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Transarterial chemoembolization versus best supportive care for patients with hepatocellular carcinoma with portal vein tumor thrombus : a multicenter study☆

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ABSTRACT

Background: This study aims to compare the efficacy and safety of treatment after transarterial chemoembolization(TACE) with best supportive care (BSC) in patients with hepatocellular carcinoma (HCC) with PVTT.

Methods: This retrospective study was conducted on 1,040 patients with HCC with PVTT who were treated either with TACE (n = 675) or BSC (n = 365). BSC did not include sorafenib. The two groups of patients were compared with or without propensity score matching. A subgroup analysis was subsequently performed by stratifying patients according to the stages of PVTT in the Cheng's PVTT classification.

Results: In PVTTtypes I-III, TACE was associated with significantly better overall survival (OS) thanBSC ($P < 0.05$). Within each type of PVTT for patients who received TACE or BSC, OS was significantly worse in patients with type IVPVTT than in any of the other three types of PVTT (all $P < 0.05$). TACE was associated with better long-termOS than BSC after propensity score matching or on stratification by the PVTT types.

Conclusion: TACE was associated with better OS than BSC in HCC patients with PVTT types I-III but not type IV. Patients with type IV PVTT showed the worst prognosis, regardless of whether TACE or BSC was used.

Introduction

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death in the world. In China, HCC is the fourth leading cause of malignancy-related morbidity and the third leading cause of malignancy-related mortality [1–3]. HCC is often

List of abbreviations in the order of appearance: AFP, alpha fetoprotein; ALB, albumin; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; CI, confidence interval; CT, computed tomography; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; OS, overall survival; MRI, magnetic resonance imaging; PVTT, portal vein tumor thrombus; TACE, transarterial chemoembolization.

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diagnosed at intermediate and advanced stages [4].

Approximately 30–50% of HCC patients have concurrent portal vein tumor thrombus (PVTT) at the time of diagnosis [5].According to Western clinical guidelines, [6,7] PVTT is a contraindication for TACE, and either sorafeniborbest supportive care (BSC)is recommended. However, several studies coming from different countries suggest that TACE is safe and effective for patients with PVTT [8–12]. The Hong Kong Liver Cancer (HKLC) staging system even recommends TACE for patients with intrahepatic vascular invasion, which is considered to be too aggressive in Western guidelines [13]. Such discrepancies highlight the need for rigorous comparisons of TACE with BSC for HCC with PVTT.

In China, sorafenib was not available until 2007. The high price of sorafenib and its limited efficacy lead to most HCC patients refuse to take sorafenib but adopt other treatments such as TACE or BSC. In this multicenter retrospective study, we compared the overall survival (OS) of HCC patients who underwent initial TACE or BSC in patients with HCC with different extents of portal invasion, including intrahepatic (Cheng's types I-II) or extrahepatic (type III-IV). Our goal was to determine whether TACE or BSC would be the more appropriate treatment for patients with HCC with different PVTT types.

Patients and methods

Ethics statement

This multi-center study was approved by the Institutional Review Board of the Tumor Hospital of Guangxi Medical University, People's Hospital of Peking University and Beijing Aerospace Center Hospital. Written informed consent was obtained from the patients for their information to be stored in the hospital database and to be used for research purposes.

Patients

We compared the efficacy and safety of treatment after TACE with BSC in patients with HCC withPVTT. Patients were further stratified using the Cheng's PVTT classification system (Fig S1 and Table 1) [14]. This system was selected because it gave more precise staging than the Japanese PVTT classification system [15].The Child-Pugh grading was used to stage liver function of the patients. HBV-positive patients received conventional anti-hepatitis B virus treatment.

This multi-center retrospective study involved all the patients who underwent initial TACE or BSC at the Affiliated Tumor Hospital of Guangxi Medical University, Peking University People's Hospital and Beijing Aerospace Center Hospital between January 2003 and December 2013. Beijing aerospace Hospital only provides BSC patients ($n = 12$). The diagnosis of HCC was confirmed by either needle biopsy or by two imaging modalities (ultrasonography, computed tomography [CT], and/or magnetic resonance imaging [MRI]) in conjunction with a serum level of alpha fetoprotein (AFP) higher than 400 ng/mL. Needle biopsy was performed in patients whose diagnosis was uncertain based on imagings and AFP levels. The PVTT extent was determined by CT and/or MRI. Patients were included in the study if they were diagnosed with HCC with any type of PVTT, and were treated with either TACE or BSC as the initial therapy. Patients were excluded if they were followed up for fewer than 6 months and were still alive at the last follow-up.

TACE and BSC

Inclusion criteria of TACE included: a) Patients aged $\geq$18 years with HCC unsuitable for resection or percutaneous ablation; b) Child-Pugh A or B liver function; c) ECOG performance status of 0 or 1; d) no previous chemotherapy, radiotherapy or transarterial embolization (with or without chemotherapy). Exclusion criteria were massive ascites, advanced liver disease, and contraindications to arteriography or TACE. Patients were excluded if they received other initial treatments such as resection, radiofrequency ablation, or sorafenib.

The Seldinger technique was used to introduce a 4 to 5 French catheter into the hepatic artery via the superficial femoral artery of the patient under local anesthesia. Hepatic arterial fluoroscopic angiography was performed to identify the feeding artery, tumor staining, and vascular anatomy of the tumor. A microcatheter was then introduced and was directed into the feeding artery. An emulsion of 5–15 mL of lipiodol and 5-fluorouracil (500 mg/m^2) with or without adriamycin (30 mg/m^2) was infused into the feeding artery until the blood flow was nearly stopped. The tumor response to TACE was assessed one month later using CT and/or MRI. TACE was repeated once every 1–2 months for a total of 2–6 cycles. Inclusion criteria of BSC included: a) any grade of liver function and any score of ECOG performance status; b) patient requested BSC.

Follow-up

After TACE, all patients attended regular follow-up visits once every 2–3 months in the first year and once every 6 months thereafter [16]. During each follow-up visits, liver function tests, serum AFP levels, abdominal ultrasonography, and CT and/or MRI were performed. Patients who failed to attend the follow-up visits were contacted by telephone.

Study endpoints

OS was the primary endpoint of this study, which was defined as the interval between the first TACE procedure (for the TACE group) or the firstin-hospital test results (for the BSC group)and the date of death. Patients who were alive at the end of follow-up were censored on February 28, 2017. The in-hospital mortality was defined as death within 1 month after the first hospitalization.

Statistical analysis

Data analysts were blinded to the TACE/BSC treatment as well as the PVTT types to the minimize risk of bias. Differences in categorical data were assessed for significance using the chi-squared test or the Fisher exact test (2-tailed), while differences in continuous data were assessed using the Mann-Whitney *U* test. Data were reported as mean $\pm$ SD, or median, range as appropriate. OS was analyzed using the Kaplan-Meier method and compared using the log-rank test. The multivariate Cox proportional hazard modeling was performed to identify independent prognostic factors based on adjusted hazard ratio and its associated 95% confidence interval (CI). All statistical analyses were performed using SPSS 20.0 (IBM, Chicago, IL, USA). For all tests, $P < 0.05$ was considered statistically significant.

To reduce the risk that our results might reflect baseline differences between patients who received TACE or BSC, further analysis using propensity score matching was performed. Patients were first assigned propensity scores along a continuous range from 0 to 1 by applying the logistic regression to clinical variables which differed significantly between the TACE and BSC groups of patients. 2:1 nearest-neighbor matches were then generated between these two groups of patients. Propensity score matching was performed by SPSS 20.0 (IBM, Chicago, IL, USA).

Table 1
Baseline characteristics of patients with HCC with portal vein tumor thrombus.

Variable	Before Propensity Matching			After Propensity Matching		
	TACE	BSC	*P*	TACE	BSC	*P*
N	675	365		350	175	
Sex, n (%)			0.564			0.992
Male	603 (89.3)	321 (88.0)		320 (91.4)	160 (91.4)	
Female	72 (10.7)	44 (12.0)		30 (8.6)	15 (8.6)	
Age, mean ± SD	55.9 ± 12.0	50.4 ± 11.9	0.689	51.7 ± 11.4	51.4 ± 11.9	0.774
Tumor size, mean ± SD	10.4 ± 4.9	10.5 ± 6.2	0.062	9.7 ± 3.5	10.3 ± 3.1	0.058
Tumor number, (%)			<0.001			0.249
Single	475 (70.3)	311 (85.2)		238 (67.9)	110 (62.9)	
Multiple	200 (29.7)	54 (14.8)		112 (32.1)	65 (37.1)	
HBsAg, n (%)			0.283			0.793
No	121 (18)	77 (21.0)		60 (16.9)	28 (16.0)	
Yes	554 (82)	288 (79.0)		290 (83.1)	147 (84.0)	
Hepatitis C antibody, n (%)			0.202			0.206
No	662 (98.1)	353 (96.7)		329 (94.0)	169 (96.6)	
Yes	13 (1.9)	12 (3.3)		21 (6.0)	6 (3.4)	
Cirrhosis, n (%)			0.196			0.558
Absent	351 (52.0)	204 (56.2)		178 (50.7)	84 (48.0)	
Present	324 (48.0)	161 (44.1)		172 (49.3)	91 (52.0)	
AFP, n (%)			0.019			0.092
≥400	566 (83.8)	285 (78.1)		262 (74.8)	128 (73.1)	
<400	109 (16.2)	80 (21.9)		68 (25.2)	47 (26.9)	
Platelets, mean ± SD	191.6 ± 94.1	198.6 ± 97.8	0.493	194.3 ± 100.1	188.0 ± 93.0	0.488
PT, mean ± SD	13.75 ± 1.99	14.05 ± 9.15	0.148	13.7 ± 2.4	13.6 ± 2.0	0.564
Total bilirubin, mean ± SD	23.87 ± 20.22	23.17 ± 20.34	0.015	24.51 ± 23.72	26.04 ± 29.16	0.521
ALB, mean ± SD	39.01 ± 10.75	37.76 ± 5.91	0.071	36.84 ± 9.1	36.8 ± 5.5	0.975
ALT, mean ± SD	74.92 ± 73.14	63.13 ± 61.19	0.031	63.2 ± 45.4	74.3 ± 83.5	0.051
Child Pugh, n (%)			0.711			0.815
A	380 (56.3)	200 (54.8)		265 (75.6)	134 (76.6)	
B	295 (43.7)	165 (45.2)		85 (24.4)	41 (23.4)	
Hypertension, n (%)			0.148			0.306
No	346 (51.3)	170 (46.6)		305 (87.1)	151 (86.2)	
Yes	329 (48.7)	195 (53.4)		45 (12.9)	24 (13.8)	
Diabetes, n (%)						0.885
No	646 (95.8)	347 (95.1)		334 (95.7)	167 (95.4)	
Yes	29 (4.2)	18 (4.9)	0.625	16 (4.3)	8 (4.6)	
Ascites, n (%)			0.019			0.822
No	661 (98.0)	360 (98.7)		341(97.4)	171 (95.4)	
Yes	14 (2.0)	5 (1.3)		9(2.6)	4(4.6)	
Esophageal varices, n (%)			0.510			0.165
No	538 (79.7)	295 (80.9)	–	272 (77.7)	145 (82.9)	–
Yes	137 (20.3)	70 (19.1)	–	78 (22.3)	30 (17.1)	–

Values are n or n (%) or mean ± SD.
ALB, albumin; ALT, alanine aminotransferase; PT, prothrombin time; AFP, alpha fetoprotein

Results

Study population

Of 1,872 HCC patients with PVTT who were treated in our hospital during the study period, 834 patients were excluded because they were treated initially with treatments other than TACE or BSC. For the remaining 1,040 patients (44%) who were included into this retrospective study, 675 patients (65%) received TACE and 365 (35%) received BSC (Fig. 1).

Clinicopathology of the entire study population

The median age of all the patients was 53 years, and more than 80% of patients were male and were positive for hepatitis B virus surface antigen (Table 1). Approximately 2% were infected with hepatitis C virus. Most baseline demographic and clinical characteristics were comparable between the TACE and BSC groups (Table 1). Patients in the TACE group showed a significantly higher incidence of multinodular tumors as well as higher levels of AFP, total bilirubin and alanine aminotransferase. Patients in the BSC group showed significantly higher incidences of portal hypertension and ascites.

Mortality and morbidity rates

For the entire study population, the BSC group showed a significantly higher in-hospital mortality rate than the TACE group (7.7% vs 2.6%; $P < 0.001$). Postoperative complications after TACE occurred in 17.1% of patients (Tables S2). In the propensity-matched patients, there were no significant differences in the mortality and the morbidity rates between the two groups of patients($P > 0.05$). Postoperative complications after TACE occurred in 13.7% of patients(Table S3).

Survival analysis of the entire study population

During a follow-up period with a median of 32 months (range, 1–120), 606 (89%) patients in the TACE group and 335 (92%) in the BSC group died. TACE showed better OS rates than BSC at 1 year (35.2% vs 26.9%), 2 years (15.9% vs 14.3%), and 3 years (11.8% vs 10.2%) ($P = 0.007$; Fig. 2A). The median OS was 9 months in the TACE group and 6 months in the BSC group. Two institutions (Affiliated Tumor Hospital of Guangxi Medical University and Peking University People's Hospital) showed similar survival results (Fig S4).

For the TACE group, OS was significantly worse in patients with

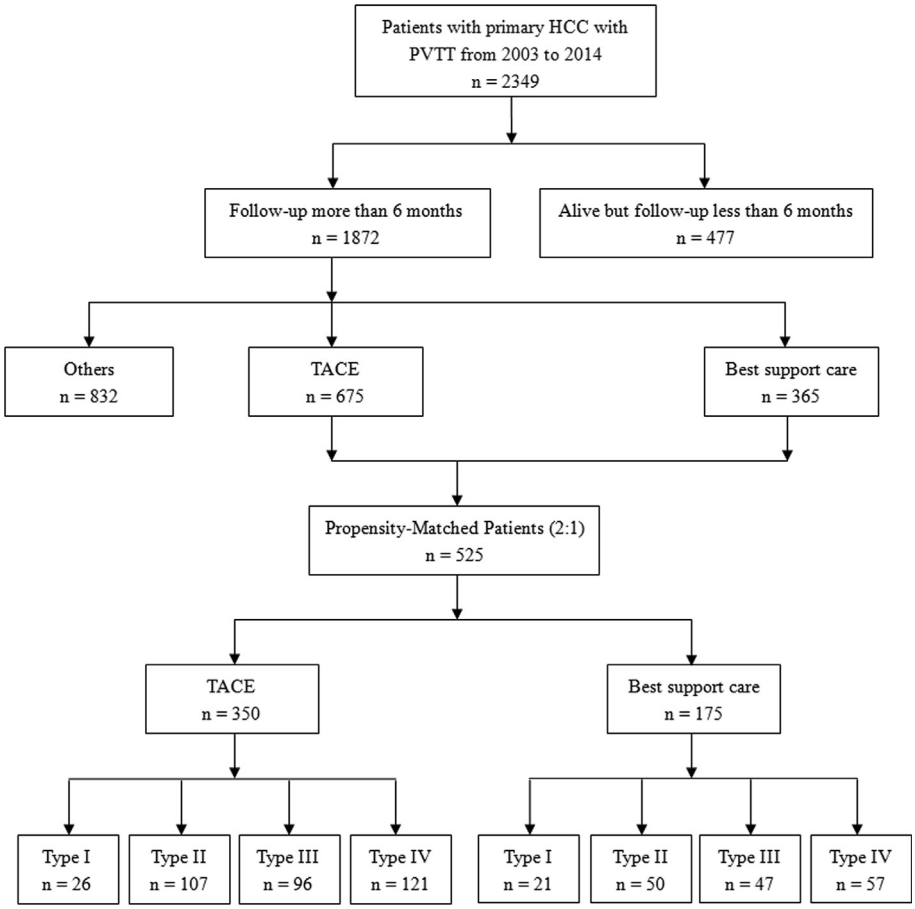

Fig. 1. Flow chart of patient selection. Type refers to the PVTT type according to the Cheng's classification system.

type IVPVTT than in the other three PVTT types (1 year, 22.5% vs 62.5%, 48.9%, and 39.0%; 2 years, 13.3% vs 46.8%,25.8%, and 17.2%; 3 years, 5.5%, vs 33.8%, 20.4%, and 10.7%, respectively) (Fig S2A). The median survival of patients with PVTT type IV, I, II and III were 6, 19, 12 and 9 months, respectively. In the BSC group, OS was significantly worse in patients with type IVPVTT than in the other three PVTT types (1 year, 15.8% vs 47.0%, 42.6%, and 27.5%; 2 years, 8.7% vs 35.3%%, 18.7%, and 12.7%; 3 years, 3.5% vs 26.4%, 14.7%, and 8.8%, respectively) (Fig S2B). The median survival of patients with PVTT type IV, I, II and III were 5, 12, 7 and 7 months, respectively. Among all the patients withPVTT type I-III, TACE was associated with markedly better OS thanBSC(Fig S3A-C). However, in patients with type IV PVTT, TACE and BSC the OS showed no significant differences (Fig S3D).

To identify potential predictors of poor OS, uni- and multivariate analyses were carried out using variables who had previously been identified to link to such risks: age, sex, tumor size and number, hepatitis, serum biochemistry, diabetes mellitus, gastrointestinal hemorrhage, hypersplenism, portal hypertension, esophageal varices, and treatment modality (Table 1). These analyses identified Child-Pugh class B and diabetes mellitus to be predictors of poor OS (Table 2).

Clinicopathology and survival analyses of the propensity-matched patients

A total of 525 trios of patients from the TACE and BSC groups (in 2:1 ratio) were generated by propensity score matching, and the members of each trio did not show any significant baseline differences from one another (Table 1). TACE resulted in better OS rates than BSC at 1 year (45.3% vs 41.1%), 2 years (27.7% vs 15.7%), and 3 years (19.3% vs 11.6%) ($P = 0.002$; Fig. 2B). The median survival was 11 months in the TACE group and 7 months in the BSC group.

Survival analysis of the propensity-matched patients with different PVTT types

For all the patients who underwent TACE, the OS rate was significantly worse in patients with type IVPVTT than in types I-III (1 year, 22.5% vs 76.9%, 60.1%, and 54.2%; 2 years, 13.3% vs 53.8%, 34.4%, and 30.2%; 3 years, 9.2% vs 37.5%, 25.8%, and 19.7%, respectively; Fig. 3A). Patients in the BSC group also showed similar results (1 year, 19.3% vs 46.1%, 46.0%, and 40.4%; 2 years, 8.8% vs 31.4%, 20.0%, and 12.8%; 3 years, 3.5% vs 21.0%, 18.0%, and 10.6%, respectively; all $P < 0.05$; Fig. 3B). The median survival associated with PVTT type IV, I, II and III were 5, 31, 14 and 13 months in the TACE group, compared to 6, 15, 12 and 11 months in the BSC group, respectively.

For the patients with PVTT types I-III, TACE was associated with significantly better OS rates than BSC(Fig. 4A–C). However, the OS rates showed no significant difference for the two treatments for patients with type IV PVTT (Fig. 4D).

Discussion

Guidelines of the European Association for the Study of the Liver [6]and the American Association for the Study of Liver Disease [7]

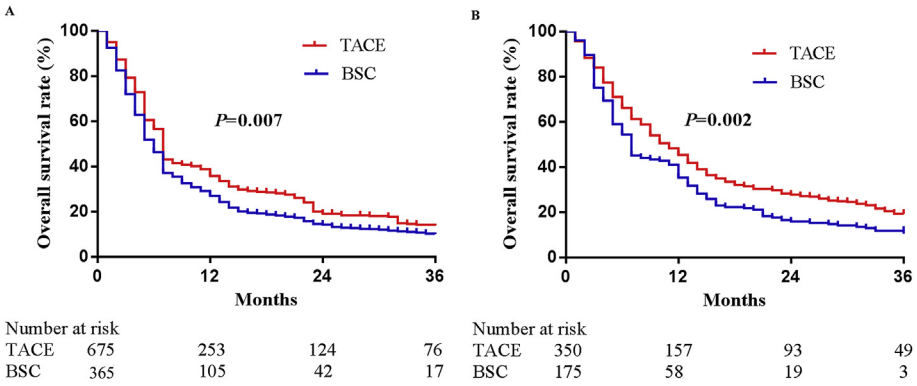

Fig. 2. Overall survival rates for all the patients with HCC with any type of PVTT ('Total') or trios of propensity score-matched patients ('Matched') treated with TACE or best supportive care (matched in 2:1 ratio).

Table 2
Uni- and multivariate analyses to identify factors influencing overall survival in total patients with hepatocellular carcinoma.

Variable	Univariate			Multivariate		
	hazard ratio	95% CI	*P*	hazard ratio	95% CI	*P*
Sex, M	0.836	0.631–1.107	0.201			
Tumor size, > 10 cm	0.947	0.799–1.123	0.531			
Tumor number, Multiple	1.454	1.204–1.758	0.048			
HBsAg, (+)	1.119	0.862–1.453	0.397			
Hepatitis C antibody, (+)	1.088	0.721–1.645	0.686			
Serum AFP, > 400 ng/mL	0.755	0.571–1.823	0.303			
Cirrhosis, (+)	1.164	0.967–1.403	0.108			
ALT, > 40U/L	1.087	0.900–1.313	0.385			
Bilirubin, > 12 mg/dL	1.071	0.876–1.311	0.500			
PT, > 13s	0.910	0.758–1.902	0.310			
ALB, > 40 g/dl	0.867	0.726–1.035	0.114			
Platelets, > 100μ/L	1.005	0.782–1.292	0.968			
Age, > 60 yr	1.001	0.839–1.194	0.993			
Present of portal hypertension	0.950	0.793–1.138	0.309			
Present of diabetes mellitus	1.495	1.021–2.197	0.032	1.278	1.081–1.496	0.004
Child-Pugh B	1.216	1.017–1.454	0.039	1.499	1.023–2.198	0.038

Values are n or n (%) or mean ± SD.
ALB, albumin; ALT, alanine aminotransferase; PT, prothrombin time; AFP, alpha fetoprotein

do not recommend TACE for patients with HCC with PVTT, but instead sorafenib or BSC. Actually, some studies have shown TACE to be safe and effective in such patients [17,18]. This reflects the lack of good medical evidence to compare TACE with BSC for such patients. Our relatively large retrospective study suggested that for patients with Cheng's PVTT types I-III, TACE resulted in significantly better OS than BSC without increasing the risks of in-hospital mortality and complications. Our findings are consistent with the findings of the HKLC staging system, which recommended TACE to be the appropriate treatment for patients with intrahepatic vascular invasion [13].

TACE effectively blocks the nutrient vessels to the tumor, thus allowing a sustainable and high-dose chemotherapy to kill HCC cells in the liver, with less damage to normal liver cells. The technique also reduces portal venous pressure and prevents intractable ascites formation and bleeding esophageal varices to occur [19]. On the basis of our findings and on published literature, clinicians should consider TACE to be an effective and safe treatment for patients with HCC with PVTT types I-III. Patients with PVTT type IV have been reported to benefit from a combination of TACE and radiotherapy [20,21].

Numerous studies have shown that sorafenib did not show any survival benefit over TACE in patients with HCC with PVTT [22–28]. Analysis of these previously published studies as shown in Table 3 suggested that sorafenib had higher median in-hospital mortality and higher complication rates than TACE [23–28]. Data in our present study also showed worse median OS rates with sorafenib than TACE at 1 year (24.3 vs 36.8%), 2 years (11.7 vs 18.6%), and 3 years (7.2 vs 12.5%), respectively. In addition, sorafenib is not well tolerated in patients with reduced liver function, [29] and it may even result in toxicity and extremely poor survival [30,31].

TACE treatment also has some limitations such as incomplete embolism which may lead to treatment failure, poor patient status, intolerance of TACE treatment and so on [16]. At present, some scholars have tried to use other treatments for HCC, such as Y90 Radioembolization. Salem et al. found an effective rate of 42% (WHO standard) or 57% (EASL standard) in 291 patients with HCC treated with Y90 radioembolization. HCC patients with Child-Pugh grade A and/or PVTT have a most benefit from Y90 radioembolization [32]. Y90 radioembolization has been identified as playing an important role in the treatment of HCC patients with PVTT and metastatic liver cancer [33,34]. However, more prospective studies with large sample size are needed.

Diabetes mellitus has been identified as a predictor of poor OS in our study, a findings which is similar to the findings published previously [15]. Diabetes mellitus may reduce OS by exacerbating any pre-existing liver damage by contributing to formation and progression of liver fibrosis [35]. The high glucose levels and hyperinsulinemia in patients with diabetes mellitus up-regulate the expression of connective tissue growth factor, [9] which

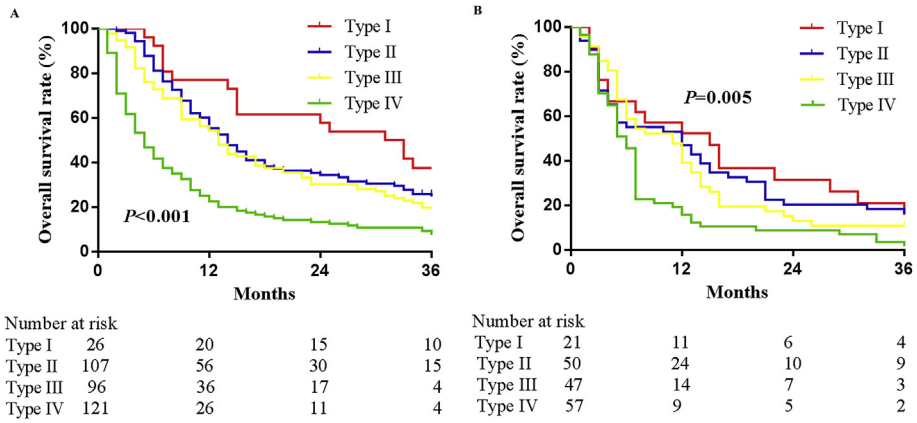

Fig. 3. Overall survival curves for propensity-matched patients with HCC with any type of portal vein tumor thrombus who received TACE (A) or best supportive care (B).

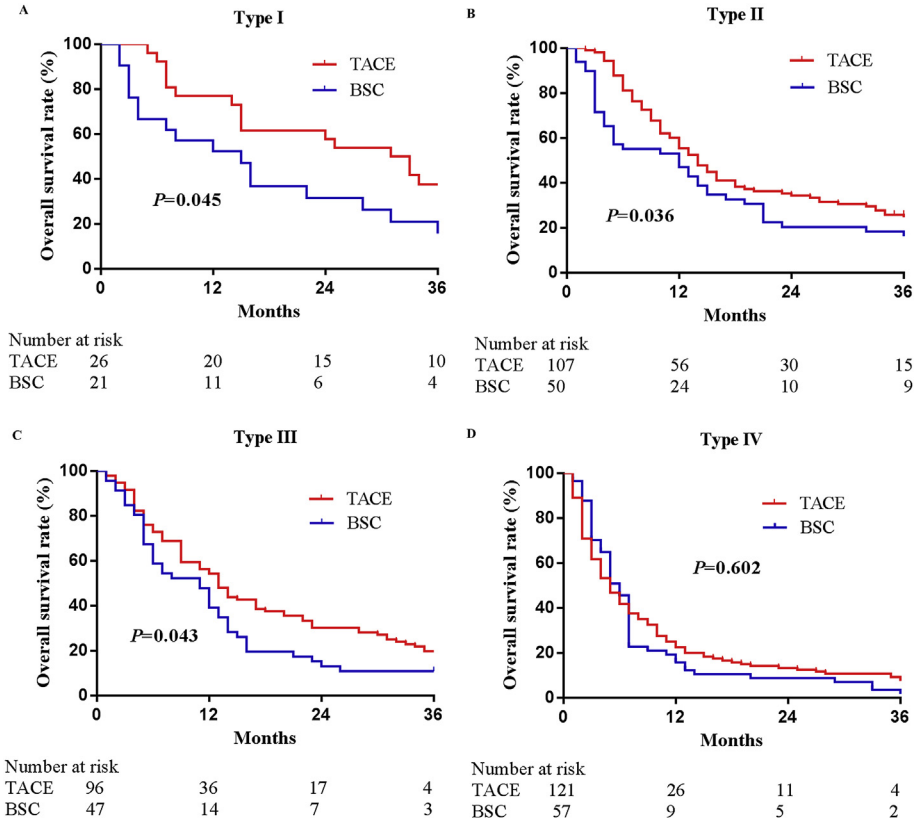

Fig. 4. Comparison of overall survival rates followingTACE or best supportive care for propensity-matched patients with HCC with PVTT type I (A), type II (B), type III (C), or type IV (D).

accelerates progression of liver fibrosis. Hyperinsulinemia and insulin resistance increase production of reactive oxygen species, thus exacerbating fibrosis and liver injury [36]. These increase the risk of liver failure, particularly in a background of cirrhosis which was present in 54% of our patients. Thus, to prolong survival of diabetic patients with HCC would require a good control of blood glucose level and provide other supportive treatment to preserve good liver function.

This study has several limitations. First, our study was retrospective, and we excluded alive patients with follow-up of less than 6 months, which was helpful in observing the morbidity and mortality of TACE. It cannot completely eliminate selection bias. Nevertheless, our study has a relatively large sample size, and propensity score analysis was used to reduce any selection bias. Second, we recruited patients into this study over a relatively long period of time, thus increasing the risk that adjustments or minor modifications in the TACE or other hospital procedures might confound our analysis. Third, we did not stratify patients by the number of TACE cycles. Thus we were unable to determine whether this affected OS. And last, high prevalence of HBV may limit extrapolation of results to other patients.

In conclusion, our results suggested that TACE was more efficacious than BSC for in treating patients with HCC with Cheng'sPVTTtypes I-III. The two treatments were similarly safe.

Table 3
Prognoses of patients with HCC with PVTT treated by sorafenib.

Study	Country	Enrollment period	Total patients	Post-treated complications, %	In-hospital mortality, %	Median survival, mon.	Overall survival (Median), %		
							1 yr	2 yr	3 yr
Giorgio 2016	Italy	2011–2014	99	29.5	4.2	7	37.3	–	–
Jeong 2013	Korea	2008–2011	143	–	3.1	4	18.7	12.3	7.2
Nakazawa 2014	Japan	2009–2011	36	27.1	–	5	21.3	17.7	8.7
Song 2015	Japan	2008–2013	110	–	5.7	6	18.4	10.2	5.1
Zhang 2015	China	2009–2013	44	59.6	–	6	23.2	18.1	11.9
Edeline 2015	France	2005–2012	89	30.7	4.3	7	28.7	17.3	10.3
Total (median)	**-**	**-**	**87**	**29.5**	**4.1**	**6**	**24.3**	**11.7**	**7.2**
Present study									
Total TACE	China	2003–2013	675	17.1	2.4	9	36.8	18.6	12.5
Total BSC	China	2003–2013	363	–	7.7	6	27.2	14.4	9.7
Match TACE	China	2003–2013	350	13.7	2.6	11	45.3	27.7	19.3
Match BSC	China	2003–2013	175	–	4.5	7	41.1	15.7	11.6

Abbreviations "-", data not reported.

There was no significant difference in OS for patients with type IV PVTT treated with either TACE or BSC. The OS rate worsened with increase in Cheng's PVTT type.

Conflict of interest

No authors declare any conflicts of interest.

Author contributions

J-Y Z, J-H Z and L-Q L conceived the study. All authors contributed to data collection, analysis, and manuscript writing. All authors approved the final version of the manuscript.

Synopsis

1. This multicenter study was conducted on 1,040 patients with HCC with PVTT who were treated either with TACE (n = 675) or BSC (n = 365).
2. We found TACE was associated with better OS than BSC inHCC patients with PVTT types I-III.
3. HCC patients with type IV PVTT showed the worst prognosis, regardless of whether TACE or BSC was used.

Role of the funding source

Data acquisition, analysis and interpretation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.03.042.

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