

Percutaneous biliary metallic stenting and ¹²⁵I seed implantation for the treatment of malignant obstructive jaundice.

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Abstract

This study aimed to investigate the feasibility and efficacy of percutaneous biliary metallic stenting and ¹²⁵I seed implantation in treatment of malignant obstructive jaundice (MOJ). Percutaneous biliary metallic stenting and ¹²⁵I seed implantation were performed in 27 patients with MOJ. Detection of liver function, routine blood test and upper abdominal CT were done to evaluate the change in bilirubin, blood components, stability of seed and stent patency. Percutaneous metallic stenting and ¹²⁵I seed implantation were smoothly performed in the biliary tract with the success rate of 100%. The mean number of ¹²⁵I seeds used was 17 per patient. The median period of follow up was 7 months (range: 3-19 months). Imaging examination showed the seeds were stable and had no displacement. The total bilirubin reduced from 369.45±87.32μmol/L before surgery to 96.03±70.14μmol/L at 1 month after surgery. Side effects of radiotherapy (such as leukopenia, nausea and vomiting) were not observed. Re-stenosis was found in 2 patients with the re-stenosis rate of 7.4%. Two patients died of systemic failure within 3 months after surgery, and the mean survival time of these patients was 201.8± 178.7 days. Percutaneous biliary metallic stenting and ¹²⁵I seed implantation are safe and feasible for patients with MOJ and may serve as a minimally invasive strategy for the prevention of re-stenosis after biliary stent implantation.

Keywords: Percutaneous biliary metallic stenting, malignant obstructive jaundice, bilirubin, invasive strategy

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Introduction

Malignant obstructive jaundice (MOJ) refers to the obstructive jaundice due to the compression of biliary ducts caused by primary cholangiocarcinoma, ampullary carcinoma, pancreatic cancer, liver cancer or lymph node metastasis of other cancers. The early diagnosis of MOJ is difficult and success rate of surgery for MOJ is low. Severe jaundice has been one of major causes of death. Since 1980s, metallic stenting has been applied in the biliary duct system. With the wide application of minimally invasive techniques in clinical practice, biliary stenting has been one of strategies for the palliative treatment of MOJ [1-3]. However, the post-operative re-stenosis and obstruction occur as an important consequence of biliary stenting. It was reported that the incidence of obstruction rate of stents was 20-80% within 6 months after biliary metallic stenting in patients with MOJ, and the obstruction is caused by overgrowth of cancer cells [3-12]. Thus, to actively control the cancer growth after stenting is a key issue for the improvement of therapeutic efficacy with the development of

radiotherapy, biliary stenting and concomitant biliary brachytherapy have been applied in the treatment of MOJ achieving favorable efficacy [13-15]. In the ¹²⁵I brachytherapy, radioactive ¹²⁵I is implanted in the cancer or at the site adherent to the cancer via a source applicator or surgery, and thus the cancer is radiated at a low dose for a long time, achieving therapeutic effectiveness [12, 16]. From 2010 to 2011, percutaneous metallic stenting and ¹²⁵I seed implantation were performed in our hospital achieving favorable efficacy.

Patients and methods

A total of 27 patients with MOJ were recruited from our hospital from May 2010 to December 2011. There were 17 males and 10 females and the median age was 66 years (range: 45-87 years). Of these patients, cholangiocarcinoma was found in 10, liver metastasis after surgery for gastric cancer in 6 and pancreatic cancer in 11. The diagnosis of cancers was confirmed by clinicopathological examination, imaging examination and blood biochemical examinations.

Radioactive seeds: The sealed radioactive ^{125}I seeds (0.8 mm×4.5 mm; cylindrical). The radiation dose was 27.4-31.5 keV, the half-life was 59.36 d and the depth of tissue penetration was 1.7 cm. These seeds were capsulated with titanium alloy and the source apparent activity was 0.3-0.8 mCi.

Puncture and drainage system: One step COOK Micro-Puncture Kit and 8.5-10.2 drainage tube were used.

Stents and balloon: The smart stent (Cordis; 8mm×80mm or 8mm×60mm) and P3 balloon (6×60mm or 8mm×60mm) were used in the surgery.

Before surgery, bleeding time, clotting time, liver and kidney function and electrocardiogram were detected, and upper abdominal CT was also performed, aiming to evaluate the site of biliary obstruction, extent of distribution of extended biliary ducts and site of cancer.

Percutaneous puncture was performed with the guidance of DSA. Then, a tube with a wire was inserted. When the tube passed through the obstructive site, a 6F tube was inserted into the biliary ducts, followed by pre-dilation at the obstructive site. Then, two superhard wires were inserted through the obstructive sites, and the long sheath of 6F tube passed through a wire and covered the obstructive site.

The 3F dilation tube of the COOK drainage kit was cut and one of terminals was sealed by heating. According to the length of obstructive lesions, the radioactive ^{125}I seeds were placed into the other terminal of this tube which was then sealed by heating. Generally, the length of ^{125}I seeds was 80~100mm.

The stent was released via the wire to cover the obstructive site. Thus, the seeds were released via the tube sheath assuring that the seeds were fixed on the biliary wall. Finally, an 8.5-10 F drainage tube was inserted into the proximal biliary tube via the wire.

After surgery, routine anti-bacterial therapy, liver-preservative and supportive therapy were performed. The external drainage was discontinued within 3-5 days depending on the color of drained bile. The drainage tube was withdrawn within 3-4 weeks.

Patients were followed up regularly and the disease conditions were monitored. Following parameters were detected: **Jaundice:** The liver function was detected at 3 days, 2 weeks, 1 month and 3 months after surgery, and the change in bilirubin was evaluated. **Blood test:** Routine blood test was performed at 2 weeks, 1 month and 3 months after surgery. **Stents:** Abdominal CT was performed at 1, 3 and 6 months after surgery, and the stability and stent patency were evaluated. The survival

time and complications related to radiotherapy were monitored during follow up.

Results

^{125}I seeds were smoothly implanted in all these patients with the success rate of 100%. The median number of seeds used was 17 per patient (range: 10-25). Imaging examination showed the seeds were stable and fixed. Two patients (7.4%) showed severe cholestasis, and the remaining patients showed significant improvement of jaundice within 1 month. The median total bilirubin reduced from $369.45\pm 87.32\mu\text{mol/L}$ before surgery to $96.03\pm 70.14\mu\text{mol/L}$ at 1 month after surgery. Side effects related to radiotherapy (such as leukopenia, nausea, and vomiting) were not observed. Of 27 patients, the median period of follow up was 7 months (range: 3-19 months). Two patients showed re-stenosis at the site of stents with the incidence of re-stenosis rate of 7.4%. Two patients died of systemic failure within 3 months after surgery. The median survival time was 201.8 ± 178.7 days. Two patients developing re-stenosis were diagnosed with hilar cholangiocarcinoma and presented with jaundice at 11 and 13 months after surgery, respectively. CT showed cancer progression. The second percutaneous catheter drainage was employed. The remaining patients survived and jaundice was not observed. Follow up continued.

Discussion

MOJ has a poor prognosis and the median survival time range 3 months to 10 months [17, 18]. Percutaneous biliary metallic stenting has been a major strategy for the treatment of MOJ. However, the stent itself has not therapeutic effect on the focal cancer. The cancer progression may eventually cause re-stenosis. It has been reported that the time of metallic stent patency is about 3-10 months [3-8], and the obstruction (re-stenosis) is usually attributed to the over-growth of cancer cells. To control the growth of focal cancer, some investigators employed afterloading technique, with which a radioactive source was placed in the drainage tube for focal radiation, achieving favorable efficacy. ^{192}Ir is frequently applied in early brachytherapy [19, 20]. Currently, radioactive ^{125}I seeds are used for brachytherapy in clinical practice [12]. The biological characteristics of ^{125}I seeds are as follows: 1) low radiation dose, continuous radiation and hyperfractionated irradiation which may delay the cell cycle, increase the repair after sublethal injury, induce the re-distribution of cell cycle and increase the sensitivity of cancer cells to radiation; 2) For cancer stem cells which are non-responsive to routine external radiation, radiation at an enough dose and for a longer time may significantly compromise the proliferation of cancer cells, and this effect is continuous and potent and may completely

remove cancer cells. To prolong the time of radiation and reduce the radiation dose may attenuate the injury to normal tissues without influence on the therapeutic effect on cancer cells. Thus, to reduce the radiation dose may increase the therapeutic ratio, which is the basis of fractionated radiation; 4) The radiation dose is at a high level in the target region but rapidly reduces in the surrounding tissues; 5) low dose radiation may release low-energy soft X-ray which may improve the biological effects; 6) radiation may destroy the nuclear DNA of cancer cells, resulting in reduction in proliferation [16]. In the present study, follow up was performed for median 7 months. Two patients developed re-stenosis with the re-stenosis rate of 7.4%. Two patients died and the survival rate was 92.5%. Our findings also supported that percutaneous metallic stenting and ¹²⁵I seed implantation could prolong the time of stent patency.

In previous studies, investigators frequently used stenting and seed implantation via an indwelling catheter for brachytherapy [21]. Although this technique is superior to seed implantation via the drainage tube, it still has disadvantages: the indwelling catheter may cause focal skin infection and reduce the quality of life; the respiration and movement may cause instability of seeds, resulting in displacement of radioactive seeds and affecting the therapeutic efficacy. In our department, modified technique was used in which two wires were used, and seeds were implanted during the stenting. The metallic stent was used to fixed seeds in the local lesions, which overcomes the discomfort due to long term catheter indwelling and at the same time increases the stability of seeds. In our study, the success rate was 100%, and imaging examinations indicated that these seeds were stable and displacement was not observed.

In our study, significant reduction in total bilirubin was observed in 92.5% of patients within 1 month after surgery, and side effects related to radiotherapy (such as leukopenia, nausea, vomiting) were not observed. This suggests that focal implantation of radioactive seeds is beneficial for the improvement of liver function and has no myelosuppressive effect.

There were still limitations in this study: the distribution of seeds was still unreasonable and these seeds failed to radical radiotherapy of focal cancer. Thus, focal implantation of seeds in the cancer after puncture or external radiation after stenting and seed implantation, and focal arterial or systemic chemotherapy may be helpful to further improve the survival time.

Our findings suggest that percutaneous metallic stenting and ¹²⁵I seed implantation are safe and feasible for patients with MOJ and may serve as a minimally invasive strategy for the prevention of re-stenosis after biliary stent implantation.

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