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CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

Safety and Feasibility of Helical I-125 Seed Implants Combined with Transcatheter Arterial Chemoembolization in Hepatocellular Carcinomas with Main Portal Vein Tumor Thrombus

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Abstract

Purpose To investigate the feasibility and safety of a helical iodine-125 (I-125) seed implant combined with transcatheter arterial chemoembolization (TACE) for the treatment of hepatocellular carcinoma (HCC) with main portal vein tumor thrombus (MPVTT).

Methods From December 2016 to February 2018, 26 cases of HCC with MPVTT patients were enrolled in this prospective study. Helical I-125 seed implants were placed into the portal vein through the percutaneous transhepatic route. Subsequently, TACE was performed. Follow-up with enhanced CT was performed every 6–8 weeks and TACE was repeated if the residual or recurrent tumor was found. Treatment response was measured with the modified response evaluation criteria in solid tumors. Complication rates and overall survival were also evaluated.

Results Implantation and TACE were successful in all patients. There were no grade $\geq$ 3 complications observed in the patients. The objective response rates (ORR) and disease control rates (DCR) of MPVTT at 3 months after implantation were 42.3% and 84.6%, respectively, whereas ORR and DCR of the liver lesions were 34.6% and 46.2%, respectively. The median overall survival was 10.7 months (95% CI 6.2–15.2 months).

Conclusion Helical I-125 seed implants can be safely placed into the human main portal vein. Helical I-125 seed implants combined with TACE for HCC with MPVTT are safe and feasible.

Keywords Hepatocellular carcinoma · MPVTT · Helical I-125 seed implant · Endovascular brachytherapy · TACE

Introduction

Hepatocellular carcinoma (HCC) is a common malignancy with 12.5–39.7% of patients presenting with portal vein tumor thrombosis (PVTT) at the time of diagnosis [1–4]. The prognosis for HCC patients with PVTT is poor with an overall survival of only 2.7–4.0 months [1–4]. While oral sorafenib has been the standard treatment, its effectiveness is limited [5, 6]. However, transarterial chemoembolization (TACE) can effectively inhibit the progression of liver disease, yet the outcome for patients with PVTT has been suboptimal [7]. There are ongoing investigations of TACE-based combined therapies, including iodine-125 (I-125) seed endovascular brachytherapy [7–15].

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Zhang et al. [12] first demonstrated TACE combined with direct implantation of I-125 seeds into the tumor thrombosis for the treatment of HCC with PVTT. The feasibility and effectiveness of the treatment were confirmed by Huang et al. [7]. However, the treatment efficacy for main portal vein tumor thrombus (MPVTT) was unsatisfactory. To improve the effectiveness of I-125 seed endovascular brachytherapy for MPVTT, I-125 seed strands combined with stents alone or stents loaded with seed were developed, which yielded satisfactory outcomes for treatment of MPVTT [13–15]. Both treatment methods relied on the stent to restore the blood flow of the portal vein from the occlusion in the hepatic arteries during TACE, in which occlusion could eventually lead to liver failure. In recent years, some studies have shown that TACE or TACE-based combination therapies were safe and effective for the treatment of HCC patients with MPVTT without stents [7, 9–12]. These studies have suggested that stents are not necessary for effective combination treatment with TACE and I-125 seed endovascular brachytherapy. Seed strands or seed alone require stents to fix and compress against the portal vein or tumor thrombosis for the therapeutic effect of endovascular brachytherapy. However, stent implantation would significantly increase the surgical damage, risk, and difficulty.

Our team has developed a helical I-125 seed implant that can self-attach and fix itself in the portal vein for endovascular brachytherapy [16]. The helical I-125 seed implant requires no stent implantation, which can minimize the surgical injury, risk, and difficulty. In this study, the feasibility and safety of helical I-125 seed implants combined with TACE are assessed for the treatment of HCC with MPVTT.

Materials and Methods

Design and Patients

This study was a single-center prospective study, which was approved by the local ethics committee. Informed consent was provided from all patients. As a prospective pilot study, the current study included all cases from a single center in a period of approximately 12 months to investigate the feasibility and safety of helical I-125 seed implants combined with TACE for the treatment of HCC with MPVTT. If there were any serious complications, such as acute liver failure, gastrointestinal perforation, acute extensive portal vein thrombosis, or abdominal hemorrhage, the treatment was considered unsafe. If there was a significant displacement of the helical implant, it was considered unfeasible.

From December 2016 to February 2018, a total of 26 cases of HCC with MPVTT were consecutively enrolled. The inclusion criteria were: (1) clinical or pathological diagnosis of HCC; (2) PVTT Cheng's classification type III [17]; (3) aged 18–75 years; (4) Child–Pugh classification A or B; (4) Eastern Cooperative Oncology Group performance status (ECOG PS) scores ≤ 2. The exclusion criteria were: (1) prior treatment for PVTT; (2) extrahepatic metastases; (3) patients with severe heart, lung, kidney, brain and other vital organ disorders; (4) presence of other malignancies; (5) TACE contraindications including (a) diffuse liver cancer or tumor volume exceeding 70% of the whole liver; (b) refractory massive ascites; (c) total bilirubin > 51 μmol/L and/or albumin < 28 g/L, which failed to improve after symptomatic treatment; or (d) active infection; (6) candidates who commenced sorafenib.

The clinical diagnosis of HCC was based on the practice guidelines of the American Association for the Study of Liver Disease (AASLD), while tumor stage was determined with the Barcelona Clinic Liver Cancer (BCLC) staging system. PVTT was classified based on tumor thrombosis type system (Cheng's classification type) [17]. Portal vein tumor thrombus was diagnosed when the filling defect in portal vein was found in the portal vein phase, and the filling defect could be enhanced in the arterial phase on contrast-enhanced CT or MRI examination. If CT or MRI examination was not clear, enhanced ultrasound examination was performed. If the thrombus was enhanced on ultrasound examination, it was considered a tumor thrombus.

Of the cases, 23 of the 26 were males. There were 19 clinically diagnosed cases, 7 pathological diagnosed cases, 15 Grade A Child–Pugh cases, 11 Grade B child–pugh cases, 11 cases without previous treatment, and 15 cases with previous treatment. All MPVTTs were Cheng's classification type III and the average length of the main portal vein tumor thrombus was 43.2 ± 8.5 mm, of which 10 were portal occlusion and 16 were stenosis. The baseline characteristics of the patients are shown in Table 1.

Helical I-125 Seed Implant Preparation and Implantation

I-125 seeds were purchased from Ningbo Junan Pharmaceutical Technology Co., Ltd. (model 6711) with 0.8 mm diameter and 4.5 mm length. Seed activity was 0.5 mCi (18.5 MBq) with a half-life of 59.6 days. I-125 emits 35.5 keV γ-ray, 27.4 keV, and 31.4 keV X-rays with an equivalent tissue half value layer (HVL) of 17 mm. The radiation dose was chosen based on the preclinical study of helical I-125 implant in pigs [16] and other clinical studies of I-125 seed strands combined with stents alone or stents loaded with seed [13–15].

Table 1 Patient characteristics

Clinical characteristics	No. of patients
Age (years)	
≤ 60	16
> 60	10
Sex	
Male	23
Female	3
HBsAg	
Negative	4
Positive	22
Child–Pugh score	
A	15
B	11
ECOG PS	
0	2
1	13
2	11
Liver cirrhosis	
No	12
Yes	14
Morphology	
Multinodular	10
Diffuse	10
Massive	6
Portal vein stenosis	
Stenosis	16
Occlusion	10
AFP, ng/mL	
≤ 400	18
> 400	8
HCC diagnostic method	
Clinical diagnosis	19
Pathological diagnosis	7
Previous treatment	
No	11
Yes	15

Liver cirrhosis, cirrhosis of the liver in this study refers to imaging diagnosis, rather than pathological diagnosis. Abbreviations: *HCC* hepatocellular carcinoma, *ECOG PS* Eastern Cooperative Oncology Group performance status scores, *BCLC stage* Barcelona Clinic Liver Cancer stage

Helical I-125 seed implants (Patent No. 201621449026.5, Zhejiang Barty Medical Technology Co., Ltd, Hangzhou, China) were composed of helical sleeves with I-125 seeds (Fig. 1). Helical sleeves (diameter and pitch of 15 mm) were made from a 4F angiocatheter, in which both ends were sealed with heat. The surgeon wore lead gloves as radiation protection measures during implantation.

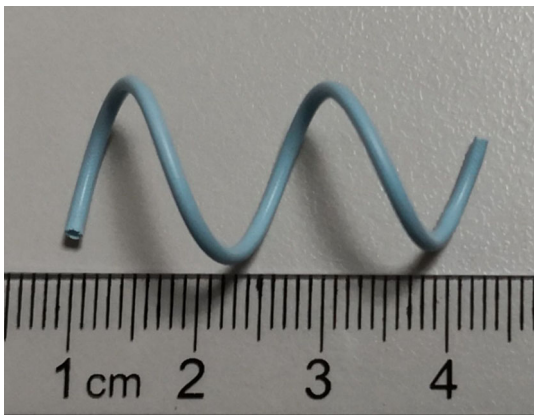

Fig. 1 Helical I-125 seed implant shaped from a 4F angiocatheter with diameter of 1.5 cm (15 mm) and pitch of 1.5 cm (15 mm)

Upon complete construction of the implant, the diameter was 20 mm (d) and the pitch was 23 mm (p). The implant would form a helical geometry that surrounded the tumor thrombosis after implantation. When the tumor thrombosis was smaller or larger than the diameter of the portal vein, the implant expanded to the diameter of the portal vein or tumor thrombosis. In addition, pitch changed with the diameter of the implant. In particular, pitch decreased with larger implant diameters and increased with smaller implant diameters. The pitch after implantation $p_{1} = \sqrt{[(p^2) + (\pi d)^2 - (\pi d_1)^2]}$, where d_1 is the diameter of main portal vein (or diameter of tumor thrombosis, whichever is largest), p is the pitch before implantation (23 mm), and d is the diameter of the helical implant before implantation (20 mm).

The number of I-125 seeds placed within the helical sleeve depended on the full length (L_1). Maximum sleeve length $L_1 = H^*[\sqrt{(p^2) + (\pi d)^2}]/p_1$, where H is the tumor thrombosis length (or treatment length), p_1 is the pitch after implantation, p is the pitch before implantation (23 mm), and d is the diameter of the helical implant before implantation (20 mm). Based on the I-125 seed length of 4.5 mm, the number of I-125 seeds was equal to L_1 divided by 4.5 (mm).

An ultrasound-guided, 22-gauge Chiba needle (Cook, Inc., Bloomington, IN, USA) was used to puncture the left or right portal vein secondary branch. A micro-guidewire was introduced to the portal vein, which was confirmed by injection of contrast agent. It was followed by replacement of a stiff guidewire. A 55-cm 4F sheath (Cook, Inc.) was then delivered along the guidewire to the portal vein, in which the tip of the sheath reached the distal end of the main tumor thrombus. The helical I-125 seed implant was loaded in the sheath and deployed in the portal vein at the site of MPVTT by pulling back sheath. Following implant

deployment, the intrahepatic puncture tract was embolized with coils.

TACE Treatment

TACE was performed directly after implantation. After diagnostic angiography, the microcatheter (Renegade, 2.8F; Boston Scientific Corporation, USA) was delivered to tumor feeding arteries, in which the mixture of lipiodol (Lipiodol ultra-fluid, 480 mg I/mL; Guerbet, France; diluted with surface water solution; lipiodol: Pirarubicin water solution ratio = 2:1) was slowly infused. Lipiodol (5–15 mL) and pirarubicin (20–40 mg) were injected. Embolization was performed by gelatin sponge particle embolic agent (350–560 μm; Hangzhou Aili Kang Pharmaceutical Technology Co. Ltd., China) until the blood supply to the tumor was stagnant. If the residual or recurrent tumor was found during the follow-up visit, TACE was repeated. TACE was not performed if liver function declined to Child–Pugh Grade C or if the ECOG PS score increased to 3 points or more.

Postoperative Treatment and TPS Dose Verification

Liver protection medication (including magnesium isoglycyrrhizinate, reduced glutathione, and ademetionine 1,4-butanedisulfonate) was given 1 week after implantation and TACE in the hospital. Anticoagulation drugs were not administered. Single-photon emission computed tomography combined with computed tomography (SPECT-CT) examination was performed on the second day after implantation to evaluate the radiation dose distribution of helical I-125 seed implant.

Abdominal contrast-enhanced CT was performed 3 days after implantation. Images (5 mm thickness) of the portal venous phase in DICOM format was imported into the three-dimensional radiation treatment planning system (TPS, FtzyPlan1.3.118, Beijing FTT Technology Co., Ltd.). The target (MPVTT) was delineated and I-125 seeds were identified. Seed activity and prescription were recorded into the TPS and the dose–volume histograms (DVH) and other dosimetry parameters (e.g., 90% target volume dose, D90) were computed.

Follow-Up and Endpoint Evaluation

The follow-up duration ranged from 3.6 to 20.0 months. Follow-up included relevant laboratory tests (blood routine, blood coagulation routine, liver, and kidney function) and chest and abdomen enhanced CT examination every 6–8 weeks. Treatment response was assessed after 3 months, which was more than a half-life. Two radiologists with more than 15 years of experience, who were blinded to the patient and clinical data, evaluated the treatment response of MPVTT and liver lesion based on modified response evaluation criteria in solid tumor (mRECIST) using objective response rate (ORR = complete response (CR) + partial response (PR)), disease control rate (DCR = CR + PR + stable disease (SD)) and progressive disease(PD). Overall survival (OS), which was defined as the time between helical I-125 seed implant implantation and the patient's death or last follow-up, was recorded. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE Version 3.0).

Statistical Analysis

Data are presented in mean ± standard deviation unless otherwise specified. All statistical analysis was performed using IBM SPSS Statistics Version 19.0 (IBM, Armonk, NY, USA). Repeated measures analysis of variance (ANOVA) was used to compare the overall differences between hematological indices at different time points. Survival was analyzed by the Kaplan–Meier test. P values < 0.05 were considered statistically significant.

Results

Helical I-125 Seed Implant Implantation

After implantation, the helical I-125 implants self-expanded and attached to the portal vein across the tumor thrombosis (Fig. 2). Implantation was successful in all patients. All patients received one helical implant. The average number of I-125 seeds in the implant was 15.6 ± 1.9 (range 12–18) and the average radioactivity of each helical implant was 7.8 ± 0.9 mCi (range 6.0–9.0 mCi). CT imaging at Day 3 showed no displacement of the helical implant that surrounded the tumor thrombosis (Fig. 3). The TPS dose calculation showed that the average D90 of the target was 60.7 ± 4.2 Gy. Day 2 SPECT-CT imaging showed a helical dose distribution that surrounded the tumor thrombosis (Fig. 4).

TACE Treatment After Implantation

Each patient received more than one TACE treatment (average number of TACE treatment = 2.9 ± 1.0 times). Eleven cases received 2 TACE, 8 cases received 3 TACE, 5 cases received 4 TACE, and 2 cases received 5 TACE.

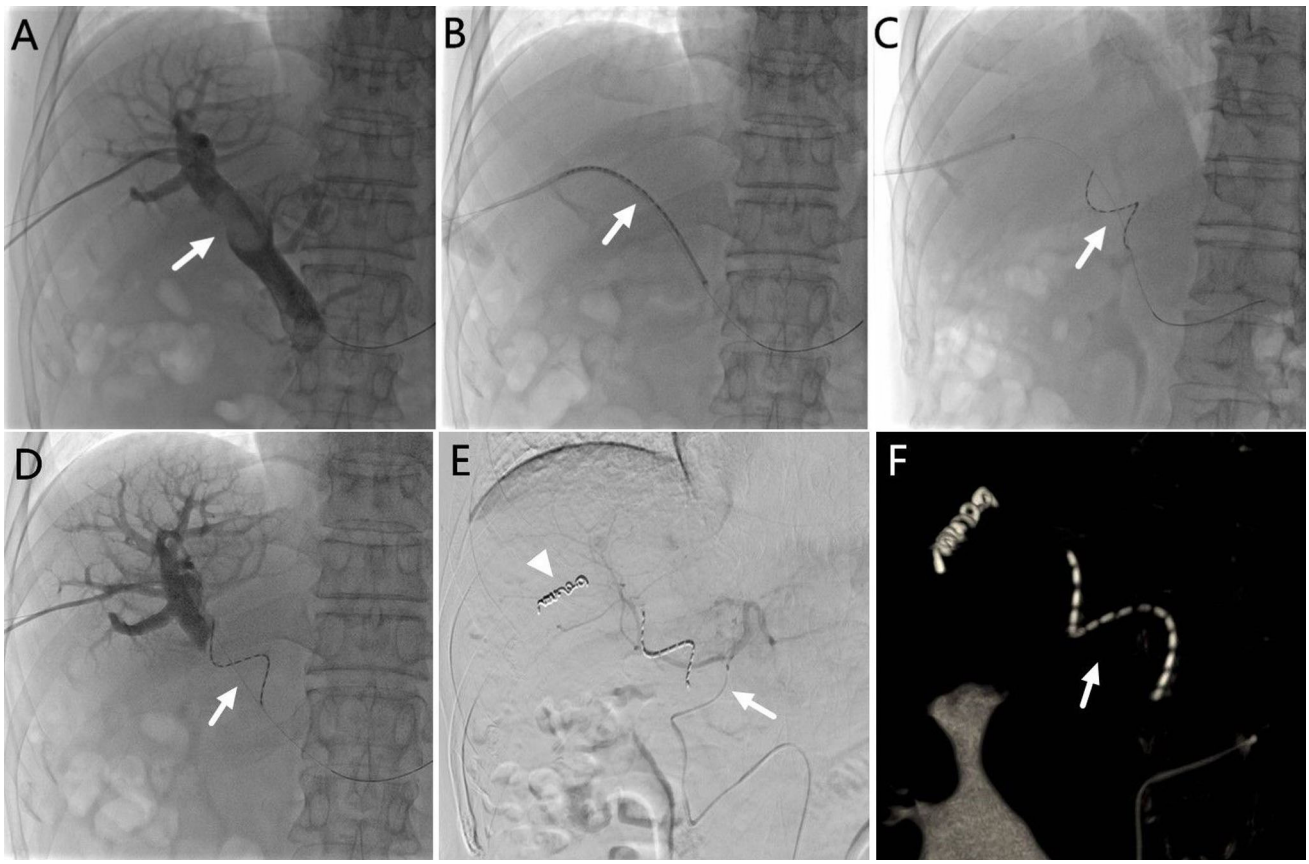

Fig. 2 Helical I-125 seed implantation through percutaneous transhepatic route. **A** Portal venography shows showed MPVTT (white arrow) and 4F catheter sheath; **B** helical I-125 implant in the full lengthen state (white arrow) inside the catheter sheath; **C** implant was unloaded into the target area from the catheter sheath forming a helical geometry (white arrow); **D** portal venogram through the sheath showed that the helical I-125 seed implant was fixed to tumor thrombosis (white arrow); **E** microcatheter (white arrow) for TACE; coil (arrow head) embolization was used in the intrahepatic puncture tract; **F** cone beam CT after implantation (white arrow)

Safety Evaluation

No abdominal bleeding, acute portal vein thrombosis, procedure-induced complications, or related death were found after helical I-125 seed implant implantation and TACE. One week after the combined treatment, the majority of patients showed various degrees of post-embolization syndrome (abdominal pain, nausea, vomiting, or fever), which were relieved after symptomatic treatment. One week and 2 months (corresponding to the first half-life of I-125) after the combined treatment, no significant differences in the blood test were found (Table 2). There were three grade I and a grade II liver toxicity. Grade I and II blood or bone marrow toxicities were found in one patient each. Grade III or higher toxicity was not found. Throughout the follow-up period, no acute liver failure, radiation-induced hepatitis, radiation-induced gastroenteritis, signs of portal vein thrombosis, abscess, septic thrombophlebitis or helical implant displacement were found.

Objective Response Rate, Disease Control Rate, and Overall Survival

Three months after the combined treatment, the ORR, DCR and PD of MPVTT were 42.3, 84.6, and 15.4%, respectively (Fig. 3), whereas the ORR, DCR, and PD of the liver lesions were 34.6, 46.2, and 53.8%, respectively. The median overall survival of the patients was 10.7 months (95% CI 6.2–15.2 months).

Discussion

In this study, all 26 implantations were successful, in which the implants self-expanded and attached to the portal vein across the tumor thrombosis for local control. Helical I-125 seed implants combined with TACE was feasible and safe for the treatment of HCC with MPVTT.

In 2011, Luo et al. [13] showed that the effectiveness of seed strands combined with stent placement in treating severely obstructed main portal vein was lower than

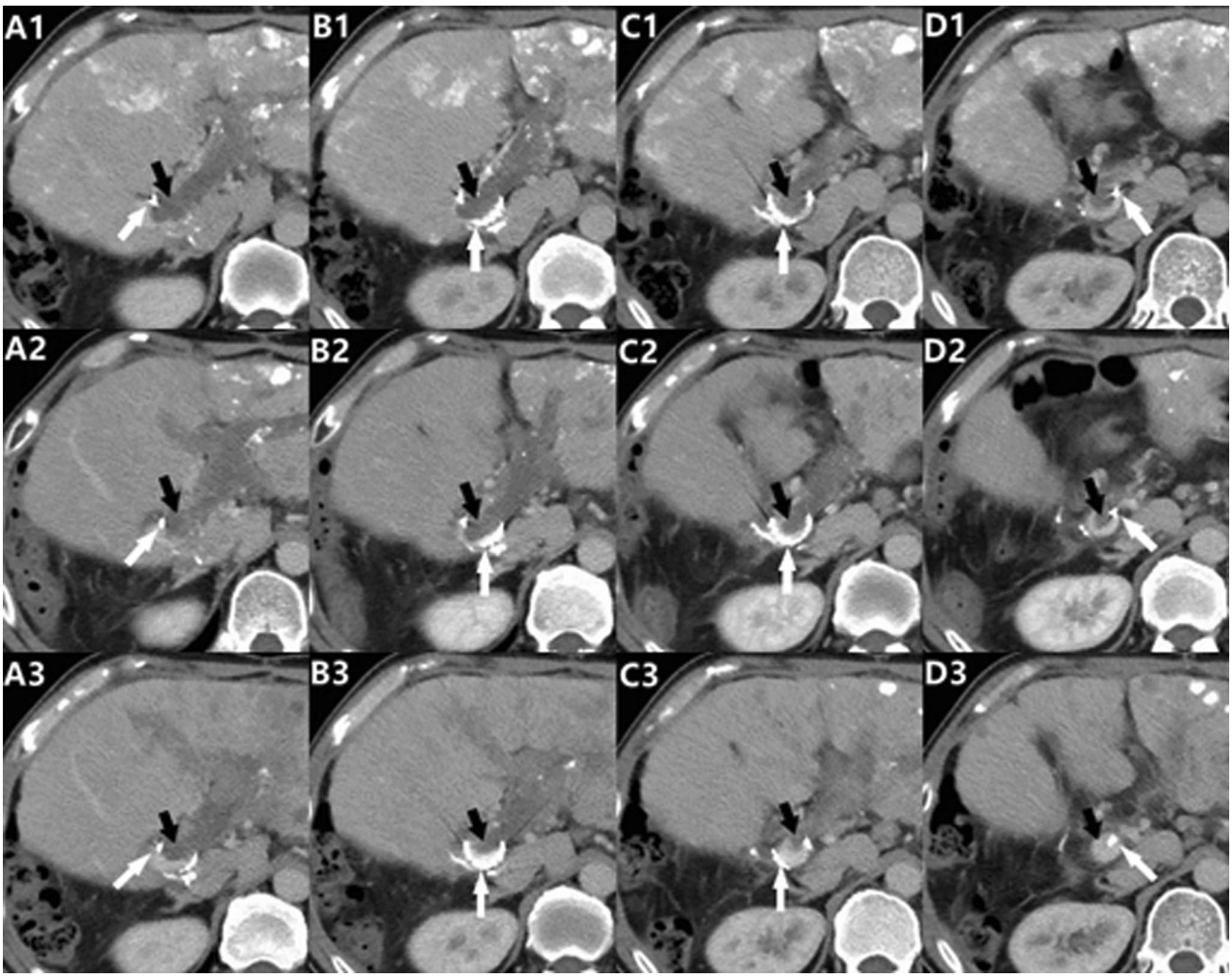

Fig. 3 Contrast-enhanced CT of the helical I-125 seed implant in main portal vein (same patient as Fig. 2) showing the implant (white arrow) wrapped around main portal vein tumor thrombosis (black arrow) in a helical geometry. A1–D1) Enhanced CT 3 days after implantation; A2–D2) Enhanced CT 1.5 months after implantation showing shrinkage of main portal vein tumor thrombosis; A3–D3) Enhanced CT 3 months after implantation showing further shrinkage of main portal vein tumor thrombosis reaching partial response

partially obstructed main portal veins. Yang et al. from the same team suggested that the seed strand alone, which lowered surgical failure and complication rates, was preferred in patients with a severely obstructed main portal vein. It was later verified that TACE, when combined with seed strand for HCC with MPVTT, in severely obstructed main portal veins was feasible, safe, and effective [18]. For safety considerations, selective TACE was preferred to avoid blocking of the arterial blood flow to normal liver tissue. Upon partial or complete blockade of the portal vein, as well as the establishment of the surrounding collateral circulation, portal vein blood flow to normal liver tissue in certain extent shall be retained. As for feasibility consideration, the seed strand was fixed and pressed against the portal vein and tumor thrombosis in the obstructed portal vein for endovascular brachytherapy. However, the seed strand may displace when the portal vein was recanalized [18]. In partially obstructed portal veins, the seed strand could not be fixed and was pressed against the portal vein and tumor thrombosis by the stent. The current study demonstrated that helical I-125 seed implants self-expanded and attached to the portal vein. The helical I-125 seed implant altered its diameter to fit the various sizes of portal veins and tumor thrombosis for endovascular brachytherapy. Implantation of the seed strand combined with stent or stent loaded with seed utilized the 10–12F catheter sheath, while the 4F catheter sheath used for the helical I-125 seed implants reduced the risk of trauma. Moreover, implantation of the seed strand combined with a stent or stent loaded with seed was complicated [13–15]. On the contrary, the helical I-125 seed implant was flexible and straight when stretched. It could reshape itself into the

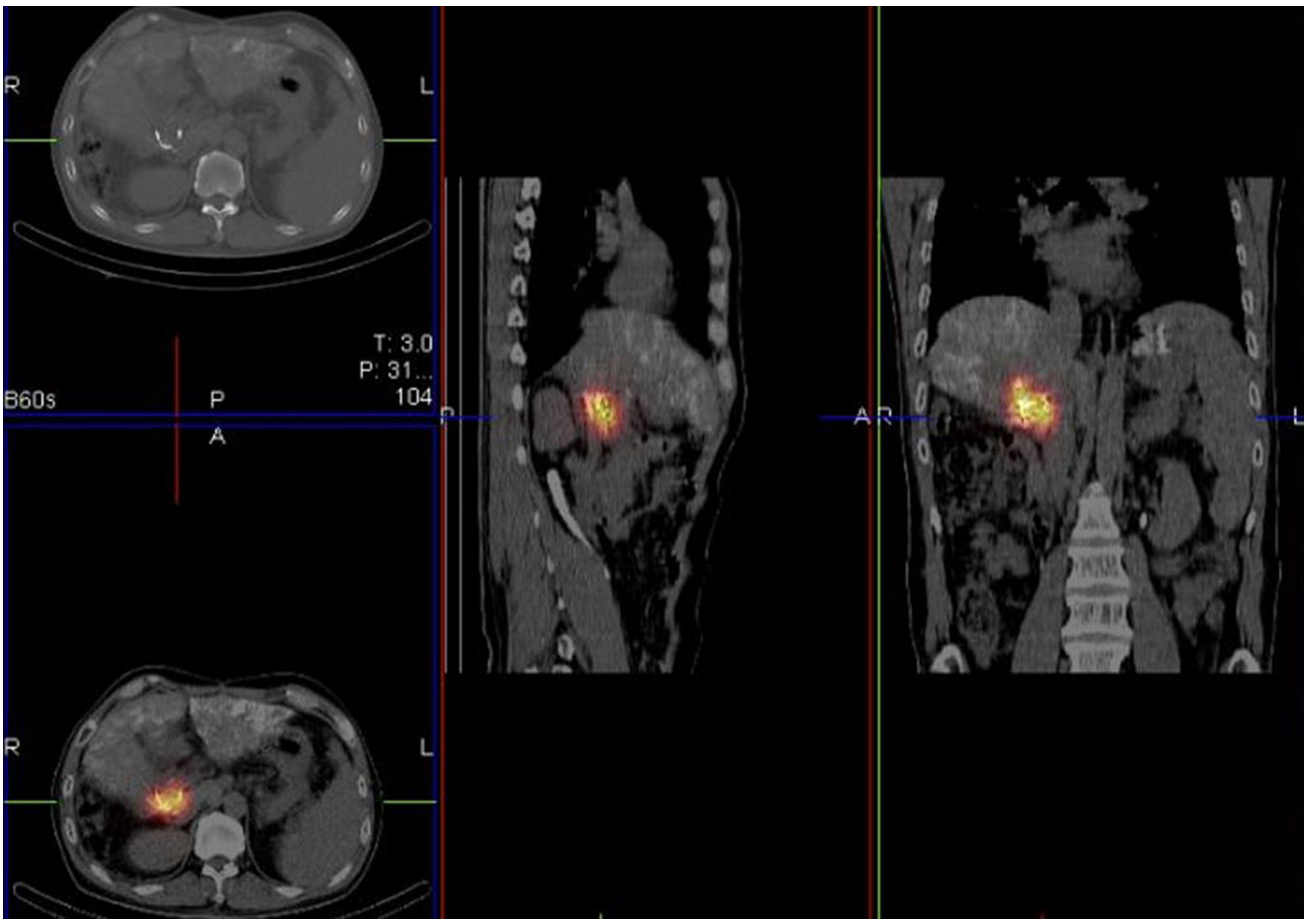

Fig. 4 SPECT-CT 2 days after implantation showed the dose distribution covering the tumor thrombosis

Table 2 Comparison of laboratory test results before, 1 week, and 2 months after implantation

	Preoperative	1 week after implantation	2 months after implantation	*P* value
White blood cell count ($\times 10^9$/L)	4.6 ± 2.2	4.9 ± 1.7	4.7 ± 1.5	0.427
Platelet count ($\times 10^9$/L)	112.3 ± 40.5	108.4 ± 50.1	109.2 ± 47.6	0.364
Alanine transaminase (U/L)	42.8 ± 7.9	50 ± 9.7	46.1 ± 8.6	0.121
Aspartate transaminase (U/L)	37.7 ± 6.7	40.3 ± 10.5	39.1 ± 7.4	0.093
Total bilirubin (μmol/L)	19.2 ± 4.6	21.2 ± 10.5	20.6 ± 8.3	0.775
Albumin (g/L)	33.7 ± 5.3	32.8 ± 4.9	32.2 ± 5.7	0.451
Prothrombin time (s)	12.5 ± 2.3	13.1 ± 4.2	12.9 ± 2.8	0.114
Creatinine (μmol/L)	70.5 ± 14.9	72.3 ± 16.7	72.5 ± 13.1	0.589

helical geometry upon release, which makes the implantation procedure much simpler.

For implantation of a seed strand with stent or stent loaded with seed that involved a metal stent, low molecular weight heparin and warfarin sequential therapy was needed for anticoagulation to prevent a thrombosis [13–15]. Numerous patients with HCC and MPVTT had multiple bleeding risk factors including portal vein hypertension, thrombocytopenia, and prolonged blood clotting. Therefore, anticoagulation therapy in these patients further increased the risk of bleeding. In this study, anticoagulation drugs were not administered. Throughout the follow-up period, no portal vein thrombosis occurred. Compared to seed strand with stent or stent loaded with seed, the helical I-125 seed implant had a simpler configuration, in which sleeve was made by a 4F angiographic catheter. For this

reason, there was a lower chance of inducing portal vein thrombosis. Thus, anticoagulation therapy was not needed to reduce the risk of bleeding by anticoagulation.

Yao et al. [19] computed the D90 to the target of 32.2 Gy in a single seed strand with seed activity of 0.7 mCi. Another study of stents loaded with seed showed dose to target was 40–50 Gy [15]. In this study, the helical I-125 seed implant delivered average D90 to the target of 60.7 Gy with seed activity of 0.5 mCi, in which the dose met the effective dose for HCC using external beam radiotherapy (40–60 Gy) [20]. This gave an ORR and DCR of MPVTT of 42.3% and 84.6%, respectively, 3 months after implantation. The median portal vein patency for the seed strand with stent and stent loaded with seed were 14.2 and 8.0 months, respectively. Compared to stent alone implantation, the seed strand with stent and stent loaded with seed significantly extended the patency of the portal vein [13–15, 21, 22]. Therefore, these three types of I-125 seed endovascular brachytherapy had better MPVTT control. Compared to TACE alone, the combination of endovascular brachytherapy and TACE significantly prolonged OS of HCC patients with MPVTT [14]. The median OS of seed strand with stent combined with TACE was 8.4–9.3 months [13, 14], while the median OS of stent loaded with seed combined with TACE was 12.5 months [15]. In this study, the median OS of the helical I-125 seed implant combined with TACE was 10.7 months. The difference in survival time among treatment techniques may be attributable to the difference in patient population and characteristics. A direct comparative study needs to be conducted in the future for objective comparison. Compared to external beam radiotherapy combined with TACE, I-125 seed endovascular brachytherapy combined with TACE in the treatment of HCC with MPVTT had a survival benefit [23]. This may be attributed to the inhibition of unsynchronized tumor growth with low-dose continual irradiation [24].

The current study was limited by it being from a small cohort with a single center. A large randomized controlled trial compared with TACE treatment alone should be included to validate the effectiveness of the combination of helical I-125 seed implants and TACE for HCC with MPVTT.

Conclusion

In conclusion, helical I-125 seed implants can be safely placed into the human main portal vein. Helical I-125 seed implants combined with TACE for HCC with MVPTT are safe and feasible.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Consent for Publication Consent for publication was obtained for every individual person's data included in the study.

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