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Adjuvant transarterial chemoembolization for patients with hepatocellular carcinoma involving microvascular invasion

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ABSTRACT

Background: Microvascular invasion (MVI) has recently been reported to be an independent prognostic factor in patients with hepatocellular carcinoma (HCC). This study compared the outcomes of adjuvant transarterial chemoembolization (A-TACE) after hepatic resection (HR) in patients with HCC involving MVI.

Methods: This prospective study involved 200 consecutive patients with MVI-HCC who underwent HR alone (n = 109) or HR with A-TACE (n = 91).The Kaplan-Meier method was used to compare disease-free survival (DFS) and overall survival (OS).

Results: The two groups showed similar DFS at 1, 2, and 3 years ($P = 0.077$). The A-TACE group showed significantly higher OS than the HR-only group ($P = 0.030$). Subgroup analysis showed that A-TACE was associated with significantly higher DFS and OS among patients with a tumor diameter >5 cm or with multinodular tumors.

Conclusions: A-TACE may improve postoperative outcomes for MVI-HCC patients, especially those with tumor diameter >5 cm or multinodular tumors.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer worldwide and the third most common cause of cancer-related deaths.[1] Liver transplantation is not an accepted conventional treatment for HCC because of scarcity of livers for donation and long waiting times.[2] Therefore hepatic resection (HR) remains the main potentially curative treatment for patients with HCC.[3,4] However, the long term prognosis after resection remains far from satisfactory due to the high incidence of tumor recurrence.[5,6] Many postoperative therapies and/or adjuvant treatments after curative resection have been reported,[7,8] but none of them is recommended by official guidelines.[9–12] Nevertheless, adjuvant transarterial chemoembolization (A-TACE) has been reported to be beneficial for patients with risk factors of recurrence after resection, such as multiple nodules of >5 cm or macrovascular invasion.[3]

One of the most critical factors predictive of HCC recurrence is microvascular invasion (MVI) by aggressive tumors.[13,14] MVI is an independent risk factor of tumor recurrence even in patients with small HCC.[15] Therefore, an efficient adjuvant therapy to prevent HCC recurrence after curative resection is urgently needed. While some small studies have suggested A-TACE as a possible adjuvant therapy, whether it reduces postoperative recurrence and prolongs overall survival in HCC patients with MVI after curative resection is unclear. Therefore, we conducted the present study to evaluate the efficacy of A-TACE for HCC patients with MVI.

Material and methods

Patients

This prospective study analyzed 952 patients diagnosed with

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HCC at the Affiliated Tumor Hospital of Guangxi Medical University between January 2012 and December 2014. Of the 952 HCC patients, 240 had MVI but clinical data were complete for only 200. These 200 patients were divided into a group who underwent HR alone (n = 109) or HR with A-TACE (n = 91).

The present study is not a randomized clinical trial. After hepatic resection, all patients with HCC involving MVI were recommended to receive adjuvant TACE. However, some patients were not received adjuvant TACE because of poor socioeconomic status or personal willingness. This study protocol was approved by medical ethics committee of Guangxi Medical University, and participants provided written informed consent before enrollment.

Patients were included in the study if their HCC and MVI had been diagnosed according to Chinese standardized pathological diagnosis.[16] MVI was defined as tumor embolus detected by microscopy only in the hepatic veins, capsule veins, portal system, or lymphatic ducts of the surrounding liver tissue. To be included, patients also had to have Child-Pugh A or B functional liver status, and they had to undergo curative resection as defined by removal of all tumor lesions, based on macroscopic inspection and negative histology resection margin; no residual tumor or portal tumor thromboses detected in postoperative imaging; and decrease of alpha-fetoprotein (AFP) levels to normal within 2 months after surgery.

Patients were excluded if they had any other malignancies, distant metastasis, lymph node involvement, or macrovascular invasion. They were also excluded if they had undergone previous HCC treatment before hepatic resection. In effect, these study criteria meant that all participants had Barcelona Clinic Liver Cancer (BCLC)-A or −B disease.

Surgical procedures

Indications for HR were absence of ascetic fluid, hepatic encephalopathy, hypersplenism, and the presence of sufficient residual liver volume, as determined by volumetric computed tomography (CT). Resection was performed as described.[17,18]

A-TACE

The Seldinger technique of A-TACE was performed as described[17,18] at one month after HR.2.A 4F-to-5F French catheter was introduced into the abdominal aorta via the right femoral artery using the Seldinger technique. Hepatic angiography was performed to detect any obvious tumor stains in the remnant liver. An emulsion of oxaliplatin or lobaplatin (25–100 mg), pirarubicin or pharmorubicin (10–50 mg), and lipiodol (2–10 mL) then was infused through the catheter. A-TACE outcomes were evaluated at 1-month follow-up by CT.

Follow-up

All patients were followed up every 2–3 months for the first two years after discharge from the hospital, and then every 3–6 months. Serum AFP levels, routine blood counts, liver and kidney functions, and prothrombin time (PT) were measured. Imaging examinations such as ultrasound, CT, or magnetic resonance imaging (MRI) was used to detected tumor recurrence or metastastic lesions. When HCC recurrence was confirmed, patients were treated aggressively with repeated hepatectomy, TACE, radiofrequency ablation, or percutaneous ethanol injection, depending on the number and diameter of the recurrent tumors as well as on liver function status.

Statistical analysis

Primary outcome measures included disease-free survival (DFS) rate and overall survival (OS) rate. Continuous data were expressed as mean ± SD. Baseline differences between the two groups were assessed for significance using the Student's *t*-test in the case of continuous variables, or the Mann–Whitney *U* test in the case of nonparametric variables. Categorical variables were compared using the chi-squared test or Fisher's exact test, and continuous variables were compared using Student's *t*-test. Survival analysis was performed by the Kaplan-Meier method and inter-group differences were assessed using the log-rank test. Uni- and multivariate analysis were used to identify prognostic risk factors of poor DFS and OS. All analyses were performed with SPSS 19.0 (IBM, Chicago, IL, USA), and $P < 0.05$ was considered significant.

Results

Patient characteristics

We conducted a prospective analysis of 952 patients (median age, 48 yr; range, 25 to 76) newly diagnosed with HCC at our hospital between January 2012 and December 2014. Of the 952 HCC patients, 317 had macrovascular invasion; 74 had distant metastasis; 118 lost to follow-up or data missing. For the rest of 443 patients, 200 had MVI only and 2430 without MVI. These 200 patients were divided into a group who underwent HR alone (n = 109, 54.5%) or HR with A-TACE (n = 91, 45.5%).

Eleven patients did not receive A-TACE after one month of resection because of postoperative complications. Postoperative complication included bile leakage (n = 2), liver damaged (n = 8) and wound infection (n = 1). These 11 patients were allocated to the HR alone group.

The two groups were comparable in baseline demographic data, tumor factors and preoperative liver function (Table 1). There were no significant differences between the two groups in age, gender, alanine aminotransferase (ALT) level, aspartate aminotransferase (AST) level, tumor capsule, tumor number, tumor diameter, intraoperative blood loss, tumor differentiation, serum albumin, platelet count, prothrombin time, serumtotal bilirubin, AFP level, HBs-Ag positivity, pancreatic transpeptidase level, or proportions of BCLC stages.

Survival analysis

Postoperative outcomes were comparable between the two groups. Median DFS was 11 months (range, 2–36) and median OS was 24 months (range, 4–36). Of the 200 patients, 30 died during follow-up, comprising 22 in the HR group and 8 in the A-TACE group. HCC recurred in 111 patients during follow-up, comprising 66 in the HR group and 45 in the A-TACE group.

Of the 200 patients, DFS rates in the HR group (109 patients) were 46.1% at 1 year, 31.7% at 2 years, and 16.7% at 3 years. The corresponding rates in the A-TACE group (91 patients) were 64.1, 27.9, and 24.4%. These two sets of DFS rates did not differ significantly ($P = 0.077$, Fig. 1A). In contrast, median OS was significantly lower for the HR group than for the A-TACE group at 1 year (89.6 *vs* 96.6%), 2 years (80.4 *vs* 91.6%), and 3 years (76.5 *vs* 89.2%; $P = 0.030$; Fig. 1B).

Subgroup analysis

Potential differences in survival between HR and A-TACE patients were explored by stratifying patients according to several risk factors for HCC recurrence, including multinodular HCC, tumor

Table 1
Clinicopathological characteristics of 200 patients with MVI-HCC.

Characteristic	HR group (n = 109)	A-TACE group (n = 91)	*P* value
Gender (Male/Female)	93/16	78/13	0.973
Age (≤50/>50 years)	67/42	52/39	0.535
Tumor size (≤5/>5 cm)	34/75	20/71	0.144
Tumor number (Single/Multiple)	84/25	68/23	0.700
BCLC stage (A/B)	76/33	54/37	0.125
Tumor capsule (Complete/Incomplete)	61/48	59/32	0.202
Blood loss (≤500/>500 mL)	89/20	73/18	0.797
Margins of resection (narrow/wide)	67/42	57/34	0.865
Extent of liver resection (major/minor)	22/87	12/79	0.190
AST (≤40/>40 U/L)	56/53	49/42	0.728
ALT (≤40/>40 U/L)	67/42	58/33	0.741
ALB (≤35/>35 g/L)	9/100	3/88	0.241
Total bilirubin (≤17.1/>17.1 μmol/L)	90/19	74/17	0.819
Prothrombin time (≤13/>13 s)	83/26	72/19	0.616
AFP (<400/≥400 ng/mL)	59/50	47/44	0.726
GGT (<50/≥50 U/L)	38/71	33/58	0.837
Platelet count (<100/≥100 × 10^9/L)	9/100	5/86	0.628
Hepatitis B status (Positive/Negative)	96/13	77/14	0.476
Liver cirrhosis (Absent/Present)	20/89	12/79	0.321

AbbreviationsAFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; A-TACE group, patients who received HR followed by adjuvant transarterial chemoembolization; BCLC, Barcelona Clinic Liver Cancer staging system; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; HR group, patients who received hepatic resection without A-TACE; MVI, microvascular invasion.

diameter >5 cm, intraoperative blood loss >500 mL, BCLC-B stage, prothrombin time >14 s, AST >40 U/L levels, and incomplete tumor capsule.

Among patients with tumor diameter >5 cm, median DFS was significantly lower in the HR group than in the A-TACE group at 1 year (38.2 *vs* 60.3%), 2 years (22.9 *vs* 24.8%), and 3 years (8.6 *vs* 24.8%; $P = 0.008$; Fig. 2A). Similarly, the corresponding median OS was also significantly lower in the HR group at 1 year (86.2 *vs* 95.7%), 2 years (75.5 *vs* 92.2%) and 3 years (69.0 *vs* 92.2%; $P = 0.033$; Fig. 2B).

Among patients with multinodular HCC, DFS rates were significantly lower in the HR group than in the A-TACE group at 1 year (30.9 *vs* 56.7%), 2 years (9.3 *vs* 7.6%), and 3 years (0 *vs* 7.6%; $P = 0.036$; Fig. 3A). Similarly, OS was significantly lower in the HR group at 1 year (87.0 *vs* 95.7%), 2 years (72.9 *vs* 95.7%) and 3 years (72.9 *vs* 95.7%; $P = 0.047$; Fig. 3B).

Significant differences in DFS or OS at 1–3 years were not found between HR and A-TACE subgroups who experienced intraoperative blood loss >500 mL, or who had BCLC-B disease, prothrombin time >14 s, AST >40 U/L, or incomplete tumor capsule.

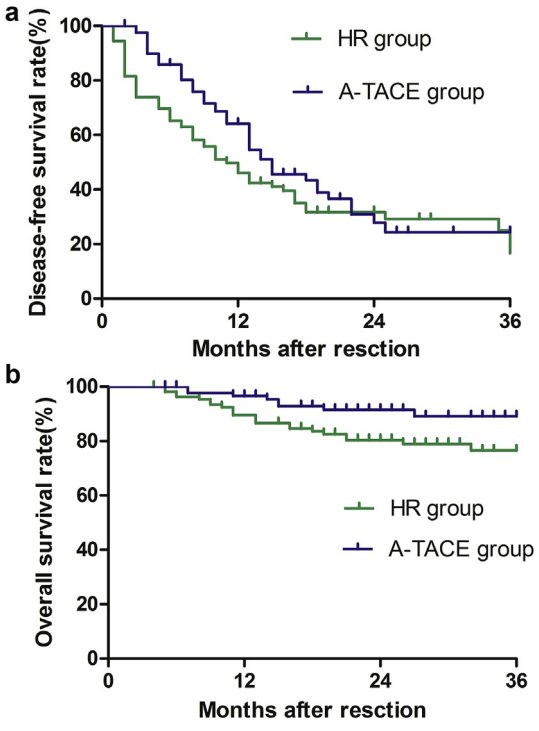

Fig. 1. Kaplan-Meier analysis of (A) disease-free survival ($P = 0.077$) and (B) overall survival ($P = 0.030$) among all patients.

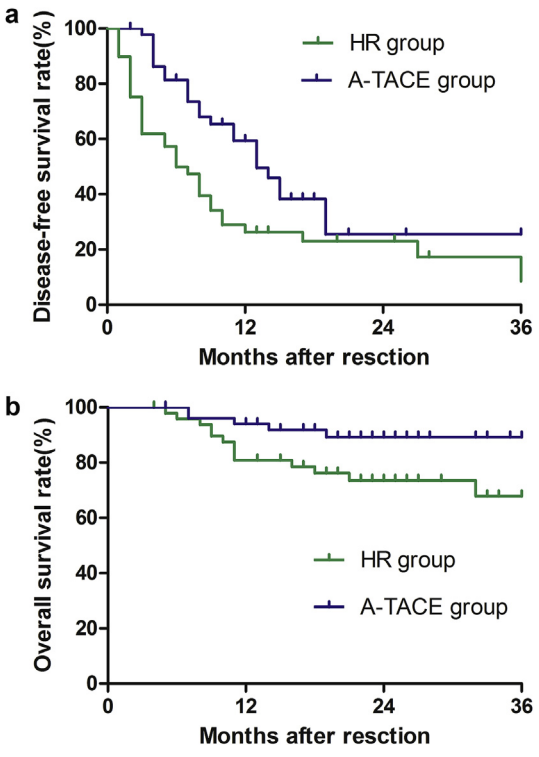

Fig. 2. Kaplan-Meier analysis of (A) disease-free survival ($P = 0.008$) and (B) overall survival ($P = 0.033$) among patients with tumor diameter >5 cm.

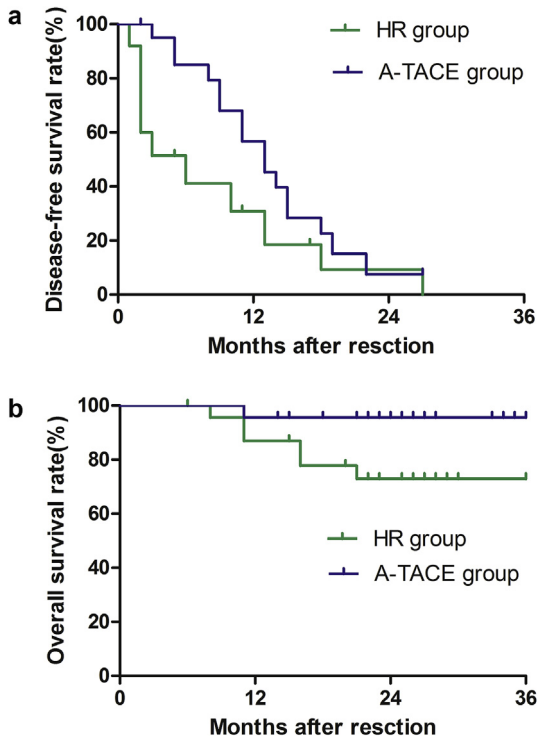

Fig. 3. Kaplan-Meier analysis of (A) disease-free survival ($P = 0.036$) and (B) overall survival ($P = 0.047$) among patients with multinodular tumors.

Prognostic factors

Univariate analysis identified the following predictors of poor DFS following hepatic resection in HCC patients with MVI: multinodular HCC, tumor diameter >5 cm, intraoperative blood loss >500 mL, BCLC-B disease, and AST >40 U/L. Tumor diameter >5 cm and intraoperative blood loss >500 mL were also identified by multivariate analysis (Table 2).

Univariate analysis identified the following predictors of poor OS: A-TACE, prothrombin time >14 s, AST >40 U/L, and incomplete tumor capsule. Multivariate analysis identified prothrombin time >14 s, AST >40 U/L levels and incomplete tumor capsule as independent risk factors of OS (Table 3).

Adverse reactions of adjuvant TACE

There was no major complication after A-TACE. On the 2nd postprocedure day, total bilirubin (25.1 ± 5.7 μmol/L) in 6 patients, ALT (107.5 ± 73.4 U/L) and AST (104.6 ± 66.4 U/L) in 26 patients transiently increased. There were 9 cases with different degrees of local pain, 4 cases with different degrees of fever (37.6–38.4 °C). After treatments, all these complications were alleviated. The morbidity rate of A-TACE was 42.86% (39/91).

Discussion

HR remains the most important curative treatment for patients with HCC, but postoperative HCC recurrence remains a major obstacle to good prognosis.[19] Although MVI occurs in up to 50% of HCC cases and is the most frequent risk factor for postoperative recurrence,[4,15] few studies have examined preventive treatments against postoperative recurrence in HCC patients with MVI.

Various treatments to prevent recurrence of HCC in general are used in the clinic, including immunotherapy, TACE, and targeted molecular therapy,[5] with TACE being the most frequently used postoperative treatment.[20] In TACE, a large amount of iodized oil and chemotherapy drugs are injected into the hepatic artery, which supplies the tumor.[6] Previous work has suggested that A-TACE does not offer significant prognostic benefit to MVI-HCC patients,[21] whereas another study suggested that A-TACE can reduce tumor recurrence in such patients.[6] Our results suggest that A-TACE may improve postoperative OS without improving DFS. The survival benefit of A-TACE was particularly evident among MVI-HCC patients with recurrence risk factors, such as tumor diameter >5 cm and multinodular disease.

Our data are consistent with the idea that A-TACE can significantly decrease early recurrence in MVI-HCC patients (Fig. 1A). Early recurrence may be a highly malignant type of recurrence pattern associated with poor survival after HR.[22,23] It may be that A-TACE significantly improves OS of MVI-HCC patients by decreasing early recurrence. This may also explain why the survival benefit of A-TACE was greater among patients with tumor size >5 cm and

Table 2
Uni- and multivariate analysis to identify risk factors of disease-free survival among MVI-HCC patients.

Variable	Univariate analyses	*P*	Multivariate analysis	*P*
	HR (95% CI)		HR (95% CI)	
Gender (Male)	0.957 (0.535–1.713)	0.883		
Age >50 years	1.126 (0.771–0.646)	0.539		
Tumor size > 5 cm	1.936 (1.226–3.057)	0.005	1.647 (1.024–2.648)	0.040
Tumor number (Multiple)	1.967 (1.311–2.952)	0.001	1.539 (0.851–2.783)	0.154
BCLC stage B	1.883 (1.291–2.746)	0.001	1.327 (0.758–2.320)	0.322
Tumor capsule (Incomplete)	1.065 (0.726–1.561)	0.748		
Blood loss >500 mL	2.163 (1.376–3.402)	0.001	1.730 (1.082–2.766)	0.022
AST > 40 U/L	1.468 (1.010–2.133)	0.044	1.248 (0.848–1.838)	0.261
ALT > 40 U/L	1.013 (0.695–1.476)	0.947		
ALB ≤ 35 g/L	0.637 (0.322–1.262)	0.196		
Total bilirubin >17.1 μmol/L	1.067 (0.669–1.704)	0.785		
Prothrombin time >14 s	0.858 (0.533–1.381)	0.528		
AFP ≥ 400 ng/mL	1.145 (0.788–1.664)	0.478		
GGT ≥ 50 U/L	1.374 (0.903–2.089)	0.138		
Platelet count < 100×10^9/L	1.321 (0.666–2.618)	0.425		
Hepatitis B status (Positive)	1.354 (0.706–2.597)	0.362		
Liver cirrhosis (Present)	1.243 (0.721–2.143)	0.434		
A-TACE	0.715 (0.489–1.045)	0.083		

AbbreviationsAFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer staging system; GGT, gamma-glutamyl transferase.

Table 3
Uni- and multivariate analysis to identify risk factors of overall survival among MVI-HCC patients.

Variable	Univariate analyses	*P*	Multivariate analysis	*P*
	HR (95% CI)		HR (95% CI)	
Gender (Male)	0.855 (0.298–2.450)	0.770		
Age > 50 years	1.467 (0.717–3.002)	0.294		
Tumor size > 5 cm	1.700 (0.694–4.165)	0.246		
Tumor number (Multiple)	0.985 (0.422–2.296)	0.972		
BCLC stage B	0.976 (0.456–2.088)	0.950		
Tumor capsule (Incomplete)	2.757 (1.312–5.796)	0.007	2.179 (1.027–4.623)	0.042
Blood loss > 500 mL	0.505 (0.153–1.664)	0.261		
AST > 40 U/L	2.338 (1.094–4.995)	0.028	2.161 (1.008–4.630)	0.048
ALT > 40 U/L	1.051 (0.506–2.181)	0.895		
ALB $\leq$ 35 g/L	0.802 (0.191–3.372)	0.764		
Total bilirubin >17.1 μmol/L)	1.436 (0.616–3.348)	0.402		
Prothrombin time > 14 s	3.096 (1.496–6.293)	0.002	2.623 (1.027–4.623)	0.009
AFP $\geq$ 400 ng/mL	1.226 (0.599–2.509)	0.576		
GGT $\geq$ 50 U/L	1.348 (0.617–2.943)	0.454		
Platelet count < 100×10^9/L	0.534 (0.186–1.535)	0.244		
Hepatitis B status (Positive)	1.446 (0.439–4.768)	0.544		
Liver cirrhosis (Present)	1.809 (0.549–5.966)	0.330		
A-TACE	0.422 (0.188–0.974)	0.036	0.472 (0.210–1.062)	0.070

Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer staging system; GGT, gamma-glutamyl transferase.

multinodular tumors, since these two factors are thought to facilitate the formation of micro-metastases that give rise to early recurrence.[24,25]

A-TACE has advantages over other anti-recurrence therapies. Its route of administration into the hepatic artery may make it particularly effective at controlling micro-metastases and killing residual cancer cells, and may help reduce systemic side effects.[26,27] At the same time, the high local delivery of chemotherapy drugs can kill normal liver cells as well as tumor cells, thus damaging residual liver function and depressing host immunity.[28,29] In addition, A-TACE is associated with higher incidence and earlier development of extra-hepatic metastases.[30] These factors should be considered when deciding whether to recommend A-TACE for patients with HCC involving MVI.

The results of this study should be interpreted with caution given that the data came from a single site. A multicenter, randomized clinical trial should be conducted in order to verify and extend our results on the impact of A-TACE for patients with MVI-HCC. Such work should aim to recruit a larger sample and follow them up for a longer period.

Despite these limitations, our study provides strong evidence that combining HR with subsequent A-TACE may lead to better OS of MVI-HCC patients (although not better DFS) than HR alone. This survival benefit was particularly evident among patients with poor prognostic risk factors. Our findings suggest that A-TACE should be considered as a potentially effective treatment to improve prognosis of MVI-HCC patients at risk of poor survival.

Disclosures

The authors declare that there are no financial and personal relationships with other people or organizations that can inappropriately influence this article.

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