A Novel Brachytherapy Biliary Drainage Catheter Loaded With 125I Seeds in Patients With Malignant Obstructive Jaundice: Preliminary Results Versus Iodine-125 Seed Strands Placement

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Abstract

Background

The placement of 125I seeds was a safe method for treating cholangiocarcinoma. The purpose of this study was to compare a novel brachytherapy biliary drainage catheter (BBDC) with an iodine-125 (125I) seed strand after self-expandable metallic stent (SEMs) implantation in terms of safety and efficacy, as treatments for patients with cholangiocarcinoma of 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 125I seeds (double-strands irradiation group) or an 125I seed strand treatment (single-strand irradiation group, control group). The outcomes were analyzed regarding the relief of obstructive jaundice, interventional-related complications, stent patency and survival time.

Results

The success rate of interventional therapy in both groups was 100% and all patients with MOJ were alleviated. The overall complication rates of BBDC group and control group were 23.1% (9/39) and 26.5% (9/34), 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).

Conclusions

This interim analysis showed that BBDC (double-stranded irradiation) can prolong the stent patency time compared with 125I seed strand treatment (single-stranded irradiation) and had the advantage of reducing jaundice, which seemed to extend survival period.

Background

Malignant obstructive jaundice (MOJ) usually results from biliary invasion or compression by cholangiocarcinoma, but less than 10–20% of the patients are eligible for radical operation[1, 2]. The implantation of the Self-expandable metallic stent (SEMS) is the main palliative treatment for patients 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 occurred in the progress of the disease will make more than 50% of patients have stent re-obstruction within 6 months[3, 4]. Hence, stents with longer patency are required to improve the survival rates of patients with MOJ. Fortunately, In 2012, Zhu et al[5] reported a radioactive biliary stent loaded with 125I seeds exhibited a significantly
prolonged stent patency compared with conventional stents. In recent years, some investigators have used the combination of $^{125}$I seeds strand and SEMs as a new therapeutic treatment for MOJ[6]. Although it is a safe treatment, the cumulative brachytherapy dose is relatively low and fibrous connective tissue in the bile duct could reduce local irradiation effect[7]. In order to eliminate these disadvantages, a novel brachytherapy biliary drainage catheter (BBDC) loaded with double $^{125}$I seed strands was designed. Of note, the efficacy and complication of the treatment for MOJ have not been largely studied to our knowledge. The aim of this study is to compare the safety, complication and efficacy of BBDC loaded with $^{125}$I seeds (double-strands irradiation group) and $^{125}$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 criterion of eligible patients were as follow: (a) aged between 43 and 80 years, (b) biliary obstruction caused by any adenocarcinoma with histological or cytological confirmation by biopsy or previous surgical procedures, (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 common bile duct. A novel brachytherapy biliary drainage catheter (BBDC). (Tuoren, Henan, China)(Fig. 1). The $^{125}$I seeds (Said Biopharmaceutical Co, Ltd. Tianjin, China) were configured in a cylindrical brachytherapy source encapsulated by titanium. The details could be found in the (supplementary information A).

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. 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 Shimadiu 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 catheter (BBDC) and Iodine-125 ($^{125}$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 could be seen in the (supplementary information B) and (Fig. 2).

**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 post-operative 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 pretreatment value within one month. Complications were classified according to the guidelines of the Society of Interventional Radiology Standards of Practice Committee[8]. Stent occlusion was defined as biliary dilatation on CT or MRI, combined with the recurrence of symptoms of malignant obstruction and an increase in serum bilirubin (> 51.3 µmol/L). The stent patency period was defined as the interval between stent placement and the development of stent occlusion.

**Statistical analysis**

Continuous variables were summarized as mean ± standard deviation (SD). The Wilcoxon Signed Rank test was used to compare the pre- and post-procedure indicators. The Fisher exact test was also used to compare postoperative complications between the two groups. Survival and stent patency time were calculated according to the Kaplan–Meier method, and a P-value of < 0.05 was considered statistically significant. The calculations were performed by the SPSS software (version 23.0, SPSS, Chicago, Illinois, USA).

**Results**

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 $^{125}$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 ± 4.72 Gy and 44.35 ± 3.55 Gy (P<0.05), as calculated by computer TPS over one month and the total number of $^{125}$I seeds embedded in the patients of both groups was 38.84 ± 2.45 and 18.86 ± 2.75, respectively (P<0.05).
| Characteristics                  | Control group ($n = 39$) | BBDC group ($n = 34$) | $P$ value |
|---------------------------------|--------------------------|-----------------------|-----------|
| **Age**                         | 57.05 ± 8.73             | 59.21 ± 7.22          | 0.408†    |
| **Sex**                         |                          |                       | 1.000*    |
| Male                            | 24                       | 21                    |           |
| Female                          | 15                       | 13                    |           |
| **Clinical symptom**            |                          |                       | 0.983*    |
| Jaundice with poor appetite     | 21                       | 19                    |           |
| Jaundice with emaciation        | 11                       | 9                     |           |
| Jaundice with recurrent fever   | 7                        | 6                     |           |
| **Location of the tumor**       |                          |                       | 0.495*    |
| Middle bile duct               | 13                       | 16                    |           |
| Distal bile duct               | 17                       | 11                    |           |
| Hilar bile duct                | 9                        | 7                     |           |
| **Stenosis length (mm), mean ± SD** | 31.31 ± 5.90             | 29.07 ± 7.76          | 0.343†    |
| **Reason for unresectability**  |                          |                       | 0.720*    |
| Metastases                      | 17                       | 13                    |           |
| Local infiltration             | 12                       | 14                    |           |
| Refusal/intolerance to surgical treatment | 10                    | 7                     |           |

* Pearson chi-square test was used.
† Independent samples t test was used.

**Clinical Success**

The hospital stay of the BBDC group and the control group was 12.53 ± 4.67 days and 11.45 ± 5.29 days, respectively ($P>0.05$). Except for one in control group died of severe gastrointestinal bleeding three weeks after the treatment, the levels of ALT, TBIL and DBIL in both group decreased significantly, and the
condition improved considerably as well ($p < 0.05$). The ALB levels in the both group were increased slightly within one week, while the ALB levels continued to increase following treatment in the both group ($p < 0.001$). (Fig. 3)

**Complications**

Procedure-related complications in the BBDC group were biliary hemorrhage, pancreatitis, cholangitis, and biliary re-intervention and the corresponding incidence were (3/34, 8.82%), (1/34, 2.94%), (2/34, 5.88%), and (4/39, 10.26%), while the incidence of control group were (2/39, 5.12%), (2/39, 5.12%), (1/39, 2.56%) and (3/34, 8.82%), respectively ($P > 0.05$).

**Stent Patency, and Survival**

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 2). 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: 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 months (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). (Fig. 4)
Table 2
Procedural details, post-procedure outcomes and follow-up data

| Characteristics                                      | Control group (n = 39) | BBDC group (n = 34) | P value |
|------------------------------------------------------|------------------------|---------------------|---------|
| 125I Seed number, (mean ± SD)                        | 18.68 ± 2.99           | 38.84 ± 2.46        | 0.002‡  |
| Cumulative dose at reference point                   | 42.55 ± 2.60           | 85.14 ± 4.72        | 0.001‡  |
| Hospital stay, day (mean ± SD)                       | 11.45 ± 5.29           | 12.53 ± 4.67        | 0.596‡  |
| Stent size (diameter × length)                       |                        |                     | 0.463#  |
| 10 × 60 mm                                           | 27                     | 20                  |         |
| 10 × 50 mm                                           | 12                     | 14                  |         |
| Complications                                        |                        |                     |         |
| Biliary hemorrhage                                  | 2                      | 3                   | 0.695*  |
| Pancreatitis                                         | 2                      | 1                   | 1.000*  |
| Cholangitis                                          | 1                      | 2                   | 1.000*  |
| Biliary re-intervention                              | 4                      | 3                   | 1.000*  |
| The reasons for death                                |                        |                     |         |
| Hepatic failure                                      | 24                     | 21                  | 0.984#  |
| Multiple organ metastasis                            | 8                      | 9                   | 0.589#  |
| Gastrointestinal hemorrhage                          | 4                      | 3                   | 1.000*  |
| Unknown cause                                        | 3                      | 1                   | 0.618*  |
| Follow-up anti-cancer treatments                     |                        |                     |         |
| Transarterial infusion chemotherapy                  | 17                     | 16                  | 0.450#  |
| Intravenous chemical therapy                         | 14                     | 12                  | 1.000#  |
| Immunotherapy                                        | 8                      | 6                   | 0.776#  |

*The Fisher exact test was used.

#Pearson chi-square test was used.

‡Difference in the variance between the two groups (Mann–Whitney test).

Discussion
Malignant obstructive jaundice (MOJ) is usually caused by Cholangiocarcinoma [9]. Regrettably, it is often detected at an unresectable stages with a poor prognosis, and the long-term survival rates remain dismal[10]. SEMs is considered to be the preferred palliative therapy for unresectable patients[11, 12]. However, doubt about the efficacy suggests that SEMs might not able to prevent excessive tumor growth [13]. Worth mentioning, 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 [4]. In addition, this therapy has shown no beneficial for prolonging survival time[14, 15]. Therefore, chemo-radiations therapy is suggested to be the 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[16, 17].

At present, a multicenter phase III clinical trial for the treatment of MOJ with radioactive stent and traditional metal stent has confirmed that inserting radioactive stent instead of uncovered SEMs could improve the patency and overall survival rate of patients with unresectable malignant biliary obstruction [18]. Unfortunately, there are two serious problems in the insertion of irradiation stents. First, $^{125}$I seeds cannot be taken out if complications occur after the treatment. Second, the seeds cannot be replaced after the $^{125}$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 192Ir radiation and paclitaxel-drug-eluting stents for malignant biliary obstruction. In the field of brachytherapy, Iodine-125 ($^{125}$I) seeds strand has been applied to the treatment of cholangiocarcinoma and portal vein tumor thrombosis with promising results[19, 20, 21]. Studies have further confirmed that intraluminal brachytherapy using a single $^{125}$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 [22, 23]. Nevertheless, single-strand $^{125}$I particles cannot solve the problem of eccentric dose distribution.

To overcome these technical limitations, a BBDC loaded with double $^{125}$I strands was designed. This design achieves drainage and brachytherapy simultaneously. Double $^{125}$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. The technical success rate (100%) and early complication rate 26.3% (5/19) were similar to the previous studies[24], 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 at the dose reference point A of 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 had resulted in 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\([25, 26]\). 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 the 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 happen to other people with closing contact of the patients may be influenced. 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 malignant biliary obstruction. However, more prospective studies are needed to further elucidate its effectiveness in the treatment of malignant obstructive jaundice.

**Abbreviations**

BBDC A novel brachytherapy biliary drainage catheter

MOJ Malignant obstructive jaundice

SEMS Self-expandable metallic stent

ECOG Eastern Cooperative Oncology Group

MRCP magnetic resonance cholangiopancreatography

ILBT Intraluminal brachytherapy

**Declarations**

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Authors’ contributions

ZL participated in the collection and analysis of data, the writing of the manuscript and specimen collection. XZ participated in data collection and analysis. DJ and YHL participated in the data analysis and manuscript revision. XH, ZL and DJ participated in manuscript editing. ZL and DJ participated in the data collection. XH participated in the study conception and supervision, data analysis and manuscript editing. All authors read and approved the final version of the manuscript.

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Availability of data and materials

The relevant raw data from this study can be 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.

Consent for publication

Not applicable.

Competing interests

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

References

1. Stain SC, Baer HU, Dennison AR, et al. Current management of hilar cholangiocarcinoma. Surg Gynecol Obstet 1992;175(6):579-88.

2. Bismuth H, Castaing D, Traynor O. Resection or palliation: priority of surgery in the treatment of hilar cancer. WORLD J SURG 1988;12(1):39-47.

3. Nam HS, Kang DH, Kim HW, et al. Efficacy and safety of limited endoscopic sphincterotomy before self-expandable metal stent insertion for malignant biliary obstruction. World J Gastroenterol 2017;23(9):1627-36.
4. Lee SJ, Kim MD, Lee MS, et al. Comparison of the efficacy of covered versus uncovered metallic stents in treating inoperable malignant common bile duct obstruction: a randomized trial. J VASC INTERV RADIOL 2014;25(12):1912-20.

5. Zhu HD, Guo JH, Zhu GY, et al. A novel biliary stent loaded with (125)I seeds in patients with malignant biliary obstruction: preliminary results versus a conventional biliary stent. J HEPATOL 2012;56(5):1104-11.

6. Ma J, Luo J, Gu J, et al. Malignant obstructive jaundice treated with intraluminal placement of Iodine-125 seed strands and metal stents: An analysis of long-term outcomes and prognostic features. BRACHYTHERAPY 2018;17(4):689-95.

7. Jiao D, Wu G, Ren J, et al. Study of self-expandable metallic stent placement intraluminal (125)I seed strands brachytherapy of malignant biliary obstruction. SURG ENDOSC 2017;31(12):4996-5005.

8. Sacks D, McClenny TE, Cardella JF, et al. Society of Interventional Radiology clinical practice guidelines. J VASC INTERV RADIOL 2003;14(9 Pt 2):S199-202.

9. Brandi G, Venturi M, Pantaleo MA, et al. Cholangiocarcinoma: Current opinion on clinical practice diagnostic and therapeutic algorithms: A review of the literature and a long-standing experience of a referral center. Dig Liver Dis 2016;48(3):231-41.

10. Wolpin BM, Mayer RJ. A step forward in the treatment of advanced biliary tract cancer. N Engl J Med 2010;362(14):1335-7.

11. van der Gaag NA, Rauws EA, van Eijck CH, et al. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med 2010;362(2):129-37.

12. Huggett MT, Ghaneh P, Pereira SP. Drainage and bypass procedures for palliation of malignant diseases of the upper gastrointestinal tract. Clin Oncol (R Coll Radiol) 2010;22(9):755-63.

13. Baron TH. Expandable metal stents for the treatment of cancerous obstruction of the gastrointestinal tract. N Engl J Med 2001;344(22):1681-7.

14. Petrowsky H, Hong JC. Current surgical management of hilar and intrahepatic cholangiocarcinoma: the role of resection and orthotopic liver transplantation. Transplant Proc 2009;41(10):4023-35.

15. Khan SA, Thomas HC, Davidson BR, et al. Cholangiocarcinoma. LANCET 2005;366(9493):1303-14.

16. Jain S, Kataria T, Bisht SS, et al. Malignant obstructive jaundice - brachytherapy as a tool for palliation. J Contemp Brachytherapy 2013;5(2):83-8.

17. Isayama H, Tsujino T, Nakai Y, et al. Clinical benefit of radiation therapy and metallic stenting for unresectable hilar cholangiocarcinoma. World J Gastroenterol 2012;18(19):2364-70.

18. Zhu HD, Guo JH, Huang M, et al. Irradiation stents vs. conventional metal stents for unresectable malignant biliary obstruction: A multicenter trial. J HEPATOL 2018;68(5):970-7.

19. Zhang Z, Zhang W, Gu J, et al. Treatment of Hepatocellular Carcinoma with Tumor Thrombus with the Use of Iodine-125 Seed Strand Implantation and Transarterial Chemoembolization: A Propensity-Score Analysis. J VASC INTERV RADIOL 2018;29(8):1085-93.
20. Fang ZT, Yan ZP, Luo JJ, et al. [Evaluation of endovascular placement of iodine-125 seed strand combined with transcatheter arterial chemoembolization for treating hepatocellular carcinoma with extensive portal vein tumor thrombus]. Zhonghua Gan Zang Bing Za Zhi 2013;21(2):146-9.

21. Luo J, Yan Z, Liu Q, et al. Endovascular Placement of Iodine-125 Seed Strand and Stent Combined with Chemoembolization for Treatment of Hepatocellular Carcinoma with Tumor Thrombus in Main Portal Vein. J VASC INTERV RADIOL 2011;22(4):479-89.

22. Zhou WZ, Fu YM, Yang ZQ, et al. Study of Percutaneous Stent Placement with Iodine-125 Seed Strand for Malignant Biliary Obstruction. Cardiovasc Intervent Radiol 2019;42(2):268-75.

23. Ma J, Luo J, Gu J, et al. Malignant obstructive jaundice treated with intraluminal placement of iodine-125 seed strands and metal stents: An analysis of long-term outcomes and prognostic features. BRACHYTHERAPY 2018;17(4):689-95.

24. Yang M, Yan Z, Luo J, et al. A pilot study of intraluminal brachytherapy using (125)I seed strand for locally advanced pancreatic ductal adenocarcinoma with obstructive jaundice. BRACHYTHERAPY 2016;15(6):859-64.

25. Chen Y, Wang XL, Yan ZP, et al. HDR-192Ir intraluminal brachytherapy in treatment of malignant obstructive jaundice. World J Gastroenterol 2004;10(23):3506-10.

26. Dvorak J, Jandik P, Melichar B, et al. Intraluminal high dose rate brachytherapy in the treatment of bile duct and gallbladder carcinomas. Hepatogastroenterology 2002;49(46):916-7.