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***Retrospective Study***

**Combined endovascular brachytherapy, sorafenib and transarterial chemobolization therapy for hepatocellular carcinoma patients with portal vein tumor thrombus**

Zhang ZH *et al*. Sorafenib, TACE and brachytherapy for HCC

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**Abstract**

***AIM***

To evaluate safety and efficacy of combined endovascular brachytherapy (EVBT), transarterial chemoembolization (TACE) and sorafenib to treat hepatocellular carcinoma (HCC) with main portal vein tumor thrombus (MPVTT).

***METHODS***

This single-center retrospective study involved 68 patients with unresectable HCC or those who were unfit for liver transplantation and percutaneous frequency ablation according to the BCLC classification, Child-Pugh classification grade A or B, Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and with MPVTT. The patients received EVBT with stent placement, TACE, and sorafenib (Group A, *n* = 37), and TACE with sorafenib (Group B, *n* = 31). The compare time to progression (TTP) and overall survival (OS) was evaluated by propensity score analysis.

***RESULTS***

In the entire cohort, the 6-, 12-, 24-mo survival rates were 88.9%, 54.3% and 14.1% in group A, and 45.8%, 0% and 0% in group B, respectively (*P* < 0.001). The median TTP and OS were significantly longer in Group A than Group B [TTP, 9.0 *vs* 3.4 mo (*P* < 0.001); OS, 10.3 *vs* 6.0 mo (*P* < 0.001)]. In the propensity score-matched cohort, the median OS was longer in group A than in group B (10.3 *vs* 6.0 mo; *P* < 0.001). Similarly, the median TTP was longer in Group A than in Group B (9.0 *vs* 3.4 mo; *P* < 0.001). Multivariate Cox analysis revealed that the EVBT combined with stent placement, TACE, and sorafenib strategy was an independent predictor of favorable OS [HR = 0.18 (*P <* 0.001)].

***CONCLUSION***

EVBT combined with stent placement, TACE, and sorafenib might be a safe and effective palliative treatment option for MPVTT.

**Key words:** Hepatocellular carcinoma; Sorafenib; Transarterial chemoembolization; Endovascular brachytherapy; Main portal vein tumor thrombus

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**Core tip:** As portal vein tumor thrombus occurs in a high proportion of hepatocellular carcinoma patients and no standard treatment has been established, we aimed to evaluate the effect of endovascular brachytherapy (EVBT) combined with stent placement, transarterial chemoembolization (TACE), sorafenib and compared it with TACE plus sorafenib alone. The results of our study revealed that EVBT along with stent placement, TACE, and sorafenib as a safe and effective palliative treatment option for main portal vein tumor thrombus.

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**INTRODUCTION**

Portal vein tumor thrombus (PVTT) occurs in a substantial proportion of patients with hepatocellular carcinoma (HCC) with 44% of the patients presenting at the time of death and about 10%-40% at the time of diagnosis[1]. In particular, HCC with tumor thrombus in the main portal trunk or the opposite side portal branch represents an end-stage condition with poor prognosis due to malignant hepatic tumor cells occluding the blood flow and deteriorating the portal hypertension[2] with a perioperative mortality rate of 0%-28% and a 5-year overall survival (OS)of 0%-26.4%[3]. As main PVTT (MPVTT) is contraindicated to surgical resection and transplantation due to a high tumor recurrence rate, no standard treatment has been established[4]. 3-dimensional conformal radiotherapy (3-DCRT)has shown survival benefits in HCC patients with PVTT[5]. However, blood flow to the obstructed main portal vein (MPV) cannot be restored immediately with radiotherapy alone. Further, PVTT is generally considered a contraindication for TACE due to the interruption of hepatic arterial flow which could result in a large segment of hepatic necrosis in patients whose blood supply is already compromised[6]. Furthermore, tumor thrombus in the MPV could not be effectively controlled by TACE combined with intra-portal stent, leading to a shorter stent patency along with increased risk of liver necrosis and treatment-related death[7],limiting its use to only selected group of patients with good hepatic function and adequate collateral circulation around the occluded portal vein[8]. Given the limitation of TACE, transarterial radioembolization (brachytherapy) has emerged as a safe and effective treatment for HCC with PVTT over TACE[9,10]. Endovascular brachytherapy (EVBT) with interstitial implantation of Iodine-125 (125I) seeds was studied extensively[11-13]. Combined endovascular implantation of 125I seed strand with stent and TACE provided long-term survival benefits and increase patency rates of the stent[14,15]. Though sorafenib has been recommended as the first-line treatment of advanced-stage disease as defined as Barcelona Clinic Liver Cancer (BCLC) stage C with PVTT, the survival outcomes obtained by sorafenib were also only modest[16]. Recent studies have reported survival benefits in patients with PVTT who underwent combinations of TACE with sorafenib, radiotherapy with sorafenib, and hepatic arterial infusion chemotherapy with sorafenib[17-19]. A recent study by Huang *et al*[20], reported survival benefit of chemoembolization plus Iodine125 seed implantation in unresectable hepatitis B-related hepatocellular carcinoma with PVTT. Reports of such combined therapeutic strategies aiming at MPVTT are obscure. Endovascular implantation of iodine-125 seeds strand and portal vein stenting followed by TACE combined with sorafenib could improve the progress free survival (PFS) of HCC patients with MPVTT[21]. In the present retrospective study, we aimed to evaluate the safety and efficacy of EVBT combined with stent placement, TACE, and sorafenib compared with TACE with sorafenib in the treatment of HCC patients with MPVTT.

**MATERIALS AND METHODS**

***Study design***

This was a single-center, retrospective study conducted on advanced HCC patients with MPVTT from January 2009 and December 2015. The study protocol was approved by the institutional ethics committee of the respective hospital. MPVTT was detected based on the presence of low-attenuation intraluminal mass expanding the main portal vein, and/or filling defects in the main portal vein, as determined with three-phase dynamic computed tomography (Figure 1).

***Patient selection and grouping***

Patients aged between 18-75 years with unresectable HCC or unfit for liver transplantation and percutaneous frequency ablation according to the BCLC classification, Child-Pugh classification grade A or B, Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; MPVTT confirmed by demonstration of tumor thrombus in MPV and HCC in three-phase dynamic CT images 7 d before treatment and those who had unilobular tumor in liver parenchyma were included in the study along with retaining the patent blood flow in the second-order branch of the uninvolved side portal vein confirmed by color doppler flow imaging (CDFI).

The patients who had undergone surgery, local-regional therapies (radiofrequency ablation, percutaneous ethanol injection, or iodine 125 seed implantation), or liver transplantation, previous sorafenib therapy, systemic chemotherapy, intra-arterial chemoinfusion, or TACE; serious medical comorbidities such as encephalopathy, uncorrectable bleeding diathesis *etc.*, currently had or had a history of malignant tumors in addition to HCC, Intrahepatic portal vein completely occluded by HCC, tumor thrombus extending into superior mesenteric vein (SMV) or splenic vein (SV), advanced liver disease, contraindication for chemoembolization (HCC burden > 70% of total liver volume, high flow intrahepatic arterial venous shunt) were excluded from the study.

Written informed consent was obtained from all eligible patients who were recommended to opt either combined EVBT-stent-TACE-sorafenib (Group A) or TACE-sorafenib (Group B) treatment. TACE-sorafenib was recommended for patients who refused EVBT-stent-TACE-sorafenib treatment.

***Treatment procedures***

**Study treatment:** Sorafenib (Nexavar®; Bayer, Leverkusen, Germany) was taken for 3 d after the first TACE procedure at a recommended dose of 400 mg twice daily in all patients and with a 3-d interruption after subsequent TACE cycles (30 d).

**Stent and iodine-125 seed:** Nitinol self-expandable stent (Luminxx III; Bard, Covington, Georgia) (diameter: 12-14 mm; length: 60-100 mm) was used. Brachytherapy source was Titanium encapsulated Model 6711 125I seed (XinKe; Shanghai, China; active length: 3.25 mm), with radioactivity and half-life of each 125I seed 25.9 MBq and 59.4 d respectively. The principal photon emissions of X-ray and gamma ray and incipient dose rates were 31.4 keV, 35.5 keV and 7 cGy/h respectively. The 240 d’ accumulated dose at 10 mm from the axis of the Iodine125 seed strand source (Z = 0, r = 10 mm) was calculated with a radiation field distribution calculation software (version 0.1, Institute of Radiation Medicine, Fudan University, Shanghai, China) based on the American Association of Physicists in Medicine TG43U1 brachytherapy formalism.

**Intra-MPV stent and 125I seed strand implantation:** In group A patients, the patent second-order branch of the intrahepatic portal vein in the unaffected side with hepatopetal flow was punctured with a 22-gauge Chiba needle (Cook, Inc., Bloomington, Indiana) under ultrasound guidance, followed by insertion of a 0.018-inch wire (Cook Inc.) into the portal vein. A 5-F calibrated pigtail catheter (Cook Inc.) was used to gauge the pressure in filling splenic mesenteric veins and portography was performed to measure the diameter and length of the obstructed MPV (stenosis). The number of 125I seeds to be implanted was calculated by the following formula:

N = Length of obstructed MPV (mm)/4.5 + 4.

These seeds were arranged linearly and sealed into a 4-F catheter continuously to construct a 125I seed strand. After 50 U/kg heparin (XinYi, Shanghai, China) was administered intravenously, two 0.035-inch, 260-cm-long stiff wires (Terumo) were inserted into the superior mesenteric vein through the 7-F sheath. After the sheath had been removed, the outer cannula of the NEFF set and a self-expendable stent of appropriate size were introduced to the MPV over one of the stiff wires, respectively. The stent was deployed from the distal MPV into the proximal patent intrahepatic portal vein. The 125I seed strand was delivered to the target position via outer cannula of the NEFF set and released between the stent and MPV (Figure 2A and B). Portography and pressure measurement were repeated.

***Transarterial chemoembolization* *procedure***

Segmental TACE was performed by experienced interventional radiologists immediately after stent and 125I seed implantation. Regardless of the type of HCC (unilobar or bilobar), all feeding arteries of tumor identified by angiography of the celiac, hepatic, superior mesenteric, left gastric and bilateral inferior phrenic artery using a 5-F RH catheter (Cook) were chemoembolized. The target artery was catheterized with a 2.7-F microcatheter (Renegade, Boston Scientific, Natick, MA). Under fluorescence imaging, mixture of 10–50 mg/m2 of epirubicin (Pharmorubicin, Pfizer, NY) and 5-20 mL of iodized oil (Lipiodol Ultrafluide, Laboratoire Guerbet, Aul-nay-sous-Bois, France) was infused at a rate of 0.5-1 mL/min through the microcatheter until stasis flow in the tumor vascularity was achieved. Finally, gelatin sponge (Jingling, Jiangsu, China) was used to embolize the feeding artery of the tumor.

***Post-procedural evaluation***

Single photon emission computer tomography (SPECT) combined with CT (SPECT/CT) scan was performed on day 1 of the therapy to evaluate the distribution of radiation by the 125I seed strand implanted in Group A patients (Figure 2C).

***Follow-up and repeat transarterial chemoembolization***

The total number of hospitalization days was 5-7 d which were prolonged if grade 3-4 adverse events occurred. All the patients were followed up every 30 d until death reported till March 1, 2016. Repeat TACE with the same protocol was performed upon detection of residual tumors or new lesions in all patients.

***Efficacy and safety endpoints***

Efficacy was evaluated as per the Modified Response Evaluation Criteria in Solid Tumor (mRECIST)[22]. The primary endpoints were OS and time to progression (TTP). OS was defined as the period from the day of the procedure to patients’ death or to their last follow-up. TTP was defined as the period from the day of the procedure until the radiologic confirmation of tumor progression in liver parenchyma. For HCC in liver parenchyma, disease control rate (DCR) was defined as the percentage of patients with complete response (CR), partial response (PR), or stable disease (SD). Tolerance and AEs were measured as secondary endpoints. Sorafenib and TACE-related AEs were monitored using the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0[23].

As MPVTT would increase the incidence of tumor dissemination, elevate portal vein pressure and impair the liver functional reserve, occurrence of events like intrahepatic HCC spread, variceal bleeding and liver function decompensation was also compared between the two groups.

***Statistical analysis***

SPSS version 22.0 (SPSS, Chicago, Illinois) was used for all the analyses. Continuous variables are presented as mean ± standard deviation, compared by *t* test and categorical variables as frequencies, compared by Chi-square test. OS and disease-free progression survival were analyzed using the Kaplan-Meier curves and log-rank test. A *P* value of less than 0.05 was considered statistically significant. Variables with *P* < 0.05 were chosen for multivariate analysis using the Cox proportional hazards model. Regression analysis was used to determine independent predictors of survival. Sex, age, type of tumor, HCC maximum diameter, degree of MPVTT, Child-Pug class, ECOG performance status, etiology of liver disease, Serum AFP level, and extrahepatic metastasis were considered within the propensity model. Propensity score matching analysis was performed, with matching ratio of 1:1 for 2 groups, using the nearest-neighbor matching method with a caliper distance of 0.2 without replacement.

**RESULTS**

***Basal characteristics of patients and tumors***

A total of 83 unresectable HCC patients were identified. Of them, 15 patients were excluded due to reasons listed in (Figure 3). Finally, 68 patients were included in this study [Group A (*n* = 37) Group B (*n* = 31)] Baseline characteristics before scores matching is shown in Table 1. After propensity score matching, we created 24 matched pairs of patients in Table 2.

***Technical Success***

The 125I seeds strand and stent placement procedure was completed in all patients in group A (technical success rate, 100%) and the TACE procedure was completed in all patients in both the groups.

***Overall survival and time to progression in the entire cohorts***

The median follow-up durations were 12.7 mo, and 5.9 mo for the prematched groups A, and B, respectively. The 6-, 12-, 24-mo survival rates were 88.9%, 54.3% and 14.1% in group A, and 45.8%, 0% and 0% in group B, respectively (*P <* 0.001). However, there were no procedure-related deaths. Kaplan-Meier curves for survival outcomes in the 2 groups are showed that significantly high OS in Group A compared to Group B (12.3 *vs* 5.2 mo; *P <* 0.001)Figure 4A.

The median TTP was longer (9.0 mo) in group A, compared to group B (3.4 mo), *P <* 0.001;Figure 4B.

***Overall survival and time to progression in matched cohorts***

In the propensity score-matched cohorts, the median OS was longer in group A than in group B (10.3 *vs* 6.0 mo; *P <* 0.001; Figure 4C). Similarly, the median TTP was longer in Group A than in Group B (9.0 *vs* 3.4 mo; *P <* 0.001; Figure 4D).

***Predictive factors for overall survival in the entire cohort***

In multivariate Cox analysis, treatment regimen (HR = 0.18, *P <* 0.001) was an independent predictor of OS for group A versus group B; Table 3.

***Iodine-125 seed strand and stent patency***

After stent placement in group A patients, the mean pressure of MPV dropped from 38.1 ± 5.8 cm. H2O (range, 23-46 cm. H2O) to 32.0 ± 5.6 cm. H2O (range, 16-37 cm. H2O) (*P* = 0.002) who were implanted with 17.2 ± 4.9 (range, 10-31) 125I seeds. The estimated mean accumulated dose (R = 10 mm, z = 0, 240 d) was 62.9 ± 2.3 Gy (range, 57.4-65.3 Gy). Stent occlusion was observed in 9 (24.3%) patients and the median stent patency period was 22.1 ± 6.1 mo (95%CI: 9.5-34.7 mo).

***Response of hepatocellular carcinoma and main portal vein tumor thrombus***

HCC responses were assessed using the mRECIST criteria. During the course of the study, 4.4 ± 3.2 and 2.9 ± 1.2 TACE procedures were performed in groups A and B, respectively. The ORR and DCR in group A were significantly higher than the rates observed in group B (ORR, 45.9% *vs* 16.1%, *P* = 0.009; DCR, 67.6% *vs* 29.0%, *P* = 0.002).

During the course of the study, the occurrence rate of complications related to MPVTT, such as intrahepatic metastasis, variceal bleeding, and liver function decompensation were observed in 15 (40.5%), 6 (16.2%), and 11 (29.7%) patients in Group A and 22 (71.0%), 18 (58.1%), and 25 (80.6%) patients in Group B, respectively (*P* = 0.012, *P <* 0.001, *P <* 0.001).

***Treatment-related toxicities***

A total of 49 TACE-related AEs occurred in (42.6% of 68 patients in groups A and B. The percentages of patients who experienced new ascites, liver dysfunction, and gastrointestinal hemorrhage were significantly higher in group B than group A.

A total of 140 sorafenib related AEs occurred in 91.2% patients. A total of 7 patients required sorafenib dose reduction to 400 mg once daily for grade 3 hand-foot skin reactions (4.2%) and grade 3 diarrhea (5.3%) reverted to a regular dose after the AEs subsided. One patient with grade 4 hypertension was subjected to a drug interruption period of 20 d after the AEs subsided (Table 4).

**DISCUSSION**

MPVTT is the most important independent prognostic factor for poor prognosis of patients with HCC[24]. Although TACE is effective and safe for intrahepatic primary HCC lesions including few cases of HCC- cholangiocellular carcinoma, its benefit in PVTT has less importance, especially in type III PVTT or MPVTT. A combined treatment of TACE with novel drugs or other therapies might be a better alternative strategy for HCC with PVTT[22-25]. Huang *et al*[20] reported better survival outcomes with TACE plus 125I-seed implantation than with TACE alone in patients with type I and II PVTT. Currently, sorafenib is the recommended standard treatment for advanced HCC with PVTT[26]. Novi *et al*[27] reported that 15 wk of sorafenib monotherapy played a key role in PVTT revascularization. TACE combined with sorafenib could be a feasible alternative treatment option in patients with HCC and PVTT in the first-order or lower order portal vein branches but not in MPVTT[12]. However, a propensity-score analysis reported a significantly shorter OS in the sorafenib group than in the radiotherapy group[28].

According to these reports, the benefits of OS and TTP were lower in patients with MPVTT than in patients with PVTT of first-order or lower order portal vein branches. The main reason being the occlusion of MPV, which is associated with an increased risk of tumor spread, elevated portal venous pressure causing variceal hemorrhage, and decreased portal flow resulting in ascites, jaundice, hepatic encephalopathy, and liver failure[29]. Restoring the flow of obstructed MPV and effectively inhibiting tumor thrombus progression might confer further survival benefit to patients with advanced HCC and MPVTT[13,21].

The strategy of implantation of 125I seed strand combined with stent placement and TACE has been reported to treat MPVTT[14,15]. This method of treatment has two advantages, firstly the blood flow to the portal vein increased immediately and the portal vein pressure elevated by MPV obstruction reduced effectively after stent deployment. Secondly, half-life of the gamma ray emitted by 125I seed is 59.4 d. A sustained radiation can inhibit tumor cell replication by inducing apoptosis. Therefore, it is rational to theorize that placing a stent to restore the blood flow of obstructed MPV and implantation of I125 seeds might inhibit the progression of tumor thrombus. This increased the safety of subsequent TACE because of previous concerns that hepatic arterial flow interruption in TACE procedure would result in serious liver necrosis in patients whose hepatic blood supply was already compromised[30].

Previously, combined brachytherapy with TACE and sorafenib showed greater OS compared to combined brachytherapy with TACE alone in HCC patients with MPVTT[31]. The success rate of TACE with stent implant and 125I implantation was 88.5% with a mOS and mTTP of 8.9 mo and 7.9 mo respectively which were higher than mOS (5.7 mo) and mTTP (5.3 mo) of TACE with portal vein stent alone[32].Further, in our study addition of sorafenib to the TACE plus portal vein tent and 125I implantation increased the OS and TTP to 10.3 mo and 9.0 mo respectively. This study reported an encouraging efficacy for the combination of sorafenib, EVBT, stent placement, and TACE in advanced HCC patients with MPVTT. The OS and TTP were longer in the EVBT-stent-TACE-sorafenib group than in the TACE-sorafenib group. Although our results show moderate sorafenib-related side effects, they were mostly manageable after TACE and were comparable among the groups. However, TACE-related toxicities were lower in combination group compared to sorafenib plus TACE group. The data also demonstrate that the combination therapy has significant benefit in term of ORR and DCR compared with sorafenib-TACE. Zhang *et al*[33] reported that sorafenib monotherapy is a better treatment strategy over sorafenib combined TACE therapy for MPVTT due to the adverse events related to TACE. However, the results of our study suggest that combining EVBT to the sorafenib-TACE combination offers added benefits to sorafenib and decreases the toxicity of TACE. Overall analysis of all the side effects observed in the sorafenib-TACE group we believe that combined endovascular brachytherapy with sorafenib and TACE may be a better approach for managing this specific subgroup of patients with advanced HCC and MPVTT.

The major limitation of this study is the single-center retrospective design, which may affect the generalization of results and small sample size. Further, cost-benefit analysis was not performed for the expensive procedures in this study, which may be a topic of interest to be covered in our future studies.

In conclusion, EVBT combined with sorafenib and TACE might be a safe and effective palliative treatment option for MPVTT.

**ARTICLE HIGHLIGHTS**

***Research background***

Despite the beneficial outcomes of individual therapies, literature pertaining to the clinical outcome of endovascular brachytherapy (EVBT) combined with stent placement, transarterial chemoembolization (TACE), and sorafenib to treat hepatocellular carcinoma (HCC) with main portal vein tumor thrombus (MPVTT) are scarce.

***Research motivation***

Recent studies have reported survival benefits in patients with PVTT who underwent combinations of TACE with sorafenib, radiotherapy with sorafenib, hepatic arterial infusion chemotherapy with sorafenib, and iodine-125 seed implantation with TACE. However, reports of such combined therapeutic strategies aiming at MPVTT are obscure. According to these previous studies, we aimed to found an effective therapy of HCC patients with MPVTT.

***Research objectives***

To evaluate safety and efficacy of combined EVBT, stent placement, TACE and sorafenib to treat HCC with MPVTT.

***Research methods***

We conducted retrospective study involving 68 patients with unresectable HCC. The patients received either EVBT with stent placement, TACE, and sorafenib or TACE with sorafenib. The compare time to progression (TTP) and overall survival (OS) was evaluated by propensity score analysis.

***Research results***

In the EVBT with stent placement, TACE, and sorafenib group, the 6-, 12-, 24-mo survival rates were 88.9%, 54.3% and 14.1% and in TACE with sorafenib group it was 45.8%, 0% and 0% respectively. The median TTP and OS were significantly longer in EVBT with stent placement, TACE, and sorafenib group (*P* < 0.001). In the propensity score-matched cohort, the median OS was longer in EVBT with stent placement, TACE, and sorafenib group (*P* < 0.001).

***Research conclusions***

EVBT combined with stent placement, TACE, and sorafenib might be a safe and effective palliative treatment option for MPVTT.

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**Table 1 Baseline characteristics of entire cohort patients *n* (%)**

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Group A**  **(*n* = 37)** | **Group B**  **(*n* = 31)** |
| Sex |  |  |
| Male | 34 (91.9) | 26 (83.9) |
| Female | 3 (8.1) | 5 (16.1) |
| Age, yr (%) |  |  |
| ≥ 55 yr | 18 (48.9) | 14 (45.2) |
| < 55 yr | 19 (51.4) | 17 (54.8) |
| Type of tumor |  |  |
| Nodular | 30 (81.1) | 29 (93.5) |
| Infiltrative | 7 (18.9) | 2 (6.5) |
| HCC maximum diameter |  |  |
| ≥ 5 cm | 26 (70.3) | 19 (61.3) |
| < 5 cm | 11 (29.7) | 12 (38.7) |
| Degree of MPVTT |  |  |
| Stenosis | 31 (83.8) | 24 (77.4) |
| Occlusive | 6 (16.2) | 7 (22.6) |
| Child-Pugh class |  |  |
| A | 33 (89.2) | 24 (77.4) |
| B | 4 (10.8) | 7 (22.6) |
| ECOG performance status |  |  |
| 0/1 | 33 (89.2) | 26 (83.9) |
| 2 | 4 (10.8) | 5 (16.1) |
| Etiology of liver disease |  |  |
| HBV | 35 (94.6) | 29 (93.5) |
| Other | 2 (5.4) | 2 (6.5) |
| Serum AFP level (in ng/mL) |  |  |
| ≥ 400 | 20 (54.1) | 17 (54.8) |
| < 400 | 17 (45.9) | 14 (45.2) |
| Extrahepatic metastasis | 3 (8.1) | 3 (9.7) |

*P* > 0.005, AFP: Alfa-fetoprotein; ECOG: Eastern cooperative oncology group; HBV: Hepatitis B virus; MPVTT: Main portal vein tumor thrombus; HCC: Hepatocellular carcinoma.

**Table 2 Baseline characteristics of propensity-matched patients *n* (%)**

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Group A**  **(*n* = 24)** | **Group B**  **(*n* = 24)** |
| Sex |  |  |
| Male | 22 (91.7) | 23 (95.8) |
| Female | 2 (8.3) | 1 (4.2) |
| Age |  |  |
| ≥ 55 yr | 14 (58.3) | 9 (37.5) |
| < 55 yr | 10 (41.7) | 15 (62.5) |
| Type of tumor |  |  |
| Nodular | 21 (87.5) | 22 (91.7) |
| Infiltrative | 3 (12.5) | 2 (8.3) |
| HCC maximum diameter |  |  |
| ≥ 5 cm | 16 (66.7) | 17 (70.8) |
| < 5 cm | 8 (33.3) | 7 (29.2) |
| Degree of MPVTT |  |  |
| Stenosis | 21 (87.5) | 19 (79.2) |
| Occlusive | 3 (12.5) | 5 (20.8) |
| Child-Pugh class |  |  |
| A | 20 (83.3) | 21 (87.5) |
| B | 4 (16.7) | 3 (12.5) |
| ECOG performance status |  |  |
| 0/1 | 20(83.3) | 22(91.7) |
| 2 | 4(16.7) | 2(8.3) |
| Etiology of liver disease |  |  |
| HBV | 22 (91.7) | 23 (87.5) |
| Other | 2 (8.3) | 1 (12.5) |
| Serum AFP level |  |  |
| ≥ 400 | 12 (50.0) | 10 (41.7) |
| < 400 | 12 (50.0) | 14 (58.3) |
| Extrahepatic metastasis | 1 (3.8) | 3 (11.5) |

*P* > 0.005, AFP: Alfa-fetoprotein; ECOG: Eastern cooperative oncology group; HBV: Hepatitis B virus; MPVTT: Main portal vein tumor thrombus; HCC: Hepatocellular carcinoma.

**Table 3 Log-rank test and cox regression analysis of factors potentially related to overall survival**

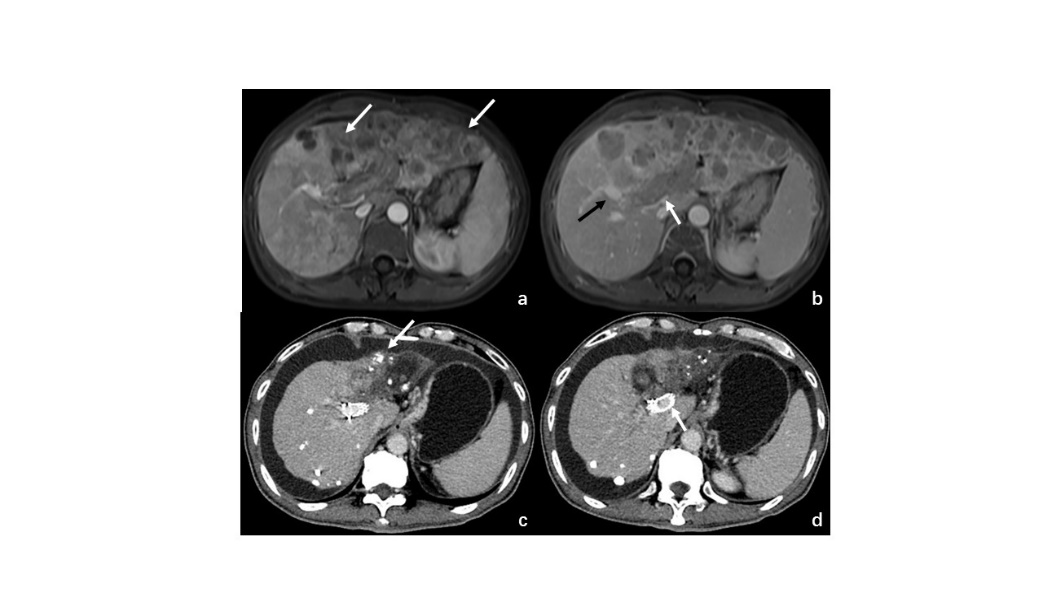
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| --- | --- | --- | --- | --- |
|  | **Group A *vs* Group B** | | | |
|  | **Log-rank test** | | **Cox regression** | |
| **Factors** | ***n*** | ***P* value** | **HR (95%CI)** | ***P* value** |
| Treatment regimen | - | < 0.001 | - | - |
| EVBT-stent-TACE-sorafenib | 37 |  | 0.18  (0.09-0.35) | < 0.001 |
| TACE-sorafenib | 31 |  | 1 | - |
| Type of tumor |  | 0.466 | - | - |
| Nodular type | 59 |  | - | - |
| Diffuse type | 9 |  | - | - |
| HCC Maximum Diameter | - | 0.320 | - | - |
| ≥ 5 cm | 45 |  | - | - |
| < 5 cm | 23 |  | - | - |
| Child-Pugh class |  | 0.298 | - | - |
| A | 57 |  | - | - |
| B | 11 |  | - | - |
| ECOG performance status | - | 0.125 | - | - |
| 0 and 1 | 59 |  | - | - |
| 2 | 9 |  | - | - |
| Extrahepatic metastasis | - | 0.742 | - | - |
| Yes | 62 |  | - | - |
| No | 6 |  | - | - |
| Serum AFP level (ng/mL) | - | 0.586 | - | - |
| ≥ 400 | 37 |  | - | - |
| < 400 | 31 |  | - | - |

AFP: Alfa-fetoprotein; ECOG: Eastern cooperative oncology group; TACE: Transarterial chemoembolization.

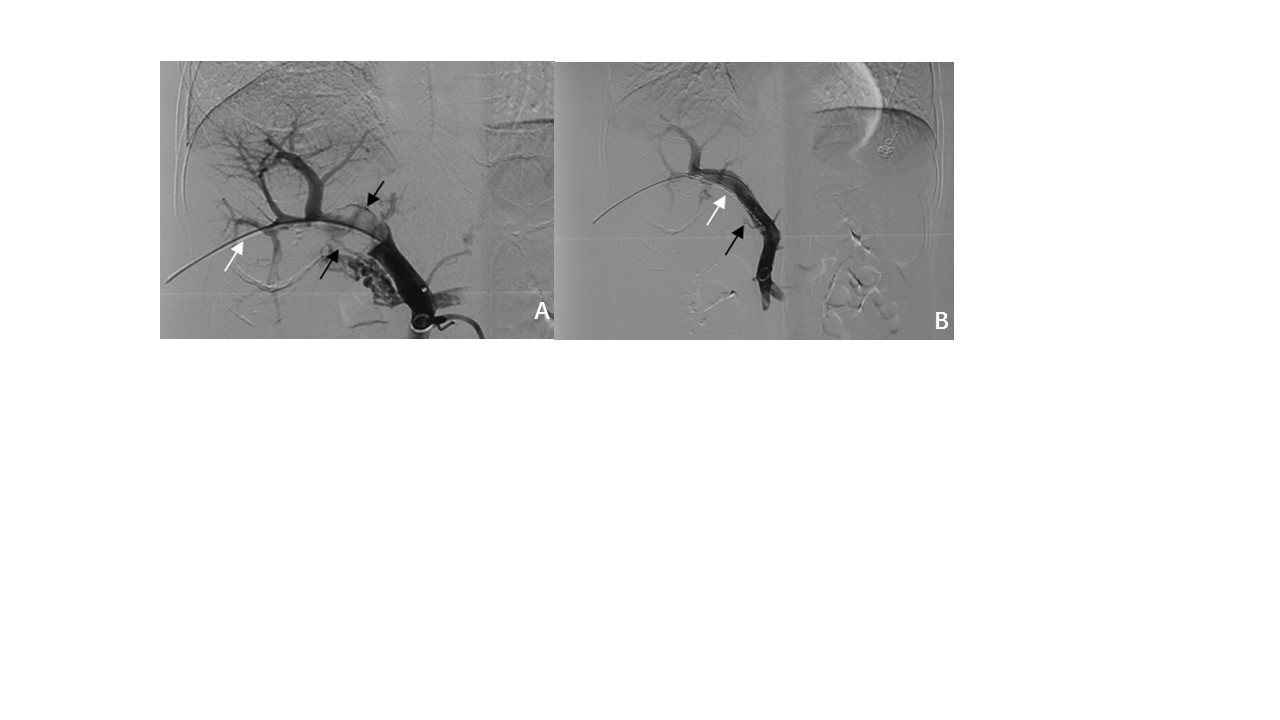
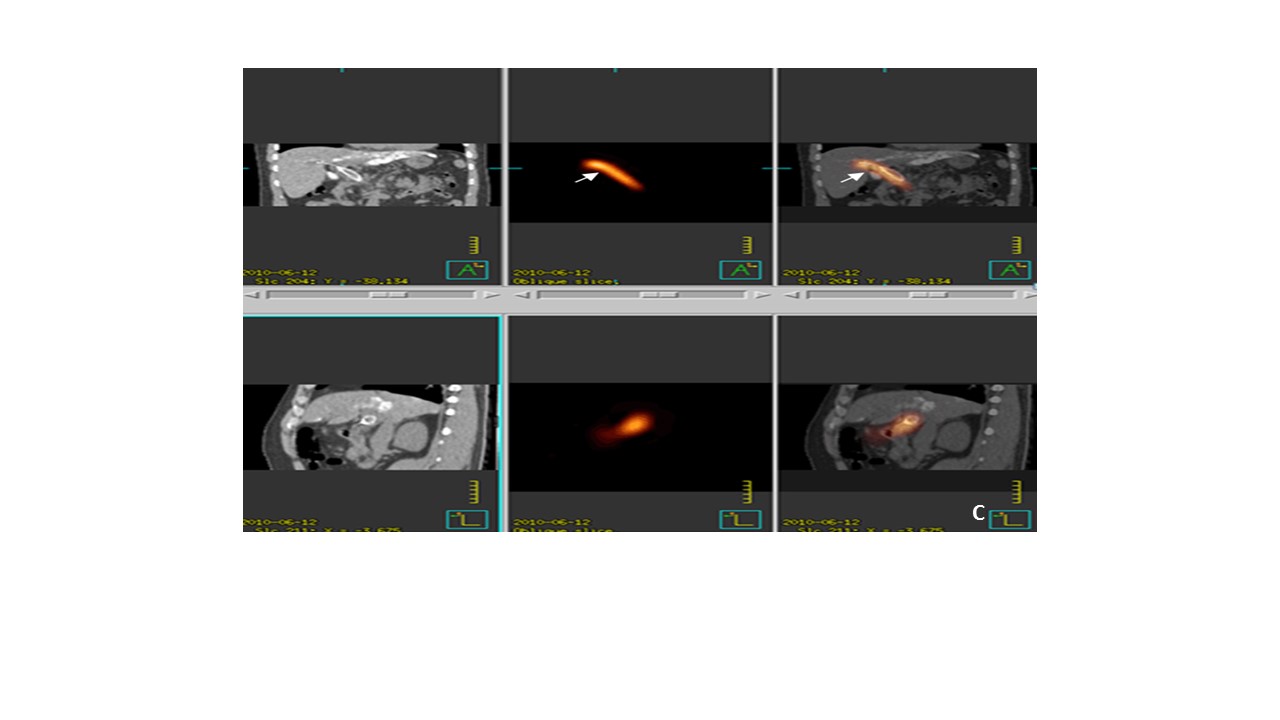
**Table 4** **Adverse events related to sorafenib administration and transarterial chemoembolization in the 2 groups *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Adverse Event** | **Group A**  **(*n* = 37)** | **Group A**  **(*n* = 31)** | ***P* value** |
| Sorafenib related AEs |  |  |  |
| Hand-foot skin reaction |  |  |  |
| Grade 1-2 | 26 (92.9) | 27 (96.4) | 0.143 |
| Grade 3-4 | 2 (7.1) | 1 (3.6) | 0.593 |
| Diarrhea |  |  |  |
| Grade 1-2 | 23 (88.5) | 18 (94.7) | 0.994 |
| Grade 3-4 | 3 (11.5) | 1 (3.6) | 0.620 |
| Hypertension |  |  |  |
| Grade 1-2 | 8 (21.6) | 6 (19.4) | 0.818 |
| Grade 3-4 | 1 (3.2) | 0 | 1.000 |
| Alopecia |  |  |  |
| Grade 1-2 | 2 (7.1) | 4 (12.9) | 0.400 |
| Grade 3-4 | 0 | 0 |  |
| Fatigue |  |  |  |
| Grade 1-2 | 9 (24.3) | 4 (12.9) | 0.354 |
| Grade 3-4 | 0 | 0 |  |
| Voice change |  |  |  |
| Grade 1-2 | 0 | 1 (3.6) | 464 |
| Grade 3-4 | 0 | 0 |  |
| Epistaxis |  |  |  |
| Grade 1-2 | 2 (7.1) | 2 (6.5) | 1.000 |
| Grade 3-4 | 0 | 0 |  |
| TACE related AEs | | | |
| New ascites | 4 (10.8) | 11 (35.5) | 0.020 |
| Liver dysfunction | 2 (16.2) | 15 (48.4) | < 0.000 |
| Gastrointestinal hemorrhage | 0 | 8 (25.8) | 0.001 |
| Hepatorenal syndrome | 0 | 2 (6.5) | 0.204 |
| Liver abscess | 0 | 0 | - |
| Spontaneous bacterial peritonitis | 0 | 0 | - |
| Inguinal hematoma | 0 | 0 | - |
| Pulmonary/cerebral oil embolization | 0 | 0 | - |

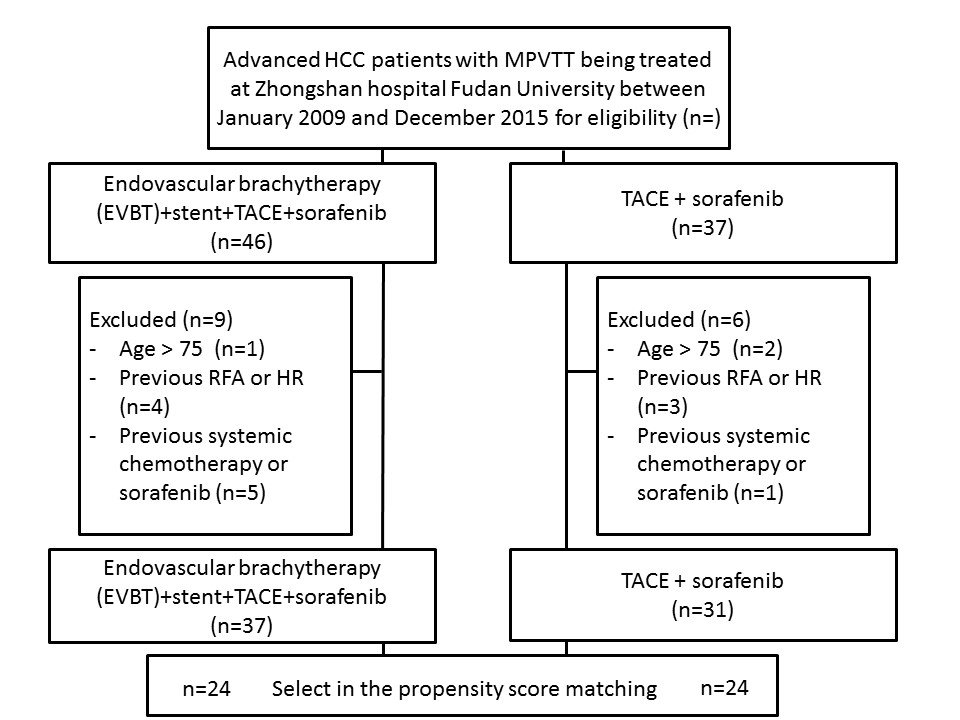
TACE: Transarterial chemoembolization.

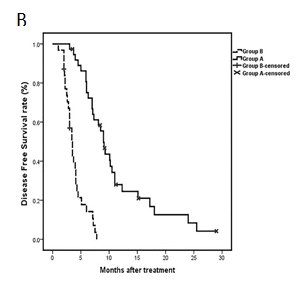
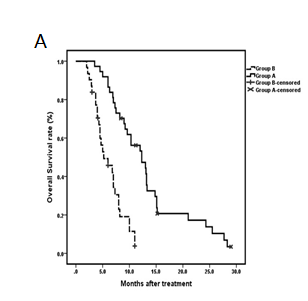


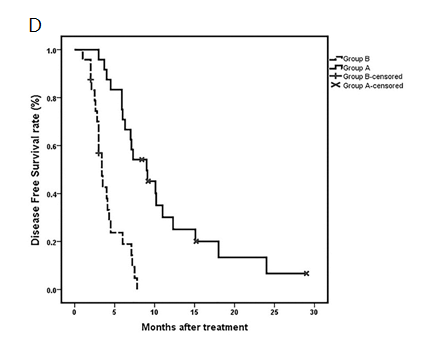
**Figure 1 Images of from a 50-yr-old man had hepatocellular carcinoma with main portal vein tumor thrombus.** A: Contrast enhanced abdominal magnetic resonance imaging before therapy. Diffuse hepatocellular carcinoma HCC (white arrow) was detected in the left lobe. B: The second order of right portal vein (black arrow) was patent. Tumor thrombus (white arrow) was observed in the left portal vein, the first order of right portal vein and main portal vein. C: Contrast-enhanced abdominal CT images 24 mo after first therapy. Deposition of iodized oil (white arrow) within tumor was observed and the left lobe was atrophied. D: The stent was still patent (white arrow). HCC: Hepatocellular carcinoma.

**Figure 2 Images of iodine-125 seed strand and stent placement.** A: After patent second-order branch of left portal vein was catheterized, a 5-F calibrated pigtail catheter (white arrow) was placed in the SV. Tumor thrombus (black arrows) in proximal MPV and sagittal segment of right portal vein was shown clearly on portography, but right portal vein was not developed. B: A 14-mm x 80-mm self-expandable stent (black arrow) and 125I seed strand (white arrow) with 20 seeds loaded were placed precisely in obstructed MPV. C: Images of SPECT/CT scan 1 d after therapy. MPV: Main portal vein; Iodine-125: 125I.

**Figure 3 Patient selection and cohorting.** MPVTT: Main portal vein tumor thrombus; HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization; EVBT: Endovascular brachytherapy.





**Figure 4 Overall survival overall cohorts and matched cohorts.** A: Kaplan-Meier curves for the overall patient cohort. OS differed between the 2 groups (OS, 12.3 *vs* 5.2 mo; *P <* 0.001);B:Kaplan-Meier curves for OS in propensity score-matched Median OS was longer in Group A than in Group B (10.3 *vs* 6.0 mo; *P <* 0.001); C: Kaplan-Meier curves for OS in propensity score-matched; D: Kaplan-Meier curves for disease free survival in propensity score-matched. OS: Overall survival.