Development of a Novel Endovascular Brachytherapy Stent: A Proof-of-concept Study

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Abstract

Background and Aims: Endovascular implantation of iodine-125 (125I) seeds strand combined with stent is an effective method of treatment for portal vein tumor thrombosis. The aim of this study was to develop a novel endovascular brachytherapy stent (EVB-Stent) and to evaluate its feasibility of use. Methods: An EVB-Stent was implanted into the main portal vein (MPV) in a live porcine model via the percutaneous transhepatic route. Blood samples were collected and tested before and after operation, as well as before euthanasia. Single-photon emission computed tomography (SPECT) combined with CT (SPECT/CT) scan were performed directly after operation and CT scan was performed 2 months after implantation. After the CT scan was performed, all animals were euthanized and histologically examined. Results: The novel stent was successfully positioned in all six pigs. No deterioration of liver function was observed during the 2-month follow-up period. SPECT/CT revealed the uniform distribution of radiation around the seeds strand, and the hottest spot was near the center of the MPV. The patency of the stented MPV was confirmed using CT scans. The tissue-accumulated absorbed dose was 31,822.11 mGy at 10 mm transversely away from the mid-point of the seeds strand, with a half-life of 59.4 days. Conclusions: A liver porcine model was used to demonstrate that the transhepatic placement of a novel endovascular brachytherapy stent, EVB-Stent, is both technically feasible and safe.

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Introduction

Hepatocellular carcinoma (HCC) is the 7th most common malignancy and the fourth leading cause of cancer-related death worldwide.1–3 Approximately 10–40% of HCC patients suffer portal vein tumor thrombus (PVTT) complication at the time of diagnosis.4 Based on Barcelona Clinic Liver Cancer staging, sorafenib is the only evidence-based and recommended treatment option for patients with vascular invasion (stage C). However, several studies have shown only modest clinical efficiency when sorafenib monotherapy has been provided for HCC patients with PVTT.4–9 In recent studies, transarterial chemoembolization (TACE) combined with sorafenib or radiotherapy has shown survival benefits for HCC patients with PVTT.7–9 Although survival benefits have been provided through the adoption of these combinations, the survival duration of HCC patients with PVTT remains poor, which may be attributed to the obstructed blood flow in the PV. Owning to compromised PV blood supply, the interruption of hepatic arterial flow may result in severe ischemic liver damage.4 Therefore, HCC patients with PVTT are generally considered as contraindicated for TACE.

In China, HCC patients with PVTT often receive treatment through multiple methods, such as surgery, external beam radiotherapy (EBRT), chemotherapy, and iodine-125 (125I) seeds strand and stent implantation.11 A recent multicenter study proved that patients with limited PVTT could benefit from liver resection.12 However, patients with main PV tumor thrombus (MPVTT), can barely meet the requirements for liver resection. A systematic review and meta-analysis compared TACE plus EBRT with TACE alone for unresectable HCC.13 The results of the study indicated that the pooled median survival for TACE plus EBRT-treated patients was significantly better than that of TACE-alone treated patients. However, the pooled analysis also showed that compared with TACE alone, TACE plus EBRT significantly increased the occurrence of gastroduodenal ulcers, as well as elevated levels of alanine aminotransferase and total bilirubin. Since normal hepatic tissues show poor tolerance to radiation, it is also impos-
Du N. et al: A novel endovascular brachytherapy stent

Figure 1. Configuration and structure of the EVB-Stent system. (A) The EVB-Stent was made using a nickel titanium alloy and consisted of a cylindrical mesh structure with two rings at its two ends. Its length of its axis was 60 mm, with a diameter of 18 mm. (B) At the two tapered ends of stent, an $^{125}$I seeds strand, which was a 4-Fr sterile plastic tube containing $^{125}$I seeds, was inserted through the two rings and fixed to the stent using sterile sutures. (C) After assembly was completed, the novel stent equipped with an $^{125}$I seeds stand was known as an EVB-Stent.

Method

Assembling of the EVB-Stent

A self-expanding Nitinol stent (Hongpu Medical Device Corporation, Shanghai, China) with a mesh-like structure, was tapered into two rings at the proximal and distal ends. The stent used in this study was 18 mm × 60 mm in size. A 4-Fr sterile plastic tube (Boston Scientific Co., Marlborough, MA, USA) containing $^{125}$I seeds was inserted through the rings at both ends and the seeds strand was fixed to the stent using sterile sutures (Fig. 1). The stent, once equipped with the $^{125}$I seeds stand, was known as an EVB-Stent.

As described in our previous study,19 Model 6711 $^{125}$I seeds (Xinke, Shanghai, China) were encapsulated in a 4-Fr sterile plastic tube (Boston Scientific Co.) to assemble the seeds strand. The radioactivity of each $^{125}$I seed was 25.9 MBq, with a half-life of 59.4 days. The principal photon emissions were 27.4–31.4 keV X-ray and 35.5 keV γ-ray. The half-value thickness of tissue for $^{125}$I seeds was 17 mm, and the initial dose rate was 7 cGy/h. The effective irradiating range was 20 mm. The number of $^{125}$I seeds was determined by the length of the plastic tube (L mm; N = L/4.5). In this study, the number of $^{125}$I seeds used in each strand was 14.
Animals

The animals selected for the experiment were six ordinary white pigs (weight 35–40 kg) provided by the Experimental Animal Center of our hospital. This study was approved by the institutional Animal Ethics Committee of our hospital. The animals were fasted for 12 h before operation. Intramuscular injection of xylazine hydrochloride (2–4 mg/kg) and diazepam (2 mg/kg) were used for sedation and anesthesia, respectively. Blood pressure, heart rate, and respiration rate were monitored during the procedure.

Interventional procedures

Under fluoroscopic and ultrasound guidance, the right intrahepatic PV was punctured using a 21G Chiba needle (Cook Medical Inc., Bloomington, IN, USA) and a 0.018-inch wire (Cook Medical Inc.) was inserted into the PV. A 6-F Neff Percutaneous Access set (Cook Medica Inc.) was introduced into the PV over the wire. Through the outer cannula of the Neff Percutaneous Access set, a 0.035-inch, 150 cm-long wire (Terumo, Tokyo, Japan) was manipulated across the MPV to the PV over the wire. After venography, the catheter was removed, and the outer cannula of the Neff Percutaneous Access set was replaced by a 7-Fr, 23 cm-long sheath (Cordis, Hialeah, FL, USA) over the wire. After 100 U/kg heparin was subcutaneously administered once a day for 2 months. The animals were sacrificed through intravenous injection of potassium chloride and necropsied, immediately. The stented animals were in good condition without a loss of appetite, vomiting, diarrhea, and weight loss after implantation. Blood samples were collected before implantation and at 1 week and 2 months after implantation, to determine liver function and blood toxicity. Single photon emission computed tomography (SPECT) combined with CT (SPECT/CT) scan was performed to evaluate the radiation distribution emitted by the 125I seeds strand immediately after implantation. Tissue accumulated absorbed doses 10 mm from the midpoint of the 125I seeds strand were theoretically calculated using 125I Radiation Field Distribution Calculation Software. CT scan was performed at 2 months post operation, and three-dimensional (3D) reconstructions were made to evaluate the patency of the stented PV. The contrast agent used was Ultravist Injection (300 mgI/mL). Intravenous access was through the femoral vein, and the dose of the contrast agent was 80 mL (2.0 mL/kg) on average, at an injection rate of 4 mL/s, delay time of arterial phase enhancement of 15 s, and a portal venous phase enhancement delay time of 50 s. After CT scans were performed, the animals were sacrificed through intravenous injection of potassium chloride and necropsied, immediately. The stented MPV and adjacent organ tissue were harvested and fixed in 10% formalin for pathological examination. Hematoxylin and eosin staining were performed, to evaluate adjunct liver tissue change and to evaluate thrombus organization within the stented PV and neointima coverage of the PV.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA) software. One-way analysis of variance was used to compare differences in hematological indices between the different time points. Measurement data are presented as mean±standard deviation. A two-sided p-value of <0.05 was considered statistically significant.

Results

The EVB-Stent was successfully implanted into the MPV of all six pigs without major complications. After stent placement, venography of the PV confirmed the proper location of the EVB-Stent in the MPV. All animals were in good condition without a loss of appetite, bleeding, weight loss, or death. Hematological indices taken throughout the examination period were summarized, and showed that no significant liver function deterioration or blood toxicity were detected (Table 1).

Table 1. Comparison of laboratory test results pre-procedure and post-procedure

|                | Preoperative | One-week post-intervention | Two-month post-intervention | p   |
|----------------|--------------|----------------------------|-----------------------------|-----|
| RBC as ×10^{12}/L | 7.2±0.3      | 6.7±0.6                   | 7.0±0.5                     | 0.261|
| HB as ×10^{9}/L  | 116.8±9.4    | 107.8±13.9                | 111.3±10.3                  | 0.352|
| WBC as ×10^{9}/L | 11.7±2.2     | 13.9±2.2                  | 11.0±1.6                    | 0.074|
| PLT as ×10^{9}/L | 514.2±82.8   | 507.1±77.4                | 513.8±67.3                  | 0.984|
| TB in μmol/L     | 9.7±0.4      | 10.4±0.6                  | 10.2±0.5                    | 0.079|
| DB in μmol/L     | 6.5±0.4      | 7.2±0.5                   | 7.0±0.5                     | 0.053|
| AST in U/L       | 37.2±1.9     | 38.0±1.9                  | 38.2±2.3                    | 0.655|
| ALT in U/L       | 44.0±2.4     | 45.2±2.1                  | 46.5±2.8                    | 0.240|
| ALB in g/L       | 23.6±1.6     | 22.9±1.4                  | 22.8±0.8                    | 0.508|

ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DB, direct bilirubin; HB, hemoglobin; PLT, platelet; RBC, red blood cell; TB, total bilirubin; WBC, white blood cell.

Journal of Clinical and Translational Hepatology 2021 vol. 9 | 711–718 713
The SPECT/CT scan showed that the EVB-Stent had been correctly placed in the MPV without collapse, occlusion, or over-expansion. Radiation emitted by the $^{125}\text{I}$ seeds strand was distributed symmetrically in the MPV, and presented as a cylindrical shape that completely covered the targeted MPV (Fig. 2). Based on the $^{125}\text{I}$ Radiation Field Distribution Calculation software, the tissue accumulated absorbed dose was 31,822.11 mGy 10 mm transverse from the midpoint of the $^{125}\text{I}$ seeds strand, with a half-life of 59.4 days (Fig. 3). The three-dimensional reconstruction CT image showed that the stented vessel remained in position and that the $^{125}\text{I}$ seeds strand was tightly fixed to the center of the stent (Fig. 4). Additionally, no malposition, collapse, thrombosis, or stenosis occurred in the stented vessels, when observed using CT scans.

Necropsy and pathological examination results showed that none of the stents were covered or occluded at the two tapered ends by neointimal overgrowth in all six pigs (Fig. 5A). However, slight intimal hyperplasia and incomplete neointimal growth covered the tapered end near the hilar side of the stent in one pig (Fig. 5B). Hematoxylin-eosin staining revealed that the central grid of the EVB-Stent and even the densest part of the stent mesh were almost completely covered by neointimal growth, which resulted in the proper incorporation of the EVB-Stent, and its surface was smooth and free from tears, peelings, or injuries (Fig. 5C–D). No obvious abnormalities were found in nearby organs, including the liver parenchyma, duodenal wall, and pancreas, as examined through gross observations and pathological analysis (Supplementary Fig. 1).

**Discussion**

In this study, we demonstrated the technical feasibility of the percutaneous transhepatic placement of a novel radioactive stent, the EVB-Stent, in the MPV of a live porcine model. Furthermore, during the 2-month follow-up period, the stented PV remained in position in all cases, with minimal neointimal growth covering it. All these results present evidence that the EVB-Stent has the potential to be used for further clinical exploration.

PVTT is a prognostic factor for poorer overall survival among patients with HCC. Stent implantation promptly restores blood flow in the obstructed MPV and provides an opportunity for TACE to be applied for tumor lesions. However, in-stent stenosis can occur due to tumor growth and/or tumor thrombosis. $^{125}\text{I}$ EVB along with $^{125}\text{I}$ seeds implantation, which can inhibit and prevent the progression of tumor thrombosis, has been provided an option to prolong stent patency.$^{21,22}$ In a previous study, better overall response rate as well as a significantly favorable level of survival

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**Fig. 2.** Images obtained by performing a SPECT/CT scan 1 day after the procedure was performed. The EVB-Stent was implanted correctly in the MPV without displacement. The radiation emitted by the $^{125}\text{I}$ seeds was homogeneously distributed and completely covered the target lesion.
were observed in patients who received TACE combined with EVB with $^{125I}$ seeds strand and stent placement. Numerous studies have demonstrated that stent devices that are combined with EVB exert therapeutic efficacy in PVTT, unresectable malignant esophageal and biliary obstruction. The eccentric distribution of the $^{125I}$ seeds strand may cause the delivery of an insufficient radiation dose to the contralateral blood vessel wall, thus compromising the therapeutic efficacy. Moreover, the eccentric distribution of the $^{125I}$ seeds in the MPV may limit the maximum dose of radiation delivered. Hence, we constructed a novel EVB-Stent to further improve the therapeutic efficacy of brachytherapy using $^{125I}$ seeds for MPVTT by improving the radiation dosage delivered. The $^{125I}$ seeds were presented as a sequential string coaxially at the center of the EVB-Stent, and the radiation emitted by the $^{125I}$ seeds was homogeneously distributed and covered the entire stent canal. To examine the safety and feasibility of the novel radioactive stent, we conducted an animal study through the percutaneous transhepatic PV deployment of the EVB-Stent in a live porcine model.

Previous experimental studies have proven that transhepatic puncture and catheterization in a porcine model can be technically feasible without bleeding complications. In our study, ultrasound was used to assess intrahepatic vascular dissection and provided clear guidance for PV puncture. Moreover, owning to fine needle puncture, no bleeding or hematoma was observed after operation. A 7-Fr long sheath was used to create a transhepatic track and the EVB-Stent was released through the long sheath. The EVB-Stent could be easily introduced into the PV without any technical difficulties or challenges. Our previous experience showed us that the procedure used for the implantation of the $^{125I}$ seeds strand combined stent was complicated to some extent. The outer cannula of the Neff set can be difficult to be delivered to the obstructed MPV and the release of the $^{125I}$ seeds strand can be complicated if the stent has already been inserted. In this study, the $^{125I}$ seeds were arranged linearly and continuously sealed into a 4-Fr sterile catheter to construct an $^{125I}$ seeds strand. Then, the strand was fixed at the center of the stent. Compared with previously used techniques, the transhepatic MPV deployment of the EVB-Stent performed in this study was relatively simple. Hence, we demonstrated the techni-
Feasibility of the transhepatic PV placement of an EVB-Stent into a pig model. However, its manipulative feasibility for HCC patients with MPVT remains to be elucidated through clinical trials.

In this study, 14 $^{125}\text{I}$ seeds were encapsulated in a 4-Fr sterile plastic tube to create a seeds strand and then fixed at the center of the stent. SPECT/CT showed that the radiation emitted by the $^{125}\text{I}$ seeds was uniformly distributed in the PV. The overall isodose of radiation can exert an elongating tumor killing effect and minimize the irradiation of the surrounding normal tissue. Moreover, the potentially irregular and asymmetric radiation emitted by the $^{125}\text{I}$ seeds at the center of the stent.

**Fig. 4.** CT images obtained 2 months after the operation was performed. Reconstruction of the CT image showed that the EVB-Stent expanded completely in the MPV, the $^{125}\text{I}$ seeds strand was fixed tightly at the center of the stent, and no thrombus was found in the entire PV.

**Fig. 5.** Necropsy and pathological examination results obtained 2 months after the procedure. (A) There was no evidence of thrombosis in the stented portal vein and on both sides of the stent. The $^{125}\text{I}$ seeds strand was completely covered by neointima, without narrowing or occlusion. (B) In one pig, slight intimal hyperplasia and incomplete neointimal cover was observed at the tapered end of the YZP-Stent near the hilar end. (C, D) Hematoxylin and eosin staining showing the central grid section of the YZP-Stent and the densest section of the stent mesh was also almost completely covered by neointimal growth, which shows the proper incorporation of the YZP-Stent. Its surface was smooth and free from tears, peelings, or injuries. (E, F) At the tapered end of stent near the hilar end, necropsy and pathological imaging showed that there was a slight intimal hyperplasia but intimal overgrowth or neointimal growth that completely covered the stent was not observed.
strand for the eccentric location in the PV can be avoided and the potential heterotopia of implanted 125I seeds strand can also be avoided. None of the animals were found to show signs of PV thrombosis after EVB-Stent placement during the 2-month follow-up period. On one hand, proper anticoagulant therapy with heparin is of great importance in preventing thrombosis. On the other hand, the anti-neointimal hyperplasia effect provided by the implantation of the 125I seeds strand allowed for a longer latency period to be achieved by the MPV stent. Moreover, the central location of the 125I seeds strand in the stented PV contributed to full conformal radiotherapy implementation on the MPV. Hence, incomplete neointimal hyperplasia coverage of the stent was observed but without thickening or resulting in PV stenosis after 2 months of deployment of the EVB-Stent.

Studies have established that persistent low-energy 125I irradiation therapy may keep tumor cells in the sensitive resting period, resulting in tumor cell apoptosis, which can induce epigenetic changes that reactivates silenced tumor suppressor genes, and damage to the DNA to kill cancer cells.14,21 For end-stage patients, the combination of EVB and PV stent implantation may not only provide a long period in which symptoms of portal hypertension are relieved but may also suppress the progression of tumor thrombus. Furthermore, compared with external radiotherapy, brachytherapy using 125I seeds provides a high local dose close to the seeds and a steep fall in the dose provided to the surrounding tissues, which exerts an adequate tumor suppression effect with limited damage exerted onto the surrounding normal tissue.15 Since 125I seeds have a long half-life (59.4 days), a sustained level of radiation can be exerted to inhibit the replication of tumor cells and induce tumor cell apoptosis.22 In this study, the EVB-Stent, which was used as a novel endovascular brachytherapy stent kit, provided three obvious advantages compared with its current usage. First, it may induce tumor cell apoptosis more effectively and inhibit the progression of tumor thrombus, since the gamma rays are evenly distributed at the center of the obstructed PV. Second, the support provided by the stent resulted in the 125I seeds strand being firmly fixed at the center of the stent without displacement. Third, the central deployment of the radiative strand provided an opportunity to further improve the antitumor effect by increasing the dosage provided by the 125I seeds without obvious damage to the PV wall.

There are several limitations in our study. First and foremost, only six pigs were used, which may introduce a case-by-case bias. Second, the use of healthy animals without tumor thrombus or portal hypertension can barely reproduce the complex environment in a real human diseased setting in which a stent must be implanted. Finally, long-term results of the efficacy and safety of the EVB-Stent transhepatic PV implantation, as well as its impact on the vessel wall over longer periods of time, are still pending. The creation of an ideal animal model with PVTT remains a daunting challenge but is urgently required to demonstrate the antitumor efficacy and safety of the transhepatic PV placement of the EVB-Stent.

Conclusions

Mid-term preclinical results demonstrated the feasibility and safety of the percutaneous transhepatic MPV implantation of a novel EVB-Stent into a live porcine model. The implantation of the stent did not produce thrombosis or stenosis. Further studies using large samples of animals with or without PVTT are needed to further assess the efficacy and safety of this innovative stent before it can be considered suitable for clinical application.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (JL, ZY), acquisition of data (ND, JM, YZ), analysis and interpretation of data (MY, WZ, ZZ), obtaining funding (ZY), drafting of the manuscript (ND, JM), critical revision of the manuscript for important intellectual content (MY, WZ), administrative, technical, or material support, study supervision (JL).

Data sharing statement

All data are available upon reasonable request.

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