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Percutaneous stenting and chemotherapy for unresectable pancreatic cancer: Comparison of irradiation stents vs conventional metal stents

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ABSTRACT

Objectives: Percutaneous stenting is a palliative method to relieve obstructive jaundice caused by unresectable pancreatic carcinoma. In this study, we aimed to compare the safety and efficacy of irradiation stents and conventional metal stents.
Methods: A total of 32 patients who received irradiation stents or conventional metal stents to treat obstructive jaundice caused by locally advanced pancreatic cancer were included in this retrospective study. Chemotherapy using gemcitabine was performed after jaundice subsided. Stent patency, technical success, survival, and complications were compared between groups.
Results: Seventeen patients were enrolled in the irradiation stent group (ISG), and 15 patients were enrolled in the uncovered stent group (USG). Median and mean stent patency time were 9.8 months (95% CI, 7.682–11.981) and 9.506 months (95% CI, 8.0–11.012) in the ISG, respectively, vs 8.8 months (95% CI, 6.528–11.072) and 7.62 months (95% CI, 5.917–9.323) in the USG, respectively ($P = 0.019$). Median and mean overall survival were 10.4 months (95% CI, 8.383–12.417) and 9.953 months (95% CI, 8.408–11.498), respectively, in the ISG vs 9.7 months (95% CI, 7.901–11.499) and 8.14 months (95% CI, 6.44–9.84), respectively, in the USG ($P = 0.027$).
Conclusions: Irradiation stents extend stent patency and overall survival compared with conventional biliary stents for the treatment of pancreatic carcinoma complicated by obstructive jaundice. Irradiation stents combined with chemotherapy may be a better choice for the treatment of obstructive jaundice caused by unresectable pancreatic carcinoma.

Introduction

Pancreatic carcinoma is a disease with a high mortality rate worldwide, ranking fourth in tumor-related deaths in the United States [1–3]. Biliary obstruction often appears when the lesion is located at the head of the pancreas. Approximately 80%–90% of patients with newly diagnosed pancreatic cancer cannot undergo surgical resection because distant metastasis or local invasion [4]. Therefore, palliative treatment for obstructive jaundice and sequential chemotherapy is the limited choice of treatment.

For these patients, percutaneous transhepatic cholangiography and drainage (PTCD) and stenting is commonly performed as a palliative procedure to relieve symptoms such as pruritus, cholangitis, and jaundice. However, restenosis may occur in metal stents because of tumor growth through the mesh [5]. Many types of modified stents, including covered stents and drug-eluding stents, have been developed to remedy this problem. Nevertheless, stent dysfunction occurs in 10%–54% of patients [6–8]. Recently, irradiation biliary stents using iodine-125 (^{125}I) seeds were developed to overcome stent restenosis [9]. Whether this method is safe and effective for unresectable pancreatic cancer requires further study. Therefore, this study was performed to evaluate the safety and efficacy of irradiation stents for the treatment of locally advanced pancreatic cancer with obstructive jaundice.

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Materials and methods

Patients

Between January 2014 and April 2016, seventy-five consecutive patients with obstructive jaundice caused by pancreatic carcinoma were treated with percutaneous stenting in our hospital. Patients were included in this study if they had obstructive jaundice caused by locally advanced unresectable pancreatic carcinoma, age range 18–80 years old, adequate cardiac, hematologic, liver, and renal function, and Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Pancreatic cancer was confirmed via biopsy with pathology indicating ductal adenocarcinoma. Exclusion criteria were ECOG performance status >2, platelet count $<50 \times 10^9$/L, renal or liver failure, cardiac dysfunction, coagulation disorder, pancreatic carcinoma with distant metastases, and other types of pancreatic carcinoma.

Finally, thirty-two patients (19 female, 13 male; age range, 35–76 years; median age, 62 years) were included in this retrospective study. Seventeen of the 32 patients underwent irradiation stent placement, while conventional metal stents were inserted in the other 15 patients. Disease stage was assessed based on contrast-enhanced computed tomography (CT) or magnetic resonance imaging findings. Baseline characteristics, including age, gender, and ECOG performance status, were similar between the groups.

The study was approved by the ethics committee review board of the Second Hospital of Shandong University and adhered to the guidelines of the Declaration of Helsinki for medical research. All patients provided written informed consent prior to the procedure.

Procedures

Irradiation stent

The irradiation stent had two overlapping parts: the inner part was an uncovered conventional SEMS (Cook), and the outer part was an ^{125}I seed–loaded stent with sheaths attached to the outer surface for seed loading (Nanjing Micro-Tech Co Ltd). These two parts were deployed in the bile duct. The length and diameter of the stents were determined based on the range and extent of the lesion according to cholangiography (Fig. 1A), magnetic resonance cholangiopancreatography, and/or contrast-enhanced CT findings. The ^{125}I seeds (4.5-mm long, 0.8-mm wide; Chinese JACO Pharmaceuticals Co Ltd) have a 59.6-day radioactive half-life and a 17-mm half-value layer of tissue. The sheaths were loaded with seeds prior to the procedure. Radiation protection equipment including radiation-proof underwear, sterile radiation protective gloves, radiation protective glasses, and radiation protection suits were used before handling seeds and implanting stents.

The number of loaded seeds depended on the length of the selected stent. A treatment planning system (TPS; University of Beijing Aeronautics and Astronautics) was used to calculate the dosage and distribution of the ^{125}I seeds.

Percutaneous transhepatic stent implantation

We chose right-sided access for the procedure. Percutaneous transhepatic cholangiography was performed using fluoroscopic guidance under intravenous anesthesia with dexmedetomidine combined with local anesthesia and lidocaine. The occluded bile duct was dilated with a balloon dilator catheter before stent insertion. Then, an outer ^{125}I seed–loaded stent was introduced over a stiff guidewire through a 10-F sheath to cover the lesion area (Fig. 1B). An inner bare SEMS (Cook) was inserted subsequently to overlap with the former stent (Fig. 1C). An uncovered SEMS (Cook) was deployed into the lesion area through a 6-F sheath after coaxial balloon dilation in the uncovered stent group (USG). A 10.2-F catheter (Cook) was retained with the distal part left in the common bile duct to perform cholangiography 7 days after the procedure in the irradiated stent group (ISG) (Fig. 1D), while an 8.5-F catheter (Cook) was retained in the USG. Contrast-enhanced CT was scheduled 1 week after the procedure, with the images imported into the TPS to demonstrate dosage and distribution of the irradiation stent (Fig. 2, Fig. 3). The catheter was removed in cases of satisfactory stent deployment and contrast runoff. Analgesics

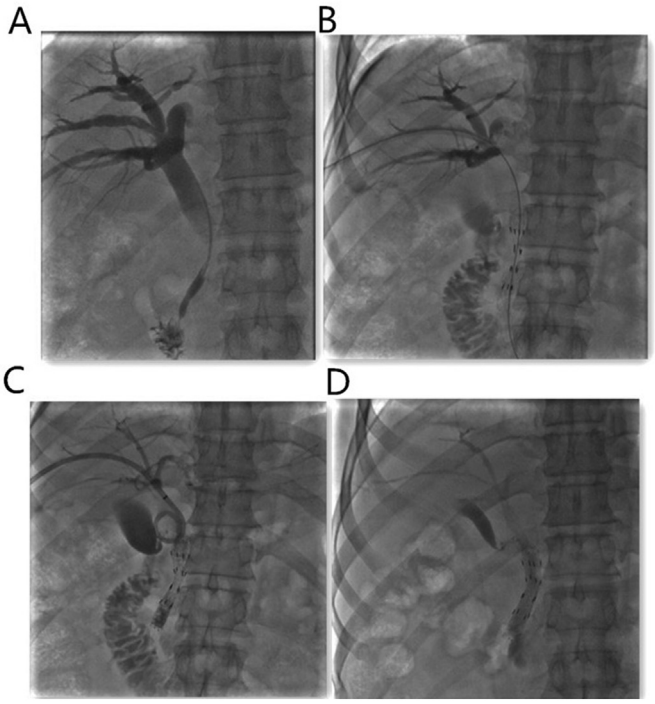

Fig. 1. A) Cholangiography showing stenosis of the common bile duct. B) The outer part of the irradiation stent inserted into the common bile duct. C) The inner part of the irradiation stent and 10.2-F catheter deployed into the common bile duct. D) Cholangiography showing that the irradiation stent was patent and well-expanded 1 week after the procedure.

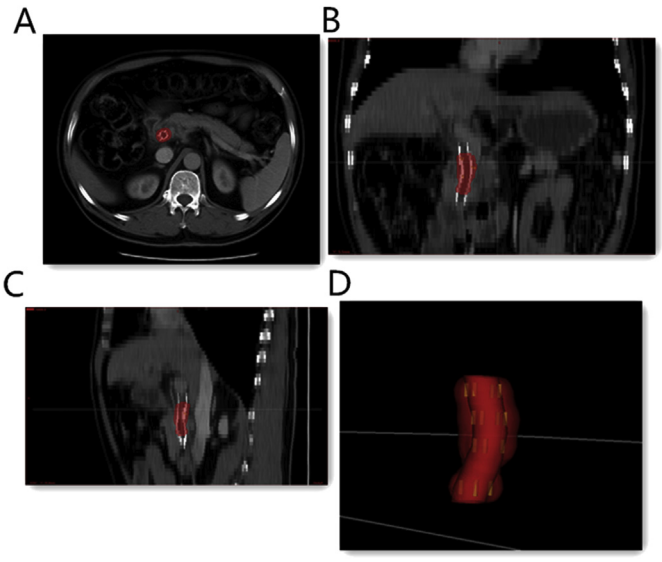

Fig. 2. Radioactivity of the irradiation stent according to the treatment planning system (TPS). A) Transverse section. B) Coronal section. C) Median sagittal section. D) Three-dimensional reconstructed image.

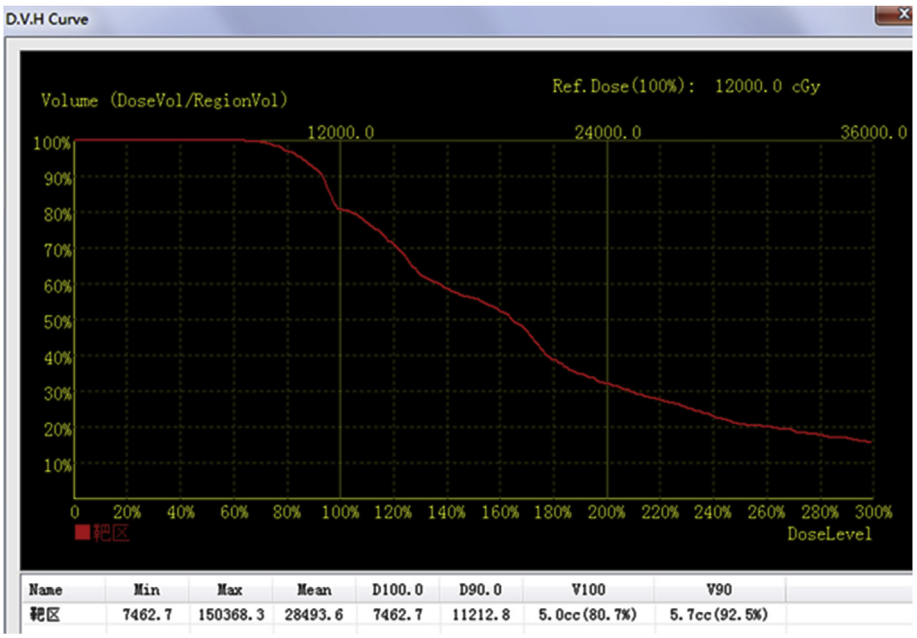

Fig. 3. Dose–volume histogram curve of the distribution of the irradiation stent according to the TPS.

were given to treat severe pain.

Endpoints and definitions

Major endpoints included overall survival, stent patency, technique feasibility, and safety. Overall survival was defined as the period between stent implantation and death. Stent patency time was defined as the period between stent implantation and recurrence of obstruction. Stent patency time was considered the same as survival time if there was no evidence to demonstrate recurrence of obstruction when the patient died. Technical efficacy correlated with the success of stent deployment to the correct location. Safety was evaluated based on the rate of procedure-related adverse events.

Follow-up

Follow-up was conducted at 1 week, 1 month, 2 months, and then every 3 months after stent implantation. Follow-up included blood laboratory examinations, clinical symptoms, and contrast-enhanced CT. Chemotherapy using gemcitabine was performed after jaundice subsided (gemcitabine 1000 mg/m^2, IV weekly × 7, one-week rest, then weekly × 3 q4W).

Statistical analysis

Continuous variables were expressed as mean ± SD. The Fisher exact test was used to compare qualitative variables, and the independent samples *t*-test was used to compare quantitative variables. Stent patency and overall survival were calculated using the Kaplan–Meier method. The log-rank test was used to compare the significance of the difference between groups. Statistical analysis was performed using SPSS version 19.0 (SPSS Inc), with all P values < 0.05 considered statistically significant for all tests.

Results

Thirty-two patients (19 female, 13 male) were included in this study. Irradiation stents were implanted in 17 patients (10 female, 7male), while 15 patients (nine female, six male) received uncovered SEMSs. The iodine-125-loaded stents were supplied by Nanjing Micro-Tech Co. Ltd free of charge. Baseline characteristics of the two groups were similar and are shown in Table 1. Irradiation stents and uncovered stents were successfully deployed in all cases (success rate, 100%).

Mean total bilirubin (TB) and conjugated bilirubin (CB) decreased from 233.40 ± 98.1 mmol/L to 34.18 ± 7.52 mmol/L, respectively, ($P < 0.01$) and from 200.75 ± 96.73 mmol/L to 26.23 ± 6.64 mmol/L, respectively, ($P < 0.01$) 1 month after the procedure in all patients. We chose stents with diameters of 10 mm and lengths of 4–8 cm. The median number of ^{125}I seeds loaded was 16, ranging from 12 to 20. Median and mean stent patency time were 9.8 months (95% CI, 7.682–11.981) and 9.506 months (95% CI, 8.0–11.012) in the ISG, respectively, vs 8.8 months (95% CI, 6.528–11.072) and 7.62 months (95% CI, 5.917–9.323) in the USG, respectively ($P = 0.019$) (Fig. 4). Median and mean overall survival were 10.4 months (95% CI, 8.383–12.417) and 9.953 months (95% CI, 8.408–11.498) in the ISG, respectively, vs 9.7 months (95% CI, 7.901–11.499) and 8.14 months (95% CI, 6.44–9.84) in the USG,

Table 1
Baseline characteristics of enrolled patients.

Characteristic	ISG (n = 17)	USG (n = 15)	*P*-value
Age, y	59.41 ± 11.29	60.07 ± 12.62	0.878[a]
Gender			0.946[b]
Male	7	6	
Female	10	9	
Bilirubin, mmol/L			
Total bilirubin	233.40 ± 98.1	232.32 ± 98.53	0.975[a]
Direct bilirubin	200.75 ± 96.73	206.55 ± 94.29	0.865[a]
Albumin, g/L	31.08 ± 2.98	30.48 ± 2.30	0.531[a]
CA19–9, U/ml	1516.28 ± 866.44	1513.82 ± 734.87	0.993[a]
ECOG performance status			0.937[b]
0	4	3	
1	5	4	
2	8	8	

CA, cancer antigen; ECOG, Eastern Cooperative Oncology Group; ISG, irradiation stent group; USG, uncovered stent group.
Data are presented as mean ± SD or number.
[a] The independent samples *t*-test was used.
[b] The Fisher exact test was used.

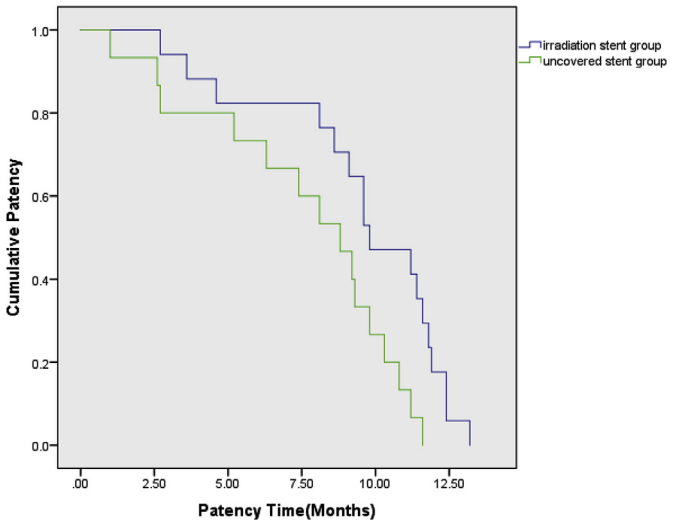

Fig. 4. Median and mean stent patency time were 9.8 months (95% CI, 7.682–11.981) and 9.506 months (95% CI, 8.0–11.012), respectively, in the ISG vs 8.8 months (95% CI, 6.528–11.072) and 7.62 months (95% CI, 5.917–9.323) in the USG (P = 0.019, log-rank test), respectively.

respectively (P = 0.027) (Fig. 5). No patients were alive at the end of follow-up.

Abdominal pain was reported by eight patients (47%) in the ISG and six patients (40%) in the USG. The symptoms subsided within 24–48 h with the use of analgesics. Fever with rigors occurred in five patients (29.4%) in the ISG and three patients (20%) in the USG during or immediately after the procedure. The symptom was alleviated by quick intravenous injection of 5 mg dexamethasone. Two patients (12%) in the ISG and one patient (7%) in the USG experienced hemobilia (grade 2 based on Common Terminology Criteria for Adverse Events 4.02) during the procedure. A vasovagal response was observed in one 62-year-old woman in the USG. Her blood pressure and heart rate declined from 120/70 mmHg and 85 bpm to 80/40 mmHg and 50 bpm, respectively. Her blood pressure and heart rate returned to normal after immediate intravenous injection of 0.6 mg atropine. The complication rates in the USG and ISG were 64.7% (11/17) and 53.3% (8/15), respectively (P = 0.72).

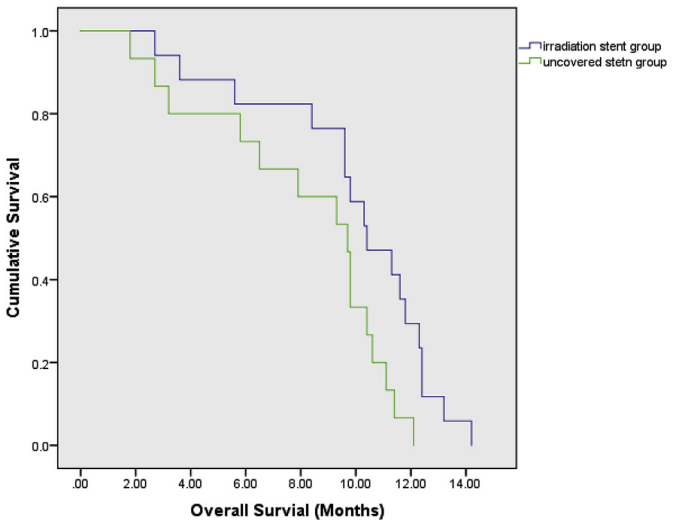

Fig. 5. Kaplan-Meier overall survival in the irradiation stent group (ISG) vs the uncovered stent group (USG). Median and mean overall survival were 10.4 months (95% CI, 8.383–12.417) and 9.953 months (95% CI, 8.408–11.498) in the ISG, respectively, vs 9.7 months (95% CI, 7.901–11.499) and 8.14 months (95% CI, 6.44–9.84) in the USG (P = 0.027, log-rank test), respectively.

Discussion

Pancreatic carcinoma is a fatal disease worldwide. Approximately 60% of patients have distant metastasis when the disease is diagnosed, while 25% of patients have locally advanced disease and are unable to undergo radical resection. Median survival is only 6–9 months [10]. Malignant obstructive jaundice occurs in 65%–75% of patients because of occlusion of the common bile duct [11].

Chemotherapy remains the primary treatment for patients with locally advanced inoperable pancreatic carcinoma [12]. Percutaneous stenting and biliary drainage with endoscopic retrograde cholangiopancreatography (ERCP) or PTCD is the essential therapy to alleviate obstructive jaundice that is often caused by cancer of the pancreatic head [13]. Nevertheless, stenting often leads to dysfunction because of tumor ingrowth and/or overgrowth, all of which has substantial impact on patient survival.

To improve stent patency time and overall survival, an irradiation stent using ^{125}I seeds as the radioactive source was developed [14]. However, whether this method is beneficial in patients with pancreatic carcinoma requires further study.

In this study, a group of patients with locally advanced pancreatic cancer and obstructive jaundice treated with irradiation stents were retrospectively analyzed. A higher stent patency rate was ensured because irradiation stenting brachytherapy has antihyperplasia and antitumor ingrowth effects.

In the 1980s, Coons and Neuhaus et al. reported their experience of applying bare metal stents for the treatment of obstructive jaundice caused by malignant tumors [15–17]. A long-term stent occlusion rate of 35% was reported in the initial study, and the main reason for occlusion was tumor overgrowth [18,19]. The polytetrafluoroethylene/fluorinated ethylene propylene–covered stent quickly relieved symptoms of obstructive jaundice and was superior to the bare stent in terms of primary stent patency time and restenosis rate. Nevertheless, the incidence of stent migration was higher than that of the bare stent [20]. The paclitaxel-eluding stent was also essentially a covered stent. Its clinical application was intended to prevent the growth of tumors into the stent lumen; however, unfortunately, the study showed that drug-eluding stents gave no particular advantage [5].

Intracavitary radiofrequency ablation, photodynamic techniques, and intraluminal irradiation have also been used to improve long-term patency of bile duct stents in patients with malignant obstructive jaundice [21]. In the treatment of malignant obstructive jaundice and portal vein tumor emboli, intraluminal irradiation with ^{125}I strands has shown encouraging results [22,23].

In most reports of biliary stent deployment for the treatment of malignant obstructive jaundice, the included tumor type was not a single tumor, but rather a variety of malignant tumors [9,14,22]. The biological behavior, survival, and radiosensitivity vary widely among tumors, and this may cause discrepancies. By contrast, in this study, only a single tumor type (pancreatic carcinoma) was analyzed.

During follow-up, we did not observe any severe complications such as pancreatitis or duodenitis. The radiation effects on the adjacent organs were minor because the irradiation distance of the 125-iodine particles is extremely short. The seeds were located in the sheath of the outer part of the irradiation stent. The rate of migration might be small because there were no cases of migration observed during follow-up.

In this study, irradiation stents obtained better results in terms of stent patency time and overall survival than did uncovered stents. The reason for this may be that iodine-125 seeds and

gemcitabine have a synergistic effect that can significantly inhibit pancreatic cancer cells, mainly through G1 cycle arrest and through induction of apoptosis [24]. The pathophysiology by which irradiated stents prolong stent patency relies on the radioactive characteristic of iodine-125 seeds; this is a low-dose rate brachytherapy with a half-life of 59.6 days with continuous release of low dose γ-radiation. Favorable biological effects of iodine-125 seeds on pancreatic cancer has been demonstrated in some studies. Wang et al. demonstrated that iodine-125 brachytherapy increased the apoptotic rate and induced programmed cell death in pancreatic tumor cells [25]. Ma et al. reported that iodine-125 irradiation changed the expression patterns of DNA methyltransferases in pancreatic cancer cells, leading to the inhibition of tumor growth [26]. The seeds were distributed evenly outside the irradiation stent, resulting in a cylindrical dose distribution shielding the stent, thereby preventing the invasion of the tumor. Similar result of the superiority of irradiated stents in prolonging stent patency were found when treating esophagus carcinoma [27]. Risk factors affecting survival time include tumor features, age, and ECOG, referring to the treatment of malignant obstructive jaundice using metal stents [28–30]. In addition to these factors, stent patency was found to be an independent risk factor for survival, with a correlation coefficient up to 0.644 [9]. In summary, the irradiation stents prevented tumor ingrowth and proliferation, prolonging stent patency, improving the physical condition of the patients, and delaying the progression of the carcinoma, thereby prolonging survival.

Currently, ERCP is recommended by National Comprehensive Cancer Network (NCCN) clinical practice guidelines as the first choice for biliary drainage of pancreatic carcinoma. ERCP-guided self-expanding metal stents (SEMS) insertion is widely performed for malignant biliary obstruction [31]. In essence, iodine-125 seed loaded stents are another type of SEMS. It is possible that this stent could potentially be placed via ERCP in the future.

There are some limitations in this study. First, this was a retrospective study with a small sample size. Therefore, the statistical analyses may not be conclusive. In addition, the results may be influenced by such factors as the distribution of the selected population. A prospective study is underway at our medical center to evaluate the efficacy of irradiation stents. Second, quality of life and costs were not assessed. Nevertheless, our study has shown promising results, including prolonged survival of irradiation stenting for the treatment of malignant obstructive jaundice caused by locally advanced pancreatic carcinoma.

In conclusion, compared with conventional bare SEMSs, irradiation stents may prolong stent patency time and improve overall survival in patients with locally advanced pancreatic carcinoma. Irradiation stents combined with chemotherapy may be a better choice for the treatment of obstructive jaundice caused by unresectable pancreatic carcinoma.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.09.006.

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