

Survival Benefits and Safety Profile of Transarterial Chemoembolization (TACE) Based Monotherapy or Multi-modal Therapies in Locally Advanced Stage Hepatocellular Carcinoma: an Observational Study from Real-World Setting

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Abstract

Background : Majority of patients with locally advanced hepatocellular carcinoma (HCC) in Asian-Pacific regions underwent transarterial chemoembolization (TACE) or TACE-based multi-modal treatments instead of molecular target therapy in clinical practice. We aimed to evaluate the treatment outcomes and safety of transarterial chemoembolization based multi-modal treatments in locally advanced HCC from a real-world setting. Methods: From January 2008 to December 2015, 552 patients with locally advanced HCC who received TACE based monotherapy or multi-modal treatments at Liver Cancer Institute, Zhongshan Hospital, Fudan University were retrospectively enrolled. The clinical outcome of these patients were evaluated among these treatment groups. Propensity score matching analysis was performed to reduce potential bias for comparing treatment modalities. Results: Of all the patients, 375 patients received TACE treatment, 83 patients received TACE followed Sorafenib treatment (TACE+Sorafenib), 30 patients received TACE followed local ablation treatment (TACE+LAT), and 64 patients received TACE followed radiotherapy (TACE+Radiotherapy). 1-, 3-, 5-year OS rates in TACE group were 50.5%, 29.8% and 24.5% vs. 74.3%, 46.6% and 37.6% in TACE+multi-modal treatment group ($P<0.001$). The median survival time was 7.5 months, 13.0 months, 16.5 months, 10.0 months for TACE alone group, TACE+Sorafenib group, TACE+LAT group, and TACE+Radiotherapy group respectively. After propensity score matching, survival benefits were verified in TACE+Sorafenib and TACE+LAT treatments group. Safety analysis showed the major adverse events rates was 3.6% in TACE alone group and 3.9% in TACE+multi-modal treatment group with no statistic difference ($P=1.0$). Conclusions: TACE+Sorafenib treatment or TACE+local ablation treatment could achieve superior survival benefits to TACE alone in the management of locally advanced HCC.

Background

Hepatocellular carcinoma (HCC) represents the second leading cause of cancer-related death worldwide(1). Although a lot of efforts have been made on HCC surveillance in the setting of viral hepatitis infection population, only a minority of HCC is diagnosed at early stage(2). Approximately 70% initially diagnosed HCC patients cannot undergo radical liver resection or liver transplantation owing to locally advanced disease, underlying liver cirrhosis or poor performance status. Consequently, HCC-associated morbidity continues to increase, especially in the Asian-Pacific area(3).

The Barcelona Clinic Liver Cancer (BCLC) staging system is the most commonly used system for newly diagnosed HCC(4). According to BCLC system, patients with Eastern Cooperative Oncology Group (ECOG) performance status of 1-2 score and/or the presence of macro-vascular invasion or extrahepatic metastasis are defined as BCLC stage C HCC(5). Based on the BCLC treatment recommendation, molecular target therapy is the only choice for patients with BCLC stage C or advanced stage HCC. This conservative recommendation excludes other alternative treatment strategy at this stage. Actually, in most Asian countries with high incidence of HCC, high medical expenses restrict the wide application of molecular target therapy. As such, many hepatologists in this area employ local-regional therapy and seek different combine therapies for better outcomes. Accordingly, Asian guidelines including the

APASL(3), JSH(6), the KLCSG-NCC(7), and the 2017 edition of Chinese HCC guideline(8) also recommended several local-regional treatments including transcatheter arterial chemoembolization (TACE), haptic arterial infusion chemotherapy (HAIC), radiotherapy in the management of advanced stage HCC. This treatment gap between western and western areas highlights the need to assess the survival benefits and safety profile of these local-regional treatments in advanced stage HCC.

Based on the opinions of Asian expert, BCLC stage C HCC could be subdivided into a locally advanced stage without extrahepatic spread and an extrahepatic advanced stage(9). It is widely accepted that local tumor control is the most important prognostic factor for HCC, because up to 92% of deaths can be directly correlated to local progression leading to liver failure rather than distant metastases(10). TACE is a first-line treatment in intermediate stage HCC, which is also the only local-regional treatment with proven survival benefit over best supportive care for advanced stage HCC (11, 12). In fact, an international large-scale BRIDGE study(13) documented that, TACE was the first treatment choice for nearly 50% of the BCLC stage C HCC patients, majority of whom were classified into locally advanced stage. Studies from different Asian-Pacific countries have explored the treatment outcomes of TACE alone or TACE-based combination treatments in the management of advanced stage HCC(14-18). However, the existing evidence in confirming the rationale of TACE in locally advanced stage HCC remain weak. Randomized controlled trials (RCTs) are the most universally accepted methods to evaluate treatment effects and clinical outcomes, however, they are conducted in highly selected populations and usually lack external validity(19). Instead, large observational studies can provide crucial real-world evidence due to the distribution of patients with different clinical features and diverse treatment modalities in clinical practice. Herein, we investigated the treatment outcome and safety profile of TACE-based monotherapy or multi-modal treatments in a large real-world cohort, aiming to provide potential multi-modality treatments for locally advanced stage HCC.

Methods

Patients

This observational study was conducted on a prospectively maintained data set of HCC patients in liver cancer institute, Zhongshan hospital, Fudan University. From January 2008 to December 2015, a total of 1327 patients were diagnosed as BCLC stage C HCC in our institute. On confirmation of BCLC stage C HCC, the patient was informed of Sorafenib administration as the first-line treatment. For those who initially refused to receive Sorafenib monotherapy, TACE was recommended as the alternative treatment choice according to 2011 edition of Chinese guideline for HCC. The most common reason for the rejection is the high cost that patients cannot afford because sorafenib is not on the list of drugs covered by medical insurance. The inclusion criteria were: 1) age more than 18 years old; 2) HCC diagnosed by either pathology or by clinical criteria according to AASLD guidelines(20); 3) patients with tumors were initially classified as locally advanced stage HCC; 4) with Child-Pugh A or B grade; 5) ECOG score 0-1; 6) had refused Sorafenib treatment and undergone TACE-based monotherapy or multi-modal therapy as initial treatment. The exclusion criteria were: 1) patients receiving liver resection prior to TACE; 2) patients

receiving liver transplantation before or after TACE; 3) being concurrent with another type of malignant tumor; 4) with severe medical comorbidities. In total, 552 consecutive patients with locally advanced HCC were included. The inclusion flowchart was illustrated in Fig.1.

Data collection

Baseline clinicopathological characteristics data were extracted from prospectively maintained database of Liver Cancer Institute, Zhongshan Hospital, including sex, age, etiology of liver disease, medical comorbidities, tumor characteristics, liver function, tumor marker, vascular invasion, lymph node involvement and extrahepatic metastasis, the presence and severity of ascites and hepatic encephalopathy, treatment details and survival outcome. For data not available in the database, manual chart abstraction was performed by the three co-authors (Bei Tang, Jia Yuan and Miao Li). This mainly included ECOG score and major complications after treatment.

Treatment

The treatment modality for individual patient was recommended by the hepatologists with more than 10 years experience and the final treatment choice was generally decided by the patients, who were informed of the advantages and disadvantages of treatments, including potential clinical benefit, treatment-related morbidity and medical costs. Patients undergoing TACE-based monotherapy or multi-modal therapy were categorized into four treatment subgroups: TACE alone, TACE+Sorafenib, TACE+local ablation treatment and TACE+Radiotherapy.

TACE alone

A total of 375 patients with locally advanced stage HCC received TACE alone. TACE was performed under the standard protocol of our department as described by Yin et al(21). Briefly, under local anesthesia, the right superficial femoral artery was punctured using Seldinger technique. A 5F or 4F catheter (Cordis®, Baltimore, USA) was introduced into the abdominal aorta under fluoroscopy guidance. Selective angiography via the common hepatic artery or the superior mesenteric artery was performed to identify the tumors and their feeding arteries. Super-selective embolization was using a microcatheter (Terumo®, Tokyo, Japan) if needed, two anticancer agents (1000 mg of 5-fluorouracil, 100-150 mg of oxaliplatin) were infused through catheter into the feeding arteries with the perfusion time at least 20 minutes. An emulsion of 5 to 20 mL lipiodol with 30 mg epirubicin was slowly injected into the feeding arteries. The dosage of lipiodol used in TACE were determined by the tumor size and extent of the lesions as well as dosages of anticancer agents adjusted according to bone marrow function and liver or renal function.

TACE+Sorafenib

A total of 83 patients received TACE combined with subsequent Sorafenib therapy in our series. Patients received TACE+Sorafenib treatment were characterized by the following features: 1) with adequate liver function defined as Child-Pugh A or B7 and ECOG score of 0-1; 2) with TACE refractory status evaluated by the JSH Consensus Guidelines(6); 3) be consent to receive Sorafenib treatment after TACE. These

patients received 3.8 ± 1.4 sessions of TACE treatments before Sorafenib medication. Sorafenib (Nexavar; Bayer, Leverkusen, Germany) was administered orally 400mg twice daily. Adverse reactions were evaluated by National Cancer Institute Common Terminology Criteria (Version 4.03). If intolerable adverse reactions occurred, the dose was reduced according to the SHARP clinical trial(22): first to 400 mg once a day then to 400 mg once every other day. If toxicity was reduced to grade 1-2, Sorafenib was resumed; otherwise, medication was stopped permanently. Patients taking Sorafenib for at least 2 months, until tumor progressed or died.

TACE+Local ablation treatment (TACE+LAT)

In our series, a total of 30 patients receiving local ablation treatment including radiofrequency ablation (RFA) as well as percutaneous ethanol injection (PEI) within one or two months following TACE. The interval of TACE and local ablation therapy was 1-2 months depending liver function status after TACE. These patients were characterized by the following features: 1) with local tumors partially response (PR) to prior TACE treatment judged by mRECIST criteria upon radiological examinations; 2) residual viable tumors could be potentially complete ablated by local ablation treatment; 3) tumors were visible through ultrasound with a safe ablation path between the lesion and skin; 4) eligible coagulation function (prothrombin activity higher than 40% or a platelet count less than 40,000/L). Among these 30 patients, 25 patients received RFA and 5 patients received PEI due to the high risk of tumor location not amenable for RFA. RFA was carried out percutaneously under local anesthesia by using the RITA system (RITA Medical Systems Inc., Mountain View, CA) or Cool Tip system (Valleylab, Boulder, CO, USA), according to the guidelines of the manufacture of the ablation device. Single needle electrodes were used with length of the burning tip of the radiofrequency probe ranging from 2 to 3 cm depending on the size of tumor. Overlap ablations were allowed to achieve complete ablation. For patients receiving PEI treatment, a volume of 2.0-5.0 ml of alcohol was injected in each procedure based on the volume of treated tumors. PEI was repeated by 4-6 sessions (mean 4.3 ± 1.7 sessions) according to institutional local regional treatment principle.

TACE+Radiotherapy

In our cohort, 64 patients with portal vein tumor embolus were treated with TACE followed radiotherapy targeting tumor embolus. 3-dimensional conformal RT (3D-CRT, n=40), and intensity-modulated RT including tomotherapy (IMRT, n=24) were carried out for these patients after TACE. These patients were characterized by Child-Pugh A or B7, ECOG score of 0-1 and no hepatic encephalopathy, uncontrolled ascites and no recent gastrointestinal bleed. The interval of TACE and radiotherapy was 4-6 weeks, depending on the liver function recovery after TACE. All patients completed the scheduled radiotherapy. A daily fraction of 2 Gy was administered to deliver a median dose of 45 Gy (95% CI 22-68 Gy). Overall radiotherapy treatment duration was 3-6 weeks.

Follow up

In follow up, patients underwent computed tomography (CT) or magnetic resonance imaging (MRI), liver function and serum α -fetoprotein (AFP) level 4 weeks after treatment, with follow-up every 2 or 3 months within the first year and six months thereafter. Survival data were collected very 6 months until death or lost follow up as censored. Chest CT scan or bone scintigraphy were performed when clinically indicated.

Statistical analysis

Continuous variables with a Gaussian distribution are provided as mean (SD). Continuous variables with no Gaussian distribution are given as median (95% CI). Categorical variables are given as the number (percentage) of patients with the respective attribute. Bivariate comparisons were performed using the t test for normally distributed continuous variables or the Mann-Whitney U test for variables not normally distributed. Bivariate comparisons of categorical variables were done with the Pearson chi test or the Fisher's exact test. OS was estimated by the Kaplan-Meier method and differences were tested by the log-rank test. Variables associated ($P < 0.10$) with survival at univariate analysis were entered into Cox multivariate regression analysis. Propensity score matching (PSM) was performed to compare treatment outcome in patients with similar clinical characteristics who underwent TACE monotherapy or TACE-based multi-modal therapy. Covariates entered into the propensity model included age, sex, etiology of liver disease, Child-Pugh grading, AFP levels, maximum tumor size, tumor number, vascular invasion and lymph node involvement. PSM analysis (1:1 ratio, with nearest-neighbour matching or calliper width of 0.1 of the standard deviation of the logit) was applied in patients undergoing TACE monotherapy and correspondent TACE-based multi-modal therapies. P value < 0.05 in a two-tailed test was considered statistically significant. All statistical analysis was performed using Stata version 14.0 (Stata Corporation, University of Texas, USA)

Results

Patient characteristics

According to the study enrollment criteria, 1060 consecutive patients with locally advanced HCC were screened in the database. 419 patients with metastatic advanced HCC were excluded from the study. 58 patients were excluded due to receiving liver resection prior to TACE. 24 Patients were excluded because of receiving liver transplantation before or after TACE. 5 patients were excluded due to decompensated liver function of Child-Pugh C grade. As a result, a total of 552 patients were enrolled into the study (Fig.1). The baseline characteristics of these 552 were summarized in Table 1. Of all the patients, 443 (80.1%) were males with a median age of 54.5 years (95% CI, 35.0-73.0 years). There were 446 patients (80.8%) who were positive for hepatitis B virus and 12 patients (2.2%) who were positive for hepatitis C. 360 patients (65.2%) had solitary tumor and 192 patients (34.8%) had multiple tumors. The median tumor size was 9.0 cm (95% CI, 2.5-15.0cm). Child-Pugh grade was A in 451 (81.7%) and B in 101 (18.3%) patients. Serum AFP levels were elevated more than 20 ng/mL in 441 (79.9%) patients. Tumor thrombosis was detected in 517 patients (93.7%) and hepatic lymph nodes involvement were found in 45 patients (8.2%).

In treatment subgroup, 375 patients received TACE alone treatment, 83 patients received TACE followed TACE+Sorafenib treatment, 30 patients received TACE+LAT and 64 patients received TACE+Radiotherapy. The characteristics of patients in different treatment subgroup were detailed in Supplemental Table 1-3.

Survival

The median duration of follow-up was 29.0 months (95% CI: 3.5-49.0 months). Overall, the median OS across the whole study population was 9.0 months (95% CI: 4.0-49.0 months). Patients in TACE group had a median OS of 7.5 months (95% CI: 4.0-37.0 months), while patients in TACE+Multi-modal treatment group had a median OS of 12.0 months (95% CI: 3.5-69.0 months).The estimated 1-, 3-, 5-year OS rates in TACE group were 50.5%, 29.8% and 24.5% vs. 74.3%, 46.6% and 37.6% in TACE+Multi-modal treatment group (Fig.2A, P<0.001). In TACE+Multi-modal treatment subgroups, the median OS were 13.0 months, 16.5 months, 10.0 months in the patients receiving TACE+Sorafenib, TACE+LAT, TACE+Radiotherapy, respectively. 1-3-5- year overall survival curves in each treatment subgroup were illustrated in Fig.2B. In treatment subgroup analysis, patients receiving TACE+LAT seemed to have a best prognosis among the multi-modal treatment subgroups. However, no statistic differences were found in log-rank test (P=0.44) . These preliminary data indicated that TACE-based multi-modal therapies could achieved a better survival outcome than TACE alone.

Cox regression analysis

To assess independent factors associated with OS, univariate and multivariate Cox regression analysis was performed. Univariate analysis revealed that gender, tumor size, AFP levels, vascular invasion type and treatment modality were predictors of OS. Further multivariate analyses confirmed that treatment modality was independent factors of OS (Table 2).

Propensity score matched Analyses

To adjust for the differences in baseline characteristics among treatment subgroups, propensity score matching analysis was used. In TACE+Sorafenib subgroup, 81 of 83 patients were matched with 81 of 375 patients receiving TACE treatment. In TACE+LAT subgroup, 26 of 30 patients were matched with 26 of 375 patients receiving TACE treatment. In TACE+Radiotherapy subgroup, 58 of 64 patients were matched with 58 of 375 patients receiving TACE treatment. After propensity score matching, the characteristics of the patients were not significantly different between each treatment subgroup and its control TACE group (Supplementary Table 1-3). The estimated 1-, 3-, and 5-year OS in each treatment subgroup before and after propensity score matching were listed in Table 3-Table 5. The survival benefits were verified in TACE+Sorafenib group (Fig.3A-3B, P=0.02) and TACE+LAT group (Fig.3C-3D, P=0.03), in comparison with TACE alone. Nevertheless,no survival difference was found between TACE+Radiotherapy group and TACE alone group (Fig.3E-3F, P=0.36).

Safety evaluation

No treatment-related mortality was found in treatment group. In the entire group, the common minor adverse events were anemia, fever, nausea, vomiting, abdominal pain, diarrhoea, weight loss, dermatological events, etc. The common major adverse events(AEs) including ascites, deterioration of liver function, gastrointestinal hemorrhage, infection and pulmonary embolism. The percentages of patients who experienced grade 3 or higher AEs were 3.7% in TACE alone group and 3.9 % in TACE+Multi-modal treatment group, which were detailed in Table 6. Although the high-grade AE rate was slightly higher in TACE+multi-modal treatment group, there was no statistic difference were found in the two groups ($P=1.0$).

Discussion

Although the treatment of HCC has advanced during the past several decades, the management of advanced stage HCC is still challenging. Advanced stage HCC encompasses a heterogeneous population and the suggested treatment for all these patients is molecular target therapy. However, one treatment type can hardly fit all this heterogeneous category of patients. To provide effective and safe multi-modal therapies for patients who dismissed molecular target therapy, we performed the present observational real-world study in locally advanced stage HCC patients. Our series indicated that TACE+Sorafenib treatment or TACE+local ablation treatment could achieve superior survival benefits to TACE alone in the management of locally advanced HCC.

Sorafenib and Lenvatinib is the first-line treatment recommended by the AASLD/EASL guidelines for advanced stage HCC(20, 23). Before the advent of Lenvatinib in 2018, Sorafenib was the only treatment option for this patient group. However, due to the modest efficacy, poor tolerability and high economical cost of Sorafenib, majority of our patients chose to receive TACE treatments. The survival analysis indicated that patients undergoing TACE treatments had a median OS of 7.5 months, slightly longer than that of Sorafenib treatment reported by SHARP clinical trial (6.5 months). Noteworthy, patients enrolled in our cohort were different in compared to those who were enrolled in SHARP clinical trial. Our patients were characterized by high percentage of macroscopic vascular invasion as well as big tumor burden (median tumor size: 9.0 cm), both associated with worsening prognosis. Whereas in SHARP clinical trial, only 36% of the patients had macrovascular invasion. In a subgroup analysis for patients with macrovascular invasion in the Asia-Pacific trial, the median OS of the patients receiving Sorafenib therapy was only 4.4 months(24), significantly shorter than that of our patients undergoing TACE treatment. These data indicated that TACE might be a potentially beneficial treatment for locally advanced stage HCC. RCTs comparing TACE with Sorafenib as first-line treatment are needed to assess the safety and treatment outcome for patients with locally advanced stage HCC, especially for those who are intolerant of or unsuitable for Sorafenib.

TACE can be carried out repeatedly for unresectable HCC, but if the effect is judged to be poor, or TACE-refractory, introduction of Sorafenib should be considered(25). Several studies reported that TACE plus Sorafenib had superior efficacy to TACE monotherapy in patients with BCLC stage B/C HCC(26-28). Recently, results from a randomized, multicenter, phase II clinical trial (TACTICS trial) revealed TACE plus

Sorafenib improved progression-free survival over TACE alone in patients with unresectable HCC(29). Consistently, in our series, the median OS in patients treated with TACE+Sorafenib were 13.0 months, longer than those of patients treated with TACE alone (7.5 months). After propensity score matching, the 1-3-5-year survival rates were still higher than those of patients undergoing TACE alone (Fig.3B, P=0.02). With regard to treatment safety, 3 out of 83 (3.6%) patients demonstrated 3-4 AEs after Sorafenib administration, similar to those of patients receiving TACE treatment (3.7%). We propose that TACE combined with subsequent Sorafenib treatment can be an effective combination therapy in locally advanced HCC, especially in patients with TACE-refractory status .

It has been identified that more than most of patients with advanced stage HCC die of liver failure result from intrahepatic tumor progression(30, 31). Thereby, we assumed that a radical treatment strategy targeting the primary tumor in the liver might be reasonable and beneficial for locally advanced stage HCC. In our cohort, 30 patients receiving TACE followed by local ablation therapy which targeted intrahepatic tumors. This exploratory treatment strategy successfully achieved a median survival time of 16.0 months, which was significantly longer than that of TACE group (7.5 months). The promising results for TACE plus local ablation treatment warrant further evaluation in large prospective clinical trials.

It has been recognized that TACE alone has limited efficacy for HCC patients with portal vein tumor thrombus(32). With recent technological advances, external radiotherapy could be considered as a complementary treatment option for patients with locally advanced stage HCC(33). Specially, for patients with portal vein tumor thrombus, focal-field radiotherapy targeting tumor thrombus can inhibit intravascular tumor growth, maintain portal blood flow and preserve liver function, thus allow additional TACE treatment(34). Investigators have demonstrated that TACE plus radiotherapy therapy is an effective treatment modality for HCC patients with macroscopic vascular invasion(34, 35). However, in our cohort, after propensity score analysis, the treatment outcome of TACE+Radiotherapy was not superior to TACE alone. With regard to treatment safety, severe liver associated AEs were found in 4 out of 64 patients (6.3%). Considering most of our patients was presented with main portal vein tumor thrombus (33 out of 64 patients), the potential treatment benefit of this treatment modality might be compromised by severe AEs induced by decompensated liver function. The effective of TACE combined with external radiotherapy still need further validation.

There are several limitations in the present study. First, due to the retrospective nature of this study, patient selection bias was inevitable. However, to reduce potential bias, we performed propensity score matching analysis to adjust confound factors affecting prognosis. Second, due to the exploratory nature of the novel combination treatment of TACE+LAT in locally advanced stage HCC, the sample size in this treatment group was relatively small. Third, our study enrolled a Chinese population of HCC patients who were mainly infected with HBV, and a variation might exist in other populations with different ethnic background. However, the strength of our study lies in the real-world evidence of multi-modal treatments in the management of life-threatening locally advanced stage HCC. The promising survival benefits gives an important insight into the effectiveness and safety of TACE based multi-modal treatment in clinical practice.

Conclusions

To conclude, our data indicated that TACE combined with Sorafenib and TACE combined with local ablation therapy could provide favorable survival benefits in locally advanced stage HCC. Since advanced stage HCC are heterogeneous patient population and the optimal treatment for these patients remains unknown, further clinical trials are warranted to develop patient-tailored treatment strategy in the future.

Abbreviations

TACE: transarterial chemoembolization; **HCC:** hepatocellular carcinoma; **BCLC:** the Barcelona Clinic Liver Cancer; **ECOG:** Eastern Cooperative Oncology Group; **HAIC:** haptic arterial infusion chemotherapy; **RCTs:** randomized controlled trials; **LAT:** local ablation treatment; **RFA:** radiofrequency ablation; **PEI:** percutaneous ethanol injection; **PR:** partially response; **3D-CRT:** 3-dimensional conformal RT; **IMRT:** intensity-modulated RT; **CT:** computed tomography; **MRI:** magnetic resonance imaging; **AFP:** α-fetoprotein; **PSM:** propensity score matching; **AEs:** adverse events.

Declarations

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Author's contributions: ZGR conceived of the study, and participated in its design and coordination. XY, BT, JY, ML, SXL participated in data acquisition. YHW, RXC, LZ, BHZ contributed to collecting all the cases. XY and BT contributed to statistical analysis. XY, BT, FZ and KSH drafted and revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics of enrolled patients.

Variable	
Age, years	54.5±35.0-73.0±
Gender	
Male	443 (80.3%)
Female	109 (19.7%)
Etiology	
Hepatitis B positive	446 (80.8%)
Hepatitis C	12 (2.2%)
Other	94 (17.0%)
ECOG score	
0	223 (40.4%)
1	329 (59.6%)
AFP, ug/mL	
Positive (>20)	441 (79.9%)
Negative (<=20)	111 (20.1%)
Total Bilirubin, umol/L	
	13.4 (6.3-32.7)
Albumin, g/L	
	38.0 (29.0-45.0)
Child-Pugh Grade	
A	451 (81.7%)
B	101 (18.3%)
Tumor number:	
Solitary	360 (65.2%)
Multifocal	192 (34.8%)
Tumor Size^a	

$\leq 5\text{cm}$ 118 (21.4%)

>5cm 434 (78.6%)

Vascular Invasion

- Absence 35 (6.3%)

-Segmental portal vein 62 (11.2%)

-Lobar portal vein 188 (34.1%)

-Main portal vein 239 (43.3%)

-Hepatic vein/Inferior Vena Cava 28 (5.1%)

Hepatic regional lymph node involvement

Absence 507 (91.8%)

Presence 45 (8.2%)

Note: Values are median (95% CI) or numbers (%).

ECOG score: Eastern Cooperative Oncology Group score; AFP: Alpha-Fetoprotein

^aTumor size was calculated as the maximum size of intrahepatic tumors

Table 2. Univariate and multivariate analysis for overall survival in patients with locally advanced stage HCC.

variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
gender	0.71	0.53-0.96	0.03			
Age (≥ 50 / <50)	1.01	0.77-1.32	0.94			
HBV infection (presence/absence)	0.93	0.74-1.16	0.51			
ECOG score (0/1)	1.21	0.92-1.58	0.16			
AFP (≥ 400 / <400)	1.33	1.02-1.72	0.03			
Child-Pugh grade (A/B)	1.16	0.86-1.56	0.33			
Tumor size (≥ 5 / $<5\text{cm}$)	1.4	1.02-1.91	0.03			
Tumor number (Solitary/Multifocal)	0.95	0.73-1.24	0.72			
Vascular invasion ^a	1.19	1.04-1.37	0.01			
Lymph node involvement	0.84	0.53-1.33	0.47			
Treatment modality	0.75	0.65-0.87	<0.001	0.8	0.69-0.93	0.003

Note: HCC: hepatocellular carcinoma; HR: hazard ratio; CI: confidence interval;

HBV: hepatitis B virus; ECOG score: Eastern Cooperative Oncology Group score

AFP: Alpha-Fetoprotein;

^aVascular invasion type includes: absence of vascular invasion; segmental portal vein invasion, branch portal vein invasion, main portal vein invasion and hepatic vein/inferior vena cava invasion.

Table 3. Comparison of survival in patients receiving TACE alone versus TACE+Sorafenib before and after PSM analysis.

Estimated OS rates	TACE	TACE+Sorafenib	Log-rank
			P value
Before PSM	n=375	n=83	0.001
1-year	50.5%	73.7%	
3-year	29.8%	47.1%	
5-year	24.5%	34.9%	
Median OS	7.5 m	13.0 m	
After PSM	n=81	n=81	0.02
1-year	51.1%	74.8%	
3-year	36.2%	50.1%	
5-year	30.1%	38.4%	
Median OS	9.0 m	14.0 m	

Note: The Kaplan-Meier method was used to assess overall survival. OS: overall survival;

TACE: Transarterial Chemoembolization; HCC: hepatocellular carcinoma; PSM: propensity score matching

Figures

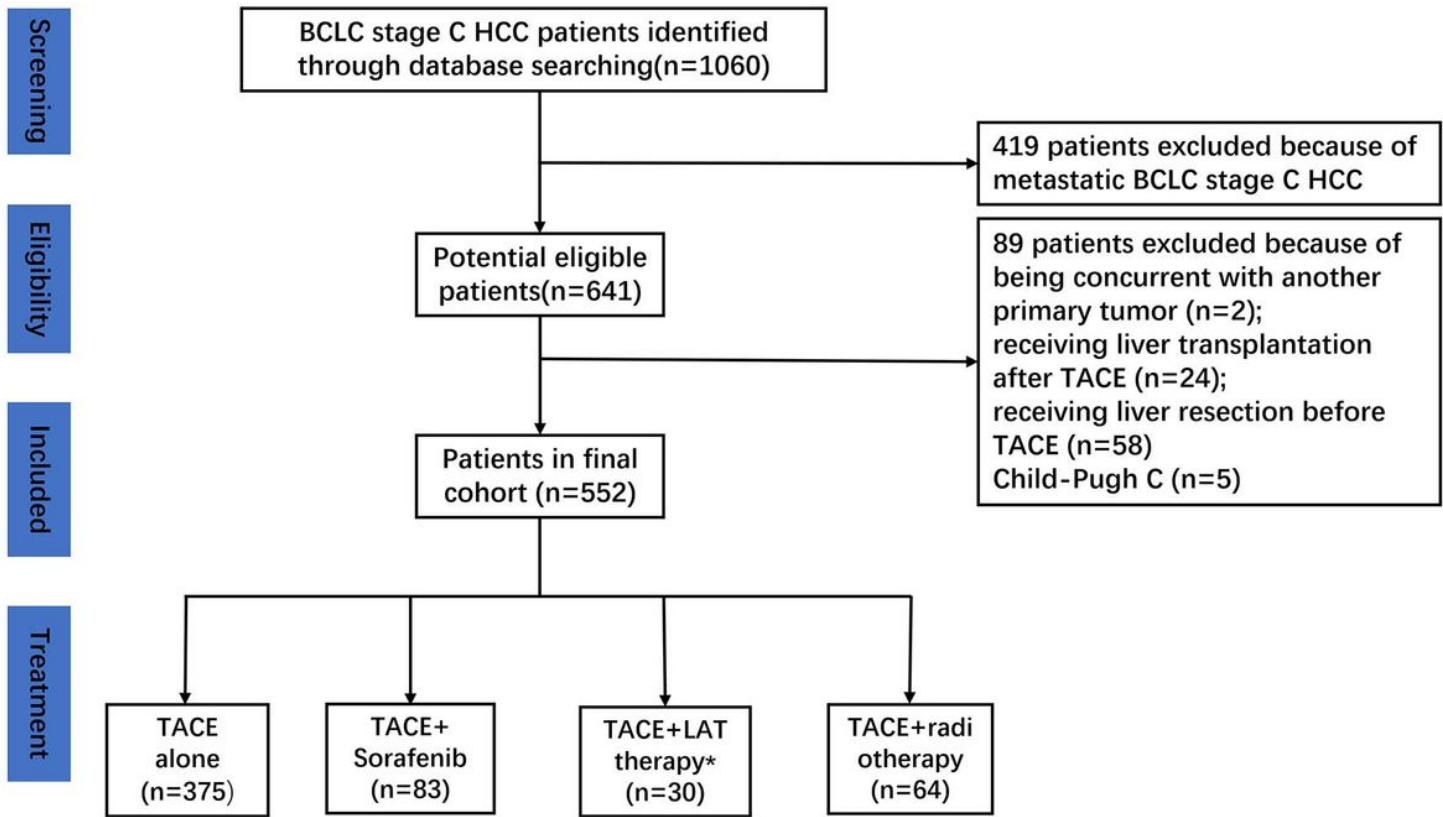


Figure 1

Flow diagram of the patient enrollment in this study. HCC: Hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer; TACE: Transcatheter arterial-chemoembolisation; *TACE+ LAT: TACE followed local ablation treatment;

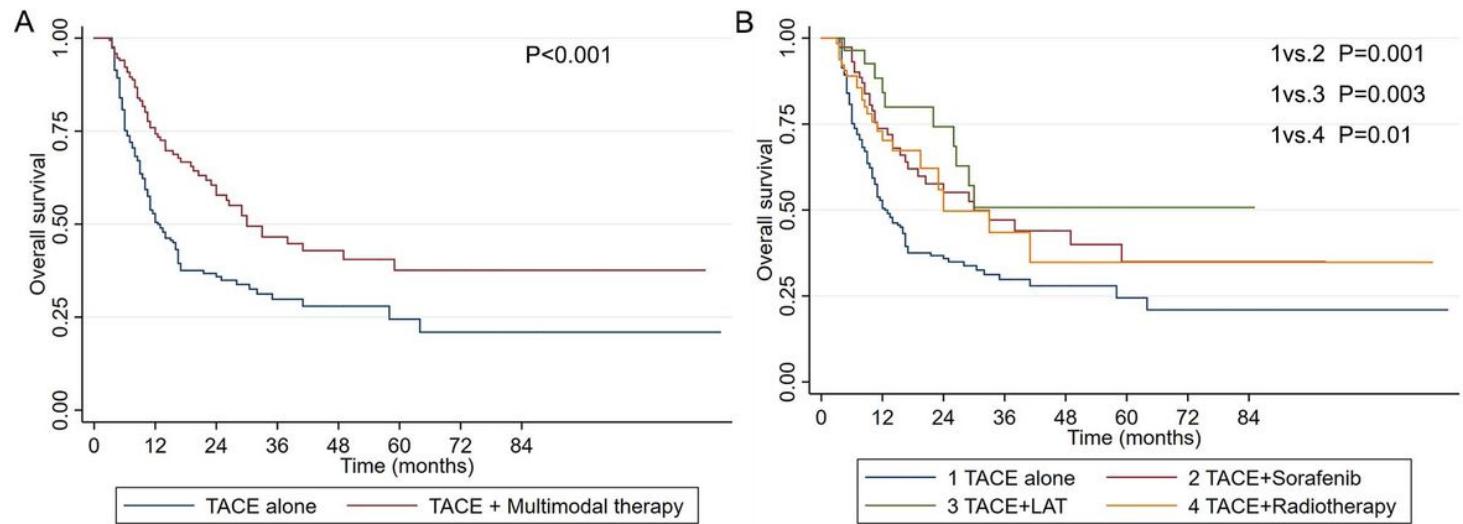


Figure 2

Overall survival of patients based on treatment modality. (A) The overall survival of patients treated with TACE+Multi-modal therapy was prolonged compared to that of patients treated with TACE alone ($P<$

0.001). (B) Overall survival curves of patients treated with TACE alone, TACE+Sorafenib, TACE+LAT, TACE+Radiotherapy were illustrated. In comparison with TACE alone, the survival rates of patients treated with TACE+Sorafenib, TACE+LAT or TACE+ Radiotherapy were higher than that of patients treated with TACE alone ($P=0.001$, $P=0.003$, $P=0.01$, respectively). TACE: Transcatheter arterial-chemoembolisation; TACE+LAT: TACE plus local ablation treatment;

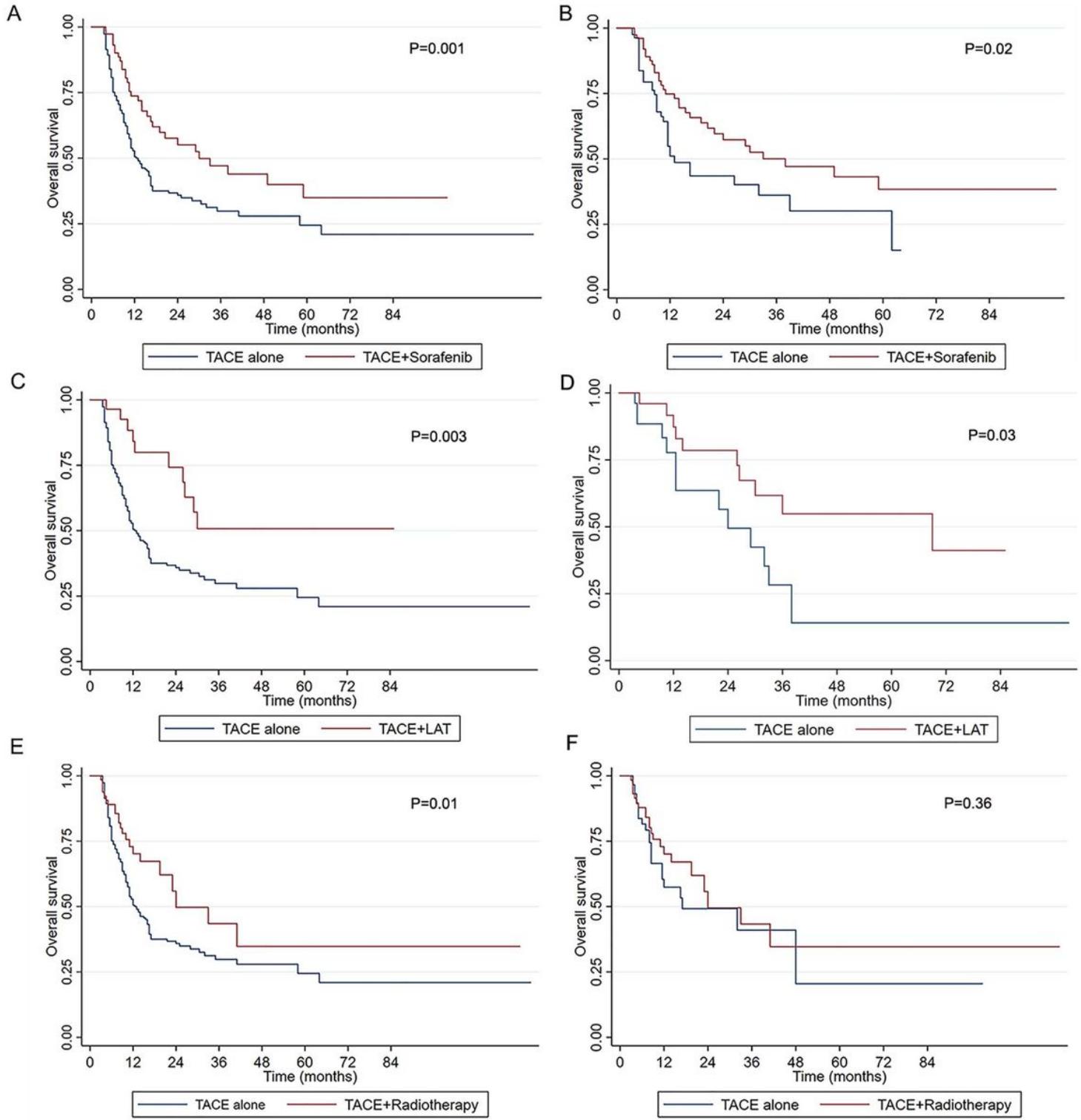


Figure 3

Overall survival of different treatment modalities upon propensity score matching (PSM) analysis. (A) and (B): Overall survival curves of patients treated with TACE or TACE+Sorafenib before (A) and after (B) propensity score matching. After PSM analysis, the survival benefit was still significant in TACE+Sorafenib treatment group compared with that of TACE alone ($P=0.02$). (C) and (D): Overall survival curves of patients treated with TACE or TACE+LAT before (C) and after (D) propensity score matching. After PSM analysis, the survival benefit was still significant in TACE+LAT treatment group compared with that of TACE alone ($P=0.03$). (E) and (F): Overall survival curves of patients treated with TACE or TACE+Radiotherapy before (E) and after (F) propensity score matching. After PSM analysis, the survival difference was not significant in TACE+Radiotherapy treatment vs, TACE alone ($P=0.36$). TACE: Transcatheter arterial-chemoembolisation; TACE+LAT: TACE plus local ablation treatment;

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTable2.doc](#)
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