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Evaluating the long-term survival benefits of high intensity focused ultrasound ablation for hepatocellular carcinoma with portal vein tumor thrombus: a single center retrospective study

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ABSTRACT

Aims: To evaluate the long-term survival benefits of high intensity focused ultrasound (HIFU) ablation in patients with hepatocellular carcinoma (HCC) combined with portal vein tumor thrombus (PVTT).

Methods: The data of patients with HCC-PVTT treated with HIFU from January 2014 to December 2019 were retrospectively analyzed. All patients received HIFU ablation for both PVTT and liver tumor in one session. Perioperative adverse events (AEs) were recorded, and follow-up was performed post-operatively. The Kaplan–Meier method was used for survival analysis.

Results: Median follow-up was 13.75 ± 1.31 months. A total of 144 patients (male/female: 122/22, age: 54.15 ± 11.84 years old) were included in the study. A total of 267 liver tumors (tumor number: 1.87 ± 1.65 , range 1–10) were treated with HIFU. The mean $\pm$ SD diameter of viable liver tumors was 100.98 ± 61.65 mm. The reported postoperative AEs of HIFU were skin edema (93.75%), local pain (69.44%) and fever (7.64%). There was no liver failure, gastrointestinal bleeding or perioperative death. The median overall survival (OS) time was 14 months, while the cumulative survival rates of 0.5, 1, 2 and 3 years were 79.0%, 58.6%, 33.3% and 5.9%, respectively. The median OS of PVTT types I, II and III was 22, 13 and 14 months, respectively, and the difference was not statistically significant ($p > 0.05$).

Conclusion: HIFU is a minimally invasive method for HCC-PVTT with fewer complications, which could prolong the OS. Patients with PVTT type III could benefit more from HIFU, compared to types I and II.

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KEYWORDS

Hepatocellular carcinoma; portal vein tumor thrombus; high intensity focused ultrasound ablation; survival analysis; thermal ablation

Background

Primary liver cancer primarily hepatocellular carcinoma (HCC), has high morbidity and mortality rates all over the world, especially in East Asia. In China, it is the fourth most common type of cancer in newly diagnosed cases and the third leading cause of cancer-related mortality [1].

Portal vein tumor thrombus (PVTT) is a frequent and mortal complication of HCC. The mean overall survival (OS) time of patients with HCC-PVTT is only 2.7 months without therapy [2–4]. These patients are prone to rapid disease progression, intrahepatic metastasis within a short time interval, portal hypertension, jaundice, peritoneal effusion and other symptoms, causing serious impact on the OS and quality of life [2].

HCC-PVTT is classified as stage C, according to the Barcelona Liver Cancer Staging System (BCLC), and stage III per the China Liver Cancer Staging System (CNLC) [5,6]. The Expert Consensus of Liver Cancer with Portal Vein Thrombus in China (2018) recommends the adaptation of a multidisciplinary therapy plan for patients with HCC-PVTT who have no opportunity for radical

surgical resection [2]. This plan includes palliative surgery, interventional embolization, targeted therapy, radiotherapy, chemotherapy, local ablation, immunotherapy, etc.

High intensity focused ultrasound (HIFU) ablation is reported to be a safe and effective treatment for liver cancer [7–10] and is recommended by the Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (China, 2019 version) [2]. It has also been reported that HIFU is safe and effective for HCC-PVTT [11–14]. However, the follow-up period of these studies so far is less than 3 years. Therefore, we do this study to investigate the long-term survival benefits of HIFU therapy in patients with HCC complicated with PVTT.

Materials and methods

Data

Patients, ethics approval and consent to participate

HCC patients with PVTT received HIFU treatment from 1 January 2014 to 31 December 2019 were included in this

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study, which was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (Chongqing, China) (538-2020) and performed in accordance with the Declaration of Helsinki. Written informed consent was provided by all patients prior to the study.

Classification standard of PVTT (Cheng's standard) [15]

- Type I₀: tumor thrombus formation is found under microscope.
- Type I: tumor thrombus involving segmental branches of portal vein or above.
- Type II: tumor thrombus involving the left and right branches of portal vein.
- Type III: tumor thrombus involving the main portal vein.
- Type IV: tumor thrombus involving the superior mesenteric vein.

Inclusion criteria and exclusion criteria

Inclusion criteria: (1) HCC diagnosed pathologically or clinically, clinical diagnosis is one of the important diagnostic methods for primary liver cancer, which is recommended by the Standardization for Diagnosis and Treatment of Primary Hepatic Carcinoma (2019 Edition). This guideline recommends a clinical diagnostic roadmap for HCC, including HCC risk factors, imaging features and serological molecular markers (AFP, PIVKA II, etc.) [6]. (2) PVTT diagnosed by enhanced MR or CT or contrast-enhanced ultrasound. (3) Child-Pugh A/B, PS score 0–2 points. (4) At least one measurable tumor. (5) Technical indications for HIFU treatment: lesions with 1 cm or over in diameter can be ablated, while visualized by localization, image fusion and real-time evaluation of HIFU treatment device system [16].

Exclusion criteria: (1) PVTT type IV. (2) Child-Pugh C, PS score 3. (3) Contraindications for anesthesia and HIFU treatment, such as active bleeding, severe cardiovascular and cerebrovascular diseases, acute infection, severe pulmonary dysfunction, etc. (4) Patients living abroad for a long time. (5) HIFU device limitations: The lesion located in a position cannot be reached by the focus of the ultrasound transducer; No safe or effective ultrasound pathway for HIFU treatment due to the occlusion of bony structures or the most important organs; the lesion cannot be effectively covered by the focal field of the HIFU device [16].

HIFU treatment

HIFU device

Focused Ultrasound Tumor Therapeutic System (Chongqing Haifu Medical Technology Co., Ltd., Chongqing, China) is equipped with a diagnostic ultrasound probe and a therapeutic transducer. The diagnostic ultrasound probe (3.5–5.0 MHz) enables real-time ultrasound imaging to determine lesion location and monitor the entire treatment process during HIFU treatment. The transducer parameters (100–300 mm in diameter, 100–250 mm in focal length, 0.5–2 MHz in frequency, 1000–20,000 W/cm² in focusing peak intensity) are key for the conversion of electric energy

into ultrasonic energy and achieving ultrasonic focusing. The focal area is an ellipsoid (3 × 8 mm). The aforementioned parameters have been described previously [17,18].

HIFU operation procedure

Preoperative plans of HIFU treatment should include intrahepatic tumor lesions and PVTT. Some patients need to follow a divided treatment plan or a partial ablation plan for intrahepatic lesions, e.g., when the diameter of intrahepatic tumor lesions is large (>15 cm), the edge of the lesions is too close to the cavity organs (such as stomach, intestine and gallbladder) (<0.5 mm), or when the lesion is complicated with severe cirrhosis or improved Child-Pugh grade B liver function after medical treatment. HIFU treatment (treatment power is less than 400 W, lasting for 2–3 s, interval of 3 s) is performed mainly by spot scanning supplemented with line scanning. The ultrasonic probe, equipped with the HIFU apparatus, is used to monitor the effect and safety of HIFU treatment in a real-time. The end of treatment is marked by mass gray-scale changes in the target area that cover the whole lesion. In absence of mass gray-scale changes during HIFU, the end of treatment is indicated by the lack of microbubble filling with sulfur hexafluoride microbubble (SonoVue, Bracco International B.V., J20180005, Gorizia, Italy) contrast-enhanced ultrasound (CEUS) in the lesions.

Other therapies

Local therapeutics

TACE/TAE and ¹²⁵I seed implantation are often used as adjuvant treatments to HIFU ablation. Their efficacy against HCC-PVTT has been reported by many researchers [2,19–21]. TACE/TAE should be performed by interventional specialists 1–4 weeks before HIFU to treat intrahepatic neoplasms. ¹²⁵I seed implantation can be performed by HIFU doctors in collaboration with nuclear medicine doctors 0–2 days before HIFU ablation, which is mainly for treating portal vein cancer thrombus.

Systemic therapy

If there are no contraindications, HBsAg positive patients are treated with antiviral drugs (entecavir or tenofovir) [6,22]. Targeted therapy is possible with oral Sorafenib (400 mg, bid), or lenvatinib (8 m, weight <50 kg or 12 mg, weight >50 kg; qd). Pembrolizumab or nivolumab or camrelizumab can be used as an immunodrug (PD-1) of choice for immunotherapy (200 mg, iv, Q3W). Systemic therapy should be performed regularly and continuously until the onset of resistance, intolerable side effects, or until patient death [6].

Follow-up and efficacy evaluation

Follow-up and efficacy evaluations were conducted by querying case records and telephone interviews. The number of viable liver tumor lesions and the maximum diameter of each lesion were measured and recorded. The sum of viable

liver tumors lesions was calculated prior to the initiation of the entire treatment plan. The first follow-up was performed 2–4 weeks after HIFU ablation, and the perioperative survival status was recorded. If the patient had died, the cause of death was recorded. Patients were followed up with every 3 months to record their survival. Follow-up ended at the patient's death or at the end of the follow-up period, i.e., 31 December 2019. Patients' survival time (from the completion of HIFU ablation to the end of follow-up) and survival status at the end of follow-up were recorded.

Adverse events

Adverse events (AEs) within seven days after HIFU ablation were recorded. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

Adverse events: (1) skin toxicity immediately after HIFU ablation, including skin edema and burns. (2) Pain (NRS scores), 1–3 for mild pain, 4–6 for moderate pain, 7–10 for severe pain. (3) Hepatic failure. (4) Fever, including: low fever 37.3–38 °C, moderate fever 38.1–39 °C, high fever 39.1–41 °C, ultra-high fever >41 °C. (5) Bleeding, including perioperative gastrointestinal bleeding, tumor rupture bleeding and portal vein vascular rupture bleeding. (6) Perioperative death, the cause being recorded. (7) Others.

Statistical analysis

Statistical analysis was performed using IBM SPSS 25.0 (IBM, Armonk, NY). The measured data are expressed as $\bar{x} \pm s$, and the rate (percentage) of counting data is expressed. Kaplan–Meier's method was used for survival analysis, reverse Kaplan–Meier's method was used for calculating median follow-up, and the log-rank test was used for differences between groups. $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

Median follow-up was 13.75 ± 1.31 months. A total of 182 (182/623) HCC patients with PVTT received HIFU ablation during the study period. One hundred and forty-four out of all the patients met the inclusion criteria (male/female: 122/22). The flowchart of enrolled patients with the exclusion criteria is shown in Figure 1. The mean age of the patients was 54.15 ± 11.84 years (27–85 years old). A total of 267 liver tumors were treated with HIFU ablation. The mean tumor number of the patients was 1.87 ± 1.65 (1–10), and the mean sum of the maximum diameter of viable liver tumors was 100.98 ± 61.65 mm (16.11–352.29 mm). More characteristics of the patient are shown in Table 1.

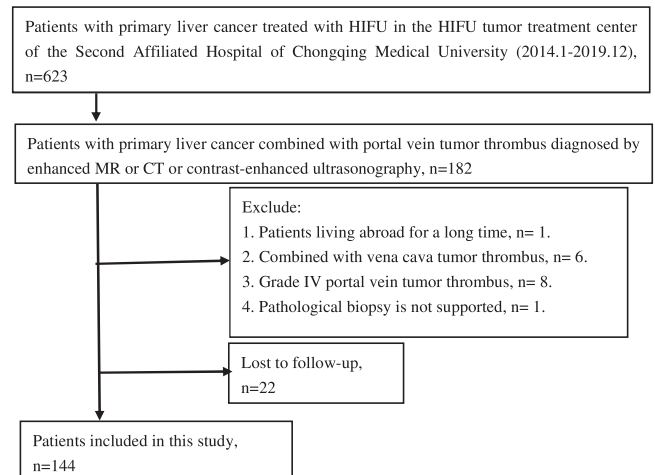


Figure 1. Flowchart of patient selection.

Table 1. Patient characteristics (n = 144).

Characteristics	Results, n (%)
Gender	
Male	122 (84.72)
Female	22 (15.28)
Age, years	
≤60	104 (72.22)
>60	40 (27.78)
Tumor diameter (mm)	
D ≤ 50	27 (18.75)
50 < D ≤ 100	57 (39.58)
D > 100	60 (41.67)
Number of tumors	
≤3	128 (88.89)
>3	16 (11.11)
PVTT type	
I	31 (21.53)
II	72 (50.00)
III	41 (28.47)
HBVsAg, +/- (%)	127 (88.19)/17 (11.81)
Extrahepatic metastasis, yes/no (%)	30 (20.83)/110 (76.39)
Other local treatment	
TACE/TAE	
Yes/no	109 (75.69)/35 (24.31)
¹²⁵ I seed implantation	
Yes/no	76 (52.78)/68 (47.22)
Systemic therapy	
Anti-hepatitis B virus	127 (88.19)
Targeted or PD-1	31 (21.53)

HIFU ablation parameters

All patients received HIFU treatment for liver tumor lesions combined with coexisting PVTT. Except for eight patients (5.56%) who received HIFU treatments twice, all other patients were treated with HIFU once. The HIFU treatment parameters included: average power of 371.42 ± 55.00 W (range 100–450 W), mean sonication time of 1581.99 ± 1289.39 s (108–6149 s), and mean time of HIFU surgery is 122.71 ± 67.47 min, and total therapeutic energy of $594,505.35 \pm 503,620.28$ J (15,300–2,533,388 J). Intravenous anesthesia and general anesthesia were used in 11 (7.64%) and 133 (92.4%) patients, respectively.

Adverse events of HIFU

The main AEs after HIFU ablation were skin edema (93.75%) and pain (69.44%). Other rare AEs included fever (7.64%),

Table 2. Perioperative adverse events of HIFU ablation.

AEs	Results, n (%)	CTCAE
Skin burn	4 (2.78)	
I	1 (0.69)	1
II	1 (0.69)	2
III	2 (1.39)	3
Pain	100 (69.44)	
Mild	88 (61.11)	1
Moderate	8 (5.56)	2
Severe	4 (2.74)	3
Fever	11 (7.64)	
Low	3 (2.08)	1
Moderate	7 (4.86)	2
High	1 (0.69)	3
Peritonitis	2 (1.39)	3
Skin edema	135 (93.75)	1
Intractable hiccups	1 (0.69)	2
Abdominal distention	5 (3.47)	2
Loss of appetite	2 (1.39)	1
Acute kidney injury	1 (0.69)	3
Liver failure	0	4
Perioperative death	0	5
Perioperative bleeding	0	4

Table 3. Overall survival of PVTT and its subgroups.

Variable	Median OS (m)	Mean OS (95%CI) (m)	OS rate (%)			
			0.5 y	1 y	2 y	3 y
I	22	27.99 ± 6.77 (14.71–41.26)	89.6	75.6	34.9	17.5
II	13	16.16 ± 1.71 (1.71–12.82)	73.7	50.1	30.4	No data
III	14	19.64 ± 3.15 (3.15–13.48)	82.3	62.2	49.8	No data
I + II	14	19.95 ± 2.92 (14.22–25.69)	78.3	57.5	30.6	6.1
I + II + III	14	20.29 ± 2.75 (14.91–25.67)	79.0	58.6	33.3	5.9

abdominal distention (3.47%), skin burn (2.78%), peritonitis (1.39%), loss of appetite (1.39%), etc.; CTCAE ≤ 3 (5.0 version) (Table 2). No serious AEs, such as liver failure, bleeding, including perioperative gastrointestinal bleeding, tumor rupture bleeding, portal vein rupture bleeding, or death, were observed during the perioperative period. Among the four patients with skin burn, two patients with grade III skin burn were cured by local surgical debridement, and the other two did not require any intervention. Complications like fever, peritonitis, intractable hiccups, abdominal distention, loss of appetite, and acute kidney injury went away within 2 weeks after HIFU treatment. Pain and skin edema occurred in the HIFU ablation area. Except for severe pain, these patients did not require any special treatment and, in most cases, resolved spontaneously within 2 weeks after HIFU treatment.

Survival

Overall survival

The median OS (MOS) time of the 144 patients with HCC combined with PVTT was 14 months. The cumulative survival rates after 0.5, 1, 2 and 3 years were 79.0%, 58.6%, 33.3% and 5.9%, respectively. The mean OS time was 20.29 ± 2.75 (95%CI: 14.91–25.67) months (Table 3).

Subgroup analysis

Subgroup of PVTT type. In the subgroup of PVTT type, the median subgroup OS was 22 months for type I, 13 months

for type II and 14 months for type III. The mean OS and cumulative survival rates of 0.5, 1, 2 and 3 years are shown in Table 3. There was no significant difference in OS among subgroups of types I, II and III PVTT ($p > 0.05$) (Figure 2(A)). In another subgroup analysis, there were 103 cases of branch tumor thrombus (type I + II) and 41 cases of main tumor thrombus (type III). The MOS was 14.0 months in patients with branch tumor thrombus (type I + II). The cumulative survival rate is shown in Table 3. There was no significant difference in OS between the two subgroups (Log-rank test, $\chi^2 = 2.43$, $p = 0.622$) (Figure 2(B)).

Subgroup of other therapy. In the subgroup of targeted treatment and/or immunotherapy and non-targeted treatment nor immunotherapy, the mean and MOS were 21.92 ± 2.48 (95%CI: 17.06–26.78) and 22.0 months, respectively, in 31 patients (21.53%) receiving targeted treatment and/or immunization. In the non-targeted treatment nor immunotherapy group (113 patients, 78.47%), the mean and MOS were 19.23 ± 2.97 (95%CI: 13.41–25.06) and 14.0 months, respectively. There was no significant difference in OS between the two subgroups (log-rank test, $\chi^2 = 3.799$, $p = 0.051$) (Figure 3(A)). In the subgroup of TACE/TAE ($n = 109$, 75.69%) and non-TACE/TAE ($n = 35$, 24.31%), there was no significant difference in OS between the two subgroups (log-rank test, $\chi^2 = 0.112$, $p = 0.738$) (Figure 3(B)). However, the mean and median tumor sizes in the TACE/TAE group were 105.84 ± 5.20 (95%CI: 95.54–116.15) and 98.56 mm, respectively. In the non-TACE/TAE group, the mean and median tumor sizes were 85.82 ± 13.43 (95%CI: 58.52–113.11) and 54.23 mm, respectively. There were significant differences in tumor size between the two subgroups (nonparametric test, $Z = 3.393$, $p = 0.001$) (Figure 3(C)). In another subgroup of ^{125}I seed-HIFU ($n = 76$, 52.78%) and non- ^{125}I seed-HIFU ($n = 68$, 47.22%), there was no significant difference in OS between the two subgroups (log-rank test, $\chi^2 = 1.75$, $p = 0.186$) (Figure 3(D)).

Discussion

There are 466,100 new diagnosed liver cancer cases and 422,100 cancer-related deaths each year in China [1]. Compared to other hepatic blood vessels, the portal vein is more susceptible to tumor thrombus formed by HCC (44.0–62.2%) [34]. Many researchers have found PVTT to be an independent risk factor for survival of HCC patients [30,31,35,36]. The treatment of HCC-PVTT is difficult and has a MOS of HCC-PVTT of only 2.7 months [2–4] without therapy. Currently, there is no unified treatment scheme for patients. HCC-PVTT is classified as stage C BCLC in European and American countries, for which targeted therapy with sorafenib is the only recommended treatment [5].

In the past 5 years, surgical treatment of liver cancer complicated with type I and type II PVTT has been recommended by consensus among Chinese experts, who believe that a radical cure is possible [2]. Su et al. found that the MOS time of surgical resection for HCC-PVTT patients is 18 months (types I + II + III) [15]. TACE and HAIC are commonly used in

Table 4. OS and AEs of various treatment options for HCC complicated with PVTT.

Author, year	Treatment strategy	Type	Patients (n)	M-OS (m)	C-OSR (%)				Adverse events, %	Refs.
					0.5 y	1 y	2 y	3 y		
Cao et al. [23]	TACE + S	NR	32	11	NR	NR	NR	NR	Hand-foot skin reactions (75), diarrhea (71.9), grade 4–5 AEs (9.3)	[23]
	TACE + A	NR	41	10	NR	NR	NR	NR	Hand-foot skin reactions (73.2), diarrhea (65.9), grade 4–5 AEs (7.2)	
Tang et al. [19]	BSC	Total	62	7.8	NR	NR	NR	NR	NR	[19]
		I	21	7.8	NR	NR	NR	NR		
		II	28	8	NR	NR	NR	NR		
		III	13	7	NR	NR	NR	NR		
	TACE	Total	62	11.3	NR	NR	NR	NR	Fever (45.16), liver dysfunction (41.94), abdominal pain (35.48), grade 3/4 AEs (16.13)	
		I	28	14.3	NR	NR	NR	NR		
		II	23	13	NR	NR	NR	NR		
		III	11	4.5	NR	NR	NR	NR		
Zhang et al. [24]	DEB-TACE + A	NR	35	18	NR	NR	NR	NR	Hand-foot skin reactions (57.1), nausea/vomiting (62.9), hypertension (45.7)	[24]
Munire et al. [25]	DEB-TACE	NR	35	13	NR	NR	NR	NR	NR	
	IMRT + S	NR	30	12	NR	48.6	23.8	NR	Leukopenia and thrombocytopenia (80), hepatic dysfunction (80.7), anorexia (60)	[25]
	IMRT	NR	46	9	NR	34.2	3.5	NR	Leukopenia (67.4), thrombocytopenia (60.9), hepatic dysfunction (58.7), fatigue (52.2)	
Ohkoshi-Yamada et al. [26]	CRT + TACE	NR	9	NR	NR	75	NR	75	NR	[26]
Li et al. [20]	TACE- ¹²⁵ I seed-implantation	NR	27	13.3	NR	NR	NR	NR	Fever (40.7), abdominal pain (33.3), nausea and vomiting (25.9), grade 3 AEs (0)	[20]
	TACE-A	NR	21	10.8	NR	NR	NR	NR	Hypertension (52.4), anorexia (42.4), fever (47.6), grade 3 AEs (52.4)	
Li et al. [27]	PVS + ¹²⁵ I + As ₂ O ₃ + TACE	NR	30	NR	43.7	31.2	NR	NR	Fever (23.3), hemorrhage (6.7), abdominal pain (10.0), grade 3–5 AEs (0)	[27]
Liang et al. [28]	eRFA + TACE	III	12	7.9	NR	NR	NR	NR	Pain and transaminase increases	[28]
Yuan et al. [29]	C + A	Total	63	14.8	87.3	60	NR	NR	Hand-foot skin reaction (52.4), abdominal pain (49.2), hepatitis (46.0), grade 3/4 AEs (28.6)	[29]
		I	32	16	96.9	68.8	NR	NR		
		II	20	15.9	95.0	65	NR	NR		
		III	11	5.8	45.5	27.3	NR	NR		
Ni et al. [30]	TACE-s-MWA	I/II	77	19	NR	NR	NR	NR	Diarrhea (55.8), fatigue (45.5), hand-foot skin (40.3), abdominal pain (19.5)	[30]
Choi et al. [31]	Sorafenib	NR	NR	7.2	NR	NR	NR	NR	Hyperbilirubinemia (34.5), hand-foot syndrome (31.0), AST elevation (27.6)	[31]
	HAIC	NR	NR	14.9	NR	NR	NR	NR	Hyperbilirubinemia (44.8), AST elevation (34.5)	
Su et al. [15]	3D-CRT	Total	134	13	NR	54	33	18	NR	[15]
		I	23	NR	NR	65	39	19		
		II	49	NR	NR	52	35	11		
		III	62	NR	NR	16	3	0		
	HR	Total	189	18	NR	62	47	43	Pulmonary infection (11), liver failure (6), grade 3–5 AEs (0)	
		I	75	NR	NR	83	53	42		
		II	77	NR	NR	55	42	25		
		III	37	NR	NR	11	0	0		
Jia et al. [32]	Yttrium-90 radioembolization (TARE)	Total	722	9.7	NR	NR	NR	NR	Fatigue, nausea/vomiting, abdominal pain	[32]
		I/II	NR	13.4	NR	NR	NR	NR		
		III/IV	NR	6.1	NR	NR	NR	NR		
Lee et al. [33]	proton beam	NR	27	13.2	NR	NR	NR	NR	Grade 3–5 AEs 0	[33]

TACE: transcatheter arterial chemoembolization; S: sorafenib; A: apatinib; BSC: best supportive care; DEB-TACE: drug-eluting transcatheter arterial chemoembolization; IMRT: intensity modulated radiation therapy; CRT: conformal radiation therapy; PVS: portal vein stenting; As₂O₃: arsenic trioxide; eRFA: endovascular radio-frequency ablation; C: camrelizumab; MWA: microwave ablation; 3D-CRT: three-dimensional conformal radiation therapy; HAIC: hepatic arterial infusion chemotherapy; HR: hepatic resection; TARE: transarterial arterial radio-embolization; COSR: cumulative overall survival rate; NR: no report.

the non-operative treatment of HCC with PVTT, often in combination with other treatment regimens, such as sorafenib, apatinib, DEB, radiotherapy, ¹²⁵I seed, RFA, MWA, etc., which

have been studied by many researchers. In these studies, the MOS is reported to be 7.9–19 months [19,20,23,24,26,28,30]. Radiotherapy is one of the therapeutic strategies for

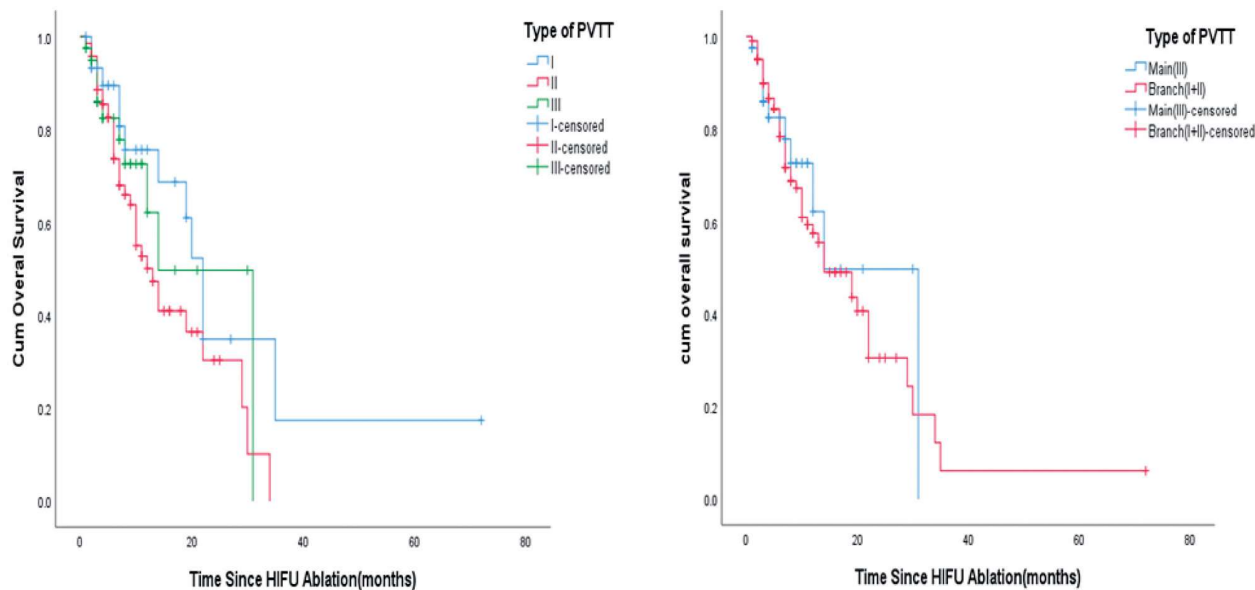


Figure 2. (A) Kaplan–Meier’s curves show OS of PVTT type I, II and III. (B) Kaplan–Meier’s curves show OS of main (type III) and branch (type I + II) PVTT.

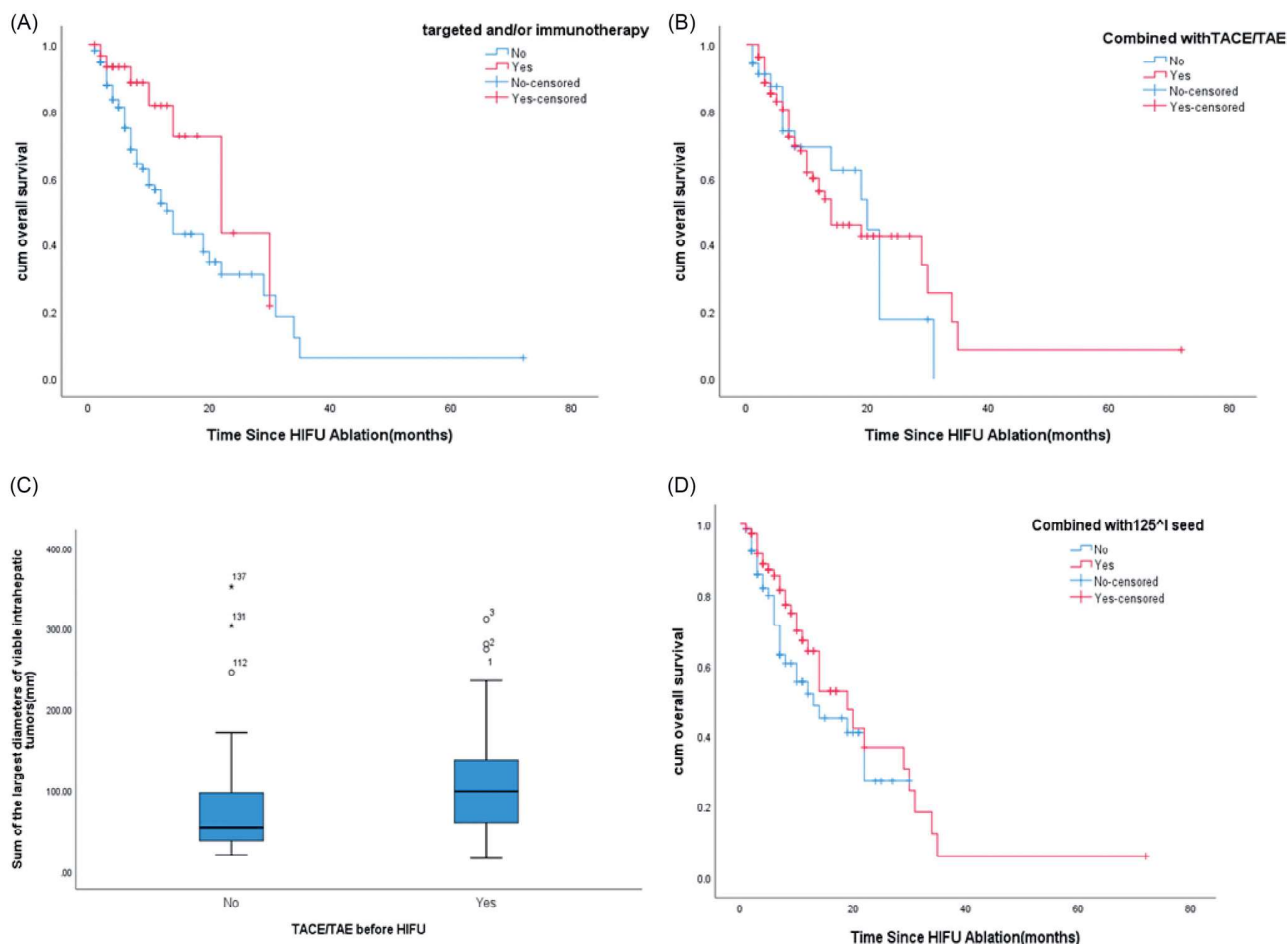


Figure 3. (A) Kaplan–Meier’s curves show OS of targeted and/or immunotherapy and non-targeted nor immunotherapy. (B) Kaplan–Meier’s curve shows the OS of TACE/TAE and non-TACE/TAE. (C) Boxplots show the tumor size of TACE/TAE and non-TACE/TAE. (D) Kaplan–Meier’s curve shows the OS of ^{125}I seed-HIFU and non- ^{125}I seed-HIFU.

HCC-PVTT patients and can also be combined with other therapeutic options. Radiotherapy includes external radiotherapy (3DCRT, IMRT, SBRT) and internal radiotherapy

(e.g., ^{125}I seed implantation therapy and YI-90 microsphere therapy (TARE)). Some studies report a MOS of 9–13.3 months [15,25–27, 32,33]. Systemic therapies, such as targeted

therapy (sorafenib, lenvatinib, apatinib, etc.), PD-1 therapy (pembrolizumab, nivolumab, camrelizumab, etc.), chemotherapy and supportive therapy, are recommended for the treatment of HCC at stage BCLC-C and CNLC-III. The MOS has been reported as 7.2–14.8 months in some researches [19,29,31].

Clinical studies have demonstrated good clinical effects of high-intensity focused ultrasound ablation in the treatment of both small and large liver cancer [9–12,18,37]. Meta-analyses have shown that HIFU combined with TACE can safely improve the long-term survival rate [7,38,39]. However, there are few studies on HIFU therapy for HCC-PVTT patients. For instance, Zhu et al. reported that PVTT were treated with HIFU [8]. Subsequently, other researchers, with follow-up of 12–36 months, found that HIFU treatment of HCC-PVTT was safe and effective and could prolong the survival of patients [12–14]. In this study, we conducted a 6-year retrospective study of HIFU therapy on 144 patients with HCC-PVTT whose mean OS was 20.29 ± 2.75 years (95%CI: 14.91–25.67), MOS was 14 months, and cumulative survival rates at 0.5, 1, 2 and 3 years were 79.0%, 58.6%, 33.3% and 5.9%, respectively. We found that these results are similar to those of other scholars, indicating that HCC patients with PVTT could benefit from HIFU treatment.

HBV infection is the main cause of primary liver cancer in China [40], and antiviral therapy is the main treatment for HCC complicated with HBVsAg positive, as recommended by liver cancer treatment guidelines [6,22,41]. In our study, 127 of the 144 patients (88.19%) were HBVsAg positive and received anti-HBV therapy.

In recent years, targeted therapy and PD-1 therapy have become the recommended systemic therapies for advanced liver cancer with reported clinical efficacy (Table 3) [20,23,29,30]. In our study, only a small proportion of patients (31 patients, 21.53%) received targeted and/or immunotherapy. Only recently (2018), new antitumor drug therapy specifications were released in China [42]. Since only some targeted or immunotherapy drugs were available for medical insurance reimbursement, some HCC-PVTT patients failed to receive any targeted therapy or treatment plan. In this study, subgroup analysis revealed a MOS time of 22 and 14 months in patients who received and did not receive targeted nor immunotherapy, respectively. The observed difference in OS between the two subgroups did not reach statistical significance ($p = 0.051$). Although there may be some bias due to the large difference in the number of cases between the two groups (31 vs. 113), we believe that patients can benefit more from combination therapy.

TACE is recommended for the treatment of HCC with PVTT. However, because the efficacy of TACE largely varies, experts suggest combining it with other therapies [2,43]. Some researchers reported that TACE-HIFU in the treatment of HCC with PVTT achieved good clinical effects without serious AEs [12,13,44]. TACE is the first-choice therapy for patients with unresectable liver cancer, liver tumor lesions with abundant blood supply, or large lesions. TACE/TAE treatment before HIFU ablation can increase the therapeutic effect [37]. HIFU alone can also achieve good ablation results in small lesions or tumors with poor blood supply [45]. In our study, 109 patients (75.69%) were treated with TACE/TAE before HIFU. In the HIFU + TACE/TAE group, the average and

median viable tumor diameters were 105.84 ± 5.20 and 98.56 mm, respectively. In the HIFU + non-TACE/TAE group, the mean and median tumor diameters were 85.82 ± 13.43 and 54.23 mm, respectively. The difference in the tumor size between the two subgroups was statistically significant (non-parametric test, $Z = 3.393$, $p = 0.001$), unlike the difference in OS (log-rank test, $\chi^2 = 0.112$, $p = 0.738$). The combination therapy achieved an equal survival benefit for patients with different tumor sizes.

Radioactive particle implantation is an alternative method for the local treatment of HCC and PVTT [2,6]. Some studies have reported that TACE/TAE + ^{125}I seed implantation has better clinical efficacy than TACE in the treatment of HCC complicated with PVTT [21,46]. Yang et al. reported 1st- and 2nd-year cumulative survival rates of 47.4% and 7.9% for HCC-PVTT patients treated by HIFU combined with ^{125}I seed implantation, respectively, with a mean OS of 11.6 ± 3.0 months. The MOS of patients with types I, II and III PVTT was 13.5, 7.0 and 4.0 months, respectively. No serious complications, such as massive bleeding, tumor embolus shedding and acute liver failure, were observed during surgery or 72 h post-operation [14]. In our study, a total of 76 patients (52.78%) received ^{125}I seed therapy before HIFU, including 15 patients (48.39%) with type I PVTT, 38 patients (52.78%) with type II PVTT and 23 patients (56.10%) with type III PVTT. There was no significant difference between the HIFU + ^{125}I seed group and the HIFU group in OS (log-rank test, $\chi^2 = 1.75$, $p = 0.186$). Both subgroups had an equal OS benefit.

Most researchers believe that there is a significant difference between the degree of invasion and prognosis of PVTT, especially type III tumor thrombus invading the main portal vein [15,19]. Some researchers reported a MOS of 4.5–7.9 months for HCC with PVTT treated with 3D-CRT, hepatectomy, TACE and other treatments [15,19,28,29,32]. Interestingly, in our retrospective study, it was found that the MOS of PVTT was 22, 13 and 14 months for types I, II and III, respectively. Table 3 displays the mean survival time and cumulative survival rate at 0.5, 1, 2 and 3 years, indicating that the three types of PVTT had the same clinical benefit. In particular, HIFU therapy for HCC patients with type III PVTT achieved a good clinical benefit and prolonged survival time. Cheng et al. reported that the growth characteristics of PVTT are reverse flow centrifugal development, with an average growth rate of $0.5 \pm 0.1 \text{ cm}^3/\text{m}$ and a monthly development length of $1.2 \pm 0.4 \text{ cm}$ [47]. Zhang found that 3 months after treating PVTT with HIFU and ^{125}I , the mean and median invasion distances of tumor thrombus were 5.94 and 0 mm, respectively [48]. Importantly, the growth rate of PVTT decreased after treatment, which is beneficial to maintain liver function and blood circulation. This result supports the clinical benefits of HIFU and ^{125}I treatment for type III HCC-PVTT patients.

Obviously, the adverse vascular events associated with HIFU ablation in PVTT patients have been the focus of attention. No HIFU-related blood vessel events have been revealed by morphology examinations (enhanced CT/MRI) or functional examination after HIFU ablation for liver and pancreatic cancer [11,49,50]. Therefore, we believe that HIFU treatment of PVTT does not increase portal vein adverse vascular events. In our study, we found no HIFU-related portal

vein AEs, such as portal vein rupture and hemorrhage or upper gastrointestinal bleeding associated with portal hypertension, which indicates that HIFU is safe for the treatment of HCC-PVTT patients.

In our retrospective study, postoperative AEs after HIFU treatment were mainly local toxic skin reactions in the treatment area, including skin edema (93.75%) and local pain (69.44%). The incidence of other AEs was low, and no AEs above CTCAE grade 4 occurred. This finding is similar to that reported by Illing et al. [51]. According to the incidence of AEs of other treatment regimens, as shown in Table 4, the patients included in our study were older (>60 years old, 27.78%), with large liver tumor lesions (intrahepatic lesions >100 cm, 41.67%), accompanied by extrahepatic metastatic lesions (20.83%) (Table 1). However, these adverse factors did not lead to an increase in AEs after HIFU ablation has small AEs and can be used in combination with other therapies to achieve a good survival benefit for patients with HCC complicated with PVTT.

Despite promising results, this study has some shortcomings. Since it is a single-center retrospective study, the possibility of potential selection bias cannot be ruled out. Second, the long-term survival benefit of patients with HCC combined with PVTT treated by HIFU ablation was investigated without comparison to patients who did not receive HIFU ablation.

Conclusion

The comprehensive modality that combines high-intensity focused ultrasound ablation with systemic therapy is an effective treatment strategy with high safety and few complications, which could prolong the OS of patients with HCC and PVTT.

Author contributions

Conception and design of the project (BJ, ZH and KZ), performance of experiments, obtainment and analysis of data (XC, YhM, JZ, WY, CBJ, LfR), writing of the manuscript (XC), and critical revision of the manuscript (KZ). All authors read and approved the final manuscript.

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Data availability statement

All data are available upon request.

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