TACE for HCC Patients with Portal Vein Tumor Thrombosis : Survival Analysis Using a New Classification

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Abstract: Background To explore the efficacy of transarterial chemoembolization (TACE) for HCC patients with different type portal vein tumor thrombosis (PVTT), to reveal which PVTT types could benefit from the treatment. **Methods** From October 2008 to December 2011, 101 HCC patients with PVTT were treated with TACE and clinical data was collected and analysed retrospectively. Survival analysis stratified by new classification of PVTT were performed. **Results** 22(21.7%), 36(35.6%), 34(33.6%) and 9(8.9%) cases were collected for types I, II, III, and IV PVTT. The 3-, 6-, 9-, 12- and 24- month survival rates were 70%, 32%, 19%, 11% and 4% respectively. The overall median survival for all patients was 4.5m and for type I-IV PVTT were 10.6, 4.6, 2.7 and 1.9 months respectively. The statistical differences between the types were significant (P<0.05) expect for PVTT-Ⅲ and PVTT-Ⅳ(P=0.618). **Conclusions** Some advanced HCC with PVTT may benefit from TACE, especial for patients with type I and II PVTT had better prognosis.

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Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related mortality worldwide [1]. As most of the patients are diagnosed at advanced stage, only 30%-40% of HCC patients are eligible to undergo curative treatment[1,2][8]. The efficacy of cytotoxic chemotherapy on HCC has not been proven in most phase III trials despite suggested effects in tumor control in phase II studies [9]. Sorafenib is currently the only systemic treatment for advanced HCC with proven efficacy, based on two recently published phase III trials[10,11,13]. Despite its proven efficacy, however, local progression remains one of the most common reasons for treatment failure in patients treated with Sorafenib, especially those with bulky intrahepatic tumor(s) [12]. Clearly, effective treatment for intrahepatic lesion to prevent local disease progression is needed to complement systemic therapy. PVTT is found in the branches or trunk of the portal vein in 40–90.2% patients with advanced liver cancer when first diagnosed [3-5]. According to the Barcelona Clinic Liver Cancer (BCLC) stage, recommendation for non-curative therapy for HCC patients with PVTT includes sorafenib, systemic chemotherapy, best supportive care and clinical trials[1]. TACE is widely used as a palliative treatment for HCC cases which are unsuitable for curative treatments. Two randomized control trials and a meta-analysis had demonstrated the effect of TACE on advanced HCC [14,24] . The goals of TACE in patients with advanced HCC include symptomatic control, improving quality of life, as well as prolonging survival through local disease control. The safety and efficacy of TACE in selected patients with PVTT were also reported [6,7]. The purpose of this retrospective study is to report the effect of TACE and to reveal which PVTT types benefit from TACE in a relatively large group of HCC patients with PVTT.

Methods

1.1 Patients From October 2008 to December 2011, 101 HCC patients with PVTT were enrolled in this study. This study conformed to the ethical guidelines of the 1975 Helsinki declaration. Informed consents were received by all patients. All of them were classified as stage C according to the BCLC staging system and received TACE procedures at our institution. All patients received routine examination including liver function test, blood biochemistry, alpha-feto-protein (AFP), hepatitis serology, abdominal color doppler ultrasound (CDUS), abdominal enhanced triple phase helical computed tomography (CT), and/or magnetic resonance imaging (MRI) before TACE. The diagnosis of HCC was based on the diagnostic criteria used by European Association for the Study of the Liver. The diagnosis of PVTT was based visible nourish artery on imaging CT, MRI, CDUS and angiography performed during TACE .

1.2 All patients satisfied the following criteria: (1) the presence of PVTT on imaging, (2) Child-Pugh class A or B liver function, (3) absence of distant metastasis, (4) Eastern Cooperative Group performance status 1-2, and (5) absence of contraindications(e.g. hepatic encephalopathy, massive

ascites, esophageal or gastric variceal bleeding, combined with serious diseases of other organs, etc.).

1.3 The extent of PVTT was classified into four types as followings: (1) type I, tumor thrombus involving segmental branches of portal vein, (2) type II, tumor thrombus involving right or left portal vein, (3) type III, tumor thrombus involving the main portal vein trunk, and (4) type IV, tumor thrombus involving the superior mesenteric vein or inferior vena cava.

1.4 Medicine regimen: iodized oil suspension included cisplatin40mg, THP 40mg, mitomycin 4mg, 48% iodipin 20ml. Injection dosage was calculated depending on the size of tumor vascular bed and the average dose was 9.5ml (rang: 5-30ml).

1.5 TACE Procedures: A 5F RH angiographic catheter was introduced into femoral artery through sheath by improved Seldinger puncture method. Then the catheter was advanced into the superior mesenteric artery to observe the presence/absence of filling defect in portal vein, time of portal vein perfusion and direction of blood flow. For the patients with delayed portal venous flow (delayed to 17s or above), embolization was performed according to tumor burden, liver function (Child-Pugh) and hepatic function reserve (ICGR15). Depending on the size, location, and arterial supply of the tumor, the tip of the catheter was advanced superselectively into the tumor-feeding branches. In patients with an arterioportal shunt, gelatin sponge embolization was initially used to occlude the shunt. After catheter placement, the emulsion of lipiodol and anticancer agents was infused. For some patient whose tumor was extremely large, thus the tumor arterial blood flow cannot reach stasis after injecting the maximum amount of iodized oil (we limitaed no more than 30 ml), embolization was then performed using absorbable gelatin sponge particles (Gelfoam; Hanzhou alc Ltd, China). Superselctive catheterization was used consistently during TACE regardless of tumor type or size to maintain hepatic function and to reduce normal hepatic parenchymal injury.

1.6 Evaluation We measured survival time from the date of PVTT diagnosis to the date of death. After TACE, liver function was monitored by serum bilirubin, ALT, serum albumin and prothrombin time. TACE-related complications were evaluated at the end of the first procedure.

1.7 Statistical analysis The probability of cumulative survival was estimated using Kaplan-Meier method; differences in the survival curves between subgroups were compared by the log-rank test. Risk factors associated with survival rates were assessed using Cox proportional hazard model. All calculations were performed using the SPSS statistical software version 17.0 (SPSS, Inc. Chicago, IL, USA). All statistical tests were two sided, and a significant difference was considered when $P < 0.05$.

Results

2.1 Baseline Characteristics of Patients

101 patients consisted of 85 males and 16 females were enrolled in this study with a mean age 53.88±11.35 (range: 30-84) years. The follow-up deadline was April 2012. At a median follow-up of 4.1 (range 1-30.8) months, 89 patients (88.1%) died. The baseline demographic information were recorded after the first treatment(**Table 1**).

Table 1 Summary of Baseline Characteristics

Parameter	Value, n	%
Age (years)	53.88±11.35	
Sex		
Male	85	84.2%
Female	16	15.8%
Viral marker		
HBsAg positive	86	85.1%
HBsAg-negative	10	9.9%
Anti-HCV positive	5	5%
Child-Pugh classification		
A	66	65.3%
B	35	34.7%
Albumin level (g/l)	35.32±5.15	
Bilirubin level(umol/l)	27.67±41.18	
PT (s)	13.24±1.77	
AFP level (ng/ml)		
<400	42	41.6%
>400	59	58.4%
Tumor number(n)		
1	24	23.8%
2	6	5.9%
>3	71	70.3%
Classification of PVTT (n)		
PVTT- Ⅰ	22	21.8%
PVTT- Ⅱ	34	33.7%
PVTT-Ⅲ	36	35.6%
PVTT-Ⅳ	9	8.9%

Variables are expressed as mean ± SD, or n ,%, PVTT, portal vein tumor thrombosis; PT, prothrombintim;

2.2 Survival Outcomes

The median overall survival for the 101 patients was 4.5 months (range, 7-925 days, 95% CI: 111.1~158.9). The 3-, 6-, 9-, 12- and 24-month overall survival rates were 70%, 32%, 19%, 11% and 4.0% respectively. The overall survival of patients by subgroup analysis was 10.6, 4.6, 2.7 and 1.9 months for type I~IV PVTT respectively and the survival curves are shown in **Figure 1**. Except the comparison between type III and IV PVTT, the compassion of any two

subgroups showed a significant statistical difference (**Table 3**).

2.3 Prognostic Factors Affecting Survival

Using Cox proportional hazards regression model analysis, four factors (PVTT type, serum bilirubin, Child-pugh status and albumin) showed statistic significance on survivals (**Table 2**). The factor "tumor numbers" did not show a significant difference (P=0.216).

Table 2 Analyses of prognostic factors using Cox proportional hazard model

Variable	P
Age	0.307
Sex	0.442
Child-Pugh	0.000
ALB	0.023
BIL	0.002
PT	0.607
Tumor number	0.216
Viral marker	0.722
AFP	0.129
Classification of PVTT	0.000

ALB, albumin; BIL, bilirubin; PVTT, portalveintumorthrombosis; PT, prothrombintime; TACE, transarterial chemoembolization

Table 3. Comparsion between any two subgroup

	PVTT- Ⅰ	PVTT-Ⅲ	PVTT-Ⅱ	PVTT-Ⅳ
	chi-square sig	chi-square sig	chi-square sig	chi-square sig
Log Rank(Mantei-Cox)				
PVTT - Ⅰ		42.552 .000	13.652 .000	33.456 .000
PVTT -Ⅲ	42.552 .000		15.562 .000	15.562 .000
PVTT - Ⅱ	13.652 .000	15.562 .000		7.645 .006
PVTT -Ⅳ	33.456 .000	.249 .618	7.645 .006	

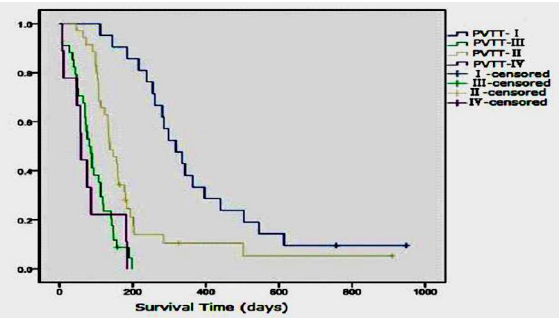

Figure 1. The overall survival of patients by subgroup analysis was 10.6, 4.6, 2.7 and 1.9 months for type I~IV PVTT respectively.

2.4 Treatment-related toxicity

During the follow-up period, we observed that approximately 70% patients had complications such as postembolization syndrome (fever, abdominal pain, and nausea/vomiting). No vascular-related complications were observed. 14 patients progressed from Child class A to Child class B and 24 patients progressed from Child class B to Child class C after TACE. No clinical, laboratory, or imaging evidence presented for acute hepatic failure, only one patient suffering upper gastrointestinal bleeding seven days after TACE (grade 3 bleeding).

Discussion

The bright spot of this study is that we observed the efficacy of TACE on unresectable advanced HCC patients with PVTT and provided first hand data about the effect of TACE on the four PVTT types which were newly suggested. Some studies reported that the new PVTT classification showed better predictive and stratified efficacy for advanced HCC patients with PVTT[19-21] but seldom applied for TACE treatment. Recent studies have shown that TACE can be performed safely in HCC patients with PVTT[7] and more survival benefit can be obtained than conventional treatment for the patients receiving surgery and TACE both compared with those receiving surgery alone[21]. Shuqun et al. [22] reported in their retrospective study that the patients receiving surgical resection were better than those of non-resection (P = 0.0006) from type I to III PVTT. Until now, few studies investigated the efficacy of TACE on advanced HCC patients with PVTT classification. From our results, PVTT classification had a good efficacy for discriminating the survival time between any two of I, II or III PVTT types, but did not show significance between type III and IV PVTT patients. However, in Shi et al.'s study, using PVTT category, a good discriminating efficacy could be obtained for resectable HCC and PVTT patients. So for patients with type III or IV PVTT of advanced HCC, other treatments rather than TACE could be considered if available. Besides, survival time of patients with PVTT on the first order branch of the portal vein (type II PVTT) was 4.6m according to our studies which suggests that other aggressive treatment could be considered alternatively. This point has been agreed upon by many scholars[7,24,25]. The survival time of our study was similar to studies which indicated that TACE can be performed safely and may improve the overall survival in HCC patients with PVTT. Niu ZJ et al.[25] have show that the overall survival of advanced HCC with PVTT I~ IV who received conservative treatment was 1.4m. Our study showed that the overall survival was 4.5 months which was significantly better than non-TACE for PVTT I- IV, but it was lower than 5.6m

reported by Chung GE et al. With similar study designs and objectives, the shorter survival time of the patients in our study may be due to the fact that we had more cases of tumor thrombus in the superior mesenteric vein and inferior vena cava(>30% vs <25%), which indicated worse survival rate. Secondly, we had 35 patients with Child-Pugh B stage and among them, 24 patients with Child-Pugh progressed from stage B to C after TACE procedures. This also proved that worse Child-Pugh class and PVTT extent are prognostic factors in predicting survival rate [7, 21, 23]. Base on previous study, the variance analysis of hepatic functional reserve by ICG15 has been under way in our centre. Some studies have shown that the survival of patients using TACE treatment was associated with many risk factors, such as tumor burden (number of the tumors, size of the tumor, tumor-to-liver volume ratio and PVTT status), liver function (Child-Pugh score) and treatment strategies[2,15-17]. Among these factors, portal vein invasion showed higher risks than other variables, and indicated a poor prognosis [18-20]. The median overall survival for patients with tumor thrombosis on main portal vein was 2.7 months. Among those patients, 47.2% (17/36) were Child-Pugh class B.

Chung GE et al showed that the median overall survival for patients with tumor thrombosis on main portal vein was 5.6 months and the patients with Child-Pugh class A in this population accounted for 69%. In addition, many of the patients in Chung GE et al.'s study had formed collateral circulation around the portal trunk. This may explain why Chung GE et al.'s study had a good prognostic factor.

Portal hypertension may affect the prognosis of TACE used on HCC patients. Of the 6 patients who died within one month after TACE, 3 patients presented with high portal pressure at first visit, which may indicate that portal hypertension may be a risk factor of TACE. In our study, only one patient experienced postoperative complication (esophageal variceal bleeding) after TACE. The low procedure-related morbidity rate of this study may be due to the application of superselective catheterization technique, the function of which is close to surgical hepatectomy and shows comparatively good efficacy. Many factors may predict the prognosis of HCC patients with PVTT who received TACE. Evaluation should be performed before TACE according to those variables.

Our study had limitations. Firstly, this study was retrospective and the patients were selected by doctor's preference. So there might be selection bias. Secondly, the cases in subgroup was comparatively small. Thirdly, our study did not have a control group. As a result, we can only analyze our result by comparing with other publications.

In conclusion, TACE is an effective treatment compared with published conservative treatment for advanced HCC with PVTT. PVTT-I and II patients had better survival and prognosis compared with type III and IV PVTT patients who had low response rate especially for the patients with Child-Pugh class B. Some factors showed statistical significance on predicting the prognosis of HCC patients with PVTT after TACE, such as the degree of liver injury, tumor burden, collateral circulation, hepatic functional reserve (ICGR15) etc. Evaluation should be performed before TACE according to those variables. With this study, we expected to obtain a relative safety range of TACE procedure applying on the patients of BCLC stage C to make more patients benefit from TACE. TACE is not a contraindication for all BCLC-C patients and the efficacy of TACE on BCLC-C patients needs to be further investigated by prospective randomized controlled trials.

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Conflicts of interest

Nothing to declare for all authors.

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