




# A Comparative Study of Self-Expandable Metallic Stent Combined with Double $^{125}\text{I}$ Seeds Strands or Single $^{125}\text{I}$ Seeds Strand in the Treatment of Advanced Perihilar Cholangiocarcinoma with Malignant Obstructive Jaundice

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**Purpose:** The purpose of this study was to compare the safety and effectiveness of a self-expandable metallic stent (SEMs) with a novel brachytherapy biliary drainage catheter (BBDC, double  $^{125}\text{I}$  seeds strands) or a single  $^{125}\text{I}$  seeds strand in the treatment of advanced perihilar cholangiocarcinoma (pCCA) with malignant obstructive jaundice (MOJ).

**Methods:** From September 2016 to December 2018, we retrospectively enrolled patients with biliary stent implantation after receiving either BBDC loaded with  $^{125}\text{I}$  seeds (double-strands irradiation group) or an  $^{125}\text{I}$  seed strand treatment (single-strand irradiation group, control group). The outcomes were analyzed regarding the relief of obstructive jaundice, and interventional-related complications. Moreover, the Kaplan–Meier method was used to analyze stent patency and survival.

**Results:** The success rate of interventional therapy in both groups was 100%, and all patients with MOJ were alleviated. According to the Common Terminology Criteria for Adverse Events (CTCAE 4.02), the grade 3 or 4 complications in the BBDC group and in the control group were 6/34 (17.65%) and 7/39 (17.95%), respectively ( $P > 0.05$ ). The median and mean overall stent patency of the BBDC group and the control group were 207 days versus 180 days, 204.212 days versus 186.278 days ( $P = 0.043$ ). The median and mean overall survivals in the BBDC group were higher than those in the control group (245 days versus 212 days, 244.883 days versus 221.844 days,  $P = 0.030$ ).

**Conclusion:** This interim analysis showed that BBDC (double-stranded irradiation) can prolong the stent patency time compared with  $^{125}\text{I}$  seed strand treatment (single-stranded irradiation) and had the advantage of reducing jaundice, which seemed to extend the survival period of advanced pCCA.

**Keywords:** restenosis, survival, jaundice, cholangiocarcinoma, brachytherapy

## Background

Malignant obstructive jaundice (MOJ) usually results from biliary invasion or compression by advanced perihilar cholangiocarcinoma (pCCA). Most patients are not cured after resection for perihilar cholangiocarcinomas; about 80% will develop recurrent disease, mostly within two years after surgery.<sup>1,2</sup> The implantation of a self-expandable metallic stent (SEMs) is the main palliative treatment for

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patients in advanced pCCA with MOJ. However, due to the stent's stimulation of the bile duct wall and the lack of therapeutic properties for the tumor, stent stenosis and granulation tissue proliferation that occur in the progress of the disease will make more than 50% of patients have stent re-obstruction within 6 months.<sup>3,4</sup> Hence, stents with longer patency are required to improve the survival rates of patients with MOJ. Fortunately, in 2012, Zhu et al.<sup>5</sup> reported that a radioactive biliary stent loaded with <sup>125</sup>I seeds exhibited significantly prolonged stent patency compared with conventional stents. In recent years, some investigators have used the combination of <sup>125</sup>I seeds strand and SEMs as a new therapeutic treatment for MOJ.<sup>6</sup> Although it is a safe treatment, the cumulative brachytherapy dose is relatively low and fibrous connective tissue in the bile duct could reduce the local irradiation effect.<sup>7</sup> To eliminate these disadvantages, a novel brachytherapy biliary drainage catheter (BBDC) loaded with double <sup>125</sup>I seed strands was designed. Of note, the efficacy and complication of the treatment for MOJ have not been largely studied to our knowledge. This study aims to compare the safety, complication and efficacy of BBDC loaded with <sup>125</sup>I seeds (double-strands irradiation group) and <sup>125</sup>I seed strand (single-strand irradiation group, control group) after SEMs was implanted in the follow up after the treatment.

## Methods

### Patients

In this retrospective study, the inclusion criteria of eligible patients were as follows: (a) aged between 43 and 80 years; (b) perihilar cholangiocarcinoma confirmed by pathological biopsy; (c) symptoms such as jaundice related to biliary obstruction; (d) Eastern Cooperative Oncology Group (ECOG) performance of 0–2; (e) patients underwent computed tomography or magnetic resonance cholangiopancreatography (MRCP) to evaluate the extent of the biliary obstruction prior to stenting; (f) unresectability or refusal to be surgically treated; (g) willing and able to comply with the study procedures and provide written informed consent to participate in the study. The exclusion criteria were as follows: (a) main portal vein tumor thrombus; (b) severe coagulation defect; (c) refractory ascites; (d) intrahepatic metastasis that extensively involves both lobes of the liver; (f) an ECOG performance of 3–4.

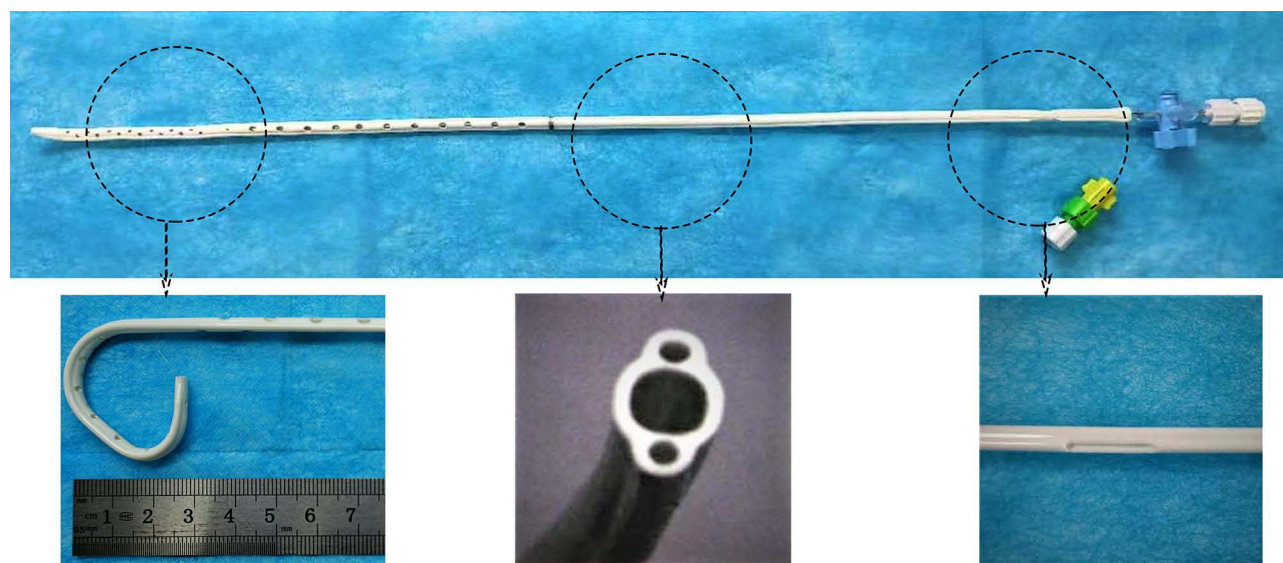
## Device

A Nitinol self-expandable stent (Niti-S Biliary stent, Taewoong, Seoul, Korea), with a diameter of 10 mm and length of 5–6 cm was used to treat the stenosis within the common bile duct. The novel brachytherapy biliary drainage catheter (Tuoren, Henan, China) used in the present study comprised three distinct ports (Figure 1). The central port [internal diameter (ID) = 2.4 mm] provides external-internal bile drainage. This was lined with several lateral holes placed 15 cm away from the distal tip of the catheter. The other two ports (ID = 0.85 mm) were designed to carry radionuclides and located close to the central port, and were 180 degrees apart. The <sup>125</sup>I radioactive seeds were inserted into both ports before deployment. The distal part of the radionuclide ports was closed at 5 cm from the tip to prevent the seeds from leaking into the duodenum. A Radiopaque marker was placed at 1 cm from the last hole to facilitate the positioning of the catheter under fluoroscopy. For the precise placement and prevention of catheter slippage, a thread and loop were employed (diameter = 2.0 cm).

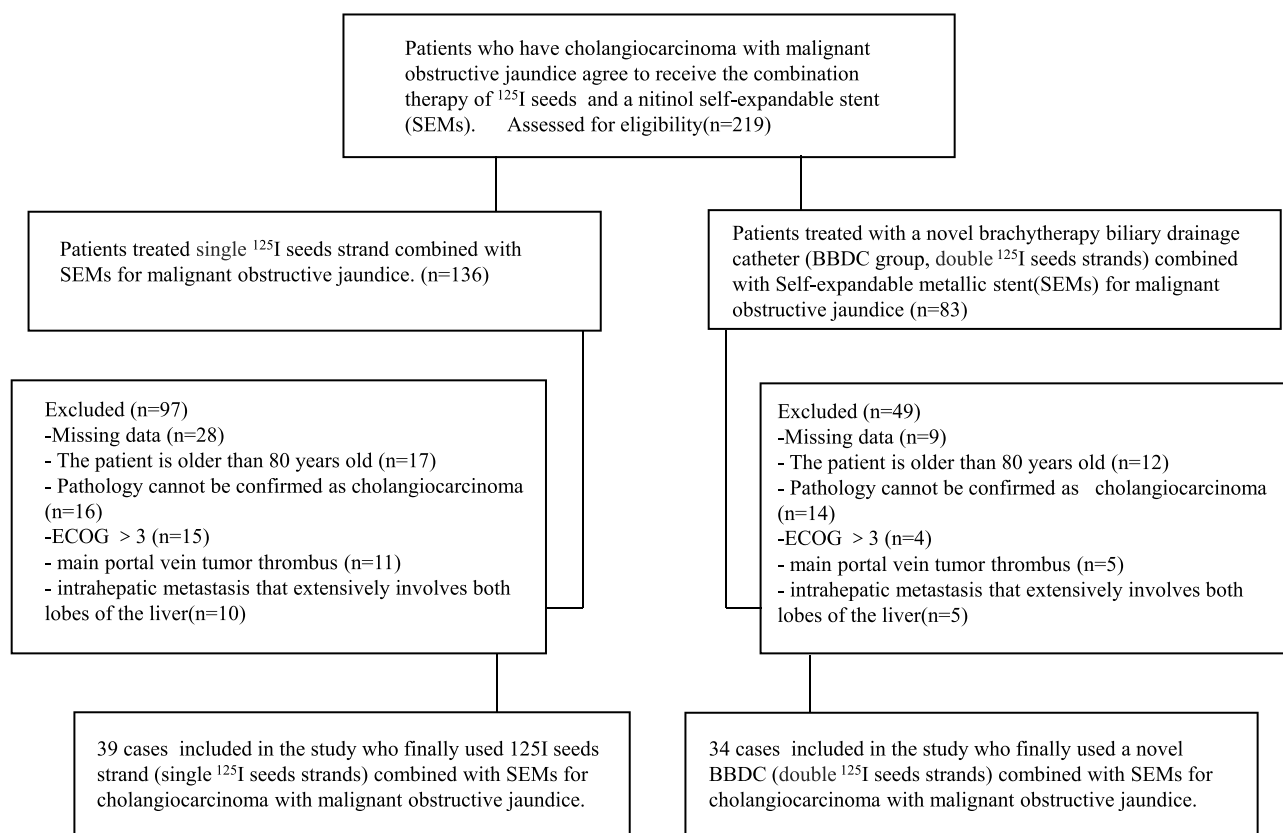
The <sup>125</sup>I seeds (Said Biopharmaceutical Co. Ltd, Tianjin, China) were configured in a cylindrical brachytherapy source encapsulated by titanium. The size of each titanium capsule was 0.8×4.5 mm. The measured emissions were low-energy (35.5 keV  $\gamma$ ) with a half-life of 59.6 days. The measured radioactivity of each seed was 0.72–0.81 mCi. The number of <sup>125</sup>I seeds to be implanted was calculated using the following formula: Number of <sup>125</sup>I seeds required = [the biliary obstruction length (mm) + 40/4.5] × 2. To prevent the seeds from withdrawing, a guidewire (0.018 inches in diameter, 20–30 length) was placed in both radionuclide ports. The ends of these ports were closed using medical adhesive tape.

## Procedures

Prior to the procedure, the extent of the tumor and the anatomy of the bile duct were evaluated by enhanced abdominal CT and/or MRCP. The treatment flow chart is shown in Figure 2. All procedures were performed under local anesthesia (2% lidocaine) and dezocine intravenous injection (5 mg). Firstly, under digital subtraction angiography (DSA) guidance (Artis Zeego, Siemens, Germany or Shimadzu Digite2400, Japan), percutaneous transhepatic cholangiography (PTC, Cook Inc., Bloomington, IN, USA) was performed to visualize the location and degree of biliary obstruction. Brachytherapy biliary drainage



**Figure 1** A novel brachytherapy biliary drainage catheter (BBDC).



**Figure 2** Treatment flow chart.

**Abbreviations:** SEMs, self-expandable stent; ECOG, Eastern Cooperative Oncology Group; BBDC, brachytherapy biliary drainage catheter.

catheter (BBDC) and Iodine-125 (<sup>125</sup>I) seed strand in bile duct placement time (1–1.5 months). Analysis of biochemical and imaging examination after one month of

interventional treatment. The details for the interventional treatment can be seen in the [Supplementary Information](#) and [Figure 3](#).

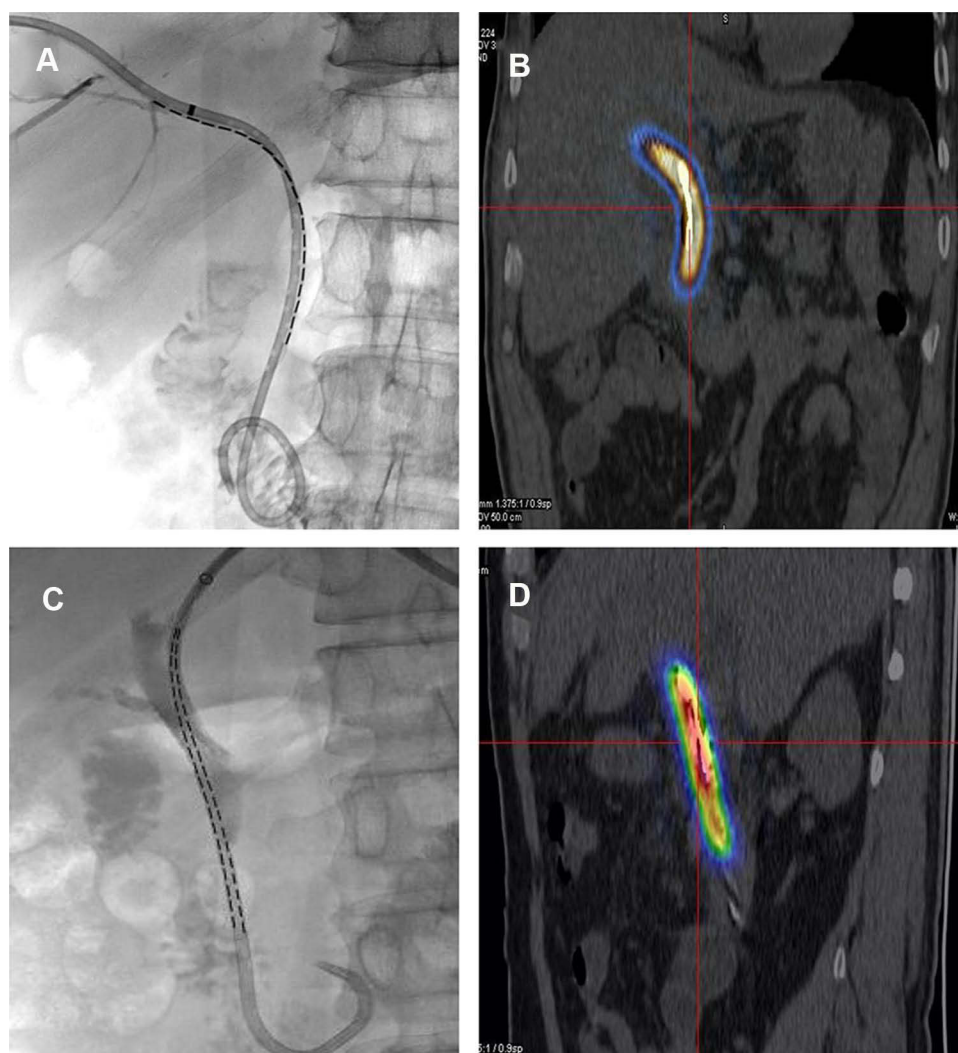
## Definitions

The primary end points were the technical success, clinical success, and stent patency. The secondary end points were complications, patient survival, and pre- and postoperative changes in the biochemical indicators. Technical success was defined as the deployment of the BBDC with favorable contrast flow through the stent at one month. Clinical success was defined as a successful BBDC removal and a reduction in serum bilirubin by at least 75% of the pre-treatment value within one month. The stent patency period was defined as the interval between stent placement and the development of stent occlusion. Complications were classified according to the Common Terminology Criteria for Adverse Events (CTCAE 4.02). Stent occlusion was defined as biliary dilation on CT or MRI, combined with the

recurrence of symptoms of malignant obstruction and an increase in serum bilirubin ( $>51.3 \mu\text{mol/L}$ ).

## Statistical Analysis

Continuous variables were summarized as mean  $\pm$  standard deviation (SD). The Wilcoxon Signed Rank test was used to compare the pre- and post-procedure indicators. The Fisher's exact test was also used to compare postoperative complications between the two groups. We calculated overall survival and stent patency at 1 year using Kaplan–Meier estimation, and we compared the two groups with the Log rank test and a  $P$ -value of  $<0.05$  was considered statistically significant. The calculations were performed by the SPSS software (version 23.0, SPSS, Chicago, IL, USA).



**Figure 3** (A, B) Single 125I seeds strand combined with self-expandable metallic stent (SEMs) for malignant obstructive jaundice (Control group); (C, D) a novel brachytherapy biliary drainage catheter (BBDC group, double-strands) combined with SEMs for cholangiocarcinoma with malignant obstructive jaundice.



## Results

### Patient Characteristics

The baseline characteristics of the BBDC group and the control group are well balanced (Table 1). The technical success rate in both groups was 100%. None of the  $^{125}\text{I}$  seeds were lost during the delivery and deployment as well as *in vivo* implantation process. The median estimated radiation doses for the reference points of the BBDC group and the control group were  $85.14 \pm 4.72$  Gy and  $44.35 \pm 3.55$  Gy ( $P < 0.05$ ), as calculated by computer TPS over one month and the total number of  $^{125}\text{I}$  seeds embedded in the patients of both groups was  $38.84 \pm 2.45$  and  $18.86 \pm 2.75$ , respectively ( $P < 0.05$ ).

### Clinical Success

The hospital stay of the BBDC group and the control group was  $12.53 \pm 4.67$  days and  $11.45 \pm 5.29$  days,

respectively ( $P > 0.05$ ). Except for one in the control group who died of severe gastrointestinal bleeding three weeks after the treatment. After 3 months of treatment, the ALT, TBIL, and DBIL of the control group decreased from  $208.87 \pm 55.76$  (U/L),  $201.77 \pm 108.98$  ( $\mu\text{mol/L}$ ), and  $167.34 \pm 102.77$  ( $\mu\text{mol/L}$ ) preoperatively to  $34.12 \pm 28.19$  (U/L),  $46.56 \pm 38.34$  ( $\mu\text{mol/L}$ ), and  $33.65 \pm 25.09$  ( $\mu\text{mol/L}$ ), respectively. Besides, the ALT, TBIL, and DBIL in the DDBC group also decreased from  $202.54 \pm 47.19$  (U/L),  $194.23 \pm 121.09$  ( $\mu\text{mol/L}$ ), and  $156.83 \pm 110.21$  ( $\mu\text{mol/L}$ ) before treatment to  $32.12 \pm 19.11$  (U/L),  $41.87 \pm 31.45$  ( $\mu\text{mol/L}$ ), and  $23.87 \pm 21.45$  ( $\mu\text{mol/L}$ ), respectively. There were significant statistical differences between the two groups before and after 3 months of treatment ( $P < 0.05$ ). Of note, the ALB levels in both groups were increased slightly within one week, while the ALB levels continued to increase following treatment in both groups ( $P < 0.001$ ). In detail, the ALB in the control group and DDBC group increased from  $31.34 \pm 4.23$  and  $32.54 \pm 5.21$  to  $37.34 \pm 5.67$  and  $39.65 \pm 6.27$ , respectively (Figure 4).

**Table 1** Patient Characteristics

Characteristics	Control Group (n = 39)	BBDC Group (n = 34)	P value
<b>Age</b>	$57.05 \pm 8.73$	$59.21 \pm 7.22$	0.408 <sup>†</sup>
<b>Sex</b>			1.000*
Male	24	21	
Female	15	13	
<b>Clinical symptom</b>			0.983*
Jaundice with poor appetite	21	19	
Jaundice with emaciation	11	9	
Jaundice with recurrent fever	7	6	
<b>Location of the tumor</b>			0.495*
Middle bile duct	13	16	
Distal bile duct	17	11	
Hilar bile duct	9	7	
<b>Stenosis length (mm), mean <math>\pm</math> SD</b>	$31.31 \pm 5.90$	$29.07 \pm 7.76$	0.343 <sup>†</sup>
<b>Reason for unresectability</b>			0.720*
Metastases	17	13	
Local infiltration	12	14	
Refusal/intolerance to surgical treatment	10	7	

**Notes:** \*Pearson chi-square test was used. <sup>†</sup>Independent samples t-test was used.

### Complications

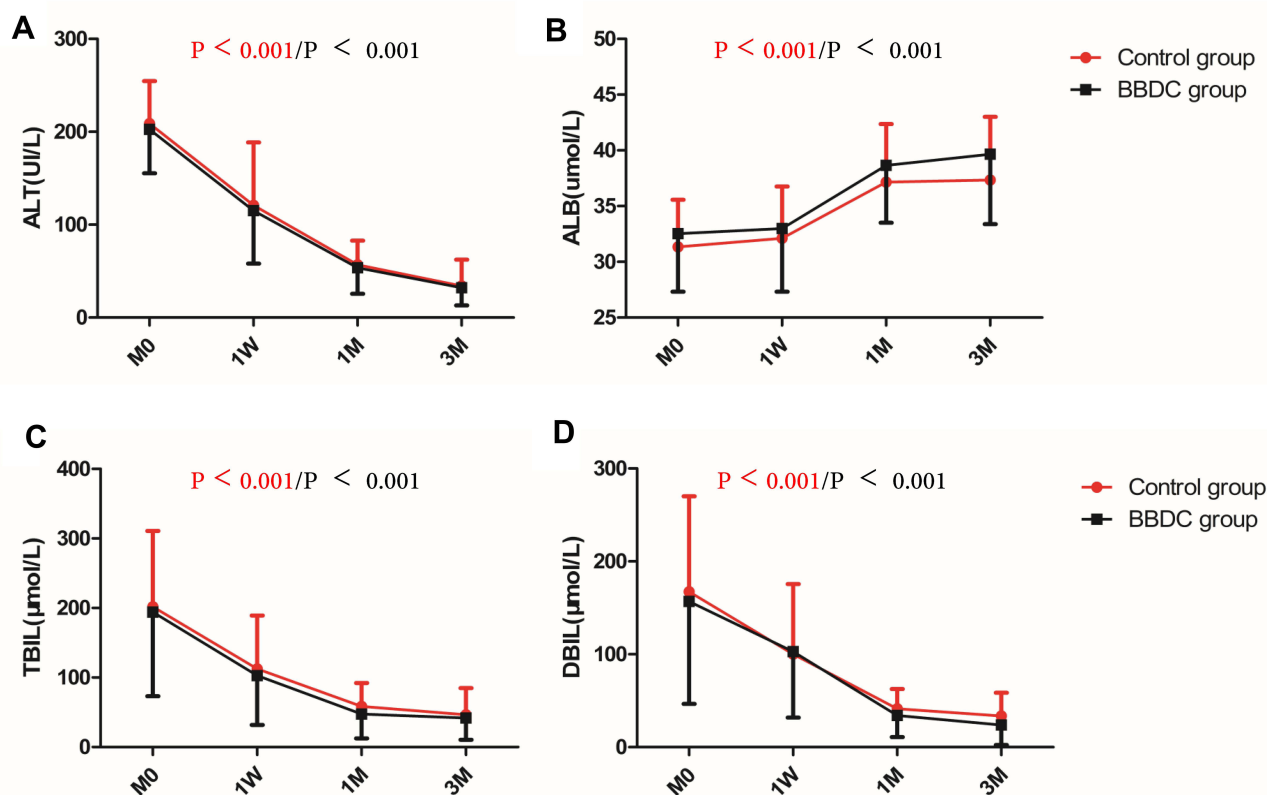
Complications were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE 4.02). The grade 3 or 4 complications in the BBDC group were biliary hemorrhage, pancreatitis, cholangitis, abdominal pain, liver abscess, and biliary leakage and the corresponding incidence were (1/34, 2.94%), (1/34, 2.94%), (2/34, 5.88%), (1/34, 2.94%), (0/34, 0.00%), and (1/34, 2.94%) while the incidence of control group were (2/39, 5.13%), (1/39, 2.56%), (1/39, 2.56%), (2/39, 5.13%), (1/39, 2.56%), and (0/39, 0.00%), respectively (Table 2).

### Post-Procedure Outcomes

During the follow up, the incidence of hepatic failure, multiple organ metastasis, gastrointestinal bleeding, and unknown death in BBDC group were (21/34, 61.76%), (9/34, 26.47%), (3/34, 8.82%), (1/34, 2.94%), respectively while the corresponding causes of death in the control group were (24/39, 61.53%), (8/39, 20.51%), (4/39, 10.25%), (3/39, 7.69%), respectively ( $P > 0.05$ ) (Table 3).

### Stent Patency, and Survival

The patency was determined by clinical findings related to biliary obstruction, results of laboratory examination and/or subsequent reexamination by cholangiography or imaging. The median stent patency was 207 days (95% CI:



**Figure 4** Changes in liver function at different times of treatment. **(A/C/D)** At 1 W, the levels of ALT, TBIL and DBIL in the BBDC group and in the control group decreased significantly and gradually returned to the normal level at 1 M and 3 M. **(B)** The ALB levels in both groups were increased slightly within one week, while the ALB levels continued to increase following treatment in both groups. However, the two groups almost reached normal levels in 3M. M0, pretreatment; 1W, the first week following treatment; 1M, the first month following treatment; 3M, the third month following treatment.

**Abbreviations:** ALT, Alanine aminotransferase; ALB, Albumin; TBIL, Total bilirubin; DBIL, Direct Bilirubin.

189.152, 224.848) in the BBDC group versus 180 days (95% CI: 170.367, 189.633) in the control group, and mean overall stent patency was 204.212 days (95% CI: 190.441, 217.983) in the BBDC group versus 186.278 days (95% CI: 173.427, 199.130) in the control group ( $P = 0.043$ , Log rank test). Additionally, the median overall survival was 245 days (95% CI: 232.010, 257.990) in the BBDC group versus 212 days (95% CI: 204.903,

219.097) in the control group, and mean overall survival was 244.883 days (95% CI: 230.414, 259.352) in the BBDC group versus 221.844 days (95% CI: 207.306, 236.383) in the control group ( $P = 0.030$ , Log rank test) (Figure 5).

## Discussion

MOJ is usually caused by cholangiocarcinoma.<sup>8</sup> Regrettably, it is often detected at an unresectable stage with a poor prognosis, and the long-term survival rates remain dismal.<sup>9</sup> SEMs is considered to be the preferred palliative therapy for unresectable patients.<sup>10,11</sup> However, doubt about the efficacy suggests that SEMs might not be able to prevent excessive tumor growth.<sup>12</sup> It is worth mentioning that the ingrowth of tumor or epithelial hyperplasia would cause further restenosis. As reported, 50% of stent restenosis occurred within 3–6 months after the treatment.<sup>4</sup> In addition, this therapy has shown no benefit for prolonging survival time.<sup>13,14</sup> Therefore, chemo-radiation therapy is suggested to be the

**Table 2** Grade 3 or 4 Complications

Complications	Control Group (n = 39)	BBDC Group (n = 34)
Biliary hemorrhage	2 (5.13%)	1 (2.94%)
Pancreatitis	1 (2.56%)	1 (2.94%)
Cholangitis	1 (2.56%)	2 (5.88%)
Abdominal pain	2 (5.13%)	1 (2.94%)
Liver abscess	1 (2.56%)	0
Biliary leakage	0	1 (2.94%)
Total	7 (17.95%)	6 (17.65%)

**Table 3** Procedural Details and Post-Procedure Outcomes

Characteristics	Control Group (n = 39)	BBDC Group (n = 34)	P value
<sup>125</sup> I Seed number, (mean ± SD)	18.68±2.99	38.84±2.46	0.002 <sup>‡</sup>
Cumulative dose at reference point	42.55±2.60	85.14±4.72	0.001 <sup>‡</sup>
Hospital stay, day (mean ± SD)	11.45±5.29	12.53±4.67	0.596 <sup>‡</sup>
Stent size (diameter × length)			0.463 <sup>#</sup>
10 × 60 mm	27	20	
10 × 50 mm	12	14	
The reasons for death			
Hepatic failure	24	21	0.984 <sup>#</sup>
Multiple organ metastasis	8	9	0.589 <sup>#</sup>
Gastrointestinal hemorrhage	4	3	1.000 <sup>*</sup>
Unknown cause	3	1	0.618 <sup>*</sup>
Follow-up anti-cancer treatments			
Transarterial infusion chemotherapy	17	16	0.450 <sup>#</sup>
Intravenous chemical therapy	14	12	1.000 <sup>#</sup>
Immunotherapy	8	6	0.776 <sup>#</sup>

**Notes:** \*The Fisher's exact test was used. <sup>#</sup>Pearson chi-square test was used. <sup>‡</sup>Difference in the variance between the two groups (Mann–Whitney test).

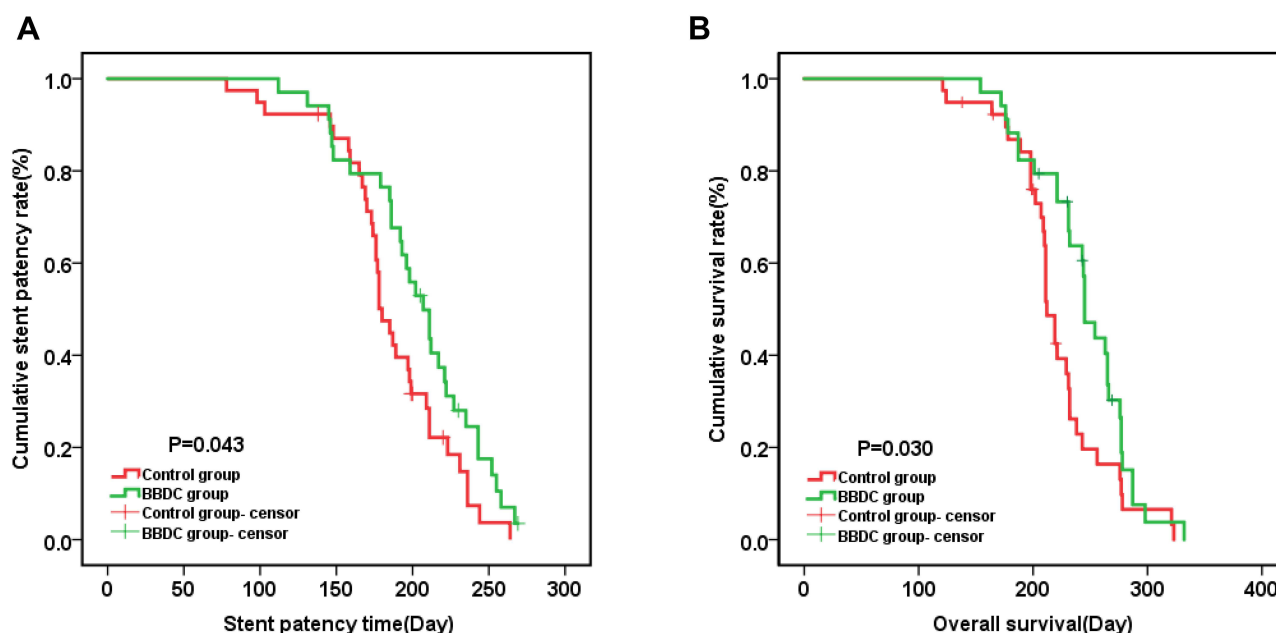
complementary treatment which can be used successively or synchronously to prolong the survival and stent patency. Compared with external irradiation, brachytherapy is a safe and effective palliative therapy, which can provide more effective treatment dose for tumor and reduce the impact on normal organs and tissues.<sup>15–17</sup>

At present, a multicenter Phase III clinical trial for the treatment of MOJ with radioactive stent and traditional metal stent has confirmed that inserting a radioactive stent instead of uncovered SEMs could improve the patency and overall survival rate of patients with unresectable malignant biliary obstruction.<sup>18</sup> Unfortunately, there are two serious problems in the insertion of irradiation stents. First, <sup>125</sup>I seeds cannot be taken out if complications occur after the treatment. Second, the seeds cannot be replaced after the <sup>125</sup>I seeds dose was completely released. In order to extend the stent patency and overall survival rate, investigators have attempted various therapies to control the growth of biliary tumors such as intraluminal radiofrequency ablation, photodynamic therapy, intraluminal high-dose-rate <sup>192</sup>Ir radiation and paclitaxel-drug-eluting stents for malignant biliary obstruction. In the field of brachytherapy, Iodine-125 (<sup>125</sup>I) seeds strand has been applied to the treatment of cholangiocarcinoma and portal vein tumor thrombosis with promising results.<sup>19–21</sup> Studies have further confirmed that intraluminal brachytherapy using a single <sup>125</sup>I seeds strand is a viable

and safe palliative treatment pressed by SEMS implantation, which can be used to treat cholangiocarcinoma and improve stent patency.<sup>6,22</sup> Nevertheless, single-strand <sup>125</sup>I particles cannot solve the problem of eccentric dose distribution.

To overcome these technical limitations, a BBDC loaded with double <sup>125</sup>I strands was designed. This design achieves drainage and brachytherapy simultaneously. Double <sup>125</sup>I strands provide better dose distribution than a single strand. In addition, the catheter can be removed or replaced when brachytherapy-related complications occur, or the intraluminal brachytherapy terminates. This retrospective study demonstrated the safety and reliability of the BBDC in the palliative treatment of malignant biliary obstruction. Besides, the technical success rate was 100% and the incidence of grade 3/4 complications in the control group versus the DDBC group was 17.95% (7/39) and 17.65% (6/34), respectively. This result was similar to the previous report,<sup>23</sup> which indicated that the three-lumen catheter would not increase the complications or reduce the success rate of clinical treatment.

All patients within 1 month of intraluminal brachytherapy (ILBT) calculated using SPECT/CT according to TPS. The estimated median radiation doses in the BBDC group and the control group were (85.14 ± 4.72) Gy and (44.35 ± 3.55) Gy, respectively (*P* < 0.05). BBDC group did better in controlling tumor ingrowth and overgrowth and resulted in



**Figure 5 (A)** Kaplan–Meier stent patency and overall survival with BBDC group versus control group. Median stent patency was 207 days (95% CI: 189.152, 224.848) in the BBDC group versus 180 days (95% CI: 170.367, 189.633) in the control group, and mean overall stent patency was 204.212 days (95% CI: 190.441, 217.983) in the BBDC group versus 186.278 days (95% CI: 173.427, 199.130) in the control group ( $P = 0.043$ , Log rank test); **(B)** Median overall survival was 245 days (95% CI: 232.010, 257.990) in the BBDC group versus 212 days (95% CI: 204.903, 219.097) in the control group, and mean overall survival was 244.883 days (95% CI: 230.414, 259.352) in the BBDC group versus 221.844 days (95% CI: 207.306, 236.383) in the control group ( $P = 0.030$ , Log rank test).

longer mean overall stent patency (204.212 vs 186.278,  $P = 0.043$ ) and overall survival (244.883 vs 221.844,  $P = 0.030$ ). Compared with High-dose-rate  $^{192}\text{Ir}$  (HDR- $^{192}\text{Ir}$ ) intraluminal brachytherapy for malignant biliary obstruction, BBDC group still had a higher overall survival rate.<sup>24,25</sup> This may be due to the SEMS combined with a novel BBDC (double- $^{125}\text{I}$  seed strands irradiation) to inhibit tumor growth and proliferation, which subsequently alleviate long-term obstructive jaundice, thereby improving patients' liver function and survival time. To date, there is no dedicated TPS for the  $^{125}\text{I}$  seed strands, and the relationship between the calculated radioactivity concentration and dose of TPS remains unclear. Therefore, further research is needed to confirm if the received radioactive dose is sufficient.

This study has several limitations. The sample size is relatively small, which reduces the statistical power of the conclusion, however some of the results have already achieved statistical significance. Selection biases might be existing in terms of the size or length of the metal stents. Second, because it is difficult to assess the tumor response after the treatment using the RECIST criteria, the objective assessment of tumor suppression by ILBT. Third, radiation might affect other people in close contact with the patients. Since the dose of the radiation on the surface of the patient's skin after placement is not accurately measured, the exact

radiation exposure to others remains unknown. However, prudent precautions have been taken to reduce the contact with others.

## Conclusion

In summary, our preliminary study showed that the newly designed BBDC loaded with  $^{125}\text{I}$  seeds provided both drainage and brachytherapy, and again demonstrated the technical feasibility and safety of BBDC for the treatment of advanced pCCA with malignant biliary obstruction. However, more prospective studies are needed to further elucidate its effectiveness in the treatment of MOJ.

## Data Sharing Statement

The relevant raw data from this study are readily available upon request for non-commercial purposes per a request from the corresponding author.

## Ethics Approval and Consent to Participate

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the First Hospital affiliated to Zhengzhou University and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study



was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University.

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## Disclosure

The authors declare that they have no competing interests to disclose.

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