Journal of Digestive Diseases 2008; **9**; 32–40 doi: 10.1111/j.1443-9573.2007.00322.x

Cryosurgery with combination of ^{125}iodine seed implantation for the treatment of locally advanced pancreatic cancer

Ke Cheng XU, Li Zhi NIU, Yi Ze HU, Wei Bing HE, Yi Song HE & Jian Sheng ZUO

Cryosurgery Center for Cancer, Fuda Cancer Hospital Guangzhou, Guangzhou, China

OBJECTIVE: To study the therapeutic value of cryosurgery with combination of ^{125}iodine seed implantation for locally advanced pancreatic cancer.

METHODS: Thirty-eight patients with locally advanced pancreatic cancer were enrolled in this study. The diagnosis was confirmed by pathology in 31 patients. Ten patients had metastases of the peripancreatic lymph node and eight had liver metastases. The therapy included cryosurgery, which was performed intra-operatively or percutaneously under guidance of ultrasound and/or computed tomography (CT), and ^{125}iodine seed implantation, which was performed during cryosurgery process or post-cryosurgery under the guidance of ultrasound and/or CT.

RESULTS: Eleven patients received intra-operative cryosurgery and 27 received percutaneous cryosurgery. Fourteen patients underwent two procedures of cryosurgery and three underwent three procedures of cryosurgery. ^{125}Iodine seed implantation was performed during the freezing procedure in 29 patients and within 3–7 days after cryosurgery in nine patients under ultrasound and CT guidance. Fifteen patients, of whom 13 had metastases of peripancreatic lymph nodes or liver received regional chemotherapy. At 3 months after therapy, a CT follow-up was performed to estimate the tumor response to therapy. Most of the patients had varying degrees of tumor necrosis. A complete response of the tumor was seen in 23.6% of patients, a partial response in 42.1%, stable disease in 26.3% and progressive disease in 7.9%. The adverse effects associated with cryosurgery mainly included pain of the upper abdomen and increased serum amylase activity. Acute pancreatitis was seen in five patients, one of whom presented a severe type of pancreatitis. During the followed-up of a median of 16 months (range of 5–37) median overall survival was 12 months, 19 patients (50.0%) survived for 12 months or longer and four survived for 24 months or longer.

CONCLUSION: As it is far less invasive than conventional pancreas resection and entails a low rate of adverse effects, cryosurgery should be the choice modality for most patients with locally advanced pancreatic cancer. ^{125}Iodine seed implantation can destroy residue survival cancer cells after cryosurgery. Hence, combination of both modalities has a complementary effect.

KEY WORDS: ^{125}iodine seed implantation, cryoablation, cryosurgery, pancreatic cancer.

Since the 1970s, along with the imaging and molecular biology technology, the diagnosis of pancreatic cancer has improved substantially. However the survival rate has not improved significantly, as most patients do not receive radical resection at the time of diagnosis and only palliative treatment can be for them prescribed, leading to overall 1-and 5-year survival rates of only 20 and 5%, respectively.[1,2] Paclitaxel and gemcitabine

Correspondence to: Ke Cheng XU, Fuda Cancer Hospital Guangzhou, 167 West Xingang Road, Guangzhou, 510300, China.
Email: xukc@vip.163.com

have been considered to be effective agents for pancreatic cancer, but response rates to this treatment have not exceeded 20%, and their effectiveness lasts less than 6 months.[3,4] It is necessary, therefore, to seek a new modality.[5,6]

We have used a combination of cryosurgery and ^{125}iodine seed implantation for the treatment of locally advanced pancreatic cancer, achieving better results. Our report on this follows.

PATIENTS AND METHODS

Patients

From 2001 to April 2007, 38 patients with locally advanced pancreatic cancer underwent cryosurgery combined with ^{125}iodine seed implantation. They were 28 men and 10 women between 29–89 years old, with a median age of 57 years. The tumor size ranged from 2.2 to 7.1 cm in diameter. The tumors of seven patients were in the head of the pancreas and the remainder were located in the body and tail of the gland. Ten patients had peripancreatic lymph node metastasis and eight had liver metastasis (with no more than four nodules). The diagnoses of all patients were based on imaging studies such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), and the diagnoses of 31 patients were proved by histology. Before hospitalization, eight patients had received 4–6 cycles of chemotherapy (gemcitabine, cisplatin, 5-fluorouracil (5-FU)). Five out of the seven patients with cancer of the pancreatic head received endoscopically placed stents for decompression of the common bile duct that was obstructed by tumors. The patients with multiple metastases (apart from metastases which had four or less than four nodules in the liver and metastases of adjacent peripancreatic lymph nodes) or with tumors which extended directly into either the stomach, spleen, colon or peritoneum were excluded from this study.

All the patients were given information of cryosurgery guidelines and the study received ethical approval.

Cryosurgery

The cryosurgery was performed with intra-operative or percutaneous approaches.

Intra-operative cryosurgery

Before the surgical procedure, the patients were administrated general anesthesia and positioned for an upper abdominal incision. The involved pancreas was exposed by the trans-peritoneal mobilization of the bowel and stomach. Once the specific pancreatic mass was identified, an 18-gauge Tru-cut (Baxter, Deerfield, IL, USA) biopsy needle was used to obtain one to two cores of tissue from the solid mass. If it was discovered that the tumor was unresectable after a thorough investigation, cryosurgery was performed in direct vision and under the guidance of ultrasound. A variable number (usually one to three) of 2- or 3-mm cryoprobes were placed directly into the pancreatic mass and positioned under ultrasound guidance. Generally, lesions smaller than 3 cm could be reliably frozen with a single, centrally placed 3-mm probe, while large lesions required multiple probes. A double freeze/thaw cycle was used with an argon gas-based cryosurgical unit (EndoCare, Irvine, CA, USA). Each cryoprobe was cooled to –160°C and the resulting ice-ball monitored with ultrasound until a frozen region encompassed the entire mass of the tumor with a safe border of at least a 0.5 cm. The tissue was then allowed to thaw slowly to 0°C. A second freezing/thawing cycle was performed after any necessary repositioning of the cryoprobes. After the freezing process was completed, the cryoprobes were removed and the entry site was occluded with thrombin-soaked gelfoam. For the metastases of peripancreatic nodes and the liver, the cryosurgery was performed simultaneously.[7,8]

Percutaneous cryosurgery

The procedure was performed under local anesthesia and under guidance of CT. The cryoprobe was often inserted using a retroperitoneal approach, based on the location of the tumor. Generally, a 2-mm or 3-mm cryoprobe was used. For tumors more than 3 cm in diameter, 2–3 probes were used. For liver metastases, simultaneous cryosurgery was performed using additional cryoprobes which were inserted through the right intercostal space. The cryosurgery procedure was the same as in intra-operative cryosurgery.[8]

Seed implantation

The procedure was performed during the cryosurgery, or percutaneously under the guidance of ultrasound or CT after cryosurgery. The ^{125}iodine seeds (Syncor Pharmaceutica, Shanghai, China) were implanted at the border line of the cryotreated tumor of the pancreas, or in the nodules of the metastases. The number of seeds depended on the size of the tumor, and every seed was implanted in between the distance of 0.5 cm.

Postoperative management

The patients were instructed to fast for three days. An analog of somatostatin was given i.v., generally for

3–4 days, or extended until the alleviation of abdominal pain and repristination of the elevated serum amylase levels. Aprotinin, an inhibitor of pancreatic enzymes, and a proton pump inhibitor were given in i.v. infusion to patients with abdominal pain and increased serum amylase levels.

Regional chemotherapy

An infusion of chemotherapeutic drugs was given through a catheter of the celiac artery using the Seldinger technique. The prescription was 5-FU 500 mg/m^2, mitomycin C 8.5 mg/m^2 and gemcitabine 500 mg/m^2, once every fortnight.

Follow-up

A postoperative follow-up was obtained at one month after treatment and every 3 months thereafter by assessment of the tumor markers, abdominal ultrasonography and CT. Some of the patients received a follow-up with positron emission tomography CT (PET-CT). The efficacy of the cryosurgery was evaluated according to the evolution of the tumor size and the survival of the patients. Changes in tumor mass were measured according to the response evaluation criteria in solid tumors (RECIST) protocol,[9] which is based on objective measurements of lesion size before and after treatment. A complete response (CR) means the disappearance of the cryotreated lesion (scar) or its reduction to less than 25% of its original size. A partial response (PR) means a greater than 30% decrease in the sum of the largest diameter of all targeted lesions. Stable disease (SD) means a less than 30% decrease in the sum of the largest diameter of all targeted lesions. Progressive disease (PD) means an increase of greater than 20% in the sum of the largest diameter of all targeted lesions.

All radiological studies were reviewed by the same radiologist with an expertise in pancreas imaging. For lesions suspected of recurrence, an ultrasound-guided liver biopsy was performed for histological study. Subsequent re-cryosurgery was performed if the histology showed positive result. A persistent nodule on radiological imaging without tumoral activity shown on PET-CT, or with reducing and normal tumor markers (CA 19-9), or no changes in the absence of other treatment for an interval of at least 6 months since cryosurgery, was considered a remnant. Tumor recurrence was estimated either by positive histology, or by the combination of an increase of the cryotreated lesion size on ultrasound, CT or PET-CT imaging and increased tumor markers, or by the discovery of metastases.

Statistical analysis

The statistical analysis was performed using SPSS (version 13.0; Chicago, IL, USA).Survival was determined according to the Kaplan–Meier method. Comparison of survival rates was obtained with the log–rank test. A *P*-value that was less than 0.05 was considered statistically significant.

RESULTS

Eleven patients received intra-operative cryosurgery and 27 underwent percutaneous cryosurgery. Among the patients who received percutaneous cryosurgery, 14 received two procedures of cryosurgery and three received three. ^{125}Iodine seed implantation was performed during the cryosurgery procedure in 29 patients and within 3–7 days after cryosurgery in nine patients under ultrasound and CT guidance. The average number of ^{125}iodine seeds implanted/patient was 28 with a range of 18–45 seeds. Fifteen patients, of whom 13 had metastases of the peripancreatic lymph nodes or the liver, received regional celiac artery chemotherapy, which was performed every fortnight as a cycle. Three patients received 1 cycle, seven received 2 cycles, three received 3 cycles and two received 4 cycles.

Response to treatment. The response of the tumor to treatment, according to the results of CT 3 months after treatment, is shown in Table 1. In most of the patients the tumors had varying degrees of necrosis. CR, PR, SD and PD were 23.6, 42.1, 26.3 and 7.9%, respectively.

Adverse reactions. Abdominal pain, which usually subsided in 2–3 days, was experienced by 73.7% of the patients. More than half the patients (55.3%) had elevated serum amylase levels, which generally ranged 1–2 folds of upper limit of the normal reference values and persisted for 5–7 days. Acute pancreatitis with acute abdominal pain, serum amylase levels elevated fourfold or more was seen in five patients (13.2%), of whom one patient developed a hemorrhage–necrosis type of pancreatitis with intra-abdominal fluid

Table 1. Response of pancreatic carcinoma to therapy

Response	No. of patients (%)
Complete	9 (23.6)
Partial	16 (42.1)
Stable disease	10 (26.3)
Progressive disease	3 (7.9)

Table 2. Adverse effects of pancreatic cryosurgery

Adverse effects	No. of patients (%)
Abdominal pain	28 (73.7)
Fever	24 (63.2)
Acute pancreatitis[†]	5 (13.2)
Increased amylase levels[‡]	21 (55.3)
Abdominal bleeding[§]	3 (7.9)
Pulmonary infection	2 (5.3)
Myocardial infarction	1 (2.6)
Cerebral infarction	1 (2.6)

[†]With abdominal pain and fever, [‡]including five patients with acute pancreatitis, [§]including three patients with abdominal pain.

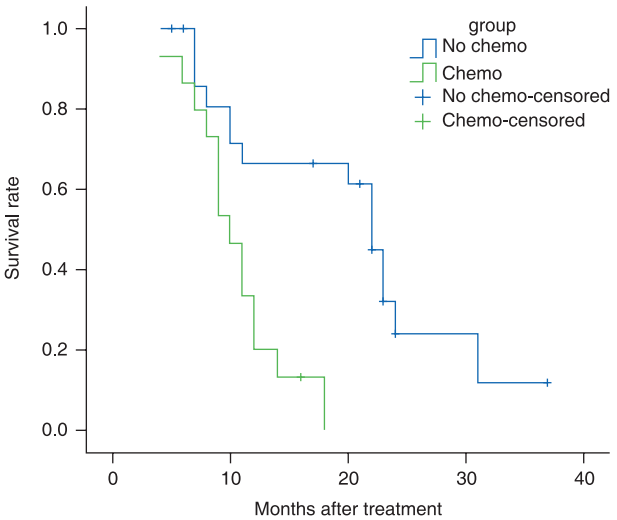

Figure 1. Survival of patients with pancreatic cancer.

effusion and serum amylase levels 12-fold the height of normal reference values. All patients with pancreatitis were cured by conservative management. Three patients (7.9%) had abdominal bleeding, however, the abdominal liquid drawn out by paracentesis showed no obvious increase in levels of amylase activity. The bleeding disappeared within four days. Most patients (63.2%) had a fever of 38–39.5°C with a temporary chill. The fever persisted for 3–4 days and generally less than 7 days. Two patients with pulmonary infection recovered with antibiotic therapy within 7–10 days. Two patients, aged 78 and 91-year old respectively had a cerebral infarction and myocardial infarction respectively (Table 2). No treatment-related mortality occurred.

Overall survival

During a median follow-up of 16 months (range of 5–37 months), the median overall survival was 12 months. There were 19 patients (50.00%) who survived for 12 months or more. The overall survival rates for 6, 12, 18, 24 and 36 months were 97, 53, 45, 20 and 7% in all patients; 93, 33, 11, 0 and 0% in 15 patients who underwent chemotherapy and 100, 67, 67, 32 and 12% in 23 patients who did not received chemotherapy, respectively. The survival curve is shown in Figure 1. The survival rate between patients who were and who were not undergoing chemotherapy was statistically significant ($P < 0.005$). Overall, 29 patients died, of whom 13 died from the spread of the cancer, 11 with liver metastases died of liver failure, three died of cardio-cerebral vascular diseases and two died of unknown causes. Among 19 patients who died within 12 months, 13 patients had liver metastases or had peripancreatic lymph node metastasis before this treatment. Four patients survived for 24 months or more, of whom two survived for 24 months and the remaining two survived for 31 and 37 months, respectively. The patient who survived the longest is alive at the time of writing with no evidence of recurrence.

Three examples of these patients are described below.

Patient 1

An 80-year-old patient had an increased bowel movement for 2 weeks. Ultrasound found a lesion of 3 × 3 cm in size within the pancreatic neck. Ultrasound-guided percutaneous biopsy showed a cystadenocarcinoma. The patient refused surgery and underwent percutaneous cryosurgery with ^{125}iodine seed implantation under CT guidance. Three months after treatment a CT scan was performed and found tumor necrosis containing ^{125}iodine particles. The patient's diarrhea subsided, his performance improved and body weight increased. A recent ultrasound and CT scan shows that the original tumor decreased to 1.5 × 1.1 cm in size (Fig. 2). The patient has had recurrence-free survival for 37 months.

Patient 2

A 61-year-old man received ultrasound and a CT scan due to abdominal pain and was found to have a tumor in the pancreatic body and tail, which was proved by biopsy to be an adenocarcinoma. The patient underwent 4 cycles of chemotherapy but the tumor showed a progressive process. A CT showed low-density areas of 4 × 5.5 cm in size in the pancreatic body and three hepatic metastases ranging in size from 2 to 5 cm. The serum CA19-9 was 512 IU. The patient underwent percutaneous cryosurgery and ^{125}iodine seed implantation under guidance of CT and ultrasound for pancreatic

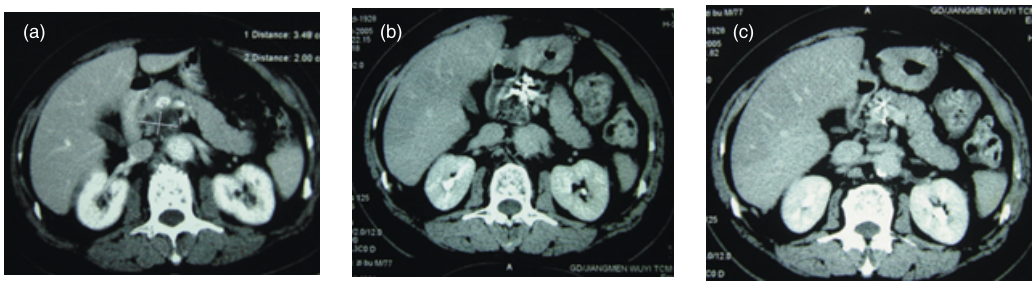

Figure 2. Pancreatic computed tomography scan in patient 1 (a) before treatment, (b) three months after treatment and (c) 12 months after treatment.

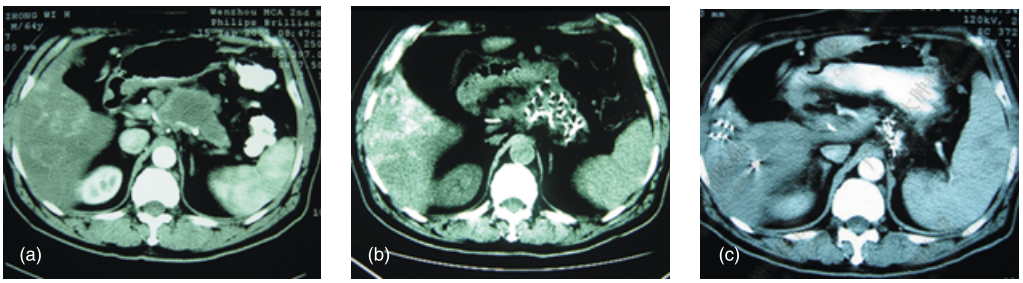

Figure 3. Computed tomography scan of patient 2 (a) before treatment, a mass was seen in pancreatic body and tail, (b) 1 month after treatment and (c) 6 months after treatment.

lesion and hepatic metastases. A repeat CT scan showed the tumor shrinkage and stabilizing in both the pancreas and liver (Fig. 3). An ultrasound-guided biopsy showed no evidence of cancer and the CA19-9 levels decreased to below 40 IU. The patient has survived for 24 months at the time of writing.

Patient 3

A 36-year-old man complained of upper abdominal pain with jaundice and decreased body weight for 2 weeks. Ultrasound and CT revealed the mass of pancreatic head with dilation of common bile duct. The serum alkaline phosphatase activity was 650 IU, CA19-9 210 IU and CEA 28 μg/L. The patient underwent a laparotomy that discovered a mass 5×5 cm in size within the pancreatic head. A biopsy showed a moderately differentiated adenocarcinoma. There was no possibility of resection for tumor. A palliative cholecystojejunostomy was performed to reduce obstructive jaundice and cryosurgery was performed for the pancreatic tumor under direct vision and ultrasound guidance, and then a trans-celiac artery infusion of chemical agents was given for four cycles. Following this treatment, the patient's symptoms significantly improved. A CT follow up was performed 3 months after the treatment and showed the shrinkage and necrosis of the pancreatic mass with a honeycomb-like change (Fig. 4). The CA 19-9 was decreased to 48 IU. The patient survived for 19 months.

DISCUSSION

Cryosurgery recently has provided a new therapeutic approach and has been used to treat many benign and malignant tumors, especially unresectable tumors.[10] Several publications have reported using this modality in the treatment of liver cancer, prostate cancer, kidney tumors and breast cancer, and have showed encouraging results.[11,12]

There have been few reports of using cryosurgery to treat pancreatic cancer. Kovach[13] reported that nine patients with unresectable pancreatic cancer underwent a total of 10 sessions of intra-operative cryosurgery under ultrasound guidance. There was no cryosurgery-related mortality and no post-cryosurgery pancreatic fistulas and pancreatitis. Following this treatment, the patients' pain was alleviated and the analgetic dose was decreased. All the patients were able to take a normal diet on their discharge from hospital. Patiutko[14] treated 30 patients with locally advanced pancreatic cancer with a combination of cryosurgery and radiation. All the patients experienced an effective control of pain, a decrease of CA 19-9, an improvement of performance

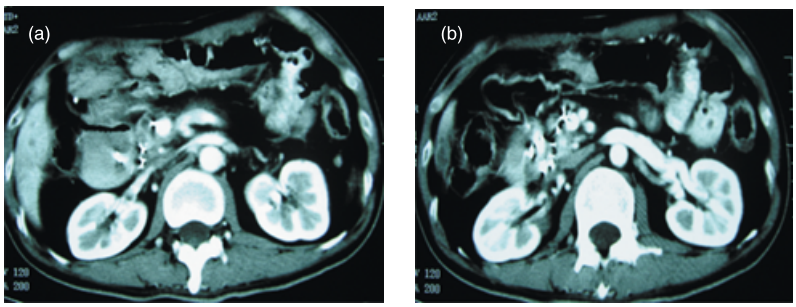

Figure 4. Computed tomography scan in patient 3 (a) before treatment, (b) three months after treatment.

and increased survival rates. Korpan[15] summarized the experience of cryosurgery for pancreatic cancer and showed that the modality was very effective for most patients.

The effectiveness of cryosurgery depends on the complete cryoablation of all targeted tissue. Tumor persistence or occurrence at the site of cryoablation often results from incomplete destruction. Temperatures lower than –40°C are assumed to be necessary to ensure tumor ablation. Ice-balls larger than the target lesions are thus necessary for complete tumor ablation, because the outer few millimeters of the ice-ball circumference are at non-lethal temperatures. Extending the ice-ball 1cm beyond the tumor borders should be adequate for ablation.[16,17] However, because the pancreas volume is relatively small, cancer often involves most of the glands and over-freezing increases complications, it is very difficult to ensure the 1-cm safety border. Therefore, we decided to try a combination of cryosurgery with ^{125}iodine seed implantation for the treatment of the pancreatic cancer.^{125}Iodine has a half-life of 59 days and radiates a short distance γ ray which results in the death of cancerous cells. ^{125}Iodine seeds are complementary to cryosurgery.[18]

In this study, 38 patients with locally advanced pancreatic cancer underwent a combination of cryosurgery and ^{125}iodine seed implantation. Eleven patients underwent intra-operative cryosurgery and 27 who underwent percutaneous cryosurgery under the guidance of ultrasound and CT. As a result, most of the tumors had different degree of necrosis. The CR, PR and SD were 23.6, 42.1 and 26.3%, respectively, and only 7.9% presented PD. During the median follow-up of 16 months (5–37 months), the median survival was 12 months for all patients, of whom 19 patients (50.00%) survived for 12 months or more. The overall survival rates for 6,12,18, 24 and 36 months were 97, 53, 45, 20 and 7%, respectively.

At present, the conventional therapies for advanced pancreatic cancer are chemotherapy and radiation. Diverse results of this treatment have been published worldwide (Table 3). Summarizing the data, median progression-free survival ranged from 3 to 10 months and the median survival was for 7 to 16 months (less than 10 months in the most reports). The objective response rate of the tumors was 22–40%, and 1-year survival was 20–78% (less than 60% in most reports).The results in this series are similar to those reported in the above publications. However, in this series, four patients survived for 24 months or more, of whom two survived for 24 months and the two others survived for 31 and 37 months, respectively. The patient who survived the longest survival was alive at the time of writing with no evidence of recurrence. The above publications report few patients with such long-term survival.

In this series there were 15 patients who underwent celiac artery regional chemotherapy. The question is whether the chemotherapy itself was responsible for the longer survival of the patients. But the most of patients who underwent chemotherapy had metastases of peripancreatic lymph nodes or the liver and survived for less than 12 months. The patients who underwent chemotherapy survived for a shorter time than those who were not given chemotherapy (Fig. 1) ($P < 0.005$).The results show that the patients with metastases of peripancreatic lymph nodes and the liver had a poor prognosis, and the chemotherapy did not result in their surviving longer.

A great deal of attention is paid to the safety of cryosurgery of pancreatic cancer. Korpan[7] performed an experimental study on dogs that received pancreatic cryosurgery with a disc cryoprobe. The cryodestruction area of the pancreatic parenchyma was clearly defined with a sharp demarcation line with good visual contours. In the following hours, the focus exposed to cold

Table 3. Treatment of advanced pancreatic carcinoma based on references

Reporter	No. of patients	Therapy	Median progressive-free survival (months)	Median survival (months)	Objective respons rate %	Survival at 12 months after treatment %
El-Rayer[19]	47	Gemcitabine, cisplatin, and 5-FU			34	
Tokuuye[20]	53	Small-field radiotherapy in combination with chemotherapy		10.2		35.2
Okusaka[21]	34	gemcitabine + 5-FU	3.2	7.1	25	14.3
Yamazaki[22]	22	Concurrent chemoradiotherapy gemcitabine		16	32	78
Isacoff[23]	50	5-FU, mitomycin dipyridamore			26	54
Park[24]	45	Gemcitabine + capecitabine	5.4	10.4	40	
Ko[25]	25	Gemcitabine + cisplatin, radiation + capecitabine	10.5	13.5		62
Polyzos[26]	32	Gemcitabine + 5-FU, folic acid, somostatin	7	7	22	20
Michael[27]	30	Gemcitabine + 13*cis*		7.8		
Furuse[28]		Intra-operative radiation, 5FU		7.8		8.1 (2-year-survival)
This series	38	Cryosurgery and ^{125}iodine seed implantation		12	CR + IR 73.6	53

become an aseptic necrosis with thrombus formation. Four weeks later, it could be seen how loose connective tissue with numerous blood vessels had developed. After 9–10 weeks tight connective tissue developed, and after 12 weeks, the transformation of the cryozone of the pancreatic parenchyma was complete. No animal in this study developed cryosurgery-related mortality or complications. No post-cryosurgery bleeding, pancreatic fistulas or secondary infection were observed. In this series there was no patient whose death was related to the cryosurgery. The main adverse effects were abdominal pain, fever and increased amylase levels. A few patients developed severe acute pancreatitis but none had a poor outcome. Therefore, the pancreatic cryosurgery seems to be a safer modality. In addition, ^{125}iodine seed implantation may be performed at the same time of the cryosurgery and is not complicated by the persistent adverse effects seen in chemo-radiotherapy. As a whole, the combination therapy consisting of cryosurgery and ^{125}iodine seed implantation is a less-invasive or mini-invasive technique.

Korpan[7,15] pointed out that there were almost no known contraindications of cryosurgery for pancreatic cancer. For most pancreatic cancers, cryosurgery can substitute for conventional surgery. This opinion needs to be confirmed. According to our experience, for unresectable pancreatic cancer, cryosurgery has the following advantages:

1. When at laparotomy the pancreatic cancer is found to be unresectable, conventional management is a bypass operation without intervention for the tumor. Cryosurgery may avoid this shortcoming and the operation therefore becomes radical, instead of merely palliative.

2. Cryosurgery is a less invasive technique and has a low rate of complications compared with conventional resection.

3. Cryosurgery may allow ablation of metastases in liver and peripancreatic lymph nodes.

4. A tumor that has been considered unresectable may undergo percutaneous cryosurgery under ultrasound or CT, which has a similar efficacy as intra-operative cryosurgery and is far less invasive.

5. Because of the "heat sink" effect created by the flow of blood in the larger vessels, cryosurgery can destroy tumors without damaging major vascular structures.

6. During percutaneous cryosurgery, other modalities such as ^{125}iodine seed implantation may be employed simultaneously.

7. It is theorized that during cryosurgery, the immune system of the host become sensitized to the tumor being destroyed by the cryosurgery. As the body absorbs the necrotic tissue, active immunity to the tumor tissue develops. Any primary tumor tissue undamaged by cryosurgery and metastases can be destroyed by the immune system after cryosurgery. That is called cryoimmunity.[29]

8. The cryoablated cancerous tissue had an increased sensitivity to chemo-radiotherapy, which creates the conditions for comprehensive therapy.[30]

The shortcoming of this study is that it does not analyze the efficacy of cryosurgery for tumors of the pancreas in different locations. It is known that the portal vein is often encased in a pancreatic tumor and tumors that are located in the body and tail of the pancreas often infiltrate the vessels of spleen. This study makes no special comment for these conditions.

In conclusion, because it is far less invasive than conventional resection for the pancreas, and due to the low rate of adverse effects from it, cryosurgery should be the preferred modality for most patients with locally advanced pancreatic cancer. ^{125}Iodine seed implantation can destroy the residual surviving cancer cells after cryosurgery. Hence, a combination of both modalities has a complementary effect.

REFERENCES

1 Xu KC, Xu P. The treatment of pancreatic cancer. In: Xu KC, Jiang SH, eds. *Modern Therapy for Digestive Diseases*. Shanghai: Shanghai Science-Education Publications, 2001; 618–24 (in Chinese).
2 Ducreux M, Boige V, Malka D. Treatment of advanced pancreatic cancer. *Semin Oncol* 2007; **34** (**2** Suppl. 1): S25–30.
3 Wilkowski R, Thoma M, Bruns C *et al*. Chemoradiotherapy with gemcitabine and continuous 5-FU in patients with primary inoperative cancer. *JOP* 2006; **7**: 349–60.
4 Eickhoff A, Martin W, Hartmann D *et al*. A phase I/II multicentric trial of gemcitabine and epirubicin in patients with advanced pancreatic carcinoma. *Br J Cancer* 2006; **94**: 1572–4.
5 Wada K, Takada T, Amano H *et al*. Trend in the management of pancreatic adenocarcinoma – Japan *vs.* US Europe. *Nippon Geka Gakkai Zasshi* 2006 Jul; **107**: 187–91.
6 Mornex CL. Chemoradiation in pancreatic carcinoma. *Cancer Radiother* 2003; **7**: 254–65.
7 Korpan NN. Pancreas cryosurgery. In: Korpan NN, ed. *Basics of Cryosurgery*. Vienna, New York: Springer-Verlag, 2001; 151–4.
8 Xu KC, Niu LZ, He WB *et al*. Pancreatic cancer. In: Xu KC, Niu LZ, eds. *Cryosurgery for Cancer*. Shanghai: Shanghai Science-Education Publications, 2007; 234–45 (in Chinese).
9 Truchida Y, Therasse P. Response evaluation criteria in solid tumors (RECIST): new guideline. *Med Pediatr Oncol* 2001; **37**: 1–3.
10 Gage AA, Baust J. Mechanisms of tissue injury in cryosurgery. *Cryobiology* 1998; **37**: 171–86.
11 Xu KC, Niu LZ, He WB *et al*. Percutaneous cryoablation in combination with ethanol injection for unresectable hepatocellular carcinoma. *World J Gastroenterol* 2003; **9**: 2686–9.
12 Mouravier V, Polascik TJ. Update on cryotherapy for prostate cancer in 2006. *Curr Opin Urol* 2006; **16**: 152–6.
13 Kovach SJ, Hendrickson RJ, Cappadona CR *et al*. Cryoablation of unresectable pancreatic cancer. *Surgery* 2002; **131**: 463–4.
14 Patiutko Iu, Barkanov AI, Kholikov TK *et al*. The combined treatment of locally disseminated pancreatic cancer using cryosurgery. *Vopr Onkol* 1991; **37**: 695–700.
15 Korpan NN, Hochwarter G. Pancreatic cryosurgery-a new surgical procedure for pancreatic cancer. *Eur J Clin Invest* 1997; **27** (Suppl. 1): A33.
16 Mala T, Samset E, Aurdal L *et al*. Magnetic resonance imaging estimated three dimensional temperature distribution in liver cryolesion. A study of cryolesion characteristics assumed necessary for tumor ablation. *Cryobiology* 2001; **43**: 268–75.
17 Seifert JK, Gerharz CD, Mattes F *et al*. A. Pig model of hepatic cryotherapy. *In vivo* temperature distribution during freezing and histopathological changes. *Cryobiology* 2003; **47**: 214–26.
18 Fu GF, Lei GY, Zhao Zl *et al*. 125 Iodine seed persistent implantation for treatment of malignant tumors. *Modern Oncol* 2004; **12** (2): 108–9 (in Chinese).
19 EI-Rayer BF, Zalupski MM, Shields AF *et al*. Phase II study of gemcitabine, cisplatin, and infusional fluorouracil in advanced pancreatic cancer. *J Clin Oncol* 2003; **21**: 2920–5.
20 Tokuuye K, Sumi M, Kagami Y *et al*. Small-field radiotherapy in combination with concomitant chemotherapy for locally advanced pancreatic carcinoma. *Radiother Oncol* 2003; **67**: 327–30.
21 Okusaka T, Ishii H, Funakoshi A, Ueno H, Furuse J, Sumii T. A phase I/II study of combination chemotherapy with gemcitabine and 5-fluorouracil for advanced pancreatic cancer. *Jpn J Clin Oncol* 2006; **36**: 557–63.
22 Yamazaki H, Nishiyama K, Koizumi M *et al*. Concurrent chemoradiotherapy for advanced pancreatic cancer: 1000 mg/m(2) gemcitabine can be administered using limited-field radiotherapy. *Strahlenther Onkol* 2007; **183**: 301–6.
23 Isacoff WH, Bendetti JK, Barstis JJ, Jazieh AR, Macdonald JS, Philip PA. Phase II trial of infusional fluorouracil, leucovorin, mitomycin, and dipyridamole in locally advanced unresectable pancreatic adenocarcinoma: *J Clin Oncol* 2007; **25**: 1665–9.
24 Park BB, Park JO, Lee HR *et al*. A phase II trial of gemcitabine plus capecitabine for patients with advanced pancreatic adenocarcinoma. *Cancer Chemother Pharmacol* 2007; **60**: 489–94.
25 Ko AH, Quivey JM, Venook AP *et al*. A phase II study of fixed-dose rate gemcitabine plus low-dose cisplatin followed by consolidative chemoradiation for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2007; **68**: 809–16.
26 Polyzos A, Tsavaris N, Vafiadis I *et al*. Phase II study of gemcitabine plus 5-fluorouracil biologically modulated by folinic acid plus long-acting formulation of octreotide

(LAR) in patients with advanced pancreatic cancer. *J BUON* 2005; **10**: 357–64.
27 Michael A, Hill M, Maraveyas A, Dalgleish A, Lofts F. 13-cis-retinoic acid in combination with gemcitabine in the treatment of locally advanced and metastatic pancreatic cancer – report of a pilot phase II study. *Clin Oncol (R Coll Radiol)* 2007; **19**: 150–3.
28 Furuse J, Ishii H, Okusaka T *et al*. Phase I study of fixed dose rate infusion of gemcitabine in patients with unresectable pancreatic cancer. *Jpn J Clin Oncol* 2005; **35**: 733–8.
29 Joosten JAA, van Muijen GNP, Wobbes T *et al*. TJM *in vivo* destruction of tumor tissue by cryoablation can induce inhibition of secondary tumor growth: an experimental study. *Cryobiology* 2001; **41**: 49–58.
30 Mir LM, Rubinsky B. Treatment of cancer with cryochemotherapy. *Br J Cancer* 2002; **86**: 658.