Original Article

Clinical outcomes of hepatocellular carcinoma patients after hepatectomy treated with TACE in combination with sorafenib: a propensity score matched analysis

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Background: To assess the long-term effects of transarterial chemoembolization (TACE) combined with sorafenib versus TACE alone procedures in recurrent patients with unresectable hepatocellular carcinoma (HCC).

Methods: A total of 381 recurrent patients treated with partial hepatectomy undergoing either TACE + sorafenib treatment or TACE alone were included in this retrospective research. To minimize bias brought on by confounding factors, propensity score matching (PSM) was used. The clinical effectiveness, complications, and negative responses of two groups were noted. Overall survival (OS) was the main result. The secondary outcome was time to target tumor progression (TTTP). The risk variables for OS were investigated using the Cox proportional hazards model.

Results: There were 32 individuals in each group following PSM. According to mRECIST (modified response evaluation criteria in solid tumors), patients receiving TACE + sorafenib had a significantly longer TTTP compared to patients receiving sorafenib alone (P=0.017). The median OS was 48.5 months with TACE plus sorafenib and 41.0 months with TACE alone. At 5 years, however, survival was comparable between groups (P=0.300). In the combination group, the most frequent side effect was hand-foot skin reaction (81.3%), whereas, in the monotherapy group, the most frequent side effect was fatigue (71.9%). In neither group were there any treatment-related fatalities.

Conclusions: Although TACE plus sorafenib did not significantly lengthen OS compared to TACE alone, it did considerably enhance TTTP.

Keywords: Hepatocellular carcinoma (HCC); recurrent; sorafenib; transarterial chemoembolization (TACE)

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Introduction

Hepatic resection is regarded as the first-line therapy for patients with hepatocellular carcinoma (HCC); notably, recurrence after resection remains a significant problem with many series reporting rates of 60–70% at 5 years (1-4). Bilobar tumor lesions, extrahepatic metastases, and portal vein invasion have been associated with a high propensity for tumor recurrence after resections (5-9). Patients with recurrent HCC are at increased risk of secondary

surgery due to the smaller size of the remaining liver after initial resection and the significantly reduced reserve and compensatory capacity of the liver. Furthermore, taking into consideration issues like quantity and location of recurring lesions unsuitable for surgery, most patients will get systemic or intra-arterial therapies (10,11).

Patients with significant unresectable or multifocal HCC without a main or lobar branch portal vein thrombus who are not candidates for local ablation might consider transarterial chemoembolization (TACE) (12-14). TACE is based on inducing tumor ischemia by cutting off the blood supply of the tumor. As a side effect of this treatment, hypoxia inducible factors are expressed by tumor after TACE (15). Angiopoietin-2 and vascular endothelial growth factor are upregulated by elevated levels of hypoxia-inducible factor 1, which worsens the prognosis for patients by promoting intrahepatic metastasis, extrahepatic metastasis, and vascular invasion (16).

A multikinase inhibitor known as sorafenib targets platelet-derived growth factor receptor-beta as well as vascular endothelial growth factor receptors 1/2/3 (17). Sorafenib has been shown to increase survival when compared to optimal supportive treatment alone. It has been proposed that giving sorafenib might help target the overexpression of TACE-induced angiogenic factors and therefore enhance the results of TACE therapy (18). The pertinent question is whether adding systemic therapy improves outcomes relative to locoregional therapy alone for individuals with liver-isolated HCC who are qualified for liver-directed nonsurgical interventions. Even though sorafenib has been the only systemic medication licensed for the treatment of HCC for 10 years, information on recurrent HCC following hepatic resection is scant.

Therefore, this study aimed to evaluate whether a combination of TACE and sorafenib can improve the outcomes in recurrent unresectable HCC patients after initial resection. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2784/rc).

Highlight box

Key findings

- Transarterial chemoembolization (TACE) + sorafenib did not significantly enhance OS in individuals who had had hepatectomy compared to TACE alone; however, time to target tumor progression was noticeably improved.

What is known and what is new?

- A prolonged duration of sorafenib treatment leads to clinical benefits.
- TACE plus sorafenib or systemic drug-TACE sequential therapy may be a viable therapeutic choice for patients who experience recurrence following hepatectomy.

What is the implication, and what should change now?

- Patients who have recurrence after hepatectomy may benefit from sequential TACE therapy with sorafenib or systemic drug-TACE therapy. Individuals with poor TACE results who have relapsed after hepatectomy may be candidates for co-administration of sorafenib.

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical Colleges (No. NCC-010299) and informed consent was obtained from all the patients.

Patient population

All patients with recurrent unresectable HCC who received TACE as first-line therapy at National Clinical Research Center for Cancer/Cancer Hospital from 2010 to 2020 were identified from an electronic database for a retrospective analysis. After a multidisciplinary tumor board debate, patients were chosen for TACE, and treatment was started after obtaining the written informed permission.

The inclusion criteria of this study were as follows: (I) patients with their first recurrence after liver resection; (II) age >18 years; (III) treated with TACE alone or TACE combined with sorafenib; (IV) sorafenib treatment for at least 4 weeks; (V) with Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1; (VI) with Child-Pugh classification of A or B. The exclusion criteria of this study are as follows: (I) patients with other malignant tumor diseases; (II) patients with serious medical comorbidities; (III) patients who received other targeting agents or immunotherapy; (IV) the period between the administration of sorafenib and the initial TACE procedure was more than a month; (V) patients who had undergone other treatments before this study; (VI) unavailability of

medical records.

TACE protocol

Regularly using the Seldinger procedure, the 5 F catheter was inserted after puncturing the femoral artery. In order to identify the tumor target vessel during angiography, the catheter was positioned near the celiac trunk artery's entrance. Into the tumor-supplying artery, super selective intubation was carried out. Oxaliplatin (50–100 mg), pirarubicin (10–40 mg), and lipiodol made up the therapy protocol (2–20 mL). The medication was chosen at the doctor's discretion, and the amount of lipiodol was determined by the size of the tumor. Following the operation, hepatoprotective hydration therapy was administered.

Sorafenib management

All patients received comprehensive information about the sorafenib therapy, including details about its effectiveness, potential side effects, and cost. Sorafenib treatment (daily dosage, 400 mg b.i.d.) was started 2–30 days after the first TACE and maintained until intolerance, refusal, or tumor progression occurred. Based on the existence of toxicity, the dose of sorafenib was reduced. If grade 3 or 4 adverse effects (AEs) occurred, a dosage change (400 mg once a day) was undertaken until the AEs were eased or eliminated. If grade 3 or 4 adverse events persisted following dosage modification, sorafenib therapy would be discontinued until the AEs were relieved or eliminated.

Follow-up

Following treatment, the standard of care clinical and radiological follow-up was set at one month and then every three months. All patients had triphasic computed tomography (CT) examinations at the initial follow-up, and subsequent follow-ups were done with either CT or magnetic resonance imaging (MRI). Retreatment was only undertaken on demand, following a multidisciplinary tumor board discussion of all available alternatives, based on the extent of remaining or recurring viable tumors and the clinical circumstances of the patients.

Data analysis

The following factors were gathered: baseline age, sex, liver function, and tumor extension; baseline demographic and clinical data; laboratory tests; periprocedural complications; target and overall tumor response; radiological tumor progression; and survival.

The main outcome in this trial was overall survival (OS), which was defined as the period from when the HCC recurrence was identified to when the patient died for any reason. The secondary outcome was time to target tumor progression (TTTP). Treatment responses were classified as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) using the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Two radiologists discussed and validated the results of contrast-enhanced CT or MRI scans.

Statistical analysis

PSM of TACE + S to TACE patients was performed with a caliper width of 0.1 and 1:1 nearest-neighbor matching. After matching, the balance of covariate distribution across groups was examined using the standardized mean difference (SMD). Data were investigated using descriptive statistics (mean and standard deviation) then compared using chi-square or Fisher exact tests for categorical data and Student's *t*-test for continuous variables. The log-rank test was used to compare the estimated Kaplan-Meier and OS curves. Using Cox proportional hazards models, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Regardless of eligibility or treatment length, all patients who received at least one dosage of the prescribed therapy were included in the safety analysis. A P value of 0.05 was used as the threshold for statistical significance in the statistical analysis, which was performed using specialized software (SAS, Cary; and Stata, Stata Corp).

Results

Patient demographic and clinical characteristics

There were 381 recurrent patients with unresectable HCC who satisfied the inclusion criteria in total, and 234 of them were disqualified based on the exclusion criteria (*Figure 1*). *Figure 2* displays the number of patients recruited over time. The median follow-up time was 33.1 months.

The study population's demographic and baseline parameters are displayed in *Table 1*. Prior to propensity matching, 32 patients received TACE combined with sorafenib compared to 115 with TACE alone. Based on

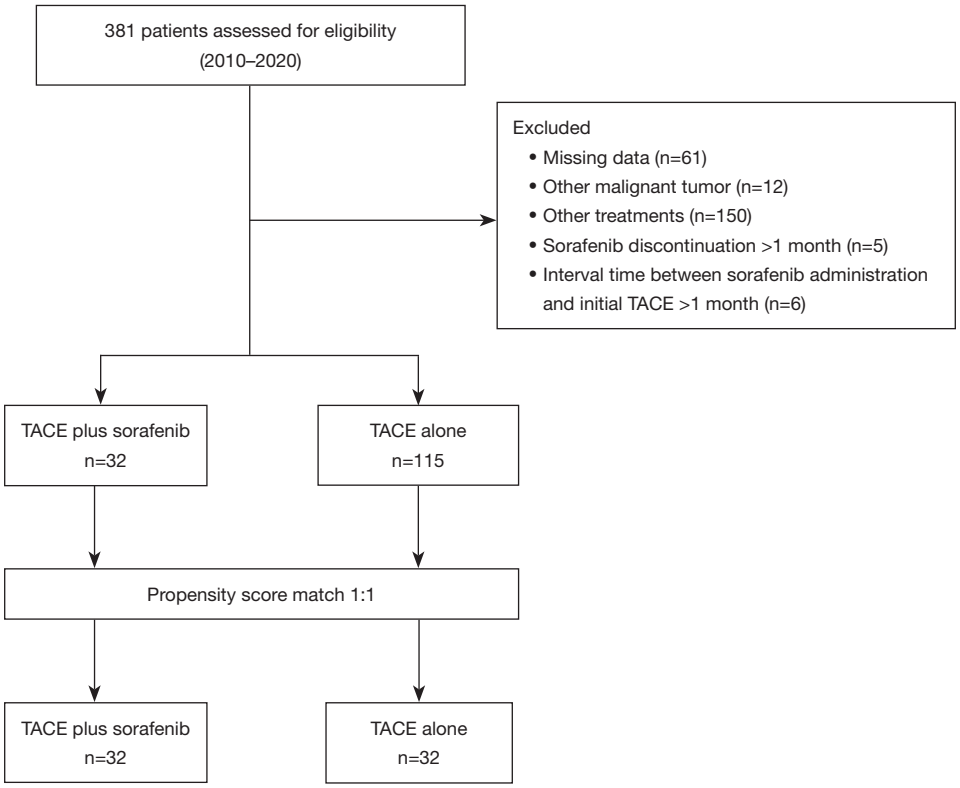

Figure 1 Flow chart of patients included in the study. TACE, transarterial chemoembolization.

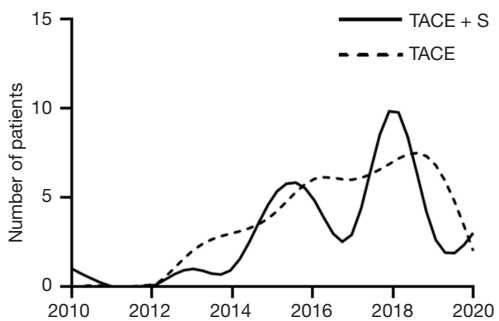

Figure 2 Patients' recruitment. TACE + S, transarterial chemoembolization plus sorafenib; TACE, transarterial chemoembolization.

the 32 patients who accepted sorafenib, 32 patients with TACE alone were matched for the analysis using the closest available neighbor approach (1:1). There were no appreciable distinctions between the two groups' baseline characteristics in the PSM cohort.

Tumor progression and survival in the matched population

For propensity-matched patients, the combination treatment group and the monotherapy group underwent a Kaplan-Meier analysis to determine OS and TTTP. At the cut-off date of September 1, 2022, 25 OS events were observed. The median OS for the TACE + sorafenib group was 48.5 months (95% CI: 39.01–58.05), compared to 41.0 months (95% CI: 34.17–53.83) for the TACE monotherapy group. As a result, TACE + sorafenib did not substantially improve survival compared to TACE alone (P=0.300) (*Figure 3*). The estimated median TTTP was 10.5 months (95% CI: 9.24–25.88) after TACE and 19.0 months (95% CI: 15.79–31.83) after TACE + sorafenib (P=0.017). Significantly longer TTTP was observed in the TACE plus sorafenib arm than in the TACE alone arm.

Prognostic factors for OS in the PSM cohort

Table 2 provides the results of the univariate and multivariate

Table 1 Baseline covariates before and after matching

Variables	Before matching			After matching		
	TACE alone	TACE + sorafenib	SMDΔ	TACE alone	TACE + sorafenib	SMDΔ
N	115	32		32	32	
Age (years)	58.27±11.88	58.09±8.79	–0.020	56.56±13.10	58.09±8.79	0.174
Gender						
Female	10 (8.7)	5 (15.6)	0.191	6 (18.8)	5 (15.6)	–0.086
Male	105 (91.3)	27 (84.4)	–0.191	26 (81.2)	27 (84.4)	0.086
Viral hepatitis						
HBV	99 (86.1)	24 (75.0)	–0.256	23 (71.9)	24 (75.0)	0.072
HCV	5 (4.3)	0 (0.0)	–0.240	0 (0.0)	0 (0.0)	
No infections	11 (9.6)	8 (25.0)	0.356	9 (28.1)	8 (25.0)	–0.072
Child-Pugh score						
A	112 (97.4)	31 (96.9)	–0.030	32 (100.0)	31 (96.9)	–0.180
B	3 (2.6)	1 (3.1)	0.030	0 (0.0)	1 (3.1)	0.180
ECOG PS						
0	114 (99.1)	32 (100.0)	0.106	32 (100.0)	32 (100.0)	0.000
1	1 (0.9)	0 (0.0)	–0.106	0 (0.0)	0 (0.0)	0.000
AFP						
<400	96 (83.5)	26 (81.2)	–0.057	25 (78.1)	26 (81.2)	0.080
≥400	19 (16.5)	6 (18.8)	0.057	7 (21.9)	6 (18.8)	–0.080
Number of nodules						
Multiple-diffuse	69 (60.0)	24 (75.0)	0.346	22 (68.8)	24 (75.0)	0.144
Single	46 (40.0)	8 (25.0)	–0.346	10 (31.2)	8 (25.0)	–0.144
Vascular invasion						
No	101 (87.8)	24 (75.0)	–0.296	25 (78.1)	24 (75.0)	–0.072
Yes	14 (12.2)	8 (25.0)	0.296	7 (21.9)	8 (25.0)	0.072
Extrahepatic metastasis						
No	102 (88.7)	25 (78.1)	–0.256	26 (81.2)	25 (78.1)	–0.076
Yes	13 (11.3)	7 (21.9)	0.256	6 (18.8)	7 (21.9)	0.076

Values are listed as number (percentage) or mean ± standard deviation unless otherwise stated. TACE, transarterial chemoembolization; SMD, standardized mean difference; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG PS, Eastern Cooperative Oncology Group Performance Status; AFP, alpha-fetoprotein.

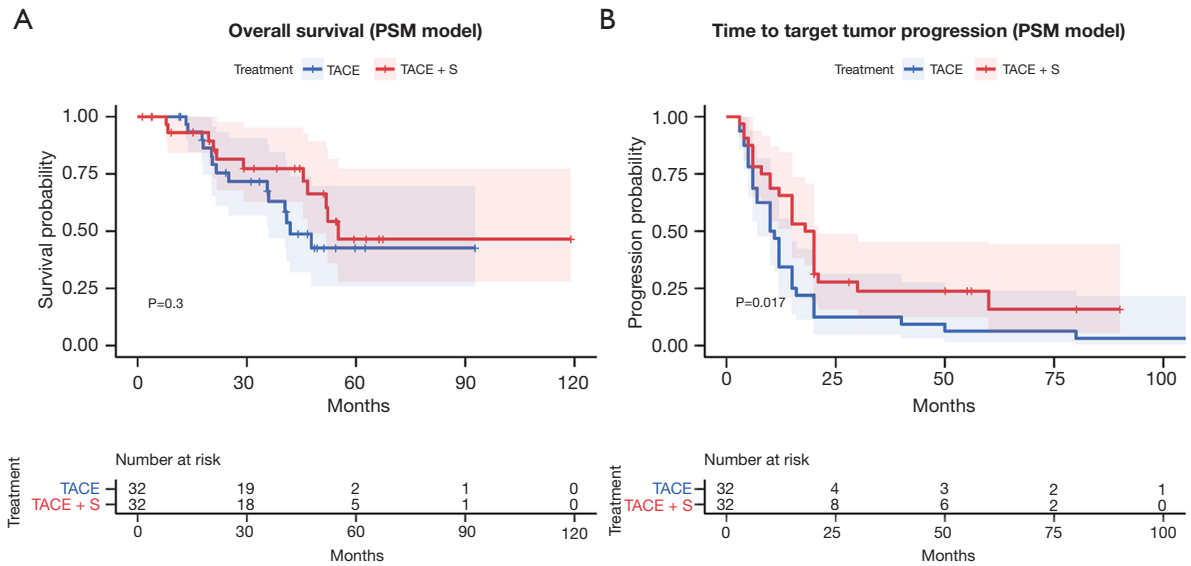

Figure 3 Kaplan-Meier analysis of overall survival in the combined treatment group and the monotherapy group for propensity-matched patients (A: refers to overall survival analysis; B: refers to time to target tumor progression analysis). PSM, propensity score matching; TACE, transarterial chemoembolization; TACE + S, transarterial chemoembolization plus sorafenib.

studies of the OS-influencing factors. The PSM cohort's univariate log-rank test analysis revealed that OS was related to the number of nodules and the degree of arterial enhancement. Multivariate Cox regression analysis revealed that TACE in combination with sorafenib did not substantially improve survival compared to TACE alone (HR =2.08; 95% CI: 0.84–5.15; P=0.11). *Figures 4,5* show forest plots of the results of the one-way and multi-way Cox regression analyses respectively.

Safety outcomes

AEs that resulted from the treatment are displayed in *Table 3*. Fatigue (71.9%) and abdominal pain (65.6%) were the two AEs that occurred the most frequently in the TACE alone group. Additionally, one patient (3.1%) experienced abdominal pain in grade 3/4. Hand-foot skin reaction (81.3%), abdominal pain (71.9%), and fatigue (62.5%) were the three most common AEs in the TACE plus sorafenib group. The most frequent grade 3/4 AEs were abdominal pain (3.1%), vomiting (3.1%), and fever (3.1%). In neither group was there a mortality connected to the treatment.

Discussion

To maximize therapeutic results, recurrent HCC typically necessitates intensive therapy. TACE is the most often utilized therapy for recurrent HCC after resection. With the publication of data revealing that the molecularly targeted drug sorafenib increases survival compared to optimal supportive treatment alone, there has been a renaissance of excitement and interest for systemic therapy of HCC (19). Real-world data are still missing, nevertheless, addressing the administration of concurrent multi-modality therapy and how this can affect resource usage and long-term effects. The results from the current study show that the concurrent treatment of sorafenib may postpone, but not avoid, tumor development following TACE.

We choose a time frame for our investigation between 2010 and 2020. This is connected to the fact that sorafenib was introduced to our institution in 2010, with an inevitable early learning curve caused by the absence of international expertise. Sorafenib is a multikinase inhibitor that, among other things, inhibits the vascular endothelial growth factor receptor. Prospective randomized studies have confirmed that in HCC in the intermediate stage, TACE plus sorafenib may be an option for treatment (19,20). The SHARP trial provided the foundation for the United States' approval of sorafenib for the systemic treatment of advanced HCC and positioned sorafenib monotherapy as a novel reference standard. In our study, recurring individuals with unresectable HCC received S-TACE (sorafenib-TACE)

Table 2 Univariate and multivariate analysis of influencing factors (Cox regression)

Characteristic	Univariable					Multivariable				
	N	Event N	HR	95% CI	P value	N	Event N	HR	95% CI	P value
Treatment										
TACE + sorafenib	32	11	–	–		32	11	–	–	
TACE	32	14	1.53	0.69, 3.40	0.30	31	14	2.08	0.84, 5.15	0.11
Age (years)	63	25	0.98	0.94, 1.02	0.25	63	25	1.00	0.95, 1.05	0.93
Gender										
Male	58	23	–	–		57	23	–	–	
Female	6	2	1.21	0.28, 5.15	0.80	6	2	1.31	0.21, 8.11	0.77
Viral hepatitis										
No infections	17	6	–	–		17	6	–	–	
HBV	47	19	1.33	0.53, 3.34	0.54	46	19	1.55	0.47, 5.09	0.47
Child-Pugh score										
A	63	25	–	–		62	25	–	–	
B	1	0				1	0			
AFP										
<400	51	19	–	–		50	19	–	–	
≥400	13	6	0.93	0.37, 2.35	0.87	13	6	0.52	0.16, 1.66	0.27
Vascular invasion										
No	49	20	–	–		48	20	–	–	
Yes	15	5	1.42	0.52, 3.85	0.49	15	5	1.16	0.38, 3.50	0.80
Number of nodules										
Single	18	5	–	–		18	5	–	–	
Multiple-diffuse	46	20	2.00	0.75, 5.35	0.04	45	20	1.85	0.48, 7.10	0.27
Extrahepatic metastasis										
No	51	19	–	–		50	19	–	–	
Yes	13	6	1.31	0.52, 3.29	0.56	13	6	1.19	0.40, 3.51	0.76
Recurrent interval	64	25	1.00	1.00, 1.00	0.28	63	25	1.00	1.00, 1.00	0.59
Angiography										
Mild	10	1	–	–		9	1	–	–	
Moderate	18	6	4.02	0.48, 33.4	0.10	18	6	3.69	0.40, 34.4	0.20
Dense	36	18	5.48	0.73, 41.1	0.03	36	18	4.57	0.46, 45.1	0.11

HR, hazard ratio; CI, confidence interval; TACE, transarterial chemoembolization; HBV, hepatic B virus; AFP, alpha-fetoprotein.

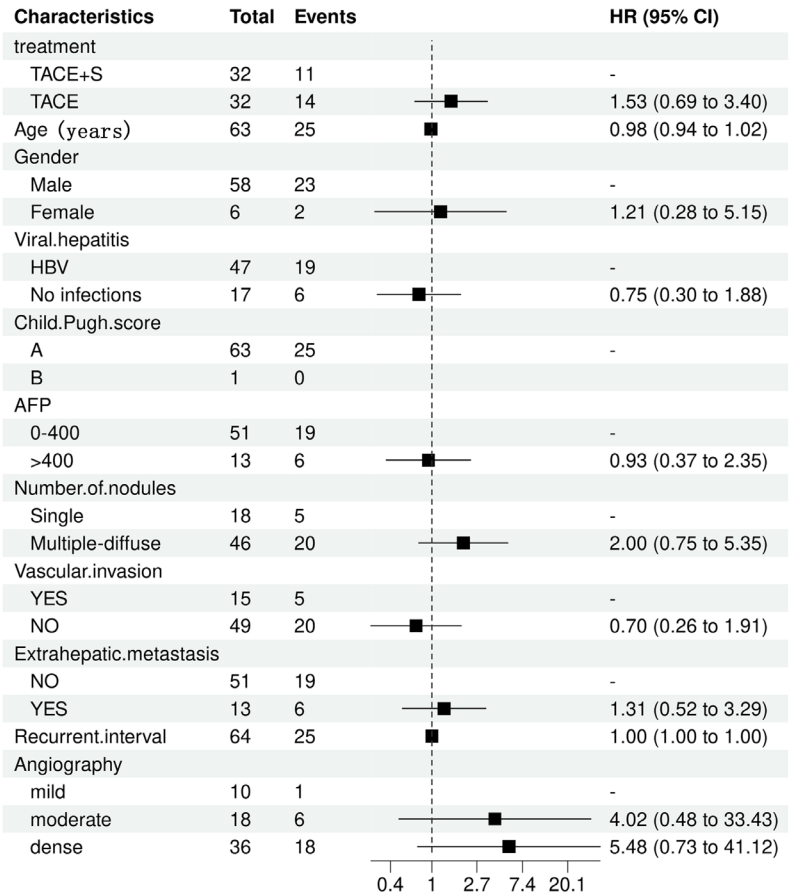

Figure 4 Forest plot of overall survival in univariate analysis. HR, hazard ratio; CI, confidence interval; TACE + S, transarterial chemoembolization plus sorafenib; TACE, transarterial chemoembolization; HBV, hepatic B virus; AFP, alpha-fetoprotein.

combination treatment with a minimal benefit over TACE monotherapy. The conclusions of a significant amount of earlier research in the TACTICS experiment are supported by these results (21). Findings from the TACTICS trial showed that TACE with sorafenib did not significantly improve OS compared to TACE alone in patients with advanced HCC. Nonetheless, when TACE and sorafenib were combined, as opposed to sorafenib alone, there was a significant improvement in tumor morphology, as evidenced by better PRs and a decrease in the incidence of PD. Given the potential of sorafenib to inhibit TACE-induced VEGF angiogenesis released by acute hypoxia, it seems that sorafenib might have stabilised disease progression after TACE session, leading to a prolonged TTTP. We tentatively put forward that effective subsequent therapy was a major factor contributing to the lack of a significant OS benefit in this trial.

The current analysis showed that the main risk factors for poor survival included the number (≥2) and the degree of arterial enhancement of the recurrent HCCs. The Child-Pugh class, vascular invasion, and tumor size have all been found to be independent predictors of outcomes in earlier studies. These findings are consistent with those findings (22,23). Interestingly, alpha-fetoprotein (AFP) was not a significant prognostic factor for survival according to the univariate analysis. This outcome might be explained by the study's limited number of cases.

The most frequent AEs reported with sorafenib usage were hand-foot skin reaction, diarrhea, alopecia, and tiredness, according to evidence from recent trials (24-28). Similar safety findings were established in the current investigation, which showed that hand-foot skin reaction was the most frequently reported drug-emergent AE, followed by abdominal pain and fatigue. In our study,

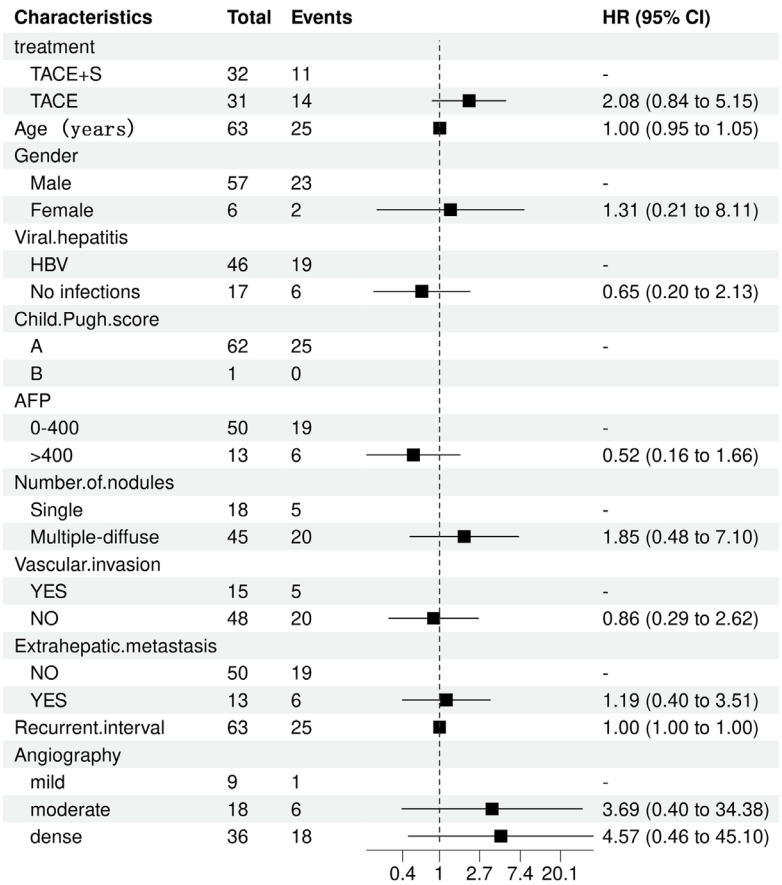

Figure 5 Forest plot of overall survival in multivariate analysis. HR, hazard ratio; CI, confidence interval; TACE + S, transarterial chemoembolization plus sorafenib; TACE, transarterial chemoembolization; HBV, hepatic B virus; AFP, alpha-fetoprotein.

the majority of these AEs were grade 1/2 and well tolerated, which seldom led to medication cessation.

This study's primary drawback stems from its retrospective methodology. Since some patients' medical records could not be located, follow-up was not uniform, and some information on locoregional and systemic treatments delivered by doctors in other institutions could have been overlooked, several individuals were removed from the study. The time frame used for the study is another drawback. Thirdly, it was unfortunate that this study only involved a limited number of patients. To validate the findings of this study, more patients must participate in external validation studies.

Despite these drawbacks, the approach of this study adds fresh information to this comparison while correlating some of the data provided by sizable prospective randomized trials (19,20,29). TACE + sorafenib failed to significantly increase OS when compared to TACE. However, considering the much enhanced lasting local tumor control that was noted, patients may benefit from using TACE with sorafenib. Future research with a larger sample size will be needed to determine whether TACE plus sorafenib is beneficial for patients with a greater liver reserve.

Conclusions

In conclusion, there was no statistically significant increase in OS with TACE plus sorafenib. Because of the considerable increase in TTTP, TACE plus sorafenib or systemic drug-TACE sequential therapy may be a viable therapeutic choice for patients who experience recurrence following hepatectomy.

Table 3 Adverse events in the combination treatment group and the monotherapy group

Adverse events	TACE + sorafenib (n=32)		TACE alone (n=32)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Diarrhea	18	0	12	0
Abdominal pain	22	1	20	1
Ascites	2	0	3	0
Vomiting	10	1	7	0
Fatigue	20	0	23	0
Fever	13	1	11	0
Headache	5	0	6	0
Upper respiratory infection	2	0	2	0
PLT decreased	3	0	4	0
WBC decreased	2	0	3	0
Anaemia	2	0	3	0
Hand-foot skin reaction	26	0	0	0
Hypertension	5	0	0	0
Hair loss	1	0	0	0
Gastrointestinal hemorrhage	2	0	1	0
Epistaxis	1	0	0	0

TACE, transarterial chemoembolization; PLT, platelet; WBC, white blood cell.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2784/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2784/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2784/coif). The authors have no conflicts of interest to declare.

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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical Colleges (No. NCC-010299) and informed consent was obtained from all the patients.

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