Original Article

Percutaneous computed tomography-guided iodine-125 seeds implantation for unresectable pancreatic cancer

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Abstract

BACKGROUND: To examine the safety and clinical efficacy of computed tomography (CT)-guided radioactive iodine-125 (^{125}I) seeds implantation for patients with unresectable pancreatic cancer. **MATERIALS AND METHODS:** A group of 26 patients with pathologically confirmed unresectable pancreatic cancer underwent percutaneous CT-guided ^{125}I seeds implantation. Part of them received transarterial chemotherapy and/or percutaneous transhepatic cholangial drainage before or after seeds implantation. The primary endpoints were the objective response rates, local control rates, and overall survival. **RESULTS:** CT scan 2 months after treatment revealed complete response (CR) in 8 patients, partial response (PR) in 9 patients. Overall response rate (CR + PR) is 65.38%. Local control rate was 88.46%. Median survival of the whole group was 15.3 months, whereas for Stage III and IV was 17.6 and 9.1 months, respectively. The estimated 1-year survival was 30.77%. **CONCLUSIONS:** We consider CT-guided ^{125}I seeds implantation as a safe, effective, uncomplicated treatment for unresectable pancreatic cancer.

Key Words: Brachytherapy, iodine, pancreas cancer, radioisotopes

Introduction

Pancreas carcinoma is known as a devastating tumor. Despite the introduction of multiple new methods and combined modalities, the prognosis remains very poor. Extensive resection of advanced pancreas cancer is associated with significant morbidity and mortality. External beam radiation therapy (EBRT) and chemotherapy are usually regarded as insensitive to pancreatic cancer and associated with more systemic side effects, although EBRT can relieve pain in up to 50–85% of patients.[1]

In China, age-standardized 5-year relative survival of pancreas cancer is only 11.7%.[2]

Radioactive iodine-125 (^{125}I) seed implantation is a relative new option for cancer, which has been proved to be effective in prostate cancer,[3] recurrent rectal cancer,[4] liver cancer, lung cancer, and soft tissue sarcoma,[5] which is characterized by its minimal trauma and fewer complications. In recent 6 years, we elaborate ^{125}I seed implantation in unresectable pancreatic cancer (Stage III and IV). In this research, we investigate the feasibility and efficacy of computed tomography (CT)-guided implantation of ^{125}I seeds as an alternative management of advanced pancreas cancer which cannot be treated surgical resection.

Materials and Methods

From December 2010 to May 2015, a total of 26 patients with unresectable pancreatic cancer (Stage III and IV) ranging in age from 48 to 86 underwent CT-guided ^{125}I seeds implantation at The Second Hospital of Shandong University. The characteristics of patients are reviewed in Table 1. Prior to CT-guided seeds implantation, patients had undergone the treatment protocol: One patient received biliary-enteric anastomosis; one received pancreatic tail resection and splenectomy combined with adjuvant chemotherapy with gemcitabine and oxaliplatin; one received percutaneous transhepatic cholangial drainage (PTCD) and bile duct stent; one received transarterial chemotherapy with gemcitabine and oxaliplatin [Table 2]. Nine patients suffered from severe pain (Numerical Rating Scale, [NRS] 7–9), six suffered from moderate dorsalgia and abdominal pain (NRS, 4–6), and other patients complained no pain.

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Treatment planning

One week before ^{125}I seeds implantation, CT scans with a 5 mm thickness slice in a prone position were performed to get a detailed tumor volume study for all patients. Transverse images of the pancreas tumor were obtained at 5 mm intervals. The radiation oncologist outlined the gross tumor volume (GTV) and areas at risk for the subclinical disease on each transverse image. The planning treatment volume (PTV) include the entire GTV and 1.0 margin [Figure 1]. The dose was prescribed as the minimal peripheral dose (MPD) encompassing the PTV. The distribution and dose of ^{125}I seeds were calculated using computerized treatment planning system (TPS) [Figure 2].

Seed implantation technique

Liquid diet 1 day and enteroclysis 12 h before the procedure is necessary. All patients received gastric tube placement and general intravenous anesthesia with propofol and dexmedetomidine. The procedure took 60–100 min in CT room. Eighteen gauge needles were inserted according to TPS plan and extended at least 0.5–1.0 cm beyond GTV [Figure 3]. The half value of 1.7 cm in tissue ^{125}I seeds (Jaco pharmaceuticals Co., Ltd., Ningbo, China, half-life: 59.6 days, energy levels 27.4–31.4 KeV) gave a characteristic sharp dose drop-off and allowed for safe handling. Seeds were implanted with a space at equal distance, usually 0.5–1.0 cm center-to-center. The number of seeds implanted ranged from 30 to 80, with a median of 53. Specific activity of the seeds ranged from 0.6 to 0.8 mCi. The MPD of ^{125}I seeds was 110–130 Gy (median 115 Gy).

Postimplant treatment

One patient received PTCD/bile duct stent. Six patients received transarterial chemotherapy with gemcitabine

Table 1: Patients and primary tumor characteristics (*n*=26)

	Number of patients	Percentage
Gender		
Male	16	62
Female	10	38
Age in years		
Median (range)	65 (48–80)	
Location		
Head	9	35
Neck	3	12
Body	9	35
Tail	3	12
Uncinate process	2	6
Pathology		
Duct adenocarcinoma	22	84
Adenosquamous carcinoma	1	4
Pleomorphic carcinoma	1	4
Poorly differentiated adenocarcinoma	1	4
Signet-ring cell carcinoma	1	4
Primary tumor stage		
Stage III	21	81
T2N1M0	3	12
T3N1M0	18	69
Stage IV		
T3N1M1	5	19
Treatment before brachytherapy		
Transarterial chemotherapy	1	4
PTCD + stent	1	4
Surgery	1	4
Surgery + chemotherapy	1	4
Treatment after brachytherapy		
PTCD + stent	1	4
Transarterial chemotherapy	6	23
PTCD + stent + transarterial chemotherapy	2	8
TACE + transarterial chemotherapy	4	15
Neurolytic celiac plexus block	1	4
KPS		
50	3	12
60	12	46
70	9	35
80	2	7

PTCD=Percutaneous transhepatic cholangial drainage; TACE=Transcatheter arterial chemoembolization; KPS=Karnofsky performance status

and oxaliplatin for 1–4 cycles. Two patients received PTCD/bile duct stent and transarterial chemotherapy with gemcitabine and oxaliplatin for 1–3 cycles. Four patients received transcatheter arterial chemoembolization and transarterial chemotherapy with gemcitabine and oxaliplatin for 1–3 cycles. One patient received neurolytic celiac plexus block with dehydrated alcohol to release severe dorsalgia and abdominal pain. The treatment characteristics and outcomes are summarized in Table 3.

Complication

At each follow-up visit, all patients were interviewed regarding clinical manifestation of pancreatitis, cholangiolitis, upper gastrointestinal bleeding or perforation, pancreatitis, pancreatic fistula, and radiation enteritis. Their complaints were documented with a modified Radiation Therapy Oncology Group scoring scale.[6]

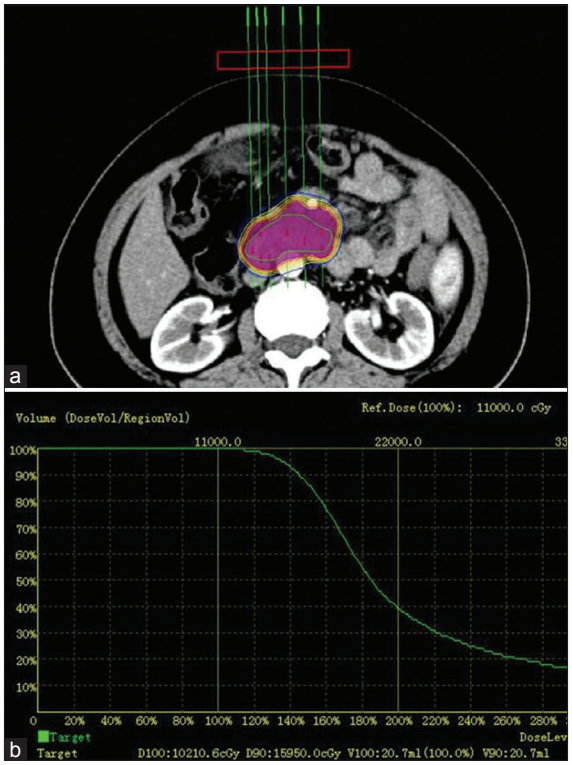

Figure 1: (a) Outlined planning treatment volume. (b) Treatment planning system curve about the distribution and dose of iodine-125 seeds

Follow-up

The median follow-up was 13.7 months (3–22 months). Patients were monitored by an interventional radiologist and radiation oncologists. Enhanced CT or magnetic resonance imaging of upper abdomen, chest X-ray, or CT were performed every 2–3 months. Tumor responses were accessed with Response evaluation criteria in solid tumors version 1.1 published in 2009.[7] Pain intensity was evaluated and grated by Adult Cancer Pain Clinical Practice Guideline.[8] NRS 1–3 is mild, 4–6 is moderate, 7–10 is severe. Overall, the pain relief response rate (RR) was defined as the sum of the complete response (CR) and partial response (PR) patients.

Statistical analysis

The follow-up time was calculated from the date of seed implantation. Survival and locoregional failure estimates were calculated according to the actuarial method of Kaplan and Meier. The primary endpoints of this study were the objective response rates, toxicities, time to progression, local control rates, and overall survival. For calculation of survival, deaths from any cause were scored as events. Local control was defined as lack of tumor progression either in or adjacent to the implanted volume.

Results

Pain relief

Among nine patients (19.2%) with severe pain before treatment, three complained mild pain (NRS 1–3) following implantation, and two had moderate pain with an NRS of

Table 2: Patients characteristics before seeds implantation

Gender	Age	Stage	Pathology	Location	Surgery	Chemotherapy	Transarterial chemotherapy	PTCD + stent
Female	73	T2N1M0	Duct adenocarcinoma	Uncinate process	No	No	No	No
Male	66	T3N1M1	Duct adenocarcinoma	Head	No	No	Gemcitabine and oxaliplatin (one cycle)	No
Male	80	T2N1M0	Adenosquamous carcinoma	Head	No	No	No	No
Male	68	T3N1M0	Duct adenocarcinoma	Head	No	No	No	No
Female	73	T2N1M0	Duct adenocarcinoma	Uncinate process	No	No	No	No
Male	80	T3N1M0	Pleomorphic carcinoma	Tail	No	No	No	No
Female	64	T3N1M0	Duct adenocarcinoma	Tail	Pancreas tail resection + splenectomy	Gemcitabine and oxaliplatin (one cycle)	No	No
Male	56	T3N1M1	Duct adenocarcinoma	Tail	No	No	No	No
Male	72	T3N1M0	Duct adenocarcinoma	Neck	No	No	No	No
Female	63	T2N1M0	Duct adenocarcinoma	Neck	No	No	No	No
Male	72	T2N1M0	Duct adenocarcinoma	Head	No	No	No	No
Female	63	T2N1M0	Duct adenocarcinoma	Head	No	No	No	8 mm×60 mm metallic
Male	64	T3N1M1	Duct adenocarcinoma	Body	No	No	No	No
Male	78	T3N1M0	Duct adenocarcinoma	Body	No	No	No	No
Female	81	T3N1M0	Duct adenocarcinoma	Head	No	No	No	No
Female	74	T3N1M0	Duct adenocarcinoma	Head	No	No	No	No
Male	71	T3N1M0	Duct adenocarcinoma	Body	No	No	No	No
Female	86	T3N1M0	Duct adenocarcinoma	Neck	No	No	No	No
Male	82	T3N1M0	Duct adenocarcinoma	Body	No	No	No	No
Male	55	T3N1M0	Duct adenocarcinoma	Body	No	No	No	No
Male	53	T3N1M1	Duct adenocarcinoma	Body	No	No	No	No
Female	48	T3N1M0	Duct adenocarcinoma	Body	No	No	No	No
Female	65	T3N1M1	Duct adenocarcinoma	Body	No	No	No	No
Male	57	T3N1M0	Duct adenocarcinoma	Uncinate process	No	No	No	No
Male	60	T3N1M0	Duct adenocarcinoma	Tail	No	No	No	No
Male	65	T3N1M1	Duct adenocarcinoma	Head	Biliary-enteric anastomosis + jejunum stoma	No	No	No

Table 3: Patients characteristics of radioactive seed implantation and outcome

Metastasis	Seed activity (mCi)	Seed (*n*)	Seed MPD (Gy)	Transartery chemotherapy	PTCD + stent	TACE	Neurolytic celiac plexus block	Cause of death	Survival (m)
No	0.8	30	110	No	No	No	No	Cachexia	11
Liver	0.8	80	120	No	No	No	No	Alive	-
No	0.6	30	110	Carboplatin (500 mg) + gemcitabine (1.6 g)	10 mm × 60 mm self-expandable	No	No	Respiratory failure	6
No	0.8	37	110	Oxaliplatin (150 mg) + gemcitabine (1.6 g) (3 cycle)	8 mm × 60 mm 10 mm × 80 mm	No	No	Cachexia	13
No	0.48	80	130	Oxaliplatin (150 mg) + gemcitabine (1.8 g)	No	No	No	Alimentary tract hemorrhage	12
No	0.8	40	110	Oxaliplatin (150 mg) + gemcitabine (1.8 g)	No	No	No	Heart Failure	3
No	0.8	50	110	No	No	No	Dehydrated alcohol (30 ml) + iodized oil (1.5 ml)	Hemorrhage shock	11
Pelvis + liver	0.6	80	110	Oxaliplatin (150 mg) + gemcitabine (1.6 g) (4 cycle)	No	Epirubicin (10 mg) + iodized oil (10 ml)	No	Liver failure	7

Contd...

Table 3: Contd...

Metastasis	Seed activity (mCi)	Seed (*n*)	Seed MPD (Gy)	Transartery chemotherapy	PTCD + stent	TACE	Neurolytic celiac plexus block	Cause of death	Survival (m)
Pelvis	0.57	32							
Liver	0.57	8							
No	0.6	60	110	No	No	No	No	Respiratory failure	3
No	0.7 0.8	50 50	110	Oxaliplatin (150 mg) + gemcitabine (1.6 g) (2 cycle)	No	Epirubicin (30 mg) + iodized oil (5 ml)	No	Cachexia	7
No	0.8	70	110	Oxaliplatin (75 mg) + gemcitabine (0.8 g)	No	No	No	Alive	-
No	0.8	50	110	Oxaliplatin (150 mg) + gemcitabine (1.8 g) (2 cycle)	No	No	No	Alive	-
Liver	0.8	53	110	No	No	No	No	Multiple organ failure	4
No	0.8	54	110	No	No	No	No	Alive	-
No	0.8	70	110	No	No	No	No	Multiple organ failure	5
No	0.8	48	110	No	No	No	No	Alive	-
No	0.8	60	110	No	No	No	No	Multiple organ failure	9
No	0.8	57	110	No	No	No	No	Multiple organ failure	3
No	0.8	70	110	No	No	No	No	Septicemia	7
No	0.8	70	110	No	No	No	No	Alive	-
Lymph nodes	0.8	64							
Lung	0.8	50	110	No	No	No	No	Multiple organ failure	6
No	0.8	70	110	No	No	No	No	Alive	-
Liver	0.8	60	110	No	No	No	No	Alive	-
No	0.8	60	110	No	No	No	No	Alimentary tract hemorrhage	6
No	0.8	50	110	No	No	No	No	Multiple organ failure	6
No	0.8	30	110	No	No	No	No	Alimentary tract hemorrhage	9

MPD=Minimal peripheral dose; PTCD=Percutaneous transhepatic cholangial drainage; TACE=Transcatheter arterial chemoembolization

4–6. In four patients, moderate pain prior to implantation became mild pain. Another two patients with moderate pain showed no change after treatment. The pain relief RR was 69.24% (9/13). The pain-free survival was 0–15 months with a median of 11 months.

Response to treatment

CT scan 2 months after treatment revealed CR in 8 patients, PR in 9 patients, stable disease in 6 patients, and progressive disease in 3 patients. Overall response rate (CR + PR) is 65.38%. Local control rate was 88.46%.

Overall survival

The follow-up period was 3–22 months. The median survival of the whole group was 15.3 months, whereas for Stage III and IV was 17.6 and 9.1 months, respectively. The estimated 1-year survival was 30.77% [Figure 3]. The median survival for pure seeds implantation is 10.7 months [Figure 4]. There is no significant difference between the seeds group and seeds–drug/PTCD combined group in terms of the median survival time.

Complications

Seven patients showed fever (low than 38.5°C) in 3–5 days after seed implantation, which was considered normal as absorption fever. Fever higher than 39.0°C, upper gastrointestinal bleeding or perforation, pancreatitis, pancreatic fistula, radiation enteritis, or cholangiolitis appeared in no patient. Five patients who received transarterial chemotherapy showed leukopenia, which was reversed with medicine, including vitamin B4 and/or Recombinant Human Interleukin-11 for Injection.

Discussion

Pancreatic carcinoma is one of the most deadly cancers and it occurs as the fifth and sixth most common causes of cancer-related death in men and women, respectively.[9] It is difficult to diagnose at its early stage because of its lack of imaging findings and typical clinical manifestations. Hence, when diagnosed, patients are in late stage with abdominal pain, abdominal distension, progressive jaundice, etc.,

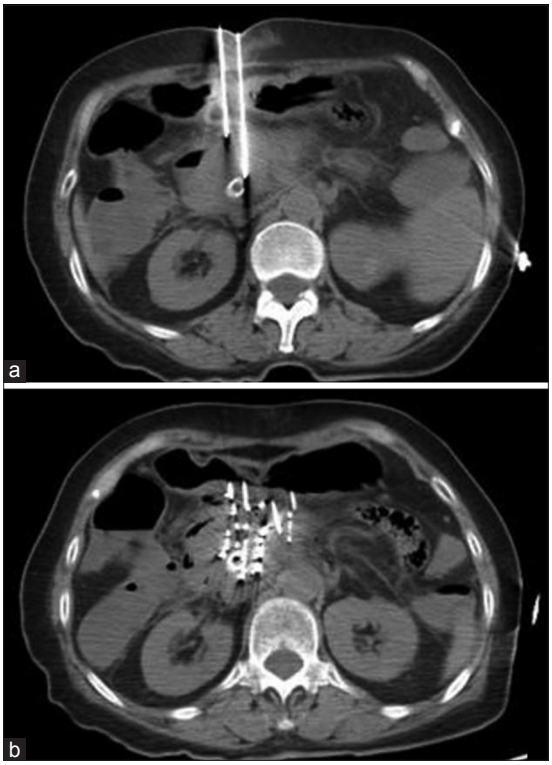

Figure 2: (a) Needles inserted according to treatment planning system plan. (b) Seeds were implanted into the lesion

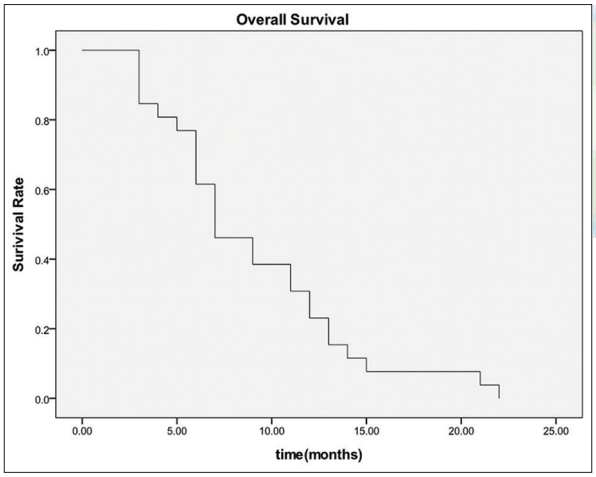

Figure 3: Overall survival of the whole group

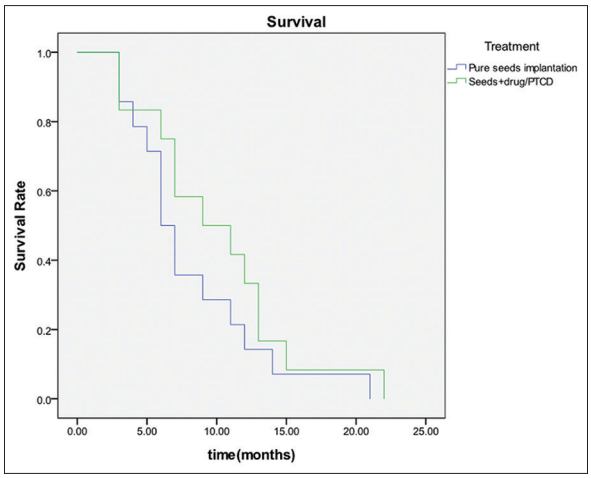

Figure 4: Survival of pure seeds implantation and seeds-drug/percutaneous transhepatic cholangial drainage

Whipple procedure, also known as Pancreaticoduodenectomy, is still the first choice for the treatment of pancreatic carcinoma, if it is resectable.[10] People always consider surgery as the best treatment for malignant tumor. However, the indication for surgery is very strict and its incidence of postoperative complications, such as longer operative time, bleeding, lower albumin, long periods to bowel movement and normal diet, is very high. Besides, in end-stage of the tumor, Stage III and IV, older patients with poor healthy are also not suitable for surgery operation.

Intravenous chemotherapy with gemcitabine is a traditional treatment for local control of advanced or metastatic pancreatic cancer. However, local recurrence and progression in the pancreas and peripancreatic lymph nodes after this treatment has been reported to be as high as 58%.[11] Moreover, as mentioned in the introduction, EBRT is usually regarded as insensitive to pancreatic cancer and associated with more systemic side effects.

Radioactive ^{125}I seed implantation, the interstitial irradiation, is a new kind of treatment for malignant tumor. Based on the TPS, percutaneous CT-guided ^{125}I seed implantation seeds can make continuous and short distance radiation, which makes tumor tissue receive the greatest degree of damage, and normal organization is not or within minor damage. Patients for whom surgery is not appropriate or who refuse surgery, ^{125}I seed implantation is a good option, with regarding interference-free and accurately predictable energy distribution, treatable size of a target lesion, and a lower rate of acute adverse effects possible by maintaining tissue continuity. In recent years, this technique has been applied in prostate cancer, primary and metastatic lung cancer, breast cancer, brain tumors, pancreatic cancer, primary and metastatic liver cancer, and soft tissue sarcoma.[12-14] However, there are few reports on CT-guided radioactive seeds implantation for pancreatic cancer.

Our data suggest that local control rates can be enhanced by the addition of transarterial chemotherapy and/or PTCD. Despite lacking definitive proof, positive results allow us to continue the use of seeds-drug/PTCD combination therapy. For patients with the first symptom of jaundice, PTCD/bile duct stent will be implied to recover the patency of bile duct and protect liver function, which helps subsequent therapy. Cron *et al*.[15] suggested that the best time for intravenous chemotherapy is within 3–4 days after implantation of ^{125}I seeds because the permeability of the surrounding vasculature is promoted by the radiation effects of the seeds at that time. In this group of patients, time of transarterial chemotherapy was uncertain, before or after the seeds implantation. The interval between transarterial chemotherapy and seeds implantation was about 1 week. The median survival time for pure seeds implantation and seeds-drug/PTCD combined therapy was 10.7 months and 15.3 months, respectively; it does not reach statistically significant but also encouraged our further evaluation.

In this group of patients, we implanted ^{125}I seeds under CT guidance and yielded good local control of the disease.

We obtained even distribution of the radioactive seeds with overall response rate of 65.38%, local control rate of 88.46%, and pain relief rate of 69.24%. Nevertheless, there were fewer complications compared with other interventional ablation procedures. From these data, it appeared that ^{125}I implantation of unresectable pancreatic tumors offered high control of the primary tumor and significant palliation of symptoms. After promising results, we will further evaluate interventional brachytherapy as an additional tool in multimodal oncologic therapy concepts.

Conclusion

This study suggested that CT-guided ^{125}I seeds implantation appeared to be safe, effective, uncomplicated, and could produce adequate pain relief for unresectable pancreatic cancer.

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