

# Study of Percutaneous Stent Placement with Iodine-125 Seed Strand for Malignant Biliary Obstruction

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Received: 20 July 2018 / Accepted: 8 November 2018 / Published online: 30 November 2018

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## Abstract

**Purpose** To evaluate the effectiveness and safety of simultaneous placement of a self-expandable metallic stents (SEMS) and iodine-125 seed strand in the management of malignant obstructive jaundice (MOJ).

**Materials and Methods** This study included 132 patients with MOJ treated from November 2015 to October 2017. Forty-five patients underwent insertion of SEMS with iodine-125 seed strands (Seeds group); the remaining 87 patients underwent SEMS placement alone (Control group). Technical success was defined as accurate, successful deployment of SEMS with or without iodine-125 seed strand; clinical success was defined as 20% reduction in serum bilirubin within 1 week after the procedure,

compared with baseline. Complications, duration of primary stent patency, and overall survival were evaluated.

**Results** Technical success was achieved in all patients in both groups. In the Seeds group, an average of 14 seeds (range 8–22) were implanted in the bile duct as a strand. Clinical success rates were similar between the groups (Seeds group, 93.3%; Control group, 95.4%). Major complications occurred in only one patient, in the Control group. The median period of primary stent patency was significantly longer in the Seeds group (194 days) than in the Control group (86 days;  $P = 0.049$ ). The median overall survival was also significantly longer in the Seeds group (194 days) than in the Control group (96 days;  $P = 0.031$ ).

**Conclusion** SEMS combined with iodine-125 seed strands is effective and safe in the management of MOJ and can improve stent patency and patient survival.

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**Keywords** Malignant obstructive jaundice · Iodine-125 seed · Self-expandable metallic stent · Stent patency · Survival

## Introduction

Malignant obstructive jaundice (MOJ) is a debilitating condition caused by various malignant lesions, including cholangiocarcinoma, pancreatic cancer, and gallbladder cancer. Only 20–30% of patients with MOJ are candidates for surgical resection at the time of diagnosis [1]. Percutaneous metallic stent placement is a widely accepted

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palliative treatment for obstructive jaundice [2]. However, stent reocclusion caused by tumor growth is a major disadvantage of this approach. Although covered self-expandable metallic stents (SEMS) have been developed to prevent tumor ingrowth, their high migration rate may counteract their benefits [3, 4]. Additionally, the current data are conflicting regarding whether covered stents prolong stent patency and survival [4–7].

Recently, intraluminal brachytherapy using iodine-125 seeds combined with SEMS has been reported for the treatment of MOJ [8–12]. These few studies have shown that combining iodine-125 seeds with SEMS might prolong stent patency and even patient survival. However, patient numbers in these studies have been small, and seed implantation techniques have differed; therefore, further investigation is warranted.

The purpose of this study was to evaluate the effectiveness and safety of simultaneous placement of SEMS and iodine-125 seed strands in the management of MOJ.

## Materials and Methods

### Patients

The study was approved by our institutional review board. We retrospectively reviewed the medical records and images of 131 patients who underwent placement of SEMS alone or SEMS combined with iodine seed strand for MOJ in our department between November 2015 and October 2017. Inclusion criteria were 1. diagnosis of MOJ on the basis of laboratory and imaging or pathological findings; 2. surgically unresectable disease; 2. no previous biliary drainage prior to admission; 3. regular follow-up. Five patients were excluded: three were lost to follow-up and two had received external drainage at other hospitals. Of the remaining 132 patients who met inclusion criteria, 87 underwent stent placement alone (Control group) and 45 received stent implantation with an iodine seed strand (Seeds group).

### Iodine-125 Seeds, and Stents

Iodine-125 seeds (Beijing Atom Hi-Tech, Beijing, China) with a radioactivity of 0.8 mCi and a half-life of 59.43 days were used. The seeds were 0.8 mm thick and 4.5 mm long. The principal photon emissions were 27.4 and 31 keV X-rays and 35.5 keV gamma rays. Three types of uncovered SEMS with a diameter of 8 mm and lengths from 40 to 100 mm were used in this study (E-Luminexx [Bard Peripheral Vascular, Tempe, AZ], S.M.A.R.T [Cordis, Milpitas, CA], and Zilver [Cook, Bloomington, IN]).

### Procedure

Before the procedure, the cause and location of the biliary stricture were evaluated on contrast-enhanced computed tomography and/or magnetic resonance cholangiopancreatography. Intravenous sedation with oxycodone and midazolam was used to alleviate pain during the procedure.

### Preparation of Iodine-125 Seed Strands

The number of iodine-125 seeds for implantation was calculated with the following formula:  $N = \text{length of stent} / 4.5$ . For stents placed across the ampulla of Vater, the number of seeds was calculated according to the length of stent within the bile duct. The seeds were loaded linearly in a 4-F catheter. The catheter was cut to match the length of the row of seeds. Both ends of the catheter fragment were then sealed with a heated vascular clamp.

### Seeds Group

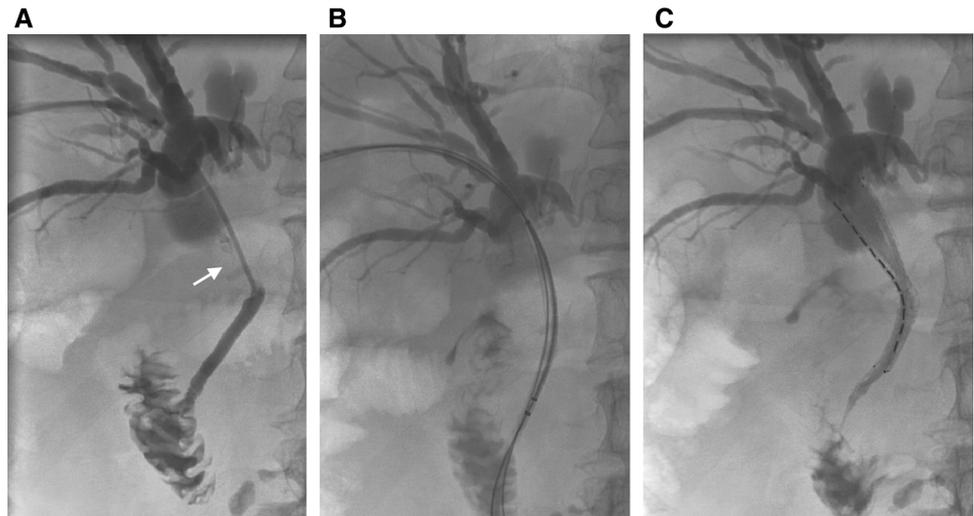
Procedures were performed under fluoroscopic guidance. The access site was chosen on the basis of pre-procedural images. The intrahepatic bile duct was punctured with a 22-G Chiba needle (Cook, Bloomington, IN), followed by insertion of a Neff percutaneous access set. The outer cannula of the Neff set was kept, and cholangiography was performed to evaluate the obstruction site. A 0.035-inch guidewire was then advanced, and the outer cannula of the Neff set was exchanged with a 5-F Headhunter or Cobra catheter to cross the obstruction site. After measurement of the length of the stricture, a long 5-F sheath was advanced over the guidewire to the duodenum; the guidewire was kept within the sheath. A stiff guidewire 260 cm long and 0.035 inches in diameter was inserted through the sheath to the distal duodenum. Next, the sheath was removed and reinserted over the short guidewire until its tip was 2–3 cm beyond the stricture. A bare SEM was advanced over the long guidewire and deployed in the center of the stricture. The stent extended 1.5–2 cm beyond the biliary stricture in each direction. After stenting, the iodine seed strand was inserted through the long 5-F sheath and placed between the biliary wall and the stent. Stent patency was confirmed with repeat cholangiography. The puncture approach was occluded with gelfoam pledgets through a sheath (Fig. 1).

### Control Group

The technique used in the Control group was similar to that described for the Seed group. After the stricture was crossed, a 6-F sheath was introduced over the 0.035-inch guidewire. Then, an uncovered SEM was inserted through the sheath and delivered across the stricture.

**Fig. 1** A 72-year-old man with unresectable esophageal carcinoma presented with obstructive jaundice.

**A** Cholangiography shows a stricture at the proximal common bile duct (white arrow). **B** Use of two guidewires to deploy a metallic stent and an iodine-125 seed strand. **C** An 8 × 6-cm self-expandable stent and a strand containing 12 iodine-125 seeds were implanted accurately. The stent was patent



Cholangiography was performed to verify stent patency. The puncture approach was occluded with gelfoam pledgets.

### Assessment and Follow-Up

Technical success was defined as successful deployment of the stent with or without iodine seed strand in the appropriate position, with good contrast passage through the stent into the intestine. Clinical success was defined as a 20% reduction in serum bilirubin level compared with preoperative baseline within 1 week after stent placement. All complications were classified as major or minor according to the reporting standards of the Society of Interventional Radiology [13]. Major complications were defined as those requiring major therapy, an unplanned increase in level of care, or prolonged hospitalization (> 48 h), and those causing permanent adverse sequelae or death. Other complications were regarded as minor.

All patients were regularly followed up through February 2018 or until patient death. The follow-up visits included outpatient and telephone interviews. Telephone interviews were performed at 2 weeks and then every 3 months after stent placement. Outpatient interviews were performed 1 month after stent implantation. If obstructive jaundice recurred (confirmed elevation of bilirubin level and dilatation of bile ducts on CT), the patient was encouraged to undergo stent revision or external drainage.

Primary stent patency was defined as the time interval between initial stent placement and recurrence of jaundice, the last follow-up, or patient death without evidence of jaundice. If a patient died without recurrent jaundice, the stent patency period was considered to equal the duration of survival. Survival was calculated from the time of initial stent placement to death from any cause or the last follow-

up visit. Data on stent patency and survival were censored for patients who remained alive at the time of this writing.

### Statistical Analysis

An independent *t* test was used to compare continuous variables. A Chi-squared test or Fisher's exact test was used to compare categorical variables, depending on the scale level. Survival curves were calculated with the Kaplan–Meier method and compared with a log-rank test. A two-tailed *P* value lower than 0.05 was considered statistically significant. All analyses were performed with SPSS version 15.0 software (SPSS, Chicago, Illinois, USA).

### Results

Among 132 patients included, 90 were men and 42 were women, with a mean age of 63.5 years (range 32–92 years). The etiologies of MOJ were cholangiocarcinoma ( $n = 50$ ), gallbladder carcinoma ( $n = 15$ ), pancreatic carcinoma ( $n = 21$ ), hepatocellular carcinoma ( $n = 16$ ), gastric cancer ( $n = 18$ ), ampullary cancer ( $n = 1$ ), and hilar node metastases from other solid malignancies ( $n = 11$ ). Diagnosis was based on pathologic results in 75 patients and on imaging and laboratory findings in 57 patients. The strictures were located at the proximal bile duct (hilar lesions) in 95 patients, at the middle and distal bile duct in 33 patients, and at the anastomotic site in four patients. According to Bismuth classification, 58 patients were type I, 28 were type II, and nine were type III.

## Technical Success

Technical success was achieved in all patients in both groups. In the Seeds group, 33 (73.3%) patients received one stent and 12 (26.7%) received two stents. In the Control group, 76 (83.9%) patients received one stent and 11 (16.1%) received two stents. In the Seeds group, two patients (type III) with left lobe atrophy and two patients (type II and III) with a large tumor mass in one lobe underwent unilateral stenting. In the Control group, three patients (type II and III) with left lobe atrophy, four patients (type II and III) with a large tumor mass in one lobe, and three patients (type II) with a history of left lobectomy underwent unilateral stenting. Stents measuring  $8 \times 60$  mm and  $8 \times 80$  mm were most commonly used in the two groups, accounting for 89.5% of stents in the Seeds group and 88.8% in the Control group. In the Seeds group, an average of 14 seeds (range 8–22) were implanted into the bile duct as a strand. The estimated mean radiation dose at the dose reference points (5 mm from the source axis) was  $72.0 \pm 6.7$  Gy (range 66.3–98.8 Gy). Baseline characteristics of the patients according to group are listed in Table 1; no significant differences in characteristics were observed between the groups ( $P > 0.05$ ).

## Clinical Success

The clinical success rate was similar between the groups [Seeds group, 93.3% (42/45); Control group, 95.4% (83/87)]. Among the seven patients who failed to achieve clinical success, a 20% reduction in serum bilirubin level occurred after more than 1 week in three patients who developed post-procedure pancreatitis and in three who developed cholangitis and were treated medically. One patient in the Control group with obviously increased bilirubin level 1 week after the procedure underwent reintervention and received a new stent because the previous stent was occluded. Liver function parameters, including total bilirubin, direct bilirubin, alanine aminotransferase, and aspartate aminotransferase, decreased significantly from before to 1 week after the procedure (Table 2,  $P < 0.05$ ).

## Complications

Major complications occurred in only one patient, in the Control group. The patient developed severe hemobilia with gastrointestinal bleeding and underwent superselective hepatic artery embolization 1 day later to treat a pseudoaneurysm caused by the puncture. Minor complications occurred in five (8.9%) patients in the Control group and in four (5.7%) in the Seeds group. No significant

difference in the incidence of complications was observed between groups (Table 3).

## Follow-Up Time, Stent Patency, and Survival

The median follow-up time after discharge was 4.5 months (range 2–12.5 months) in the Seeds group and 7.5 months (range 2–12.5 months) in the Control group. The median duration of primary stent patency was significantly longer in the Seeds group (194 days) than that in the Control group (86 days,  $P = 0.049$ ; Fig. 2). Recurrent obstructive jaundice occurred in five patients in the Seeds group and in four patients in the Control group. In the Seeds group, two patients underwent stent revision with a new stent, two patients received external drainage, and one patient received only conservative treatment because of large ascites and poor general condition. In the Control group, stent revision was performed in three patients and external drainage in one patient. During the study period, 24 patients in the Seeds group and 66 patients in the Control group died. The causes of death in the Seeds group included disease progression ( $n = 11$ ), liver failure ( $n = 5$ ), multiple organ failure ( $n = 3$ ), infection ( $n = 3$ ), and alimentary tract hemorrhage ( $n = 2$ ). In the Control group, causes of death were disease progression ( $n = 35$ ), liver failure ( $n = 11$ ), multiple organ failure ( $n = 8$ ), infection ( $n = 7$ ), and alimentary tract hemorrhage ( $n = 5$ ). The median overall survival in the Seeds group was significantly longer (194 days) than that in the Control group (96 days,  $P = 0.031$ ; Fig. 3).

## Discussion

In the current study, we compared the clinical outcomes of patients who received seeds with stent insertion versus those who received stent insertion alone. The results showed that primary stent patency and median overall survival were significantly longer in the Seeds group than in the Control group. To the best of our knowledge, this study included the largest number of patients treated with stent insertion combined with seed strand placement. Our results are in line with previous limited reports [8–12].

Uncovered metallic stent placement is currently a widely accepted treatment for MOJ. However, stent reocclusion caused by tumor growth or normal tissue hyperplasia is a major disadvantage of this approach [14–16]. Covered metallic stents have been used to overcome this problem. However, covered stents have a higher incidence of stent migration than uncovered stents and may block ducts, causing cholecystitis, pancreatitis, and other complications [3, 17]. Furthermore, a covered stent only

**Table 1** Patients' characteristics, according to treatment group

	Seeds	Control	<i>P</i> value
Pt. no.	45	87	
Age (year)	61.7(32–87)	64.4(35–92)	0.91
Gender (M/F)	31/14	59/28	0.90
Obstruction causes			0.67
HCC	7(15.6%)	9(10.3%)	
Cholangiocarcinoma	18(40.0%)	32(36.8%)	
Gastric cancer	7(15.6%)	11(12.6%)	
Gallbladder cancer	6(13.3%)	9(10.3%)	
Pancreatic carcinoma	4(8.9%)	17(19.5%)	
Ampullary cancer	0	1(1.1%)	
Others	3(6.7%)	8(9.2%)	
Pathology confirmed	25(55.6%)	50(57.5%)	0.83
Combined intrahepatic mass lesion	14(31.3%)	25(28.7%)	0.84
ECOG			0.50
0	3(6.7%)	2(2.3%)	
1	30(66.7%)	62(71.3%)	
2	12(26.6%)	23(26.4%)	
Further chemotherapy	4(8.9%)	11(12.6%)	0.58
Obstruction location			0.92
Proximal bile ducts (hilar lesions)	33(73.3%)	62(73.8%)	
Middle and distal bile duct	11(24.4%)	22(26.2%)	
Anastomotic	1(2.2%)	3(3.6%)	
Obstruction length (cm)	4.1(2–7)	3.7(1–8)	0.80
Stent number			0.44
One stent	33(73.3%)	76(83.9%)	
Two stents	12(26.7%)	11(16.1%)	
Stent size (mm)			0.83
8 × 60	23(40.4%)	45(45.9%)	
8 × 80	28(49.1%)	42(42.9%)	
8 × 100	3(5.3%)	4(4.1%)	
8 × 40	3(5.3%)	7(3.1%)	

*HCC* hepatocellular carcinoma, *ECOG* Eastern Cooperative Oncology Group

physically prevents tumor ingrowth; a method that could cause tumor regression would be preferable.

Iodine-125 seed implantation has been widely used as brachytherapy for the treatment of malignant tumors [18–20] and shows several advantages for brachytherapy of MOJ. First, its small size makes it easy to load and insert into the bile duct. Secondly, the method can deliver high doses of radiation to the adjacent tumor tissue, while sparing normal tissues located at more distant locations [8]. Thirdly, seed insertion represents a form of conformal radiotherapy, which could minimize treatment inaccuracy resulting from patient movement.

The use of iodine-125 seeds combined with SEMS for the management of MOJ was first reported in 2012, but was not fully investigated [8–12, 21, 22]. Currently, there are three methods of fixing iodine-125 seeds in the bile duct:

seed fixation in a drainage catheter through a stent, seed fixation in a stent, and seed fixation between a stent and the bile duct wall. Chen et al. [8] first reported the technique of fixing the seeds in a drainage catheter through a stent. They found that the mean stent patency was significantly longer in the Seeds group than in the stent-alone group (10.2 vs 7.2 months, respectively). Two later studies using the same technique confirmed this finding and also found that patients treated with seeds had longer survival than those treated with stents alone [10, 11]. Zhu et al. [22] evaluated a new irradiation stent for loading iodine-125 seeds and demonstrated that stent patency and patient survival were markedly longer in the study group than in the Control group (7.4 vs 2.5 months and 7.4 vs 2.5 months, respectively). In 2017, Hasimu et al. [9] reported the technique of fixing the seed strand between the stent and the bile duct

**Table 2** Liver function parameters before and 1 week after the procedure, according to group

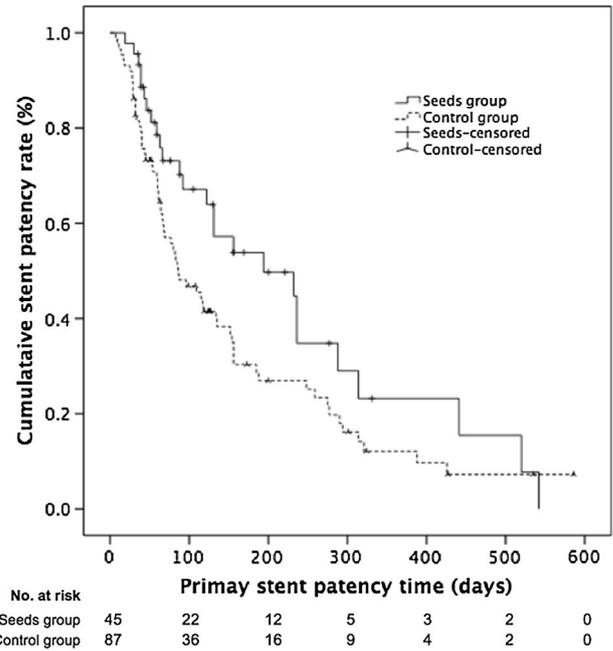
	Seeds	Control	<i>P</i> value
<b>ALT (U/L)</b>			
Before	112.5 ± 92.0	116.8 ± 82.5	0.56
After	66.9 ± 61.8	61.3 ± 50.1	0.48
<i>P</i> value	0.00	0.00	
<b>AST (U/L)</b>			
Before	128.9 ± 87.4	124.4 ± 80.1	0.50
After	73.0 ± 60.4	70.9 ± 64.1	0.71
<i>P</i> value	0.00	0.00	
<b>TBIL (μmol/L)</b>			
Before	238.6 ± 139.2	238.8 ± 135.9	0.90
After	153.7 ± 105.2	164.7 ± 111.9	0.29
<i>P</i> value	0.00	0.00	
<b>DBIL (μmol/L)</b>			
Before	165.9 ± 89.9	170.1 ± 96.4	0.94
After	106.0 ± 78.6	116.5 ± 81.7	0.45
<i>P</i> value	0.00	0.00	

ALT alanine aminotransferase, AST aspartate aminotransferase, TBIL total bilirubin, DBIL direct bilirubin

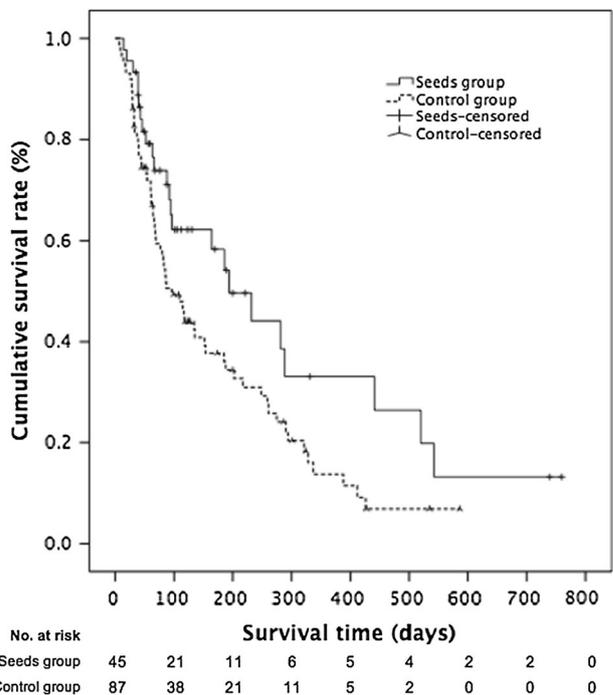
**Table 3** Post-procedural complications, according to group

	Seeds	Control	<i>P</i> value
Major complication	0 (0)	1 (1.1%)	
Severe hemobilia	0 (0)	1 (1.1%)	1.0
Minor complication	4 (8.9%)	5 (5.7%)	
Pancreatitis	2 (4.4%)	1 (1.1%)	0.27
Cholangitis	1 (2.2%)	3 (3.4%)	1.0
Cholecystitis	1 (2.2%)	1 (1.1%)	1.0

wall, which also resulted in longer stent patency and patient survival. In the present study, we adopted a similar technique to that of Hasimu’s study and found that the median duration of stent patency and overall survival were significantly longer in the Seeds group than in the Control group (194 vs 86 days and 194 vs 96 days, respectively). Compared with the previous two techniques, the technique of fixing seeds between the stent and the bile duct wall has several advantages. First, an external drainage catheter is not needed with this technique, which greatly improves quality of life. Secondly, the dual-stent design of the new irradiation stent is unsuitable for patients with hilar strictures of Bismuth type III or higher grade [10]. In addition, the seed strand length was about 1.8 cm longer than the stricture in previous studies [8, 9], whereas in this study,



**Fig. 2** Kaplan–Meier estimation of primary stent patency. Duration of stent patency in the Seeds group was longer than that in the Control group (*P* = 0.049)



**Fig. 3** Kaplan–Meier estimation of patient survival. Survival time in the Seeds group was longer than that in the Control group (*P* = 0.031)

the strand length matched the stent length, unless the stent crossed the ampulla of Vater, in which case the strand length matched the length of stent within the bile duct. Because a longer seed strand contains more seeds, it can

offer a higher radiation dose and may better prevent tumor growth and normal tissue hyperplasia.

The major and minor complication rates in this study were similar to those of previous studies [1, 8, 10]. Patients who received a seed strand combined with a stent did not have a higher complication rate than patients who received a stent alone, indicating that insertion of a seed strand in the bile duct is safe.

This study has several limitations. First, because this was a retrospective study and thus had no randomization, there could be bias in patient selection. Most of the procedures in the Control group were performed early in the study period, and most in the Seeds group were performed later in the study period. Secondly, the number of seeds implanted in this study was chosen according to the length of the lesion and the stent. This number should be accurately determined, but a specific treatment planning system for hollow organs is currently unavailable. Thirdly, tumor response to seed radiation was not evaluated, because it was very difficult to evaluate the lesions with RECIST criteria [23].

## Conclusion

In conclusion, the preliminary results of this study demonstrated that combining SEMS with an iodine-125 seed strand is effective and safe in the management of MOJ, improving not only stent patency but also patient survival.

**Funding** This study was supported by the Six Talent Peaks Project in Jiangsu Province (CN) (No. 2013-WSN-038).

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethical Approval** All procedures performed in this study were in accordance with the ethical standards of ethical committee of the First Affiliated Hospital of Nanjing Medical University and with the 1964 Helsinki Declaration and its later amendments.

**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 this study.

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