Sigdel *et al. BMC Cancer* (2025) 25:229
https://doi.org/10.1186/s12885-025-13627-w

BMC Cancer

RESEARCH Open Access

Biliary metallic stent combined with radioactive 125I seeds strands for malignant hilar obstruction

Milan Sigdel[1], Chengzhi Zhang[1], Rongna Hou[1], Mengyao Song[1], Zhanguo Sun[1] and Dechao Jiao[1*]

Abstract

Background To evaluate the safety and efficacy of biliary metallic stent (BMS) combined with radioactive ^{125}I seed strands (RISS) for malignant hilar obstruction (MHO).

Method From January 2016 to January 2022, 317 patients with MHO underwent percutaneous trans-hepatic biliary drainage at our center. Among them, 40 patients underwent BMS combined with RISS treatment (experimental group), and 52 patients underwent BMS alone (control group). Primary endpoints were technical success, complications and stent patency time (SPT). Secondary endpoints were clinical success and overall survival (OS).

Results The technical success (100% vs. 100%) and clinical success rate (92.50% vs. 90.04%) showed no statistically significance between the experimental and control groups ($P > 0.05$). The Grade 3–5 early and late complications showed no significance between both groups ($P > 0.05$). The SPT [(8.2 ± 0.39) vs. (5.8 ± 0.33) months] and OS [(13.6 ± 0.81) vs. (11.7 ± 0.44) months)] of the experimental group showed significantly longer than that of the control group (($P < 0.05$). Multivariate analysis revealed higher Bismuth type as an independent predictor for shorter OS (HR: 1.846, 95% CI: 1.019–3.341, $P = 0.043$) and SPT (HR: 1.959, 95% CI: 1.269–4.420, $P = 0.009$).

Conclusion Biliary metallic stent (BMS) placement combined with radioactive iodine-125 seed strands (RISS) is a safe and effective treatment option for patients with malignant hilar obstruction (MHO). However, multicenter randomized controlled trials are required to further validate the effectiveness and long-term benefits of this therapeutic approach.

Keywords Obstructive jaundice, ^{125}I seeds, Bile duct stent, Malignant hilar obstruction

Introduction

Malignant hilar obstruction (MHO) is caused by a heterogenous group of highly aggressive tumors that includes primary biliary cancer (Klatskin tumor), gallbladder cancer and metastatic cancer. It accounts for 50–70% of all neoplasms within the biliary tract and contributes to 2% of cancer-related death worldwide [1]. MHO is often diagnosed at an advanced stage because of its silent clinical character and non-specific symptoms [2]. The management of MHO is particularly challenging given its aggressive nature and complex anatomical relationships with hepatic and portal vessels [3]. Complete resection is considered the most effective therapy; however, only 20–30% of patients are eligible for resection at diagnosis stage. The five-year survival rate is only 20–35% and a recurrence rate as high as 70% in the past clinical study [4]. For the remaining unresectable patients, biliary metallic stent (BMS) placement is considered to be the

*Correspondence:
Dechao Jiao
jiaodechao007@126.com
[1]Department of Interventional Radiology, First Affiliated Hospital of Zhengzhou University, No. 1 Jianshe East Road, Zhengzhou City, China

preferred palliative treatment [5], which can effectively relieve the symptoms of biliary obstruction and improve the quality of life for patients, but it has no therapeutic effect on tumors [6]. Moreover, the efficacy of BMS is limited by tumor ingrowth and epithelial cell hyperplasia, leading to a 50% stent restenosis rate within 3 months [7]. Therefore, efforts to prolong the stent patency and patient survival needs to be explored.

Iodine-125 (^{125}I) is widely used in treating malignancies, either in the form of radioactive ^{125}I seeds implantation for solid organs or in the form of radioactive ^{125}I seed strands (RISS) in hollow organs such as the ureter, bile duct and blood vessels [8–10]. Our team demonstrated that radioactive ^{125}I seeds can significantly inhibit the proliferation, migration and invasion of MHO cells and promote apoptosis at previous study [11]. Inspired by the results, our team had used a method where multiple radioactive ^{125}I seeds were inserted into a 3 F catheter to form RISS, and such device were used together with BMS, which allowed the RISS to come into close contact with the intra-luminal tumor and exert local brachytherapy. Meanwhile, the BMS plays a physical role in maintaining the patency of lumen. Due to the effect of RISS, the invasion of tumors into the lumen will be greatly reduced, thereby prolonging the patency time of the BMS.

Materials and methods

Design and participants

A single center, retrospective analysis was done in this study and the data were collected form the First Affiliated Hospital of Zhengzhou University's electronic information system. From January 2016 to January 2022, 317 patients with MHO underwent percutaneous trans-hepatic biliary drainage at our center. Among them, 40 patients underwent BMS combined with RISS treatment (experimental group), and 52 patients underwent BMS treatment alone (control group). The stricture length (33.30 ± 7.1 mm vs. 34.29 ± 7.4 mm, $p = 0.52$) and diameter (27.61 ± 7.82 mm vs. 27.90 ± 8.45 mm, $p = 0.84$) showed no significant differences between the experimental and control group respectively.

In our institution, the decision-making process involves adherence to established institutional criteria for patient management. Patients are fully informed about their condition, potential risks, and benefits associated with the RISS procedure. The final treatment decision are made collaboratively, based on patient consent and a multidisciplinary team (MDT) review, considering tumor characteristics, prior treatments, performance status, and anatomical suitability. The inclusion and exclusion criteria were as follows:- Inclusion Criteria were: (1) age range 18–80 years old; (2) histopathology confirmed malignancy; (3) clinical symptoms directly related to obstructive jaundice; (4) dilation of peripheral bile ducts on pre-treatment imaging; (5) surgically unresectable or refusal to surgical treatments. The exclusion criteria were: (1) benign biliary obstruction; (2) presence of a BMS, or prior bile duct surgery; (3) massive ascites; (4) Bismuth type IV MHO; (5) Local tumor diameter > 4 cm; (6) Eastern Cooperative Oncology Group Performance score ≥ 3. The workflow and the baseline characteristics of all patients are list in Fig. 1; Table 1, respectively.

Pre-procedure

GTV was defined as the gross tumor volume visualized through imaging (CT/MRCP). With reference to International Commission on Radiation Units and Measurements (ICRU) report (No.58), to acquire the clinical target volume (CTV), the gross tumor volume (GTV) was expanded by 5 mm in all directions. The ^{125}I seed (model 6711; size: 0.8 mm ×4.5 mm; Chinese Atomic Energy Science Institution, Beijing, China) was a cylindrical radioactive source encapsulated by titanium, which has a half-life of 59.4 days and an effective irradiation radius of 15 mm was used. For the preparation of RISS, the head of the 3 F catheter (length = 40 cm, Cook, USA) was sealed using the heat burning method, and then multiple radioactive ^{125}I seed were inserted into the catheter one by one without gaps between seeds. The total number of ^{125}I seeds was calculated using the following formula: seeds number = (biliary obstruction length + 20 mm)/4.5 mm. Then, the unfilled portion of the catheter was cut off, and the tail end of the catheter was sealed again using the heat burning method to form RISS with both ends closed. Throughout the study a self-expandable BMS (Taewoong, Seoul, Korea) [8 mm×(50–80) mm] was used to reopen the MHO, both in experimental and control group. Treatment Planning System (TPS) (BT-RSI model TPS, Beijing, China) was used to ensure that the prescribed irradiation dose was delivered precisely to the tumor site. The TPS was utilized to calculate dose distribution, taking into account the tumor size (GTV), Clinical Target Volume (CTV), and organs at risk (OARs), such as the portal vein. It also ensured that the dosimetry at critical reference points was within safe limits.

Procedures

Before the procedure, biochemical indicators [white blood cell (WBC), platelet (PLT), hemoglobin (Hg), Prothrombin time (PT), total bilirubin (TBIL), direct bilirubin (DBIL), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and CA 19 – 9] were tested, and enhanced MR/CT were obtained to evaluate of the correlation of tumor extent and dilated biliary tree. The larger liver lobe was selected as the drainage liver, and an appropriate approach was selected to avoid vessels and lung damages. A satisfactory pain control was

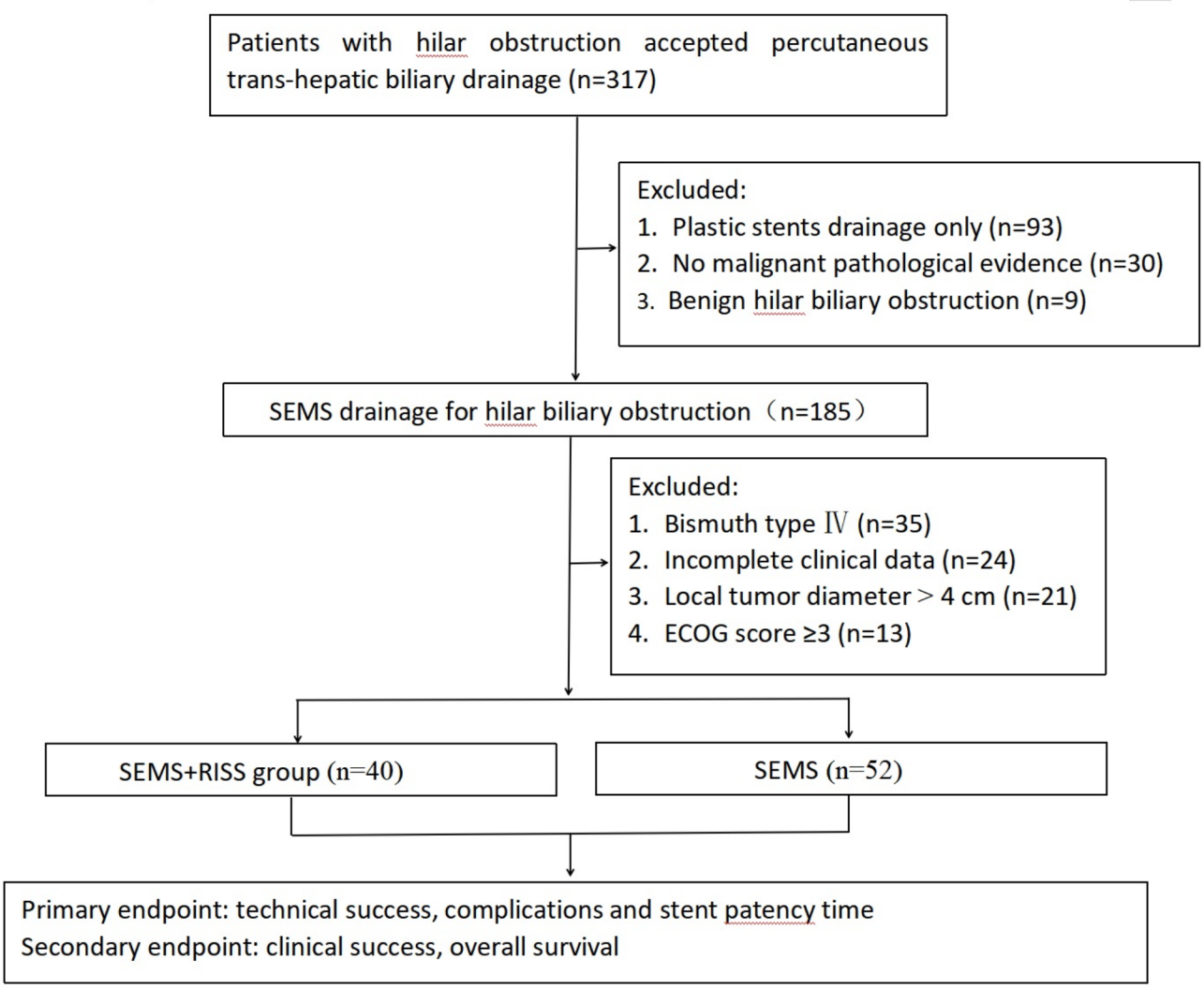


Fig. 1 The workflow of the study

done by the mixture of dexmedetomidine hydrochloride (400 μg) and deszocin (10 mg) infused (4–8 ml/h, total volume 50 ml) by a medical pump. All interventional procedures were done by Dechao Jiao and Zhanguo Sun, who had 15 and 9 years of biliary intervention experiences under the fluoroscopy (Artis Zeego, Siemens, Germany) and ultrasound (DP8800, Mindray, China) guidance. 2% lidocaine (10 ml) was used for local anesthesia, and the dilated perihepatic biliary branch was punctured by a 21G Chiba needle (Cook, USA), 5–10 ml contrast agent (Hengrui, 270mgI/100 ml) was injected to confirm the biliary information. A 0.018-inch platinum guidewire (35 cm in length, Cook, USA) was used to introduce through the 21G Chiba needle and a 6 F sheath (Cook, USA) was exchanged along the 0.018-inch guidewire. 0.035 inch guidewire (Terumo, Japan) was inserted into the 6 F sheath, and 6 F sheath was exchanged for a 5 F Cobra catheter (90 cm in length, Cook, USA); the guidewire and catheter were manipulated with each other to reopen the MBO. If required, an intra-luminal biliary forceps biopsy was done according to our previous study [12]. When the malignant evidence was confirmed, the 8 F sheath (length 23 cm, Cordis, USA) guidewire was exchanged to establish the following manipulation access. Both 0.035-inch guidewire (guidewire-1 is soft guidewire, guidewire-2 is strength guidewire) were inserted into the bile duct through the 8 F sheath. After withdrawing the 8 F sheath, the 6 F sheath was advanced along the guidewire-1 and 6 F BMS delivery system was advanced along the guidewire-2. A 6–8 mm balloon (Boston Scientific, USA) dilation catheter was used when BMS delivery system was inserted in case of difficulty. Under the guidance of real-time fluoroscopy, the BMS was successfully released across the biliary stricture, and then the RISS was pushed through the 6 F sheath to the biliary stricture part while withdrawing the 6 F sheath. An 8.5 F external

Table 1 Baseline data characteristics

Characteristics	BMS with RISS group (*n* = 40)	BMS alone group (*n* = 52)	*P* value
Age (year)	64.28 ± 8.89	63.27 ± 9.91	0.46
Sex (Male/female) (n, %)	26(65%)/14(35%)	30(57.7%)/22(42.3%)	0.47
Diagnosis (CC/GBC/Metastasis) (n, %)	15(37.5%)/13(32.5%)/12(30.0%)	22(42.3%)/16(30.8%)/14(26.9%)	0.89
Bismuth type (Type I/II/III) (n, %)	18(45%)/12(30%)/10(25%)	21(40.4%)/15(28.8%)/16(30.8)	0.88
Clinical staging (Stage III/ IV)	17(42.5%)/23(57.5%)	20(38.5%/32(61.5)	0.69
Stricture length (mm)	33.30 ± 7.1	34.29 ± 7.4	0.52
Stricture diameter (mm)	27.61 ± 7.82	27.90 ± 8.45	0.84
ECOG score (Score 0/1/2) (n, %)	8(20%)/23(57.5%)/9(22.5%)	12(23.1%)/25(48.1%)/15(28.8%)	0.66
Biochemical indicators			
WBC ($\times 10^{12}$/L)	6.16 ± 1.39	6.16 ± 1.46	0.95
Platelet ($\times 10^{9}$/L)	168.55 ± 27.23	168.58 ± 27.15	0.98
Hemoglobin (g/L)	124.13 ± 11.41	124.90 ± 15.58	0.93
Prothrombin time(s)	18.82 ± 2.36	18.56 ± 2.64	0.57
TBIL (μmol/L)	201.38 ± 60.78	203.60 ± 63.25	0.79
DBIL (μmol/L)	159.70 ± 53.80	160.35 ± 54.48	0.93
Albumin (g/L)	38.65 ± 2.60	38.79 ± 2.54	0.73
ALT (U/L)	97.96 ± 35.54	94.21 ± 33.47	0.71
AST (U/L)	87.62 ± 23.57	87.06 ± 35.59	0.51
CA19-9 (U/ml)	555.55 ± 205.76	558.03 ± 239.88	0.79

RISS: Radioactive ^{125}I seeds strands; BMS: Biliary metallic stent; ECOG: Eastern Cooperative oncology group;

WBC: White blood cell; PLT: Platelet; TBIL: Total bilirubin; DBIL: Direct bilirubin; ALT: Alanine aminotransferase;

AST: Aspartate aminotransferase; CC: Cholangiocarcinoma; GBC: Gall bladder cancer

or inter-external drainage tube was advanced along guidewire-2 and then fixed externally (Fig. 2). Removing the biliary drainage tube one month later after confirmation of stent patency by cholangiography. Single-photon emission computerized tomography (SPECT) was used to verify the position of the RISS, and estimated radiation dose at the reference point (5 mm from the RISS) was calculated using a computerized treatment planning system (BT-RSI model TPS, Beijing, China). 1 month later, laboratory values (WBC, PLT, Hg, PT, TBIL, DBIL, and albumin, ALT, AST and CA 19 – 9) were analyzed between the two groups. Routine follow-up occurred every 1 month to evaluate the SPT. Follow-up was performed by telephone or by visiting the patients or their relatives.

Study endpoints and definitions

The primary endpoints were technical success, complications and SPT. Secondary endpoints were clinical success and overall survival (OS). Technical success was defined as the successful deployment of the BMS and RISS. Clinical success was defined as a decrease of TBIL levels by at least 50% of pre-treatment value within 1 month. Early and late complications were defined as those occurring within and after 1 month of BMS placement according to the guidelines of the Society of Interventional Radiology Standards of Practice Committee [13]. Only grade 3–5 complications were recorded. BMS occlusion was defined as the recurrence of symptoms of obstructive jaundice with bilirubin level more than three times the normal and biliary dilatation on the MR/CT. The SPT was defined as the interval from stent placement to occlusion. The OS was defined as the interval from the stent placement to patient's death.

Statistical analysis

Statistical procedures were performed using the statistical package of SPSS (version 23.0, SPSS, Chicago, Illinois). Baseline characteristics were calculated by Chi-Square or independent samples t-test. The data before and after the procedure in the same group was compared with the Wilcoxon Signed-Rank test. The difference in the variance (difference between pre-procedure and post-procedure) between the two groups was compared with Mann–Whitney test. Technical success, clinical success and complications were compared with Fisher exact test. OS and SPT were compared with the Kaplan–Meier method. Statistically significant factors in univariate analysis were included in multivariate cox regression analysis. A cox proportionate hazard model was used to estimate the hazard ratio. A *P* value of less than 0.05 was considered to be significantly different.

Results

The clinical data of 92 patients with MHO in our department from January 2016 to January 2022 were retrospectively analyzed. Among them, 52 patients underwent BMS treatment alone, and 40 patients underwent BMS combined with RISS treatments (Figs. 3, 4 and 5). The left/right puncture approaches were 6/34 and 11/41 at

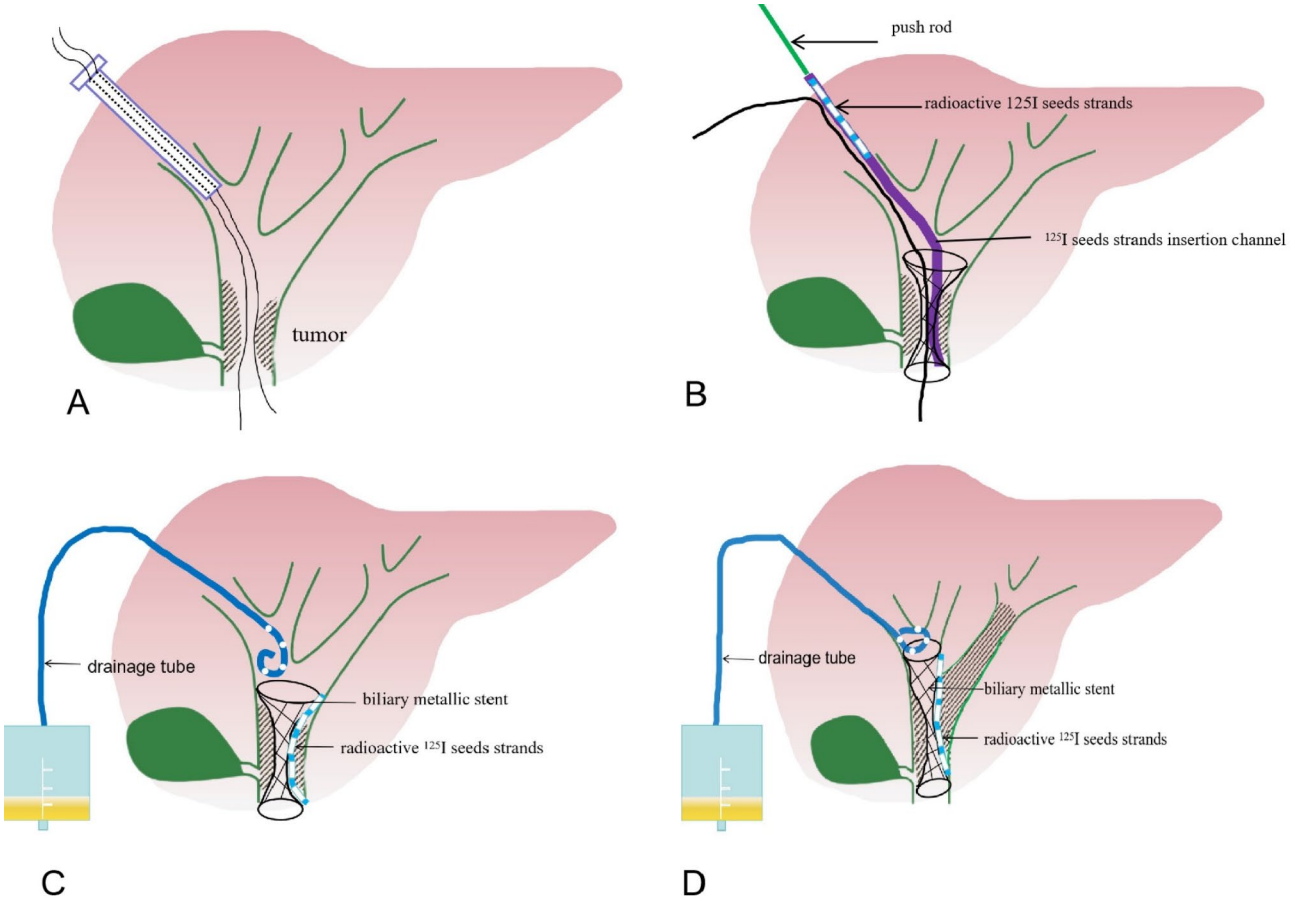


Fig. 2 Schematic diagram of biliary metal stent (BMS) deployment and radioactive ^{125}I seeds strand (RISS) placement. (**A**) Double guidewires were inserted into the bile duct through a 8 F short sheath (**B**). BMS was deployed with the help of strength guide wire. 6 F sheath was advanced along the soft guidewire and then RISS was pushed through the sheath after removing the guidewire. (**C**) Final representation of BMS together with RISS and drainage catheter in Bismuth I/II type. (**D**) Final representation of BMS together with RISS and drainage catheter in Bismuth III type

experimental and control group, respectively, which showed no significance ($p > 0.05$). The technical success of both groups were 100%, which showed no significance ($p > 0.05$). One month after surgery, all biliary stents were unobstructed and biliary drainage tubes could be successfully removed. However, three (7.5%) in the experimental group and 5 (9.6%) patients in the control group were defined as clinical failure due to bilirubin decrease that did not reach 50% of preoperative levels, so the clinical success rates were 92.50% and 90.04%, respectively, which showed no statistically significance between the two groups ($P > 0.05$) (Table 2). Pre and postoperative comparison of biochemical and tumor marker all revealed significant difference in the same group ($p < 0.05$), but there was no statistically significant difference in the decrease of preoperative and postoperative indicators of TBIL, DBIL, ALT, and CA 19 – 9 between the experimental group and the control group (Table 3) ($P > 0.05$).

The stent occlusion due to tumor ingrowth and debris formation was 27.5% (11 of 40 patients) in experimental group and 52% (27 of 42 patients) in control group ($p < 0.05$). One case in experimental group encountered a partial stent migration after on weeks follow-up. This did not result in any clinical complications or impact the treatment efficacy. As for early Grade 3–5 complications, there were biliary infection ($n = 2$), recurrent biliary bleeding ($n = 4$) and cholangitis ($n = 7$) were observed at both groups, but it showed no significance between both groups (all $P > 0.05$). As for Grade 3–5 late complications, there were cholangitis ($n = 7$), cholecystitis ($n = 3$), pancreatitis ($n = 2$) and ^{125}I strands displacement ($n = 1$) were observed at both groups, but it also showed no significance (all $P > 0.05$), which suggested that the use of the RISS did not increase the complication rate (Table 4). There were no cases of stent-related perforation, liver abscess or biliary fistula.

The SPT [(8.2 ± 0.39) vs. (5.8 ± 0.33) months)] and OS [(13.6% ± 0.81) vs. (11.7 ± 0.44) months)] of the experimental group showed significantly longer duration than that of the control group ($P < 0.05$) (Fig. 6). The estimated radiation dose at the dose reference points (5 mm

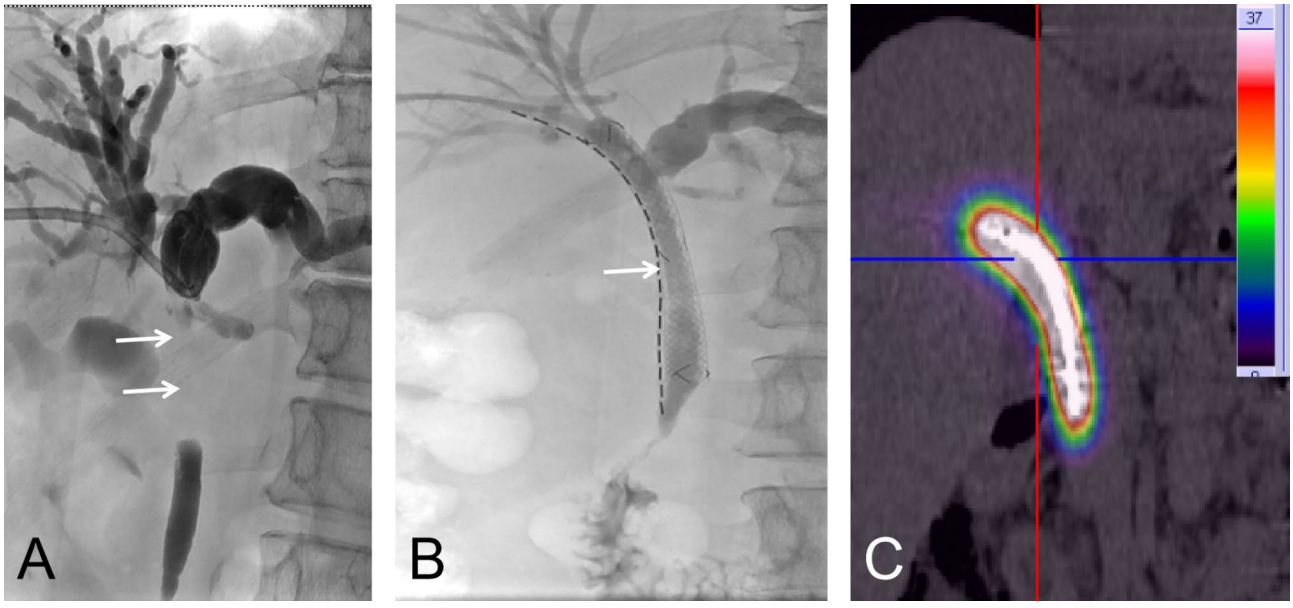


Fig. 3 Woman, 56 years old (Experimental group). (**A**) Percutaneous transhepatic cholangiography was performed to visualize the tumor location (arrow) under fluoroscopy. (**B**) Postoperative cholangiography RISS (arrow) together with BMS and restoration of biliary patency. (**C**) Coronal sections showing Gamma rays on SPECT with a high local dose and an extremely low dose to the normal surrounding tissues

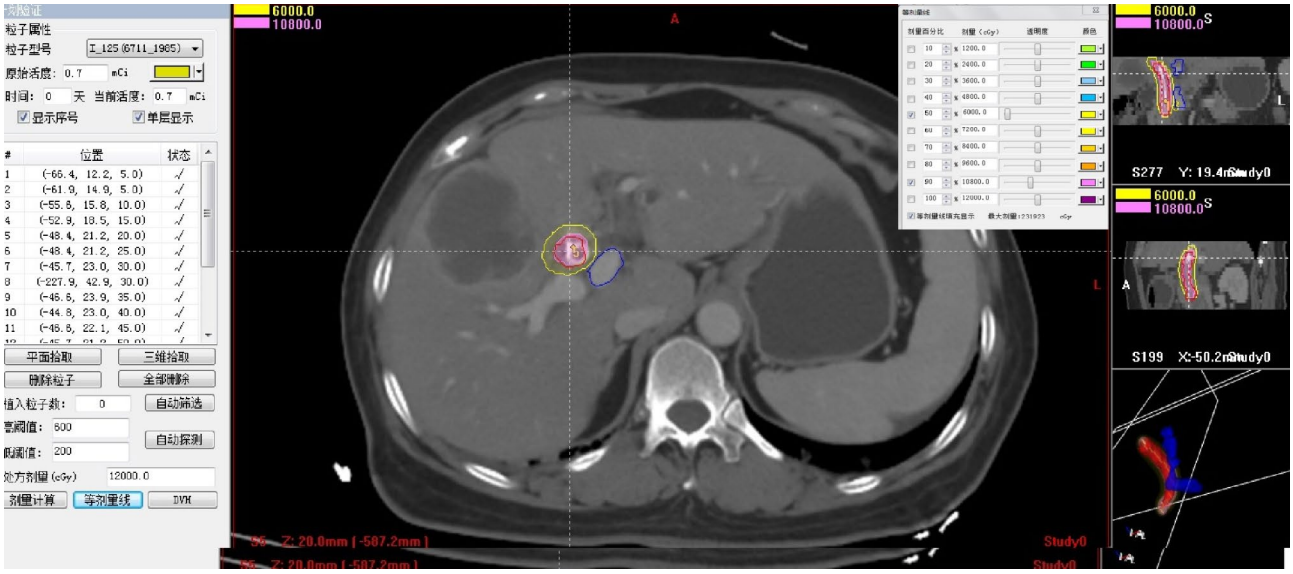
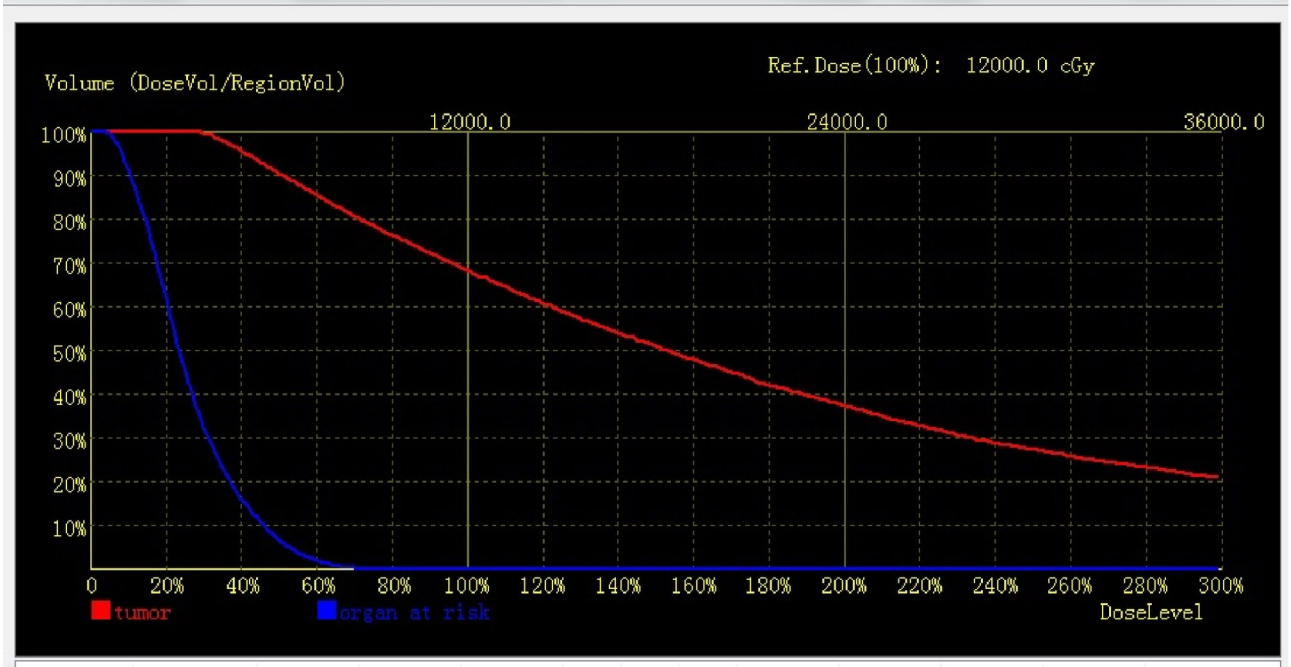


Fig. 4 Local cumulative dose 5 mm (dose reference point) from RISS was calculated by brachytherapy treatment plan system

from the source axis) and organ at risk (portal vein) was (58.20 ± 4.22) Gy (range 50.9–65.3 Gy) and (10.51 ± 0.92) Gy (range 8.2–12.5 Gy), respectively. There were a total of 66 deaths throughout the study including 32 patients [progression of disease ($n = 25$), multiple organs failure ($n = 7$)] in the experimental group and 34 patients [progression of disease ($n = 24$), multiple organs failure ($n = 8$), and respiratory infection ($n = 2$)] in the control group. Univariate and multivariate Cox regression analysis for factors relevant to SPT and OS are shown in Tables 5 and 6 respectively. Bismuth type remained a significant independent predictor of both OS (HR: 1.846, 95% CI: 1.019–3.341, $P = 0.043$) and SPT (HR: 1.959, 95% CI: 1.269–4.420, $P = 0.009$) in multivariable analysis.

Discussion

MHO are usually caused by adenocarcinomas involving the proximal bile duct. For decades, increasing efforts had been made to understand the complexity of MHO and to develop new diagnostic tools and therapies that might improve clinical outcomes [14]. Radical resection was preferred for resectable tumors, but complications



Name	Plan	Min	Max	Mean	CI	EI	HI	D50.0	D80.0	D90.0	D100.0	V80
tumor	Plan0	3149.1	196253.5	27997.4	0.42	0.44	0.26	18339.4	8599.7	6124.9	3149.1	19.9cc(76.4%
organ a...	Plan0	521.9	9210.1	3138.9	0.00	1.43	0.00	2827.2	1737.6	1276.7	521.9	0.0cc(0.0%)

Fig. 5 Dose volume histogram of the dose reference point and organ at risk (portal vein)

Table 2 Intra- and post- operation parameters

Characteristics	RISS combined with BMS group($n=40$)	BMS alone group($n=52$)	*P* value
Technical success (%)	100%	100%	-
Clinical success (yes/no, %)	37/3 (92.50%)	47/5 (90.04%)	0.74
Puncture approach (Left/right)	6/34	11/41	0.45
Procedural time (min) (range)	50.72 (39–71)	42.76 (36–64)	0.00
Biochemical indicators at 1 month			
WBC ($\times10^{12}$/L)	6.07 ± 1.19	5.75 ± 1.15	0.25
PLT($\times10^{9}$/L)	168.48 ± 24.87	167.23 ± 28.08	0.70
Hemoglobin (g/L)	127.88 ± 10.16	130.96 ± 14.51	0.41
Prothrombin time(s)	17.50 ± 1.18	18.10 ± 1.55	0.49
TBIL (μmol/L)	80.39 ± 26.84	79.72 ± 29.65	0.49
DBIL (μmol/L)	55.34 ± 19.21	53.01 ± 23.40	0.30
Albumin (g/L)	39.84 ± 2.19	39.81 ± 2,22	0.80
ALT (U/L)	48.35 ± 11.63	45.89 ± 13.49	0.21
AST (U/L)	47.28 ± 10.62	49.52 ± 11.42	0.36
CA19-9 (U/ml)	152.10 ± 42.93	221.90 ± 101.09	0.00
Post-procedural chemotherapy (Yes/no, %)	23(%)/17(%)	38(%)/14(%)	0.11
Median patency time(month, 95%CI)	8.2 ± 0.39 (7.41–8.98)	5.8 ± 0.33 (5.14–6.45)	0.00
Median overall survival (month, 95%CI)	13.60 ± 0.81 (12.01–15.19)	11.70 ± 0.44 (10.82–12.57)	0.02

WBC: White blood cell; PLT: Platelet; TBIL: Total bilirubin; DBIL: Direct bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase

(14–36%) often arise. Despite new interventions like portal vein embolization [15] and bile duct reconstruction [16] had been carried out, tumor recurrence still exceeded 50% yielding a 5-year OS below 20%. For unresectable tumors, palliative care involved endoscopic or transhepatic interventions with BMS placement which can decrease the elevated biliary pressure, leading to liver function recovery and improvement of quality of life for patients [17]. Although BMS placement is a minimally invasive intervention with efficient biliary drainage, stent occlusion by tumor overgrowth, tissue reactive hyperplasia and debris can occur resulting in hyperbilirubinemia

Table 3 Comparison of important biochemical and tumor marker indicators

Characteristics	BMS with RISS group($n=40$)	BMS alone group($n=52$)	*P* value
TBIL(μmol/L)			0.45
Pre-treatment	201.38 ± 60.78	203.60 ± 63.25	
Post-treatment at 1 month	80.39 ± 26.84	79.72 ± 29.65	
P value	0.00	0.00	
DBIL(μmol/L)			0.48
Pre-treatment	159.70 ± 53.80	160.35 ± 54.48	
Post-treatment at 1 month	55.34 ± 19.21	53.01 ± 23.40	
P value	0.00	0.00	
ALT(U/L)			0.42
Pre-treatment	97.96 ± 35.54	94.32 ± 33.47	
Post-treatment at 1 month	48.35 ± 11.63	45.89 ± 13.49	
P value	0.00	0.00	
CA19-9 (U/ml)			0.39
Pre-treatment	555.55 ± 205.76	558.03 ± 239.88	
Post-treatment at 1 month	152.10 ± 42.93	221.90 ± 101.09	
P value	0.00	0.00	

TBIL: Total bilirubin; DBIL: Direct bilirubin; ALT: Alanine aminotransferase; CA19-9: Carbohydrate Antigen 19 – 9

Table 4 Postoperative complications (Grade 3–5) between two groups

Characteristics	BMS with RISS group($n=40$)	BMS alone group($n=52$)	*P* value
Early complications (n, %)			
Biliary infection	1 (2.5)	1 (1.9)	0.85
Recurrent bile duct bleeding	2 (5)	2 (2.8)	0.78
Cholangitis	3 (7.5)	4 (7.6)	0.97
Late complications (n, %)			
Cholangitis	3 (7.5)	4 (7.6)	0.97
Cholecystitis	1 (2.5)	2 (2.8)	0.71
Pancreatitis	1 (2.5)	1 (1.9)	0.85
^{125}I strands migration	1 (2.5)	0	0.25

again. Therefore main goal to prolong the OS is by ensuring long-term patency of the stent. In our study, RISS is like a linear radioactive protective wall that suppresses tumor growth, reducing tumor growth into the BMS, and it can emit γ-ray within a defined perimeter and therefore has the following advantages [18]: (1) precise targeting to biliary tumor without damage to surrounding vital organs like the portal vein, pancreas and spinal cord; 2) RISS can be prepared easily and suitable for promotion in grassroots hospitals; 3) such procedures can be performed under local anesthesia as a day care surgery; 4) RISS is flexible and is suitable for the curved structure of bile duct. The cost of RISS may vary based on factors such as the number of iodine-125 seeds required, additional imaging guidance, and regional price differences. In comparison to SEMS-only placement (approximately $11,000) in our institution, RISS placement is estimated to incur an additional cost ranging from $4,000 to $8,000. This includes the cost of iodine-125 seed strands ($43 per seed), procedural charges ($1,200), additional instruments such as guidewire and catheters ($1,000–$3,000), and SPECT/CT verification ($1,000). However, these costs may be balanced by improved stent patency and a reduced need for re-intervention over time.

Chen Y et al. [19] were first to evaluate the effects of RISS on the bile duct in a study involving 16 healthy pigs. The study demonstrated that the peak of biliary injury occurred at 15 days, with significant epithelial cell repair beginning at 30 days and near-complete recovery observed by 60 days. Notably, no severe complications such as bile duct perforation or bleeding were identified, indicating that the damage caused by radioactive iodine-125 seeds to the normal bile duct wall is mild, temporary, and reversible. In 2012, Chen Y et al. [20] firstly reported the feasibility of BMS with RISS for malignant obstruction among 34 patients, and SPT of the brachytherapy ($n=17$) and conventional stents ($n=17$) were 10.2 and 7.2 months, respectively ($p=0.03$). In 2015, Zhang W firstly reported a case report of two RISS and two stents in the right and left intrahepatic bile ducts for the treatment of a 75 old man with hilar cholangiocarcinoma (Bismuth type IV). Considering the simplicity and convenience of this operating method, and the significant improvement in SPT, more and more centers adopted this combined method to treat malignant obstructive jaundice. The clinical studies published in recent year are summarized in Table 7 [21–25]. The technical success rate was 100% with complication range ranging from 8.3 to 35.5%. SPT and OS were ranged from 5.8 to 12.3 months and 7.3 to 13.1 months respectively. The results of our current study fall within previously reported range. Stent patency time (SPT) was significantly longer in the experimental group (8.2 months), possibly due to the combination of the metal stent's radial force, and the I-125 seeds' radiation, which inhibited tumor growth around the stent. This dual effect helped prevent early re-obstruction and prolonged SPT compared to the control group. In this study, Bismuth type remained a consistent and independent predictor of both OS and SPT, while stricture length lost statistical significance after multivariate adjustment. The observed discrepancy may be attributed to the anatomical complexity captured by Bismuth classification, which could influence both the extent of stricture and prognosis. This finding aligns with previous research [21–25], highlighting the challenge of maintaining stent function in more advanced biliary strictures. Additionally, the lack of a significant impact in post-procedural chemotherapy on stent patency suggests

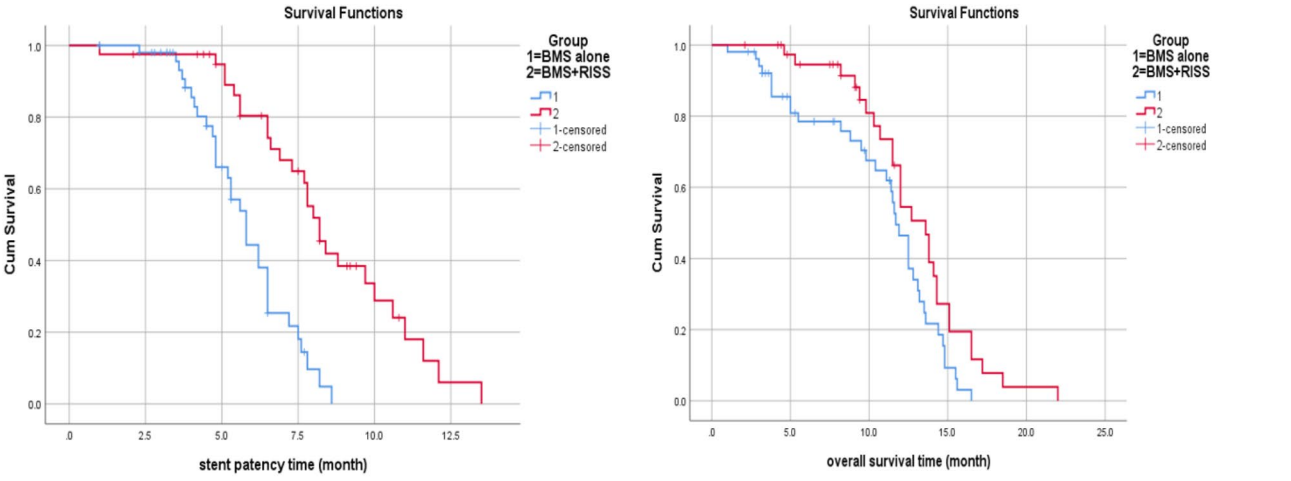


Fig. 6 Stent patency time and overall survival in both groups

Table 5 Univariate and multivariate analysis of prognostic factors of SPT

Factors			Univariate analysis		Multi variate analysis	
		No of cases	Median SPT (95% CI)	*P* value	HR (95% CI)	*P* value
Age (year)	< 65	50	7.30 (6.18–8.41)	0.866		
	≥ 65	42	6.50 (4.53–8.46)			
Gender	Male	56	7.60 (6.68–8.51)	0.777		
	Female	36	6.60 (4.61–8.38)			
Diagnosis	CC	37	6.50 (5.99–8.60)	0.272		
	Others	55	7.30 (5.78–7.41)			
Bismuth type	I-II	66	7.50 (6.29–8.70)	0.038	1.959 (1.269, 4.420)	0.009
	III	26	5.10 (4.58–5.61)			
Stricture length	< 30 cm	24	8.20 (7.51–8.83)	0.027	0.928 (0.441, 1.953)	0.844
	≥ 30 cm	68	6.50 (5.84–7.15)			
Stricture diameter	< 25 cm	51	7.50 (5.83–9.16)	0.690		
	≥ 25 cm	41	6.60 (5.52–7.67)			
Clinical stage	Stage 3	37	6.50 (5.19–7.80)	0.538		
	Stage 4	55	6.90 (5.76–8.03)			
Post-procedural chemotherapy	Yes	31	5.80 (4.95–6.65)	0.510		
	No	61	7.70 (6.67–8.73)			
ECOG stage	Stage 0	20	5.80 (4.32–7.27)	0.935		
	1 and 2	72	7.30 (5.86–8.73)			
CA 19 – 9 (U/mL)	< 520	46	7.60 (5.97–9.22)	0.242		
	≥ 520	46	6.50 (5.99-7.00)			

ECOG: Eastern Cooperative oncology group; CA 19 – 9: Carbohydrate Antigen 19 – 9

that while chemotherapy is essential for managing the underlying cancer, it may not directly enhance stent performance. This possibly highlights the mechanical nature of stent-related outcomes, where procedural factors and stricture severity play a more significant role than adjunct therapies. Furthermore, when we compared the difference in the reduction of preoperative and postoperative indicators of TBIL, DBIL, ALT, and CA 19 – 9 within 1 month between the experimental and control group, no statistically significance were observed. This suggests that both method showed the same drainage function for short-term, but due to longer SPT of the brachytherapy stent, liver function can be maintained in a normal state for a long time, and further anti-tumor treatments can be received, providing a basis for prolonging OS.

Taking inspiration from RISS and BMS, Zhu et al. [26] developed a new biliary stent that can loaded ^{125}I seeds. Which consists of a framework stent loading ^{125}I seeds and conventional stent. Balloon dilation should be done to assist the inner stent fully deployment. Furthermore, such complex design increases the cost and operational difficulty, so only experienced operators can master the implementation, but this functional stent has shown better clinical results than conventional stents, indicating

Table 6 Univariate and multivariate analysis of prognostic factors of OS

Factors		Univariate analysis			Multi variate analysis	
		No of cases	Median OS (95% CI)	*P* value	HR (95% CI)	*P* value
Age (year)	< 65	50	12.00 (10.27–13.72)	0.210		
	≥ 65	42	12.50 (9.94–15.05)			
Gender	Male	56	12.80 (10.98–14.61)	0.649		
	Female	36	11.90 (10.91–12.88)			
Diagnosis	CC	37	13.10 (10.70–15.50)	0.838		
	Others	55	11.90 (10.53–13.26)			
Bismuth type	I - II	66	13.10 (11.13–15.06)	0.023	1.846 (1.019–3.341)	0.043
	III	26	11.30 (9.18–13.41)			
Stricture length (mm)	< 30	24	12.80 (11.15–14.41)	0.036	0.661 (0.361–1.121)	0.181
	≥ 30	68	11.70 (9.63–12.76)			
Stricture diameter (mm)	< 25	51	13.10 (10.00-16.19)	0.283		
	≥ 25	41	12.00 (10.76–13.23)			
Clinical stage	Stage 3	37	11.90 (9.98–13.81)	0.538		
	Stage 4	55	12.50 (10.88–14.11)			
Post-procedural chemotherapy	Yes	31	13.50 (12.60-14.39)	0.099		
	No	61	11.70 (9.92–13.48)			
ECOG stage	Stage 0	20	14.40 (12.34–16.45)	0.357		
	1 and 2	72	11.70 (10.91–12.48)			
CA 19 – 9 (U/mL)	< 520	46	12.00 (9.53–14.46)	0.569		
	≥ 520	46	12.80 (10.95–14.64)			

ECOG: Eastern Cooperative oncology group; CA 19 – 9; Carbohydrate Antigen 19 – 9

Table 7 Clinical controlled studies studies on study of RISS and BMS

Year/author/ study design	Group information (*n*)	Tumor Composition (*n*)	Obstruction location (*n*)	Technical success (%)	Median SPT	Median OS	AE (*n* or %)
2017/Jiao D/PS[21]	BMS + RISS (31) BMS (30)	PS (40) Non-PS (21)	Hilar (12) Non-hilar (49)	100 vs. 100	368 vs. 220 d	355 vs. 209 d	Early AE: 35.5vs 25.8% Late AE: 30.0 vs. 23.3%
2020/Zhou C/RS[22]	BMS + RISS (40) BMS (36)	PS (41) Non-PS (35)	Hilar (76) Non-hilar (0)	100 vs. 100	387 vs. 121 d	177 vs. 123 d	AE: 50.0 VS 38.9%
2020/Pan T/RS[23]	BMS + RISS (30) BMS (54)	Not supplied	Not supplied	100 vs. 100	231 vs. 110 d	310.6 vs. 173.2 d	AE: 13.3 vs. 11.1%
2021/Li J/RS[24]	BMS + RISS (48) BMS (62)	Not supplied	Not supplied	100 vs. 100	175 vs. 120 d	209 vs. 202 d	AE:8.3 vs. 8.1%
2023/Sheng Y/RS[25]	BMS + RISS (34) BMS (25)	PS (22) Non-PS (37)	Hilar (52) Non-hilar (7)	100 vs. 100	289 vs. 88 d	221 vs. 78 d	AE: Cholangitis (5.1 vs. 4%); self-limited hemobilia (5.9 vs. 0%); severe pain (8.8 vs. 8%); liver abscess (2.9 vs. 0%)

PC: Primary Cholangiocarcinoma; BMS: biliary metallic stent; RISS: Radioactive 125I seeds strands; d:day; AE: adverse event

that this is a very promising research and development direction. However, both the stent and ^{125}I seeds will require a significant fusion of medical and engineering techniques to solve the disadvantages. As for the cumulative dose, the estimated radiation dose at the dose reference points reached 58.2 Gy in our study, surpassing the achievable doses in traditional radiotherapy (40–50 Gy) and High-Dose Rate Brachytherapy with ^{192}Ir (30–35 Gy) [27, 28]. This difference together with continuous radiation from the ^{125}I seeds over time helped delay tumor growth and maintain stent patency for a longer period.

Complications related to adjacent organs like duodenitis, bowel obstruction and gastrointestinal bleeding did not occur during the follow-up period which can be considered as an advantage of RISS against traditional radiotherapy. The RISS was not routinely removed in this study as it is designed to deliver continuous low-dose radiation over time. Removal was only considered in cases of complete migration which did not occurred. Partial migration occurred in one patient after 4 weeks was seen during follow-up but no discomfort symptoms were observed.

In addition to ^125I brachytherapy, other local treatments for malignant hilar obstructions (MHO) such as Photodynamic Therapy (PDT), Radiofrequency Ablation (RFA), and Stereotactic Body Radiation Therapy (SBRT) are outgrowing. PDT is effective for selective tumor necrosis with minimal damage to adjacent structures but is limited by, shallow tissue penetration and photosensitivity [29]. A recent study which included 55 studies for unresectable extrahepatic cholangiocarcinoma showed a pooled OS of 11.9 months (95% CI: 10.7–13.1) compared to 8.1 months (95% CI: 6.4–9.9) for PDT and RFA combined with SEMS respectively [30]. Takenaka et al. reported SPT between 90 and 230 days and OS ranging from 147 to 342 days with RFA and SEMS use in similar settings [31]. SBRT allows precise and high-dose radiation delivery and has shown a promising results in preliminary study involving MHO. Frakulli et al. [32] in their study involving 10 studies utilizing SBRT for cholangiocarcinoma, reported a median overall survival (OS) of 15 months; however, clinically significant late toxicities were reported in multiple studies, including duodenal complications like obstruction and ulceration reaching as high as 22.2% and biliary stenosis up to 8.3%. While these local treatment shows potential, future studies directly comparing these treatments will help determine the optimal treatment approach.

In conclusion, this study suggests that biliary metallic stent (BMS) placement combined with radioactive iodine-125 seed strands (RISS) is a safe and feasible treatment approach for patients with malignant hilar obstruction (MHO), showing potential benefits in stent patency and overall survival. However, due to the single-center retrospective design, small sample size, and procedures performed exclusively by highly experienced interventional radiologists, the findings should be interpreted with caution. Larger, multicenter prospective studies are necessary to confirm the efficacy and broader applicability of this treatment strategy.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Milan Sigdel, and Dechao Jiao. The first draft of the manuscript was written by Milan Sigdel, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All authors acknowledge the preprint publication.

Funding

Major Science and Technology Projects in Henan Province (221100310100).

Data availability

In addition to the raw data in the manuscript, the datasets used are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committees of the First Affiliated Hospital of Zhengzhou University. The requirement for informed consent was waived by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University because of the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 5 April 2024 / Accepted: 3 February 2025
Published online: 10 February 2025

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