Combined Iodine-125 Seed Strand, Transarterial Chemoembolizaiton, Lenvatinib and Anti-PD-1 Antibodies Therapy for Unresectable Hepatocellular Carcinoma and Vp4 Portal Vein Tumor Thrombus: A Real-world Study

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Abstract

Purpose

To evaluate the safety and efficacy of interventional therapy (iodine-125 seed strand [with or without stent] implantation plus transarterial chemoembolization) combined with systemic therapy (lenvatinib plus anti-PD-1 antibody) as first-line treatment for hepatocellular carcinoma (HCC) patients with Vp4 portal vein tumor thrombus (PVTT).

Methods

From December 2018 to June 2021, 75 patients with HCC and Vp4 PVTT were included in this single-center retrospective study. Forty-one patients underwent interventional therapy combined with lenvatinib and anti-PD-1 antibody (group A; n = 41), while 34 cases underwent interventional therapy combined with lenvatinib (group B; n = 34). Stent occlusion rates and overall response rates (ORRs) for intrahepatic tumors and PVTT were compared. Median overall survival (mOS) and median progression-free survival (mPFS) were compared by using Kaplan-Meier method.

Results

The technique was performed successfully in all patients. ORRs for intrahepatic tumors (58.5% vs 11.8%, $p < .001$) and PVTT (76.9% vs 33.3%, $p < .001$) were significantly higher in group A compared with group B. Stent occlusion rates were 17.8% and 39.3% in groups A and B, respectively ($p = .076$). The mOS and mPFS were significantly longer in group A compared with group B (mOS, 17.7 ± 1.7 vs 11.2 ± 0.9 months, $p = .003$; mPFS, 16.8 ± 1.6 vs 7.0 ± 1.0 months, $p < .001$). Multivariate analysis found that treatment regimen and sex were two independent prognostic factors of OS.

Conclusions

Interventional therapy (iodine-125 seed strand [with or without stent] implantation plus transarterial chemoembolization) combined with systemic therapy (lenvatinib plus anti-PD-1 antibody) is safe and effective as first-line treatment for HCC patients with Vp4 PVTT.

Introduction

Portal vein tumor thrombus (PVTT), a common pattern in advanced hepatocellular carcinoma (HCC), is found in 10 ~ 40% of patients [1]. The prognosis of patients with PVTT in the main trunk (Vp4 PVTT) remains poor. The median overall survival (mOS) of these patients is only 2.7 ~ 4.0 months if untreated [2]. The perioperative mortality rate is 0%-28%, with a 5-year OS rate of 0%-26% [3, 4].

Based on the SHARP and REFLECT trials [5, 6], sorafenib and lenvatinib were recommended as first-line systemic therapy for patients with advanced unresectable HCC [7]. However, Kaneko et al reported a mOS of only 5.5 months in patients with Vp3/4 PVTT administered sorafeinib and lenvatinib [8].

Linear iodine-125(^{125}I) seed strand combined with stent implantation plus transarterial chemoembolization was proposed by Luo et al [9] for patients with HCC and Vp4 PVTT. Recently, Zhang et al [10] conducted a retrospective study that combined sorafenib with this interventional treatment strategy. This combined therapy prolonged the mOS to 12.3 months in these patients. Immune checkpoint inhibitor (ICI) therapy, particularly applying antibodies targeting the programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) pathway, has been a significant component of numerous combination regimens in advanced HCC [11–13].

This study performed to evaluate the safety and efficacy of interventional therapy (^{125}I seed strand [with or without stent] implantation plus transarterial chemoembolization) combined with systemic therapy (lenvatinib plus anti-PD-1 antibody) as first-line treatment for HCC patients with Vp4 PVTT.

Materials And Methods

This was a single-center retrospective study. Local institutional review board approval was obtained. We reviewed the electronic medical records of 95 consecutive patients with hepatitis B-related HCC and Vp4 PVTT, who were administered interventional therapy (^{125}I seed strand [with or without stent] implantation plus transarterial chemoembolization) combined with systemic therapy (lenvatinib plus anti-PD-1 antibody) (group A) or interventional therapy (^{125}I seed strand [with or without stent] implantation plus transarterial chemoembolization) combined with systemic therapy (lenvatinib) (group B) from December 2018 to June 2021. Before treatment initiation, the benefits, and potential adverse events (AEs) related to both combination regimens were explained thoroughly to the patients. The final choices were made by the patients. All patients provided written informed consent.

Patients

Intrahepatic HCC was diagnosed based on the American Association for the Study of Liver Disease guidelines [14]. According to the standard recommended by Shah et al [15], a PVTT was considered to be neoplastic if at least one of the following criteria was met: (a) expansion of the involved vessel (vessel diameter ≥ 1.8 cm for the MPV, ≥ 1.6 cm for the right portal vein (PV), or ≥ 1.8 cm for the left PV; (b) clear evidence of enhancement on dynamic contrast-enhanced CT images during the arterial phase of dynamic imaging, compared with baseline images (≥ 20 HU on CT). Otherwise, the PVTT was bland. The extent of PVTT was classified as follows: Vp0, no PVTT; Vp1, segmental PV invasion; Vp2, right anterior or posterior PV; Vp3, right or left PV; Vp4, main trunk and/or contralateral portal vein branch to the primarily involved lobe [16]. In this study, Vp4 PVTT was classified as follows: Vp4 I PVTT, tumor thrombus

extended to main trunk of portal vein, but not extended to contralateral portal vein branch; Vp4 II PVTT, tumor thrombus extended to main trunk and contralateral portal vein branch.

Inclusion criteria were: (1) between 18 and 75 years of age; (2) a single tumor ≥ 5.0 cm or multiple nodular tumors > 3.0 cm; (3) Vp4 PVTT; (4) patent second-order branch of the portal vein prior to PVTT; (5) Child-Pugh class A or B; and (6) an Eastern Cooperative Group performance status (ECOG) score of 0–2. These points represent eligibility criteria for the treatment.

Exclusion criteria were: (1) Vp1-3 PVTT; (2) completely occluded portal vein; (3) hepatic encephalopathy, severe ascites, esophageal, gastric fundal variceal bleeding or other serious medical comorbidities; (4) previous local-regional therapy (transarterial chemoembolization, radiofrequency ablation [RFA], microwave ablation [MWA], cryoablation, yttrium-90 [90Y] radioembolization, stereotactic body radiotherapy [SBRT], hepatic artery infusion chemotherapy [HAIC], or liver transplantation); (5) previous systemic therapy (tyrosine kinase inhibitors [TKIs], systemic chemotherapy, or immunotherapy); or (6) malignant tumor other than HCC.

According to the inclusion and exclusion criteria, 75 patients were included in this study (Group A, n = 41; and Group B, n = 34; Fig. 1). Baseline characteristics are presented in Table 1.

Table 1
Baseline characteristics of the patients in 2 groups, n (%)

Characteristic	Group A (n = 41)	Group B (n = 34)	*p*-value
Sex			1.000
Male	36(87.8)	30(88.2)	
Female	5(12.2)	4(11.8)	
Age			0.882
≥55y	21(51.2)	18(52.9)	
<55y	20(48.8)	16(47.1)	
Tumor size *(mm)			0.321
≥10cm	17(41.5)	18(52.9)	
<10cm	24(58.5)	16(47.1)	
PVTT type *			0.163
Vp4 I	28(68.3)	28(82.4)	
Vp4 II	13(31.7)	6(17.6)	
Child-Pugh class			1.000
A	39(95.1)	32(94.1)	
B	2(4.9)	2(5.9)	
ECOG performance status			0.401
0/1	39(95.1)	30(88.2)	
2	2(4.9)	4(11.8)	
Serum AFP level			0.150
≥400	21(51.2)	23(67.6)	
<400	20(48.8)	11(32.4)	
Extrahepatic metastasis			0.722
Yes	5(12.2)	3(8.8)	

AFP = α-fetoprotein; ECOG = Eastern Cooperative Oncology Group; PVTT = portal vein tumor thrombus.

*Tumor size, the maximum diameter of the largest target index lesion.

*Vp4 I = tumor thrombus extended to main trunk of portal vein, but not extended to contralateral portal vein branch; Vp4 II = tumor thrombus extended to main trunk and contralateral portal vein branch

Characteristic	Group A (n = 41)	Group B (n = 34)	*p*-value
No	36(87.8)	31(91.2)	
AFP = α-fetoprotein; ECOG = Eastern Cooperative Oncology Group; PVTT = portal vein tumor thrombus.			
*Tumor size, the maximum diameter of the largest target index lesion.			
*Vp4 I = tumor thrombus extended to main trunk of portal vein, but not extended to contralateral portal vein branch; Vp4 II = tumor thrombus extended to main trunk and contralateral portal vein branch			

Interventional Therapy

The protocol for ^{125}I seed strand (with or without stent) implantation and transarterial chemoembolization procedure was the same in both groups.

^{125}I seed properties

Model 6711 ^{125}I seeds (XinKe; Shanghai, China) were used in this study. The radioactivity of each ^{125}I seed was 25.9 MBq with a half-life of 59.4 days. Principal photon emissions were 27.4 and 35.5 keV X-rays and gamma-rays, respectively. The half-value thickness of the tissue for ^{125}I seed was 17 mm, and the incipient dose rate was 7 cGy/h. The 240-day intended dose at 10 mm from the axis of the ^{125}I seed strand was calculated with a radiation calculation software (version 0.1) based on the American Association of Physicists in Medicine TG43U1 brachytherapy formalism [17].

The production process of ^{125}I seed strands was as follows [9]: (a) a 4-F flexible compliant cannula (Boston Scientific, Natick, Massachusetts) was sealed at one end with an alcohol lamp; (b) ^{125}I seeds were loaded into the tube linearly, and the number of ^{125}I seeds loaded (N) was determined as N = L / 4.5 + 4, where L (mm) is the length of the obstructed PV; (c) the other end was cut and sealed.

^{125}I seed strand (with or without stent) implantation

Vp4 I PVTT cases

In the 2 groups, patients with Vp4 I PVTT received ^{125}I seed strand and intra-main trunk of portal vein (MPV) stent implantations. The method of ^{125}I seed strand and stent implantations in contralateral branch and MPV was adapted the technique proposed by Luo et al [9]. The contralateral secondorder branch was punctured with a 21-gauge Chiba needle (Cook, Bloomington, Indiana) under ultrasound guidance, followed by the insertion of a 0.018-inch wire (Cook) into the MPV. A 6-F NEEF set (Cook) was introduced into the MPV over the wire. Through the outer cannula of the 6-F NEEF set, a 0.035-inch wire (Terumo, Tokyo, Japan) combined with a 4-F Cobra catheter (Cordis, Miami Lakes, Florida) was manipulated across the obstructed MPV into the superior mesenteric vein (SMV). The 4-F Cobra catheter and the 6-F NEEF set were removed, and a 6-F sheath (Cordis) was introduced through the wire. Portography was performed to measure the diameter and length of the obstructed MPV by a 4-F pigtail

catheter (Cook) placed in the SMV. Two 0.035-inch stiff wires (Terumo) were inserted into the SMV through the 6F sheath. After the sheath removal, the 6-F NEFF set and a self-expandable stent (Bard, New Jersey, America) of appropriate size were introduced into the MPV over one of the stiff wires, respectively. The stent was deployed from the distal MPV into the contralateral fist-order branch of the portal vein. A ^{125}I seed strand was delivered to the target position via the outer cannula of the 6-F NEFF set and released between the stent and the MPV. Portography was repeated through the 4-F pigtail catheter (Cook). The puncture tract was next occluded by 3 × 140 mm Nester coils (Cook).

Then, another ^{125}I seed strand was implanted into the ipsilateral portal vein branch. This method was adapted the technique proposed by Zhang et al [18]. The ipsilateral second-order portal vein branch was punctured with a 21-gauge Chiba needle (Cook) under ultrasound guidance. With confirmed access, a 0.018-inch wire (Cook) was manipulated to cross the obstructed segment of ipsilateral portal vein branch and positioned into the MPV. A 6-F NEFF set (Cook) was introduced into the ipsilateral portal vein over the 0.018-inch wire. Then, the 0.018-inch wire was replaced by a 0.035-inch wire (Cook). Another ^{125}I seed strand was pushed to the target position of PVTT in ipsilateral portal vein branch by the inner core of the 6-F NEFF set. Then, the outer cannula of the 6-F sheath was retreated slowly until the strand was completely released. The position of the strand should completely cover the macroaxis of PVTT in ipsilateral portal vein branch. The trailing part of the strand was fixed into the hepatic parenchyma through the liver elasticity. Finally, the transhepatic puncture track was occluded by 3 × 140 mm Nester coils (Cook) (Fig. 2a-d).

Vp4 II PVTT cases

Patients with Vp4 II PVTT received ^{125}I seed strand (without stent) implantation. The contralateral second-order portal vein branch was punctured with a 21-gauge Chiba needle (Cook) under ultrasound guidance. A ^{125}I seed strand was implanted from MPV to contralateral branch by the same method which performed in ipsilateral portal vein branch of Vp4 I PVTT cases. The position of this strand should completely cover the macroaxis of PVTT in MPV and contralateral branch. Then, the ipsilateral second-order branch was punctured, another ^{125}I seed strand was implanted into the ipsilateral portal vein branch by the same method and this strand should completely cover the macroaxis of PVTT in ipsilateral portal vein branch (Fig. 3a-d).

Transarterial Chemoembolization

Transarterial chemoembolization was provided after the ^{125}I seed strand (with or without stent) implantation immediately. This method was adapted the technique proposed by Zhang et al [18]. Hepatic angiography was performed to evaluate tumor vascularity. A chemotherapeutic emulsion consisting of 10–50 mg epirubicin (Pharmorubicin; Pfizer, New York) and 4–10 ml lipiodol (Lipiodol; Guerbet, Roissy, France) was slowly injected at a rate of 0.5-1.0 mL/min under fluoroscopic guidance via a 2.4-F microcatheter (Merit Medical, USA) until saturation of the tumor-supplying arteries. The dose of iodized oil was calculated as 1.0-1.5 ml per cm in dimeter of tumor. If the tumor had a rich blood supply, more oil

was needed and vice versa. The dose of epirubicin was calculated as 10–50 mg/m^2 of body surface area. Then, 350-560-μm gelatin sponge particles (Jingling, Jiangsu, China) were used to embolize the residual feeding artery of tumor.

Systemic Therapy

In group A, all patients received lenvatinib 3 days after the first interventional procedure. Lenvatinib was orally administered at 8 mg/day in patients weighing < 60 kg and at 12 mg/day in those ≥ 60 kg. In patients developing AEs (grade ≥ 2), dose reduction or temporary interruption was maintained until the symptoms resolved to grade 0–1. AEs were assessed by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v4.03).

In group A, patients received anti-PD-1 inhibitor injection in 3–7 days after the first interventional procedure. They were monitored regularly, including repeat safety evaluation 2–3 days prior to each anti-PD-1 antibody treatment cycle. Anti-PD-1 antibodies were intravenously administered as follows: nivolumab (Bristol-Myers Squibb, USA) 3 mg/kg or camrelizumab (Hengrui Medicine, China) 200 mg [19] every 2 weeks, or pembrolizumab (MSD, USA) 200 mg, sintilimab (Innovent Biologics, China) 200 mg [20] or toripalimab (Junshi Bioscience, China) 240 mg [21] every 3 weeks. In patients developing AEs (grade 2), temporary interruption was maintained until the symptoms resolved to grade 0–1. In patients developing AEs (grade 3–4), anti-PD-1 inhibitor injection was ceased permanently.

Post-procedure Management

Single photon-emission computer tomography combined with CT (SPECT/CT) was performed on day 1 to evaluate the location and distribution of radiation by the ^{125}I seed strand. Laboratory tests (including hepatic and renal functions, complete blood count, and coagulation parameters) were performed 3–7 days after the initial procedure.

Follow-up and Repeated Transarterial Chemoembolization

The follow-up period was defined as the time from the initial interventional procedure to death or the last follow-up date. Each follow-up session included a detailed medical history, physical examination, laboratory tests, and contrast-enhanced CT or MRI. Follow-up was conducted every 30–45 days after the initial procedure. Patients with residual viable tumors or recurrent tumors in the hepatic parenchyma on CT or MRI images underwent repeated transarterial chemoembolization in case the Child-Pugh status remained at class A or B. No other interventional therapy was provided except for transarterial chemoembolization.

Evaluation

The primary endpoint was overall survival (OS, defined as the time from the initial interventional procedure to death from any cause). Secondary endpoint was progression-free survival (PFS, defined as the time from the initial interventional procedure until tumor progression or death from any cause).

Intrahepatic tumor response was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to modified Response Evaluation Criteria in Solid Tumor (mRECIST) criteria.

In Vp4 I PVTT patients who administered ^{125}I seed strand and stent implantations, treatment response in PVTT was evaluated by the rate of stent occlusion and the median stent patency time. Because PVTT changed into an irregular shape and was positioned between the stent and the portal vein wall after stent implantation, it is hard to calculate the diameter of tumor thrombus precisely. Stent occlusion was defined with no contrast medium detected inside the stent on the portal phase of contrast-enhanced CT or contrast-enhanced MRI images, or no blood flow signal detected by color doppler flow imaging (CDFI). Stent patency time was determined from the day of stent placement to stent occlusion or the day of last follow-up.

In Vp4 II PVTT patients who administered ^{125}I seed strand (without stent) implantation, treatment response in PVTT was evaluated by contrast-enhanced CT or MRI, and the product of the largest perpendicular diameters of the PVTT was calculated and compared to the initial value, irrespective of the vascular site [22]. A complete response (CR) was defined as complete PVTT disappearance, a partial response (PR) as a ≥ 30% decrease of PVTT diameter, stable disease (SD) as between a 30% decrease and a 20% increase in thrombus diameter, and progressive disease (PD) as ≥ 20% increase in PVTT diameter.

Overall response rate (ORR) was defined as the percentage of patients who had a best tumor response rating of CR or PR. Disease control rate (DCR) was defined as the percentage of patients achieving CR, PR or SD as the best tumor response.

Statistical Analysis

All statistical analysis was performed with SPSS (version 23.0, Chicago, Illinois). Continuous variables were presented as mean ± standard deviation and were compared by independent or paired samples *t* test. Categorical variables were presented as frequency and compared by the Chi-square test. Median PFS (mPFS), mOS and median stent patency times were analyzed by the Kaplan-Meier method and the log-rank test. A *p*-value < 0.05 was considered statistically significant. Factors statistically significant at *p*-value < 0.10 in univariate analysis were entered a multivariable Cox proportional hazards model.

Results

Technical Success

In both groups, 56 patients with Vp4 I PVTT received ^{125}I seed strand and stent implantation plus transarterial chemoembolization (28 in groups A and B, respectively), and 19 with Vp4 II PVTT received ^{125}I seed strand implantation plus transarterial chemoembolization (13 and 6 in groups A and B, respectively). The mean number of ^{125}I seeds loaded were 38.6 ± 14.0 (range, 20–60) and 32.8 ± 15.0

(range, 16–60) in groups A and B, respectively ($p = 0.314$). The mean intended doses were 64.9 ± 1.0 Gy (range, 63.5–66.5 Gy) and 64.5 ± 1.2 Gy (range, 63.2–66.5 Gy) in groups A and B, respectively ($p = 0.159$). No dislodge of ^{125}I seed strand was observed in SPETCT/CT and CT images. Totally 75 patients in both groups received a total of 258 transarterial chemoembolization procedures (137 and 121 in groups A and B, respectively). Mean 3.3 ± 1.9 (range 1–11) and 3.6 ± 1.7 (range 1–8) transarterial chemoembolization procedures were performed in groups A and B, respectively ($p = 0.610$).

Immunotherapy

In group A, 8 patients received pembrolizumab injection, 9 received toripalimab injection, 10 received sintilimab injection, 8 received camrelizumab injection, and 6 received nivolumab injection.

Tumor Response

Treatment responses for intrahepatic tumors in all patients and PVTT in Vp4 II PVTT patients are presented in Table 2. ORRs for intrahepatic tumors and Vp4 II PVTT were 58.5% and 76.9% in group A, and 11.8% and 33.3% in group B, respectively ($p < 0.001$, $p = 0.129$). DCRs for intrahepatic tumors and Vp4 II PVTT were 73.2% and 92.3% in group A, and 28.6% and 83.3% in group B, respectively ($p < 0.001$, $p = 1.000$).

Table 2
Response of intrahepatic tumor and Vp4 II PVTT

Response	**Intrahepatic tumor**			**Vp4 II PVTT***		
	Group A n = 41	Group B n = 34	P-value	Group A n = 13	Group B n = 6	p-value
CR	3	0		2	0	
PR	18	4		8	2	
SD	6	5		2	3	
PD	14	25		1	1	
ORR* (%)	58.5	11.8	0.000	76.9	33.3	0.129
DCR* (%)	73.2	26.8	0.000	92.3	83.3	1.000

CR = complete response; DCR = disease control rate; PD = progressive disease; PR = partial response; SD = stable disease. *ORR = (CR + PR)/n. *DCR = (CR + PR + SD)/n. * Vp4 II PVTT = tumor thrombus extended to main trunk and contralateral portal vein branch.

In Vp4 I PVTT patients, stent occlusion by tumor invasion was observed in 5 (17.8%) group A and 11(39.3%) group B patients ($p = 0.076$). The cumulative stent patency rates at 3-, 6-, 9- and 12-months were 100.0%, 96.3%, 88.2% and 88.2% in group A, and 96.3%, 81.5%, 71.9% and 65.4% in group B, respectively. The median stent patency time was not reached in group A and was 14.0 ± 1.5 months in group B (95%CI, 11.1–16.9 months; $p = 0.029$). (Fig. 4a)

In group A, a Vp4 I PVTT patient who received ^{125}I seed strand and stent implantation plus transarterial chemoembolization with PR intrahepatic tumor response was administered liver transplantation at 11 months after the initial interventional therapy. And a Vp4 II PVTT patient in group A who received ^{125}I seed strand implantation plus transarterial chemoembolization with PR intrahepatic and PVTT tumor responses was administered surgical resection of intrahepatic tumor at 11.7 months after the initial interventional therapy. No patient received surgical resection or liver transplantation in group B.

Survival

The mean follow-up times were 14.4 ± 5.2 and 11.6 ± 5.2 months in groups A and B, respectively. During the follow-up period, 25 (61.0%) and 30 (88.2%) patients died in groups A and B, respectively ($p = 0.008$). Overall survival rates at 3-, 6-, 9- and 12-months were 97.6%, 95.1%, 87.8% and 70.7% in group A, and 97.1%, 82.4%, 61.8% and 47.1% in group B, respectively ($p = 0.003$). The causes of death are presented in Table 3.

Table 3
The causes of death in 2 groups, n (%)

Causes of death	Group A (n = 25)	Group B (n = 30)	p-value
Tumor progression	7(28.0)	16(53.3)	0.058
hepatic failure	7(28.0)	6(20.0)	0.487
Variceal bleeding	6(24.0)	5(16.7)	0.498
Hepatic encephalopathy	1(4.1)	1(3.3)	1.000
Liver abscess	0(0.0)	1(3.3)	1.000
Respiratory failure	1(4.1)	1(3.3)	1.000
Myocardial infarction	2(8.0)	0(0.0)	0.202
Cerebral hemorrhage	1(4.1)	0(0.0)	0.455

The mOS was 17.7 ± 1.7 months (95%CI, 14.3–21.1 months) in group A and 11.2 ± 0.9 months in group B (95%CI, 9.5–12.9 months) ($p = 0.003$) (Fig. 4b). Meanwhile, the mPFS was 16.8 ± 1.7 (95%CI, 13.7–19.8) and 7.0 ± 1.0 (95%CI, 5.1–8.9) months in groups A and B, respectively ($p < 0.001$) (Fig. 4c).

In univariate analysis, treatment regimen and sex statistically significant at $p < 0.10$ and they were entered a multivariable Cox proportional hazards model. Multivariate analysis found that the treatment regimen and sex were two independent prognostic factors of OS. (Table 4)

Table 4
Log-rank test and Cox regression analysis of factors potentially related to OS

	All patients (n = 75)				
		Log-rank test		Multivariate	
Factors	No. of Patients	Median OS (95%CI)	p-value	HR (95%CI)	p-value
Sex			0.056		0.047
Male	66	15.5 ± 1.6(12.3–18.7)		0.471(0.224–0.989)	
Female	9	11.2 ± 2.5(6.2–16.2)		1	
Age			0.812		
≥55y	39	14.0 ± 2.5(8.9–19.0)			
< 55y	36	14.5 ± 1.2(12.1–16.9)			
Treatment regimen			0.003		0.003
Group A	41	17.7 ± 1.7(14.3–21.1)		0.438(0.254–0.755)	
Group B	34	11.2 ± 0.9(9.5–12.9)		1	
Tumor size *(mm)			0.183		
≥ 10cm	35	11.2 ± 1.7(7.8–14.6)			
< 10cm	40	15.8 ± 0.9(14.0-17.6)			
PVTT type *			0.972		
Vp4 I	56	14.5 ± 1.4(11.8–17.2)			
Vp4 II	19	13.0 ± 3.7(5.8–20.2)			
Serum AFP level			0.396		

AFP = α-fetoprotein; CI = confidence interval; HR = hazard ratio; PVTT = portal vein tumor thrombus.

*Tumor size, the maximum diameter of the largest target index lesion.

*Vp4 I = tumor thrombus extended to main trunk of portal vein, but not extended to contralateral portal vein branch; Vp4 II = tumor thrombus extended to main trunk and contralateral portal vein branch

	All patients (n = 75)		
≥ 400	44	13.0 ± 2.5(8.1–17.9)	
< 400	31	15.5 ± 1.9(11.8–19.2)	
Extrahepatic metastasis			0.488
Yes	8	8.0 ± 0.9(6.2–9.8)	
No	67	14.5 ± 1.3(12.0–17.0)	
AFP = α-fetoprotein; CI = confidence interval; HR = hazard ratio; PVTT = portal vein tumor thrombus.			
*Tumor size, the maximum diameter of the largest target index lesion.			
*Vp4 I = tumor thrombus extended to main trunk of portal vein, but not extended to contralateral portal vein branch; Vp4 II = tumor thrombus extended to main trunk and contralateral portal vein branch			

Complications

No serious complications related to interventional treatment, including acute hepatic failure, liver abscess, intraperitoneal bleeding, and radiation hepatitis, were observed. The incidence rates of fever, vomiting and upper-abdominal pain were 24.4%, 31.7% and 53.7% in group A, and 28.6%, 22.8% and 60.0% in group B, respectively. They were all resolved after symptomatic treatment.

In 2 groups, all recorded AEs related to systemic treatment are shown in Table 5. Seven (17.1%) and 12 (35.3%) patients occurred 11 and 13 AEs related lenvatinib in group A and B, respectively ($p = 0.292$). Grade 3 diarrhea and hypertension occurred in 1 patient each and led to lenvatinib dose reduction. In group A, 4 (9.8%) patients occurred 4 anti-PD-1 antibody related AEs. Grade 3 immunological enteritis and immunological myocarditis occurred in 1 patient each, and anti-PD-1 antibody injection was ceased permanently.

Table 5
Adverse events related to systemic therapy in 2 groups, n (%)

	Group A (n = 41)	Group B (n = 34)	*p*-value
Lenvatinib related AEs			
Diarrhea			
Grade 1–2	2(4.9)	4(11.8)	0.401
Grade 3–4	1(2.4)	0(0.0)	1.000
Hand-foot skin reaction			
Grade 1–2	2(4.9)	3(8.8)	0.654
Grade 3–4	0(0.0)	0(0.0)	
Hypertension			
Grade 1–2	4(9.8)	5(14.7)	0.723
Grade 3–4	0(0.0)	1(2.9)	0.453
Duodenal ulcer			
Grade 1–2	1(2.4)	0(0.0)	1.000
Grade 3–4	0(0.0)	0(0.0)	
Leukopenia and thrombocytopenia			
Grade 1–2	0(0.0)	1(2.9)	0.453
Grade 3–4	0(0.0)	0(0.0)	
Anti-PD-1 antibody related AEs			
Immunological hypothyroidism			
Grade 1–2	1(2.4)		
Grade 3–4	0(0.0)		
Immunological enteritis			
Grade 1–2	0(0.0)		
Grade 3–4	1(2.4)		
Immunological myocarditis			
Grade 1–2	0(0.0)		
Grade 3–4	1(2.4)		

	Group A (n = 41)	Group B (n = 34)	*p*-value
Immunological pneumonia			
Grade 1–2	1(2.4)		

These patients were all relieved by symptomatic treatment (grade 1AEs) and lenvatinib dose reduction and/or anti-PD-1 antibody cease (grade ≥ 2 AEs). No grade 4 AE occurred, and no patient died of AEs in this study.

Discussion

This study demonstrated that interventional therapy (^{125}I seed strand [with or without stent] implantation plus transarterial chemoembolization) combined with systemic therapy (lenvatinib plus anti-PD-1 antibody) is a safe and effective treatment strategy for HCC patients with Vp4 PVTT.

The prognosis of advanced HCC remains poor, especially for patients with PVTT. Furthermore, mOS is shorter in patients with Vp4 PVTT than in those with Vp0-3 PVTT [23, 24]. The main reason for the poor prognosis is MPV occlusion, which is associated with increased risk of tumor spread, elevated portal venous pressure causing variceal hemorrhage, and decreased portal flow resulting in ascites, jaundice, hepatic encephalopathy, and liver failure[9]. However, without treatment the interval between the formation of segmental PVTT and complete obstruction is < 6 weeks [25]. These previous studies implied that there are two key points in the treatment strategy for patients with Vp4 PVTT: first, restoring the flow of obstructed portal vein; second, inhibiting intrahepatic tumor and PVTT progression.

Luo et al [9] proposed stent and ^{125}I seed strand which implanted from contralateral branch to MPV combined with transarterial chemoembolization treatment for HCC patients with Vp4 I PVTT. Even though, this interventional treatment strategy prolonged the mOS to 9.3 months. The mPFS was only 1.8 months and stent occlusion by tumor invasion occurred in 68.1% patients. Based on this interventional technique, two improvements were made in this study: (*i*) in patients with Vp4 I PVTT, except for the stent and ^{125}I seed strand which implanted from contralateral branch to MPV, another ^{125}I seed strand was implanted into the ipsilateral branch which inhibited the progression of tumor thrombus in ipsilateral branch and prolonged the stent patency time; (*ii*) in patients with Vp4 II PVTT, because of the contralateral branch occlusion these patients had lost the possibility of stent implantation to restore the blood flow of MPV. Two ^{125}I seed strands which implanted into MPV and bilateral branch inhibited the progression of PVTT and allowed time for the portal vein to establish more collateral circulation. To a certain extent, patent MPV or enough collateral circulation provided grantee for normal liver function. Based on the normal liver function, transarterial chemoembolization and systemic therapy could be provided to control tumor progression more safely.

According to BCLC stage, sorafenib and lenvatinib were recommended as first-line systemic therapy for patients with HCC and PVTT [7]. More recently, ICI therapy plus TKIs have been recommended as a new effective systemic treatment strategy for patients with advanced HCC. One of the underlying mechanisms is that anti-VEGF therapies can reduce VEGF therapy-mediated immunosuppression within the tumor and its microenvironment may enhance anti-PD-1/PD-L1 efficacy by reversing VEGF-mediated immunosuppression and promoting tumor T-cell infiltration [26]. In the IMbrave150 study, ORRs were 33.2% and 13.3% in the atezolizumab-bevacizumab and sorafenib groups, respectively, and OS was significantly longer with atezolizumab-bevacizumab [27]. In the exploratory analysis of IMbrave150, the mOS of Vp4 HCC patients is only 7.6 m in the atezolizumab-bevacizumab group and 5.5 m in the sorafenib group ($p = 0.104$) (2021 ASCO 4047 poster). In a phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable HCC, the ORR was 46% and the median OS was 22 months [28]. Huang et al. performed a real-world study that analyzed HCC patients with macrovascular tumor thrombus (MVTT) administered lenvatinib plus anti-PD-1 antibodies as first-line treatment. This combination therapy resulted in better tumor responses in MVTT (ORR for MVTT, 54.5%) than in intrahepatic tumor (32.8%) and lung metastases (37.5%) [21]. Based on these results, whether combined interventional therapy with ICI therapy and TKIs could provide more effective tumor control rate and prolong the mOS for patients with Vp4 PVTT.

Recently, Gao et al reported transarterial chemoembolization combined with lenvatinib and sintilimab for unresectable HCC with a mOS of 23.6 months and ORR of 46.7% [29]. Ju et al reported transarterial chemoembolization combined with apatinib and camrelizumab for advanced HCC with a mOS of 24.8 months which longer than apatinib plus camrelizumab (13.1 months) [30]. According to these result, transarterial chemoembolization combined TKIs and anti-PD-1 antibody might be an effect combined therapy for advanced HCC. However, Vp4 PVTT patients were excluded by these studies. In our study, the MPV was restored in patients with Vp4 I PVTT, and enough collateral circulation formed in patients with Vp4 II PVTT. These two advantages provided the guarantee for normal liver function. Thus, in our study, patients received transarterial chemoembolization combined with lenvatinib and anti-PD-1 antibody (group A) or with Lenvatinib only (group B) to control intrahepatic tumor. Patients in group A had significantly better intrahepatic tumor control (ORR for intrahepatic tumors, 58.5% vs 11.8%). As a result, group A patients had significantly longer mOS and mPFS than group B cases (mOS, 17.7 vs 11.2 months; mPFS, 16.8 vs 7.0 months). In group A, a patient received liver transplantation and another patient received surgical resection. This result implied us that this combined therapy could provide opportunities of tumor down-staging and surgical treatment for patients with Vp4 PVTT.

In addition, radiation therapy (RT) has been demonstrated to enhance the priming and effector phases of antitumor-T-cell response, rendering it an attractive therapeutic tool that can be combined with PD-1/PD-L1 inhibitors [31]. Two preclinical studies supported the rational combination of RT and PD-1/PD-L1 inhibitors in HCC [32, 33]. ^{125}I seed strand implantation is a type of endovascular brachytherapy. X-rays and gamma-rays emitted by ^{125}I seeds could continuously irradiate the PVTT. In the current study, patients administered ^{125}I seed strand and stent implantations had a lower rate of stent occlusion in group A

compared with group B (17.8% vs 39.3%). In Vp4 II PVTT patients who administered ^{125}I seed strand implantation without stent placement also had a better tumor response for PVTT in group A than in group B (76.9% vs 33.3%). Therefore, ^{125}I seeds may also enhance the therapeutical effect of anti-PD-1 antibodies. More experimental investigations should be conducted to confirm this conclusion.

In addition, 7(17.1%) and 12(35.3%) patients occurred 11 and 13 AEs related lenvatinib in group A and B, respectively. The occurrence rate of AEs related to lenvatinib did not increase in patients combined lenvatinib and anti-PD-1 antibodies. Hence, this combined treatment regimen in group A is safe for patients with HCC and Vp4 PVTT.

There were several limitations in the current study. First, this study had a retrospective design, which may affect its generalizability. Second, the sample size was limited, which may affect the survival results. Third, more techniques could be used to evaluate the volume and activity of PVTT more precisely in a future study. Therefore, our next step is to conduct a single-center prospective, randomized, controlled trial to evaluate the long-term efficacy of this encouraging combination therapy in improving survival in HCC patients with Vp4 PVTT.

Conclusion

In conclusion, the interventional therapy (^{125}I seed strand [with or without stent] implantation plus transarterial chemoembolization) combined with systemic therapy (lenvatinib plus anti-PD-1 antibody) in patients with HCC and Vp4 PVTT is safe and effective. To our knowledge, this is the first report of patients with HCC and Vp4 PVTT administered this combination therapy as first-line treatment.

Abbreviations

AEs: Adverse events;AFP: Alpha-fetoprotein; CDFI: Color doppler flow imaging; CR: Complete response; DCR: Disease control rate; ECOG: Eastern Cooperative Oncology Group; HAIC: Hepatic artery infusion chemotherapy; HCC: Hepatocellular carcinoma; ICI: Immune checkpoint inhibitor; ^{125}I: Iodine-125; MOS: Median overall survival; MPFS: Median progression-free survival; MWA: Microwave ablation; NCI: National Cancer Institute; ORRs: Overall response rates; PD: Progressive disease; PD-1: Programmed cell death-1; PD-L1: Programmed cell death ligand-1; PR: partial response; PV: Portal vein; PVTT: Portal vein tumor thrombus; RFA: Radiofrequency ablation; SBRT: Stereotactic body radiotherapy; SMV: Superior mesenteric vein; SD: Stable disease; TKIs: Tyrosine kinase inhibitors; ^{90}Y: Yttrium-90

Declarations

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Not Applicable

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding authors on reasonable request.

Authors' contributions

ZHZ conceived and designed the experiments. WZ, JQM, and MJY performed the analysis. ZHZ, SNH, JZY, and XZ wrote the paper and prepared figures. QXL, LXL, JJL, XDQ and ZPY reviewed the draft. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of the Zhongshan Hospital of Fudan University and was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Consent for publication

Consent to publish this retrospective clinical study.

Competing interest

The authors declare no conflict of interest.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics. 2012. CA Cancer J Clin. 2015;65(2):87–108.
2. Katagiri S, Yamamoto M. Multidisciplinary treatments for hepatocellular carcinoma with major portal vein tumor thrombus. Surg Today. 2014;44(2):219–26.
3. Ikai I, Hatano E, Hasegawa S, Fujii H, Taura K, Uyama N, Shimahara Y. Prognositic index for patients with hepatocellular carcinoma combined with tumor thrombosis in the major portal vein. J Am Coll Surg. 2006;202(3):431–8.
4. Wu CC, Hsieh SR, Chen JT, Ho WL, Lin MC, Yeh DC, Liu TJ, P'eng FK. An appraisal of liver and portal vein resection for hepatocellular carcinoma with tumor thrombi extending to portal bifurcation. Arch Surg. 2000;135(11):1273–9.
5. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J-F, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378–90.

6. Kudo M, Finn RS, Qin S, Han K-H, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomized phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163–1173.
7. Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018; 29(Suppl 4):iv228-iv255.
8. Kaneko S, Tsuchiya K, Yasui Y, Inada K, Kirino S, Yamashita K, et al. Strategy for advanced hepatocellular carcinoma based on liver function and portal vein tumor thrombosis. Hepatol Res. 2020;50(12):1375–1385.
9. Luo J-J, Zhang Z-H, Liu Q-X, Zhang W, Wang J-H, Yan Z-P. Endovascular brachytherapy combined with stent placement and TACE for treatment of HCC with main portal vein tumor thrombus. Hepatol Int. 2016;10(1):185–95.
10. Zhang Z-H, Liu Q-X, Zhang W, Ma J-Q, Wang J-H, Luo J-J, Liu L-X, Yan Z-P. Combined endovascular brachytherapy, sorafenib, and transarterial chemobolization therapy for hepatocellular carcinoma patients with portal vein tumor thrombus. World J Gastroenterol. 2017;23(43):7735–7745.
11. Rimassa L, Pressiani T, Merle P. Systemic treatment options in hepatocellular carcinoma. Liver Cancer. 2019;8(6):427–446.
12. Finn RS, Zhu AX, Farah W, Almasri J, Zaiem F, Prokop LJ, Murad MH, Mohammed K. Therapies for advanced stage hepatocellular carcinoma with macrovascular invasion or metastatic disease: A systematic review and meta-analysis. Hepatology. 2018;67(1):422–435.
13. Brown ZJ, Greten TF, Heinrich B. Adjuvant treatment of hepatocellular carcinoma: prospect of immunotherapy. Hepatology. 2019;70(4):1437–1442.
14. Bruix J, Sherman M, Practice Guidelines Committee, American Association for the Study of Liver Disease. Management of hepatocellular carcinoma. Hepatology. 2005;42(5):1208–36.
15. Shah ZK, McKernan MG, Hahn PF, Sahani DV. Enhancing and expansile portal vein thrombosis: value in the diagnosis of hepatocellular carcinoma in patients with multiple hepatic lesions. Am J Roentgenol. 2007;188(5):1320–3.
16. Kudo M, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, Kojiro M, Makuuchi M, HCC Eepert Panel of Japan Society of Hepatology. Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis. 2011;29(3):339–64.
17. Yang M, Yan Z, Luo J, Liu Q, Zhang W, Ma J, Zhang Z, Yu T, Zhao Q, Liu L. A pilot study of intraluminal brachytherapy using ^{125}I seed strand for locally advanced pancreatic ductal adenocarcinoma with obstructive jaundice. Brachytherapy. 2016;15(6):859–864.
18. Zhang Z-H, Zhang W, Gu J-Y, Liu Q-X, Ma J-Q, Liu L-X, Wang J-H, Luo J-J, Yan Z-P. Treatment of Hepatocellular Carcinoma with Tumor Thrombus with the Use of Iodine-125 Seed Strand Implantation and Transarterial Chemoembolization: A Propensity-Score Analysis. J Vasc Interv Radiol. 2018;29(8):1085–1093.

19. Qin S, Ren Z, Meng Z, Chen Z, Chai X, Xiong J, et al. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomized, phase 2 trial. Lancet Oncol. 2020;21(4):571–580.
20. Hoy SM. Sintilimab: First Global Approval. Drugs. 2019;79(3):341–346.
21. Keam SJ. Toripalimab: First Global Approval. Drugs. 2019;79(5):573–578.
22. Huang C, Zhu X-D, Shen Y-H, Wu D, Ji Y, Ge N-L, Chen L-L, Tan C-J, Zhou J, Fan J, Sun H-C. Organ specific responses to first-line Lenvatinib plus anti-PD-1 antibodies in patients with unresectable hepatocellular carcinoma: a retrospective analysis. Biomarker Research. 2021;9(1):19.
23. Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. World J Gastroenterol. 2006;12(47):7561–7.
24. Liu L, Zhang C, Zhao Y, Qi X, Chen H, Bai W, He C, Guo W, Yin Z, Fan D, Han G. Transarterial chemoembolization for the treatment of advanced hepatocellular carcinoma with portal vein tumor thrombosis: prognostic factors in a single-center study of 188 patients. Biomed Res Int. 2014;2014:194278.
25. Ohnishi K, Okuda K, Ohtsuki T, Nakayama T, Hiyama Y, Iwama S, Goto N, Nakajima Y, Musha N, Nakashima T. Formation of hilar collaterals or cavernous transformation after portal vein obstruction by hepatocellular carcinoma. Gastroenterology. 1984;87(5):1150–3.
26. Hegde PS, Wallin JJ, Mancao C. Predictive markers of anti-VEGF and emerging role of angiogenesis inhibitors as immunotherapeutics. Semin Cancer Biol. 2018;52(Pt 2):117–124.
27. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-K, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382(20):1894–1905.
28. Finn RS, Ikeda M, Zhu AX, Sung MW, Baron AD, Kudo M, et al. Phase Ib Study of Lenvatinib Plus Pembrolizumab in patients with unresectable hepatocellular carcinoma. J Clin Oncol. 2020;38(26):2960–2970.
29. Cao F, Yang Y, Si T, Luo J, Zeng H, Zhang Z, Feng D, Chen Y, Zhang J. The Efficacy of TACE Combined With Lenvatinib Plus Sintilimab in Unresectable Hepatocellular Carcinoma: A Multicenter Retrospective Study. Front Oncol. 2021;11:783480.
30. Ju S, Zhou C, Yang C, Wang C, Liu J, Wang Y, Huang S, Li T, Chen Y, Bai Y, Yao W, Xiong B. Apatinib Plus Camrelizumab With/Without Chemoembolization for Hepatocellular Carcinoma: A Real-World Experience of a Single Center. Front Oncol. 2022;11:835889.
31. Jun G, Le TQ, Massarelli E, Hendifar AE, Tuli R. Radiation therapy and PD-1/PD-L1 blockade: the clinical development of an evolving anticancer. J Immunother Cancer. 2018;6(1):46.
32. Friedman D, Baird JR, Young KH, Cottam B, Crittenden MR, Friedman S, Gough MJ, Newell P. Programmed cell death-1 blockade enhanced response to stereotactic radiation in an orthotopic murine model of hepatocellular carcinoma. Hepatol Res. 2017;47(7):702–714.
33. Kim K-J, Kim J-H, Lee SJ, Lee E-J, Shin E-C, Seong J. Radiation improves antitumor effect of immune checkpoint inhibitor in murine hepatocellular carcinoma model. Oncotarget. 2017;8(25):41242–41255.

Figures

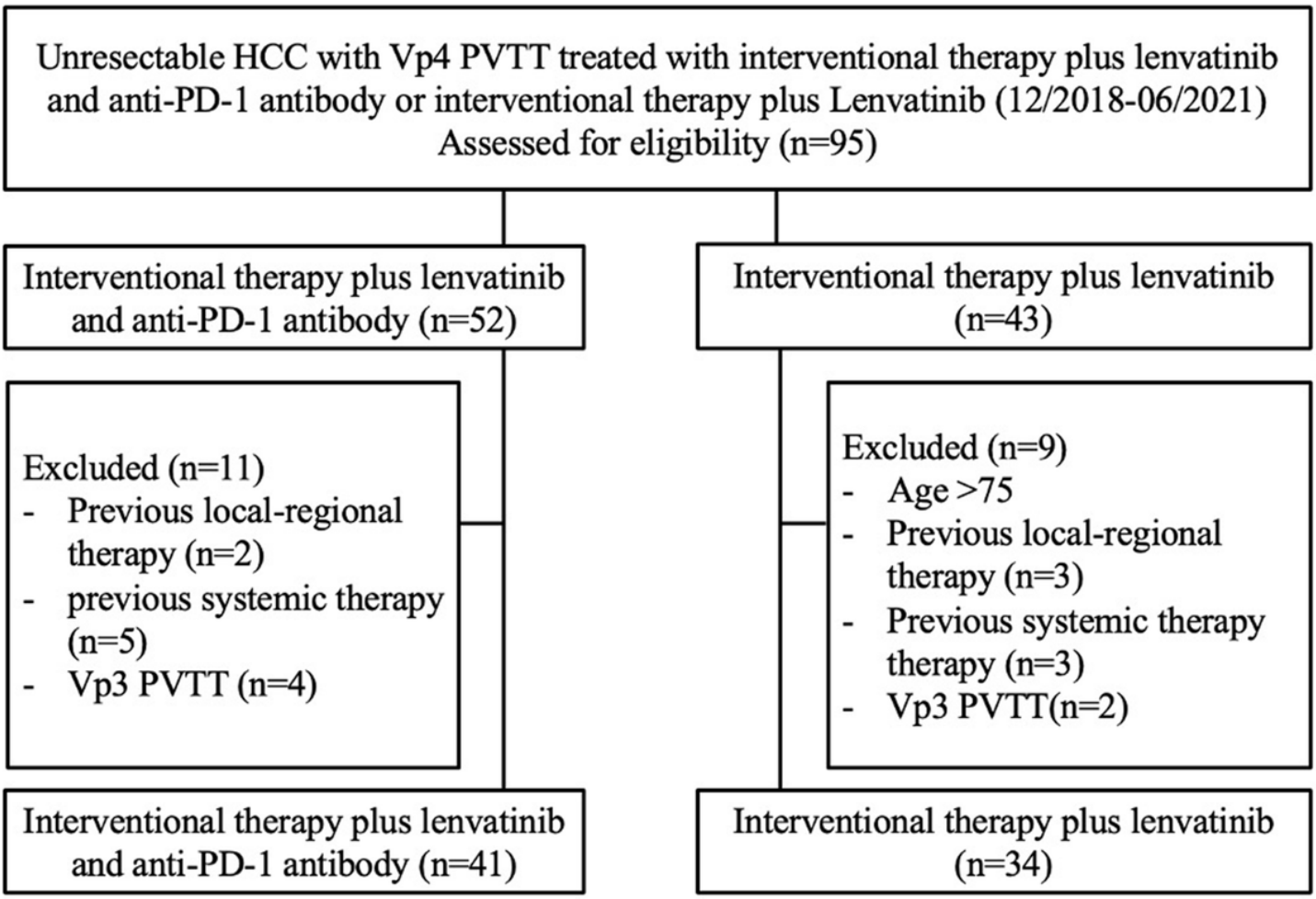

Figure 1

Patient selection flow chart.

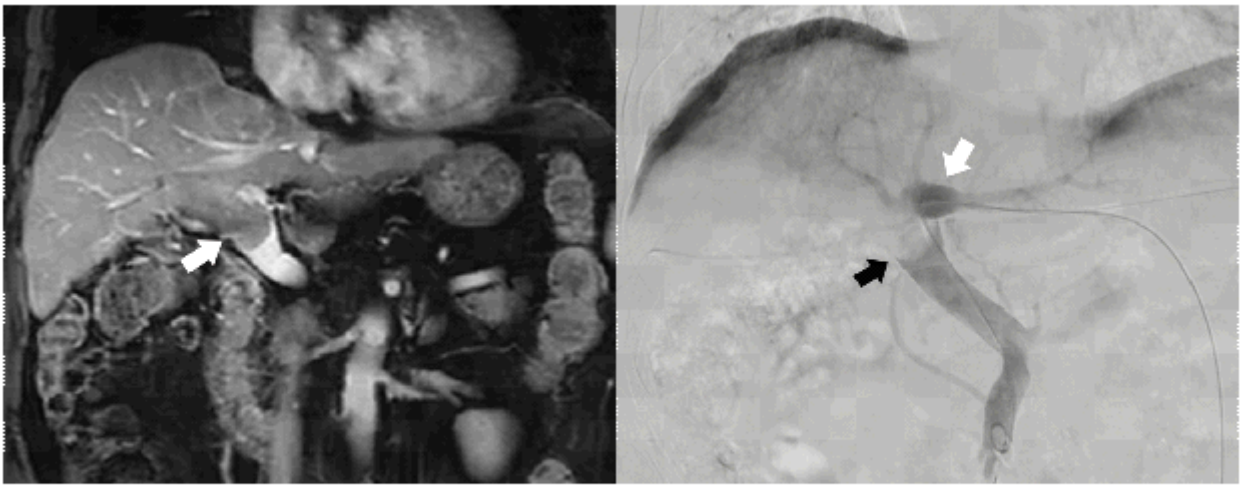

Fig 2 (a)

Fig 2 (b)

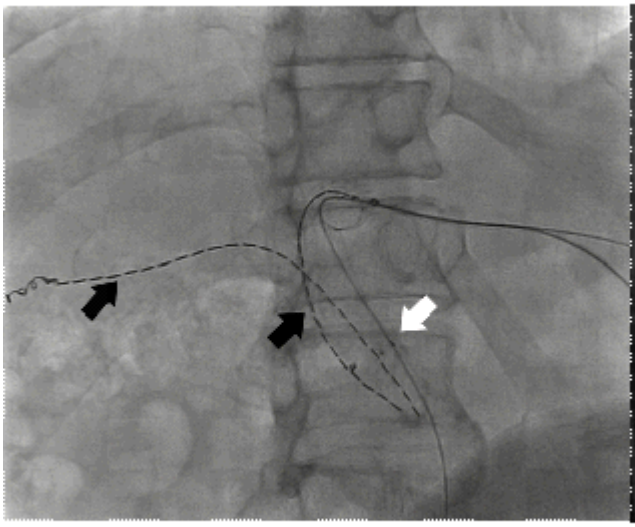

Fig 2 (c)

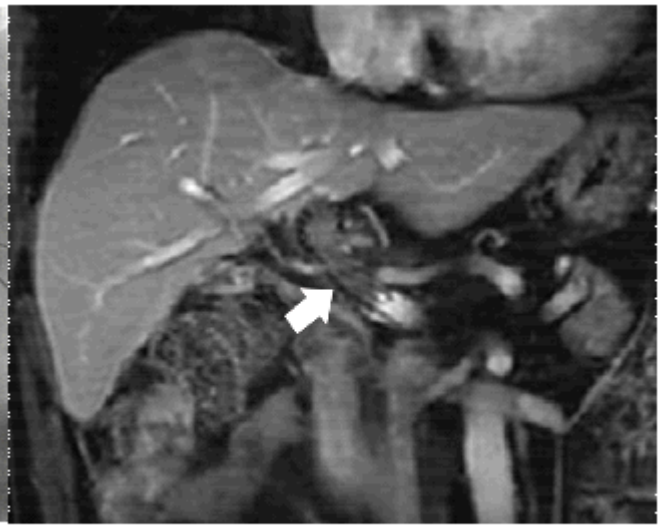

Fig 2 (d)

Figure 2

(a) The MRI images of a 62-yea-old man shows the tumor thrombus had invaded into the MPV from right portal vein (white arrow); (b) The portal venography shows the left portal vein is still patent (white arrow) and tumor thrombus in MPV(black arrow); (c) A ^{125}I seed strand (black arrow) and a stent (white arrow) are placed from left portal vein to MPV and another ^{125}I seed strand is placed into right portal vein (black arrow); (d) In MRI images performed 11 months after the initial procedure shows the stent is still patent.

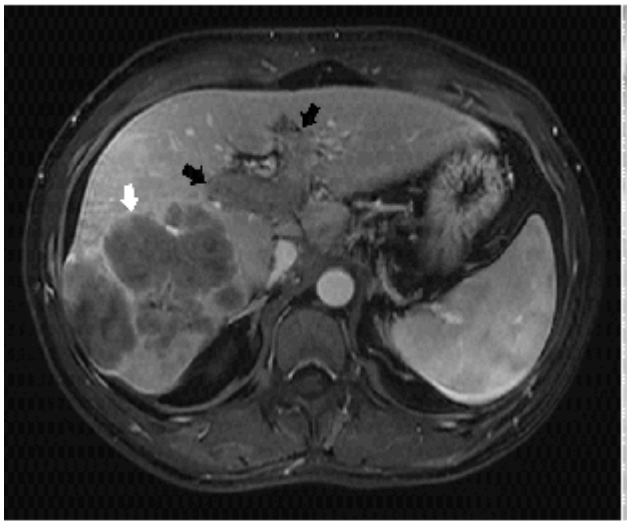

Fig 3 (a)

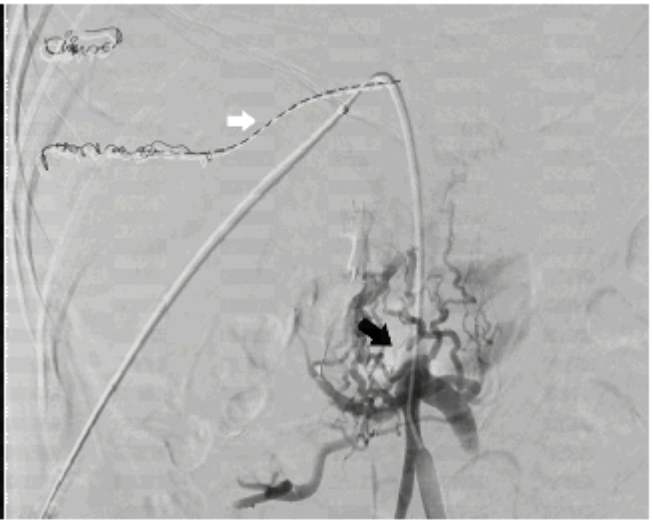

Fig 3 (b)

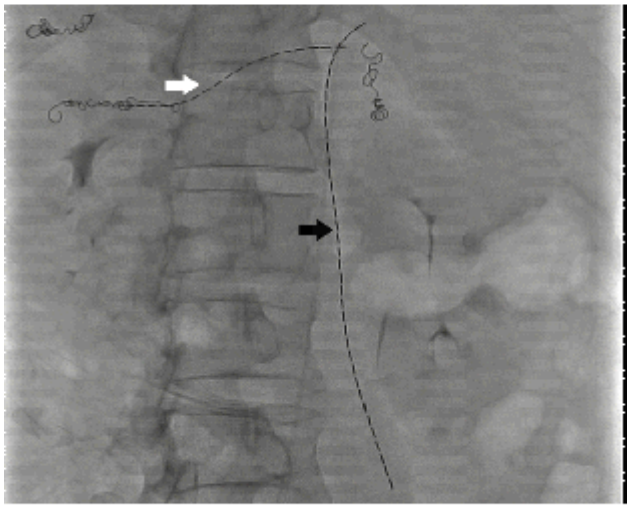

Fig 3 (c)

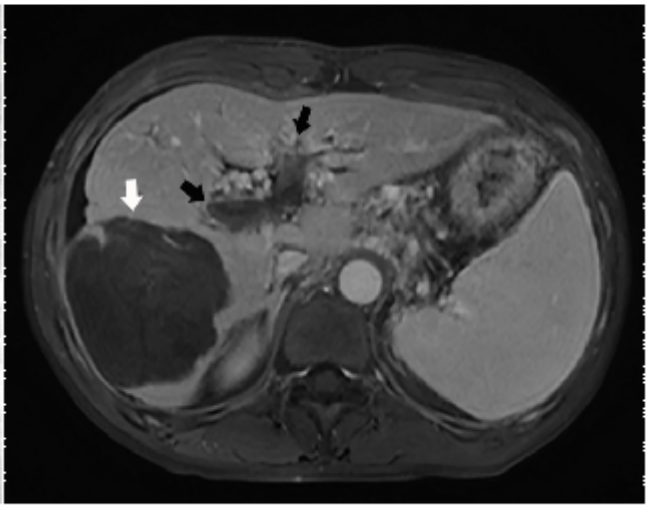

Fig 3 (d)

Figure 3

(a) The MRI images of a 45-year-old man shows a large massive-type tumor in liver right lobe (white arrow), PVTT has invaded from right portal vein to left portal vein (black arrow); (b) The portal venography shows the MPV has been occluded by PVTT(black arrow); (c) A ^{125}I seed strand is placed into right portal vein (white arrow), and another ^{125}I seed strand is placed from left portal vein to MPV (black arrow); (d) The MRI images performed 9 months after the initial procedure, there is no obvious enhancement of intrahepatic tumor (white arrow), the diameter and enhancement degree of PVTT decreased obviously (black arrow).

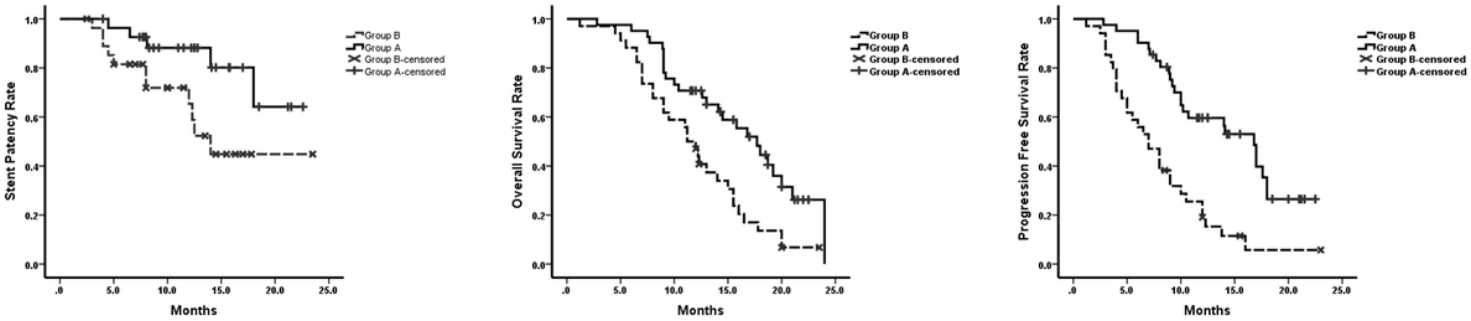

Figure 4

(a) The median stent patency time was not reached in group A and was 14.0 ± 1.5 months in group B (95%CI, 11.1-16.9 months; p = .029)

(b) The mOS was 17.7 ± 1.7 months (95%CI, 14.3-21.1 months) in group A and 11.2 ± 0.9 months in group B (95%CI, 9.5-12.9 months) (p = .003)

(c) The mPFS was 16.8 ± 1.7 (95%CI, 13.7-19.8) and 7.0 ± 1.0 (95%CI, 5.1-8.9) months in groups A and B, respectively (p < .001).