



Efficacy and safety of apatinib combined with transarterial chemoembolization (TACE) in treating patients with recurrent hepatocellular carcinoma

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Background: Apatinib, a vascular endothelial growth factor receptor 2 (VEGFR-2) inhibitor, has shown promising therapeutic effect for hepatocellular carcinoma (HCC). This prospective clinical study was implemented to evaluate the efficacy and safety of apatinib combined with transarterial chemoembolization (TACE) versus TACE alone in treating patients with recurrent HCC after hepatectomy.

Methods: Eligible patients with postoperative recurrent HCC from January 2018 to January 2020 were enrolled at the Xinqiao Hospital of Army Medical University. Patients were randomized 1:1 into TACE plus apatinib group or TACE-alone group. The clinical information of patients was collected, and the patients were followed up until untreatable progression or the end of the study. Adverse events (AEs), overall survival (OS) and progression-free survival (PFS) between the two groups were evaluated. In addition, the objective response rate (ORR) and the disease control rate (DCR) were determined according to the modified Response Evaluation Criteria In Solid Tumors (mRECIST). Among those indexes, PFS was the primary endpoint.

Results: This study enrolled 80 patients with recurrent HCC, and the demographics and primary tumor characteristics were balanced between the two groups. However, TACE plus apatinib treatment could significantly improve the median PFS of patients when compared with the TACE-alone group (17.2 *vs.* 12.5 months, $P=0.041$). The 1- and 2-year overall survival (OS) rates showed a tendency of improving in the TACE plus apatinib group, but not significantly (95.0% *vs.* 85.0%, and 90.0% *vs.* 75.0%; both $P>0.05$). Furthermore, the TACE plus apatinib treatment did significantly increase the short-term ORR and DCR when compared with the TACE-alone group (all $P<0.05$). And no unexpected toxicity or procedure-related mortality was occurred during this study.

Conclusions: The combination treatment of apatinib and TACE might be safe and of potential benefit on patients with intrahepatic recurrent HCC.

Keywords: Hepatocellular carcinoma (HCC); transarterial chemoembolization (TACE); apatinib

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Introduction

Hepatocellular carcinoma (HCC) is one of the fastest growing malignant diseases in the world (1,2). Despite the efforts made towards achieving a long-term cure, postoperative tumors recur in more than 50% patients within 5 years (3). This necessitates further treatment by performing re-resection or salvage transplantation (4,5). However, not all patients are amenable to further surgery due to limited preservation of liver function, difficult tumor location, and/or unavailability of liver transplantation.

Transarterial chemoembolization (TACE) has been developed as a readily available treatment option with good tolerance, limited liver toxicity, and demonstrated efficacy for intermediate-stage HCC, even in recurrent patients with borderline liver function (5-7). However, the local hypoxia environment caused by interventional embolization could stimulate tumor angiogenesis and increase the expression of vascular endothelial growth factor (VEGF), which in turn promotes tumor recurrence and metastasis (8,9). Short-term tumor progression has been reported in some patients after TACE treatment, and the overall effect remains unsatisfactory (8,10). Therefore, it is reasonable that the therapy of TACE combined with anti-angiogenic drugs would be conducive to augment the clinical benefit of TACE alone.

Apatinib, a novel oral anti-angiogenic small molecule that blocks VEGFR-2, has been approved as a 3rd line or beyond therapy in treating patients with advanced gastric or gastroesophageal junction adenocarcinoma in China (11). Studies have shown the promising therapeutic potential of apatinib on various types of cancers, including HCC (12,13). Moreover, the strategy of apatinib combined with TACE has been elaborated to be safe and effective on patients with intermediate or advanced HCC (14-18). Nevertheless, there was no study have focused on evaluating the efficacy of TACE plus apatinib in treating patients with postoperative recurrent HCC.

Therefore, this prospective clinical study was conducted to evaluate the efficacy and safety of TACE with apatinib versus TACE alone in treating patients with recurrent HCC.

We present the following article in accordance with the CONSORT reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-7244>).

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Methods

Participants

Patients with recurrent HCC defined by clinical, biochemical, and imaging evaluation between January 2018 and January 2020 at the Xinqiao Hospital of Army Medical University, were randomized (1:1) into TACE plus apatinib group or TACE-alone group by using the block randomization method. No patient was allowed to switch groups once randomized. The clinical information of the patients was prospectively collected, and all participants were followed up until the end of the study or untreatable progression, which was defined as untreatable tumor progression, transient deterioration to Child-Pugh C, or appearance of vascular invasion/extra-hepatic metastases. The study was registered on the Chinese Clinical Trial Registry (<http://www.chictr.org.cn>; no. ChiCTR-IPR-17012667). All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The protocol was approved by the China Ethics Committee of Registering Clinical Trials (ethics committee approval no. ChiECRCT-20170060). And all the patients provided written informed consent before enrollment.

Inclusion and exclusion criteria

Eligible patients needed to meet the following criteria: (I) aged 18 years or older; (II) diagnosed with HCC by two imaging modalities or biopsy; (III) intrahepatic recurrence after hepatic resection; (IV) Barcelona Clinic Liver Cancer (BCLC) stage B/C; (V) Child-Pugh class A/B; (VI) could not tolerate or refuse performing re-resection or salvage transplantation; (VII) adequate organ function; (VIII) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-2; and (IX) no vascular invasion or extra-hepatic metastasis. Patients were excluded if they met any of the following criteria: (I) combined use of other anticancer therapy after the surgery; (II) accompanied by other malignancies; (III) severe coagulation disorders; (IV) serious medical comorbidity; and (V) a large amount of ascites or refractory ascites.

Therapeutic methods

TACE procedure

TACE was performed following a previously reported method (14). Briefly, the modified Seldinger technique was used for hepatic artery catheterization. Both superior mesenteric and common hepatic arteriography were performed with a 5- or 4-F catheter to assess the overall anatomy, tumor burden, and the patency of the portal vein. Next, conventional super-selective catheterization was carried out for the hepatic artery and other feeding arteries. Then, hepatic artery infusion chemotherapy was performed using 50 mg of lobaplatin (Hainan Changan International Pharmaceutical Co., Ltd., Hainan, China). Subsequently, chemoembolization was performed with 50 mg of epirubicin (Shenzhen Wanle Pharmaceutical Co., Ltd., Guangdong, China) mixed with 5–10 mL of ethiodized oil (Jiangsu Hengrui Medicine Co., Ltd., Jiangsu, China), followed by the application of 8Spheres microspheres 100–300 μm in diameter (Jiangsu Hengrui Medicine Co., Ltd., Jiangsu, China), until blood flow in the feeding arteries stagnated. The dose of ethiodized oil was determined by the surgeon according to tumor size, blood supply of tumor, and other factors. In order to prevent nausea and vomiting after each TACE procedure, symptomatic treatments were applied to protect the gastric and liver function. Further TACE were performed on an “on-demand” basis as previously reported (19).

Apatinib administration

Oral apatinib (Jiangsu Hengrui Medicine Co., Ltd., Jiangsu, China) at a dose of 500 mg qd was given to patients in the TACE plus apatinib group beginning the third day after the first TACE treatment and was suspended 3 days before and after the following TACE treatment procedure. Dosage modified to 250 mg qd or temporary interruption were permitted in patients with grade 3–4 adverse events (AEs) or treatment-related intolerance until the adverse symptoms remitted to a grade ≤ 2 . Medication of apatinib was continued until significant disease progression, drug intolerance, consent withdrawal, or patient death.

Clinical and laboratory evaluation

The entire medical history and related records of each patient were collected. The clinical data included age, gender, ECOG PS and Child-Pugh score, BCLC stage and recurrence time. The laboratory data included α -fetoprotein (AFP), and hepatitis B surface antigen (HBsAg) status.

Moreover, imaging data concerning tumor size and tumor number were collected through abdominal contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI).

To assess the tumor response, evaluation by CT/MRI every 4–12 weeks after TACE treatment was administrated according to the modified response evaluation criteria in solid tumors (mRECIST, 2008). In addition, the overall survival (OS, defined as the interval between the first TACE procedure and the time of all-cause death) and PFS (defined as the time from the first TACE procedure to disease progression or all-cause death) were appraised in the two groups, while PFS was the primary endpoint. Toxicities were assessed on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, and all serious AEs and their severities were recorded.

Sample size

The sample size was based on the primary efficacy endpoint, PFS. The expected median PFS for TACE plus apatinib and TACE alone was assumed to be 18 and 10 months, respectively. The allocation ratio was 1:1. The required number of patients was 80 with a dropout rate of 10% to achieve 80% power at a one-sided α value of 0.15.

Statistical analysis

All statistical analyses were conducted using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean \pm standard deviation or median (first-third quartile), and were compared with an independent *t*-test or Mann-Whitney U test. Categorical variables are expressed as percentage (number/total), and were compared with chi square or Fisher's exact test. Survival curves were plotted for both groups using Kaplan-Meier analysis with the log-rank test. All statistical analysis was based on a two-tailed hypothesis test and a P value < 0.05 was considered statistically significant.

Results

Clinical characteristics

Between January 2018 and January 2020, 80 patients with recurrent HCC who met the selection criteria were included in the present study and randomly assigned to TACE plus apatinib (n=40) group or TACE-alone group

(n=40). The two groups showed no significant differences in baseline demographic or laboratory characteristics, including age, gender, Child-Pugh classification, ECOG PS, BCLC stage, level of AFP, tumor number, tumor size, hepatic cirrhosis, hepatitis B, and recurrence time (Table 1).

PFS and OS

The median PFS was significantly improved in the TACE plus apatinib group compared with the TACE-alone group [17.2 months, 95% confidence interval (CI): 13.6–20.8 vs. 12.5 months, 95% CI: 11.3–13.7, hazard ratio (HR) =0.563, 95% CI: 0.336–0.943, P=0.041] (Figure 1). At the end of the follow-up, more patients survived in the TACE plus apatinib group than in the TACE-alone group [90.0% (36/40) vs. 75.0% (30/40)], but the median OS has not yet been reached in either group, and the differences were not statistically significant (HR =0.360, 95% CI: 0.113–1.150, P=0.072) (Figure 2). The 1- and 2-year OS rates in the two groups were 95.0% vs. 85.0% (P=0.136) and 90.0% vs. 75.0% (P=0.077), respectively.

Tumor response

Changes could be observed before and after TACE procedure in tumors in both groups on abdominal contrast-enhanced CT or MRI scans (Figure 3A,B,C,D,E,F,G,H). At 1 month and 3 months after the treatment, the tumor responses of all patients were evaluated in both groups according to the mRECIST (Table 2). None of the patients achieved complete response (CR). The TACE plus apatinib group had a significantly higher 1-month objective response rate (ORR) and 1-month disease control rate (DCR) than the TACE group (75.0% vs. 50.0%, P=0.021; 90.0% vs. 72.5%, P=0.045, respectively) (Table 2); and the 3-month ORR and DCR showed similar trends (55.0% vs. 32.5%, P=0.043 and 75.0% vs. 52.5%, P=0.036, respectively) (Table 2).

AEs

Two categories of AEs were considered in this study: postembolization syndrome (PES) and apatinib-related AEs. Features of PES typically include fever, abdominal pain, nausea and vomiting, and myelosuppression. No significant difference was found in the incidence of PES between the two groups (all P>0.05) (Table 3).

The incidence of apatinib-related AEs was 80.0% (32/40)

in the TACE plus apatinib group (Table 3). Treatment-related AEs in the TACE plus apatinib group included the following: hand-foot syndrome (16/40, 40.0%), hypertension (11/40, 27.5%), fatigue (10/40, 25.0%), diarrhea (9/40, 22.5%), oral ulcer (9/40, 22.5%), and proteinuria (6/40, 15.0%). The majority of toxicities were grade 1–2, which is consistent with the known toxicities associated with apatinib. Once the patients developed grade 3 AE, the dose of apatinib was reduced from 500 mg qd to 250 mg qd until remission of symptoms, and the patients could then resume apatinib at 500 mg per day.

Thus, no patient developed grade 4 toxicity. Nevertheless, the addition of apatinib to TACE significantly increased the incidence of apatinib-related complications compared to treatment with TACE alone (all P<0.05, Table 3). No unexpected toxicity or procedure-related mortality was observed in either group, and all AEs were effectively alleviated after symptomatic treatment.

Discussion

HCC recurrence is a critical failure for patients treated with surgical resection (20). Various therapies, such as re-resection, salvage liver transplantation, TACE, radiofrequency ablation, radiotherapy, and systemic therapy (sorafenib or FOLFOX4 chemotherapy) have been applied for intrahepatic tumor recurrence after hepatic resection, and comparisons among these treatment modalities have been reported (4,5,7,21,22). However, there is currently no agreement on a standard guideline in clinical practice for intrahepatic recurrent HCC after hepatectomy.

TACE has been used as a common treatment for recurrent HCC when tumors are unresectable or transplantation is infeasible by virtue of its strong cytotoxic and ischemic antitumor effect, minimal invasiveness, and repeatability (7,23). On the other hand, TACE may promote an embolization-induced local hypoxic environment which can in turn cause neovascularization in tumors (8,9). Previous studies also confirmed that the overexpression of an angiogenic factor, VEGF, could promote recurrence and metastasis in remnant peripheral tumor tissues (24,25). Therefore, inhibiting VEGF pathway may be a crucial strategy for improving the long-term benefit of patients treated with TACE.

Sorafenib is an anti-angiogenic agent, which inhibits multi-kinases, inhibiting RAF kinase, VEGFR-2, VEGFR-3, and PDGFR-b tyrosine kinase in particular. It has been the first-line option for use as an oral targeted

Table 1 Baseline characteristics of the two groups

Characteristic	TACE group (n=40)	TACE plus apatinib group (n=40)	P value
Age, median [year]	51 [33–67]	53 [31–68]	0.438
Gender, n (%)			0.502
Male	22 (55.0)	19 (47.5)	
Female	18 (45.0)	21 (52.5)	
Child-Pugh classification, n (%)			0.531
A	35 (87.5)	33 (82.5)	
B	5 (12.5)	7 (17.5)	
ECOG PS, n (%)			0.576
0–1	31 (77.5)	33 (82.5)	
2	9 (22.5)	7 (17.5)	
BCLC stage, n (%)			0.330
B	33 (82.5)	36 (90.0)	
C	7 (17.5)	4 (10.0)	
Level of AFP ($\mu\text{g/L}$), n (%)			0.108
<400	12 (30.0)	19 (47.5)	
\geq 400	28 (70.0)	21 (52.5)	
Tumor number, n (%)			0.370
Single	17 (42.5)	21 (52.5)	
Multiple	23 (57.5)	19 (47.5)	
Tumor size (cm), n (%)			0.606
<5	29 (72.5)	31 (77.5)	
\geq 5	11 (27.5)	9 (22.5)	
Hepatic cirrhosis, n (%)			0.502
Yes	21 (52.5)	18 (45.0)	
No	19 (47.5)	22 (55.0)	
Hepatitis B, n (%)			0.617
Yes	30 (75.0)	28 (70.0)	
No	10 (25.0)	12 (30.0)	
Recurrence time (year), n (%)			0.256
<1	26 (65.0)	21 (52.5)	
\geq 1	14 (35.0)	19 (47.5)	

TACE, transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; PS, performance score; BCLC, Barcelona Clinic Liver Cancer; AFP, α -fetoprotein.

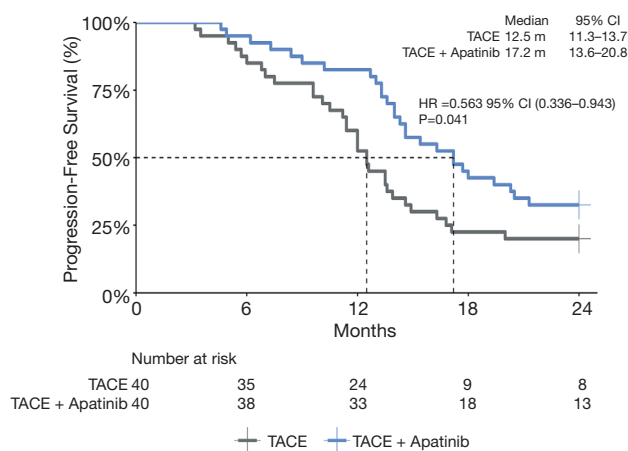


Figure 1 Progression-free survival (PFS) in the transarterial chemoembolization (TACE) plus apatinib and TACE-alone groups. The Kaplan-Meier analysis was used to evaluate PFS in patients. The log-rank test was used to compare treatments. CI, confidence interval; HR, hazard ratio.

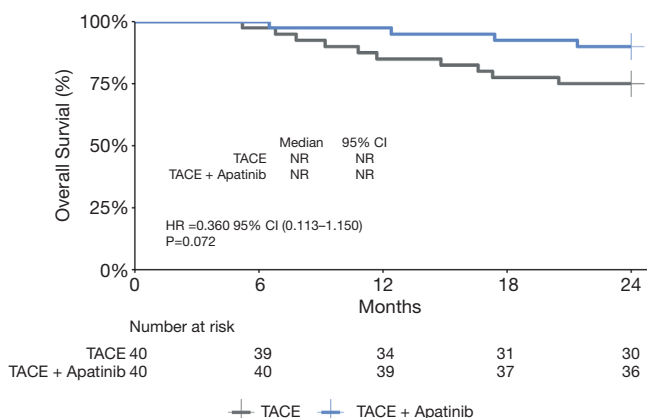


Figure 2 Overall survival (OS) in the transarterial chemoembolization (TACE) plus apatinib and TACE-alone groups. The Kaplan-Meier analysis was used to evaluate OS in patients. The log-rank test was used to compare treatments. CI, confidence interval; NR, not reached; HR, hazard ratio.

agent approved to treat advanced HCC (26). Several analyses have demonstrated that the addition of sorafenib to TACE could produce a synergistic enhancement effect, considerably enhancing OS, time to progression (TTP), and ORR for intermediate- or advanced-stage HCC (27–29). Nevertheless, the data in STORM trial showed there was no significant advantage of sorafenib for HCC following

resection or ablation (30). In addition, the remarkable adverse effects and high resistance rate have significantly hampered its use (31,32). Consequently, more effective and less expensive treatments are urgently needed to be explored.

As a highly selective VEGFR-2 blocker, the affinity of apatinib to VEGFR-2 tyrosine kinase is 10 times greater than that of sorafenib (33). Numerous clinical studies have confirmed the efficacy of apatinib for advanced HCC, and further research has corroborated the benefits of TACE plus apatinib for intermediate or advanced HCC (14–16,18). Recently, the RESCUE trial showed that the treatment of apatinib combined with camrelizumab, an anti-programmed death-1 monoclonal antibody, was controllable safe and showed a good curative effect in advanced HCC (34). Therefore, apatinib seems to have a good value in the treatment of HCC.

This prospective randomized controlled study was conducted to investigate the effect of apatinib used concurrently with TACE on recurrent HCC. We found that the apatinib plus TACE treatment resulted in an mPFS benefit of 4.7 months and achieved a higher ORR and DCR when compared with TACE-alone treatment. The results may attribute to the follows: strict inclusion and exclusion criteria, good condition of patients, lack of vascular invasion and extra-hepatic metastasis, and the use of 8Spheres microspheres in TACE treatment ensuring an excellent embolization effect. However, the secondary endpoint of OS was not significantly different between the two groups, which might be partly attributed to the consequence of the limited sample size and the short follow-up time of the study.

Furthermore, the treatments were controllable safe in this study as all serious AEs were effectively alleviated after symptomatic care. The incidence of PES post-embolization showed no significant difference between the two groups. The rate of apatinib-related AEs was higher in the TACE plus apatinib group, with the majority of AEs classified as grade 1–2. No grade 4 AE occurred in this study, which may be explained by the dosage reduction of apatinib once grade 3 AE occurs. Furthermore, no unexpected toxicity or procedure-related mortality was observed.

So far, there is little study regarding on the effect of combination therapy of TACE and anti-angiogenic drugs on patients with recurrence HCC post-hepatectomy. The preliminary results of our study showed that the combination of TACE and apatinib can significantly prolong the mPFS in patients with recurrence HCC,

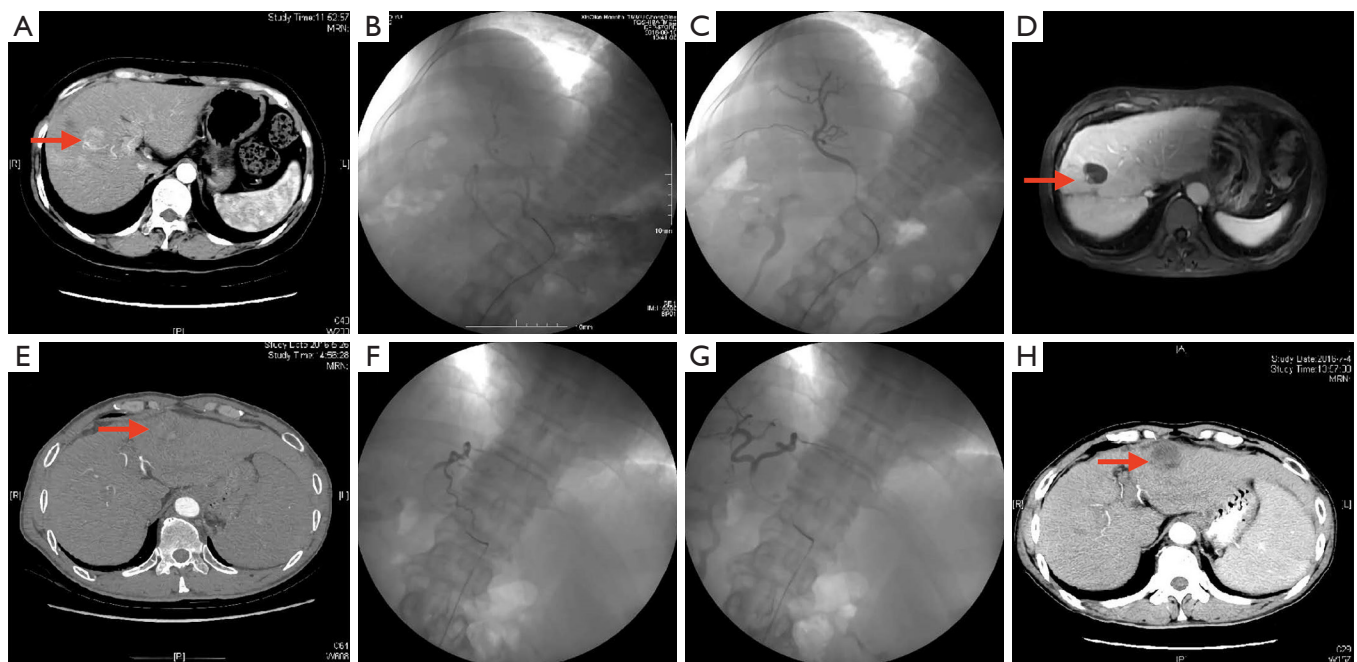


Figure 3 Results of imaging with abdominal contrast-enhanced confidence interval (CT) or magnetic resonance imaging (MRI) in a representative case before transarterial chemoembolization (TACE) and after treatment in both groups and the digital subtraction angiography changes during TACE treatment. Imaging changes before and after TACE in the TACE-alone group (A,D) and TACE plus apatinib group (E,H). The digital subtraction angiography changes before and after embolization during TACE treatment in the TACE-alone group (B,C) and the TACE plus apatinib group (F,G). Arrow, the location of tumor.

Table 2 Tumor responses in the two groups

Tumor responses	TACE group (n=40)	TACE plus apatinib group (n=40)	P value
One-month			
CR	0	0	
PR	20 (50.0%)	30 (75.0%)	
SD	9 (22.5%)	6 (15.0%)	
PD	11 (27.5%)	4 (10.0%)	
ORR	50.0%	75.0%	0.021
DCR	72.5%	90.0%	0.045
Three-month			
CR	0	0	
PR	13 (32.5%)	22 (55.0%)	
SD	8 (20.0%)	8 (20.0%)	
PD	19 (47.5%)	10 (25.0%)	
ORR	32.5%	55.0%	0.043
DCR	52.5%	75.0%	0.036

TACE, transarterial chemoembolization; one-month, the first month after TACE treatment; three-month, the third month after TACE treatment; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate, defined as CR+PR; DCR, disease control rate, defined as CR + PR + SD.

Table 3 Adverse events in the two groups

Adverse events	TACE group (n=40)	TACE plus apatinib group (n=40)	P value
Postembolization syndrome, n (%)			
Fever	10 (25.0)	13 (32.5)	0.459
Abdominal pain	14 (35.0)	10 (25.0)	0.329
Nausea and vomiting	11 (27.5)	14 (35.0)	0.469
Myelosuppression	5 (12.5)	7 (17.5)	0.531
Drug-related adverse events, n (%)			
Fatigue	0	10 (25.0)	<0.001
Hand-foot syndrome	0	16 (40.0)	<0.001
Diarrhea	0	9 (22.5)	0.001
Hypertension	0	11 (27.5)	<0.001
Proteinuria	0	6 (15.0)	0.011
Oral ulcer	0	9 (22.5)	0.001

TACE, transarterial chemoembolization.

suggested that the combination therapy might be safe and of potential benefit in treating patients with intrahepatic recurrent HCC, could be used as a new treatment option for intrahepatic recurrence.

However, our study's findings are limited by the small sample size and a short follow-up time of its design. Therefore, multicenter, randomized, controlled studies with a larger sample size are needed in the near future to further assess the effects and safety of combining TACE and apatinib in treating recurrent HCC.

Conclusions

In summary, the results of this study indicated that TACE plus apatinib might be safe and of potential benefit to patients with intrahepatic recurrent HCC after hepatectomy.

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Footnote

Reporting Checklist: The authors have completed the

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Data Sharing Statement: Available at <http://dx.doi.org/10.21037/atm-20-7244>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-7244>). The authors have no conflicts of interest to declare. The abstract of the study has been orally presented at the ESMO 22nd World Congress on Gastrointestinal Cancer, and has been published in a supplement to the *Annals of Oncology*. The work described was original research that has not been published in whole previously, and not under consideration for publication elsewhere.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The protocol was approved by the China Ethics Committee of Registering Clinical Trials (ethics committee approval no. ChiECRCT-20170060), and all the patients provided written informed consent before enrollment.

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