ANTICANCER RESEARCH *37*: 4649-4653 (2017)
doi:10.21873/anticanres.11867

Clinical Study on Using ^{125}I Seeds Articles Combined with Biliary Stent Implantation in the Treatment of Malignant Obstructive Jaundice

TAO WANG*, SHENG LIU*, YAN-BO ZHENG, XUE-PENG SONG, BO-LIN SUN, WEN-JIN JIANG and LI-GANG WANG

Department of Interventional Therapy, Yuhuangding Hospital, Yantai, P.R. China

Abstract. *Aim: To study the feasibility and curative effect of ^{125}I seeds articles combined with biliary stent implantation in the treatment of malignant obstructive jaundice. Patients and Methods: Fifty patients with malignant obstructive jaundice were included. Twenty-four were treated by biliary stent implantation combined with intraluminal brachytherapy by ^{125}I seeds articles as the experimental group, while the remaining 26 were treated by biliary stent implantation only as the control group. The goal of this study was to evaluate total bilirubin, direct bilirubin and tumor markers (cancer antigen (CA)-199, CA-242 and carcinoembryonic antigen (CEA)), as well as biliary stent patency status and survival time before and after surgery. Results: Jaundice improved greatly in both groups. The decreases of CA-199 and CA-242 had statistical significance (p=0.003 and p=0.004) in the experimental group. The ratio of biliary stent patency was 83.3% (20/24) in the experimental group and 57.7% (15/26) in the control group (p=0.048). The biliary stent patency time in the experimental group was 1~15.5 (mean=9.84) months. The biliary stent patency time in the control group was 0.8~9 (mean=5.57) months, which was statistically significant (p=0.018). The median survival time was 10.2 months in the experimental group, while 5.4 months in control group (p<0.05). Conclusion: ^{125}I seeds articles combined with biliary stent implantation significantly prolongs biliary stent patency time and survival time for patients with malignant obstructive jaundice possibly by inhibiting the proliferation of vascular endothelial cells and the growth of tumor.*

Malignant obstructive jaundice refers to the bile duct obstruction caused by a variety of malignant lesions, most of which will not be diagnosed until reaching an advanced stage. Unfortunately, only 7% of patients with this condition have the opportunity of radical surgery (1, 2). Biliary stent implantation technique can restore the physiological drainage of bile (3, 4). ^{125}I seeds articles combined with biliary stent implantation technique has been demonstrated in the past as a potential approach that can ease the jaundice recurrence due to the stent blockage; it also has therapeutic effects on the primary tumor via the radiation effects (5, 6). We have been evaluating this technique in the clinical condition. From September 2010 to February 2013, we applied ^{125}I seeds articles combined with biliary stent implantation treatment to 24 patients with malignant obstructive jaundice, together with a control group. Here, we report the efficacy and clinical outcome of the findings.

Materials and Methods

Clinical data. From September 2010 to February 2013, 50 patients (29 male and 21 female; aged between 41 to 80 (mean=57.3) years) with malignant obstructive jaundice were treated in our Hospital. All patients were confirmed by laboratory and pathological or imaging examination as malignant obstructive jaundice. The etiology of the jaundice include 18 cases of cholangiocarcinoma,14 cases of pancreatic head carcinoma,12 cases of hilar lymph node metastasis and 6 cases of ampullary carcinoma. Among the 50 patients with malignant obstructive jaundice, 24 cases (experimental group) were treated with ^{125}I seeds articles combined with biliary stent implantation. The remaining 26 cases were treated with biliary stent implantation (control group). All 50 patients had progressive jaundice on admission with skin and icteric sclera. Among the patients, there were 28 cases of right upper abdominal tenderness, 12 with epigastric tenderness and 10 with no clear abdominal symptoms. Fifteen patients had fever and 6 cases had ascites-positive syndrome. Preoperative imaging examination of all the

*These Authors contributed equally to this study.

Correspondence to: Yan-bo Zheng, MD, Ph.D., Department of Interventional Therapy, Yuhuangding Hospital, No. 20 Yuhuangding East Road, Zhifu District, Yantai 264000, P.R China. Tel: +86 18253560686, Fax: +86 05356240341, e-mail: 18253560686@163.com

Key Words: Neoplasms, jaundice, obstructive, ^{125}I seeds, stents, treatment outcome.

patients showed different degrees of intrahepatic bile duct dilation. According to Bismuth classification, 17 cases were type I, 15 cases type II, 10 cases type IIIa, 8 cases type IIIb, whereas no case of type IV existed. The serum total bilirubin and direct bilirubin of all patients increased. Twenty cases were Child-Pugh classification of liver function grade B, while 23 cases were grade C. None of the routine blood tests, hemagglutination tests or pre-transfusion tests had surgical contraindications.

Materials and equipment for interventional treatment. ^{125}I seeds: sealed seed source, produced by Beijing Zhibo Hi-Tech Biotechnology Co., Ltd. (Beijing, China) was selected. Size: length=4.5 mm, diameter=0.8 mm. Package: titanium shell as the external package. Carrier: radioactive material adsorbed on silver bars. Half-value layer=0.03 mm lead. Activity=0.7 mCi. Ray energy=27.4~35.5 keV. Tissue penetration=17 mm. Half-life period= 60.1 days. MTN-DR biliary stent was selected for the biliary internal stent, produced by Micro-Tech Co., Ltd. (Nanjing, China) with 4 specifications, including 8 mm × 40 mm, 8 mm × 60 mm, 10 mm × 40 mm and 10 mm × 60 mm. Other auxiliary materials included 180 cm and 260 cm ultra smooth loach guide wire, 4F elbowed catheter, 8.5 F bile duct drainage kit and puncture introduction system. The contrast medium used was ioversol.

Preoperation preparations. Full set of biochemical examinations, routine blood tests, four blood coagulation indices, carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 242 (CA242) and carcinoembryonic antigen (CEA) examination were all routinely tested before operation. Liver computed tomography (CT) and magnetic resonance imaging (MRI) scans were obtained to understand the extent of intrahepatic bile duct dilatation, obstructive position and the position and extent of the nearby primary lesion. This information was also used to clarify the length of bile duct obstruction segment, select the appropriate biliary stent and determine the number of ^{125}I seeds according to the length of the stent.

Surgical procedures. (i) Percutaneous intrahepatic bile duct puncture and drainage and biliary stent implantation: the conventional method of bile duct puncture in the obstruction with biliary stent implantation and placement of 8.5 F internal and external bile duct or external drainage tube for bile drainage was adopted. If the patient had concurrent biliary infection and hemobilia, the drainage time could be appropriately extended. (ii) ^{125}I seeds articles preparation and implantation: the transparent fine flexible tube in the bile duct drainage tube kit as the carrier of the seeds was used. The distance from the lateral end of the drainage tube to the medial end of the stent was measured to allow production of a suitably sized transparent fine flexible tube. This tube was used to contain the required seeds. It was required that after the placement of seeds articles, the seed section inside the transparent fine flexible tube to be located precisely in the inside of the stent, with both ends being 5 mm beyond the stent, before closing the fine flexible tube. The internal drainage was regarded as successful if the patients showed no signs of discomfort 1-2 days after the drainage procedure. At this point, ^{125}I seeds articles were then placed through the drainage tube, which delivered the prepared ^{125}I seeds articles accurately to the bile duct obstruction position. The seeds articles end and the end of the drainage tube fastened with each other, so as to prevent the movement of the seeds articles and affix commonly to the skin surface with butterfly stickers.

Postoperative treatment. Postoperative hepatoprotective action of the hemostatic system and jaundice-relieving treatment supplemented by nutritional support were routinely given to patients in both groups. Clinical monitoring was routinely carried out for signs of hemobilia, fever, chills, abdominal discomfort, diarrhea, hemafecia or any other symptoms related to the disease and procedure. Two months after the operation and under sterile conditions, ^{125}I seeds articles were removed from the patients in the experimental group and the bile duct drainage tubes were removed from the control group.

Follow-up and evaluation of curative effect. Follow-up time was up to September 2013 or until the death of the patients. All patients completed the follow-up. The follow-up information included the change in biliary stent patency time, total bilirubin (TBIL), direct bilirubin (DBIL), CA199, CA242 and CEA. Stent patency time criteria were: a) After stent placement, TBIL and DBIL value dropping to normal to the relapse of obstructive jaundice; or significant decrease (>100 μmol/l) or decreasing to 50% of the original level to increasing again; b) No jaundice at the time of death; c) After the stent placement patients remain alive and without evidence of jaundice up to the end of follow-up (September 2013) (7).

Statistical method. All data were analyzed by SPSS 18.0 (SPSS Inc., Chicago, IL, USA); *t*-test or χ^2 test was used for intergroup analysis where appropriate. Kaplan-Meier method was used for survival analysis. The test level was α=0.05.

Results

Treatment and procedure. Twenty patients in the experimental group were implanted with thirty ^{125}I seeds articles successfully, with 450 seeds in total, thus, with a success rate of 100%. During the follow-up period, none of the patients had seed articles shedding or seed migration. All 50 patients of the study were successfully implanted with a biliary stent, including the placement of a common bile duct stent in 25 patients, combined stent for left and right hepatic duct in 15 patients, right hepatic duct stent in 8 patients and left hepatic duct stent in 2 patients.

Change in TBIL and DBIL of the two groups of patients before and after treatment. In the experimental group, TBIL before treatment, 1 month and 2 months after surgery was 412.26±102.30 μmol/l, 205.52±58.45 μmol/l and 120.02±35.13 μmol/l, respectively. This decrease was statistically significant (p=0.027). In control group, TBIL before treatment, 1 month and 2 months after surgery was 424.22±111.20 μmol/l, 212.28±62.45 μmol/l and 134.45±40.63 μmol/l, respectively, representing a significant difference in the decrease of TBIL after treatment (p=0.026). For the DBIL, the change in experimental group from before treatment to 1 month and 2 months after surgery was 218.64±118.45 μmol/l, 105.19±58.36 μmol/l and 71.35±36.87 μmol/l, respectively (p=0.033), whereas, for the control group, 221.25±114.57 μmol/l, 98.76±43.98 μmol/l and 82.65±39.25 μmol/l, respectively (p=0.035).

Table I. *Comparison of the change in tumor markers of the patients in experimental and control group before and after treatment.*

Group	CA-199 (U/ml)		CA-242 (U/ml)		CEA (ng/ml)	
	Before treatment	2 months after surgery	Before treatment	2 months after surgery	Before treatment	2 months after surgery
Experimental group	130.58±59.41	43.72±10.68[a]	28.61±13.08	5.98±1.36[b]	4.69±1.25	2.81±0.54
Control group	128.48±61.31	125.95±58.21	31.25±10.08	28.62±11.47	5.36±1.14	4.90±0.63

CA, Cancer antigen; CEA, carcinoembryonic antigen. Note: Compared to before treatment status, [a]p=0.003, [b]p=0.004.

Change in tumor markers of the two groups of patients before and after treatment. As seen in Table I, a statistically significant decrease in CA-199 (p=0.003) and CA-242 (p=0.004) was demonstrated in the experimental group 2 months after surgery. Interestingly there was no significant change with CEA (p=0.238). The control group had a different response, since there was no statistical significance in any of the three biomarkers tested 2 months after surgery (p>0.05).

Comparison of the ratio of biliary stent patency and biliary stent patency time in the two groups. There was a significant increase in the ratio of biliary stent patency 83.3% (20/24) in experimental group compared to the control group (57.7%, 15/26) (p=0.048). The biliary stent patency time in the experimental group was 1~15.5 (mean=9.84) months, significantly longer than that in the control group (0.8~9 (mean=5.57) months) (p=0.018).

The two treatments employed resulted in different patient survival time. By the end of the follow-up period, the survival rate was 33.3% (8/24) in the experimental group and 19.2% (5/26) in the control group. The cause of death in both groups was multiple organ failure. The median survival time was 10.2 months in the experimental group and 5.4 months in the control group (Figure 1), a significant difference in the survival time of the two groups (p<0.05, log-rank test).

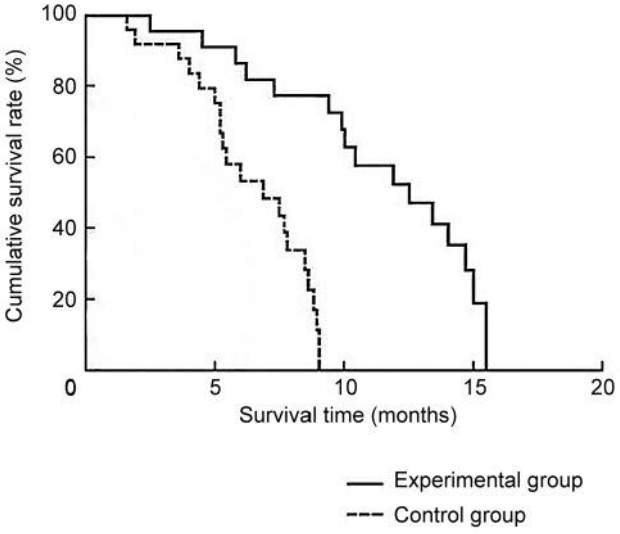

Figure 1. *Survival curves of patients in the experimental and control group.*

Discussion

Biliary stent implantation for the treatment of malignant obstructive jaundice is known to improve the patients' quality of life, prolong survival time and prepare and provide conditions for further chemotherapy, radiotherapy and other treatments (8-10). However, stent restenosis has become a major limiting factor to providing a lasting benefit. Invasive growth of tumor is the main cause of stent stenosis, together with inflammation and granulation tissue formation (11-14). Studies by Isayamaet *et al*. showed that the implanted stent graft can prevent the invasion of the tumor tissue to the stent interior and cause stent blockage (13). However, due to the position of its placement, the stent graft may block the collateral bile duct, affecting the bile flow, or even causing acute cholecystitis, pancreatitis and other serious complications. Furthermore, due to the low coefficient of friction, stent graft has higher incidence of migration relative to the bare stent. In their study, Han *et al*. treated a total of 12 patients with stent restenosis due to various etiologies by two stent implantations and achieved good curative effect (15).

Seed implantation therapy is one form of interstitial brachytherapy (16, 17). Compared with external irradiation, it has a direct effect on the lesion, so that the dose of radiation inside the tumor is much higher than the surrounding normal tissue. This would give the advantage of reducing the radiation damage to the surrounding normal tissue; continuously released radiation has fragmentation effects on all stages of tumor cells and significantly improves the biological effects, *i.e.*, oxidize the tumor to produce hypoxia cells, thereby increasing the sensitivity of the tumor cell to radiation (18). Guo *et al*. treated 38 malignant obstructive

jaundice patients after biliary stent implantation with external radiotherapy, transcatheter arterial chemoembolization and (or) perfusion chemotherapy (19). Their study demonstrated an improvement in survival time. However, for the patients with malignant obstruction, the traditional external radiotherapy requires considerable attention to the duodenum, stomach, liver, kidney and other organs in the choice of the radiation dose. When the radiation dose exceeds 50 Gy, the probability of the occurrence of gastrointestinal ulcer, hemorrhage and radiation enteritis increased significantly (20). Therefore, the application of the traditional radiotherapy is subject to great restrictions. In this study, the ^{125}I seeds implanted in the lumen of the bile duct can release 80% of its own energy within 1 cm, without damaging the surrounding organs, such as the pancreas and intestine. ^{125}I radioactive seeds can also inhibit the proliferation of bile duct epithelial cells, thereby reducing the re-blockage of biliary stent due to tissue proliferation. Chang *et al*. adopted the indwelling catheter device to load the radioactive seeds and performed endovascular brachytherapy on the tumor at the stenosis of biliary tract (21). The initial treatment effect was satisfactory; however, the subcutaneous implantation of indwelling catheter device caused pain and discomfort, which may lead to early removal, thus affecting the curative effect.

In the present study, the ^{125}I seeds articles made use of the original fine flexible tube of the bile duct drainage tube as the carrier of seeds, which could be served along the bile duct drainage tube to the stenosis position. The end of the tube could be completely combined with the bile duct drainage tube, allowing good fixation, so as to simplify the operation procedure of the placement of seeds articles. Chen *et al*. performed transcatheter arterial chemoembolization on 39 patients with malignant obstructive jaundice after implantation of biliary stent, which could also control the primary tumor effectively and prolong the recurrence time of jaundice (22). The aforementioned methods had good therapeutic effects on the external biliary stricture due to intrahepatic solid tumors, enlarged hilar lymph nodes and pancreatic head carcinoma. However, there were limitations for the invasive growth tumor along the bile duct wall. As most of such tumors did not exceed 1 cm in diameter, it was difficult to implant seeds directly into the tumor. In our study, we selected tumor cases with the obstruction position of the invasive growth tumor along the bile duct wall and diameter <1.5 cm, which significantly improved the jaundice of the 50 patients in the group after treatment. Both the stent patency time and the stent patency rate in the experimental group were superior over the control group. The benefit for the experimental group also displayed significant benefit in the rate of reduction of tumor markers, CA-199, CA-242 and CEA. It was pleasing to see that these benefits were well-reflected in the survival of the patients, as the patients, in the experimental group, survived almost twice as long as the control group.

In conclusion, ^{125}I seeds articles combined with biliary stent implantation is a safe and effective method for patients with malignant obstructive jaundice. It prolongs the biliary stent patency time and patients' survival time. It is likely that the treatment effectively inhibits the proliferation of vascular endothelial cells and the growth of tumor cells. This study, limited by the sample size and short follow-up time, would warrant further in-depth study with a larger sample size and longer follow-up time in the future.

Acknowledgements

Thanks are due to the medical technicians in the interventional catheter room for assistance with the operation. The Authors express their heartfelt thanks to all patients who participated in the study.

References

1 Wasan SM, Ross WA, Staerkel GA and Lee JH: Use of expandable metallic biliary stents in resectable pancreatic cancer. Am J Gastroenterol *100*: 2056-2061, 2005.

2 Stern N and Sturgess R: Endoscopic therapy in the management of malignant biliary obstruction. Eur J Surg Oncol *34*: 313-317, 2008.

3 Kim HS, Lee DK, Kim HG, Park JJ, Park SH, Kim JH, Yoo BM, Roe IH, Moon YS and Myung SJ: Metallic stents in malignant biliary obstruction: Prospective long-term clinical results. Am J Roentgenol *168*: 41-745, 1997.

4 Chen Y, Wang XL, Yan ZP, Wang JH, Cheng JM, Gong GQ and Luo JJ: The use of ^{125}I seed strands for intraluminal brachytherapy of malignant obstructive jaundice. Cancer Biother Radiopharm *27*: 317-323, 2012.

5 Nag S, Dehaan M, Scruggs G, Mayr N and Martin EW: Long-term follow-up of patients of intrahepatic malignancies treated with iodine-125 brachytherapy. Int J Radiat Oncol Biol Phys *63(Suppl 1)*: S281, 2006.

6 Zhu HD, Guo JH, Zhu GY, He SC, Fang W Deng G, Qin YL, Li GZ, Coldwell DM and Teng GJ: A novel biliary stent loaded with ^{125}I seeds in patients with malignant biliary obstruction: Preliminary results versus a conventional biliary stent. J Hepatol *56*: 1104-1111, 2012.

7 Zhang M: Percutanenous transhepatic biliary drainage combined with radioactive seed ^{125}I implantation in treatment of malignant obstructive jaundice. Arch China-Japan Union Hospital Jilin University *2009*: 25, 2009.

8 Jain S, Kataria T, Bisht SS, Gupta D, Vikraman S, Baijal S and Sud R: Malignant obstructive jaundice – Brachytherapy as a tool for palliation. J Contemp Brachytherapy *5*: 83-88, 2013.

9 Mattiucci GC, Autorino R, D'Agostino GR, Deodato F, Macchia G, Perri V, Tringali A, Morganti AG, Mutignani M and Valentini V: Chemoradiation and brachytherapy in extrahepatic bile duct carcinoma. Crit Rev Oncol Hematol *90*: 58-67, 2014.

10 Yoon WJ, Ryu JK, Yang KY, Paik WH, Lee JK, Woo SM, Park JK, Kim YT, Yoon YB: A comparative study on the efficacy of covered metal stent and plastic stent in unresectable malignant biliary obstruction. Clin Endosc *45*: 78-83, 2012.

11 Liu Y, Liu JL, Cai ZZ, Lu Z, Gong YF, Wu HY, Man XH, Jin ZD and Li ZS: A novel approach for treatment of unresectable extrahepatic bile duct carcinoma: Design of radioactive stents and an experimental trial in healthy pigs. Gastrointest Endosc *69*: 517-524, 2009.
12 Kaassis M, Boyer J, Dumas R, Ponchon T, Coumaros D, Delcenserie R, Canard JM, Fritsch J, Rey JF and Burtin P: Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. Gastrointest Endosc *57*: 178-182, 2003.
13 Wadsworth CA, Westaby D and Khan SA: Endoscopic radiofrequency ablation for cholangiocarcinoma. Curr Opin Gastroenterol *29*: 305-311, 2013.
14 Isayama H, Komatsu Y, Tsujino T, Sasahira N, Hirano K, Toda N, Nakai Y, Yamamoto N, Tada M, Yoshida H, Shiratori Y, Kawabe T and Omata M: A prospective randomised study of "covered" versus "uncovered" diamond stents for the management of distal malignant biliary obstruction. Gut *53(5)*: 729-734, 2004.
15 Han XW, Li YD, Ma N, Xing GS, Ma B and Wu G: The interventional treatment for biliary re-stenosis after metallic stents placement in patients with malignant obstruction due to cholangio carcinoma. J Intervent Radiol *11*: 354-356, 2002.
16 Mohiuddin M, Rosato F, Barbot D, Schuricht A, Biermann W and Cantor R: Long-term results of combined modality treatment with I-125 implantation for carcinoma of the pancreas. Int J Radiat Oncol Biol Phys *23*: 305-311, 1992.
17 Mattiucci GC, Autorino R, Tringali A, Perri V, Balducci M, Deodato F, Gambacorta MA, Mantini G, Tagliaferri L, Mutignani M and Morganti AG: A Phase I study of high-dose-rate intraluminal brachytherapy as palliative treatment in extrahepatic biliary tract cancer Brachytherapy *14(3)*: 401-404, 2015.
18 Popescu CC, Wise J, Sowards K, Meigooni AS and Ibbott GS: Dosimetric characteristics of the Pharma Seed model BT-125-I source. Med Phys *27*: 2174-2181, 2007.
19 Lu ZM, Guo QY, Liu ZY, Liao W and Zhang J: The result of percutaneous interwentional therapy for malignant biliary obstruction. Chin J Med Imaging *11(2)*: 125125-125127, 2003.
20 Qiu GQ, Chen YQ, Wu XA, Luo PF, Gao CL, Zhang ZY, Hong JY, Wan YF, Lin ZC and Liu T: Clinical observation of biliary stent plus conformal radiation for therapy of malignant obstructive jaundice. Clin J Med Offic *37*: 969-971, 2009.
21 Chang G, You Y, Meng FZ and Yang ZG: Treatment of malignant obstructive jaundice: biliary stent implantation+ intraluminal brachytherapy by I-125 seeds. Chin J Med Imaging Technol *23*: 439-441, 2007.
22 Chen Y, Yan ZP, Wang JH, Wang XL, Cheng JM, Gong GQ, Liu QX, Qian S, Liu Z and Luo JJ: Epirubicin in the treatment of malignant obstructive jaundice. Chin J Oncol *28(5)*: 397-399, 2006.

Received May 2, 2017
Revised June 1, 2017
Accepted June 7, 2017