Diagn Interv Radiol 2021; 27: 50–58

INTERVENTIONAL RADIOLOGY
ORIGINAL ARTICLE

CT-guided ^{125}I brachytherapy combined with chemotherapy for the treatment of unresectable or locally advanced pancreatic carcinoma

Ma Luo
Jiawen Chen
Zhihui Zhong
Fujun Zhang

PURPOSE
We aimed to explore the feasibility and clinical effectiveness of percutaneous CT-guided iodine-125 (^{125}I) brachytherapy combined with chemotherapy for the treatment of patients with unresectable or locally advanced pancreatic carcinoma (PC).

METHODS
We retrospectively reviewed 66 patients with Stage III and IV PC who had received chemotherapy. A total of 35 (53%) patients receiving ^{125}I brachytherapy and chemotherapy (gemcitabine + cisplatin, GP) were classified as Group A, and 31 (47%) patients who received GP chemotherapy alone were categorized as Group B. The evaluated indications were local control rate (LCR), local progression-free survival (LPFS), overall survival (OS), treatment-related complications, and the degree of symptom relief. Kaplan-Meier curves, log-rank test and Cox regression models were generated and used for further analysis to identify predictors of outcomes.

RESULTS
The median follow-up time was 6.00±0.84 months. The 1-, 3-, 6-, 12- and 18-month LCRs for Group A were 100% (35/35), 89.3% (25/28), 71.4% (15/21), 37.5% (3/8) and 33.3% (1/3), respectively; and those for Group B were 87.1% (27/31), 69.6% (16/23), 41.2% (7/17), 14.3% (1/7) and 0% (0/3), respectively. The LCR differed at 1-, 3- and 6-months (p = 0.032; p = 0.009; p = 0.030; respectively). The median LPFS was 7.00±0.30 months and 5.00±0.75 months for Groups A and B (p = 0.023), respectively; however, the median OS of the groups were not significantly different (8.00±0.77 months vs. 6.00±1.04 months. p = 0.917). No life-threatening complications occurred during or after the procedures. Patients in Group A experienced better pain control and relief of abdominal distension than those in Group B.

CONCLUSION
CT-guided ^{125}I brachytherapy is a feasible, safe, and valuable treatment for patients with unresectable PC.

Pancreatic carcinoma (PC) is the fourth most common cause of cancer-related death in both males and females (1). Abdominal pain, distension and fatigue are relevant symptoms. However, these symptoms usually occur with advanced disease due to the deep located anatomy of the pancreas, making tumors difficult to detect (2). Tumors are inclined to invade vessels, nerves and lymphatic system, explaining its characteristics of being peripancreatic and extrapancreatic. Once these situation occur, unresectable disease is diagnosed based on certain criteria (3).

For unresectable PC (UPC), some patients may refuse or give up their treatments because of its late stage when diagnosed, and poor general condition. An improvement of local control is an important part of disease management. The current treatment is multimodality therapy, including chemotherapy, irreversible electroporation, radiotherapy, and supportive care. However, the prognosis is poor, with a 1-year survival rate of 20% and a 5-year survival rate of less than 5% (4, 5). The first-line therapy for UPC with or without metastasis is chemotherapy, including gemcitabine with cisplatin or paclitaxel, FOLFIRINOX or FOLFOX. Despite advancements in chemotherapy, many patients are not able to tolerate treatment, mainly due to their poor mental and physical health at the time of diagnosis and the severe toxicities, including myelosuppression and vom-

From the Department of Interventional Radiology (F.Z. ✉ *zhangfj@sysucc.org.cn*), Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China.

Received 20 July 2019; revision requested 02 October 2020; last revision received 23 February 2020; accepted 03 March 2020.

Published online 25 November 2020.

DOI 10.5152/dir.2020.19371

You may cite this article as: Luo M, Chen J, Zhong Z, Zhang F. CT-guided ^{125}I brachytherapy combined with chemotherapy for the treatment of unresectable or locally advanced pancreatic carcinoma. Diagn Interv Radiol 2021; 27: 50–58.

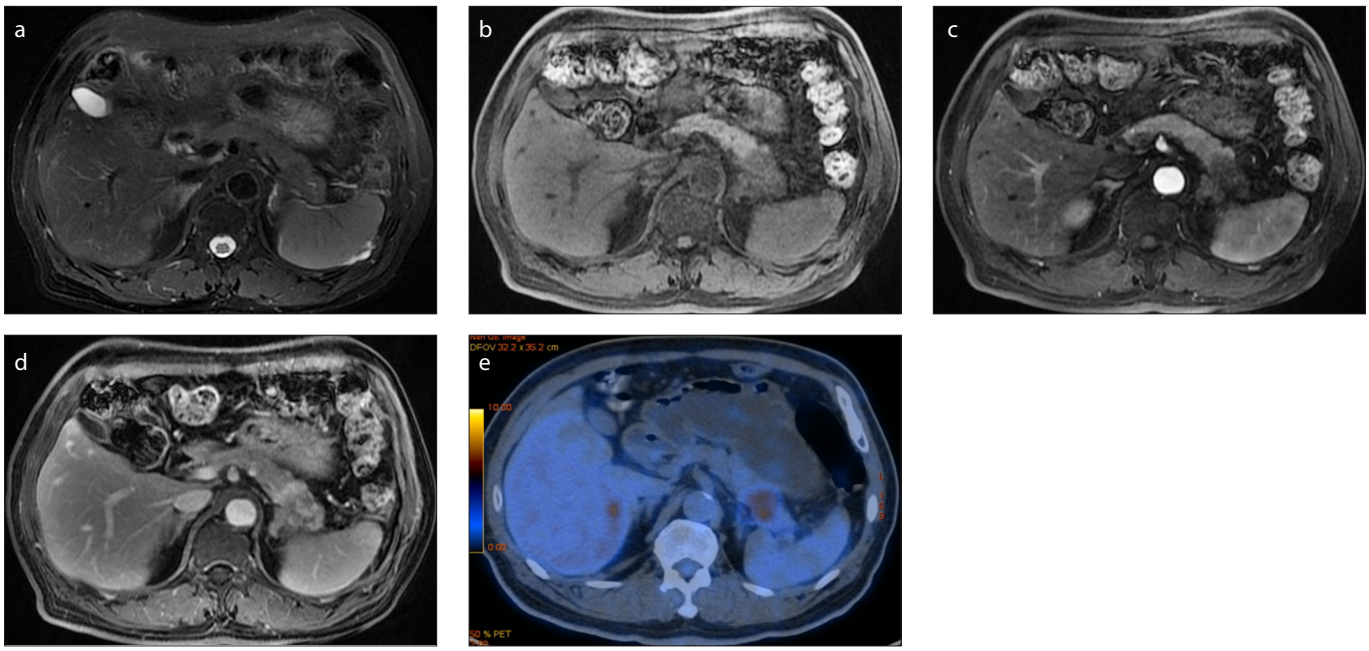

Figure 1. a–e. A 67-year-old male pancreatic carcinoma (PC) patient with high-grade adenocarcinoma confirmed by histopathology. Axial fat-suppressed T2-weighted image **(a)** shows an elliptical shaped lesion in the pancreatic tail with slightly higher signal intensity. On axial fat-suppressed T1-weighted image **(b)**, the lesion is hypointense. In the arterial phase **(c)**, the lesion is slightly enhanced and its signal intensity is lower than the normal intensity of the pancreas. In the equilibrium phase **(d)**, the lesion is clear with delayed enhancement compared with the arterial phase, which is a typical imaging characteristic of PC. On the PET-CT image **(e)**, the lesion shows high metabolic activity. There was a small hypermetabolic nodule in liver Segment V/VI, indicating a metastatic lesion. This patient was classified with unresectable PC Stage VI.

iting. Irreversible electroporation, a local destructive therapy, is based on the transmission of high-voltage current pulses direct through the tumor tissue, leading to alteration of irreversible permeation in the integrity of cell membrane and cell death (6). Nevertheless, this procedure is often implemented under laparotomy and the expense is high. New technologies in external beam radiotherapy have also been developed, such as stereotactic body radiotherapy and cyberknife. However, PC is relatively insensitive to external radiation. Also, the higher the dose received, the higher the risk of severe adverse effects, especially to cardinal organs such as the intestine and liver. Thus, the dose has to be controlled and rapidly reduced, ultimately increasing the risk of residual tumor and treatment failure.

Main points

- ^{125}I brachytherapy is a feasible method for treating unresectable or locally advanced pancreatic carcinoma.
- ^{125}I brachytherapy combined with chemotherapy can achieve good local disease control compared with chemotherapy alone, but the overall survival cannot be improved by this combination treatment.
- ^{125}I brachytherapy shows favorable clinical symptoms relief without increasing complications.

Iodine-125 (^{125}I) brachytherapy, a treatment as internal radiotherapy, has been considered a useful and minimally invasive modality. It has been shown to be a safe and effective option for many types of tumors such as those on brain, thoracic, prostate and soft tissue (7–10), and remarkable advantage of few complications and side effects (11, 12). Under the real-time imaging guidance (CT or ultrasound), the ^{125}I seed-specific needle is used to insert the seed into the tumor tissue. When the needle reaches the target area according to the preoperative plan, the ^{125}I seed is released by a single use of implantation gun after pulling out the needle core. Each seed is implanted one by one within the tumor by drawing back the needle along the needle track. The ^{125}I seed continuously emits X-rays and γ-rays within the target area, with a half-life of 59.6 days and a radiation diameter of 1.7 cm. The miniature seed has higher local radiation energy than conventional radiotherapy, while decreasing rapidly with increasing distance from the target area. CT is characterized by clear images, real-time observations, thin slices, and good tissue contrast on enhancement scanning. These characteristics make it possible for CT-guided ^{125}I brachytherapy to safely and visibly cover the target lesion completely, avoiding injury to the adjacent tissues. However, there have been few reports about CT-guided ^{125}I brachytherapy combined with chemotherapy for this disease. The aim of our study was to evaluate and determine the effectiveness and feasibility of this combination treatment for UPC.

Methods

Data collection

This study was approved by the ethics committees of our center, in accordance with the Helsinki Declaration. Written informed consent was waived because it was a retrospective study, and patient data were kept strictly confidential. From January 2006 to November 2017, patients diagnosed with UPC were reviewed retrospectively. The inclusion criteria: (a) Stage III (tumor invading the celiac axis or the superior mesenteric artery with or without spreading to lymph nodes) or Stage IV (metastasis) (based on the American Joint Committee on Cancer TNM Staging of Pancreatic Cancer, 8th ed., 2017) that was ineligible for surgical resection (Fig. 1) and receiving at least two cycles of chemotherapy (gemcitabine with cisplatin initially, GP); (b) ≤2 sites of metastasis; (c)

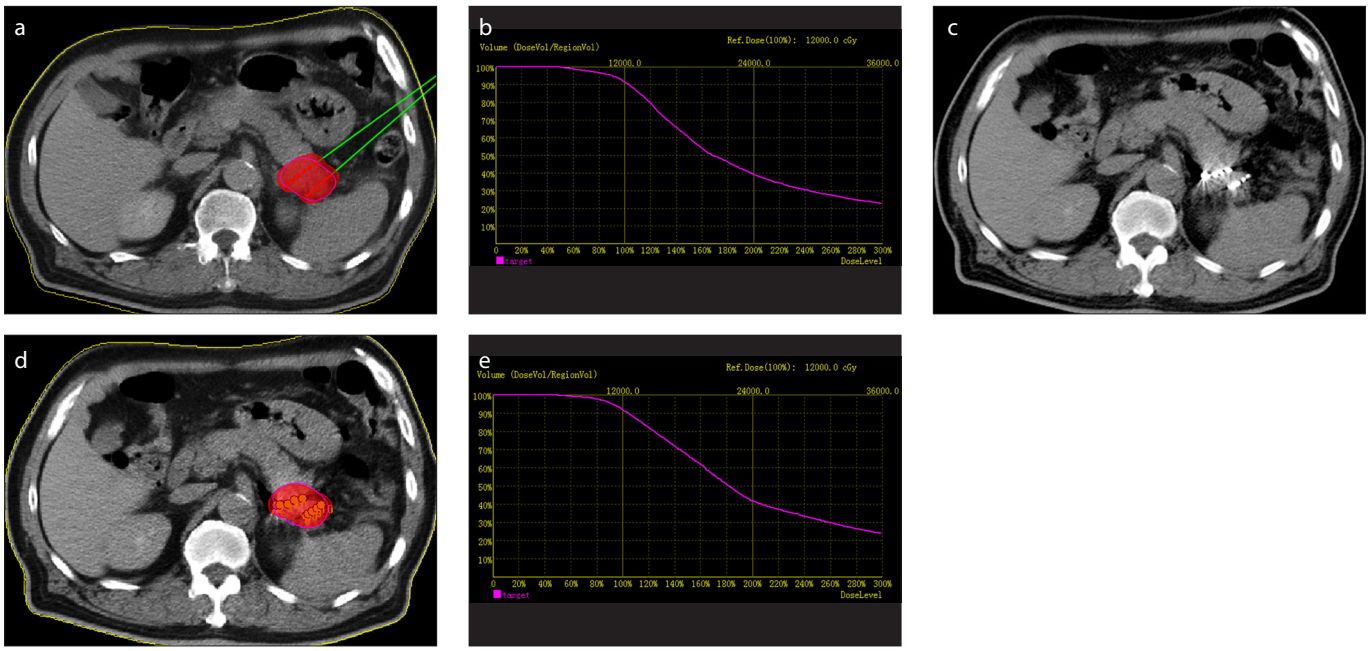

Figure 2. a–e. Treatment planning system verification. Image **(a)** shows a tumor in the pancreatic tail. *Purple lines* represent the tumor's contour; the *red area* received 90% of the prescribed dose. Preoperative dose volume histogram (DVH) **(b)** determined the prescribed dose as 120 Gy with target = tumor. A total of 90% of the tumor area (D90 = 124.1 Gy) received 124.1 Gy, and 91.7% of the tumor area received 100% of the prescribed dose (V_{100} = 91.7%). Postoperative CT image **(c)** shows two rows of seeds in the pancreatic tail. Image **(d)** shows postoperative distribution of implanted seeds. Postoperative DVH **(e)** determined D_{90} = 125.2 Gy, V_{100} = 92%. The distribution of the postoperative dose was coincident with the preoperative dose.

histopathological confirmation; (d) receiving ^{125}I seed treatment; (e) platelet count >70.0×10^9/L, prothrombin time <18 s and international normalized ratio <1.5; (f) alanine transaminase and aspartate transaminase <50 U/L, total bilirubin <50 μmol/L, serum albumin >28 g/L, normal kidney function. For patients who had moderate or severe pain after one cycle of chemotherapy and refused to take more dosages of analgesic, after fully informing of the potential risks for brachytherapy and obtaining their informed consent, ^{125}I seed was added to their treatment before the second cycle of chemotherapy (7–10 days interval); those who refused to receive ^{125}I brachytherapy were continued on chemotherapy. The remaining cycles of chemotherapy were continued in all patients until disease progression was detected. The exclusion criteria were: (a) lack of detailed clinical information or loss to follow-up; (b) more than 2 sites of metastasis; (c) incomplete or intolerant for two cycles of chemotherapy; (d) previous radiotherapy; (e) massive ascites or cachexia; (f) Karnofsky performance status <70, and severe heart, liver, or renal disorder.

Chemotherapy

Gemcitabine: 1000 mg/m^2/once a week/3 weeks (d_1, d_8, d_{15}), then ceased for 1 week. Cisplatin: 25 mg/m^2/once a day/3 days (d_{1-3}).

^{125}I seed implantation

^{125}I seeds (Yunke Pharmaceutical Limited Liability Company) were designed as cylindrical titanium packages (diameter, 0.8 mm; length, 5.0 mm). The particle, which contained ^{125}I radionuclide silver rod (diameter, 0.5 mm; length, 3.0 mm) as the central source, was implanted with a mean energy of 27–32 KeV, and effective diameter of 1.7 cm. The initial activity and half-life for each seed was 0.6 mCi and 59.6 days, respectively; 88%–94% of the dose was delivered within 6–8 months.

CT images (5 mm sections) were obtained from all patients <1 week preoperatively, then imported into a treatment planning system (TPS) (Beijing Atom and High Technique Inc.) to optimize the treatment plan of each patient. Careful delineation of the gross tumor volume (GTV) and planned target volume (PTV) in each CT slice was verified by an interventional oncologist and clinical physicist. GTV was delineation of the whole lesion visualized on CT. PTV was defined as beyond the edge of the GTV of 1.0 cm. The number of ^{125}I seeds needed and the total dose activity were calculated using the TPS to develop a dose-volume histogram, observe the dose distribution, and adjust the needle to obtain optimal dose distribution in the PTV. The dose transmitted to the PTV was 95% of the prescribed dose, with a mean dosage of 120 Gy in this study.

On the days of the procedure, contrast-enhanced CT scanning was performed to obtain clear delineation of the tumor and important vessels. After administering 10 mL 1% lidocaine for local infiltration anesthesia, several 18 G spinal needles were used for the percutaneous puncture to the farthest tumor edge, keeping approximately 1 cm distance between each needle. An implantation gun was used to release the ^{125}I seeds into the tumor after pulling out the needle core. Every seed was released by drawing back the needle, and seeds were kept adjacent at distances of 5 mm. After completing the procedure, repeated CT scans were performed and transmitted to TPS for dose verification (Fig. 2) and check for any complications.

Pre- and postoperative management

Patients were asked to fast 24 h prior to the procedure. Octreotide was given one day before the procedure. Oral laxatives and cleansing enemas were used one night before the procedure to flush out the intestine and reduce the complications.

During seed implantation and in the following 24 h, patients underwent electrocardiograph monitoring. After the procedure, they were strictly confined to hospital bed

and prohibited from drinking and eating until anal exhaust. Antibiotics, hemostasis, inhibition of gastric acid and digestive enzyme secretion, and fluid therapy were given as needed.

Follow-up and evaluation criteria

All patients underwent contrast-enhanced CT or MRI at follow-up. The tumor response of ^{125}I seed was evaluated after the first and second month of seed implantation. The tumor response of chemotherapy was evaluated every two courses of chemotherapy (8 weeks) in both groups. The observed outcomes included local control rate (LCR), local progression-free survival (LPFS), overall survival (OS), degree of symptom relief, and complications. The primary endpoint was LPFS that was defined as the start of ^{125}I seed treatment to the date of either local disease progression or the last follow-up. OS was defined as the date from ^{125}I seed treatment to the date of death. Tumor response (including the primary tumor and the whole body lesion) was evaluated according to the RECIST 1.1. The complete response (CR), partial response (PR), stable disease (SD) and progression disease (PD) were classified accordingly. LCR was defined as the proportion of cases with absence of tumor progression (CR+PR+SD). The major clinical symptoms were pain (including flank pain and stomachache), abdominal distension, fatigue, and inappetence. Pain distribution before and after treatment was divided into three classifications based on the visual analogue scale, respectively: 0–3 was mild; 4–6 was moderate; and 7–10 was severe. Symptoms for abdominal distention, fatigue and inappetence between pre-treatment and post-treatment were categorized by using a four-point categoric scale (worst=1, bad=2, mild=3, and normal=4). Symptom distribution was re-evaluated and recorded after one month of treatment in both groups. The differences in symptom changes between the Group A and Group B, and pre- and post-treatment were calculated and compared.

Statistical analysis

Statistical analyses were performed using SPSS Statistics Software Version 22.0 (SPSS) and GraphPad Prism version 6.01 (GraphPad Software). Descriptive statistics of the data were presented as n (%). Test of normality (Shapiro-Wilk) was used to determine whether the variable had normal distribution. If variable was normally distributed, it was shown as mean ± standard deviation, and independent sample *t* test was used for the comparison. Otherwise, variable was shown as median (min–max), and Wilcoxon's signed rank test was used for the two dependent sample comparison and Mann-Whitney U test was used for the two independent sample comparison. Follow-up time and survival related outcomes were indicated as median ± standard error of median. Patient characteristics and the LCR were analyzed by the Pearson's chi-square test or Fisher Freeman Halton exact test when necessary. Kaplan-Meier analysis and log-rank test were used to compare LPFS and OS between groups. Multivariable Cox proportional hazards model by using stepwise forward logistic regression was applied to investigate the relationship between variables and LPFS, and the *p* value of the model was shown at last step. Values of $p < 0.05$ (two-sided) were considered statistically significant.

Table 1. Patient characteristics

Characteristics	Group A, n (%)[a]	Group B, n (%)[a]	*p*
Age			
Mean ± SD	56.60±11.41	59.84±11.26	0.251[b]
Sex			0.258
Male	26 (74.3)	19 (61.3)	
Female	9 (25.7)	12 (38.7)	
Stage			0.678
III	13 (37.1)	10 (32.3)	
IV	22 (62.9)	21 (67.7)	
Lesion diameter (cm)			
Median (min–max)	4.90 (3.10–7.20)	4.79 (3.20–6.90)	0.783[c]
Tumor location			0.420
Pancreatic head	17 (48.6)	12 (38.7)	
Pancreatic body or tail	18 (51.4)	19 (61.3)	
Histology			0.671
Low grade	13 (37.1)	14 (45.2)	
Middle grade	15 (42.9)	10 (32.3)	
High grade	7 (20.0)	7 (22.6)	
CA_{19-9} pre-treatment			0.153
≤35 U/mL	6 (17.1)	10 (32.3)	
>35 U/mL	29 (82.9)	21 (67.7)	
TBIL pre-treatment			0.538
≤21 µmol/L	26 (74.3)	25 (80.6)	
>21 µmol/L	9 (25.7)	6 (19.4)	
Cycles of chemotherapy (GP)			0.936
2	5 (14.3)	6 (19.4)	
3	8 (22.9)	8 (25.8)	
4	9 (25.7)	8 (25.8)	
5	6 (17.1)	5 (16.1)	
6	7 (20.0)	4 (12.9)	

[a]Descriptive statistics of categorical variables were expressed as n (%).
[b]The independent samples t test was used for the age comparison between two groups.
[c]The Mann-Whitney U test was used for the lesion diameter comparison between two groups.
SD, standard deviation; CA19-9, carbohydrate antigen 19-9; TBIL, total bilirubin; GP, gemcitabine + cisplatin.

Results

There were 35 patients (53%) receiving combination treatment (Group A, ^{125}I seed and GP chemotherapy) and 31 patients (47%) receiving GP chemotherapy

Table 2. Comparison of clinical efficacy between the two groups

	Group A, n (%)					Group B, n (%)					
Follow-up period	CR	PR	SD	PD	LC	CR	PR	SD	PD	LC	*p*
Primary tumor[a]											
1 month	0 (0)	12 (34.3)	23 (65.7)	0 (0)	35/35 (100)	0 (0)	5 (16.1)	22 (71)	4 (12.9)	27/31 (87.1)	0.032
3 months	1 (3.6)	9 (32.1)	15 (53.6)	3 (10.7)	25/28 (89.3)	0 (0)	0 (0)	16 (69.6)	7 (30.4)	16/23 (69.6)	0.009
6 months	2 (9.5)	7 (33.3)	6 (28.6)	6 (28.6)	15/21 (71.4)	0 (0)	0 (0)	7 (41.2)	10 (58.8)	7/17 (41.2)	0.030
12 months	0 (0)	2 (25)	1 (12.5)	5 (62.5)	3/8 (37.5)	0 (0)	0 (0)	1 (14.3)	6 (85.7)	1/7 (14.3)	0.754
18 months	0 (0)	1 (33.3)	0 (0)	2 (66.7)	1/3 (33.3)	0 (0)	0 (0)	0 (0)	3 (100)	0/3 (0)	0.821
Overall response[b]											
1 month	0 (0)	10 (28.6)	18 (51.4)	7 (20)	28/35 (80)	0 (0)	5 (16.1)	19 (61.3)	7 (22.6)	24/31 (77.4)	0.505
3 months	0 (0)	5 (17.9)	12 (42.9)	11 (39.3)	17/28 (60.7)	0 (0)	6 (26.1)	8 (34.8)	9 (39.1)	14/23 (60.9)	0.815
6 months	0 (0)	1 (4.8)	5 (23.8)	15 (71.4)	6/21 (28.6)	0 (0)	2 (11.8)	3 (17.6)	12 (70.6)	5/17 (29.4)	0.831
12 months	0 (0)	0 (0)	0 (0)	8 (100)	0/8 (0)	0 (0)	0 (0)	0 (0)	7 (100)	0/7 (0)	1.000
18 months	0 (0)	0 (0)	0 (0)	3 (100)	0/3 (0)	0 (0)	0 (0)	0 (0)	3 (100)	0/3 (0)	1.000

LC was calculated as: (CR+PR+SD)/total in each group.
[a]Treatment response evaluation was performed only for the primary tumor by using RECIST 1.1.
[b]Treatment response evaluation was performed for the whole body lesion by using RECIST 1.1.
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; LC, local control.

Table 3. Results of univariate and multivariate analyses for LPFS

	LPFS	
	Multivariate	
Variable	HR (95% CI)	*p*
Sex (female vs. male)		0.204
Age (≤60 years vs. >60 years)		0.568
Stage (III vs. IV)	0.668 (0.437–0.904)	0.026
CA_{19-9} pre-treatment (U/mL) (≤35 vs. >35)		0.278
Tumor location (head vs. body + tail)		0.134
Tumor size (cm) (≤5 vs. >5)	0.509 (0.306–0.818)	0.006
Tumor differentiation (low vs. middle + high)		0.051
Large vessel encapsulated (no vs. yes)		0.322
^{125}I brachytherapy (no vs. yes)	1.398 (1.091–1.821)	0.012
Puncture through liver (no vs. yes)		0.662

LPFS, local progression-free survival; HR, hazard ratio; CI, confidence interval; CA19-9, carbohydrate antigen 19-9.

alone (Group B), respectively. There were 45 (68.2%) male and 21 (31.8%) female patients. The mean age was 56.6±11.4 years (range, 39–82 years) for Group A and 59.8±11.3 years (range, 29–77 years) for Group B. All patients received 2–6 cycles of GP chemotherapy. The patients' detailed characteristics are listed in Table 1.

At 1-, 3-, 6-, 12- and 18-months, the LCRs for Group A were 100% (35/35), 89.3% (25/28), 71.4% (15/21), 37.5% (3/8) and 33.3% (1/3), respectively; and those for Group B were 87.1% (27/31), 69.6% (16/23), 41.2% (7/17), 14.3% (1/7) and 0% (0/3), respectively (Table 2). Patients in Group A achieved better LCR than those in Group B; this difference was evident at 1-, 3- and 6-months ($p = 0.032$; $p = 0.009$; $p = 0.030$; respectively). Kaplan–Meier curves showed that the median LPFS for Groups A and B was 7.00±0.30 months and 5.00±0.75 months, respectively. LPFS was significantly longer in Group A than that in Group B ($p = 0.023$; Fig. 3 and 4).

Kaplan–Meier curves showed that the median OS for Groups A and B was 8.00±0.77 months and 6.00±1.04 months, respectively. There was no statistical difference in OS between two groups ($p = 0.917$; Fig. 5). In the multivariate model, stage III (HR=0.668; $p = 0.026$), tumor size ≤5cm (HR=0.509; $p = 0.006$) and receiving ^{125}I brachytherapy (HR=1.398; $p = 0.012$) were identified as independent predictors of longer LPFS (Table 3). Forest plot subgroup analysis of factors associated with LPFS is shown in Fig. 6.

No life-threatening complications such as death, massive hemorrhage or peritonitis occurred during or after the seed implantation. One patient (2.9%) suffered seed migration, which was located in the peri-intestine after the procedure for two months; the patient did not experience discomfort or severe complications during the follow-up period.

Before treatment, the symptoms between the two groups did not show significant difference. The symptom relief distribution for pain and abdominal distension after ^{125}I treatment in Group A was significantly better than that in Group B. Fatigue and inappetence were not statistically different between the two groups (Table 4 and 5).

Discussion

Radiation, a physical factor to which cell division is sensitive, is able to efficiently inhibit cell proliferation and promote apoptosis. The X-rays and γ-rays can directly induce DNA single-strand and double-strand breaks of cells. Additionally, there is an in-

Table 4. Relief of clinical symptoms in each group

Group	Variable	Pre-treatment Median (min–max)	Post-treatment Median (min–max)	*p* *
Group A	Pain	7 (2–10)	5 (1–10)	<0.001
	Distension	2 (1–4)	3 (1–4)	0.001
	Fatigue	2 (1–4)	3 (1–4)	0.654
	Inappetence	3 (1–4)	2 (1–4)	0.282
Group B	Pain	9 (3–10)	7 (2–10)	0.002
	Distension	2 (1–4)	2 (1–4)	0.705
	Fatigue	2 (1–4)	2 (1–4)	0.414
	Inappetence	2 (1–4)	2 (1–4)	0.180

* The Wilcoxon's signed rank test was used between pre-treatment and post-treatment for each symptom.

Table 5. The comparison of clinical symptom relief between two groups

	Pain Median (min–max)	Distension Median (min–max)	Fatigue Median (min–max)	Inappetence Median (min–max)
Pre-treatment				
Group A	7 (2–10)	2 (1–4)	2 (1–4)	3 (1–4)
Group B	9 (3–10)	2 (1–4)	2 (1–4)	2 (1–4)
p *	0.050	0.172	0.968	0.249
Post-treatment				
Group A	5 (1–10)	3 (1–4)	3 (1–4)	2 (1–4)
Group B	7 (2–10)	2 (1–4)	2 (1–4)	2 (1–4)
p *	0.034	0.007	0.878	0.340

*The Mann-Whitney U test was used between Group A and Group B for each symptom.

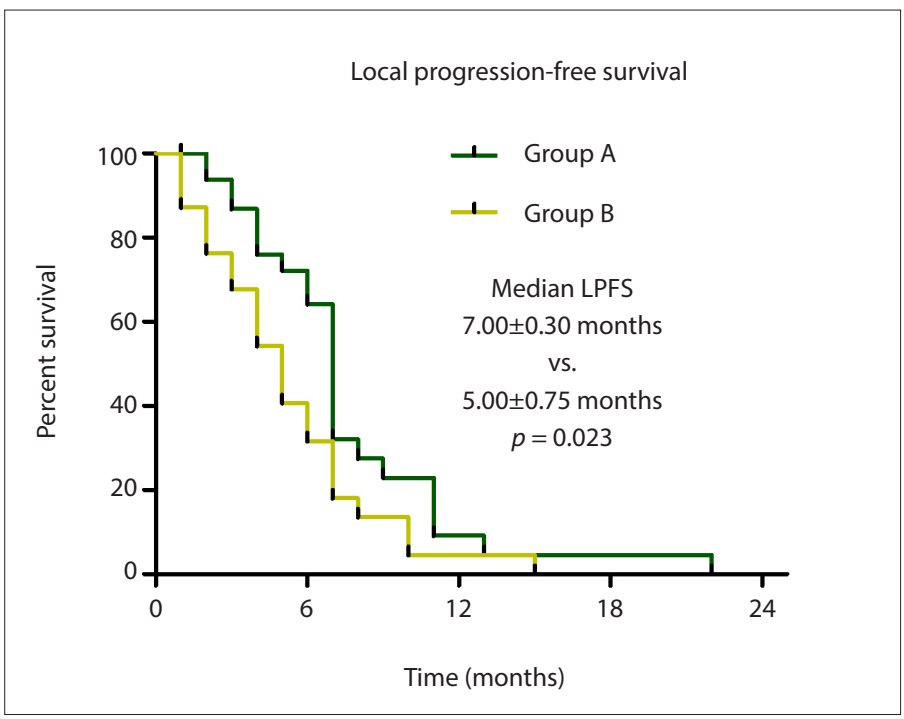

Figure 3. Local progression-free survival (LPFS) in Groups A and B. There was statistical difference between the two groups with the median LPFS 7.00±0.30 months vs. 5.00±0.75 months, respectively ($p = 0.023$).

direct effect on cell damage. Ionization, especially as a result of forming free radicals and hydroxyl radicals from water molecules after absorbing radiation energy, can destruct the DNA structure. These events can initialize the cell cycle checkpoint which is sensitive to DNA damage. When repairment was insufficient to counteract this lethal damage, the cell cycle was blocked and cell division was terminated. However, for surrounding normal tissues that receive sublethal doses of radiation, slow-emitting radiation from ^{125}I seed allows them to repair and recover in ample time (13). Compared with external radiotherapy, ^{125}I seed implantation has advantages. First, ^{125}I seed can continuously damage tumor cells by keeping them in a resting period, as harmful irradiation is constantly released. Second, rays from the seed can target the local tumor with overlapping high doses, after which the radioactive energy rapidly decreases with an increase in distance. Third, ^{125}I seed treatment has low dependence on oxygen for its killing effect in the hypoxic environment within the tumor, promoting the apoptosis of tumor cells (14).

^{125}I seed, a local treatment, has been widely applied in many cancerous diseases as it has been shown to be effective and safe (7, 11, 15). With the advent of TPS, the operation procedure and dose distribution have become normalized, accurate and repeatable. Importantly, this modality can be used in patients who are not eligible for other treatments, providing more salvageable options based on their disease and intention. There is an interval of about 1–2 months from original seed implantation to therapeutic effectiveness due to continued and slow emission of the radiation; the half-life of ^{125}I seed is 59.6 days. Similarly, there is an interval of about 8 months from the start of therapeutic effects of the seed to the end of its activity. During this three to four half-life cycles, nearly 90% of the radiation decays. Unlike external radiation, the accumulation of low-dose consecutive radiation from ^{125}I seed within the tumor tissue can result in tumor cell devitalization gradually. Localized inflammatory reaction also takes place, which is replaced by fibrous tissue later turning into scar and tumor shrinkage. This pathophysiologic process makes radiologic tumor response visible in the later period, explaining why the LPFS and LCR in Group A were superior to those in Group B, particularly the LCR within the first 6 months.

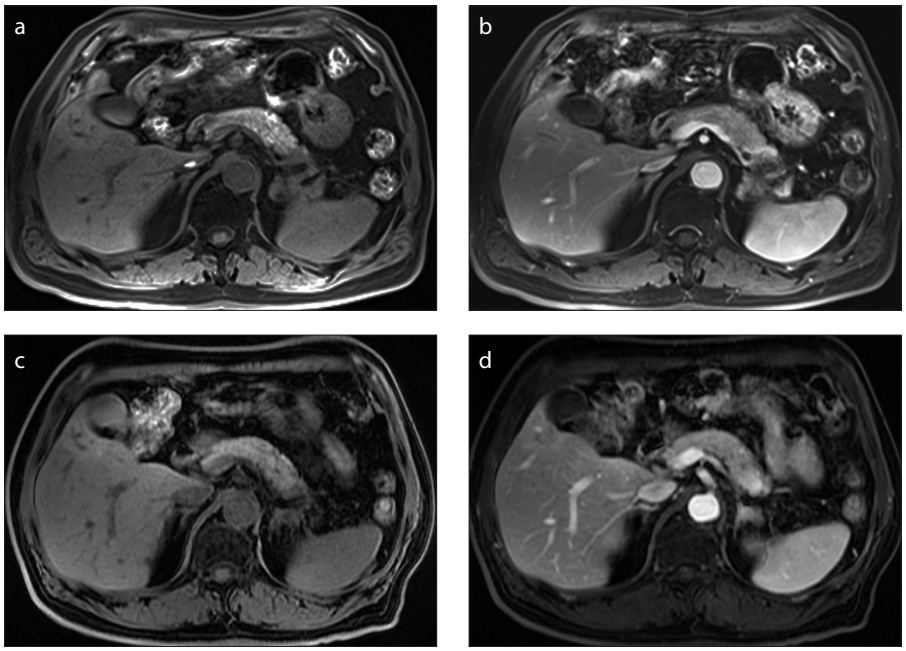

Figure 4. a–d. Patient follow-up after ^{125}I treatment. Images **(a, b)** were acquired one month after ^{125}I seed implantation. On axial fat-suppressed T1-weighted image **(a)**, the lesion shows heterogeneous hypointensity. In the equilibrium phases **(b)**, the lesion shows heterogeneous enhancement. However, the degree and extent of enhancement is lower and smaller than those in the preoperative images, indicating a therapeutic response. Images **(c, d)** were acquired three months after seed implantation. On axial fat-suppressed T1-weighted image **(c)**, the lesion shows heterogeneous hypointensity. In the equilibrium phases **(d)**, the lesion is still hypointense without enhancement compared with the surrounding tissues and preoperative images, indicating no tumor residual.

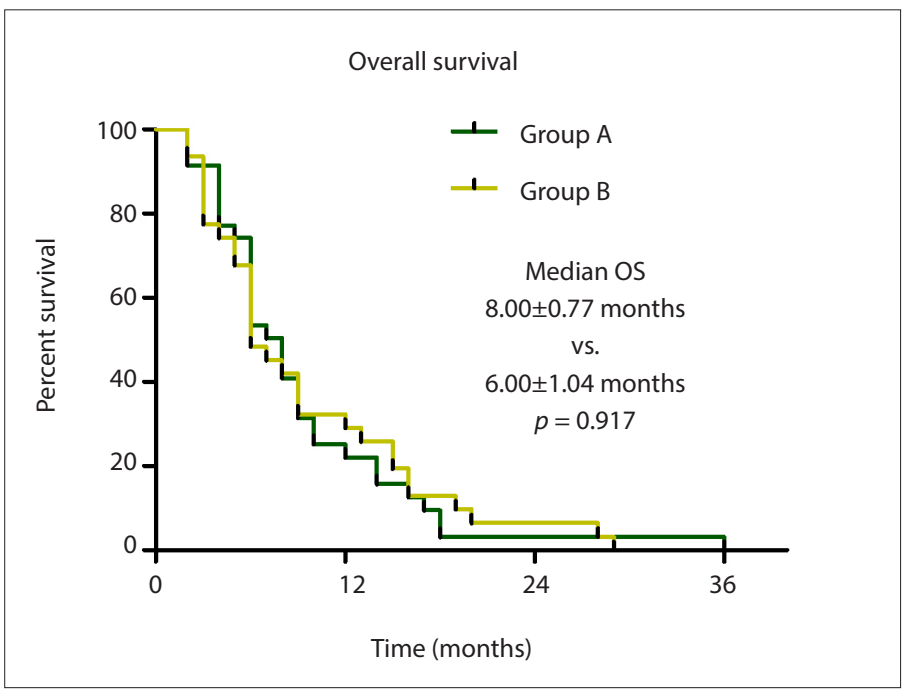

Figure 5. Overall survival (OS) in Groups A and B. There was no statistical difference between the two groups with the median OS determined as 8.00±0.77 months vs. 6.00±1.04 months, respectively ($p = 0.917$).

The median OS and 1-year OS rates were in line with or similar to those previously reported (16–19). However, the overall 2-year survival rates were less than these previous studies. Two possible reasons for these differences were as follows. First, our study had patients with Stage III and IV unresectable disease, whereas other studies included patients with Stage I and II disease (20, 21). The second reason might be differences in treatment. The treatment in some studies was adjuvant with radiotherapy (16), and comparison between pancreaticoduodenectomy and seed implantation has also been made (22). These curative options could strengthen therapeutic efficacy of primary tumor and eliminate the viable tumor compared with ^{125}I therapy alone. The results from Group B treated with chemotherapy alone were in accordance with other studies. The prognosis with gemcitabine alone is poor (~5–6 months). However, the addition of other chemotherapeutic drugs can increase the median survival time to 7.5–9 months (23, 24). The median PFS for gemcitabine alone is shorter than that with gemcitabine combination chemotherapy (3.8 vs. 5.3 months) (25). The median LPFS in our study was 7.0 months in Group A. Therefore, it is reasonable to assume that chemotherapy combined with brachytherapy can lead to longer local disease control.

There have been few studies focused on the effectiveness of this combination therapy in PC. Zou et al. (19) and Xu et al. (26) compared OS using radiofrequency ablation with ^{125}I seed treatment and cryoablation with ^{125}I seed implantation, respectively. However, these were all local therapies. In Wang et al. (21) and Yu et al. (27), they used only single therapy of seed implantation to evaluate therapeutic efficacy in PC. When we used enhanced-CT guidance to direct our procedure, compared with ultrasound guidance, CT could not only avoid the interference of intestinal gas and echo influence from ultrasound, but also eliminate measurement variations caused by different sonographers. It is more accurate to verify postoperative TPS and obtain uniform image each time for evaluation. In our study, we calculated the LCR at 1-, 3-, and 6-months, as it is more reasonable to assess this index within 6 months because the seed is in the "active" stage.

The major complications for ^{125}I seed implantation such as death and massive bleeding are rare. The incidence of minor complications is relatively low. In the study by Yu et al. (16), one patient had massive hemorrhaging of the upper gastrointestinal tract and three patients had a small amount of bleeding between bowel clearances. In the study of Zou et al. (19), two patients had biliary leakage, and one had acute pancreatitis. These may have been due to intestinal gas interfering with ultrasound when implanting

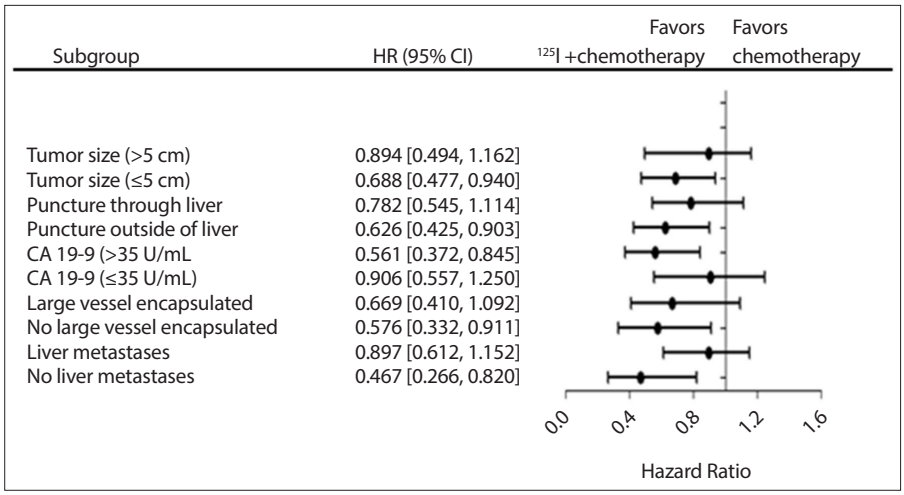

Figure 6. Forest plot of subgroup analysis for local progression-free survival.

the seed or ablative injury in the peripheral tract tissue. Also, prior cholangio-jejunostomy in their study complicated the original anatomic structure around the pancreas.

Pain relieved by ^{125}I seed had also been previously reported (28, 29). In the study by Wang et al. (17), pain was present in 57.1% (8/14) of patients prior to treatment. In his study, the rate of pain remission was nearly 50% during the follow-up period. The mechanism of ^{125}I seed for pain and distension relief might be related to tumor shrinkage and tumor cell growth inhibition caused by radiation damage. With decreasing tumor size or viable tumor area, the compression of the neural plexus around the pancreas and gastrointestinal tract and the effect on secretion were alleviated and modulated.

This study has several limitations. This was a single-center retrospective study with a small sample size. In addition, although we strictly followed the TPS as much as possible, unavoidable change of posture and breath movement might cause considerable dose deviation from the prescribed plan and affect accuracy. Moreover, radioactive tolerance or failure could be seen in some patients (30, 31). Molecular expression and cell activity might be two crucial aspects of this phenomenon. More signal pathway research is encouraged to continue the clarification of this basic mechanism in future. Finally, the curative efficacy of CT-guided and ultrasound-guided seed implantation was not compared, which should be performed in later studies for precise and optimal options in subsequent treatments.

In conclusion, CT-guided ^{125}I brachytherapy is a feasible and safe alternative method for treating UPC. It results in good LPFS and relief of clinical symptoms without decreasing OS or increasing complication.

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017; 67:7–30. [Crossref]
2. Low G, Panu A, Millo N, Leen E. Multimodality imaging of neoplastic and nonneoplastic solid lesions of the pancreas. Radiographics 2011; 31:993–1015. [Crossref]
3. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic adenocarcinoma, version 2.2017, nccn clinical practice guidelines in oncology. J Natl Compr Canc Netw 2017; 15:1028–1061. [Crossref]
4. Brennan DD, Zamboni GA, Raptopoulos VD, Kruskal JB. Comprehensive preoperative assessment of pancreatic adenocarcinoma with 64-section volumetric CT. Radiographics 2007; 27:1653–1666. [Crossref]
5. Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. J Clin Oncol 2007; 25:2607–2615. [Crossref]
6. He C, Wang J, Sun S, et al. Irreversible electroporation versus radiotherapy after induction chemotherapy on survival in patients with locally advanced pancreatic cancer: A propensity score analysis. BMC Cancer 2019; 19:394. [Crossref]
7. Hu X, Qiu H, Zhang L, et al. Recurrent gliomas: Comparison of computed tomography (CT)-guided 125I seed implantation therapy and traditional radiochemotherapy. Cancer Biol Ther 2012; 13:840–847. [Crossref]
8. Stewart A, Parashar B, Patel M, et al. American brachytherapy society consensus guidelines for thoracic brachytherapy for lung cancer. Brachytherapy 2016; 15:1–11. [Crossref]
9. Demanes DJ, Ghilezan MI. High-dose-rate brachytherapy as monotherapy for prostate cancer. Brachytherapy 2014; 13:529–541. [Crossref]
10. Mo Z, Zhang T, Zhang Y, et al. Feasibility and clinical value of CT-guided (125)I brachytherapy for metastatic soft tissue sarcoma after first-line chemotherapy failure. Eur Radiol 2018; 28:1194–1203. [Crossref]
11. Yan H, Xiang Z, Zhong Z, et al. CT-guided (125) I brachytherapy in the treatment of distant metastases in the oral cavity and maxillofacial region. Transl Oncol 2017; 10:90–98. [Crossref]
12. Wang G, Zhang F, Yang B, et al. Feasibility and clinical value of CT-guided (125)I brachytherapy for bilateral lung recurrences from colorectal carcinoma. Radiology 2016; 278:897–905. [Crossref]
13. Zhang FJ, Li CX, Zhang L, Wu PH, Jiao DC, Duan GF. Short- to mid-term evaluation of CT-guided 125i brachytherapy on intra-hepatic recurrent tumors and/or extra-hepatic metastases after liver transplantation for hepatocellular carcinoma. Cancer Biol Ther 2009; 8:585–590. [Crossref]
14. Cron GO, Beghein N, Crokart N, et al. Changes in the tumor microenvironment during low-dose-rate permanent seed implantation iodine-125 brachytherapy. Int J Radiat Oncol Biol Phys 2005; 63:1245–1251. [Crossref]
15. Xiang Z, Li G, Liu Z, et al. 125I brachytherapy in locally advanced nonsmall cell lung cancer after progression of concurrent radiochemotherapy. Medicine (Baltimore) 2015; 94:e2249. [Crossref]
16. Yu YP, Yu Q, Guo JM, Jiang HT, Di XY, Zhu Y. (125) I particle implantation combined with chemoradiotherapy to treat advanced pancreatic cancer. Br J Radiol 2014; 87:20130641. [Crossref]
17. Wang J, Jiang Y, Li J, Tian S, Ran W, Xiu D. Intraoperative ultrasound-guided iodine-125 seed implantation for unresectable pancreatic carcinoma. J Exp Clin Cancer Res 2009; 28:88. [Crossref]
18. Stathis A, Moore MJ. Advanced pancreatic carcinoma: Current treatment and future challenges. Nat Rev Clin Oncol 2010; 7:163–172. [Crossref]
19. Zou YP, Li WM, Zheng F, et al. Intraoperative radiofrequency ablation combined with 125 iodine seed implantation for unresectable pancreatic cancer. World J Gastroenterol 2010; 16:5104–5110. [Crossref]
20. Zhongmin W, Yu L, Fenju L, Kemin C, Gang H. Clinical efficacy of CT-guided iodine-125 seed implantation therapy in patients with advanced pancreatic cancer. Eur Radiol 2010; 20:1786–1791. [Crossref]
21. Wang H, Wang J, Jiang Y, et al. The investigation of 125i seed implantation as a salvage modality for unresectable pancreatic carcinoma. J Exp Clin Cancer Res 2013; 32:106. [Crossref]
22. Liu K, Ji B, Zhang W, Liu S, Wang Y, Liu Y. Comparison of iodine-125 seed implantation and pancreaticoduodenectomy in the treatment of pancreatic cancer. Int J Med Sci 2014; 11:893–896. [Crossref]
23. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase iii trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol 2006; 24:3946–3952. [Crossref]
24. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: Results of a gercor and giscad phase III trial. J Clin Oncol 2005; 23:3509–3516. [Crossref]

25. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol 2009; 27:5513–5518. [Crossref]
26. Xu K, Niu L, Mu F, Hu Y. Cryosurgery in combination with brachytherapy of iodine-125 seeds for pancreatic cancer. Gland Surg 2013; 2:91–99. [Crossref]
27. Yu YP, Yu Q, Guo JM, Jiang HT, Di XY, Zhu Y. Effectiveness and security of CT-guided percutaneous implantation of (125)i seeds in pancreatic carcinoma. Br J Radiol 2014; 87:20130642. [Crossref]
28. Wang C, Chen Z, Sun W, et al. Palliative treatment of pelvic bone tumors using radioiodine ((125)I) brachytherapy. World J Surg Oncol 2016; 14:294. [Crossref]
29. Yao L, Cao Q, Wang J, et al. CT-guided (125) I seed interstitial brachytherapy as a salvage treatment for recurrent spinal metastases after external beam radiotherapy. Biomed Res Int 2016; 2016:8265907. [Crossref]
30. Yan H, Mo Z, Xiang Z, et al. CT-guided (125)I brachytherapy for locally recurrent nasopharyngeal carcinoma. J Cancer 2017; 8:2104–2113. [Crossref]
31. Jin Z, Guan L, Xiang GM, Gao BA. Radiation resistance of the lung adenocarcinoma is related to the akt-onzin-pou5f1 axis. Biochem Biophys Res Commun 2018; 499:538–543. [Crossref]