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Transarterial Chemoembolization in Unresectable Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis: A Tertiary Care Center Experience

Yashwant Patidar[1] Basavaraj[1] Amar Mukund[1] Shiv K. Sarin[2]

[1]Department of Interventional Radiology, Institute of Liver and Biliary Sciences, New Delhi, India
[2]Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India

Address for correspondence Yashwant Patidar, MD, Department of Interventional Radiology, Institute of Liver and Biliary Sciences, D-1 Vasant Kunj, New Delhi, 110070, India (e-mail: dryashwantpatidar@gmail.com).

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Abstract

Background Portal vein tumor thrombosis (PVTT) is a common complication of hepatocellular carcinoma (HCC) occurring in 30 to 40% of cases. The presence of PVTT in HCC is regarded as an advanced disease that confers poor prognosis and survival. Transarterial chemoembolization (TACE) has traditionally been considered to be contraindicated in cases of PVTT, due to the risk of hepatic infarction, and further deteriorate liver function. We evaluated safety, technical efficacy, and outcomes of TACE in HCC with PVTT.

Methods From search results of the hospital database, out of 652 patients who underwent TACE for HCC, 73 patients of HCC with PVTT were retrospectively evaluated. Post-TACE tumor response by computed tomography (CT)/magnetic resonance imaging (MRI) imaging as per modified response evaluation criteria in solid tumors (mRECIST) criteria, if any occurrence of acute hepatic failure was assessed. Prognostic factors influencing survival were also determined.

Results In our study population, the mean age of the patients was 58 years. The 12- and 24-month survival rates were 59 and 14%, respectively, with an overall median survival of 12.3 months. A total of 58.9% patients had branch portal vein tumor thrombus and 41.1% had tumor thrombus in the main portal vein. We did not encounter any mortality or acute liver failure following TACE in a 30-day period. Both univariate and multivariate analysis revealed Child–Pugh score (p = 0.01) and the extent of tumoral thrombus (p 0.004) as a significant prognostic factor. Patients with branch PVTT, no ascites, and Child–Pugh A had better survival than those having main portal vein tumor thrombus, ascites, and Child–Pugh B.

Conclusion Our study concluded that TACE can achieve good disease control and improved survival in HCC with portal vein invasion despite being considered as a relative contraindication. Technical expertise, selection of patients, such as superselective catheterization and preserved liver function, are the key factors for a safe therapeutic procedure. Child–Pugh score and extent of portal vein invasion were the significant prognostic factors determining survival.

Keywords
- hepatocellular carcinoma
- portal vein tumor thrombosis
- transarterial chemoembolization

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common causes of malignancy-related deaths worldwide. The incidence is higher in Asian countries compared with Europe and the United States.[1-3] The incidence of portal vein tumor invasion, in general, has been reported up to 30 to 40% in patients with HCC.[4,5] The presence of portal vein tumor thrombus in HCC patients indicates a poorer prognosis reducing their overall survival to approximately 2 to 4 months with the best supportive care.[6,7] Transarterial chemoembolization (TACE) has been recommended as the first line of management in unresectable HCC. As per the Barcelona Clinic Liver Cancer (BCLC) staging system, portal vein tumor thrombosis (PVTT) in HCC is considered as a relative contraindication for transarterial chemoembolization due to the potential risk of hepatic infarction and worsening liver function following embolization. Officially, BCLC staging system does not endorse intra-arterial therapy (IAT) in this group of patients, but certain studies have reported evidence supporting this treatment.[8,9] The dual advantage of TACE is that it allows to administer locally high concentration of chemotherapeutic drugs directly to the tumor and thus reducing the systemic toxicity of these agents. Recent advances in technology and the use of micro catheters for superselective catheterization of arteries have given an edge to perform TACE in patients of HCC with PVTT.[9] Few studies including meta-analyses have reported that TACE can be performed safely for HCC with PVTT with survival benefits in selected Child–Pugh class-A and -B patients.[10,11] The current study was undertaken with the objectives of evaluating the efficacy, safety, and survival outcomes of TACE in HCC patients complicated by portal vein tumor thrombus.

Study Population and Methods

Patient Selection

This is a retrospective study done at a dedicated hepatobiliary tertiary care teaching hospital. The study was approved by the institutional review board. We searched through the hospital database system for patients with HCC who underwent TACE between 2011 and 2019. There were a total of 653 patients with unresectable HCC treated with TACE, comprising of 1,032 TACE sessions. Out of which, 73 patients of HCC with PVTT were enrolled in this study (22 patients received conventional TACE and 51 patients received drug-eluting beads TACE) (►**Fig. 1**).

Inclusion criteria were serum bilirubin <3 mg/dL, aspartate aminotransferase (AST), or alanine aminotransferase (ALT) <5 times upper limit of normal, the Eastern Cooperative Oncology Group (ECOG) performance status 0–2, and Child–Pugh A/B. Patients were excluded if they had surgical resection/liver transplantation/RFA/locoregional therapy/sorafenib or systemic chemotherapy prior to TACE, refractory ascites, clinical encephalopathy, extrahepatic metastasis, and complete portal vein thrombus extending up to splenic–superior mesenteric vein (SMV) confluence and contraindications to TACE.

All patients included in the study were biopsy proven and/or had triphasic imaging confirmation of the tumor. We reviewed baseline imaging and relevant laboratory parameters such as serum alpha-fetoprotein (AFP), complete blood count, and liver function tests. Portal vein tumor thrombus was interpreted on computed tomography (CT)/magnetic resonance imaging (MRI) by observing filling defects in the portal vein due to intraluminal mass causing expansion of portal vein with thread and streaks type of enhancement. We followed PVTT classification system developed by the Liver Cancer Study Group of Japan for assessing the degree of extent of PVTT[12] (Vp0: no tumor thrombus in the portal vein; Vp1: presence of tumor thrombus distal to but not in the second-order branches of PV; Vp2: the second-order branches of PV; Vp3: first-order branches of the PV; Vp4: main trunk of the PV).

Procedure

Standard angiographic technique was used to access the common femoral artery. Celiac and mesenteric arteriograms were taken to assess arterial anatomy and tumor vascularisation. Superselective cannulation of the segmental and subsegmental hepatic artery branches feeding the tumor was done using a microcatheter (Progreat 2.7 Fr coaxial microcatheter system, Somerset, New Jersey, United States: Terumo Medical Corporation) and embolized with doxorubicin and Lipiodol emulsion (Guerbet, Paris, France) in 1:1 ratio or drug-eluting beads (Hepaspheres; Merit Medical Systems Inc.) of size 30 to 60 µm loaded with 50 mg of doxorubicin, which were mixed with nonionic iodinated contrast material in a ratio of 1:1. Any extrahepatic blood supply to the tumor (the inferior phrenic, intercostal arteries, or internal mammary), the respective arteries were cannulated and embolized in the same way. Stasis or near stasis (sluggish) of blood flow was considered as the end-point of embolization. After the procedure, the femoral arterial sheath was removed. Hemostasis was achieved through manual compression or vascular closure device.

Postprocedure Assessment and Follow-up

All patients had their serum bilirubin, AST, and ALT measured on days 2 to 5 post-TACE to monitor parenchymal injury and risk of acute liver failure as per CTCAE (common terminology criteria for adverse events version 4.0, for toxicities), any adverse events related to the procedure within 1 month were also sorted. All the patients were followed-up with contrast-enhanced CT or MRI done at 1, 3, and 6, months, and annually thereafter. The treatment response was evaluated by the modified response evaluation criteria in solid tumors (mRECIST) criteria. Repeat TACE sessions were performed if the patients have residual tumor on imaging at 1 month and thereafter unless the patient had developed contraindication for TACE or showed absence of radiological response or AST >25% elevation or worsening of Child–Pugh score. Follow-up of patients was done until their death or cut-off date of the study.

Statistical Methods

Survival analysis was done by using the Kaplan–Meier method. All analyses were done using SPSS software version 22. Univariate and multivariate survival analyses were performed on selected variables, including Child–Pugh score, ascites status, ECOG performance status, and PVTT (branch vs. MPV), and p-value <0.05 was interpreted as statistically significant (►**Fig. 1**).

Results

Our study group comprised of 69 males and 4 females with a median age of presentation of 58 years (►**Table 1**). The most common etiology was hepatitis B virus (HBV)-related infection accounting for 32.9% of cases. A total of 60% of patients had multifocal tumors. There were 49 and 24 patients of Child–Pugh classes A and B, respectively. Forty-eight patients had ascites. For the purpose of number and uniform comparison, we combined Vp1 to Vp3 as a branch portal vein and compared with Vp4 as the main portal vein thrombus. Tumor thrombus involving portal vein branches (Vp1–3) were 43 patients (58.9%), and that involving the main portal vein was 30 (41.1%). The average number of TACE sessions was two (range: 1–5). We also collected available protein-induced by vitamin-K absence II (PIVKA II) data from patients, only 22 patients had PIVKA II assay with a mean of 109.9 mAU/mL. We found no procedure-related deaths or major complications such as acute liver failure/encephalopathy following TACE at 1 month. Minor adverse effects observed were related to postembolization syndrome such as fever (33%), nausea and vomiting (21%), abdominal pain (10%), combined symptoms (17%), transient elevation in liver enzymes (grades 2 and 3 as per CTCAE version 4.0; 14%), and none (5%). At 1-month follow-up, 3 patients showed complete response who had Vp1 type tumor thrombus (►**Fig. 2**), 67 of them showed partial response, and 3 patients showed stable disease (►**Table 2**). Meantime to tumor progression was 6.3 months (6.3 ± 2.8 months).

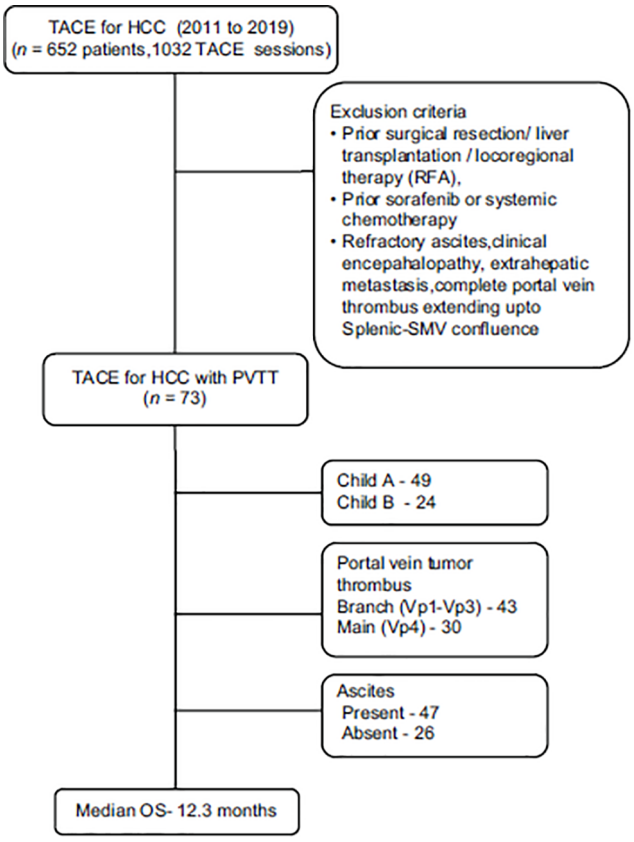

Fig. 1 Univariate and multivariate survival analyses were performed on selected variables as appropriate. HCC, hepatocellular carcinoma; OS, overall survival; PVTT, portal vein tumor thrombosis; SMV, superior mesenteric vein; TACE, transarterial chemoembolization; vp, Portal vein invasion; RFA, Radiofrequency ablatio.

Survival

Overall survival rates at 12 and 24 months were 59 and 14%, respectively, with a median survival of 12.3 months (95% confidence interval [CI]: 11–14; p = 0.01; ►**Fig. 3**). Survival analysis revealed significant correlation with child pugh score (p = 0.004) and branch versus MPV PVTT (p = 0.004) and ascites (p = 0.050). The median survival time of patients with Child–Pugh A versus B was 12.9 ± 0.6 and 9.2 ± 1.01 months (p = 0.004), respectively. The median survival time of patients with branch versus main PVTT was 13 ± 1.1 and 9.1 ± 1.2 months (p = 0.004), respectively. Patients without ascites had longer median survival time than patients with ascites (13 versus 10 months) with p = 0.050 (►**Fig. 4**).

Prognosis Predictive Factors

Univariate and multivariate survival analyses (►**Table 3**) were performed on selected variables including ascites status, Child–Pugh score and PVTT (branch vs. MPV), and ECOG performance status. Child–Pugh score (p = 0.004), (branch vs. MPV) PVTT (p = 0.004), and ascites (p = 0.050) showed statistically significant correlation with survival in univariate analysis. However, on multivariate analysis Child–Pugh score

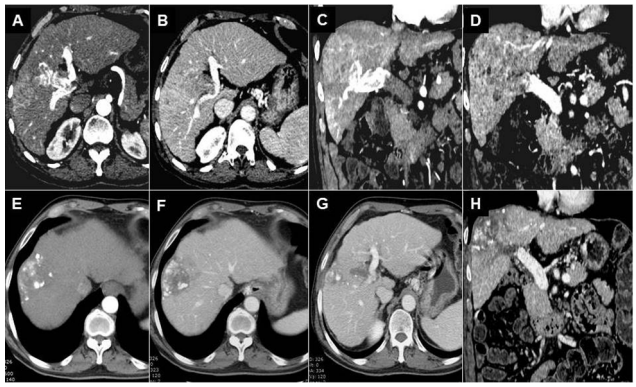

Fig. 2 (A–H) HCC with Vp1 type PVT: baseline CT images in the noncontrast axial phase image (**A**), arterial phase axial (**B**), portal venous phase axial (**C**), and portal venous phase coronal image (**D**) showing a large lesion in segment VIII of liver displaying arterial phase enhancement and venous phase washout suggestive of HCC with associate Vp1 PVT. Post-TACE follow-up CT noncontrast axial (**E**), arterial phase axial (**F**), portal venous phase axial (**G**), and portal venous phase coronal image (**H**) showing complete lipiodol deposition and no any enhancement s/o complete response. CT, computed tomography; HCC, hepatocellular carcinoma; PVT, portal vein tumor; TACE, transarterial chemoembolization.

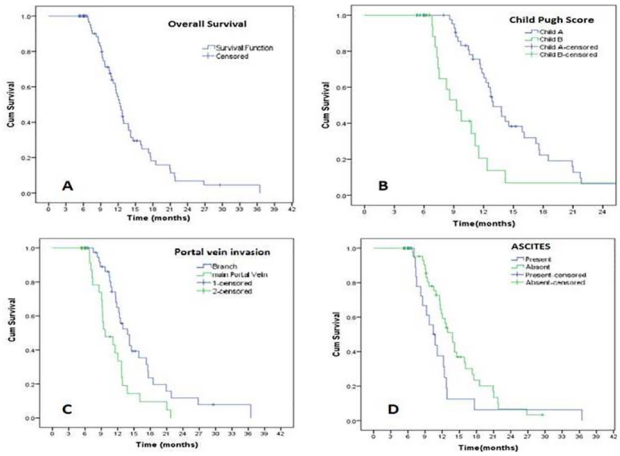

Fig. 3 (**A–D**): Kaplan–Meier survival curves: (**A**) overall survival, (**B**) branch versus main portal vein tumor thrombosis (PVTT), (**C**) Child–Pugh A versus B, and (**D**) ascites present versus absent.

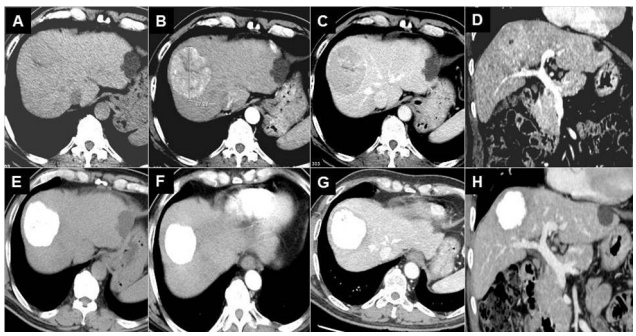

Fig. 4 (A–H) HCC with Vp3 type PVT: pre-TACE—Axial (**A** and **B**) and coronal (**C** and **D**) images showing HCC in right lobe of liver invading portal vein (Vp3) with arterioportal shunting. Post-TACE follow-up 6 month CT Axial (**E–G**) and coronal (**H**) images showing the reduced size of target lesion without any enhancement s/o complete response. CT, computed tomography; HCC, hepatocellular carcinoma; PVT, portal vein tumor; TACE, transarterial chemoembolization; vp,Portal vein invasion.

($p = 0.01$) and (branch vs. MPV) portal vein tumor thrombus ($p = 0.004$) were significant prognostic predictive factors.

Discussion

HCC has a high propensity for vascular invasion. HCC with vascular invasion is classified as advanced stage. Portal vein invasion is the most common followed by hepatic veins and IVC invasion.[13] HCC complicated by portal vein thrombosis presents as a challenging complication to treat as these patients have worsened liver function, compromised blood supply, and also they are at higher risk due to associated comorbid conditions such as portal hypertension. These patients have lesser tolerance to treatment and have a worse prognosis with a median survival time of 2 to 4 months with supportive management.[14] The BCLC staging system considers PVTT as a relative contraindication for TACE and recommend sorafenib as a mainstay of therapy. This recommendation is based on the reason that liver is at increased risk of liver infarction and liver failure following TACE in HCC with PVTT.[15,16] Advances in technical skills and availability of superselective microcatheters have allowed to selectively target tumors and perform TACE sparing the uninvolved liver. Till date, very few studies have evaluated the safety and of TACE in HCC with PVTT.[17-19] This study was undertaken to establish support, further strengthen and validate the evidence for the safety and efficacy of TACE in HCC with PVTT. Similar to Acharya, hepatitis B infection was the major cause

Table 1 Baseline characteristic of patients

Variable	Baseline Mean ± SD/*n* (%)
Age (y)	58.5 ± 11.2
Sex	
Male	69 (94.5)
Female	4 (5.5)
Etiology of cirrhosis	
HCV	11 (15.1)
HBV	24 (32.9)
Ethanol	16 (21.9)
NASH	18 (24.7)
Cryptogenic	4 (5.5)
ECOG PS	
0	37 (50.7)
1	30 (41.8)
2	6 (8.2)
Child class	
A	49 (67.1)
B	24 (32.9)
Average number of TACE sessions	2
Tumor distribution	
Solitary	39 (39.87)
Multifocal	44 (60.3)
Ascites	
Yes	48 (67.1)
No	25 (32.9)
AFP (ng/mL)	Pre-TACE: 1,210 (median)
	Post-TACE: 850 (median)
Serum bilirubin (mg/dL)	1.26 ± 0.5
AST (IU/L)	75.5 ± 30.06
ALT (IU/L)	50.4 ± 23.9
Portal vein invasion	
Vp1	3 (4.1)
Vp2	15 (20.5)
Vp3	25 (34.2)
Vp4	30 (41.9)

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECOG PS, Eastern Cooperative Oncology Group-performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; SD, standard deviation; TACE, transarterial chemoembolization; NASH,Non-alcoholic steatohepatitis.

of HCC in our study, reportedly being the most common cause of HCC in India.[20] Comparison of our study outcomes was made with several studies in regard to the survival period (►**Table 4**). Patients with Child–Pugh score A had better survival than Child–Pugh score B (13 vs. 9 months) similar to Georgiades et al,[21] whereas Chern et al[22] reported better survival in patients without ascites compared with those with ascites. In our study also, we found improved survival in patients presenting without ascites than with ascites (13 vs. l0 months). A meta-analysis by Silva et al,[10] showed patients with tumor thrombus involving MPV had poor survival compared with branch portal vein. Similarly, in our study, patients with branch portal vein involvement had better survival than tumor thrombosis involving the main portal vein (13 vs. 9.1 months). Our analysis in these 73 patients revealed significant improvement of 1-year survival rate (59%) with a median survival of the entire group of 12.3 months similar to the study done by Kim et al[23]; Yoo et al[24] reported favorable outcomes in patients without extrahepatic metastasis that partly explains improved median overall survival in our study, as we had excluded patients with extrahepatic metastasis. Postprocedure treatment response in all cases were done at 1 month with continued follow-up till death or study end period with cases having minimum of 6 months of follow-up. Our overall treatment response was based on mRECIST criteria given by Lencioni and Llovet.[25] Three of our patients with Vp1 type of thrombus showed complete response; among them two showed progression at an interval of 8 and 16 months, while one showed no recurrence and progression-free survival for 2 years at

Table 2 mRECIST response rates

mRECIST response	Frequency
CR	3 (4.1%)
PR	67 (91.7%)
SD	3 (4.1%)
Total	73

Abbreviations: mRECIST, modified response evaluation criteria in solid tumors; SD, standard deviation; CR, Complete response; PR,Partial response.

Table 3 Univariate and multivariate survival analysis

	No of patients	No of deaths	Univariate analysis			Multivariate analysis		
			HR	95% CI	*p*	HR	95% CI	*p*
Ascites								
No	47	34	1	0.9–3.3	0.050	1	0.7–2.7	0.7
Yes	26	17	1.8			1.2		
ECOG PS								
0	37	18	1	0.6–2.4	0.46	1	0.6–2.3	0.2
1	30	27	1.2	0.8–6.1	0.09	0.95	0.8–6.2	0.1
2	6	6	2.3			2.5		
Child–Pugh								
A	48	35	1	1.3–4.5	0.004[a]	1	1.07–6.3	0.01
B	25	16	2.4			2.4		
PVTT								
Branch	43	29	1	1.05–3.5	0.004[a]	1	1.3–4.3	0.004
Main	30	22	2.1			2.3		

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group-performance status; HR, hazard ratio; PVTT, portal vein tumor thrombosis.
[a]Statistically significant correlation in both univariate and multivariate analysis.

Table 4 Comparative studies

Studies	No. of patients	Median OS (mo)	Survival rates (%)		Prognostic factors
			1 year	2 years	
Georgiades et al[21]	32	11	25	12.5	Child–Pugh score
Chung et al[29]	110	6	30	18	Tumor extent
Chern et al[22]	50	6.2	22	10	Ascites and response to treatment
Kim et al[23]	49	15	59	28	Treatment type
Yadav et al[30]	17	10	47	–	Child Pugh score and ascites
Our study	73	12.3	59	13	Child–Pugh score, extent of portal vein invasion

Abbreviation OS, overall survival.

follow-up. Sixty-seven patients had partial response and three patients had stable disease with varying lengths of time to tumor progression with a mean time to tumor progression of 6.3 months. Technically, the procedure was successful in all cases. Georgiades et al[21] and Chung et al[26] have postulated that there is a gradual formation of periportal collateral circulation and/or portal vein recanalization in these patients, thereby reducing the risk of acute liver failure. We did not encounter any mortality or acute liver failure following TACE in a 30-day period. No immediate procedure-related complications, like access site hematoma, pseudoaneurysm, Arteriovenous fistula, or arterial dissection, were reported. Postembolization syndrome was noted in majority of cases with transient elevation of liver enzymes upto grade 2.3 as per CTACE version 4.0; however, returned to near-baseline values in subsequent days with conservative management. Although recommendations suggest sorafenib as a targeted therapy in advanced HCC with portal vein invasion, the medial survival time with sorafenib is short which is around 6 months.[27] Cho et al[28] compared TARE versus sorafenib for HCC with PVT and found no significant difference in median overall survival and time to progression between two groups. Medial overall survival was (13.8 vs. 10 months) and time to progression was 6 versus 6 months. Our patients had a median overall survival of 12.3 months with time to progression of 6.3 months. Hence, we believe that transarterial chemoembolization is noninferior to TARE and better than sorafenib treatments with regard to survival and time to progression. TACE should be considered as the first-line treatment in patients of HCC with PVTT having good hepatic functional reserve without ascites which is safe and effective. Our study had few limitations like retrospective analysis and few patients received sorafenib treatment after TACE which could have influenced the obtained results.

Conclusion

To conclude, our study demonstrated that TACE can be safely performed in HCC with portal vein tumor thrombus and offers good disease control. The efficacy and survival outcomes of TACE in these patients are similar to other alternative treatment modalities described in the literature. Superselective catheterization technique and preserved liver function favor TACE as the first line of treatment in patients of HCC with PVTT. Child–Pugh score and extent of portal vein invasion are an important determinant of prognosis and survival.

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Conflicts of Interest
There are no conflicts of interest.

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