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Original Article

Indications and treatment of hepatocellular carcinoma with portal vein tumor thrombus based on two classifications

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Abstract: Background: The exact indication of surgery for hepatocellular carcinoma (HCC) patients combined with portal vein tumor thrombus (PVTT) remains controversial. Purpose: To investigate the effect of location and extention of PVTT on the prognosis of HCC patients underwent surgery compared with transarterial chemoembolization (TACE). Methods: During January, 2009 and December, 2011, 320 HCC patients with PVTT were divided into surgery group (n = 160) and TACE group (n = 160) and respectively studied. Two PVTT classifications (I-IV and Vp1-Vp4) were used. The cumulative survival rates of HCC patients with different types of PVTT after surgery were compared with TACE. Also for patients underwent surgery, the postoperative survival rates of HCC patients with different types of PVTT were compared. Results: The survival after surgery were significantly better than TACE in HCC patients with type I/II or Vp1/Vp2/Vp3 PVTT ($P<0.05$). However, surgery failed to achieve better survival than TACE in HCC patients with type III/IV/Vp4 PVTT ($P>0.05$). For patients underwent surgery, postoperative survival rates in HCC patients with type I/II or Vp1/Vp2/Vp3 PVTT were significantly higher than type III/IV or Vp4 PVTT ($P<0.05$). Conclusion: PVTT without extending to the main trunk of portal vein (type I/II or Vp1/Vp2/Vp3) should be recommended as an important indication of surgery for HCC patients. For PVTT extending to the main trunk of portal vein or bellow (type III/IV or Vp4), HCC patients may have lost the optimal opportunity of surgery.

Keywords: Hepatocellular carcinoma, portal vein tumor thrombus, surgery, indication, prognosis

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide as more than 700,000 cases are diagnosed yearly [1], and the third leading cause of cancer-related death [2]. Tumor thrombus has been detected in about 30% of HCC patients at the time of diagnosis [3]. When the vascular invasion occurs in the portal vein system especially the tumor thrombus involve the main trunk of portal vein, the prognosis is extremely poor because tumor cells may spread along the portal vein, leading to extensive intra-hepatic metastasis. Further, the obstruction of portal vein thrombus to the portal vein can lead to portal hypertension, then results in badly deterioration and impairment of liver function, refractory ascites, esophageal-gastric varices, acute bleeding and its related death [4-6]. According to the "Barcelona" group (Barcelona Classification of Liver Cancer, BCLC), the portal vein tumor thrombus (PVTT) is generally considered as an absolutely contradiction for surgeries or TACE in HCC patients [7], a mean survival period of only 2.7-4.0 months was reported without treatment [8, 9].

With advances in surgical techniques [10], radical resection has become feasible to remove gross tumors and PVTT. The tumor thrombus can be removed safely by an embolectomy, though it has extended to the main trunk of portal vein. Thus, PVTT is no longer considered as an absolute contraindication to surgery. Some studies [11-13] have shown that, the liver resection especially embolectomy still provided benefits of releasing the portal hypertension,

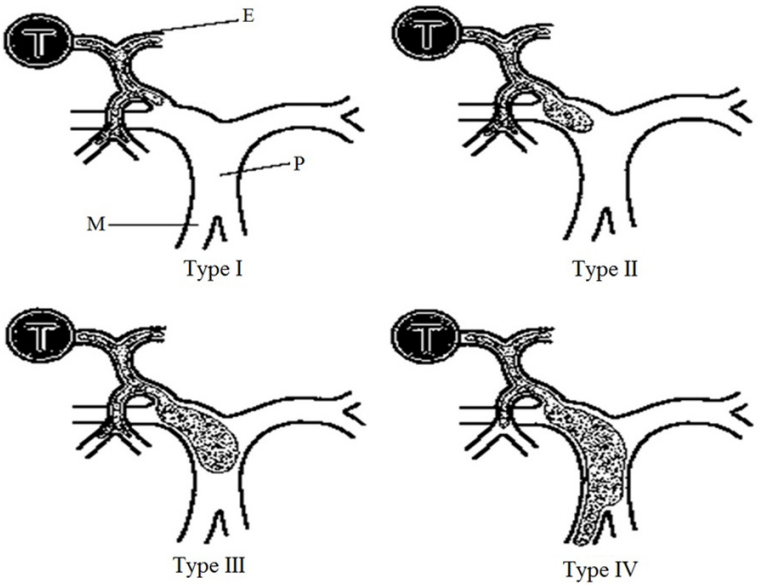

Figure 1. Type I-IV classification of PVTT. Type I: tumor thrombus involving segmental branches of portal vein or above; Type II: tumor thrombus involving lobe large branches of portal vein; Type III: tumor thrombus involving the main trunk of portal vein; Type IV: tumor thrombus involving the superior mesenteric vein or inferior vein cava. T: primary tumor; P: portal vein; M: inferior vena cava, E: branches of portal vein.

refractory ascites and liver function impairment, also reducing the incidence of acute bleeding resulted by esophageal-gastric varices and its related death for HCC patients with portal vein system invasion, even the tumor thrombus has invaded into the main trunk of portal vein or bellow. Also, several studies [14-16] have reported that transarterial chemoembolization (TACE) provides a benefit of prolonging survival for HCC patients with PVTT and it is no longer considered as a contradiction to HCC with PVTT. Thus, the efficacy of surgery and TACE to prolong the survival period for HCC patients with PVTT remains controversial.

This study aimed to respectively compare the cumulative survival outcomes of liver surgery and TACE for HCC patients with PVTT by using two PVTT classifications, and to identify the proper indication for liver surgery in HCC patients with PVTT.

Subjects and methods

General information

During January 2009 to December 2011, 320 patients diagnosed with HCC merged with PVTT who were admitted to the Department of Hepatobiliary Surgery and Department of Interventional Therapy in our hospital were enrolled in this study. 160 patients were treated with surgery and 160 with TACE therapy. Ultrasonograpgy (US), computed tomograghy (CT), magnetic resonance imaging (MRI), and CT or MRI during angiography were performed. Based on the location and extention of PVTT, two PVTT classifications recommended by Chinese scholars Cheng *et al* (type I-IV) [17] (**Figure 1**) and the classification system of Liver Cancer Study Group of Japan (type Vp1-4) [18] (**Figure 2**) were used. Laboratory tests including alpha-fetoprotein, serum total bilirubin (TBil), albumin (ALB), prothrombin time (PT) and HBV-DNA copies and Eastern Cooperative Oncology Group performance status (ECOG score), and Child-Pugh grade were used in the decision. Inclusion criteria: (1) diagnosed to be HCC with PVTT if the preoperative assessment was content with the following conditions: i) ultrasound (including ultrasound contrast), CT, MRI, or hepatic artery angiography prompted compliance with HCC typical radiographic performance, and tumor thrombus was found in the main trunk of portal vein or 1-2 grade branch; ii) naked eye found main portal vein or PVTT with 1-2 grade branch in the surgery; (2) for patients underwent surgery, solitary tumor with complete capsule could be visually R0 radical removed, and tumor thrombus could be removed together with the tumor or cleared from the portal vein by an embolectomy; postoperative pathologically confirmed that the tumor tissue was type HCC. When patients suffered other tumors or extra-hepatic metastasis, ECOG score ≥ 2, Child-Pugh Score ≥ 10 (Child-Pugh stage C), or combined with chemo/radio therapy were excluded. Propensity Score Matching (PSM) [19] was performed to balance the selection difference and reduce the selection bias between the two groups. This study was conducted in accordance with the declaration of Helsinki, and approval from the Ethics Committee of Guangxi Medical University. Written informed consent was obtained from all participants.

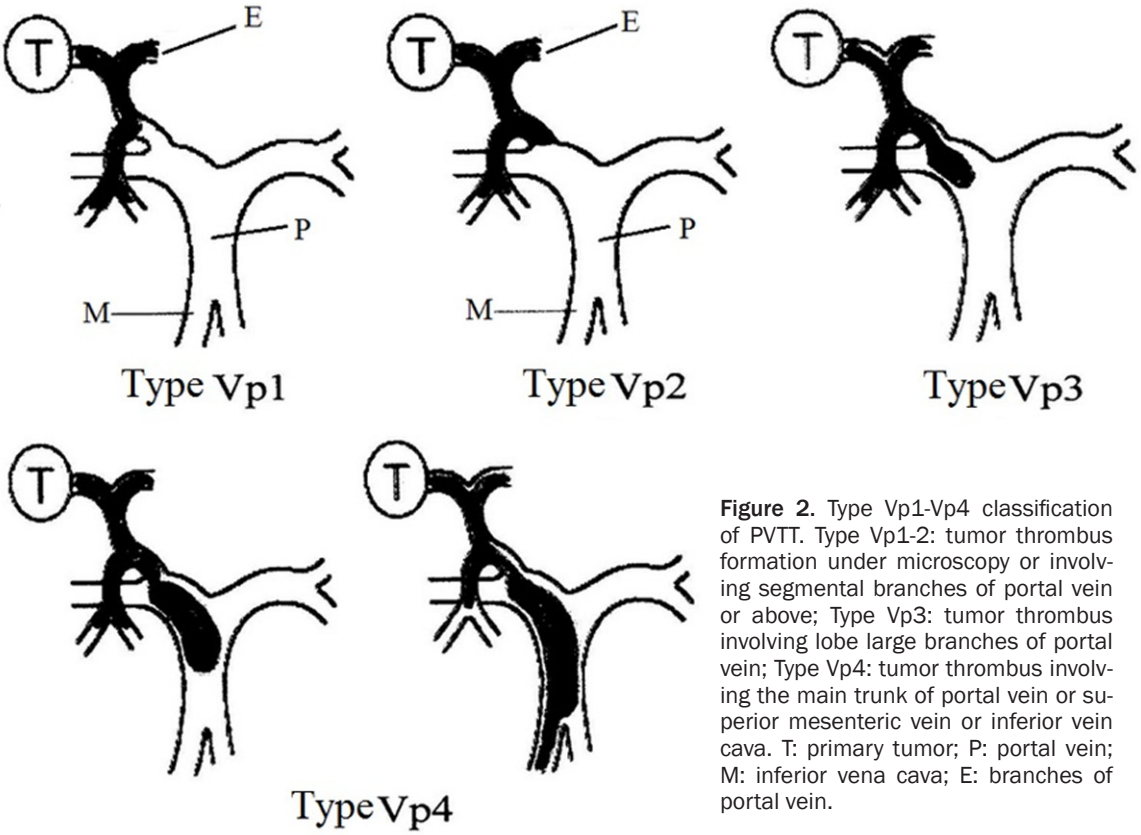

Figure 2. Type Vp1-Vp4 classification of PVTT. Type Vp1-2: tumor thrombus formation under microscopy or involving segmental branches of portal vein or above; Type Vp3: tumor thrombus involving lobe large branches of portal vein; Type Vp4: tumor thrombus involving the main trunk of portal vein or superior mesenteric vein or inferior vein cava. T: primary tumor; P: portal vein; M: inferior vena cava; E: branches of portal vein.

Operation

Tumor resection was performed by using the electrosurgical instrument ultrasonic knife, Ligsure, CUSA combined with traditional forceps to remove the tumor. Hemostasis on the raw liver surface was done with suturing, electric coagulation, and fibrin glue. Pringle's maneuver was routinely used with a clamp/unclamp time of 10 minutes/5 minutes. The operative procedure for PVTT was decided based on the location and extend of tumor thrombus: (1) when tumor thrombus located within the liver parenchyma and resection line, it was resected together with the solitary tumor. (2) When tumor thrombus located outside the liver resection line, we opened the stump section of portal vein from the hepatic section on the basis of blocking portal vein branches of the healthy side, used tweezers to remove the tumor thrombus or sucked by aspirator. If tumor thrombus attached to the wall of portal vein and was difficult to remove, stone forceps would be used. Finally we loosed the door vein blocked belt, it could be seen that stump end of the portal vein had fan-shaped blood gushing, which proved that tumor embolus has been completely removed, and continuously sutured with suture line without damaging to the vascular to shut off the stump. (3) When tumor thrombus had involved into the main trunk of portal vein but not involved in the branches of healthy side, we block portal vein branch of the healthy side, then longitudinally incised along the main trunk of portal vein, took out the tumor thrombus and finally closed wall of portal vein by a continuous suture. (4) When tumor thrombus had grown into the main trunk of portal vein and inferior cava, we blocked the portal vein branch of the retention sides to reduce bleeding, then longitudinally cut open along the main trunk of portal vein and removed the tumor thrombus, finally closed wall of portal vein by a continuous suture. Ultrasound was generally used to detect whether tumor thrombus was completely removed.

Follow-up

Contrast-enhanced computed tomograghy (CT), Magnetic Resonance Imaging (MRI), Laboratory tests including alpha-fetoprotein, serum total bilirubin (TBil), albumin (ALB), prothrombin time (PT) and HBV-DNA copies were routinely per-

Table 1. Baseline characteristics of patients between surgery group and TACE group after PSM matching

Index	Surgery (n = 160)	TACE (n = 160)	P
Age, years	52.17±21.09	53.01±21.27	0.819
Males, n (%)	121 (75.6%)	122 (76.2%)	0.852
WBC, 10^9/L	6.49±2.48	6.61±2.19	0.746
Hb, g/L	126.87±35.28	130.12±36.21	0.736
PLT, 10^9/L	251.11±73.56	260.13±80.18	0.735
PT, s	12.73±3.92	12.68±3.16	0.746
TBil, μmol/L	15.21±6.76	16.10±7.72	0.476
ALB, g/L	45.01±21.32	44.75±23.54	0.853
ALT, IU/L	39.16±15.49	40.12±14.76	0.876
AST, IU/L	40.73±17.21	39.98±16.86	0.716
HBV DNA	5765.00 (649.50-39800.00)	5870.00 (687.50-41000.00)	0.862
AFP, ng/mL	549.00 (26.25-850.00)	580.00 (29.45-900.00)	0.764
Child-Pugh Score	7.23±3.58	7.49±3.98	0.591

formed in the first month after surgery and then every three months in the first 2 years. After 2 years, at each of these follow-up visits above were performed every 6 months. Recurrence was defined as appearance of new lesions detected by radiologicl images with HCC features after radical resection. When intra-hepatic recurrence was confirmed, patients were treated aggressively with surgery, radiofrequency ablation, percutaneous ethanol injection or TACE therapy depending on the size, number of recurrent tumors, location, liver function status, extra-hepatic disease, and portal vein tumor thrombus. Palliative treatment was given to patients with poor liver function or general status, and advanced disease.

Statistical analysis

Normally distributed data were expressed as mean ± standard deviation (SD), asymmetrical distributed data were expressed as median (range). The baseline characteristics between groups were using independent sample t tests. After the univariate analyses conducted by cox model regression, the factors which found to be significantly associated with OS were tested by multivariate analysis by a stepwise cox model. All the data were calculated by using SPSS 21.0, P<0.05 was considered as statistically significant.

Results

Baseline characteristics

Propensity Score Matching (PSM) [19] was performed to balance the selection difference and reduce the selection bias between the two groups. Laboratory tests, radiological imaging performance, and other baseline characteristics were matched according to surgery group: TACE group = 1:1. Finally, 160 patients of each were enrolled in the surgery group and TACE group. The baseline characteristics data were well matched between the two groups after PSM matched (P>0.05), the baseline balance was improved significantly (**Table 1**).

Survival difference comparison of TACE surgery and each PVTT type

The median survival period of HCC patients combined with type I PVTT in the surgery group was 31.3 months (CI 95%: 6.2~56.4 months), and the 1-, 2-, 3-year survival rates were 76.6%, 57.4%, 38.3%, while the median survival period of patients in TACE group was 13 months (4.3 to 21.7 months), and the 1-, 2-, 3-year survival rates were 58.3%, 16.5%, 5.5% (P = 0.012). The median survival period of type II PVTT patients in the surgery group was 17.4 months (9.2 to 25.6 months), and the 1-, 2-, 3-year survival rates were 68.5%, 40.8%, 30.6%, while the median survival period of TACE group was 8 months (6.1 to 9.9 months), the 1-, 2-, 3-year survival rates were 36%, 8.9% and 6.0% (P<0.0001). After surgery, the survival rates were significantly higher than TACE in HCC patients combined with type I and II PVTT (P<0.05). The median survival period of patients with type III PVTT in the surgery group was 4 months (3.3 to 4.7 months), and the 1-, 2-, 3-year survival rates were 8.3%, 0% and 0%,

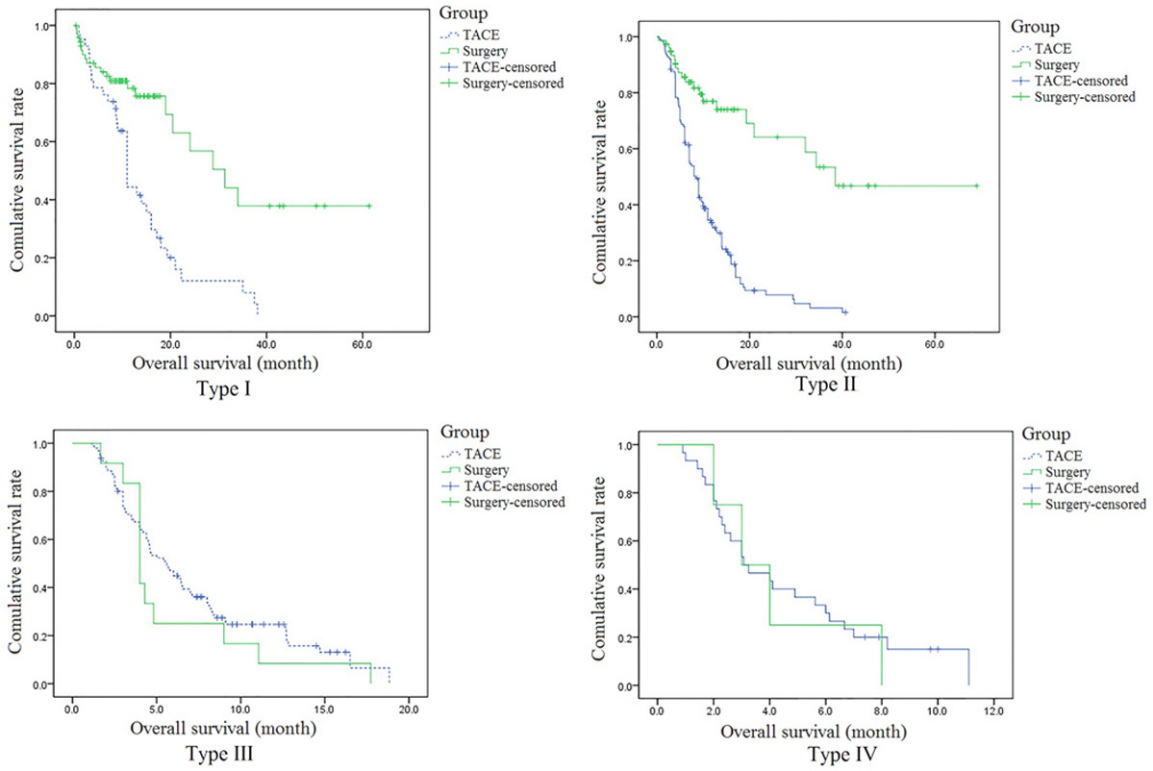

Figure 3. Cumulative survival rates of type I-IV PVTT patients in surgery and TACE groups after matching.

Table 2. Outcomes after surgery and TACE based on different PVTT types

Outcome		Type						
		I (68)	II (73)	III (19)	IV (6)	Vp1-2 (68)	Vp3 (73)	Vp4 (25)
Liver resection		68	73	0	0	68	73	0
Liver resection + embolectomy		0	0	19	6	0	0	25
Complications	Hemorrhage	0	3	2	2	0	3	4
	Liver function failure	0	0	2	2	0	0	4
	Bile leakage	1	2	1	1	1	2	2
	Pleural effusion	20	27	11	5	20	27	16
Cumulative survival after surgery	1-year	76.6%	68.5%	8.3%	0.23%	77.3%	67.5%	5.6%
	2-year	57.4%	40.8%	0%	0%	53.6%	42.1%	0%
	3-year	38.3%	30.6%	0%	0%	39.7%	30.2%	0%
Cumulative survival after TACE	1-year	58.3%	36.0%	22.4%	0.35%	56.1%	35.8%	11.4%
	2-year	16.5%	8.9%	0%	0%	17.2%	8.1%	0%
	3-year	5.5%	6.0%	0%	0%	4.5%	6.4%	0%

while the median survival period of the TACE group was 5.6 months (4.3 to 6.9 months), and the 1-, 2-, 3-year survival rates were 22.4%, 0% and 0%, (P = 0.372). The median survival period of patients with type IV PVTT in the surgery group was 3 months (1.9 to 4.2 month), while the median survival period of the TACE group was 3.1 months (1.6 to 4.6 months) (**Figure 3**). However, the survival period in this two groups were no more than 12 months (**Table 2**). No significant difference of survival rates was found between the surgery group and TACE group in HCC patients combined with type III and IV PVTT (P>0.05).

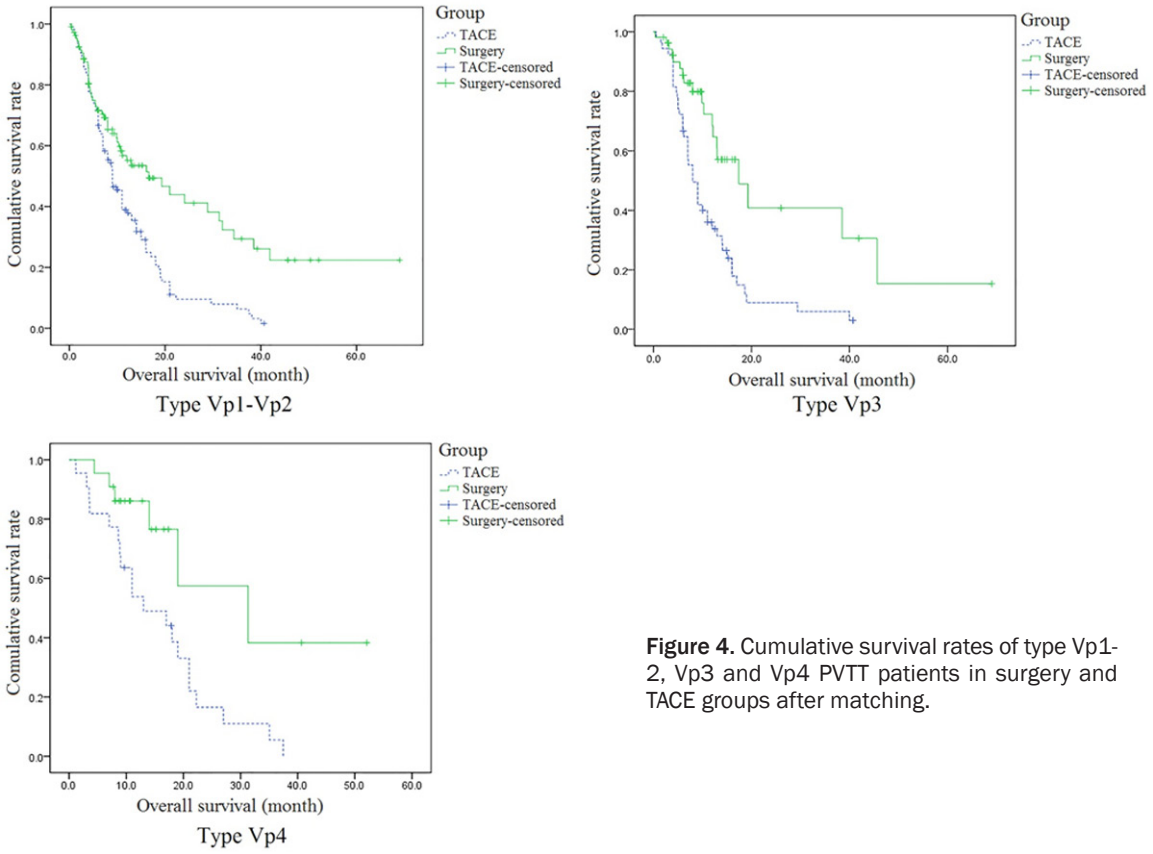

Figure 4. Cumulative survival rates of type Vp1-2, Vp3 and Vp4 PVTT patients in surgery and TACE groups after matching.

The median survival period of HCC patients with Vp1-Vp2 type PVTT in the surgery group was 32.4 months (CI 95%: 6.3~59.1 months), and the 1-, 2-, 3-year survival rates were 77.3%, 53.6% and 39.7%, while the median survival period of the TACE group was 13.9 months (4.5 to 24.1 months), and 1-, 2-, 3-year survival rates were 56.1%, 17.2% and 4.5%, (P = 0.002). The median survival period of the Vp3 type PVTT patients in surgery group was 16.3 months (8.2 to 26.8 months), and the 1-, 2-, 3-year survival rates were 67.5%, 42.1% and 30.2%, while the median survival period of the TACE group was 8.3 months (6.0 to 10.4 months), and the 1-, 2-, 3-year survival rates were 35.8%, 8.1% and 6.4% (P<0.0001). The survival rates of patients with Vp1-Vp2 and Vp3 type PVTT in the surgery group was superior to that of the TACE group. The median survival period of Vp4 type PVTT patients in the surgery group was 2.6 months (1.1 to 5.7 months), and 1-, 2-, 3-year survival rates were 5.6%, 0% and 0%, while the median survival period of the TACE group was 2.8 months (1.3 to 4.9 months), and 1-, 2-, 3-year survival rates were 11.4%, 0% and 0%, (χ^2 = 766, P = 0.186) (**Figure 4**). Similarly, the survival period of patients with type Vp4 PVTT after surgery and TACE were all no longer than 12 months (**Table 2**). The survival rate of type Vp4 PVTT patients in surgery group had no significant difference compared with TACE group.

Our results based on these two PVTT classifications both prompted that when tumor vascular invasion only occurred in the first branch of the portal vein or above (type I/II or type Vp1-3), surgery still gain a benefit of prolonging the cumulative survival than TACE. However, when tumor thrombus extended to the main trunk of portal vein (type III/IV or type Vp4), surgery failed to provide better survival than TACE.

Impact of PVTT types as an independent prognostic factor on HCC patients underwent surgery

The postoperative 1-year overall survival rates of patients with type I-IV PVTT were 76.6%, 68.5%, 8.3%, 0.23%, and 57.4%, 40.8%, 0%, 0% for the 2-year survival rates, 38.3%, 30.6%,

Table 3. Comparison of cumulative survivals among type I-IV PVTT after Long-rank test

Type	I		II		III		IV	
	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
I			3.520	0.061	26.740	0.000	13.590	0.000
II	3.520	0.061			12.791	0.000	8.059	0.005
III	26.740	0.000	12.791	0.000			1.265	0.261
IV	13.590	0.000	8.059	0.005	1.265	0.261		

Table 4. Comparison of cumulative survivals among type Vp1-Vp4 PVTT after Long-rank test

Type	Vp1-2		Vp3		Vp4	
	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
Vp1-2			3.750	0.064	19.710	0.001
Vp3	3.750	0.064			8.013	0.001
Vp4	19.710	0.001	8.013	0.005		

0%, 0% for the 3-year l survival rate. The postoperative overall survival rates of patients with type I/II PVTT were significantly higher than that of patients with type III and IV PVTT, but no significant difference existed between type I and II (P = 0.061). The 1-year overall survival rates after surgery of patients with Vp1-Vp2, Vp3 and Vp4 PVTT were 77.3%, 67.5% and 5.6%, while 53.6%, 42.1% and 0% for the 2-year overall survival rate, and 39.7%, 30.2% and 0% for the 3-years overall survival rate. The overall survival rates after surgery of patients with Vp1-Vp2, Vp3 PVTT were significantly higher than that of Vp4 type patients (**Tables 3** and **4**; **Figure 5**). No significant differences of survival rates were found between Vp1-Vp2, Vp3 groups (P = 0.064).

Our results based on these two PVTT classifications both indicated that when the tumor thrombus had involved in main trunk of portal vein, the survival were obviously worse than PVTT did not extend to the main trunk of portal vein in HCC patients underwent surgery.

Discussion

In patients diagnosed to be HCC, about 30 percent already had vein tumor thrombus [3]. Merged PVTT often prompted poor prognosis because the cancer cells would proliferate through the portal system and result in a wide range of intra-hepatic metastasis. Moreover, the portal vein obstruction would cause portal hypertension, leading to aggravate the risk of refractory ascites, further damaged to liver function, incidence of acute variceal bleeding and its related death [4-6]. Based on the "Barcelona" group, patients with PVTT were considered to have lost the optimal opportunity of either radical surgery or TACE and into the last stage of the HCC [7].

However, with the more sophisticated development of surgery techniques [10], curative liver resection and embolectomy by portal incision and other technologies, liver resection has now reached "liver cancer without surgical restricted" level. Many oriental scholars argued that portal vein thrombus was not longer an absolute or related contraindication to liver resection. Chinese scholars Cheng *et al* [17] and Liver Cancer Study Group of Japan [18] believe that surgery still provides benefit for patients. The reasons may be that, after removal of tumor thrombus, portal vein hypertension and refractory ascites will be released, and the incidence of acute gastric bottom-esophageal varices and its related sudden death will be reduced. Moreover, removal of solitary tumor and PVTT would reduce the deterioration and impairment of liver function; promote recovery of liver function and efficacy of postoperative adjuvant therapy such as postoperative TACE, radiofrequency ablation, anhydrous ethanol injection and sorafenib. Anyway, the efficacy and proper indication of liver resection for HCC patients with PVTT remains to be discussed.

According to the location and extend of tumor thrombus invades into the portal vein system, Chen *et al* [17] proposed a I-IV PVTT classification and they suggested when tumor thrombus only invades the first branch of portal vein and above (type I/II), or even did not exceed the 2 cm below of the main trunk of portal vein (type IIIa), liver resection including remove the tumor thrombus still gain a benefit of prolonging the cumulative survival for HCC patients. But when tumor thrombus has extended 2 cm bellow of the main trunk of portal vein (type IIIb) or inferior cava (type IV), HCC patients may have lost

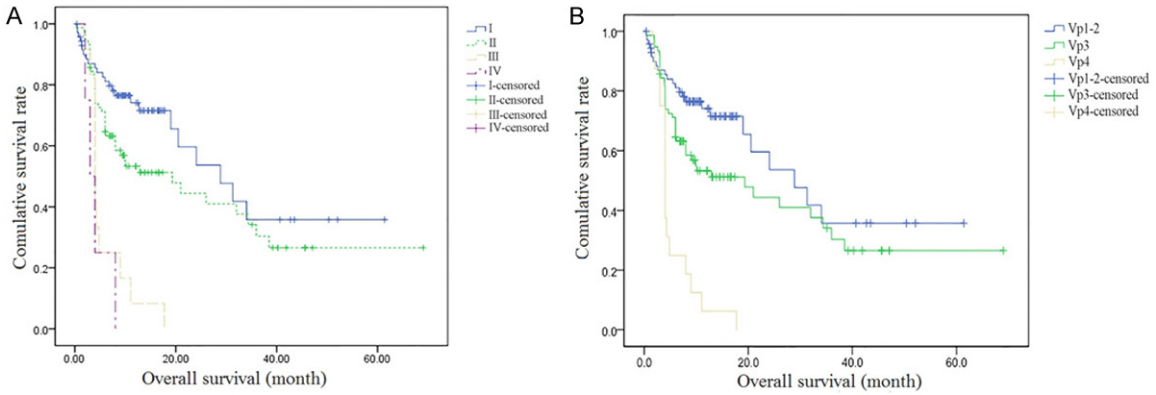

Figure 5. Cumulative survival rates of PVTT patients in surgery and TACE groups after matching. A. Type I-IV PVTT patients; B. Type Vp1-2, Vp3 and Vp4 PVTT patients.

the opportunity of radical liver resection because surgery failed to achieve a better survival than other treatments. The I-IV PVTT classification defined by Chen *et al* [17] was usually used by many Chinese clinician teams. The studies of Peng *et al* [20] showed that the 1-, 3-, 5-year survival rate after surgery of patients with type I PVTT was significantly better than patients treated by TACE therapy (81.5% vs. 41.1%, 51.2% vs. 8.9%, 39.7% vs. 3.6%, P<0.05). The 1-, 3-, 5-year survival rates after surgery of patients with type II PVTT was also significantly superior to that patients treated by TACE (46.3% vs. 37.9 %, 17.2% vs. 6.0%, 17.2% vs. 0%, P<0.05). But the survival rates of patients with type III and type IV PVTT after surgery were not statistically better than TACE in 1-year (III type: 32.5% vs. 36.1%; IV type: 21.7% vs. 30.4%), 3-year (III type: 3.6% vs. 4.2%; IV type: 0.0% vs. 4.3%) and 5-year (III type: 3.6% vs. 0.0%; IV type: 0.0% vs. 0.0 %) survival rates. His studies suggested that patients with type I and type II PVTT is proper to undergo surgery, while patients with type III and IV PVTT has lose the optimal chance of surgery.

Our studies after PSM match found similar results with their research. We found that the survivals were obviously better in HCC patients combined with type I/II PVTT underwent surgery than TACE. The median survival period of HCC patients with type I PVTT after surgery was 31.3 months (95% CI: 6.2~56.4 months), 1-, 2- and 3-year survival rates were 76.6%, 57.4%, 38.3%, while the median survival period after TACE treatment time was 13 months (95% CI: 4.3~21.7 months), and the 1-, 2- and 3-year survival rates were 58.3%, 16.5%, 5.5% (P = 0.012). The median survival period of HCC patients with type II PVTT after surgery was 17.4 months (95% CI: 9.2~25.6 months), and the 1-, 2- and 3-year survival rates were 68.5%, 40.8%, 30.6%, while the median survival period after TACE was 8 months (95% CI: 6.1~9.9 months), and the 1-, 2- and 3-year survival rates were 36%, 8.9% and 6.0% (P<0.0001). However, the survival of HCC patients combined either type III or IV PVTT was no better after surgery compared with TACE. The median survival periods of HCC patients with type III PVTT after surgery compared TACE were 4.7 months (95% CI: 3.34.3~6.9 months) vs. 5.6 months (95% CI: 4.3~6.9 months) after TACE; and the 1-, 2- and 3-year survival rates were 8.3% vs. 22.4%, 0% vs. 0%, 0% vs. 0% (P = 0.372). Similarly, the median survival period of HCC patients with type IV PVTT after surgery compared with TACE were 3 months (95% CI: 1.9 to 4.2 months) vs. 3.1 months(CI 95%: 1.6~4.6 months); 1, 2, 3-year survival periods were all not longer than 12 months; P = 0.740).

Japanese scholars usually used Vp1-Vp4 type PVTT classification system proposed by the Liver Cancer Study Group of Japan [18]. Minagawa *et al* [21] respectively studied 45 HCC patients merged PVTT but not invaded into the main trunk of portal vein, the average survival time of 18 cases treated by preoperative TACE + surgery was 3.4±2.7 years, the 1-, 3- and 5-year survival rates were, 82.0%, 42.0%, 42.0%. While 27 patients who did not undergo surgery (10 cases treated with TACE, 12 cases treated with chemotherapy, 5 cases treated

with hepatic artery or portal vein ligation), the average survival time was 0.36±0.26 years, the 1-, 3- and 5-year survival rates were 7.0%, 0% and 0%. His research showed that when tumor thrombus did not involve in the main trunk of portal vein, surgery is more effective to prolong the survival of HCC patients than other treatments. Our research showed that the median survival period of HCC patients merged Vp1-Vp2 type PVTT in surgery group was 32.4 months (95% CI: 6.3~59.1 months), and the 1-, 2- and 3-year survival rates were 77.3%, 53.6% and 39.7%, while the median survival period in TACE group was 13.9 months (4.5 to 24.1 months), and the 1-, 2- and 3-year survival rates were 56.1%, 17.2%, 4.5%, (P = 0.002). The median survival period of HCC patients accompanied with Vp3 type PVTT in surgery group was 16.3 months (8.2 to 26.8 months), and the 1-, 2- and 3-year survival rates were 67.5%, 42.1%, 30.2%, while median survival time in TACE group was 8.3 months (range 6.0 to 10.4 months), and the 1-, 2- and 3-year survival rates were 35.8%, 8.1%, 6.4%, (P<0.0001). The survival of Vp1-Vp2, Vp3 PVTT after surgery was significantly better than TACE. The median survival period of HCC patients with Vp4 type PVTT in surgery group was only 2.6 months (1.1 to 5.7 months), and the 1-, 2- and 3-year survival rates were 5.6%, 0%, 0%, while the median survival time in TACE group was 2.8 months (1.3 to 4.9 months), and the 1-, 2- and 3-year survival rates were 11.4%, 0%, 0% (P = 0.186). However, the cumulative survival periods of patients in the two groups were all not more than 12 months. The survival of Vp4 type PVTT patients in the surgery group was no significant better compared with TACE group.

In our study, type I-IV and Vp1-Vp4 PVTT classifications were used. Our founding revealed surgery was more effective to prolong the survival period in HCC patients until tumor thrombus invaded into the main trunk of portal vein (type I/II or Vp1-3) compared with TACE. But after tumor thrombus extended to the main trunk of portal vein and bellow (type III/IV or Vp4) surgery failed to provide better survival than TACE. The prognosis was really poor and a median survival time of only less than 6 months were shown in both surgery and TACE groups. The reason might be that when tumor thrombus involved the main trunk of portal vein or bellow (type III or Vp4), blockage in the main trunk of portal vein would cause portal hypertension, resulted in badly damage of liver function, refractory ascites, acute gastric bottom-esophageal varices and its related death. Further, the tumor cells would likely to spread out along the portal vein system and lead to intra/extra-metastasis. These Factors eventually affected the cumulative survival.

Shi *et al* [22] reported the 1-, 3-year disease-free survival rates of I-IV-type PVTT patients after surgery were 21.1%, 13.6%, 3.0%, 0% and 4.4%, 6.4%, 0%, 0%; the 1-, 3-year overall survival rates were 52.1%, 38.2%, 24.7%, 18.3% and 25.1%, 17.7%, 3.6%, 0%. His study indicated that the postoperative survival rates of HCC patients combined with type I, II PVTT were significantly better than that of III and IV type PVTT. Chen *et al* [23] divided HCC patients into two groups: tumor thrombus exceeded 1 cm and less than 1 cm of the main trunk of portal vein. the 1-, 2-, 3- and 5-year overall survival rates after surgery of tumor thrombus involving less than 1 cm of the main trunk of portal vein was significantly higher than the patients with PVTT exceeded 1 cm (58.7%, 39.9%, 22.7%, 18.1% vs. 39.5%, 20.4%, 5.7%, 0%). The recurrence rates of patients with tumor thrombus involving portal vein exceeded 1 cm in 6 months after surgery was significantly higher than patients with tumor thrombus involving portal vein less than 1 cm (11.3% vs. 76.9%, 45.0% vs. 78.8%). He suggested that until tumor thrombus exceeded 1 cm of the main trunk of portal vein, HCC patients were still suitable for surgery. While tumor thrombus exceeded more than 1 cm, patients would lose the optimal opportunity for radical resection. Our study also showed similar results: after surgery, the 1-year overall survival rates of I-IV type tumor thrombus patients were 50.3%, 34.2%, 21.6%, 16.7%, 2-year was 32.1%, 26.8%, 10.5%, 3.6%, and 3-year was 22.6%, 18.1%, 3.9%, 0%. When tumor thrombus involved in the main trunk of portal vein, the postoperative overall survival rates decreased significantly.

Kazuhiro *et al* [24] reported that the postoperative survival period of HCC patients with tumor thrombus invaded into the first branch of portal vein and above (type Vp1-Vp3) was only 398 days, but it was still significantly higher than

that in patients with tumor thrombus had involved the main trunk of portal vein (type Vp4: 248 days). He argued that tumor thrombus invading into the main trunk of portal vein and bellow (type Vp4) was a contradiction for surgery. Ban *et al* [25] revealed that when the tumor thrombus involved the first branch of portal vein (Vp3 type), the 3-year, 5-year survival rates of HCC patients were not statistical higher compared with patients with tumor thrombus extended to the main trunk of portal vein (type Vp4) (3-year survival rate: 35.3% vs. 41.8%; 5-year survival rate: 21.2% vs. 20.9%). He believed that when tumor thrombus invaded into the first branch of portal vein (Vp3 type), the patient would had already lost the optimal opportunity of surgery. In our study, the postoperative overall survival rates of HCC patients with Vp1-Vp2, Vp3, Vp4 PVTT after 1 year were 48.6%, 36.1%, 15.9%, while 30.4%, 27.3%, 6.1% after 2 years and 20.5%, 18.2%, 1.2% after 3 years. The survival rates after surgery between patients with Vp1-Vp2 and Vp3 type PVTT had no significant difference (P = 0.061). However, the survival rate of patients with Vp4 PVTT after surgery was significantly lower than that of patients Vp1-Vp2 and Vp3 PVTT (P<0.0001). Thus, the postoperative survival was obviously worse when the tumor thrombus invaded into the main trunk of portal vein.

In this study, two kinds of PVTT classifications proposed by Chinese scholar Chen *et al* [17] and Liver Cancer Study Group of Japan [18] were used for analysis. Results of these two PVTT classifications Both showed that: (1) live resection including embolectomy was more effective in prolong the cumulative survival period in HCC patients until the tumor thrombus invaded into the main trunk of portal vein compared with TACE. But when the tumor thrombus extended to the main trunk of portal vein, surgery failed to achieve the benefit of better survival compared than TACE; (2) for patients underwent surgery, when tumor thrombus invaded into the main trunk of portal vein, the postoperative survival rates was significantly lower than tumor thrombus not extend to the main trunk of portal vein. However, some scholars augured that although surgery would not prolong the survival period of HCC patients with PVTT invaded into the main trunk of portal vein, it still provided a benefit of improving their survival quality. When the tumor thrombus was removed, portal vein hypertension and the liver function deterioration would be released, and the incidence of intractable ascites, esophageal variceal bleeding would be reduced. But on the other hand, surgery would also increase the risk of postoperative complications and liver failure [24, 26].

In conclusion, based on the results of this study by using two PVTT classifications, PVTT was no longer an absolutely or related contradiction for surgery in HCC patients. Until invades into the main trunk of portal vein, PVTT (I/II or Vp1/Vp2/Vp3) should be recommended as an important indication of surgery for HCC patients. But when the PVTT extends to the main trunk of portal vein or bellow (III/IV or Vp4), HCC patients might be have lost the optimal opportunity of surgery. Surgery should be carefully selected unless emergent removal of the PVTT [24, 26] because surgery could not prolong the survival period but may increase the risk of postoperative complications and liver failure. In this study, the recent receipt of PSM method applications in the medical field was used for comparative analysis of pre-treatment to effectively reduce the confounding bias of observational studies, and in order to reach originally expected balance between groups by randomized controlled trial. Nevertheless, PSM method still could not completely replace the randomized controlled trials; the study of this problem still needed a lot of randomized controlled clinical trials in order to obtain more convincing evidence.

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Disclosure of conflict of interest

None.

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