 months. Postoperative antiviral treatment was rarely administered.

Treatment of Recurrence

In patients who showed recurrence or resectable extrahepatic metastasis after initial treatment, HR was performed if it was judged feasible on the basis of liver function reserve and residual liver volume, which were evaluated according to the same criteria as those used at the time of initial resection.[19,20] If this HR could not be performed because of poor liver function or other unfavorable factors, then TACE, microwave coagulation therapy, or sorafenib therapy were applied.

Statistical Analysis

All demographic and clinicopathological data had been prospectively collected in computer databases before this retrospective analysis. Differences between categorical data were analyzed using the chi-squared and Fisher exact test (2-tailed). Continuous data were expressed as median (range). Differences between continuous data were analyzed using the Mann-Whitney U test. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis was carried out using the Cox proportional hazards model to generate adjusted hazard ratios and 95% confidence intervals. A P value of less than 0.05 was set as the significance threshold.

To reduce bias in patient selection, propensity analysis was carried out using logistic regression to create propensity scores for HR and TACE patients in an observational database.[21,22] Logistic regression was applied to clinical variables differing significantly between HR and TACE patients with HCC, and propensity scores were generated along a continuous range from 0 to 1. The model was then used to provide a one-to-one nearest-neighbor match between patients undergoing HR or TACE.[23,24]

For all tests, a 2-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS 17.0 statistical package (IBM).

Comprehensive MEDLINE Review

We comprehensively searched the MEDLINE database using the following medical subject headings (MeSH): *hepatocellular carcinoma* or *liver cancer* or *primary liver carcinoma* and *liver resection* or *hepatic resection* or *surgery*. Manual searching of relevant references and review articles was also performed. Studies were included in our review if they (*a*) evaluated the efficacy of HR for primary BCLC stage B/C HCC, (*b*) were published in English, and (*c*) were published between January 2000 and April 2013, to ensure comparability with our retrospective clinical study. Studies evaluating HR to treat recurrent HCC or studies involving fewer than 50 patients were excluded. In the case of multiple studies based on the same population, we selected the study with the largest number of participants.

RESULTS

Characteristics of the Entire Study Population

From January 2000 to December 2007, 4535 patients with HCC from southern China were enrolled in the prospective databases of the 3 study hospitals. On the basis of the inclusion criteria, 1259 patients (28%) were enrolled in this retrospective study. Of these patients, 908 (72%) received HR, whereas 351 (28%) underwent TACE (Fig. 1). HCC diagnosis was confirmed in TACE patients by needle biopsy (10.1%) or using 2 imaging techniques in conjunction with a serum level of AFP higher than 400 ng/mL (89.9%).

Baseline demographic and clinicopathological data for the 1259 patients are shown in Table 1. Patients in the TACE group were significantly older and had larger tumor size and higher levels of alanine aminotransferase and total bilirubin (all $P < 0.001$). More patients in the HR group were positive for hepatitis B surface antigen ($P = 0.018$). There were no significant differences in gender, number of tumors, hepatitis C antibody positivity, serum AFP or albumin level, distribution of cancer stages or frequencies of diabetes mellitus (DM), macrovascular invasion, or esophageal varices (all $P > 0.05$).

Mortality and Morbidity in the Entire Study Population

No significant differences between the HR and TACE groups were observed in 30-day mortality (1.9% vs 1.7%, $P = 0.847$) or 90-day mortality (3.1% vs 2.8%, $P = 0.827$) (Table 1). Postoperative

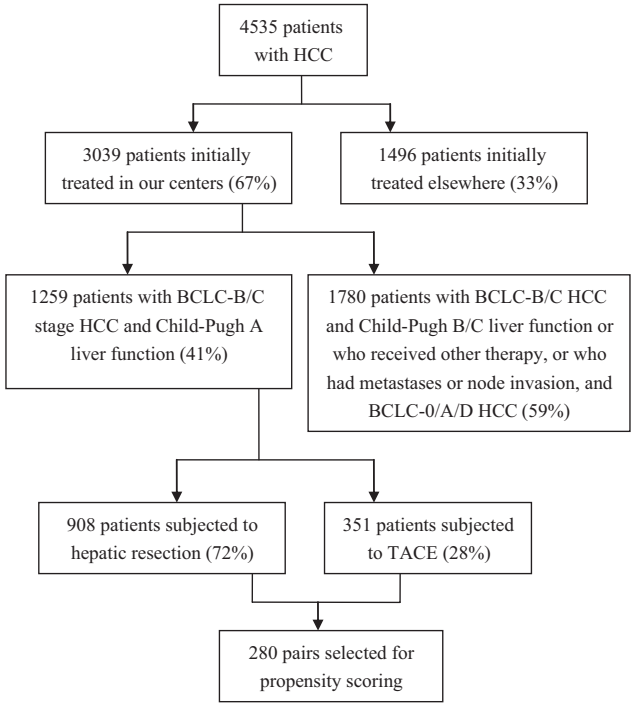

FIGURE 1. The patient databases included 4535 HCC patients. On the basis of the inclusion criteria, 908 (72%) and 351 (28%) BCLC stage B/C HCC patients underwent HR or TACE. In the propensity score model, 280 pairs of matched patients were generated for baseline-adjusted analyses.

complications were assessed using the Clavien-Dindo classification. Most complications were grade I or II (Table 2). Patients in the HR group had a significantly higher rate of postoperative complications (27%) than did patients in the TACE group (19%). The most frequent complications in HR patients were pulmonary infection (7.0%) and liver function failure (4.0%); the most frequent complications in TACE patients were liver function failure (4.6%) and puncture hematoma (4.6%).

Survival Analysis of the Entire Study Population

During a follow-up period lasting a median of 31.2 months (range, 1–120.3), 575 (63%) patients in the HR group and 285 (81%) in the TACE group died. Overall survival was significantly better in the HR group than in the TACE group ($P < 0.001$; Fig. 2). In fact, the HR group showed a survival benefit over TACE at 1 year (88% vs 81%), 3 years (62% vs 33%), and 5 years (39% vs 16%) ($P < 0.001$). Median survival time in the HR group was 47.4 months, compared with 23.7 months in the TACE group ($P < 0.001$). The 1-, 3-, and 5-year recurrence rates of patients in the HR group were 32%, 58%, and 74%. Among patients with recurrence, 83% were amenable to TACE and underwent the procedure.

Additional survival analysis was performed by including factors linked to survival, including age, gender, tumor size and number, hepatitis, serum biochemistry, DM, macrovascular invasion, esophageal varices, and treatment modality (Table 3). Univariate analysis identified the following prognostic factors predicting increased risk of mortality in the total population: age 60 years or older, tumor size 10 cm or bigger, tumor number 3 or more, serum AFP 400 ng/mL or more, serum alanine aminotransferase more than 80 U/L, serum bilirubin more than 1.2 mg/dL, DM, macrovascular invasion, esophageal varices, and TACE treatment. The multivariate Cox proportional hazards model identified several independent predictors of poor prognosis (Table 4): serum AFP 400 ng/mL or more, DM, macrovascular invasion, esophageal varices, and TACE treatment.

Characteristics and Survival Analysis of Propensity-Matched Patients

Propensity analysis based on variables associated with therapeutic strategy and long-term prognosis identified 280 matched pairs of patients from each treatment group. When only these pairs were considered, the 2 treatment arms did not show significant baseline differences in age, gender, tumor size or number, serum biochemistry, DM, macrovascular invasion, esophageal varices, or tumor staging (Table 1). Comparison of long-term survival in the 2 propensity-matched groups is shown in Figure 2. As observed in the overall study population, patients selected in the propensity-matching model who underwent HR showed significantly better long-term survival than did those who underwent TACE ($P < 0.001$). Overall survival of HCC patients undergoing HR and TACE was 87% and 80% (1 year), 54% and 32% (3 years), and 34% and 15% (5 years), respectively. The HR and TACE groups had similar rates for 30-day mortality (1.8% vs 2.1%, $P = 0.716$) and 90-day mortality (2.5% vs 3.2%, $P = 0.612$). However, the postoperative complication rate was significantly higher in the HR group (25%) than in the TACE group (18%; $P = 0.032$). The multivariate Cox proportional hazards model identified serum AFP 400 ng/mL or more, DM, macrovascular invasion, esophageal varices, and TACE treatment as mortality risk factors (Table 4).

Subgroup Analysis of the Entire Study Population

To explore more deeply the efficacy of HR for treating BCLC stage B/C HCC, we performed subgroup analyses on the basis of tumor size and number, as well as the presence or absence of macrovascular invasion (BCLC stage B/C) and PHT.

Subgroup Analysis by Tumor Size

Patients in each group were divided into subgroups with tumor size 10 cm or bigger or smaller than 10 cm. Among patients with tumor size 10 cm or more, HR provided better long-term survival than did TACE ($P < 0.001$; Fig. 3A), and HR showed a survival benefit at 1 year (86% vs 80%), 3 years (54% vs 30%), and 5 years (34% vs 16%). Similarly, among patients with tumor size smaller than 10 cm, HR provided better long-term survival ($P < 0.001$; Fig. 3A). HR showed a survival benefit at 1 year (89% vs 83%), 3 years (65% vs 37%), and 5 years (40% vs 18%). The prognosis of patients with large ($\geq$10 cm) HCC was poorer than that of patients with smaller ($<$10 cm) HCC (Table 3).

Subgroup Analysis by Tumor Number

Patients receiving each kind of treatment were divided into subgroups with 3 or more tumors or less than 3 tumors. Among patients with 3 or more tumors, survival was significantly higher in the HR subgroup at 1 year (90% vs 59%), 3 years (52% vs 11%), and 5 years (33% vs 6%) ($P < 0.001$) (Fig. 3B). Similarly, among patients with less than 3 tumors, survival was significantly higher in the HR subgroup at 1 year (88% vs 83%), 3 years (62% vs 35%), and 5 years (39% vs 17%) ($P < 0.001$) (Fig. 3B). Patients with multinodular HCC showed poorer overall survival than those with less than 3 neoplasms (Table 3).

Subgroup Analysis by Macrovascular Invasion

Patients were stratified on the basis of the absence of macrovascular invasion (BCLC-B) or on its presence (BCLC-C).

TABLE 1. Preoperative Clinicopathologic Data of Patients With BCLC Stage B/C HCC and Child-Pugh A Liver Function Who Received HR or TACE

	Before Propensity Matching			After Propensity Matching		
Variable	**HR ($n = 908$)**	**TACE ($n = 351$)**	***P***	**HR ($n = 280$)**	**TACE ($n = 280$)**	***P***
Age, median (range), yr	44 (17–78)	53 (19–82)	<0.001	53 (19–78)	52 (19–82)	0.628
Gender, M/F, *n* (%)	824 (91)/84 (9)	326 (93)/25 (7)	0.228	257 (92)/23 (8)	259 (93)/21 (7)	0.753
Tumor size, median (range)	8 (4–20)	10 (4–20)	<0.001	9 (4–20)	10 (4–18)	0.674
Tumor number, <3/ ≥3, *n* (%)	845 (93)/63 (7)	319 (91)/32 (9)	0.189	256 (91)/24 (9)	255 (91)/25 (9)	0.881
Hepatitis B surface antigen positivity, +/−, *n* (%)	844 (93)/64 (7)	312 (90)/39 (11)	0.018	244 (87)/36 (13)	247 (88)/33 (12)	0.700
Hepatitis C antibody positivity, *n* (%)	17 (2)	9 (3)	0.439	7 (3)	7 (3)	1.000
Serum AFP, *n* (%), ng/mL						
≥400	434 (48)	158 (45)	0.375	125 (45)	123 (44)	0.865
<400	474 (52)	193 (55)		155 (55)	157 (56)	
Platelet count ($\times 10^3$), *n* (range), μ/L	212.0 (59.0–528.0)	198.0 (37.0–530.0)	< 0.001	211.5 (59.0–523.0)	199.0 (39.0–521.0)	0.079
Prothrombin time, median (range), s	13.2 (10.0–19.0)	11.9 (7.9–16.1)	0.764	12.8 (10.5–17.8)	13.1 (8.3–16.0)	0.781
Albumin level, median (range), g/dL	3.9 (2.8–4.7)	3.9 (2.2–5.1)	0.775	3.9 (2.9–4.7)	3.9 (2.2–5.1)	0.317
Median alanine aminotransferase, U/L (range)	51 (13–320)	58 (0–260)	<0.001	53 (13–310)	58 (0–260)	0.459
Total bilirubin level, median (range), mg/dL	1.3 (0.5–4.0)	1.7 (0.3–22)	<0.001	1.5 (0.5–4.0)	1.6 (0.3–4.5)	0.483
Diabetes mellitus, *n* (%)	118 (13)	56 (16)	0.173	46 (16)	44 (16)	0.818
Macrovascular invasion, *n* (%)	248 (27)	85 (24)	0.264	72 (26)	71 (25)	0.923
BCLC stage B/C, *n* (%)	660 (73)/248 (27)	266 (76)/85 (24)	0.264	208 (74)/72 (26)	209 (75)/71 (25)	0.923
Grade of esophageal varices,* *n* (%)	0.469		0.680			
F0	742 (82)	274 (78)		221 (79)	216 (77)	
F1	90 (9.9)	44 (12.5)		28 (10)	36 (12.9)	
F2	58 (6.4)	24 (6.8)		22 (7.9)	18 (6.4)	
F3	18 (2.0)	9 (2.6)		9 (3.2)	10 (3.6)	
30-d mortality, *n* (%)	17 (1.9)	6 (1.7)	0.847	5 (1.8)	6 (2.1)	0.716
90-d mortality, *n* (%)	28 (3.1)	10 (2.8)	0.827	7 (2.5)	9 (3.2)	0.612
Postoperative complications, *n* (%)	243 (27)	67 (19)	0.005	70 (25)	50 (18)	0.032
Survival time, median (range), mo	47 (1–120)	24 (1–91)	< 0.001	41 (1–120)	23 (1–80)	< 0.001

*Evaluated using gastroesophageal fiberscopy and/or computed tomography.

TABLE 2. Postoperative Complications Assessed by the Clavien-Dindo Classification in Patients With BCLC Stage B/C HCC and Child-Pugh A Liver Function Who Received HR or TACE

	No. (%) Patients		
Grade	**HR ($n = 908$)**	**TACE ($n = 351$)**	***P***
Grade I	64 (7.0)	35 (10.0)	0.001
Grade II	125 (13.8)	19 (5.4)	
Grade III-a	27 (3.0)	4 (1.1)	
Grade III-b	15 (1.7)	8 (2.3)	
Grade IV-a	32 (3.5)	15 (4.3)	
Grade IV-b	6 (0.7)	3 (0.9)	
Grade V	17 (1.9)	6 (1.7)	

Among patients with macrovascular invasion HCC, overall survival was found to be significantly better after HR than after TACE (1 year, 81% vs 68%; 3 years, 46% vs 22%; 5 years, 20% vs 5%; $P < 0.001$) (Fig. 3C). Similarly, among patients without macrovascular invasion HCC, overall survival was better for the HR group than the TACE group (1 year, 91% vs 85%; 3 years, 67% vs 36%; 5 years, 44% vs 19%; $P < 0.001$) (Fig. 3C). Patients with macrovascular invasion HCC had poorer prognosis than did those without invasion (Table 3).

Subgroup Analysis by PHT

Among the subgroup of patients with PHT, survival was significantly better in the HR group than in the TACE group ($P < 0.001$;

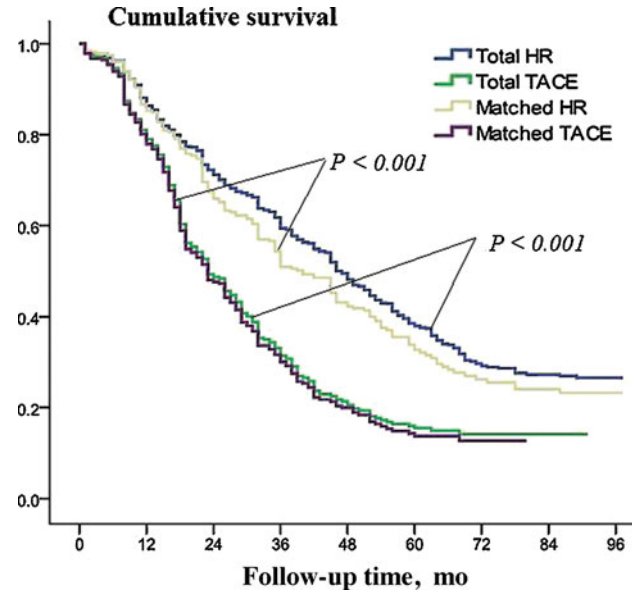

FIGURE 2. Overall survival curves for patients with BCLC stage B/C HCC who were treated with HR or TACE. Separate curves are shown for the entire patient population ($P < 0.001$) and for propensity-matched patients ($P < 0.001$).

TABLE 3. Univariate Analysis of Clinicopathological Prognostic Factors for Overall Survival

	Before Propensity Matching				After Propensity Matching			
Variable and Value Categories	**N**	**3-yr OS, %**	**5-yr OS, %**	***P***	**N**	**3-yr OS, %**	**5-yr OS, %**	***P***
Age, yr								
≥60	244	38	20	0.025	154	42	24	0.741
<60	1015	45	28		406	43	25	
Gender								
M	1150	43	26	0.714	516	44	25	0.159
F	109	50	24		44	39	20	
Tumor size, cm								
≥10	430	37	21	0.002	269	38	21	0.062
<10	829	47	29		291	48	28	
Tumor number								
≥3	95	31	23	0.017	49	26	17	0.023
<3	1164	45	26		511	45	25	
Hepatitis B surface antigen								
+	1156	43	26	0.091	491	41	23	0.037
−	103	56	23		69	61	32	
Hepatitis C antibody								
+	26	66	39	0.133	14	85	55	0.052
−	1233	43	26		546	42	24	
Serum AFP, ng/mL								
≥400	592	35	21	<0.001	248	36	19	0.001
<400	667	51	31		312	49	29	
Albumin, g/dL								
>4	469	45	28	0.206	222	45	28	0.360
≤4	790	43	25		338	42	22	
Alanine aminotransferase (U/L)								
>80	213	34	20	0.005	117	35	19	0.082
≤80	1046	46	27		443	45	26	
Bilirubin, mg/dL								
>1.2	750	40	23	0.001	387	41	23	0.128
≤1.2	509	49	30		173	48	28	
Diabetes mellitus								
Yes	174	35	16	0.001	90	40	16	0.056
No	1085	45	28		470	44	26	
Macrovascular invasion								
Yes	333	33	16	<0.001	417	48	29	<0.001
No	926	47	29		143	27	10	
PHT								
Yes	253	28	12	<0.001	129	25	12	<0.001
No	1016	48	29		437	48	28	

OS indicates overall survival.

TABLE 4. Multivariate Analysis of Clinicopathological Factors Predictive of Poor Overall Survival

	Before Propensity Matching			After Propensity Matching		
Variable	**Hazard Ratio**	**95% Confidence Interval**	***P***	**Hazard Ratio**	**95% Confidence Interval**	***P***
Age ≥ 60 yr	1.081	0.909–1.287	0.377	0.919	0.733–1.151	0.463
Tumor size ≥ 10 cm	1.015	0.873–1.181	0.844	1.056	0.864–1.292	0.594
Tumor number ≥ 3	1.196	0.908–1.574	0.203	1.356	0.954–1.929	0.090
Serum AFP ≥ 400 ng/mL	1.443	1.258–1.654	<0.001	1.357	1.110–1.660	0.003
Alanine aminotransferase > 80 U/L	1.052	0.875–1.265	0.590	1.004	0.783–1.287	0.977
Bilirubin > 1.2 mg/dL	1.064	0.919–1.232	0.405	1.141	0.912–1.427	0.248
Diabetes mellitus	1.342	1.108–1.626	0.003	1.321	1.011–1.724	0.041
Macrovascular invasion	1.414	1.210–1.653	<0.001	1.648	1.309–2.075	<0.001
PHT	1.504	1.272–1.773	<0.001	1.702	1.342–2.157	<0.001
TACE treatment	1.642	1.399–1.927	<0.001	1.812	1.480–2.220	<0.001

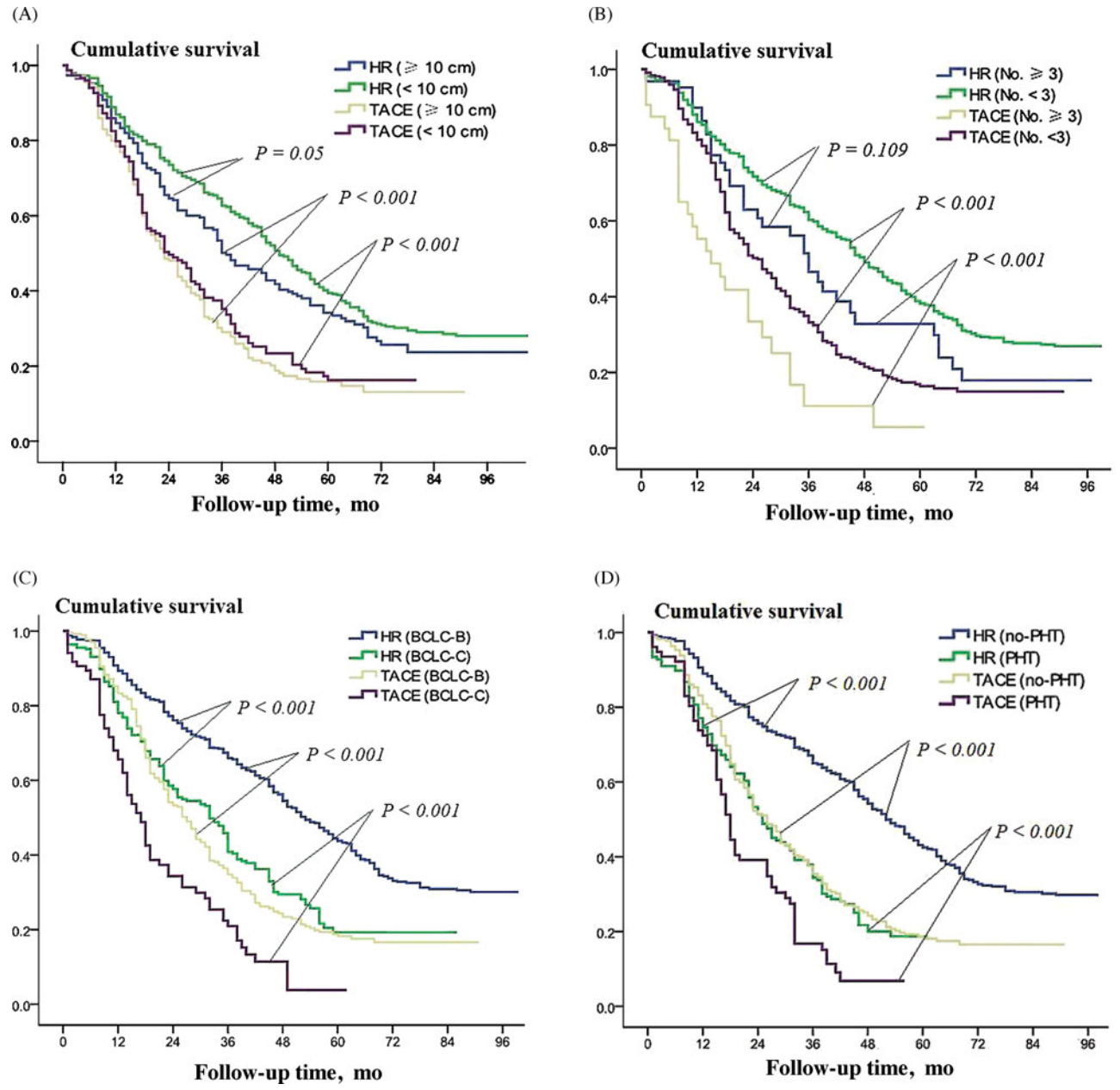

FIGURE 3. Overall survival curves of subgroups of patients with BCLC stage B/C HCC who underwent HR or TACE. Subgroups were defined according to (A) tumor size, (B) tumor number, (C) BCLC stage, and (D) presence or absence of PHT.

Fig. 3D). HR showed a survival benefit at 1 year (76% vs 73%), 3 years (38% vs 17%), and 5 years (16% vs 7%). Similarly, among patients without PHT, HR showed survival benefit at 1 year (91% vs 82%), 3 years (67% vs 38%), and 5 years (43% vs 20%) ($P < 0.001$; Fig. 3D).

Literature Review

A total of 36 eligible studies were found to satisfy the inclusion criteria, and key demographic and clinicopathological data were extracted (Table 5). Studies were organized into subgroups depending on whether they involved large and/or multinodular HCC,[18,25–52] HCC with macrovascular invasion,[18,25,34,53–56] and HCC with PHT.[35,57–59] Most patients in included studies were from southeast Asia, the region with the highest prevalence of HCC, and most had large and/or multiple HCC.

The majority of the studies reported a hospital mortality less than 5%. However, when HR was used to treat HCC with PHT, hospital mortality was reported to rise to 11%.[57,58] Overall survival after HR was 70% to 80% (1 year), about 50% (3 years), and about 30% (5 years). Patients with large and/or multinodular HCC showed better long-term survival than did those with HCC with macrovascular invasion or PHT. Patients with macrovascular invasion HCC showed the worst long-term survival.

TABLE 5. Outcomes of HR for Patients With BCLC Stage B/C HCC in the Recent Literature

Study	Patient Origins	Recruitment Period	*N*	No. With Cirrhosis, %	HCC Characteristics	Hospital Mortality, %‡	Overall Survival, %		
							1 yr	3 yr	5 yr
Single large and/or multinodular HCC									
Chang et al[25]	Taiwan	1991–2006	318	97 (31)	BCLC-B HCC	About 2.7	81	59	47
Chen et al[26]	Central China	1996–2003	1143	897 (78)	Tumor size ≥ 5 cm	0.7	71	59	39
Cheng et al[27]	Taiwan	1999–2005	104	22 (21)	Tumor size > 5 cm	7.3 and 7.9*	90 and 88*	—	66 and 53*
Cho et al[28]	Korea	1998–2001	61	35 (58)	Tumor size 5–10 cm	1.6	85	59	53
Choi et al[29]	Korea	1996–2006	50	13 (26)	Tumor size ≥ 10 cm	0	70	50	40
Delis et al[30]	Greece	2002–2008	66	59 (89)	Tumor size > 5 cm	0	69	37	32
Hanazaki et al[52]	Japan	1983–1997	133	69 (52)	Tumor size ≥ 5 cm	6.0	—	38	28
Ho et al[31]	Taiwan	1981–2000	294	188 (64)	Tumor No. ≥ 2	—	77	52	37
Hsu et al[32]	Taiwan	2002–2010	268	—	Beyond the Milan criteria	2.7	81	63	43
Huang et al[33]	Taiwan	2001–2005	139	80 (58)	Tumor size > 10 cm or adjacent organ invasion, or ruptured tumor	4.3	62	39	29
Ikai et al[34]	Japan	1992–2003	4972	—	Tumor size 5–10 cm	—	81	56	42
			2127	—	Tumor size > 10 cm	—	67	43	32
			3174	—	Tumor No. ≥ 3	—	75	48	30
Ishizawa et al[35]	Japan	1994–2004	126	103 (82)	Multiple HCC	—	—	72 and 33†	58 and 19†
Lee et al[36]	Korea	1997–2003	100	—	Tumor size > 10 cm	2.0	66	44	31
Liau et al[37]	USA	1985–2002	82	8 (10)	Tumor size ≥ 10 cm	2.0	68	48	33
Lin et al[38]	Taiwan	2001–2007	93	—	BCLC-B HCC	5.4	83	49	30
Mok et al[39]	Taiwan	1990–2001	56	28 (50)	Tumor size > 10 cm	1.8	61	25	25
Ng et al[40]	Asia, Europe, USA	1982–2001	380	101 (26)	Single nodule > 5 cm or multinodular	2.7	74	50	39
Pandey et al[41]	Singapore	1995–2006	166	80 (48)	Tumor size ≥ 10 cm	3.0	—	—	29
Pawlik et al[42]	Asia, Europe, USA	1981–2000	300	—	Tumor size ≥ 10 cm	5.0	65	37	27
Poon et al[43]	Hong Kong	1991–2000	120	32 (27)	Tumor size > 10 cm	5.0	61	38	28
Shimada et al[44]	Japan	1988–2004	86	9 (10)	Tumor size ≥ 10 cm	1.2	—	—	32
Torzilli et al[18]	Europe, USA, China and others	1990–2009	737	360 (56)	BCLC-B HCC	3.0	88	71	57
Truant et al[45]	France	2000–2010	52	—	Tumor size ≥ 8 cm	9.6	—	—	43
Wang et al[46]	Taiwan	1986–2002	243	—	BCLC-B HCC	—	82	64	51
Yamashita et al[47]	Japan	1995–2007	53	—	Tumor size ≥ 10 cm	3.8	74	43	35
Yang et al[48]	Eastern China	1985–1996	86	—	Tumor size ≥ 15 cm	3.5	58	36	18
Yang et al[49]	Central China	1992–2002	260	198 (76)	Tumor size > 5 cm	2.3	87	56	38
Yeh et al[50]	Taiwan	1982–2001	211	63 (30)	Tumor size ≥ 10 cm	4.3	48	24	17
Zhou et al[51]	Eastern China	1964–1999	621	About 503 (81)	Tumor size ≥ 10 cm	4.5	68	37	26
This study	Southern China	2000–2010	660	514 (78)	BCLC-B HCC	2.6	91	67	44
HCC with macrovascular invasion									
Chang et al[25]	Taiwan	1991–2006	160	60 (40)	BCLC-C HCC	About 2.7	58	34	29

(*continued*)

TABLE 5. (*Continued*)

Study	Patient Origins	Recruitment Period	*N*	No. With Cirrhosis, %	HCC Characteristics	Hospital Mortality, %‡	Overall Survival, %		
							1 yr	3 yr	5 yr
Huang et al[56]	West China	1998–2008	116	41 (35)	With tumor size > 15 cm	3.4	71	23	11
Ikai et al[34]	Japan	1992–2003	976	—	First-order branches or main trunk of portal vein	—	50	26	18
Pawlik et al[53]	Asia, Europe, USA	1984–1999	102	—	Major vascular invasion	5.9	45	17	10
Shi et al[54]	Eastern China	2001–2003	406	320 (79)	Involving segmental branches, right/left portal vein, main portal vein trunk, or superior mesenteric vein	0.2	34	13	—
Torzilli et al[18]	Europe, USA, China, and others	1990–2009	297	169 (64)	BCLC-C HCC	3.0	76	49	38
Yang et al[55]	Eastern China	2001–2007	511	392 (77)	Advanced HCC	2.3	70	41	31
This study	Southern China	2000–2010	248	198 (80)	Major vascular invasion	4.4	81	46	20
HCC with PHT									
Capussotti et al[57]	Italy	1985–2003	99	99 (100)	Portal hypertension	11.1	—	45	29
Cucchetti et al[58]	Italy	1997–2007	89	89 (100)	Portal hypertension	11.9	—	62	52
Ishizawa et al[35]	Japan	1994–2004	136	123 (90)	Portal hypertension	—	—	71 and 59†	56 and 41†
Santambrogio et al[59]	Italy and France	1997–2012	63	63 (100)	Portal hypertension	4.0	—	66	48
This study	Southern China	2000–2010	166	173 (100)	Portal hypertension	10.3	77	38	17

*Hemi-/extended hepatectomy group and central hepatectomy group.
†Child-Pugh class A cirrhosis and Child-Pugh class B cirrhosis.
‡Mainly 90-d mortality.

DISCUSSION

According to the guidelines of the European Association for the Study of the Liver[60] and the American Association for the Study of Liver Disease,[8] which are based on the BCLC classification, HR is indicated only for those patients with early-stage HCC. However, some new seminars[61–63] have stated that tumor size should not be used as a selection criterion for HR if tumor location and liver function allow resection, and therefore that patients with single large HCC may be considered for HR. Nevertheless, HR is not recommended as the first-line treatment for single large, multinodular, and macrovascular invasion HCCs.[64,65] Moreover, PHT in cirrhotic patients is considered a relative contraindication for HR according to the guidelines of European Association for the Study of the Liver/American Association for the Study of Liver Disease.

In this retrospective clinical study of a large cohort of patients from a region in which more than 90% of HCC is related to hepatitis B, we found that HR led to better overall survival than did TACE, both for the entire study population as well as for a propensity-matched subpopulation. Subgroup analyses based on tumor size and number and on the presence or absence of macrovascular invasion and PHT gave similar results. The 1-, 3-, and 5-year overall survival of our HR patients was similar to that reported by other studies identified in a comprehensive review of MEDLINE (Table 6). Therefore, the recommendation of the consensus of the Asian Pacific Association for the Study of the Liver,[66] the Japan Society of Hepatology,[67] and the American Hepato-Pancreato-Biliary Association[68] seems reasonable: in terms of long-term survival, HR is the best treatment for selected patients with large solitary, multinodular, or macrovascular invasion HCC. In our view, when determining the HR suitability of these patients, preoperative liver function and postoperative residual liver volume are the 2 most important criteria. As long as these parameters are adequate, we suggest that there is no absolute contraindication of HR for HCC.

HR is considered the most effective treatment for HCC,[18,69,70] but perioperative morbidity and mortality have traditionally posed significant risks. Although the postoperative complication rate in our HR group (26.8%) was significantly higher than that in the TACE group (18.5%), improvements in surgical technique and perioperative care have lowered the mortality of HR for HCC. As a result, HR performed correctly on carefully selected patients is safe and effective even for HCC patients with large and multinodular tumor burden, macrovascular invasion, and compensated liver cirrhosis.[54,70] In fact, perioperative mortality can be zero in some centers.[71,72] By comparison, TACE-related mortality ranges from 0% to 9.5% and is primarily the result of liver failure.[73]

Our results suggest that the decision whether to perform HR should not be constrained by tumor size or number. Resection led to significantly better survival than did TACE, both for patients with small (<10 cm) HCC and those with large (≥10 cm) HCC (Fig. 3A; both $P < 0.001$), even though patients with large HCC treated by either technique showed worse survival. These findings, together with those of other studies,[18,25–30,32–34,36–52] lead us to conclude that tumor size alone should not be considered a contraindication of HR. In addition, survival was better after HR than after TACE for patients treated for multiple (≥3) HCCs and those treated for single/double (<3) HCCs (Fig. 3B; both $P < 0.001$), although survival after both techniques was worse after resection for 3 or more HCCs than after resection for less than 3 HCCs (Fig. 3B; $P = 0.109$). These findings suggest that multinodularity by itself should not be considered an exclusion criterion against HR.[31,34,56]

Our results further suggest that the decision whether to perform HR should not be determined solely by the presence or absence of macrovascular invasion in HCC. Under the BCLC classification system used in this study, such invasion is the defining difference between stage B and stage C, yet HR was associated with better survival than TACE for both stages (Fig. 3C; both $P < 0.001$). Nevertheless, HR was not equally effective for all patients: patients with BCLC stage B HCC showed better survival than did those with BCLC stage C cancer (Fig. 3C; $P < 0.001$). These findings are consistent with several multicenter studies[18,25,34,53–56] identified in our MEDLINE literature search, which reported that HR for HCC with macrovascular invasion can be performed relatively safely with lower than 5%

TABLE 6. Efficacy of HR and TACE in the Total Population, Propensity-Matched Population and Subgroups

		No.	1 yr (%)	3 yr (%)	5 yr (%)	*P*
Total population ($N = 1259$)	HR	908	88	62	39	<0.001
	TACE	351	81	33	16	
Matched population ($N = 560$)	HR	280	87	54	34	<0.001
	TACE	280	80	32	15	
Subgroup analysis						
Tumor size						
≥10 cm	HR	229	86	54	34	<0.001
	TACE	201	80	30	16	
<10 cm	HR	679	89	65	40	<0.001
	TACE	150	83	37	18	
Tumor number						
≥3	HR	63	90	52	33	0.001
	TACE	32	59	11	6	
<3	HR	845	88	62	39	<0.001
	TACE	319	83	35	17	
BCLC stage B	HR	660	91	67	44	<0.001
	TACE	266	85	36	19	
Macrovascular invasion (BCLC stage C)	HR	248	81	46	20	<0.001
	TACE	85	68	22	5	
Portal hypertension						
Yes	HR	173	76	38	16	<0.001
	TACE	80	73	17	7	
No	HR	735	91	67	43	<0.001
	TACE	271	82	38	20	

mortality, and with long-term survival far superior to that of TACE or other therapies (Table 5).

In our patient population with HCC, as in most parts of China, hepatitis B virus infection is endemic and screening is not routinely performed. This may help to explain why 243 (19%) of our patients had esophageal varices (Table 1). Our results suggest that PHT should not by itself be an exclusion criterion for HR. In our study, HR led to better long-term survival than TACE in patients with or without PHT (Fig. 3D; both $P < 0.001$), although survival after either technique was lower for patients with PHT than for those without it (Fig. 3D; $P < 0.001$). These findings are consistent with studies from Europe and Asia, which found 5-year survival to be about 50% for patients with PHT treated by HR.[35,58,59] While we interpret these findings to mean that PHT per se is not a contraindication to HR in patients with HCC and cirrhosis, we do emphasize the need for preoperatively assessing the likelihood that perioperative liver function and postoperative residual liver volume will be sufficient. This is particularly important for reducing the risk of hepatic mortality in patients with PHT, because these factors are associated with severe cirrhosis.

Our multivariate Cox modeling to identify prognostic factors in HCC patients came to similar conclusions as previous studies: patients with high preoperative AFP level[74,75] and DM[76,77] had significantly worse outcomes than did other patients after HR. In contrast to previous studies, our modeling did not show large tumor size[30,45] and multinodularity[25,35,40] to be poor prognostic factors. Our modeling further identified 2 other independent predictors of poor prognosis: macrovascular invasion and PHT. Our finding of macrovascular invasion as a poor prognostic predictor is supported by numerous studies outside China.[42,47,57] Macrovascular invasion is attributed to HCC recurrence, which is the primary cause of postoperative death. Our finding of PHT as a poor prognostic factor may reflect the high 90-day mortality among patients with PHT treated with HR (10.2%, 17/166) or TACE (6.5%, 5/77). Liver failure and varices rupture are 2 major causes of mortality in these patients. Some studies have also indicated that PHT is an independent factor related for morbidity.[78–80]

One of the major limitations of our clinical study is the particular characteristics of our patient population, which shows one of the highest incidences of HCC in the world. All patients in our consecutive series had Child-Pugh class A disease. Nearly half (41%) of the patients in our study arrived with BCLC stage B/C HCC (Fig. 1), and fully 26% had BCLC stage C disease. Nevertheless, our findings are in accord with an extensive literature search in which we identified studies conducted with diverse patient populations around the world. Therefore, we believe our results are relevant for other populations. Another limitation is that analysis involving multicentric tumors was not conducted because of the insufficiently detailed data. Further studies should do this.

Given its retrospective design, our study was probably subject to selection bias. On the contrary, the established efficacy of HR and the heterogeneity of patients with HCC that require HR or TACE make it difficult to conduct a randomized controlled trial comparing the efficacy of the 2 techniques. Therefore, we used a propensity-scoring model to verify our results obtained with the entire study population. Another limitation of our study is that the use of postoperative adjuvant treatment, such as TACE and interferon, and postrecurrence retreatment with resection or other local therapies complicated efficacy comparisons between HR and TACE. Future studies should take into account the frequently multidisciplinary approach used to improve prognosis of patients with advanced HCC.

CONCLUSIONS

In this way, our clinical and literature studies suggest that HR should be considered a fundamental part of total curative treatment of HCC. Compared to TACE, HR can provide significant survival benefit for patients with HCC involving large solitary tumors, multinodular tumors, macrovascular invasion, and PHT. It is important that such patients have at least Child-Pugh class A liver function.

ACKNOWLEDGMENTS

The authors thank Dr Armando Chapin Rodríguez for his contribution in language editing, which substantially improved the quality of the manuscript.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics. *CA Cancer J Clin.* 2013;63:11–30.
2. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med.* 1996;334:693–699.
3. Thelen A, Benckert C, Tautenhahn HM, et al. Liver resection for hepatocellular carcinoma in patients without cirrhosis. *Br J Surg.* 2013;100:130–137.
4. Hasegawa K, Kokudo N, Makuuchi M, et al. Comparison of resection and ablation for hepatocellular carcinoma: a cohort study based on a Japanese nationwide survey. *J Hepatol.* 2013;58:724–729.
5. Lim KC, Chow PK, Allen JC, et al. Systematic review of outcomes of liver resection for early hepatocellular carcinoma within the Milan criteria. *Br J Surg.* 2012;99:1622–1629.
6. Fan ST, Poon RT, Yeung C, et al. Outcome after partial hepatectomy for hepatocellular cancer within the Milan criteria. *Br J Surg.* 2011;98:1292–1300.
7. Lencioni R, Chen XP, Dagher L, et al. Treatment of intermediate/advanced hepatocellular carcinoma in the clinic: how can outcomes be improved? *Oncologist.* 2010;15 (suppl 4):42–52.
8. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology.* 2011;53:1020–1022.
9. Cillo U, Vitale A, Grigoletto F, et al. Prospective validation of the Barcelona Clinic Liver Cancer staging system. *J Hepatol.* 2006;44:723–731.
10. Cabibbo G, Enea M, Attanasio M, et al. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. *Hepatology.* 2010;51:1274–1283.
11. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatology.* 2002;35:519–524.
12. Befeler AS, Di Bisceglie AM. Hepatocellular carcinoma: diagnosis and treatment. *Gastroenterology.* 2002;122:1609–1619.
13. Hassoun Z, Gores GJ. Treatment of hepatocellular carcinoma. *Clin Gastroenterol Hepatol.* 2003;1:10–18.
14. Zhong JH, Gong WF, Ke Y, et al. Comparison of long-term survival of patients with BCLC stage B hepatocellular carcinoma after liver resection or transarterial chemoembolization. *PLoS One.* 2013;8:e68193.
15. Yeh FS, Yu MC, Mo CC, et al. Hepatitis B virus, aflatoxins, and hepatocellular carcinoma in southern Guangxi, China. *Cancer Res.* 1989;49:2506–2509.
16. Wang JS, Huang T, Su J, et al. Hepatocellular carcinoma and aflatoxin exposure in Zhuqing Village, Fusui County, People's Republic of China. *Cancer Epidemiol Biomarkers Prev.* 2001;10:143–146.
17. Kikuchi LO, Paranagua-Vezozzo DC, Chagas AL, et al. Nodules less than 20 mm and vascular invasion are predictors of survival in small hepatocellular carcinoma. *J Clin Gastroenterol.* 2009;43:191–195.
18. Torzilli G, Belghiti J, Kokudo N, et al. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations? An observational study of the HCC East-West Study Group. *Ann Surg.* 2013;257:929–937.
19. Hsieh CB, Yu CY, Tzao C, et al. Prediction of the risk of hepatic failure in patients with portal vein invasion hepatoma after hepatic resection. *Eur J Surg Oncol.* 2006;32:72–76.
20. Minagawa M, Makuuchi M, Takayama T, et al. Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. *Ann Surg.* 2003;238:703–710.
21. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res.* 2011;46:399–424.
22. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med.* 1998;17:2265–2281.
23. Mirici-Cappa F, Gramenzi A, Santi V, et al. Treatments for hepatocellular carcinoma in elderly patients are as effective as in younger patients: a 20-year multicentre experience. *Gut.* 2010;59:387–396.

24. Hung HH, Chiou YY, Hsia CY, et al. Survival rates are comparable after radiofrequency ablation or surgery in patients with small hepatocellular carcinomas. *Clin Gastroenterol Hepatol.* 2011;9:79–86.
25. Chang WT, Kao WY, Chau GY, et al. Hepatic resection can provide long-term survival of patients with non-early-stage hepatocellular carcinoma: extending the indication for resection? *Surgery.* 2012;152:809–820.
26. Chen XP, Qiu FZ, Wu ZD, et al. Long-term outcome of resection of large hepatocellular carcinoma. *Br J Surg.* 2006;93:600–606.
27. Cheng CH, Yu MC, Wu TH, et al. Surgical resection of centrally located large hepatocellular carcinoma. *Chang Gung Med J.* 2012;35:178–191.
28. Cho YB, Lee KU, Lee HW, et al. Outcomes of hepatic resection for a single large hepatocellular carcinoma. *World J Surg.* 2007;31:795–801.
29. Choi GH, Han DH, Kim DH, et al. Outcome after curative resection for a huge (>or = 10 cm) hepatocellular carcinoma and prognostic significance of gross tumor classification. *Am J Surg.* 2009;198:693–701.
30. Delis SG, Bakoyiannis A, Tassopoulos N, et al. Hepatic resection for hepatocellular carcinoma exceeding Milan criteria. *Surg Oncol.* 2010;19:200–207.
31. Ho MC, Huang GT, Tsang YM, et al. Liver resection improves the survival of patients with multiple hepatocellular carcinomas. *Ann Surg Oncol.* 2009;16:848–855.
32. Hsu CY, Hsia CY, Huang YH, et al. Comparison of surgical resection and transarterial chemoembolization for hepatocellular carcinoma beyond the Milan criteria: a propensity score analysis. *Ann Surg Oncol.* 2012;19:842–849.
33. Huang JF, Wu SM, Wu TH, et al. Liver resection for complicated hepatocellular carcinoma: challenges but opportunity for long-term survivals. *J Surg Oncol.* 2012;106:959–965.
34. Ikai I, Arii S, Okazaki M, et al. Report of the 17th nationwide follow-up survey of primary liver cancer in Japan. *Hepatol Res.* 2007;37:676–691.
35. Ishizawa T, Hasegawa K, Aoki T, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology.* 2008;134:1908–1916.
36. Lee SG, Hwang S, Jung JP, et al. Outcome of patients with huge hepatocellular carcinoma after primary resection and treatment of recurrent lesions. *Br J Surg.* 2007;94:320–326.
37. Liau KH, Ruo L, Shia J, et al. Outcome of partial hepatectomy for large (>10 cm) hepatocellular carcinoma. *Cancer.* 2005;104:1948–1955.
38. Lin CT, Hsu KF, Chen TW, et al. Comparing hepatic resection and transarterial chemoembolization for Barcelona Clinic Liver Cancer (BCLC) stage B hepatocellular carcinoma: change for treatment of choice? *World J Surg.* 2010;34:2155–2161.
39. Mok KT, Wang BW, Lo GH, et al. Multimodality management of hepatocellular carcinoma larger than 10 cm. *J Am Coll Surg.* 2003;197:730–738.
40. Ng KK, Vauthey JN, Pawlik TM, et al. Is hepatic resection for large or multinodular hepatocellular carcinoma justified? Results from a multi-institutional database. *Ann Surg Oncol.* 2005;12:364–373.
41. Pandey D, Lee KH, Wai CT, et al. Long term outcome and prognostic factors for large hepatocellular carcinoma (10 cm or more) after surgical resection. *Ann Surg Oncol.* 2007;14:2817–2823.
42. Pawlik TM, Poon RT, Abdalla EK, et al. Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. *Arch Surg.* 2005;140:450–457; discussion 457–458.
43. Poon RT, Fan ST, Wong J. Selection criteria for hepatic resection in patients with large hepatocellular carcinoma larger than 10 cm in diameter. *J Am Coll Surg.* 2002;194:592–602.
44. Shimada K, Sakamoto Y, Esaki M, et al. Role of a hepatectomy for the treatment of large hepatocellular carcinomas measuring 10 cm or larger in diameter. *Langenbecks Arch Surg.* 2008;393:521–526.
45. Truant S, Boleslawski E, Duhamel A, et al. Tumor size of hepatocellular carcinoma in noncirrhotic liver: a controversial predictive factor for outcome after resection. *Eur J Surg Oncol.* 2012;38:1189–1196.
46. Wang JH, Changchien CS, Hu TH, et al. The efficacy of treatment schedules according to Barcelona Clinic Liver Cancer staging for hepatocellular carcinoma: survival analysis of 3892 patients. *Eur J Cancer.* 2008;44:1000–1006.
47. Yamashita Y, Taketomi A, Shirabe K, et al. Outcomes of hepatic resection for huge hepatocellular carcinoma (≥10 cm in diameter). *J Surg Oncol.* 2011;104:292–298.
48. Yang JM, Kan T, Chen H, et al. Hepatectomy in the treatment of very big primary liver cancer: report of 86 cases. *Hepatobiliary Pancreat Dis Int.* 2002;1:42–45.
49. Yang LY, Fang F, Ou DP, et al. Solitary large hepatocellular carcinoma: a specific subtype of hepatocellular carcinoma with good outcome after hepatic resection. *Ann Surg.* 2009;249:118–123.
50. Yeh CN, Lee WC, Chen MF. Hepatic resection and prognosis for patients with hepatocellular carcinoma larger than 10 cm: two decades of experience at Chang Gung memorial hospital. *Ann Surg Oncol.* 2003;10:1070–1076.
51. Zhou XD, Tang ZY, Ma ZC, et al. Surgery for large primary liver cancer more than 10 cm in diameter. *J Cancer Res Clin Oncol.* 2003;129:543–548.
52. Hanazaki K, Kajikawa S, Shimozawa N, et al. Hepatic resection for large hepatocellular carcinoma. *Am J Surg.* 2001;181:347–353.
53. Pawlik TM, Poon RT, Abdalla EK, et al. Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: results of a multicenter study. *Surgery.* 2005;137:403–410.
54. Shi J, Lai EC, Li N, et al. Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. *Ann Surg Oncol.* 2010;17:2073–2080.
55. Yang T, Lin C, Zhai J, et al. Surgical resection for advanced hepatocellular carcinoma according to Barcelona Clinic Liver Cancer (BCLC) staging. *J Cancer Res Clin Oncol.* 2012;138:1121–1129.
56. Huang J, Hernandez-Alejandro R, Croome KP, et al. Hepatic resection for huge (>15 cm) multinodular HCC with macrovascular invasion. *J Surg Res.* 2012;178:743–750.
57. Capussotti L, Ferrero A, Vigano L, et al. Portal hypertension: contraindication to liver surgery? *World J Surg.* 2006;30:992–999.
58. Cucchetti A, Ercolani G, Vivarelli M, et al. Is portal hypertension a contraindication to hepatic resection? *Ann Surg.* 2009;250:922–928.
59. Santambrogio R, Kluger MD, Costa M, et al. Hepatic resection for hepatocellular carcinoma in patients with Child-Pugh's A cirrhosis: is clinical evidence of portal hypertension a contraindication? *HPB (Oxford).* 2013;15:78–84.
60. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol.* 2001;35:421–430.
61. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet.* 2012;379:1245–1255.
62. European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol.* 2012;56:908–943.
63. de Lope CR, Tremosini S, Forner A, et al. Management of HCC. *J Hepatol.* 2012;56 (suppl 1):S75–S87.
64. Bruix J, Llovet JM. Major achievements in hepatocellular carcinoma. *Lancet.* 2009;373:614–616.
65. Forner A, Reig ME, de Lope CR, et al. Current strategy for staging and treatment: the BCLC update and future prospects. *Semin Liver Dis.* 2010;30:61–74.
66. Omata M, Lesmana LA, Tateishi R, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. *Hepatol Int.* 2010;4:439–474.
67. Kudo M, Izumi N, Kokudo N, et al. Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. *Dig Dis.* 2011;29:339–364.
68. Jarnagin W, Chapman WC, Curley S, et al. Surgical treatment of hepatocellular carcinoma: expert consensus statement. *HPB (Oxford).* 2010;12:302–310.
69. Lau WY, Leung TW, Lai BS, et al. Preoperative systemic chemoimmunotherapy and sequential resection for unresectable hepatocellular carcinoma. *Ann Surg.* 2001;233:236–241.
70. Truty MJ, Vauthey JN. Surgical resection of high-risk hepatocellular carcinoma: patient selection, preoperative considerations, and operative technique. *Ann Surg Oncol.* 2010;17:1219–1225.
71. Jarnagin WR, Gonen M, Fong Y, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg.* 2002;236:397–406; discussion 406–397.
72. Imamura H, Seyama Y, Kokudo N, et al. One thousand fifty-six hepatectomies without mortality in 8 years. *Arch Surg.* 2003;138:1198–1206; discussion 1206.
73. Marelli L, Stigliano R, Triantos C, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. *Cardiovasc Intervent Radiol.* 2007;30:6–25.
74. Witjes CD, Polak WG, Verhoef C, et al. Increased alpha-fetoprotein serum level is predictive for survival and recurrence of hepatocellular carcinoma in non-cirrhotic livers. *Dig Surg.* 2012;29:522–528.
75. Tamura Y, Suda T, Arii S, et al. Value of highly sensitive fucosylated fraction of alpha-fetoprotein for prediction of hepatocellular carcinoma recurrence after curative treatment. *Dig Dis Sci.* 2013;58:2406–2412.
76. Shau WY, Shao YY, Yeh YC, et al. Diabetes mellitus is associated with increased mortality in patients receiving curative therapy for hepatocellular carcinoma. *Oncologist.* 2012;17:856–862.

77. Yang WS, Va P, Bray F, et al. The role of pre-existing diabetes mellitus on hepatocellular carcinoma occurrence and prognosis: a meta-analysis of prospective cohort studies. *PLoS One.* 2011;6:e27326.
78. Boleslawski E, Petrovai G, Truant S, et al. Hepatic venous pressure gradient in the assessment of portal hypertension before liver resection in patients with cirrhosis. *Br J Surg*. 2012;99:855–863.
79. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology*. 1999;30:1434–1440.
80. Figueras J, Llado L, Ruiz D, et al. Complete versus selective portal triad clamping for minor liver resections: a prospective randomized trial. *Ann Surg*. 2005;241:582–590.

