

A Novel Approach for Treatment of Unresectable Pancreatic Cancer: Design of Radioactive Stents and Trial Studies on Normal Pigs

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Abstract Purpose: Patients diagnosed with pancreatic cancer typically have a poor prognosis. The aims of these studies were to design radioactive stents and to evaluate the feasibility and safety of the stents in animals.

Experimental Design: To combine the effects of stents and brachytherapy, plastic stents with inserted iodine-125 seeds were designed and tested in 18 normal pigs. The pigs were divided into five groups on the basis of radiation dose. The estimated radiation dose at a 5-mm radial distance from the axis of the seeds was 50 Gy in group A, 100 Gy in group B, 150 Gy in group C, and 200 Gy in group D, with four pigs in each group. In the control group ($n = 2$), the same plastic stents with non-radioactive seeds were implanted in the pancreatic duct.

Results: The procedures were successfully done on 14 of 18 (78%) pigs, whereas pancreatic duct perforation occurred in four pigs (22%). The thickened wall of the dilated pancreatic duct was clearly observed in the control group. However, the normal morphologic structure of the pancreatic duct wall disappeared in the experimental groups. Histopathologic examination revealed that the stents were surrounded with necrotic tissues and lateral fibrous tissues. During the follow-up period, the width of outside fibrous tissues gradually increased.

Conclusions: These results indicate that the radioactive stents are safe in all dose groups, and it is feasible to design a special radioactive stent for each patient according to the size, shape, and position of the pancreatic tumor.

Pancreatic cancer is an uncommon disease that is generally diagnosed at an advanced stage. Surgical resection is currently considered to be the best treatment, but the majority of patients are not suitable for curative resection due to advanced disease at diagnosis, poor patient condition, and/or tumor location (1, 2). Moreover, the life expectancy of pancreatic cancer patients is short; thus, the therapeutic goal is often palliative. An endoscopic procedure combined with chemoradiotherapy is currently used in the treatment of unresectable pancreatic cancer. Palliative surgery and endoscopic drainage can be done for the treatment of obstructive jaundice and other symptoms (1, 3). Drainage with stents in the bile duct and the pancreatic duct has become a favored palliative drainage procedure.

Radiotherapy with either external beam, intraluminal brachytherapy, or interstitial brachytherapy has been found to be effective to improve local control in patients with advanced pancreatic cancer (4–6). The combination of intraluminal brachytherapy and stent drainage seems to be effective in

preventing local tumor growth and suitable for patients with poor performance status.

To combine the effects of both stents and brachytherapy for preventing local tumor growth, special plastic stents were designed with inserted γ -emitting iodine-125 (^{125}I) seeds. The purpose of this study was to evaluate the safety and tissue response following the placement of the radioactive stents in normal porcine pancreatic ducts to provide information for their future clinical application.

Materials and Methods

Design of ^{125}I radioactive plastic stents. The stents were made of polyurethane, which had a negligible influence in shielding the γ -rays (7). Each plastic stent was composed of a drainage tube and stabs at both ends based on normal pancreatic duct stents. One thin channel was made in the wall of the stent that was parallel to the drainage lumen. Irradiance windows were established in the lateral wall of the channel. The diameter of the channel (0.7 mm) was slightly smaller than the diameter of the radioactive seeds (0.84 mm). The length and width of the windows were also slightly smaller than the sizes of radioactive seeds. The plastic stent was dipped into hot water, and the radioactive seeds were then inserted into the channel and positioned at the irradiance windows. This thermal loading procedure results in a tight fit of the seeds within the stents and prevents seed migration at the body temperature of pigs (about 37°C). The design assures that all seeds directly contact one side wall of the pancreatic ducts and that the lateral wall of pancreatic ducts receives enough radiation (Fig. 1A).

According to the experiment plan, two kinds of pancreatic duct stents were designed. The external diameter of the plastic stent was 3.2 mm

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according to the normal size of the porcine pancreatic duct (8). The diameter of the drainage lumen was 1.8 mm. There was a 0.7-mm channel in the lateral wall of the stent for radioactive seeds. In lower-dosage groups (50 and 100 Gy), the length of stents was 34 mm. Three irradiance windows 4.0 mm in length and 0.5 mm in width were arrayed equidistantly on the outside wall of the channel. The distance between the centers of the irradiance windows was 10 mm, and the distance between each end of the stent and the irradiance windows was 5 mm. The length of the stabs was 7 mm. In higher-dosage groups (150 and 200 Gy), the stent length was 39 mm. Six irradiance windows of the same size were equidistantly arrayed on the lateral wall of the channel. The distance between the centers of the irradiance windows was 5 mm, and the distance between each end of the stent and the irradiance windows was 5 mm. The length of the stabs was 7 mm (Fig. 1B).

The radioactive ^{125}I seeds (China Institute of Atomic Energy, Beijing, China) were 4.5 mm long and 0.84 mm thick, and their half-life was 59.7 days. γ -Rays emitted by ^{125}I had an average energy of 27 keV. The seeds could be easily inserted into the lumen of the channel using a modified needle. For the control group, the same method was used to insert the non-radioactive seeds into the lumen of the channels of the plastic stents.

Radiation dosimetry. Brachytherapy was delivered by ^{125}I seeds inserted into the plastic stent. The target volume for treatment was the distal pancreatic duct with a margin of 5 mm in the pancreatic head area. The dose reference point was selected as 5 mm from the source axis. The number and position of ^{125}I seeds were calculated on the pancreatic head area of each pig using a computerized treatment planning system (Kelinzhong Institute of Atomic Energy, Beijing, China; NO. YZB/1466-70-2004). The dose distribution was optimized, and the dose-volume histogram for the target was generated according to the reference plan with modified peripheral loading (9, 10). All dose calculations were hypothetical and were generated by means of the computerized treatment planning system.

The doses at the reference point were varied in four different groups by changing the source activity and the distance between the seeds. The source region was assumed to be distributed uniformly over the surface. The individual plans were calculated by taking into account the seed number,

position, and activity. The difference among the plans at each dosage was calculated by a computerized treatment planning system according to computerized tomography scans of the abdomens of the pigs.

The estimated radiation dose at a 5-mm radial distance from the axis of the seeds was 50 Gy in group A, 100 Gy in group B, 150 Gy in group C, and 200 Gy in group D. In group A ($n = 4$), the radioactivity of the seeds was 0.5 mCi, the interval distance was 10 mm, and the seed number was 3. The treatment volume was $6.0 \pm 0.1 \text{ cm}^3$, and the volume percentage that received 100% dose (V_{100}) was $19.5 \pm 0.7\%$. In group B ($n = 4$), there were three 0.8-mCi seeds spaced 10 mm apart. The treatment volume was $6.1 \pm 0.3 \text{ cm}^3$, and the V_{100} was $18.5 \pm 1.2\%$. In group C ($n = 4$), there were six 0.6-mCi seeds spaced 5 mm apart. The treatment volume was $6.2 \pm 0.3 \text{ cm}^3$, and the V_{100} was $18.3 \pm 0.9\%$. In group D ($n = 4$), there were six 0.8-mCi seeds spaced 5 mm apart. The treatment volume was $6.2 \pm 0.2 \text{ cm}^3$, and the V_{100} was $18.8 \pm 1.7\%$. In the control group, plastic stents with six non-radioactive seeds spaced 5 mm apart were implanted in the pancreatic ducts of two pigs.

Animals and stent implantation. The experimental procedures in this study were approved by the Animal Use and Care Committee of the Second Military Medical University, China. Eighteen healthy pigs were divided into five groups on the basis of radiation dose, weighing from 20 to 22 kg (mean weight, 21.5 kg); 3% pentobarbital (1 mL/kg) was injected into the abdominal cavity followed by sedation with an i.m. injection of 250 mg ketamin-HCl. Cardiac and respiratory variables were monitored throughout the procedures. A duodenoscope (TGF240, Olympus) with a 4.2-mm working channel was inserted into the duodenum through the mouth, esophagus and stomach. Then, the opening of the pancreatic duct in the descending part of the duodenum was located. A guide wire was manipulated into the pancreatic duct through a catheter. A plastic dilating bougie (2.5 mm) was then inserted over the wire into the distal pancreatic ducts. Through the guide wire, the radioactive stent was inserted into the working channel. The radioactive stent was then advanced into the distal portion of the pancreatic ducts using a plastic pusher. Forty-eight hours later, the position of the stent and seeds was confirmed using radiography (Fig. 2). During all the procedures, the operator

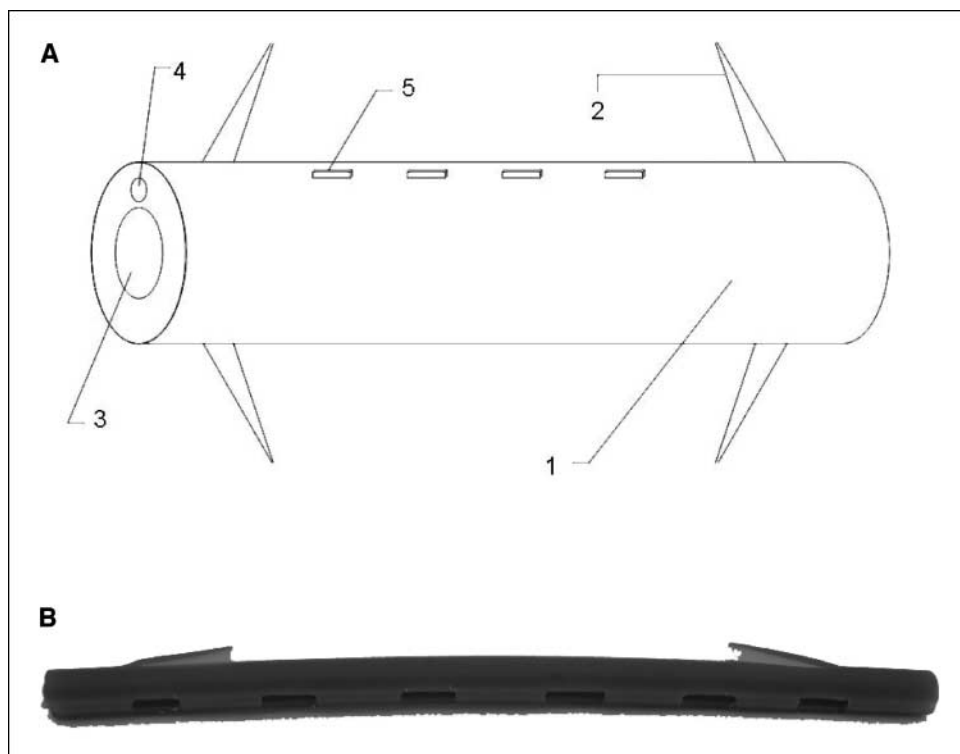


Fig. 1. A, schematic illustration of a radioactive stent. The radioactive seeds were inserted into the channel and were partially exposed in the irradiance windows. 1, stent wall; 2, stab; 3, drainage lumen; 4, seed channel; 5, irradiance window. B, an example of the radioactive stents in the higher-dosage group with six ^{125}I seeds.

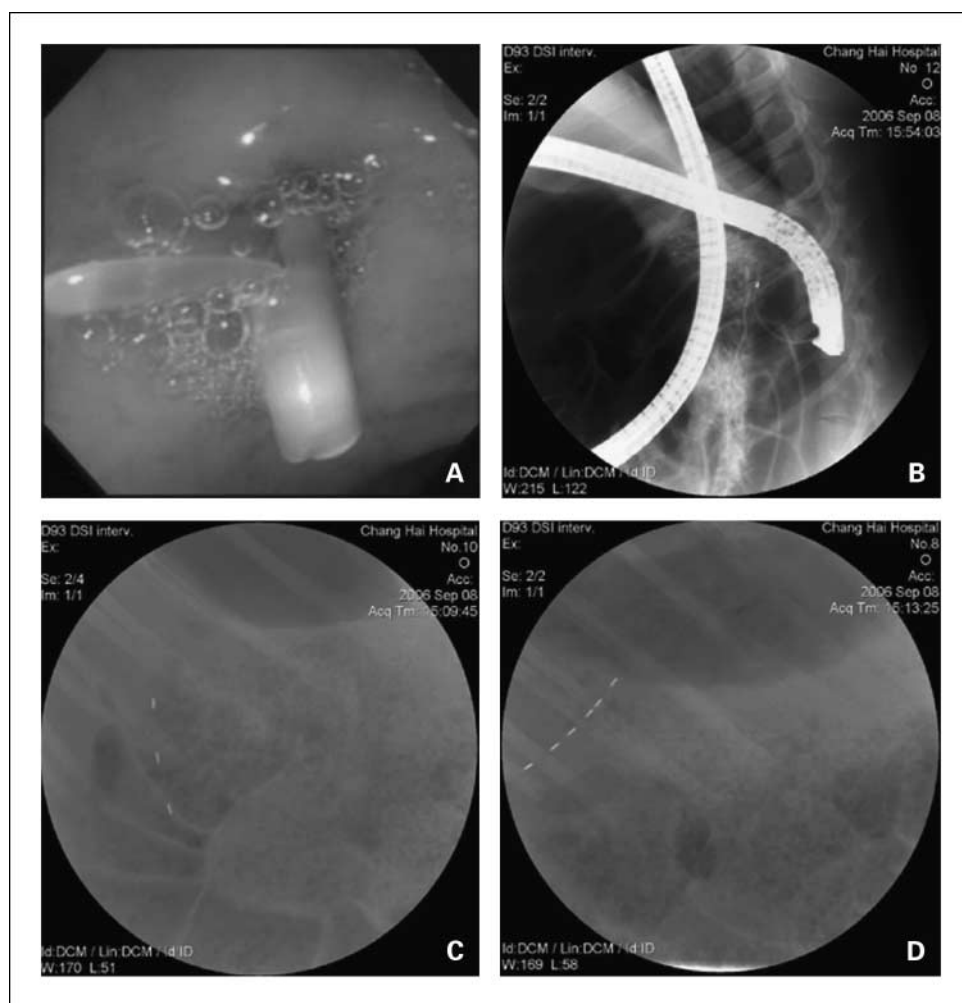


Fig. 2. Representative images illustrating the experimental results. *A*, endoscopic photograph after the placement of a radioactive stent in a pig. *B*, pancreatic ductography picture after cannulation. *C* and *D*, plain radiography shows radioactive stents placed in the pancreatic ducts of pigs. Because X-rays can easily permeate the polyurethane material, only the radioactive seeds are visible in the radiograph.

wore a lead apron and lead gloves, and the radiation dose absorbed by the operator was measured by a BIRM personal thermoluminescence dosimeter worn on the waist (LiF/Mg, Cu, P TL detector; Institute of Radiation Medicine Academy of Military Medical Sciences, Beijing, China).

After the implantation, the animals were observed for clinical symptoms of acute pancreatitis (loss of appetite, altered consciousness, and irritability). Prior studies of interstitial brachytherapy of ^{125}I seeds have found that tissue damage occurred maximally at 14 days (11). Routine blood tests, serum amylase, biochemical variables, IgG/IgA/IgM levels in the blood, and kidney and liver function were monitored at baseline, at 48 h, and on 7, 14, 21, 30, and 60 days after placement of the stent.

Follow-up. After implantation, the 18 pigs were kept alive and observed for three different time periods. One pig from each group with radioactive stents ($n = 4$) and one pig with a non-radioactive stent were followed for 14 days. Two pigs from each group with radioactive stents ($n = 8$) were followed for 30 days. One pig from each group with radioactive stents ($n = 4$) and one pig with a non-radioactive stent were followed for 60 days.

Histologic studies. At the end of their follow-up period, the pigs were euthanized by an i.v. injection of pentobarbital followed by 20 mEq of potassium chloride. All animals underwent a postmortem to exclude intra-abdominal hemorrhage, pancreatic fistula, or peritonitis. During autopsy, the liver, bile ducts, head of the pancreas, stomach, and duodenum were examined for perforation, stricture, or dilation and damage of the surrounding structures. The portion of the

pancreatic ducts containing the stent was dissected out and immediately fixed in a 4% formaldehyde solution. The specimens were embedded in methylmethacrylate for 30 days. The sample was then processed for sectioning and staining with H&E. This procedure was in accordance with the radiation safety rules of our institution. Histologic evaluation was done under a light microscope. The extent of necrosis induced by brachytherapy and the intensity of the inflammation of the parenchyma adjacent to the targeted area were assessed by a single pathologist blinded to the type of inserted stent.

Results

General evaluation of stent implantation. The porcine pancreatic duct is not fused with the common bile duct. As the procedure was similar to minor papilla cannulation by endoscopic retrograde cholangiopancreatography in human patients, the implantation of the radioactive stent in each pig was technically difficult, although most procedures were done successfully. One stent was misplaced in the cavity of the duodenum and was taken back successfully using a snare. The personal thermoluminescence dosimeter on the operator was collected and processed after the placement of stents was completed, and the average effective dose to the surgeon for individual implantation procedures was 0.023 mSV, which indicates a minimal radiation hazard to the operator.

The 150- and 200-Gy stents were longer than the lower dosage stents, and due to the fragility of the pancreatic tissue, it is quite easy to perforate the pancreas during deep insertion of longer stents. One pig in group D died 2 days after the procedure due to perforation of the pancreatic duct; thus, results were obtained from 17 of the original 18 pigs. The deep insertion of long stents caused perforation of the pancreatic duct in three pigs from groups C and D.

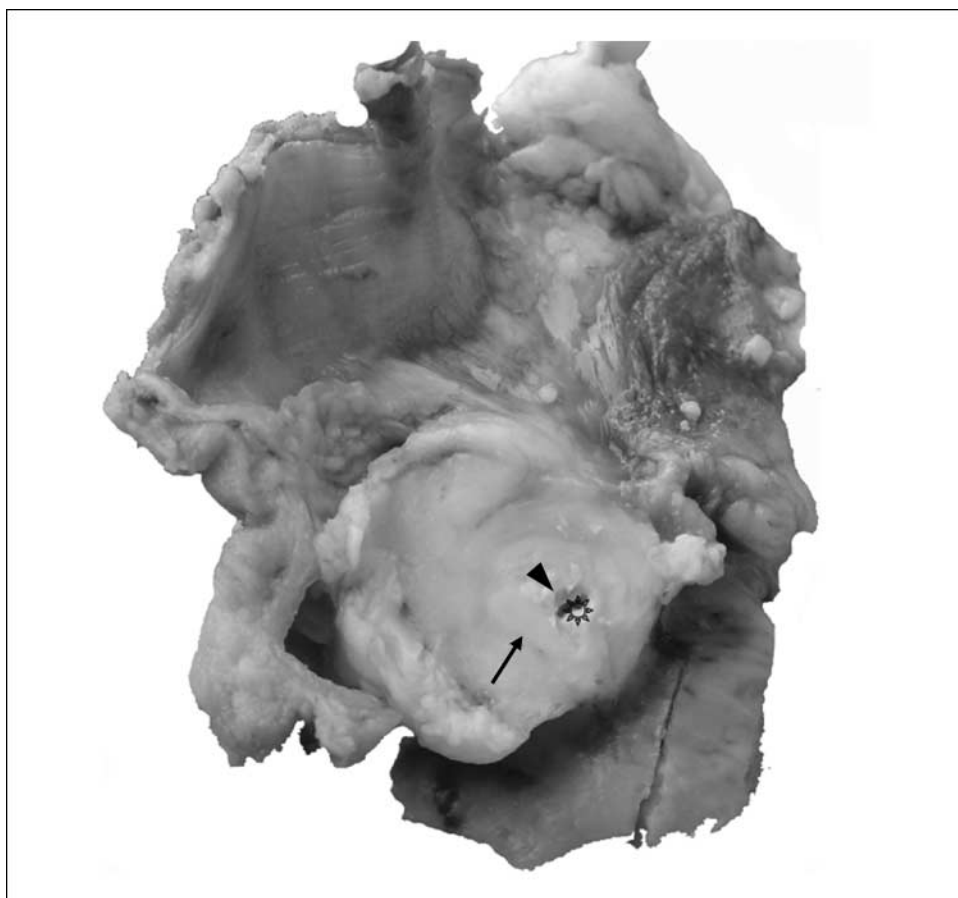
During the first 3 days after implantation, most pigs showed various degrees of loss of appetite and discomfort. In the three pigs with perforations, these symptoms lasted about 7 days. All symptoms disappeared after 2 weeks. If the thermoluminescence dosimeters showed the possibility of stent migration, the animals would be immediately sacrificed after X-ray confirmation.

Fourteen-day follow-up. In the 14-day observation group, there were no clinical signs of peritoneal bleeding or infection in any of the five pigs over the entire observation period. The migrated 200-Gy stent was found in the cavity of the small intestine on the 12th days. After euthanasia, no ecchymosis was observed on the surface of the pancreas in the 50, 100, or 150 Gy pigs, but the 200 Gy pig had a little hyperemia and edema on the surface of the pancreas. There was no blood or fluid in the abdominal cavity of any of the pigs. There were no effusion, hemorrhage, or necrosis in the adjacent duodenum, stomach, liver, or right kidney. None of the stents were obstructed, although there were some ivory necrotic tissues in the stent lumens and food debris could also be seen in the gaps

of two stents. The pancreatic duct proximal to the stent insertion sites was dilated, and the thickened wall of the pancreatic ducts was clearly observed in the control group. However, the structure of the pancreatic duct wall disappeared in the experimental groups. Histopathologic examination revealed that the stents were surrounded with necrotic tissues and lateral fibrous tissues composed of granulation tissue and macrophages. All seeds were identified and retrieved safely after the experiments. No signs were observed of tarnishing, distortion, or rupture of the seeds in the stents.

Thirty-day follow-up. In the 30-day observation group, 6 of the 8 (75%) pigs survived the entire observation period and were sacrificed on the 30th day. Another two pigs (25%) did not complete the observation process, as the migration of one 100-Gy stent was found on the 27th day, and one 150-Gy stent was found to have migrated on the 24th day. The head areas of the pancreas in the 200-Gy group became rigid and white, and in one pig of the 200-Gy group, the proximal pancreatic duct was dilated, and a cyst mass was found on the pancreas tail. There were four unmigrating stents that remained in the pancreatic ducts and were not obstructed: 50 Gy ($n = 2$), 100 Gy ($n = 1$), and 150 Gy ($n = 1$). The two 200-Gy stents did not migrate either, but they were obstructed, and their lumens were full of necrotic material and food debris. The epithelial tissue of the pancreatic ducts in all groups also disappeared. The outside fibrous tissues that surrounded the necrotic areas were thicker and more obvious than those at 14 days (Fig. 3). Because of the cylindrical distribution of the radiation dose, the pancreases

Fig. 3. Photograph of a section of pancreatic head area in the 50-Gy group at 30 d. The necrotic tissues (*arrowhead*) and lateral fibrous tissues (*arrow*) surround the area of the prior stent (*).



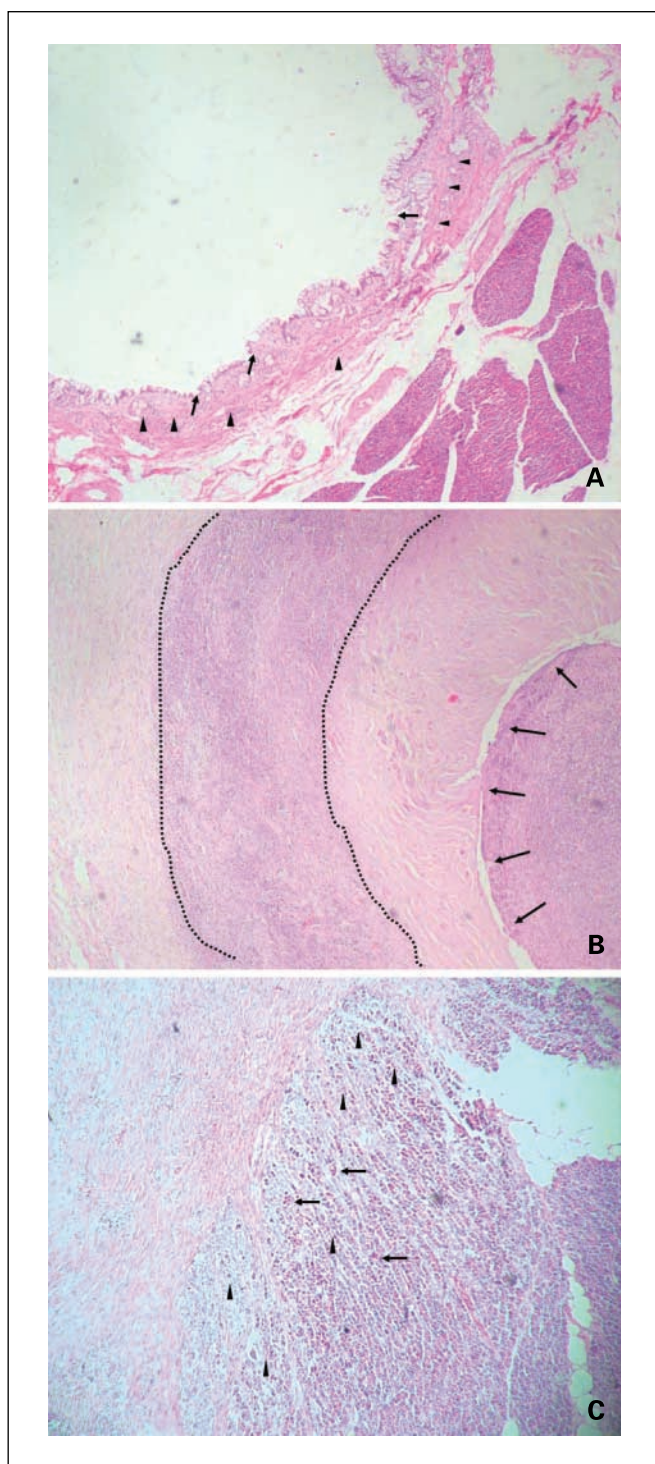


Fig. 4. Micrographs of tissue sections of the pancreatic duct and the surrounding area after the implantation of the stents. *A*, photograph of a tissue section of the pancreatic duct around a non-radioactive stent in the control group at the 14-d follow-up showing the atrophy of cellula columnoepithelialis of the pancreatic duct (arrows) and infiltration of inflammatory cells and hyperplasia of fibroblasts in the submucosal layer (arrowheads). *B*, photograph of a section of pancreatic tissue around a radioactive stent in the 100-Gy group at the 30-d follow-up showing the three tissue layers around the stent. From left to right, they are fibrous tissue, cell debris, and necrotic tissue. Caducous necrosis tissue at the position of stents is on the far right (arrows mark the border of this tissue). *C*, photograph of a section of pancreatic tissue around a radioactive stent in the 200-Gy group at the 60-d follow-up showing atrophy of the acinus outside the fibrosis layer (arrowheads). All sections were stained by H&E. Magnification, $\times 40$ (*A* and *B*) and $\times 100$ (*C*).

were excised and were then incised in the plane of the seeds. In the perforated pancreas specimen, sections were chosen at a distance of 1 to 1.5 cm from the perforation.

Sixty-day follow-up. In the 60-day observation group, 3 of 5 (60%) pigs completed the entire observation process and were sacrificed on the 60th day. Another two pigs (40%) did not survive the entire period. One pig died 2 days after implantation due to a perforation. Migration of one 150-Gy stent was found on the 50th day. At necropsy, the appearances of the abdominal cavities of the pigs were similar with those on 30 days, although the fiber layers were slightly thicker. There was also a cyst mass with the same structure in the tail of the pancreas. Similar to the 14-day follow-up, no structural changes were observed in the radioactive seeds removed from the stents.

Microscopic examination. Examination with a light microscope revealed that there were no obvious morphologic changes in adjacent organs, such as the duodenum, stomach, liver, and right kidney, among animals in all three follow-up groups (14, 30, and 60 days).

On the 14-day follow-up, atrophy of the columnar epithelium of the pancreatic duct was observed in the control group. Focal necrosis could also be found in some local areas. Infiltration of inflammatory cells and hyperplasia of fibroblasts could be seen on the submucosal layer (Fig. 4A). At 60 days, the layer of fibrous tissues in the submucosal layer was obviously thickened. The structure of the epithelium of the pancreatic duct disappeared in all experimental groups. Three layers were arrayed around the stents, with different thickness according to the dose given. From inside to outside, these layers were necrotic tissue, cell debris, and fibrous tissues composed of granulation tissue and macrophages (Fig. 4B). In the 150- and 200-Gy groups, atrophy of the pancreatic islet and acinus outside the fibrous layer could be observed (Fig. 4C). On the 14-day follow-up, vascular proliferation and hyperemia in the connective tissue surrounding the pancreatic ducts and the glandular lobule were obvious. However, these characteristics were gradually reduced and had almost completely disappeared at 60 days. At the same time, hyperplasia of the granulation tissue gradually increased, and the fibrous layer became the thickest at 60 days.

The results of pathologic examination showed that the maximal tissue damage occurred at 14 days. During the follow-up period, the necrotic tissue could sometimes fall off. Because of the positioning of the radioactive seeds, histologic analysis revealed that the necrotic layer was thicker close to the irradiance windows. The thickness of necrotic layer in experimental groups ($n = 4$) at 14 days was 2.7 mm (50 Gy), 3.7 mm (100 Gy), 4.7 mm (150 Gy), and 5.2 mm (200 Gy). The thickness of the fibrosis layer was correlated with the ability for tissue repair and the length of follow-up time. On the 30-day follow-up, the thickness of the fibrosis layer in all four groups ($n = 8$) was 1.9 ± 0.1 mm (50 Gy), 2.8 ± 0.4 mm (100 Gy), 3.1 ± 0.3 mm (150 Gy), and 3.8 ± 0.3 mm (200 Gy). On 60 days, the thickness of the fibrosis layer in three pigs was 3.5 mm (50 Gy), 4.5 mm (100 Gy), and 5.6 mm (150 Gy).

Blood tests. Blood tests were conducted frequently throughout the experiment. Blood electrolyte levels, IgG/IgA/IgM levels, and the markers for kidney and liver function were monitored at baseline, at 48 h, and on 7, 14, 21, 30, and 60 days after

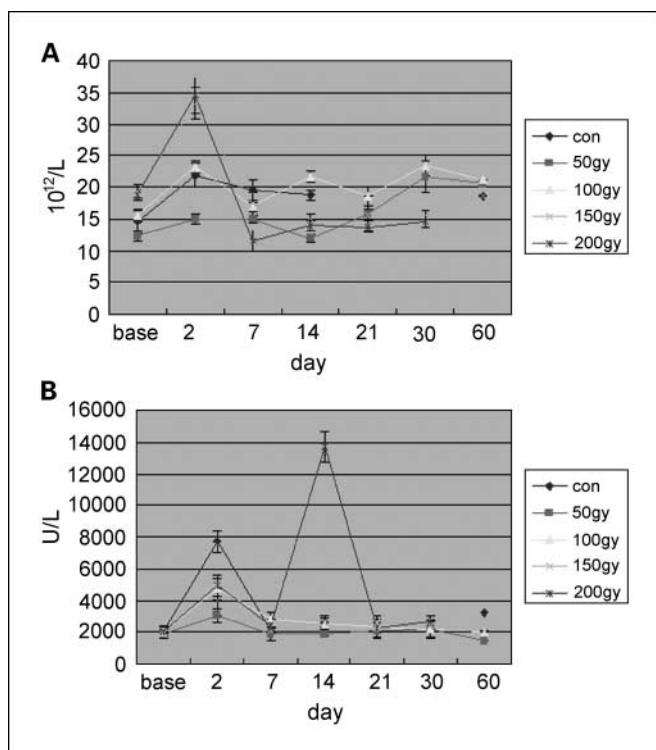


Fig. 5. Levels of WBC (A) and serum amylase (B) in five groups of pigs during the follow-up period. In both charts, there are no data at 21 or 30 d in the control group or at 60 d in the 200-Gy group. Points, mean in each group; bars, SE.

placement of the stent. The blood tests did not detect any obvious abnormality during the follow-up period, which indicated that the radioactive stents had a negligible influence on the function of adjacent organs. Compared with the baseline levels, WBC counts increased in all groups on the 2nd day after implantation. However, WBC levels almost completely returned to baseline in all pigs by the 7th day after implantation. The change of the serum amylase levels of the pigs was similar to that of WBC. However, the serum amylase levels of two pigs in the 200-Gy group increased again at 14 days, which was perhaps due to the high radioactive dosage and/or pancreatic duct perforation (Fig. 5).

Discussion

Intraluminal and interstitial brachytherapies have been found effective when used as palliative therapy to improve local control in patients with locally advanced pancreatic cancer. It has been reported that intraluminal brachytherapy from the duct of Wirsung and the common bile duct are safe and feasible for the treatment of pancreatic head carcinoma (12, 13). Intraluminal brachytherapy using γ -emitting radioisotopes, such as ^{192}Ir or ^{60}Co , combined with radiation therapy has been reported to be useful, resulting in the improvement of local tumor control (12, 14, 15). Intraluminal sources could be inserted through a pancreatic stent, nasopancreatic drain, nasobiliary drain, bile duct stent, or transhepatic percutaneous drainage (12, 14, 15). However, it has been reported that intracorporeal radiotherapy or brachytherapy have no influence on survival time (15). The main

drawback of this treatment is that it has to be repeated several times over a period of 2 to 3 weeks, which requires maintaining an external catheter.

Interstitial brachytherapy has been considered a useful method for the local control of malignant pancreatic tumors (6, 16). Clinically, the technique has also been used to control malignancies of the prostate, breast, brain, and rectum (17–20). After radioactive seed placement, the target tissue is continuously exposed to γ -rays, which produces more localized tissue injury and tumor ablation than intraluminal brachytherapy. The puncture upon implantation is an invasive interventional method and may be complicated by gastrointestinal bleeding and ulceration of the gastrointestinal mucosa, especially at high doses (15, 21).

Radioactive stents are a rapidly evolving field of research and clinical treatment, with a number of different irradiation techniques being used clinically. Won et al. reported that a self-expandable covered metallic stent impregnated with the β -emitting radionuclide ^{166}Ho can be safely used as an intraluminal brachytherapy for esophageal cancer (22). The same method was used to produce radioactive stents with different dosages implanted into the common bile duct of dogs (23). The method has been proved to be safe and can increase the rate of patency over normal metallic stents. The disadvantages of using β -emitting radionuclides as a long-term brachytherapy agent are their short half-life and short penetration depth. Some researchers reported that interstitial brachytherapy with γ -emitting radionuclides, such as ^{125}I and ^{103}Pd , seem to be useful for local pancreatic tumor regression (6, 24).

The lumens of the polyethylene stents were sometimes occluded during the follow-up period. Two 200-Gy stents were occluded at both ends at 30 days, whereas the lumens of the other four stents in the lower dosage groups were still open at that time, suggesting that the higher dose of radiation could be the main reason. This idea is supported by the examination of the blocked stents at the end of the experiments, which showed that the stents were blocked by necrotic tissue caused by irradiation and refluxed duodenal contents. Moreover, it has been reported that the mean time for stent occlusion in the treatment of chronic pancreatitis is 9 weeks (25, 26), much longer than the occlusion time seen here. This data further support the conclusion that the higher dose of radiation is the main reason for the blockage of the stents. Therefore, the prevention of blockage of the radioactive stents in the pancreatic ducts will be a concern for their future clinical application.

The greatest merit of this study is the combination of a stent with local brachytherapy achieved by radioactive seeds, both of which have been widely used in the clinic. Therefore, prior radioactive stents should be tested in the laboratory environment (22, 23). According to the location of pancreatic cancer in a patient's computerized tomography scan, a special treatment plan can be formulated for the patient through treatment planning system. To our knowledge, the current study is the first on radioactive stents designed for pancreatic cancer and tested in normal pigs.

This study has some limitations. First, the effect of the radioactive stents on the common bile duct could not be evaluated, although liver function studies were done during the follow-up period. This was done because the radioactive stent was placed in the pancreatic duct, and the porcine pancreatic duct is not fused with the common bile duct as it

is for humans. Second, the control group was too small (only two pigs) to evaluate the response to the mechanical effect of the non-radioactive stents. The number of pigs with radioactive stents in the different follow-up groups was also small. Third, the early abscission and migration of stents should be considered. Finally, this study was only done on healthy pigs, and a tumor group was not included in the study to show the effects of the radioactive seeds on the reduction of tumor mass.

In conclusion, this study showed that it is feasible to combine the benefits of stents and brachytherapy into a new radioactive stent in the porcine pancreatic duct, suggesting that radioactive stents might have a similar, if not better, radiation effect as intraluminal and interstitial brachytherapies in the treatment of pancreatic cancer. This study also showed that the radioactive stents were safe to the animals in all doses of ^{125}I studied because no serious complications were detected in the important organs around the pancreatic ducts.

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