

Hepatic resection versus transarterial chemoembolization for patients with Barcelona Clinic Liver Cancer intermediate stage Child-Pugh A hepatocellular carcinoma

YIN-NONG ZHAO¹, YONG-QUAN ZHANG², JIA-ZHOU YE¹, XING LIU¹, HONG-ZHI YANG², FENG-YUN CONG², BANG-DE XIANG¹, FEI-XIANG WU¹, LIANG MA¹, LE-QUN LI¹ and HAI-HONG YE²

¹Department of Hepatobiliary Surgery, Affiliated Tumor Hospital of Guangxi Medical University, Nanning, Guangxi 530021; ²Department of Hepatobiliary Surgery, The Affiliated Minzu Hospital of Guangxi Medical University, Nanning, Guangxi 530001, P.R. China

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Abstract. The present study aimed to compare the overall and recurrence-free survival rates following hepatic resection (HR) and transcatheter arterial chemoembolization (TACE) in patients with Barcelona Clinic Liver Cancer (BCLC) classified intermediate-stage Child-Pugh A hepatocellular carcinoma (HCC). A total of 443 patients were examined, among whom 274 underwent HR, whereas 169 received TACE. The overall survival, recurrence-free survival between groups and subgroups, and risk factors with respect to mortality and recurrence, were analyzed. The 1-, 3- and 5-year overall and recurrence-free survival rates were 70, 46 and 37% and 73, 52, and 37%, respectively after HR, compared with 38, 15, and 12% and 44, 25 and 16%, respectively after TACE. Overall and recurrence-free survival rates were significantly increased following HR compared with TACE. Subgroup analysis in the multi-nodule group showed that the 1-, 3- and 5-year overall survival rates were 68, 38 and 30% after HR, compared with 36, 10 and 0% following TACE. In the solitary tumor group, 1-, 3- and 5-year overall survival rates were 71, 50 and 38% after HR, and 41, 22 and 15% after TACE. The overall survival rate after HR was significantly increased compared with that after TACE in the solitary tumor and multi-nodule

groups. The risk factors for mortality include solitary tumor diameter >10 cm, multi-nodules, serum albumin level ≥ 35 g/l, prothrombin time >13 sec, alphafetoprotein levels >400 ng/ml, and patients with hepatitis B virus. Solitary tumor diameter >10 cm, multi-nodules, and hepatitis B virus ($P < 0.001$) were found to be associated with higher recurrence of HCC. Overall and recurrence-free survival rates were improved after HR compared with those after TACE in BCLC stage B, Child-Pugh A, HCC patients.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most frequently occurring malignant tumor, with 500,000 patients succumbing to the disease globally each year (1,2). Although safe and efficient therapies, including radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and percutaneous ethanol injection have been reported, surgical resection remains the predominant modality applied for the treatment of the majority of patients with HCC patients as a result of advantages, such as low mortality and recurrence rates (3).

Hepatic resection (HR) is based on the tumor stage and the possibility of the preservation of liver function. In accordance with clinicopathologic parameters, several prognostic systems for HCC have been proposed. The most widely known and assessed systems adopted in various countries and areas are TNM (4), Okuda stage (5), Cancer of the Liver Italian Program (CLIP) (6,7), Chinese University Prognostic Index (8) and Barcelona Clinic Liver Cancer (BCLC) (9) and estrogen receptor classification (10). With an advanced capability to consider factors with respect to tumor stage, liver function and physical status, and its provision of treatment recommendations for the corresponding stage, the BCLC classification system is the most widely accepted treatment algorithm (11). Typically, HR is only favorable for the treatment of patients with early-stage HCC who have good liver function, as identified by a single nodule ≤ 5 cm or up to 3 nodules ≤ 3 cm, Child-Pugh A or B and a performance score of 0 (10). RFA and liver transplantation are recommended for patients at the early stage but with poor liver function [portal hypertension/increased

Correspondence to: Professor Le-Qun Li, Department of Hepatobiliary Surgery, Affiliated Tumor Hospital of Guangxi Medical University, 71 Hedi Road, Nanning, Guangxi 530021, P.R. China

E-mail: lequnli@yeah.net

Professor Hai-Hong Ye, Department of Hepatobiliary Surgery, The Affiliated Minzu Hospital of Guangxi Medical University, 232 Mingxiu Road, Nanning, Guangxi 530001, P.R. China

E-mail: haihongye@yeah.net

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total bilirubin (T.BIL)] (12). However, for intermediate-stage patients (a single nodule >5 cm or multi-nodular tumors; Child-Pugh A or B with a performance score of 0, no portal hypertension and distant metastasis) (10), TACE is indicated as the first-choice treatment. With the exception of the Barcelona group, several groups have recommended that BCLC stage B HCC should be considered a contraindication for HR (11,13). However, a number of authors argue that HR offers advantages with respect to patients with large tumors (>5 cm, and as large as >10 cm) and those with multi-nodular HCC (14,15). As a result of the variation in recommendations, the role of surgical resection remains controversial.

The present retrospective study was conducted to clarify the role of surgical resection and evaluate the long-term and recurrence-free survival rates of HR compared with TACE in patients with BCLC intermediate-stage Child-Pugh A HCC.

Patients and methods

Patients. The database from the Affiliated Tumor Hospital and the Affiliated Minzu Hospital of Guangxi Medical University (Nanning, China) was retrospectively reviewed. A total of 1,340 patients with HCC were examined between January 2003 and December 2008. Among the patients analyzed, 669 were diagnosed to be under the resectable intermediate stage (BCLC stage B) and underwent HR or TACE as an initial treatment according to their preference, once they were informed of the surgical risks and presented with the guidelines for HCC treatment. The present study was conducted in accordance with the Declaration of Helsinki, and approval was obtained from the Ethics Committee of the Affiliated Minzu Hospital of Guangxi Medical University. Written informed consent was obtained from all participants.

Among the 669 patients, 323 patients who had Child-Pugh B liver function (n=70), had undergone treatment with RFA (n=26) and pre-operative TACE (n=45) or who were not followed up (n=82), were excluded. Subsequently, 443 patients with resectable intermediate-stage HCC with Child-Pugh A liver function were included, among whom 235 patients with solitary tumor and 9 patients with multi-nodules underwent treatment with HR, and 144 patients with solitary tumor and 25 patients with multi-nodules received TACE.

Diagnosis for all patients with HCC was based on the post-operative pathological findings or the diagnosis and treatment of primary liver cancer standardization expert consensus guidelines as follows: i) Concordant results obtained from two radiology techniques with contrast enhancement in the arterial phase and washout in the venous phase; and ii) typical image findings using an imaging technique, with an alphafetoprotein (AFP) level of >400 ng/ml.

Surgical resection. Indications for surgery in patients with BCLC stage B Child-Pugh A HCC were based on tumor location, number of tumors, absence of ascites, T.BIL <3 mg/dl modified through Makuuchi's principle (16), and an appropriate amount of residual liver volume evaluated by volumetric CT, as previously described (17). Surgery was performed under general anesthesia through a bilateral subcostal incision with midline extension or with reversed L-shaped laparotomy. Intra-operative ultrasound was routinely performed. HR with

a resection margin of ≤ 1 cm was performed, through which the primary tumor was eradicated and no residual tumor remained. Portal vein tumor thrombus, bile duct thrombus, hepatic vein tumor thrombus, and inferior vena cava tumor thrombus were not detected. The Pringle maneuver was used for 15 to 20 min and a 5 min clamp-free interval was performed to reduce blood loss. One or two 10 Fr Jackson-Pratt wound drains were applied after surgery.

TACE. Indications for TACE in patients with BCLC stage B Child-Pugh A HCC were based on the tumor location, number of tumors, absence of ascites, and T.BIL <3 mg/dl. TACE was performed subsequent to a diagnostic hepatic angiography. Contrast medium was injected into the arteries via a 4.1-French RC1 catheter, which was introduced into the abdominal aorta via the right superficial femoral artery using the Seldinger technique. The number, location, and size of tumors, as well as the arterial branches supplying the tumors, were identified. Iodized oil (10-20 ml), gelfoam particles with doxorubicin (30-50 mg) and cis-platinum (50-100 mg) were injected into the arterial branches. A follow-up computed tomography (CT) scan after 3 weeks in order to evaluate the effect of TACE. The TACE procedure was repeated if the tumors did not shrink and if liver function was satisfactory. The number of TACE cycles varied between 1 and 7 cycles.

Follow-up. Serum AFP was routinely measured, and B-mode ultrasound, dynamic CT, or MRI was performed a month after surgery or TACE. The possibility of recurrence was regularly monitored by measuring serum AFP levels every 1 and 3 months. Suspected intrahepatic recurrence was confirmed by dynamic CT and MRI or angiography. Equivocal situations were confirmed by pathological diagnosis through imaging-guided fine-needle aspiration cytology. Patients with recurrence were treated by TACE, RFA, or HR, regardless of their initial treatments. All patients were followed-up until April 2012.

Statistical analysis. Data were statistically analyzed using SPSS statistical software (version 18.0; SPSS, Inc., Chicago, IL, USA). Baseline characteristics between the two groups were compared using the Student's t-test and chi-square test. Survival time was defined as the period between the date of the initial HR or TACE and the date the patient succumbed to HCC, or as the end of the study for patients who survived. Recurrence-free survival was defined as the time from the date of the initial HR or TACE until the date of recurrence, or as the end of the study for patients who did not experience recurrence. Survival rates were estimated using the Kaplan-Meier method and compared using the log-rank test. The relative risks of mortality and recurrence were calculated using Cox's regression model and were compared using the log-rank test. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Baseline characteristics. Baseline characteristics of the 443 patients who underwent HR (n=274) and TACE (n=169) were determined and are presented in Table I. No difference in

Table I. Characteristics and preoperative demographic data for patients with BCLC-B stage Child A HCC patients in the HR and TACE groups.

	HR (n=274)	TACE (n=169)	P-value
Age (years)	45.7±11.9	49.2±12.7	0.144
Male/female	260 (94.9%)/14 (5.1%)	161 (95.4%)/8 (4.6%)	0.905
Tumor size (cm)	8.2±2.4	8.9±2.7	0.101
Tumor number			0.234
=1	235 (85.8%)	144 (85.2%)	
>1	39 (14.2%)	25 (14.8%)	
Total bilirubin (umol/l)	13.5±5.6	14.6±7.3	0.872
Serum albumi (g/l)	39.4±5.8	38.7±5.4	0.585
Alanineamino transferase (U/l)	49.1±25.4	57.2±25.1	0.250
Platelet count (x10 ⁹ , g/l)	208.6±80.7	196.9±88.8	0.527
Prothrombin time(s)	13.3±1.7	13.1±1.8	0.879
Alphafetoprotein (ng/ml)			0.736
≥400	155 (56.8%)	97 (57.7%)	
<400	119 (43.2%)	72 (42.3%)	
Hepatitis B virus			0.778
(+)	228 (83.2%)	137 (81.3%)	
(-)	56 (16.8%)	62 (19.7%)	

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; HR, hepatic resection; TACE, transcatheter arterial chemoembolization.

age, gender, tumor size, tumor number, T.BIL, albumin (ALB), alanine transaminase, blood platelet, prothrombin time, AFP, and hepatitis B surface antigen was found between the HR and TACE groups.

Survival. The 1-, 3- and 5-year overall survival rates and recurrence-free survival rates were 70, 46 and 37%, and 73, 52 and 37% in the HR group compared with 38, 15 and 12%, and 44, 25 and 16%, respectively, in the TACE group. The respective mean overall and recurrence-free survival periods were 31.9 and 32.6 months in the HR group, and 14.3 and 13.4 months in the TACE group. Overall survival ($P<0.0001$; Fig. 1) and recurrence-free survival rates ($P<0.0001$; Fig. 2) were significantly increased in the HR group, compared with the TACE group.

Overall survival was also analyzed in the subgroups. In the multi-nodule group, the respective 1-, 3-, and 5-year overall survival rates were 68, 38 and 30% in the HR group, compared with 36, 10 and 0% in the TACE group. Mean overall survival periods for the HR and TACE groups were 28.1 and 11.5 months, respectively. In the solitary tumor group, the respective 1-, 3-, and 5-year overall survival rates were 71, 50 and 38% in the HR group compared with 41, 22 and 15% in the TACE group. Mean overall survival periods for the HR and TACE groups were 32.6 and 14.8 months, respectively. Overall survival in both the solitary (Fig. 3) and multi-nodule tumor groups (Fig. 4) was significantly longer after HR compared with that of patients who underwent TACE (both $P<0.0001$).

Prognostic factors. Cox regression analysis indicated that the following were independent risk factors for survival: Solitary

tumor diameter >10 cm, the presence of multi-nodules, serum ALB levels ≥ 35 g/l, prothrombin time >13 sec, AFP levels >400 ng/ml, and hepatitis B virus. Therefore, solitary tumor diameter >10 cm, multi-nodules, hepatitis B virus, and TACE ($P<0.001$) are associated with higher recurrence of HCC (Tables II and III).

Discussion

The findings of the present study showed that the respective 1-, 3- and 5-year overall survival rates were 70, 46 and 37% in the HR group, compared with 38, 15 and 12% in the TACE group. The mean overall survival period was 31.9 months in the HR group, compared with 14.3 months in the TACE group. In the subgroup analysis, the 1-, 3- and 5-year overall survival rates were longer after HR than after TACE in both the solitary tumor group (HR, 71, 50, and 38%; TACE, 41, 22, and 15%) and the multi-nodule group (HR, 68, 38, and 30%; TACE, 36, 10 and 0%).

A higher recurrence rate of HCC was observed in the TACE group compared with the HR group. The respective 1-, 3- and 5-year recurrence-free survival rates were 73, 52 and 37% in the HR group, compared with 44, 25 and 16% in the TACE group. The mean recurrence-free survival period was 32.6 months in the HR group compared with 13.4 months in the TACE group. Both overall survival and recurrence-free survival rates were significantly longer in the HR group compared with those of the TACE group. Therefore, these findings indicated that HR may be superior to TACE for the treatment of patients with BCLC intermediate stage Child-Pugh A HCC. However, no difference was observed in the mortality rates during

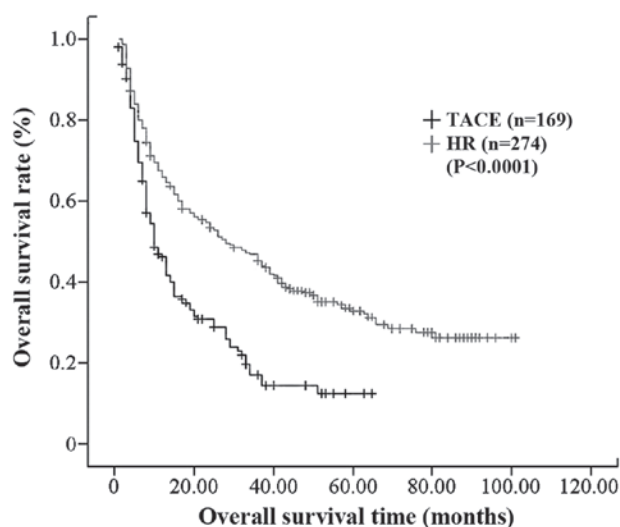


Figure 1. Overall survival curves in the TACE and HR groups. TACE, transcatheter arterial chemoembolization; HR, hepatic resection.

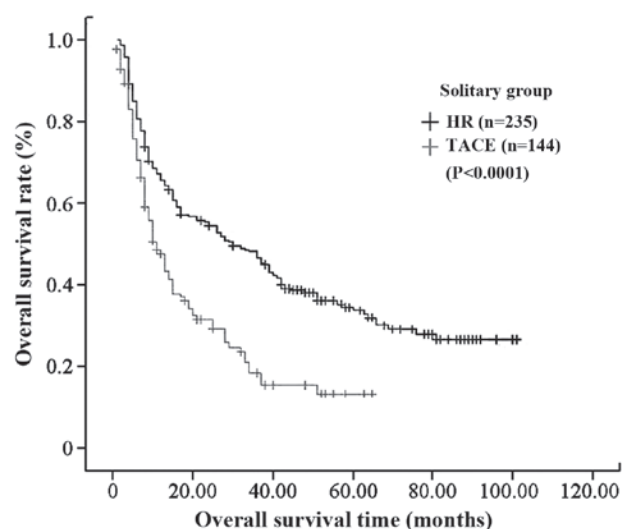


Figure 3. Overall survival curves following TACE or HR in the solitary tumor group. TACE, transcatheter arterial chemoembolization; HR, hepatic resection.

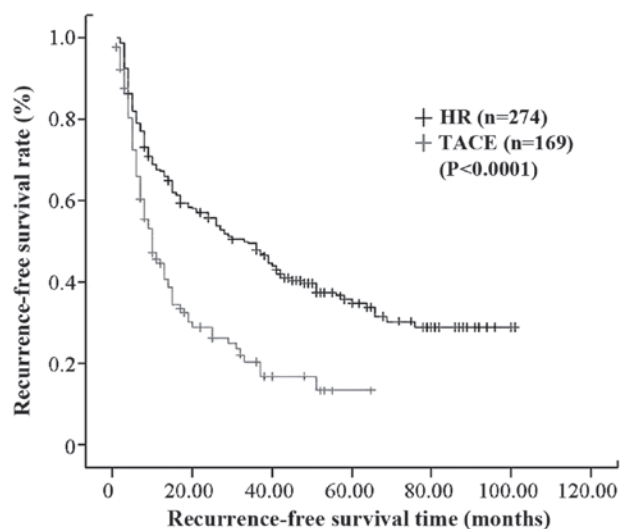


Figure 2. Recurrence-free survival curves in the TACE and hepatic resection groups. TACE, transcatheter arterial chemoembolization; HR, hepatic resection.

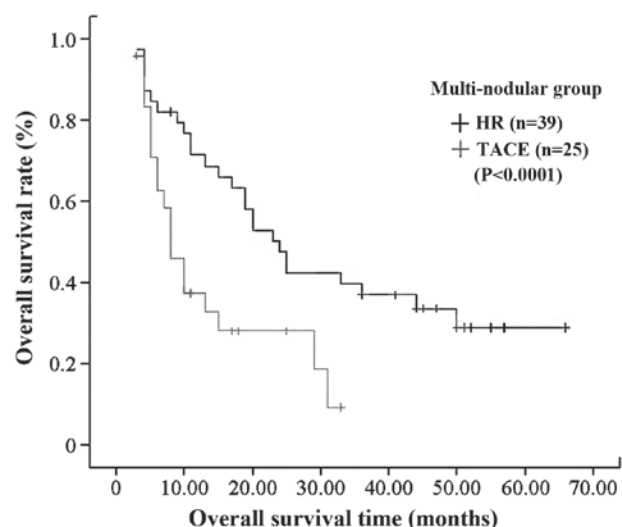


Figure 4. Overall survival curves following TACE or HR in the multi-nodular group. TACE, transcatheter arterial chemoembolization; HR, hepatic resection.

hospitalization between the two groups. The present study found that the treatment modality was an independent prognostic factor of overall survival based on the Cox regression model (HR vs. TACE, RR=1.001; $P=0.025$).

The liver's blood supply is provided by the portal vein and hepatic artery. Typically, ~75% of the blood in the liver is supplied from portal vein, whereas the remaining 25% arrives through the hepatic artery. However, 95-99% of blood in HCC is supplied by the hepatic artery, and only a small amount is provided by the portal vein (18,19). Iodized oil (10-20 ml), gelfoam particles with doxorubicin (30-50 mg), and cis-platinum (50-100 mg) were injected into the arterial branches via TACE in the present study. Based on the fact that lipiodol selectively accumulates in tumors when delivered intra-arterially and is a carrier for anti-cancer drugs, TACE is able to provide direct therapeutic efficacy by blocking vessels that deliver nutrients to tumors, and providing large

doses of sustainable chemotherapy without affecting normal liver cells (20-22). However, TACE is only a palliative treatment, as the vessels delivering nutrients to tumors are not able to be completely blocked as a result of the nutrient vessels from the portal vein. Thus, tumor necrosis is not completely achieved. The risk of tumor recurrence increases as a result of tumor blood vessel collateral circulation. Llovet *et al* (23) revealed that TACE induces extensive tumor necrosis in 30-50% of patients; however, a complete response has only been achieved in <2% of patients. Whether TACE is able to provide a long-term survival benefit has yet to be elucidated, however a number of authors have reported the 5-year overall survival rates for patients with HCC who underwent TACE to be between 6 and 19% (24,25), which is similar to the findings of the present study (12%). However, it has been suggested that repetitive TACE may damage the remnant liver parenchyma,

Table II. Cox regression model for factors associated with survival and recurrence for patients included in the study.

Pre-operative demographic data	RR value	95% for CI	P-value
Mortality			
Age (≥ 60 vs. < 60 years)	0.998	0.989-1.008	0.754
Male vs. female	0.932	0.902-0.981	0.644
Tumor size (> 10 vs. ≤ 10 cm)	1.087	1.039-1.137	< 0.0001
Tumor number ($= 1$ vs. > 1)	1.045	1.012-1.086	0.025
Total bilirubin (> 17.1 vs. ≤ 17.1 $\mu\text{mol/l}$)	1.013	0.993-1.034	0.191
Serum albumin (≥ 35 vs. < 35 g/l)	0.975	0.952-0.997	0.028
Alanine amino transferase (> 40 vs. ≤ 40 U/l)	1.000	0.997-1.002	0.752
Platelet count (> 100 vs. $\leq 100 \times 10^9$ g/l)	1.000	0.998-1.001	0.756
Prothrombin time (> 13 vs. ≤ 13 sec)	1.033	1.001-1.067	0.045
Alphafetoprotein (> 400 vs. < 400 ng/ml)	0.965	0.921-1.001	0.041
Hepatitis B virus (+ vs. -)	0.982	0.936-1.082	0.031
Hepatic resection vs. TACE	1.001	0.998-1.003	0.025
Recurrence			
Age (≥ 60 vs. < 60 years)	1.002	0.971-1.008	0.631
Male vs. female	0.941	0.903-0.981	0.069
Tumor size, cm (> 10 vs. ≤ 10 cm)	1.063	0.989-1.116	< 0.0001
Number of tumors ($= 1$ vs. > 1)	1.042	0.982-1.098	< 0.0001
Total bilirubin (> 17.1 vs. ≤ 17.1 $\mu\text{mol/l}$)	0.951	0.932-0.993	0.326
Serum albumin (≥ 35 vs. < 35 g/l)	1.003	0.986-1.009	0.052
Alanine amino transferase (> 40 vs. ≤ 40 U/l)	0.984	0.961-1.020	0.491
Platelet count (> 100 vs. $\leq 100 \times 10^9$ g/l)	1.005	0.997-1.012	0.738
Prothrombin time (> 13 vs. ≤ 13 sec)	0.966	0.939-0.994	0.352
Alphafetoprotein (> 400 vs. < 400 ng/ml)	0.977	0.935-1.015	0.361
Hepatitis B virus (+ vs. -)	0.962	0.922-0.981	0.048
Hepatic resection vs. TACE	1.065	0.971-1.111	< 0.001

RR, risk ratio; CI, confidence interval; TACE, transcatheter arterial chemoembolization.

particularly in cirrhotic patients, which may result in the impairment or deterioration of liver function (26,27).

By contrast, with the advances made in terms of surgical techniques and pre-operative care, HR remains widely accepted as the standard modality for the treatment of the majority of HCC patients, as it improves their long-term survival (28). A number of scholars believe that patients with HCC with sufficient preservation of the liver function may still be cured (13,29-31). Assessment of the residual liver function is a crucial indicator for HR. HR has been performed in patients with BCLC intermediate stage large and multi-nodular HCC. Lin *et al* (29) reported the 3-year survival rate of patients with BCLC stage B HCC after initial HR to be 49% compared with 2% for patients who underwent TACE. However, the patients in the TACE group exhibited lower serum ALB and larger tumor sizes, resulting in a less favorable prognosis (29). Ng *et al* (11) revealed that HR is efficient and safe for the treatment of patients with HCC with a diameter of > 5 cm or multiple -nodules (> 3). Furthermore, the 5-year survival rate for HCC patients who underwent HR was 39% (13), which was similar to the findings of the present study. Ho *et al* (30) suggested that HR was able to prolong the survival of patients with BCLC-B HCC with multi-nodules compared with TACE.

Wang *et al* (31) retrospectively analyzed the survival time of patients with intermediate stage HCC, and found the 5-year survival rates for patients with HCC BCLC stage-B after initial HR to be 50.5%, compared with 16.9% in patients who received TACE.

The BCLC classification encompasses the tumor stage, liver function, and physical status, as well as the recommendation of treatment modalities for the corresponding stages and is accepted as one of the most reliable staging and treatment strategy systems for HCC (9). Considering the high risk of hepatic decompensation after surgical resection, patients with BCLC intermediate-stage HCC are not suitable candidates for HR. In particular, the livers of patients with cirrhosis have a reduced effective remnant liver volume of regenerative reserve. In the present study, CT or MRI was employed to measure the remnant liver volume of patients with BCLC intermediate stage Child-Pugh A HCC who may be classified as having resectable HCC (20). HR was performed in patients with multi-modal and large tumors (> 5 cm), or if the tumor size was > 10 cm after volumetric CT and MRI scans. With the advancements made with respect to pre-operative measurements and surgical techniques, the current results indicate that HR is a promising option in patients with BCLC intermediate

Table III. Cox regression model for factors associated with the survival and recurrence of hepatic cellular carcinoma in patients included in the present study.

Pre-operative demographic data	RR value	95% CI	P-value
Mortality			
Tumor size (>10 vs. ≤10 cm)	1.087	1.039-1.137	<0.0001
Number of tumors (=1 vs. >1)	1.045	1.012-1.086	0.025
Serum albumin (≥35 vs. <35 g/l)	0.975	0.952-0.997	0.028
Prothrombin time (>13 vs. ≤13 sec)	1.033	1.001-1.067	0.045
Alphafetoprotein (>400 vs. <400 ng/ml)	0.965	0.921-1.001	0.041
Hepatitis B virus (+ vs. -)	0.982	0.936-1.082	0.031
Hepatic resection vs. TACE	1.001	0.998-1.003	0.025
Recurrence			
Tumor size (>10 vs. ≤10 cm)	1.063	0.989-1.116	<0.0001
Tumor number (=1 vs. >1)	1.042	0.982-1.098	<0.0001
Hepatitis B virus (+ vs. -)	0.962	0.922-0.981	0.048
Hepatic resection vs. TACE	1.065	0.971-1.111	<0.001

RR, risk ratio; CI, confidence interval; TACE, transcatheter arterial chemoembolization.

stage Child-Pugh A HCC who have adequate liver function preservation. In particular, HR improves the survival-time and has a lower recurrence rate compared with TACE.

In the present study, Cox regression model analysis revealed that a solitary tumor diameter >10 cm, multi-nodules, serum ALB level ≥35 g/l, prothrombin time >13 sec, AFP level >400 ng/ml, infection with hepatitis B virus, cirrhosis, and the treatment modality (TACE) were independent risk factors for poor survival. Solitary tumor diameter >10 cm, multi-nodules, hepatitis B virus, and TACE were found to be associated with high recurrence. The use of TACE as a therapeutic intervention and predictor of recurrence has generated widespread interest. Xia *et al* (32) indicated that the serum levels of angiogenic factors in post-TACE patients were significantly higher than those of post-operative patients. Serum levels of vascular endothelial cells in patients post-TACE were found to be significantly lower compared with those of post-operative patients. By contrast, HR was more efficacious in terms of preventing the renaissance of vessels and recurrence of HCC.

Although the present study was conducted across two centers, limitations such as selection bias in terms of the patients' choice of treatment between HR and TACE, the different stages of liver function and the tumor location must be noted. Although the present study compared the baseline characteristics and pre-operative demographic data and found no significant difference between the groups with patients with the same stage of liver function, there may still be heterogeneity between the patients (33). Multi-institutional prospective randomized control trials are required to clarify the role of HR for patients with BCLC intermediate stage Child-Pugh A HCC.

The present study demonstrated that HR was superior in terms of resulting in longer overall survival and recurrence-free survival compared with TACE in patients with BCLC intermediate stage Child-Pugh A HCC. Therefore, HR has the potential to be an alternative treatment applied to selected patients with BCLC intermediate stage Child-Pugh A HCC.

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