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Original Article

Effect of transjugular intrahepatic portosystemic shunt combined with ^{125}I particle implantation on portal vein tumor thrombus in hepatocellular carcinoma

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Abstract: Objective: The efficacy of transjugular intrahepatic portosystemic shunt (TIPS) combined with ^{125}I particle implantation in the treatment of portal vein tumor thrombus (PVTT) in hepatocellular carcinoma was discussed and analyzed in this study. Methods: A total of 127 patients with primary hepatocellular carcinoma (PHC) complicated with PVTT admitted to our hospital from March 2017 to June 2018 were enrolled. The patients were classified into an observation group (n=69) and a control group (n=58) in the light of the different treatment methods. The control group patients were treated with TIPS alone, and the observation group patients received ^{125}I particle implantation on the basis of TIPS in the control group. Subsequently, the clinical therapeutic efficacy, perioperative indicators, postoperative complications, quality of life and survival of patients before and after treatment were compared between the two groups. Results: The remission rate in the observation group was remarkably higher than that of the control group ($P<0.05$), and the difference in the overall response rate (ORR) of the two groups of patients was not statistically significant ($P>0.05$). The AFP, PLT, WBC and the diameter of the main portal vein in the two groups dropped substantially compared to those before treatment ($P<0.05$), and the AFP and the diameter of the main portal vein in the observation group were notably lower than those in the control group ($P<0.05$). After treatment, the ALT, AST and TBiL of the two groups were remarkably higher than those before treatment ($P<0.05$), and these indicators in the observation group were apparently higher than those in the control group ($P<0.05$). There was no significant difference in the incidence of postoperative gastrointestinal bleeding, fever, granulocytopenia and abnormal hepatic dysfunction between the observation group and the control group ($P>0.05$). The functional assessment of cancer therapy-hepatobiliary (FACT-Hep) scores of the two groups 6 months after operation was substantially lower than pre-op scores ($P<0.05$), and the observation group had apparently lower postoperative scores than the control group ($P<0.05$). The progression-free survival (PFS) and overall survival (OS) in the observation group were critically superior to those in the control group ($P<0.05$). Conclusion: TIPS combined with ^{125}I particle implantation in the treatment of PHC patients with PVTT can help improve patients' clinical treatment efficacy after surgery while prolonging their postoperative survival. The treatment is safe and worthy of clinical promotion.

Keywords: Transjugular intrahepatic portosystemic shunt (TIPS), ^{125}I particles implantation, hepatocellular carcinoma, portal vein tumor thrombus (PVTT), curative effect, prognosis

Introduction

Primary hepatocellular carcinoma (PHC) is one of the most common clinical malignancies with a high incidence and mortality. Patients with PHC often (up to 60%) have portal vein tumor thrombus (PVTT) when they are diagnosed. The presence of PVTT often leads to poor clinical prognosis when compared with PHC patients without PVTT. PVTT is considered a risk factor for tumor recurrence, metastasis, and blood-borne transmission, especially when the tumor thrombus grows along the trunk of the portal vein. PVTT, a kind of intrahepatic metastasis, can cause liver failure and bleeding from esophageal and gastric varices etc., thus threatening the life of patients [1, 2]. Therefore, the early intervention of PVTT is beneficial to improve the clinical prognosis and quality of life of PHC patients [3].

Traditional surgical resection is only applicable to patients with Child-Pugh A grade of liver function. However, some issues including large sur-

gical trauma and the recurrence of PVTT might impair its clinical application [4]. Intrahepatic portal vena cava shunt via jugular vein (TIPS) is safer and shows better short-term efficacy in improving portal vein hypertension in patients when compared to traditional surgical resection. However, due to the proliferation of tumor and endothelial cells, patients are still prone to stenosis after surgery [5, 6]. Thus, the inhibition of portal vein tumor cells should be conducted with the TIPS simultaneously. Currently, several methods such as radiation therapy (RT), transarterial chemoembolization (TACE), and radioembolization (RE) have been applied for the anti-PVTT treatment. Among those methods, radiotherapy using radioactive ^{125}I particles can kill portal vein tumor cells, inhibit the regeneration of endothelial cells and extend the patency period of the stent [7].

In this study, we evaluated the therapeutic effect of TIPS combined with ^{125}I particle implantation on patients with PVTT. The combination of those therapies significantly improves the patients' clinical efficacy and survival when compared to the patients who only received TIPS.

Materials and methods

Clinical data

In this retrospective analysis, a total of 127 patients with primary hepatocellular carcinoma (PHC) complicated with PVTT admitted to our hospital from March 2017 to June 2018 were enrolled. The patients were classified into an observation group (n=69) and a control group (n=58) in the light of the different treatment methods. The ethics committee of our hospital approved this study (No. ECZZX-2017031).

Inclusion and exclusion criteria

Inclusion criteria: (1) PHC patients with PVTT that confirmed by CT, MRI or pathological diagnosis; (2) patients with the presence of radiographically measurable lesions; (3) patients with MPVTT confirmed by imaging, and no treatment experiences of other PVTT; (4) patients with PHC who were not eligible for surgical resection or liver transplantation according to the Barcelona Clinic Liver Cancer (BCLC) classification criteria, or who had clear indications for surgery and were unwilling to undergo surgical treatment; (5) patients who voluntarily signed the informed consent forms.

Exclusion criteria: (1) patients with distant metastasis; (2) patients with tumor thrombus extending to the lower part of the main trunk of the portal vein and superior mesenteric vein or splenic vein; (3) patients with contraindications for TIPS; (4) patients with expected survival of less than three months.

Surgical treatment

The control group received TIPS only, and the surgical guidance equipment was GE Innova3100 digital subtraction angiography. The modified Seldinger technique was adopted to puncture the right internal jugular vein of the patient, and the RUPS 100 cannula (COOK Company, USA) was inserted into the inferior vena cava. The hepatic vein opening was explored with a guide wire and catheter, and the hepatic venography was performed accordingly. The patient's right hepatic vein or middle hepatic vein was chosen as the starting point for puncture, and the intrahepatic portal vein branch was punctured through the liver parenchyma according to the anatomic relationship between the hepatic vein and portal vein shown by CT or MRI (the ideal target path of the puncture was the left branch which avoids the tumor position). After successful puncture, the double J tube was introduced into splenic vein or superior mesenteric vein via catheter to conduct the portal venography and measurement of portal vein pressure. If the patient's angiography showed obvious varicose veins at the esophageal and gastric fundus during operation, the veins were completely embolized with embolic materials such as spring coil and medical tissue glue. According to the patient's liver function reserve, portal vein pressure and hemodynamics, balloons with different inner diameters were applied to expand shunt (7 mm × 80 mm balloon was routinely used, Johnson & Johnson, USA). Subsequently, the different specifications of vascular bare stents and covered stents were inserted according to the length of shunt (Bard, USA). The portal vein pressure after shunt was measured after the accurate position and well deployed of the stent was confirmed by portal vein angiography. The opera-

tion was completed after the ideal decrease of portal vein pressure, unobstructed shunt and successful variceal vein embolization. After surgery, the patients received routine ornithine aspartate and oral lactulose to prevent hepatic encephalopathy, strengthened liver protection treatment and given albumin supplementation appropriately as needed.

The observation group received ^{125}I radioactive particles in addition to the TIPS treatment in the control group. After the shunt channel was successfully established by TIPS, the catheter and particle releasing gun were connected between the stent and the cancer thrombus. While the catheter was slowly retreated, the ^{125}I particles were released through the catheter until the proximal end of the main portal vein and branch to the cancer thrombus, and the radioactive particles were arranged in the entire cancer thrombus as consecutive and orderly as possible. After the implantation, the patient underwent portal vein pressure measurement and portal venography again. If applied in combination with percutaneous hepatic portal vein puncture, the percutaneous hepatic portal vein catheter was removed after the completion of TIPS. During the extraction process, the liver puncture channel was strictly blocked to avoid bleeding in the abdominal cavity or chest cavity. CT scan was performed to confirm that no bleeding or particle metastasis had occurred. The postoperative dose assessment of Radiation Therapy Planning System (TPS), quality verification, routine postoperative hemostasis, liver protection, antiemetic, anti-infection, and supportive treatment were performed on patients, and ECG monitoring was continued for 12 h.

Treatment of tumor

In addition, the transcatheter arterial chemoembolization (TACE) or hepatic artery embolization (TAE), radiofrequency ablation (RFA) and targeted therapy were given according to the patient's condition. For Child-Pugh A patients, TACE treatment was given before or after TIPS according to the size of lesion. For child-Pugh grade C patients, TAE was administered after liver function recovery after TIPS. Patients with lesion diameter ≤5 cm and with abundant blood supply were treated with TACE or TAE at an interval of 3-15 d before RFA. For patients with lesion diameter >5 cm, one or several applications of TACE or TAE were performed. After imaging showed that the lesion had no hepatic artery supply or the catheter could not enter the lesion supply artery, radiofrequency RFA was performed on the part of lesions that showed survival in imaging. Sorafenib targeted therapy can be performed after surgery according to the patient's condition (or the patient's will). The treatment regimen was 400 mg orally, twice a day for 6 months, and the dose can be adjusted on the basis of patient's situation.

Follow-up visit

The deadline for follow-up was set to April 1, 2021. After 1, 2, 3, 6, 9, 12, 15, 18, 21, 24 months, the patient's liver and kidney function, complete blood count, coagulation function, blood fetoprotein (AFP) and upper abdominal enhanced MR were checked to keep track of the changes of intrahepatic lesions after treatment and the status of portal vein thrombus. The efficacy of HCC treatment was evaluated using the modified RECIST criteria proposed by the American Association of Liver Diseases in 2008. If the remaining lesions in the liver were enhanced at arterial stages or new lesions appeared, and the patients could tolerate it, the TACE treatment can be performed again. Patients' OS and PFS were recorded. OS refers to the period from the start of treatment to death due to any cause, and PFS refers to the time from the start of treatment to the first occurrence of disease progression or death from any cause.

Evaluation of clinical efficacy

The curative effect of the patient was evaluated by two physicians with associate senior professional titles or above in combination with the patient's preoperative and postoperative imaging performance. Complete remission (CR): postoperative imaging examination showed the disappearance of MPVTT. Partial remission (PR): imaging examination showed that the diameter of the MPVTT was less than that at pre-operation and did not develop to the distal portal vein. Stable disease (SD): Imaging examination showed that the diameter of the MPVTT did not change much or develop to the distal end of portal vein. Progressive disease (PD): Imaging examination demonstrated that the

lesion developed to the distal end of portal vein or the diameter of MPVTT increased compared with that before surgery. Remission rate = (CR+PR)/number of cases × 100%, total response rate = (CR+PR+SD)/number of cases × 100%.

Observation of indicators

The levels of serum alpha fetoprotein (AFP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), platelet count (PLT), leukocyte count (WBC) and the diameter of the portal vein were compared between the two groups before and 8 weeks after operation. The patients' fasting venous blood was extracted before surgery and 8 weeks after surgery to detect AFP, which was conducted by Roche Cobas e601 electrochemiluminescence immunoassay analyzer and its supporting kits. ALT, AST and TBiL were detected by Beckman Coulter AU5800 automatic biochemical analyzer. PLT and WBC were detected by hematology analyzer. The diameter of the portal vein trunk was measured by color Doppler ultrasonography.

Observation of complications

The incidence of postoperative complications in the two groups of patients was observed and compared accordingly.

Comparison of quality of life

The quality of life of the two groups was compared before surgery and 6 months after surgery. The index was evaluated by FACT-Hep Scale, which included daily activities, social/family life, emotional status, activity ability and additional symptoms of hepatocellular carcinoma. The scale has a total of 46 items, each of which has a score of 0 to 4 point(s), with a total score of 0 to 185 point(s). A lower score indicates a better quality of life of the patient.

Statistical analysis

SPSS 25.0 was applied for data processing and analysis. The measurement data were expressed as ($\bar{x}\pm s$) and compared with t test, while the counting data were expressed by percentage and compared using χ^2 test. The intergroup comparison was conducted using the independent sample t test, while the intragroup comparison was performed using the paired sample t test. Kaplan-Meier survival curve was drawn for survival, and Log-rank test was used for comparison of PFS/OS. *P<0.05* indicated statistically significant differences.

Results

Clinical data

The differences in the baseline data, such as gender, age, Child-Pugh grade, number of lesions, location of PVTT, maximum lesion diameter, and alpha-fetoprotein (APF) between the two groups of patients were not statistically significant (all *P>0.05*), as shown in **Table 1**.

Clinical efficacy

The treatment conditions of the observation group were as follows: 9 cases of CR (13.04%), 34 cases of PR (49.28%), 23 cases of SD (33.33%), 3 cases of PD (4.35%), the remission rate was 62.32%, and the overall response rate (ORR) of treatment was 95.65%. The treatment results of the control group were as follows: 5 cases of CR (8.62%), 21 cases of PR (36.21%), 26 cases of SD (44.83%), 6 cases of PD (10.34%), the treatment remission rate was 44.83%, and the ORR was 89.66%. A typical case of combining TIPS with ^{125}I nanoparticle implantation is shown in **Figure 1**. **Figure 1A** shows the structure and location of tumors by CT. Then the TIPS and implantation of ^{125}I were conducted under the image guidance (**Figure 1B-D**). The postoperative abdominal CT (**Figure 1E**) was done to check whether there was bleeding or particle diffusion.

The remission rate in the observation group was remarkably higher than that in the control group (*P<0.05*), but the difference in ORR of the two groups of patients was not statistically significant (*P>0.05*) (**Table 2**).

Comparison of indicators between the two groups before and after treatment

Before treatment, there were no statistically significant differences in AFP, ALT, AST, TBiL, PLT, WBC and portal vein trunk diameter between the two groups (all *P>0.05*). The indicators of AFP, PLT, WBC and portal vein trunk diameter in the two groups decreased substantially compared to those before treatment

Table 1. Comparison of general data between the two groups of patients

general information	Observation group (n=69)	Control group (n=58)	t/χ^2	*P*
Gender				
Male	39	35	0.189	0.663
Female	30	23		
Age (yrs, $\bar{x}\pm s$)	52.96±11.52	50.41±13.41	1.150	0.252
Child-Pugh classification (n, %)				
Grade A	18	13	0.280	0.780
Grade B	42	38		
Grade C	9	7		
Number of lesion (n, %)				
1	43	37	0.142	0.887
1~3	19	15		
>3	7	6		
Location of PVTT (n, %)				
Left branch of portal vein	30	24	0.578	0.563
Right branch of portal vein	27	20		
Left and right branches of portal vein	12	14		
Maximum diameter of lesion (cm, $\bar{x}\pm s$)	7.44±3.00	7.95±2.54	1.018	0.311
AFP (ng/ml, $\bar{x}\pm s$)	798.59±81.29	795.14±104.05	0.210	0.834

Note: AFP refers to alpha fetoprotein.

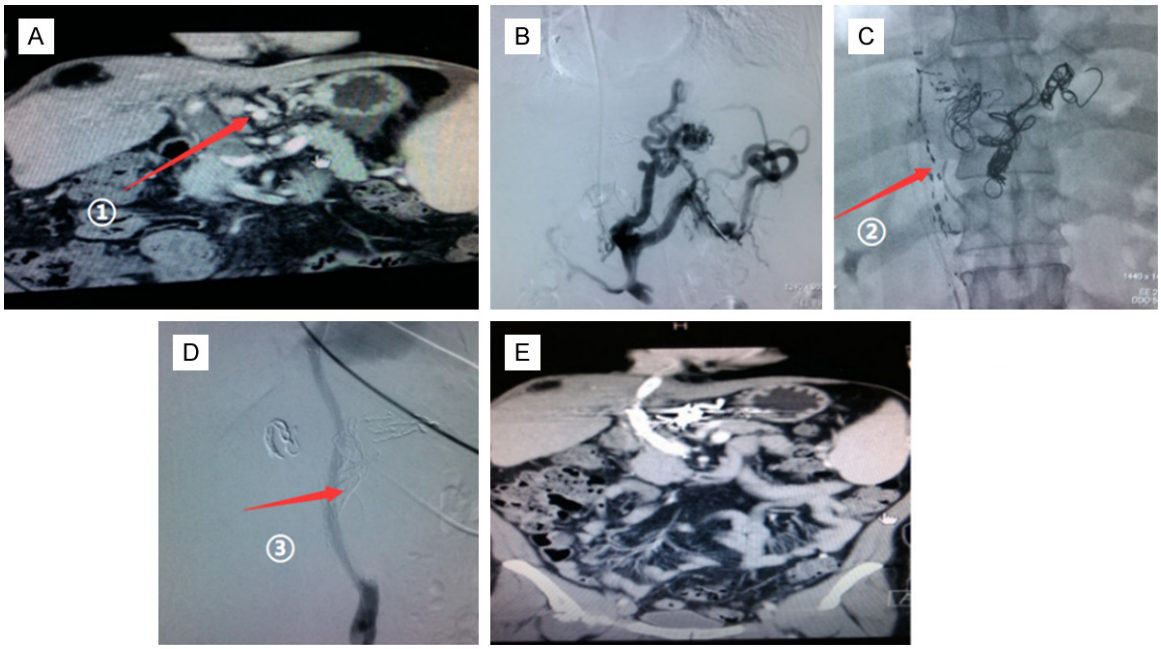

Figure 1. Typical pathological performance before and after surgery. A. Enhanced CT portal vein main tumor thrombus, low-density area after cryotherapy of liver cancer. B-D. TIPS operation process and portal vein I125 seed implantation. E. Postoperative abdominal CT. ① Main portal vein tumor thrombus. ② Main portal stent and particle distribution. ③ Hilar secretion.

(*P<0.05*), and the observation group had notably lower indicators than the control group (*P<0.05*). After treatment, the ALT, AST and TBiL of the two groups were remarkably higher

Table 2. Comparison of clinical efficacy between the two groups

Group	Number of cases	CR	PR	SD	PD	Remission rate (%)	ORR (%)
Observation group	69	9 (13.04)	34 (49.28)	23 (33.33)	3 (4.35)	62.32	95.65
Control group	58	5 (8.62)	21 (36.21)	26 (44.83)	6 (10.34)	44.83	89.66
χ^2	-	-	-	-	-	3.886	0.931
P	-	-	-	-	-	0.049	0.335

than those before treatment (*P<0.05*), and indicators in the observation group were apparently higher than those in the control group (all *P<0.05*) (**Table 3**).

Comparison of postoperative complications

There was no significant difference in the incidence of postoperative gastrointestinal hemorrhage, fever, granulocytopenia and abnormal hepatic dysfunction between the observation group and the control group (*P>0.05*) (**Table 4**).

Comparison of quality of life between the two groups before and after treatment

There was no statistically significant difference in preoperative functional assessment of cancer therapy-hepatobiliary (FACT-Hep) score between the two groups (*P>0.05*). Six months after operation, the FACT-Hep scores of patients in both groups were significantly lower than those before operation (*P<0.05*), and the scores of the observation group patients were notably lower than those of the control group (*P<0.05*) (**Figure 2**).

Comparison of PFS between the two groups

As shown in **Figure 3**, the PFS in the observation group was around 22 months, while that in the control group was only about 15 months (χ^2=12.779, *P*=0.000).

Comparison of OS between the two groups

As shown in **Figure 4**, the median OS in the observation group was around 26 months which was 5 months more than that of the control group (χ^2=5.682, *P*=0.017).

Discussion

Hepatocellular carcinoma with tumor thrombus in the main portal vein is one of the most difficult clinical diseases to treat. This disease negatively affects patient's liver function and usually causes severe malignant portal hypertension as well as other complications such as upper gastrointestinal bleeding, massive chest and ascites, thus seriously affecting the patient's survival and quality of life [8, 9].

Based on the growth characteristics of portal vein thrombus with liver cancer, the classification criteria was established for 8 subtypes of tumor thrombus which comprised five stages from I0 to IV [10]. This classification contributes to improve the treatment effects and clinical prognosis of patients with different types of tumor thrombus. For example, proper treatment for hepatocellular carcinoma complicated with type IIA-IIIA tumor thrombus is critical in extending the survival. While, without effective treatment, the patient may rapidly develop into type IV and lose the opportunity for treatment [11]. By analyzing the image of 130 cases of liver cancer portal vein tumor thrombi [12], it was found that tumor thrombus developed in reverse blood flow by using portal vein wall as the stent with average growth rate of 0.5±0.1 cm^3/month. Therefore, it is necessary to control the growth of tumor thrombi after surgical resection.

The previous treatments included surgery, ^{131}I-lipiodol internal irradiation, TACE, and TACE plus radiation therapy, but the therapeutic outcome was not desirable [13, 14]. Recently, several teams [15, 16] have made a breakthrough in treating hepatocellular carcinoma complicated with portal artery thrombus by combining stent implantation with TACE. The major limitation of this method includes the difficulty of operation and it is unsuitable for Type III patients. Type III patients with severe accumulation of cancer thrombus in the main portal vein are mostly accompanied by liver cirrhosis, branch cancer thrombus or cancer thrombus at the proximal end of the main portal vein and ascites, therefore portal

Table 3. Comparison of indicators between the two groups before and after treatment ($\bar{x}\pm s$)

Group	Timing	AFP (ng/ml)	ALT (U/L)	AST (U/L)	TBiL (μmol/L)	PLT (× 10^9/L)	WBC (× 10^9/L)	Diameter of main portal vein (mm)
Observation group (n=69)	Pre-operation	798.59±81.29	54.58±7.88	68.35±5.91	21.24±2.24	158.96±23.67	5.17±0.95	13.93±1.11
	8 weeks after operation	173.39±32.01*	116.18±21.68*	120.15±15.46*	37.73±4.43*	108.99±21.04	3.93±0.83	10.99±0.76*
	t	55.066	22.182	25.997	27.593	13.107	8.165	18.154
	P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Control group (n=58)	Pre-operation	795.14±104.05	56.75±7.14	66.46±6.60	20.53±2.51	165.75±22.36	5.28±1.01	13.59±1.01
	8 weeks after operation	240.51±36.66	79.66±15.20	89.52±14.78	30.66±3.22	109.65±22.03	3.81±0.89	11.95±0.82
	t	38.288	10.390	10.850	18.896	13.611	8.316	9.601
	P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note: Compared with the control group in the same period, t-text, *$P<0.05$.

Table 4. Comparison of postoperative complications between the two groups [n (%)]

Group	Number of cases	Gastrointestinal hemorrhage	Fever	Granulocytopia	Abdominal bleeding
Observation group	69	7 (10.14)	19 (27.54)	8 (11.59)	3 (4.35)
Control group	58	4 (6.90)	21 (36.21)	5 (8.62)	2 (3.45)
χ^2	-	0.420	1.098	0.303	0.039
P	-	0.517	0.295	0.582	0.843

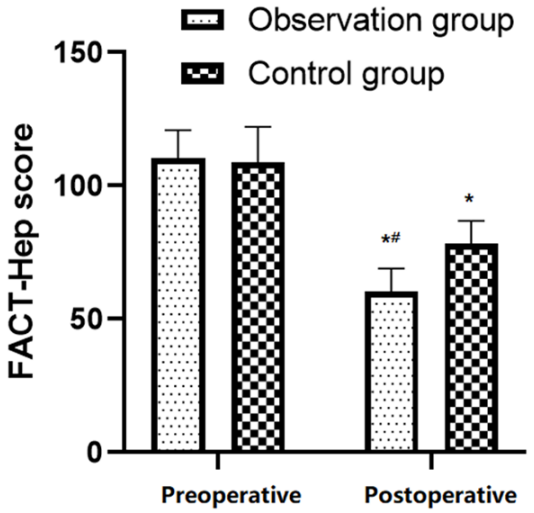

Figure 2. Comparison of quality-of-life scores between the two groups before and after treatment (points). Note: Compared with preoperative, paired t test, $^{*}P<0.05$; compared with control group, independent t test, $^{\#}P<0.05$.

vein stenting is not preferred [17-20]. In contrast, TIPS can better reduce patients' portal vein pressure, prevent and treat portal hypertension, improve patients' quality of life, help restore their liver function, and provide opportunities for the treatment of primary lesions. The success rate of TIPS surgical treatment was about 97% [21].

It has been shown through ultrasound studies that the diameter of the main portal vein in patients with liver cirrhosis is 8-14 mm, and the radiation radius of ^{125}I particles is 8.5 mm (i.e., diameter 17 mm). Therefore, the implantation of ^{125}I particles for treating PVTT can effectively cover the tumor thrombus. There were also studies shown that it was safe and feasible to implant the appropriate dose of particles in the blood vessel lumen [22, 23].

To improve the symptoms of portal vein hypertension for type III patients with severe PVTT, especially for patients with poor foundation (some patients in this study had child-Pugh grade C) [24, 25], we explored the therapeutic effects of combination of TIPS and ^{125}I radiation. This study demonstrated an exploratory analysis of the effects of TIPS combined with ^{125}I particles implantation on the efficacy and prognosis of hepatocellular carcinoma with PVTT. The results demonstrated that the short-term remission rate of patients treated with TIPS combined with ^{125}I particle implantation was remarkably higher than that treated with TIPS alone, and the AFP, portal vein main diameter reduction and the improvement of quality of life were better than the control group. The results are consistent with those published studies [26], that the continuous release of gamma rays from radioactive iodine particles in the portal vein destroys the DNA helix of tumor cells. This can exert a direct killing effect on cancer thrombus, produce more accurate radiotherapy effect, relieve portal hypertension and reduce the damage to surrounding tissues, thus contributing to the improvement of clinical treatment effect.

With the improvement of portal hypertension symptoms and the benefit of tumor treatment, patients' quality of life can be further improved. It is noteworthy that levels of serum ALT, AST and TBiL in patients treated with TIPS combined with ^{125}I particle implantation were higher than those treated with TIPS alone, which suggests that radioactive iodide may cause radioactive damage to hepatocytes. However, this damage can still be ameliorated by clinical drug treatment [27], and was within the tolerable range of patients. In terms of postoperative follow-up, the PFS and OS of patients in the observation group were remarkably superior to those in the control group.

The combination of TIPS and ^{125}I particle implantation improved the patient's portal

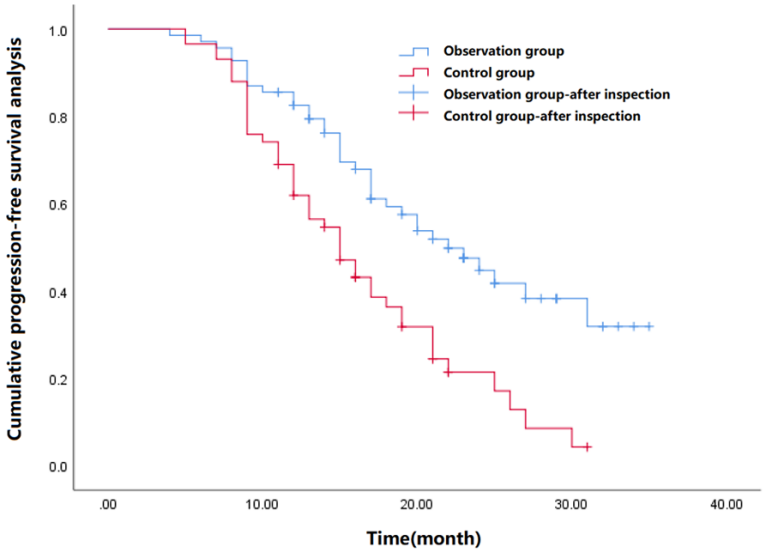

Figure 3. Postoperative progression-free survival of the two groups of patients.

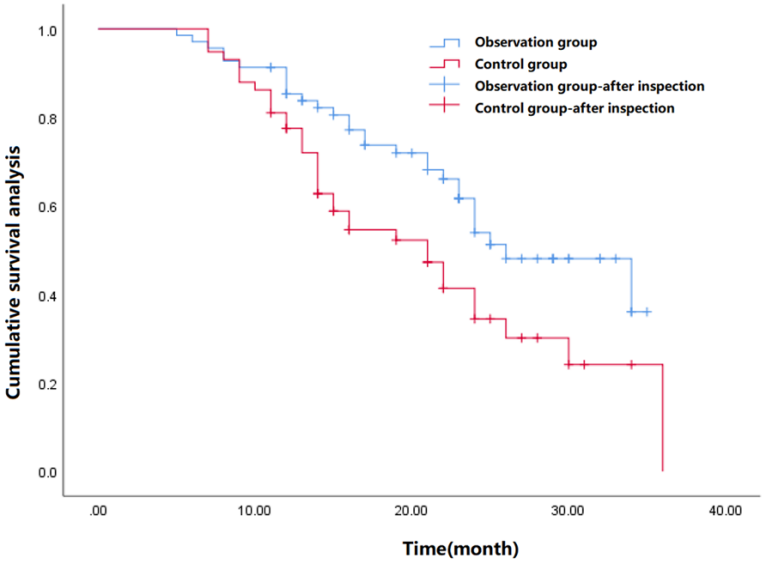

Figure 4. The overall survival of the two groups of patients after surgery.

hypertension and exerted continuous inhibitory effect on tumor thrombus. The progression of PVTT is a key factor for the prognosis of patients. Therefore, the combination of the two treatments can effectively prolong the survival of patients after surgery, which is consistent with the expected results of this study. However, we also realize some limitations in our study. First, the relatively small sample size limited the persuasion of the results. Second, there is a lack of animal studies to further demonstrate the mechanism of this combination therapeutic.

Sorafenib targeted therapy can be performed after surgery according to the patient's condition (or the patient's will). Sorafenib acts on RAF kinase, vascular endothelial growth factor receptor, platelet-derived growth factor receptor-β, etc., to inhibit the growth of tumor cells and prevent the formation of new blood vessels, so as to improve the survival of patients after surgery.

In summary, the combination of TIPS and ^{125}I particle implantation in the treatment of PHC patients with PVTT can help improve their clinical efficacy and quality of life while prolonging their postoperative survival. The treatment is safe and worthy of clinical promotion.

Disclosure of conflict of interest

None.

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