

Research Paper

Transarterial Chemoembolization (TACE) Combined with Sorafenib *versus* TACE Alone for Unresectable Hepatocellular Carcinoma: A Propensity Score Matching Study

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Abstract

Objective: To compare the outcomes of transarterial chemoembolization (TACE) combined with sorafenib *versus* TACE alone for treating patients with unresectable hepatocellular carcinoma (HCC).

Methods: This retrospective analysis included all patients receiving either TACE plus sorafenib therapy or TACE alone for unresectable HCC between February 2008 and August 2015 at the First Affiliated Hospital of Soochow University, China. Propensity score matching (PSM) was carried out to reduce bias due to confounding variables. The primary outcome was overall survival (OS), calculated from the date of the first TACE treatment until the date of death of any cause. A multivariate Cox proportional hazards analysis was conducted to examine determinants of OS.

Results: A total of 308 patients were included in the study: 61 receiving TACE plus sorafenib treatment and 247 receiving TACE monotherapy. The PSM cohort included 61 subjects receiving TACE plus sorafenib and 122 subjects receiving TACE alone. In the overall analysis that included all patients, the median OS in the combination group was significantly longer than that in the monotherapy group (29.0 ± 7.2 vs. 14.9 ± 1.1 months; $P = 0.008$). In the PCM cohort, the median OS was also significantly longer in the combination group (29.0 ± 7.2 vs. 14.9 ± 1.5 months; $P = 0.018$). Subgroup analysis revealed longer OS in patients receiving combination treatment in both the BCLC-B and BCLC-C subgroups ($P < 0.05$ for both). Multivariate analyses in the PSM cohort revealed that treatment methods ($P = 0.003$), number of nodules ($P = 0.010$), tumor size ($P = 0.012$), vascular invasion ($P = 0.005$), and number of TACE ($P = 0.029$) were independent prognostic factors of OS. The most common adverse events were hand-foot skin reaction (75.4%) and diarrhea (47.5%) in the combination group, and fatigue (19.0%) and liver dysfunction (18.2%) in the monotherapy group. There were no treatment-related deaths in either group.

Conclusion: The combined use of TACE and sorafenib is generally well tolerated and could significantly increase OS of patients with unresectable HCC.

Key words: hepatocellular carcinoma; transarterial chemoembolization; sorafenib; survival; propensity score

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related deaths worldwide [1]. More than 80% of HCC cases occur in sub-Saharan Africa and Eastern

Asia, and China accounts for approximately 50% of all cases [2]. Curative treatments for HCC include surgical resection, liver transplantation, or local ablation therapy for early HCC [3]. However, many

patients are diagnosed at an advanced stage of HCC and, therefore, are not candidates for these radical treatment options at the time of diagnosis [4].

Transarterial chemoembolization (TACE) is a major treatment modality for unresectable HCC. The Barcelona Clinic Liver Cancer (BCLC) staging system recommends TACE as a standard treatment for stage B HCC [5]. TACE is also used as an important locoregional treatment for patients with advanced HCC, including those with vascular invasion or metastases [6, 7]. TACE exerts its effects by administering intra-arterial cytotoxic chemotherapeutic agents, followed by embolization, creating vascular occlusion and inducing ischemia and necrosis of the HCC lesion [8]. Two randomized controlled trials (RCTs) have confirmed that TACE improved survival of unresectable HCC patients compared to symptomatic treatment [9, 10].

Sorafenib is currently the only first-line multi-kinase inhibitor approved for use in HCC [11]. Sorafenib inhibits the activity of the Raf serine-threonine kinase and receptor tyrosine kinases, including vascular endothelial growth factor receptor (VEGFR)-1/2/3, platelet-derived growth factor receptor-beta (PDGFR- β), c-KIT, FLT-3, and RET [11, 12]. These kinases are involved in tumor cell signaling, proliferation, angiogenesis and apoptosis. Thus, sorafenib could inhibit tumor growth and neo-angiogenesis. RCTs have shown that it is efficacious for prolonging time to progression (TTP) and median overall survival (OS) of patients with advanced HCC [13, 14].

The combination of TACE with sorafenib is appealing based on a strong scientific rationale. In fact, TACE causes hypoxia within the tumor, resulting in local and systemic increases in VEGF, which may facilitate disease progression and metastasis [15, 16], whereas sorafenib can inhibit the activity of VEGF receptors; thus, the combination therapy may have synergistic effect. Indeed, several prospective studies have shown the safety and potential survival benefits of the use of this combination therapy in patients with unresectable HCC [17-19]. However, a phase III study and a meta-analysis did not find an improvement in OS with the combined therapy [20, 21]. Therefore, whether the combination of TACE and sorafenib in patients with unresectable HCC could improve the survival outcomes remain controversial.

The purpose of this study was to compare OS of unresectable HCC treated with TACE combined with sorafenib *versus* TACE monotherapy using propensity score matching (PSM). In addition, we further explored predictors of OS.

Materials and Methods

The study design and patient population

The current retrospective study included all adult patients (18 years or older) with unresectable HCC who were admitted to our department from February 2008 to August 2015. HCC was diagnosed by the practice guidelines of the American Association for the Study of Liver Disease [22].

Patients included in our study met the following criteria: 1) patients were treated with TACE alone or TACE combined with sorafenib instead of any other interventional procedures such as radio-frequency ablation, microwave ablation, iodine-125 seed implantation or percutaneous ethanol injection; 2) Child-Pugh class A or B; 3) Eastern Cooperative Oncology Group performance status (ECOG PS) score of no more than 2; 4) sorafenib treatment at least 5 weeks; 5) patients showed disease progression despite previous surgical treatment. Patients were excluded if they had any of the following reasons: 1) sorafenib was discontinued or the interval between sorafenib administration and initial TACE procedure lasted for more than one month; 2) patients with secondary malignancy; 3) patients who received other targeting agents or immunotherapy.

The study protocol was approved by the Institutional Ethics Review Board of the First Affiliated Hospital of Soochow University (Suzhou, Jiangsu Province, China). Given the retrospective study design, the requirement to obtain informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki on human research.

TACE

The femoral artery was punctured using the Seldinger technique. Angiography of the celiac, hepatic, and superior mesenteric arteries was performed to identify all tumor-feeding arteries by using a 5-Fr catheter. After identification of the target artery, segmental and subsegmental tumor feeding arteries was catheterized using a 2.3-Fr to 2.8-Fr tip microcatheter. An emulsion of chemotherapeutics and iodized oil was slowly injected to the tumor feeding arteries through the microcatheter. The super selective TACE procedure was the preferred modality whenever technically feasible. The treatment regimen was comprised of oxaliplatin (50-100 mg) and pirarubicin (10-40 mg) with lipiodol (2-20 mL). Drug was selected at physician discretion, and the dose of lipiodol was selected by tumor size. Gelatin sponge or polyvinyl alcohol particles (300-500 μ m) were injected to embolize tumor-feeding arterioles if necessary, until there was no tumor staining with repeat

angiography. In patients with tumor thrombosis in the main portal branch and/or Child-Pugh B liver function, gelatin sponge particles were not used. Contrast agent-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was performed 6-8 weeks after the procedure. When residual viable tumors were confirmed or new lesions developed in patients with adequate hepatic function, "on demand" TACE were repeated carried out.

Sorafenib therapy

All patients were given detailed information of sorafenib treatment including its efficacy, potential adverse effects, and costs. The use of sorafenib in addition to TACE was recommended by the physicians and the final treatment decision was generally made by the patients or their family members. Sorafenib was administered orally at a dose of 400 mg twice daily within 3 -5 days after the first TACE, and then discontinued the day before each next TACE, and resumed within 3 - 5 days after each repeated TACE. To ensure maximum patient safety, the dose of sorafenib was reduced, or treatment was delayed or temporarily discontinued when we observed grade 3 or 4 toxicity according to the National Cancer Institute Common Toxicity Criteria Adverse Events (CTC AE) version 3.0. Treatment was continued until disease progression, unacceptable toxicities, or death.

Safety assessment

Treatment-emergent adverse events (AEs) were graded by the CTC AE, version 3.0. Vital signs and AEs were monitored throughout the study. Safety assessments were based mainly on the occurrence, frequency, and severity of AEs. For all AEs, where necessary, patients were withdrawn from the study. Safety assessments were analyzed mainly using descriptive statistics.

Follow-up

Subjects underwent monthly follow-up that included complete blood cell count, prothrombin time, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, albumin, and serum alpha-fetoprotein (AFP). Liver contrast-enhanced CT or MRI was performed every 6-8 weeks to evaluate treatment response. If necessary, chest CT and/or a bone scan were also performed to identify extrahepatic metastasis. Tumor response was according to the Modified Response Evaluation Criteria in Solid Tumors (mRECIST) for HCC [23]. February 28, 2017 was the final date of follow-up. OS was calculated the date of the first TACE treatment until the date of death of any cause. Patients who were lost to follow-up were censored at the last date

they were known to be alive, and patients who remained alive were censored at the time of data cutoff.

Statistical analysis

Statistical analysis was performed using the SPSS version 22.0 (IBM Corp, Armonk, NY, USA). PSM was carried out, as previously described [24]. Propensity scores for all patients were calculated using a logistic regression model. The covariates in the analysis included sex, age, viral hepatitis, Child-Pugh score, serum AFP levels, BCLC stage, ECOG PS, number of nodules, tumor size, liver cirrhosis, vascular invasion, extrahepatic metastasis, number of TACE procedure, and previous tumor treatment. The nearest neighbor match in accordance with 1:2 ratios balanced the baseline characteristics of the patients. Differences in baseline characteristics of patients of the two groups were compared using Fisher's exact or χ^2 test for categorical variables and Student's t-test for continuous variables. OS was analyzed using Kaplan-Meier (KM) analysis followed by a log-rank test. Prognostic factors for OS were performed using univariate and multivariate analyses in the propensity score-matched cohort. Variables that showed statistical significance ($P \leq 0.05$) in the univariate analysis were entered into multivariate Cox regression models to look for predictors of efficacy. The outcomes were reported using hazard ratios (HRs) and associated 95% confidence intervals (95% CI). A two-sided P value ≤ 0.05 was taken as statistically significant.

Results

Patient demographic and clinical characteristics

Totally 363 patients with unresectable HCC met the inclusion criteria, of whom 55 were excluded according to the exclusion criteria (Figure 1). A total of 308 patients were included in the data analysis: 61 receiving TACE combined with sorafenib and the remaining 247 receiving TACE alone. One hundred eighty (58.4%) patients had BCLC stage B disease and the remaining 128 (41.6%) had stage C disease. Thirty (49.2%) subjects receiving TACE plus sorafenib had stage B disease and 31 (50.8%) had stage C disease; the median number of TACE sessions was 2 (range: 1-9). Sorafenib therapy was initiated for 56 patients (91.8%) within 5 days after the first TACE session (range 3-5 days). The treatment of the remaining 5 patients (8.2%) was delayed due to TACE-induced adverse effects, but all received sorafenib therapy within 14 days (range 6-14 days) after the completion of TACE. During the treatment, 19 (31.1%) and 5 (8.2%) patients required dose reductions and drug interruptions due

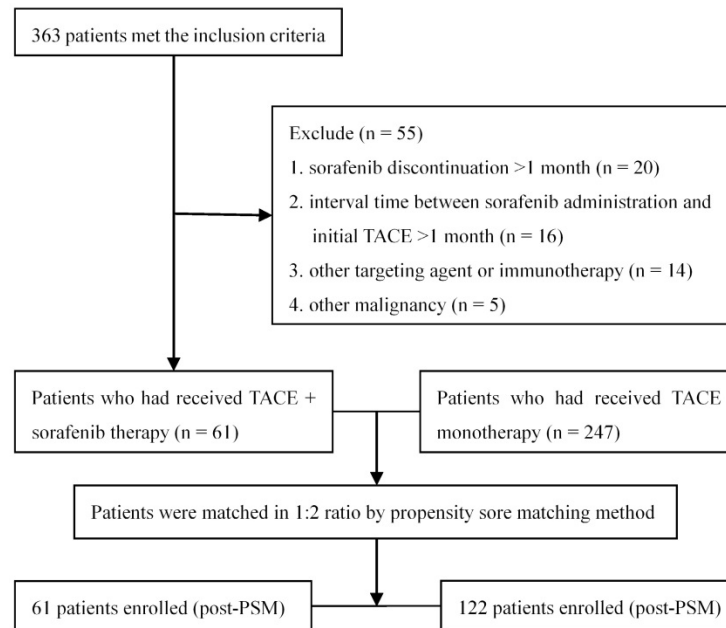


Figure 1. The study flowchart.

to severe sorafenib-related adverse events, respectively. The median duration of sorafenib treatment was 11.7 months (range 2.5-65.6 months). In the 247 subjects receiving TACE alone, the median number of TACE sessions was 3 (range: 1-18).

Table 1. Baseline characteristics of patients before and after propensity score matching.

Variables	TACE+Sorafenib (n=61)	TACE alone (pre-match, n=247)	P value	TACE alone (matched, n=122)	P value
Sex					
Male	48(78.7%)	209(85.0%)	0.265	102(83.6%)	0.415
Female	13(21.3%)	38(15.0%)		20(16.4%)	
Age					
<60y	39(63.9%)	148(59.9%)	0.565	71(58.2%)	0.455
≥60y	22(36.1%)	99(40.1%)		51(41.8%)	
Viral hepatitis					
HBV	50(82.0%)	192(77.7%)	0.470	93(76.2%)	0.376
HCV	5(8.2%)	13(5.3%)		9(7.4%)	
No infections	6(9.8%)	42(17.0%)		20(16.4%)	
Child-Pugh score					
A	55(90.2%)	219(88.7%)	0.738	111(91.0%)	0.857
B	6(9.8%)	28(11.3%)		11(9.0%)	
Serum AFP levels					
<400ng/ml	42(68.9%)	119(48.2%)	0.014	77(63.1%)	0.443
≥400ng/ml	19(31.1%)	128(51.8%)		45(36.9%)	
BCLC staging					
B	30(49.2%)	150(60.7%)	0.101	72(59.0%)	0.207
C	31(50.8%)	97(39.3%)		50(41.0%)	
ECOG PS					
0	36(59.0%)	166(67.2%)	0.237	69(56.6%)	0.751
1-2	25(41.0%)	81(32.8%)		53(43.4%)	
Number of nodules					
Single	40(65.6%)	127(51.4%)	0.047	77(63.1%)	0.744
Multiple-diffuse	21(34.4%)	120(48.6%)		45(36.9%)	
Tumor size					
≤5cm	26(42.6%)	57(23.1%)	0.002	45(36.9%)	0.453
>5cm	35(57.4%)	190(76.9%)		77(63.1%)	
Liver cirrhosis					
Yes	31(50.8%)	169(68.4%)	0.010	70(57.4%)	0.400

No	30(49.2%)	78(31.6%)		52(42.6%)	
Vascular invasion					
Yes	20(32.8%)	71(28.7%)	0.536	33(27.0%)	0.420
No	41(67.2%)	176(71.3%)		89(73.0%)	
Extrahepatic metastasis					
Yes	14(23.0%)	15(6.1%)	0.000	15(12.3%)	0.063
No	47(77.0%)	232(93.9%)		107(87.7%)	
Number of TACE procedure					
≤3	48(78.7%)	169(68.4%)	0.115	93(76.2%)	0.709
>3	13(21.3%)	78(31.6%)		29(23.8%)	
Previous tumor treatment (Surgical)					
Yes	29(47.5%)	45(18.2%)	0.000	45(36.9%)	0.166
No	32(52.5%)	202(81.8%)		77(63.1%)	

TACE: transarterial chemoembolization; HBV: hepatitis B virus; HCV: hepatitis C virus; BCLC: Barcelona Clinic Liver Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status.

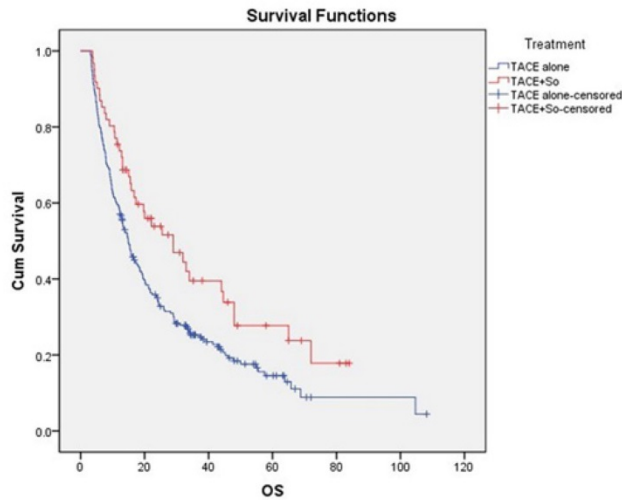
The demographic and baseline characteristics of the study population are shown in Table 1. The two groups differed significantly in serum AFP levels, number of nodules, tumor size, liver cirrhosis, extrahepatic metastasis, and previous tumor treatment. After matching by the nearest available neighbor method (1:2), based on the number of 61 patients who accepted sorafenib, 122 patients with TACE alone were matched for the analyses. In the PSM cohort, there were no significant differences among the baseline characteristics between the two groups.

OS

The median OS was 29.0 ± 7.2 (95% CI, 14.945-43.055) months in subjects receiving TACE plus sorafenib and 14.9 ± 1.1 (95% CI, 12.694-17.106) months in subjects receiving TACE alone, strongly favoring the combination treatment (HR = 0.628, 95%

CI: 0.445-0.888; $P = 0.008$; Figure 2A). In the PSM cohort, the median OS was 29.0 ± 7.2 (95% CI, 14.945-43.055) months in the combination group and 14.9 ± 1.5 (95% CI, 12.025-17.775) months in the TACE monotherapy group, also strongly favoring the combination treatment (HR = 0.684, 95% CI: 0.470-0.997; $P = 0.018$; Figure 2B).

A



B

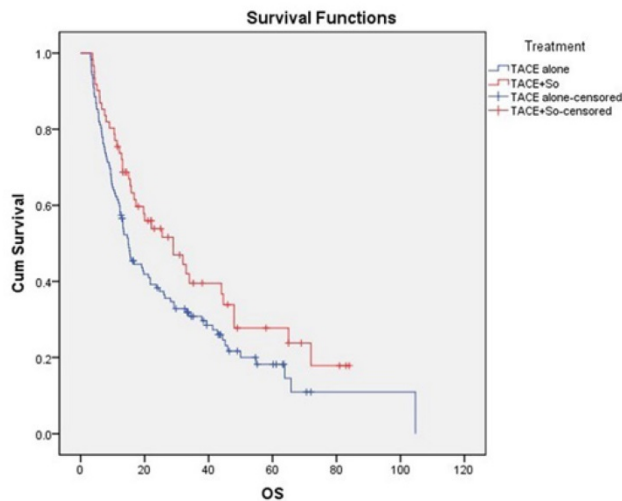


Figure 2. Kaplan-Meier analysis of overall survival (OS) in the combined treatment group and the monotherapy group for all patients (A) and propensity-matched patients (B). Both non-matched and matched models reveal significant differences in OS between the combined treatment group and the monotherapy group (non-matched model: 29.0 ± 7.2 months for the combined treatment group vs. 14.9 ± 1.1 months for the monotherapy group, $P = 0.008$; matched model: 29.0 ± 7.2 months for the combined treatment group vs. 14.9 ± 1.5 months for the monotherapy group, $P = 0.018$).

Safety

Treatment-emergent adverse events (AEs) are shown in Table 2. The two most frequent AEs in the TACE alone group were fatigue (19.0%) and liver dysfunction (18.2%). In addition, grade 3/4 liver dysfunction occurred in 8.9% of the patients; no other

grade 3/4 AEs were reported. In the TACE plus sorafenib group, hand-foot skin reaction (75.4%), diarrhea (47.5%), and liver dysfunction (32.8%) were the most three most frequent AEs. Grade 3/4 hand-foot skin reaction (18.0%), liver dysfunction (13.1%) and diarrhea (9.8%) were the most common grade 3/4 AEs. There was no treatment-related death in either group.

Table 2. Adverse events in the combination treatment group and the monotherapy group.

Adverse events	TACE + sorafenib (n=61)		TACE alone (n=247)	
	All grade (n)	Grade 3/4 (n)	All grade (n)	Grade 3/4 (n)
Hand-foot skin reaction	46 (75.4%)	11 (18.0%)	0	0
Diarrhea	29 (47.5%)	6 (9.8%)	3 (1.2%)	0
Hypertension	10 (16.4%)	3 (4.9%)	2 (0.8%)	0
Alopecia	19 (31.1%)	2 (3.3%)	0	0
Gastrointestinal bleeding	2 (3.3%)	0	5 (2.0%)	0
Liver dysfunction (AST and/or ALT increase)	20 (32.8%)	8 (13.1%)	45 (18.2%)	22 (8.9%)
Fatigue	15 (24.6%)	0	47 (19.0%)	0

Subgroup analysis

In the BCLC-B subgroup, before matching, the median OS was 33.0 ± 9.8 (95% CI, 18.688-43.312) months in the TACE plus sorafenib group and 21.2 ± 2.3 (95% CI, 16.696-25.704) months in the TACE monotherapy group (HR = 0.547, 95% CI: 0.317-0.943; $P = 0.027$; Figure 3A). After PSM, the median OS was 33.0 ± 9.8 (95% CI, 18.688-43.312) months in the combination group and 25.3 ± 6.7 (95% CI, 13.135-39.465) months in the monotherapy group (HR=0.620, 95% CI: 0.345-1.114; $P = 0.041$; Figure 3B).

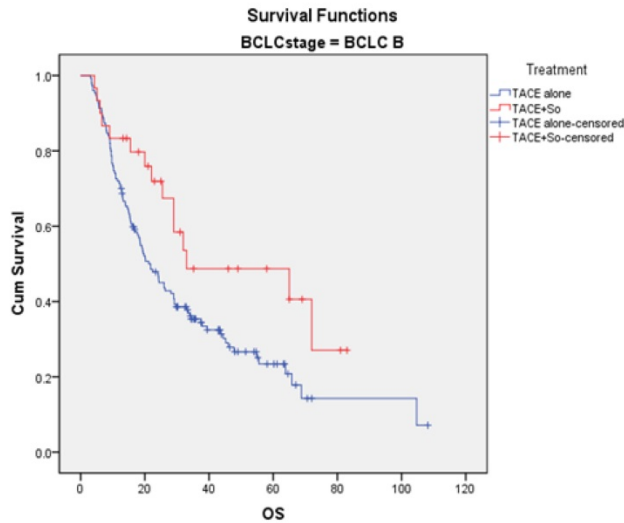
In the BCLC-C subgroup, before matching, the median OS was 15.8 ± 2.0 (95% CI, 11.820-19.780) months in the TACE plus sorafenib group and 7.8 ± 1.1 (95% CI, 5.607-9.993) months in the TACE monotherapy group (HR=0.507, 95% CI: 0.320-0.801; $P = 0.003$; Figure 4A). After PSM, the median OS was 15.8 ± 2.0 (95% CI, 11.820-19.780) months in the combination group and 8.3 ± 1.4 (95% CI, 5.528-11.072) months in the monotherapy group (HR = 0.544, 95% CI: 0.328-0.902; $P = 0.016$; Figure 4 B).

Prognostic factors for OS in the PSM cohort

Univariate and multivariate analyses of the factors influencing OS are summarized in Table 3. Univariate log-rank test analysis of the PSM cohort showed that OS was associated with treatment methods, serum AFP levels, BCLC stage, number of nodules, tumor size, liver cirrhosis, vascular invasion, number of TACE, and previous tumor treatment ($P \leq 0.05$ for all). Multivariate Cox regression analysis indicated the following independent factors: treatment methods [HR 0.618; 95% CI (0.419-0.912); $P = 0.003$], number of nodules [HR 2.491; 95% CI

(1.705-3.638); $P = 0.010$], tumor size [HR 2.130; 95% CI (1.343-3.378); $P = 0.012$], vascular invasion [HR 2.575; 95% CI (1.676-3.957); $P = 0.005$], and number of TACE [HR 0.621; 95% CI (0.405-0.953); $P = 0.029$].

A



B

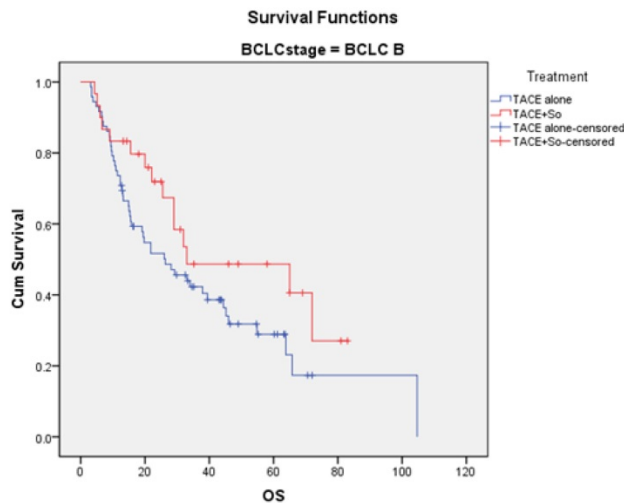


Figure 3. Kaplan-Meier analysis of OS in BCLC-B subgroup. (A) Median OS was 33.0 ± 9.8 months in the combined treatment group compared with 21.2 ± 2.3 months in the monotherapy group in the non-matched model ($P = 0.027$). (B) Median OS was 33.0 ± 9.8 months in the combined treatment group compared with 25.3 ± 6.7 months in the monotherapy group in the matched model ($P = 0.041$).

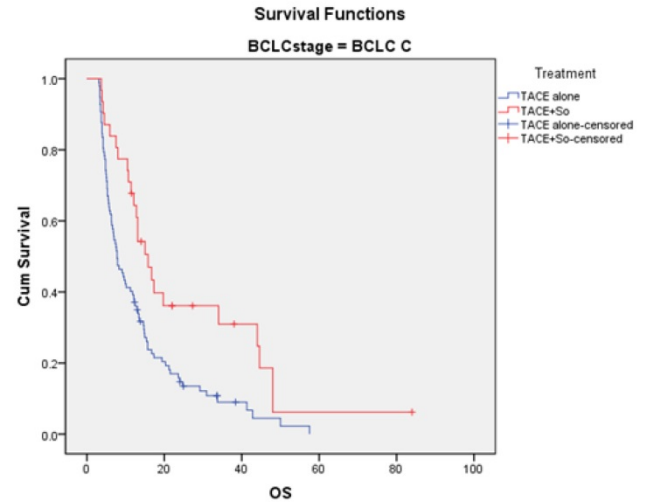
Table 3. Univariate and multivariate analyses of potential prognostic factors for overall survival

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Treatment methods	0.684 (0.428-0.908)	0.008	0.618 (0.419-0.912)	0.003
Gender	1.558 (0.967-2.510)	0.069	-	-
Age	1.066 (0.752-1.510)	0.721	-	-
Viral hepatitis	0.872 (0.577-1.319)	0.517	-	-
Child-Pugh score	0.618 (0.354-1.080)	0.091	-	-
Serum AFP levels	1.563 (1.100-2.221)	0.013	1.350 (0.957-1.903)	0.087

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
BCLC staging	2.435 (1.714-3.457)	0.004	1.183 (0.696-2.013)	0.535
ECOG PS	1.355 (0.931-1.853)	0.287	-	-
Number of nodules	1.950 (1.369-2.778)	0.026	2.491 (1.705-3.638)	0.010
Tumor size	2.422 (1.671-3.511)	0.006	2.130 (1.343-3.378)	0.012
Liver cirrhosis	1.542 (1.095-2.170)	0.015	1.523 (1.010-2.297)	0.054
Vascular invasion	3.097 (2.154-4.451)	0.011	2.575 (1.676-3.957)	0.005
Extrahepatic metastasis	1.500 (0.952-2.364)	0.081	-	-
Number of TACE	0.663 (0.444-0.989)	0.044	0.621 (0.405-0.953)	0.029
Previous tumor treatment	0.628 (0.440-0.897)	0.010	1.492 (0.928-2.399)	0.099

Treatment methods: TACE + sorafenib vs TACE alone; HR: hazard ratio; 95% CI: 95% confidence interval.

A



B

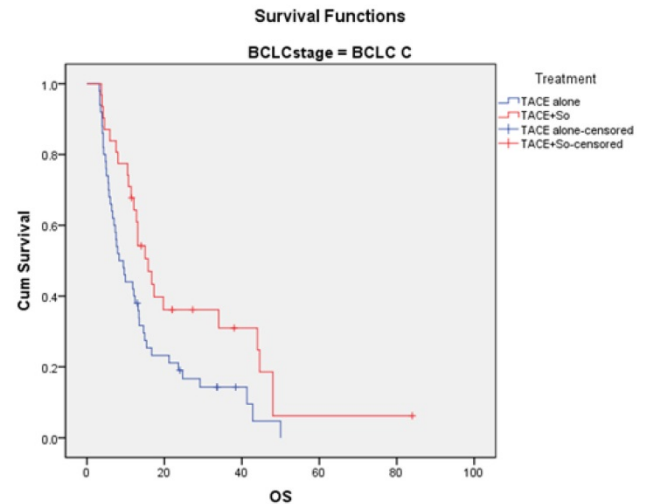


Figure 4. Kaplan-Meier analysis of OS in BCLC-C subgroup. (A) Median OS was 15.8 ± 2.0 months in the combined treatment group compared with 7.8 ± 1.1 months in the monotherapy group in the non-matched model ($P = 0.003$). (B) Median OS was 15.8 ± 2.0 months in the combined treatment group compared with 8.3 ± 1.4 months in the monotherapy group in the matched model ($P = 0.016$).

Discussion

This retrospective study demonstrated that the combination treatment with TACE and sorafenib

significantly improved OS *versus* TACE monotherapy in patients with unresectable HCC. This survival advantage was still present even after adjustment of baseline characteristics through PSM.

The survival advantage of combined TACE and sorafenib treatment seen in our study is encouraging. The median OS in our subjects receiving TACE plus sorafenib was numerically longer than 7.5-27 months reported in previous studies [25-27]. Such a discrepancy could reflect differences between the current and previous studies. Firstly, in this study, the median duration of sorafenib treatment was 11.7 months, which is longer than that of the above mentioned studies [25, 27]. It may be the key reason for the success of the combined treatment group. The negative results of the two RCTs, Post-TACE and TACE-2, may be due to the short duration of sorafenib administration [28]. Recently, the preliminary results of the TACTICS trial also supported our viewpoint [29]. Additionally, due to the plasma concentration of VEGF was markedly elevated after TACE treatment [16], patients in our study received timely sorafenib treatment within 3-5 days after the first TACE. Meng et al. [30] demonstrated that earlier administration of sorafenib after the first TACE may lead to a greater survival benefit in patients with HCC.

In subgroup analysis, the median OS of BCLC-B patients was significantly longer in the combined treatment group than in the TACE monotherapy group before and after PSM, suggesting that BCLC stage B HCC patients could benefit from the combination therapy. This finding has also been supported by a recent PSM study [31]. In addition, a meta-analysis of 1254 patients with intermediate stage HCC confirmed that the combination therapy of TACE plus sorafenib can improve OS [32]. Similarly, in the BCLC-C subgroup, the combination therapy of TACE plus sorafenib significantly improved OS *versus* TACE alone, a finding also confirmed in the PMS cohort. Numerous clinical studies have demonstrated that TACE combined with sorafenib is superior to TACE or sorafenib monotherapy in prolonging OS in advanced HCC patients [33-35]. These findings are further supported by two meta-analyses of RCTs [36, 37].

Our multivariate analysis indicated that the combination treatment with TACE and sorafenib was an independent predictor for OS. In addition, number of nodules, tumor size, vascular invasion, and number of TACE were also significant predictors of OS. These findings are similar to those of a recent study showing TACE plus sorafenib treatment, Child-Pugh class, vascular invasion, tumor number and tumor size as independent predictors of prognosis [38]. Differing results in terms of the number of TACE may be due to

differences in patient response to TACE, hepatic reserve function and patient compliance.

Evidence from recently studies have suggested that common AEs are associated with the use of sorafenib, the most common being hand-foot skin reactions, diarrhea, alopecia, and fatigue [39, 40]. Similar safety outcomes were found in the current study, which revealed hand-foot skin reaction and diarrhea to be the most common drug-emergent AEs, followed by alopecia and fatigue. Hypertension and gastrointestinal bleeding were also observed in a small fraction of patients. Most of these AEs in our study were grade 1/2 and well tolerated, which seldom contributed to the discontinuation of therapy.

The current study has some limitations that must be considered. Due to the retrospective nature of this study, there was selection bias in determining treatment modalities. The choice of sorafenib was based on physician discretion and patient financial capability, which introduced a selection bias that could have influenced the difference in survival between the two groups. To minimize the bias, we conducted PSM, which supported the advantage of combination treatment. Secondly, all subjects received treatment at the same research site, and the sample size is relatively small, and the results of which on its own cannot represent the entire population. Thirdly, as BCLC stage B and C HCC include a broad spectrum of tumors, the composition of our sample was mixed. The heterogeneity of our patients precluded a stratified analysis for patients with different extents of disease.

In conclusion, the current study indicated that addition of sorafenib to TACE therapy is generally well tolerated and could increase OS of patients with unresectable HCC. Further multi-center, prospective, randomized, controlled trials are required to confirm our preliminary findings, as well as to identify suitable candidates for treatment.

Abbreviations

TACE: transarterial chemoembolization; HCC: hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer; RCT: randomized controlled trial; VEGFR: vascular endothelial growth factor receptor; TTP: time to progression; OS: overall survival; PSM: propensity score matching; ECOG PS: Eastern Cooperative Oncology Group performance status; CT: computed tomography; MRI: magnetic resonance imaging; CTC AE: Common Toxicity Criteria Adverse Events; AEs: adverse events; AST: aspartate aminotransferase; ALT: alanine aminotransferase; AFP: alpha-fetoprotein; mRECIST: Modified Response Evaluation Criteria in Solid Tumors; HR: hazard ratio; CI: confidence intervals.

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Competing Interests

The authors have declared that no competing interest exists.

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