

Efficacy and safety of TACE in combination with sorafenib for the treatment of TACE-refractory advanced hepatocellular carcinoma in Chinese patients: a retrospective study

Jianbing Wu*
An Li*
Jiajin Yang*
YanJun Lu
Jie Li

Department of Oncology,
The Second Affiliated Hospital
of Nanchang University, Nanchang,
Jiangxi, People's Republic of China

*These authors contributed
equally to this work

Background: Transarterial chemoembolization (TACE) and sorafenib (SOR) are well-established treatments for hepatocellular carcinoma (HCC). This study evaluates the efficacy and safety of SOR combined with TACE in the treatment of patients with TACE-refractory, advanced-stage HCC.

Methods: This retrospective study included 61 patients with TACE-refractory advanced HCC. Patients were divided into TACE + SOR (n=30) and TACE (n=31) treatment groups. Patient demographic and clinical characteristics, overall survival (OS), time to progression (TTP), disease control rate (DCR), and adverse events (AEs) were compared between the two groups.

Results: Compared with TACE alone, the 5-year OS and TTP were prolonged in the TACE + SOR group (median OS: 17.9 vs 7.1 months, $P < 0.001$; median TTP: 9.3 vs 3.4 months, $P < 0.001$). Multivariate analysis showed that Child–Pugh class A (hazard ratio [HR], 0.234; 95% confidence interval [CI], 0.092–0.595), Eastern Cooperative Oncology Group performance status 1 (HR, 0.355; 95% CI, 0.153–0.826), alpha-fetoprotein < 400 ng/mL (HR, 0.349; 95% CI, 0.177–0.689), and TACE + SOR treatment (HR, 0.151; 95% CI, 0.071–0.322) were independent, positive predictive factors of OS.

Conclusion: The OS and TTP in the combined treatment group were significantly improved when compared with the TACE group. However, no significant difference in DCR was found between these two groups. While no AEs occurred in the TACE group, two patients in the TACE + SOR group experienced severe AEs which were effectively mitigated by lowering the dose of SOR. Thus, SOR in combination with TACE is a safe and effective treatment for advanced-stage, prior-TACE-resistant HCC.

Keywords: hepatocellular carcinoma, sorafenib, transarterial chemoembolization, overall survival, time to progression, TACE-refractory, adverse events

Background

Hepatocellular carcinoma (HCC) is one of the most ubiquitously occurring malignancies worldwide. Its geographical distribution is not uniform and it is known to be particularly common in Asian countries due to the increased prevalence of hepatitis B virus infections within this region.^{1,2} Less than 25% of all HCC patients can be cured by treatments such as surgical resection, liver transplant, and lesion ablation.³ Unresectable HCC (on which surgical procedures cannot be performed successfully) is associated with an alarmingly high rate of morbidity and mortality.^{4,5} Thus, its effective treatment and resolution is an important contributor to the longevity and quality

Correspondence: Jianbing Wu
Department of Oncology, The Second
Affiliated Hospital of Nanchang
University, No. 1 Mingde Road,
Nanchang, Jiangxi 330006, People's
Republic of China
Tel +86 135 0791 7177
Email hhgwbj@163.com

of life of a fairly large subset of the population. Currently, most patients with advanced HCC undergo treatment such as transarterial chemoembolization (TACE),⁶ hepatic arterial infusion chemotherapy,⁷ and systemic chemotherapy including molecular targets in order to prolong survival and to provide symptomatic relief.^{8–14}

TACE is considered the standard treatment for unresectable HCC and it has been shown to provide a modest survival benefit in patients with advanced stage of the disease.^{15,16} It is also a very important palliative procedure which is carried out during the treatment and management of HCC in Asian countries such as the People's Republic of China, Japan, and Korea. However, it is associated with a high rate of treatment failure, which may be attributed to tumor neo-angiogenesis (resulting from hypoxia induced by TACE).^{12,13} Currently, sorafenib (SOR), a multi-kinase inhibitor that prevents tumor cell proliferation by targeting the RAF-MEK-ERK signaling pathway, also blocks the vascular endothelial growth factor receptor (VEGFR)-1/2/3 and platelet-derived growth factor receptor- β , thereby inhibiting neo-angiogenesis.¹⁷ SOR constitutes the first line of treatment against unresectable HCC throughout the world.^{18,19} It can also work as an adjuvant to TACE in patients diagnosed with advanced stage of the disease by reducing post-TACE angiogenesis, thus potentially restricting tumor recurrence.¹⁸

Recently published studies have shown that TACE combined with SOR is superior to TACE or SOR monotherapy in prolonging overall survival (OS) and time to progression (TTP) in patients with advanced HCC.^{9,10,19,20} These findings were further supported by two meta-analyses of randomized controlled trials, published by Zhang et al²¹ and Fu et al.⁹ Moreover, SOR also showed significantly improved OS and TTP in patients with intermediate or advanced HCC that is refractory to TACE.^{10,22,23}

Nevertheless, in patients with advanced HCC refractory to TACE, a standard therapeutic regimen has not been established due to lack of clinical investigations and randomized controlled trials.²⁴ Thus, the aim of this study was to retrospectively analyze the efficacy of TACE in combination with SOR for the treatment of patients with TACE-refractory advanced HCC.

Methods

Study design and patient population

This retrospective analysis of patients diagnosed with advanced HCC according to the previously published Japan Society of Hepatology criteria²⁵ and treated with TACE at the Second Affiliated Hospital of Nanchang University was

conducted between April 2009 and February 2014. The study included advanced-stage HCC patients diagnosed with Child–Pugh class A/B HCC and having Eastern Cooperative Oncology Group performance status (ECOG-PS) scores between 0 and 2 (defined as progression or tumor shrinkage rate <25%). The extent of devascularization was measured by using dynamic-enhanced computed tomography (CT)/magnetic resonance imaging (MRI) screening (in order to visualize active vascular tissue) every 4–6 weeks. Modified Response Evaluation Criteria for Solid Tumors (mRECIST) were used in order to determine inclusion. Exclusion criteria included pregnancy and the presence of malignant tumors in any other organ.

Based on the above criteria, 61 eligible patients with TACE-refractory advanced HCC were included in this study. Whether the patients were refractory to TACE was determined, and if not they were excluded. If patients were TACE refractory, the stage of disease was ascertained based on the Barcelona Clinic Liver Cancer (BCLC) criteria. In Asia, (particularly Japan, Korea, and the People's Republic of China), TACE is still the main treatment for advanced-stage HCC patients, (provided their level of hepatic function is conducive to TACE treatment) and is used in order to prolong survival. Since 2008, SOR has been used to treat HCC patients and several patients were admitted to the hospital. However, very few presented with advanced-stage HCC which was shown to be TACE refractory. Thus, 30 SOR + TACE-treated (TACE + SOR group) HCC patients and 31 TACE-treated (TACE group) patients were enrolled at the same baseline. Treatment in both groups included TACE with iodinated oil, and epirubicin or cisplatin 5-fluorouracil.²⁶

The study protocol was approved by the ethics committee of the Second Affiliated Hospital of Nanchang University. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (the Second Affiliated Hospital of Nanchang University) and with the Helsinki Declaration of 1975, revised in 2008. The need for written informed consent was waived due to the retrospective nature of the study. Disease history, physical examination, serum laboratory tests, and radiologic investigations (CT and MRI) were collected from patient hospital records.

TACE group

Patients in the TACE group received standard super-selective TACE treatment, as described previously.²⁷ All TACE procedures were performed on demand (repeated TACE was performed if required after identifying a viable tumor or

local or distant intrahepatic recurrence). The decision to treat patients with TACE was based on discussions involving a multidisciplinary tumor board. In addition, a CT or MRI scan was performed within 4 weeks of TACE therapy in order to monitor the response of the tumor to treatment.

TACE + SOR group

In the TACE + SOR group, oral administration of SOR (Bayer HealthCare AG, Berlin, Germany; 200 mg/pill) was initiated at a dose of 400 mg twice a day for 2 weeks post-super-selective TACE therapy. Treatment interruption and dose reduction were considered for patients who experienced intolerable adverse events (AEs). The initial dose of SOR was resumed once AEs abated. If required, or if obvious clinical disease progression was apparent, TACE was performed again.

Follow-up period

All patients were followed up every 4–6 weeks (starting immediately after treatment) by examining blood samples for tumor markers and performing contrast-enhanced CT or MRI.

Primary and secondary efficacy assessment

The primary outcome was OS, which was defined as the time taken to identify a patient as TACE refractory until the occurrence of death due to any cause or until the last follow-up for patients who were still alive on August 31, 2015.

Secondary outcomes included TTP and disease control rate (DCR). TTP was defined as the time taken to identify patients as TACE refractory until radiological diagnosis of progression of the tumor according to the mRECIST criteria.²⁸ In patients who were dead or lost to follow-up, the withdrawal date was considered as the last time radiological assessment was conducted. DCR was defined as the proportion of patients with advanced HCC who achieved either partial response (PR) or complete response (CR) or progression-free stable disease (SD) posttreatment.

Tumor response was assessed according to the mRECIST criteria²⁸ based on dynamic CT or MRI results collected during follow-up visits. CR was defined as the disappearance of enhanced tumor areas during the arterial phase, reflecting complete tissue necrosis. PR was defined as decreased tumor area by at least 30% and progressive disease (PD) was defined as an increase of at least 20% (of the sum of the longest diameter) in enhanced tumor areas. SD was defined as neither sufficient shrinkage (qualified as PR) nor a sufficient increase in tumor (qualified as PD).

Safety assessment

AEs were evaluated on the basis of the National Cancer Institute Common Terminology Criteria for AEs version 3.0. According to these criteria, grade 1 and 2 AEs are mild or moderate and require only symptomatic treatment, grade 3 AEs are severe and require specific medical treatments, grade 4 AEs are life-threatening or disabling AEs, and grade 5 AEs include death related to treatment. For the present study, only AEs deemed to be related to TACE or SOR treatment were considered.

Statistical analyses

Continuous parameters were expressed as medians and ranges and categorical variables were expressed as numbers or frequencies. Categorical variables were analyzed using the chi-square test whereas continuous variables were analyzed using the Student's *t*-test. Survival curves were analyzed based on the Kaplan–Meier model using the log-rank test. Univariate analysis was performed to identify factors predicting OS. Factors with $P < 0.10$ were further tested in a multivariate logistic regression analysis to identify the factors independently associated with OS using the backward conditional method. Cox regression was used for multivariate analysis. All statistical analyses were performed with SPSS 17.0 (IBM, Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

Results

Patient demographics and clinical characteristics

Sixty-one patients met the inclusion criteria and there were no significant differences in baseline characteristics (gender, age, diagnosis of hepatitis, histology of HCC, cirrhosis, Child–Pugh class, ECOG-PS, alpha-fetoprotein [AFP], and number of previous TACE) between the two groups (Table 1). TACE was performed 87 times in the TACE + SOR group (mean of 2.23 procedures per patient; range 1–7) and 58 times in the TACE group (mean of 1.87 procedures per patient; range 1–4). The larger number of TACE procedures in the TACE + SOR group may be attributed to the fact that the combined treatment group had a longer OS. Of the 61 patients analyzed, 50 patients died during the study period, 6 patients survived, and 5 patients were lost to follow-up. The median follow-up period was 11.3 months.

Comparison of OS and TTP between the two groups

In comparison with the TACE group, the 5-year OS of the TACE + SOR group was significantly longer (log-rank

Table 1 Patient demographics and clinical characteristics

Characteristics	TACE + SOR n=30	TACE n=31	P-value
Gender (male), n (%)	25 (83.33)	28 (90.32)	0.419
Age, n (%)			0.900
>50 years	15 (50)	15 (48.39)	
<50 years	15 (50)	16 (51.61)	
Histology of HCC, n (%)	11 (36.67)	5 (16.63)	0.068
Cirrhosis	8 (26.67)	13 (41.94)	0.210
Child–Pugh class, n (%)			0.142
A	28 (93.33)	25 (80.65)	
B	2 (6.67)	6 (19.35)	
ECOG-PS, n (%)			0.806
1	24 (80)	24 (77.42)	
2	6 (20)	7 (22.58)	
BCLC stage C, n			0.495
Vascular invasion	13	19	
Extrahepatic spread	19	20	
AFP, n (%)			0.375
<400 ng/mL	14 (46.67)	11 (35.48)	
>400 ng/mL	16 (53.33)	20 (64.52)	
Hepatitis, n (%)	27 (90)	30 (96.77)	0.285
Number of previous TACE, n (%)			0.837
<2	22 (73.33)	22 (70.97)	
>2	8 (26.67)	9 (29.03)	

Abbreviations: TACE, transarterial chemoembolization; SOR, sorafenib; BCLC, Barcelona Clinic Liver Cancer; ECOG-PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma.

test, $P<0.001$; Figure 1). The median survival time was 17.9 months in the TACE + SOR group versus 7.1 months in the TACE group. The 1- and 2-year survival rates were 60% and 20% for the TACE + SOR group, compared with 16.7% and 3.3% in the TACE group, respectively.

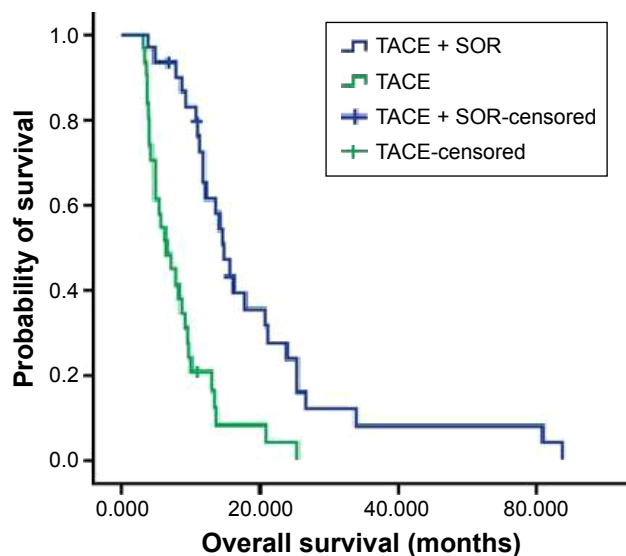


Figure 1 Kaplan–Meier analysis of OS for the TACE + SOR and TACE groups.
Note: A significant increase in OS is observed in the combined treatment group.
Abbreviations: TACE, transarterial chemoembolization; SOR, sorafenib; OS, overall survival.

TTP in the TACE + SOR group was significantly longer compared with the TACE group (log-rank test, $P<0.001$; Figure 2). The median TTP was 9.3 months for the TACE + SOR group versus 3.4 months for the TACE group.

Comparison of tumor response between the two groups

According to mRECIST, in the TACE + SOR group, five patients (16.7%) showed PR, 17 patients (56.7%) showed SD, and eight patients (26.6%) showed PD. In the TACE group, two patients (6.5%) showed PR, 14 patients (45.1%) showed SD, and 15 patients (48.4%) showed PD. The DCR was not significantly different between the two treatment groups (73.4% vs 51.6%, $P=0.08$).

Safety assessment and AEs

The occurrence of any AE was routinely checked prior to each TACE session. However, abnormal liver function or post-embolization syndrome (nausea, vomiting, fever, and abdominal pain) was not included as part of the safety analysis since such events are known to occur shortly after TACE. No patient from the TACE group experienced any AE of grade 3 or higher. However, two patients from the TACE + SOR group experienced severe AE (one patient with grade 3 hand–foot syndrome and one patient with diarrhea). In 18 patients (60%), the dosage of SOR had to be reduced due to AEs such as liver dysfunction, hand–foot syndrome, or rashes. Treatment was discontinued in five patients (16.7%) due to AEs such as hand–foot syndrome, diarrhea, or rashes.

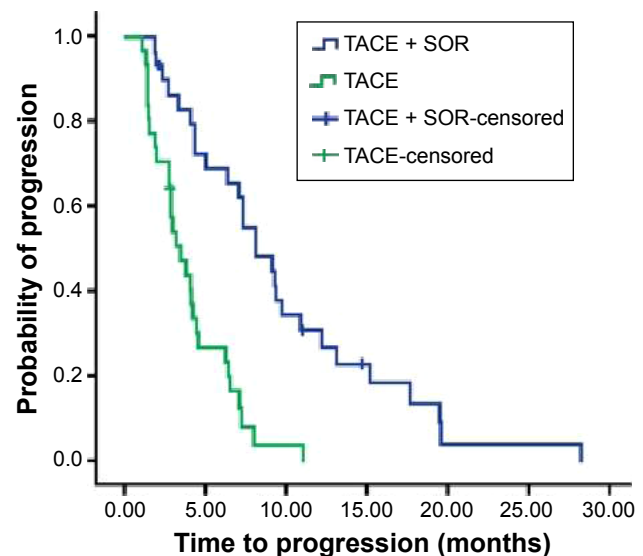


Figure 2 Kaplan–Meier analysis of TTP for the TACE + SOR and TACE groups.
Note: A significantly longer TTP is observed in the combined treatment group.
Abbreviations: TACE, transarterial chemoembolization; SOR, sorafenib; TTP, time to progression.

However, in all the patients who were required to reduce the dosage of SOR or who discontinued the drug, SOR treatment was resumed when the AE was effectively lowered to grade 1 after treatment.

Prognostic factors affecting survival

Univariate and multivariate analyses of the factors influencing OS have been summarized in Table 2. Univariate analysis showed that age, ECOG-PS, Child–Pugh class, hepatic vein invasion, AFP level, TACE + SOR versus TACE, and the number of previous TACE procedures were factors associated with OS (all $P < 0.10$). Multivariate analysis showed that Child–Pugh class A (hazard ratio [HR], 0.234; 95% confidence interval [CI], 0.092–0.595; $P = 0.002$),

ECOG-PS 1 (HR, 0.355; 95% CI, 0.153–0.826; $P = 0.016$), AFP < 400 ng/mL (HR, 0.349; 95% CI, 0.177–0.689; $P = 0.002$), and TACE + SOR treatment (HR, 0.151; 95% CI, 0.071–0.322; $P < 0.001$) were independent predictive factors of OS.

Discussion

This retrospective study sought to investigate the efficacy and safety of TACE + SOR versus TACE alone in the treatment of patients with TACE-refractory advanced HCC. These analyses showed that OS and TTP in the combined treatment group were significantly improved when compared with TACE treatment alone. However, no significant difference in the DCR was observed between the two treatment groups,

Table 2 Univariate and multivariate analyses of prognostic factors affecting survival in TACE-refractory advanced HCC

Variables	Univariate Cox analysis			Multivariate Cox analysis		
	Median OS (month)	95% CI	P-value	HR	95% CI	P-value
Gender						
Male	11.37	9.059–13.681	0.44			
Female	14.6	0.0–30.538				
Age						
>50 years	16.2	10.579–21.821	0.08	0.54	0.276–1.056	0.072
<50 years	9.6	7.296–11.904				
Histology of HCC						
Yes	14.9	12.506–17.294	0.112			
No	9.6	6.992–12.208				
Cirrhosis						
Yes	13.53	6.583–20.477	0.865			
No	11.37	9.469–13.271				
Child–Pugh class						
A	13.47	9.757–17.183	0.002	0.234	0.092–0.595	0.002
B	3.9	1.714–6.086				
ECOG-PS						
1	13.47	9.51–17.43	0.021	0.355	0.153–0.826	0.016
2	8.7	3.309–14.091				
Cause of BCLC stage C						
Vascular invasion	9.27	6.308–12.232	0.035	0.961	0.484–1.909	0.91
Extrahepatic spread	14.6	9.75–19.45				
AFP						
<400 ng/mL	17.9	8.722–27.078	0.006	0.349	0.177–0.689	0.002
>400 ng/mL	9.6	7.938–11.262				
Diagnosis of hepatitis						
Yes	11.8	8.454–15.146	0.914			
No	9.27	0.677–17.865				
Number of previous TACE						
<2	11.1	7.509–14.691	0.075	1.548	0.773–3.099	0.217
>2	14.6	3.611–25.589				
Treatment						
TACE + SOR	17.9	11.101–24.699	0.000	0.151	0.071–0.322	0.000
TACE	7.1	4.343–9.857				

Abbreviations: TACE, transarterial chemoembolization; SOR, sorafenib; BCLC, Barcelona Clinic Liver Cancer; ECOG-PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; CI, confidence interval; HR, hazard ratio; OS, overall survival.

and this might be due to the relatively small sample size of the study and loss of patients to follow-up. Any high-grade AEs that occurred in the combined treatment group were either well tolerated or controlled by adjusting the dose of SOR.

Findings of the present study are consistent with previous studies that demonstrate the effectiveness of TACE + SOR in patients with advanced HCC refractory to TACE.²⁹ A previously published case series reported the beneficial effects of SOR for the treatment of TACE-refractory HCC.¹⁰ In addition, a retrospective study showed that the DCR for SOR was 60.4%, the median TTP was 3.9 months, and the median OS was 16.4 months in patients who were refractory to TACE.²² Another study of TACE followed by SOR treatment showed similar results: median OS time (861 vs 467 days) was longer with TACE + SOR treatment than with TACE alone,¹⁰ which is in agreement with the results from this study. Arizumi et al showed that switching to SOR after becoming refractory to TACE could improve OS in intermediate-stage HCC compared with continuing TACE.³⁰ An analysis of the results from the GIDEON trial showed that TACE + SOR was a well-tolerated and viable therapeutic approach for the treatment of HCC.³¹ A meta-analysis showed that TACE + SOR improved TTP compared to TACE alone, but this analysis did not show any improvement in OS,³² while meta-analyses by Zhang et al²¹ and Hu et al⁹ showed that TACE + SOR improved both OS and TTP compared with TACE alone. This discrepancy could be due to a number of factors, including the studies being included and the populations being studied.

Although the use of TACE seems to be beneficial in some patients with advanced disease, the objective response rates of TACE were reported to be only 15%–61% and CR is observed in only 20%–35% of patients. In addition, HCC recurs in some patients due to the transient devascularization effect of TACE.³³ The administration of multiple TACE sessions is more likely to cause liver failure, which in turn affects survival. Therefore, it is important to determine which patients are refractory to TACE so that an appropriate treatment regimen may be selected. However, there is no global, standardized definition for failure of TACE treatment. Therefore, the best course of treatment for such patients remains ambiguous. In this study, patients who showed tumor progression or a tumor shrinkage rate of <25% of the corresponding hypervascular lesions (visualized using dynamic CT and/or MRI 1–3 months after TACE) were defined as TACE refractory. However, according to the consensus-based 2010 clinical practice guidelines proposed by the Japanese Society of Hepatology,³⁴ refractory to TACE was

defined as ≥ 2 consecutive incomplete necrotic reactions or the appearance of a new lesion, vascular invasion, or extrahepatic metastases. Additional studies and/or international guidelines are needed to define this parameter.

The selection of the most suitable treatment option for patients who are refractory to TACE treatment is an important issue that concerns clinicians and oncologists. SOR may be effectively administered as a molecular target in patients who are refractory to TACE and who present with HCC involving vascular invasion and extrahepatic metastasis.^{24,34,35} The present study was based on the hypothesis that SOR could inhibit VEGFR activity after TACE and thus prevent angiogenesis and tumor recurrence in advanced HCCs refractory to TACE; the results support this hypothesis since OS and TTR were both longer in the TACE + SOR group compared with the TACE alone treatment group.

Previous studies indicate that SOR combined with TACE may increase the possibility of liver dysfunction. However, no grade 4 AE was observed in this study and the most common grade 1 or 2 AEs were hand–foot syndrome, rashes, and hypertension. Only two grade 3 events were observed, indicating that TACE combined with SOR was well tolerated by patients with TACE-refractory HCC. The conclusion is supported by meta-analyses that showed that AEs were more frequent in patients receiving TACE + SOR compared with TACE alone.^{9,21,32} However, an analysis of the results of the GIDEON trial showed that there was no significant difference in the occurrence of AEs between TACE + SOR and TACE treatment alone.³¹

Although this study successfully highlights the improvement in patient outcomes achieved as a result of the use of combination therapy, it is not without limitations. The retrospective nature of the study may have introduced a selection bias which could not be accounted for in the analyses. In addition, the sample size was small and taken from a single center. Since five patients were lost to follow-up, there was a further reduction in the sample size used to compute patient outcomes. Results from prospective, multicenter studies such as OPTIMIS can confirm the positive effects of TACE in combination with SOR in patients with TACE-refractory advanced HCC.³¹

In conclusion, TACE combined with SOR showed some benefits in patients with TACE-refractory advanced HCC, resulting in prolonged TTP and OS compared with TACE treatment alone. The occurrence of high-grade AEs was rare in both treatment groups. In addition, Child–Pugh class, ECOG-PS scores, AFP levels, and type of treatment (TACE + SOR or TACE alone) were independent predictive factors of OS in this study.

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The study was approved by the ethics committee of the Second Affiliated Hospital of Nanchang University. The data sets used and/or analyzed in the current study are available with the corresponding author.

Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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