Original Article

Pilot trial of endoscopic ultrasound-guided interstitial chemoradiation of UICC-T4 pancreatic cancer

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Abstract:
Background and aims: Both interstitial brachytherapy and interstitial chemotherapy are effective in improving local control in patients with local UICC-T4 pancreatic cancer. In this study, we report the results of endoscopic ultrasound (EUS)-guided interstitial chemoradiation (EUS-ICR) in patients with advanced pancreatic cancer, with respect to tumor response, clinical response, safety, and complications.
Patients and methods: A total of 8 patients (3 men, 5 women; median age of 69) with T4 pancreatic adenocarcinoma were the subjects of this study. A mean of 18 radioactive seeds and 36 intratumoral implants for sustained delivery of 5-fluorouracil in each patient were implanted into the tumors using EUS-guided needle puncture. The mean total implanted radioactive activity was 13.68 mCi, the mean total dose of intratumoral 5-fluorouracil was 3.6 g, and the mean volume of implants was 28 cm^3. The conditions of the patients were followed-up by examination and imaging tests every two months. Clinical endpoints included the Karnofsky performance status, pain response, tumor response (assessed by computed tomography and/or EUS), and survival.
Results: During a median follow-up period of 8.3 months, the objective tumor response was classified as "partial" in 1 of 8 patients (with a median duration of partial response of 3 months), "minimal" in 2 patients, and indicative of "stable disease" in 3 of 8 patients. Clinical benefit was shown in 4 of 8 patients, which was mostly due to pain reduction, and lasted for 3.5 months. No local complications or hematologic toxicity occurred.
Conclusions: EUS-ICR had a moderate local anti-tumor effect, showed some clinical benefits in 4 of the 8 patients, and was well tolerated by all the patients in this study.

Keywords:
endoscopic ultrasound; interstitial therapy; pancreatic cancer

Introduction

Interstitial brachytherapy and interstitial chemotherapy are useful methods in improving local control of malignant tumors.[1-8] After radioactive seed placement, the target tissue is exposed to a steady emission of gamma rays, which leads to localized ablation. A method for local sustained release of chemotherapeutic agents by their incorporation into biodegradable polymers has been developed. The implantation of a drug-impregnated polymer at the tumor site allows prolonged local exposure with minimal systemic exposure. This technique is used in clinical practice to control malignancies in the prostate, breast, and brain.[4-8] The recent developments in linear array technology have expanded the clinical utility of endoscopic ultrasound (EUS) by enabling image-guided biopsy and fine-needle therapy.[9-14] In a previous study, we showed that EUS-guided radioactive seed implantation is a safe but mildly effective method for patients with pancreatic cancer. Chemotherapeutic implant placement can also be safely performed in the pancreas under EUS guidance.[3,4,15] We investigated the possibility of implanting both radioactive seeds and chemotherapeutic implants at the same time because there is always a synergy between brachytherapy and chemotherapy. In the present study, we evaluated the results of using EUS-guided interstitial chemoradiation (EUS-ICR) in patients with advanced pancreatic cancer, with respect to tumor response, clinical response, safety, and complications. The study was approved by the Institutional Review Board of China Medical University.

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Patients and methods

Patients

Patients were eligible for enrollment in this study if they were over 18 years of age and had histologically been confirmed with adenocarcinoma of the pancreas that was bidimensionally measurable using computed tomography (CT) or EUS. The tumors, which were at the UICC-T4 stage, involved the celiac or superior mesenteric artery. Written informed consent was obtained before patients were admitted into the study. Patients with unresectable pancreatic cancer should have a Karnofsky performance status (KPS) score of 60 or better and were expected to survive for more than 2 months. Pregnant women and patients with distant metastasis (e.g., liver, lung) were excluded, as were patients who had received prior therapy within 28 days of study enrollment. Laboratory requirements for inclusion included the following: white blood cell count greater than 3×10^9/L, platelet count greater than 100×10^9/L, hematocrit greater than 33%, hemoglobin level greater than 10^5 g/L, prothrombin time within 3 s of control, and serum creatinine less than or equal to 133 mol/L. Abdominal CT and EUS were performed in all patients. EUS-guided fine needle aspiration was performed if there was no prior histological diagnosis of pancreatic adenocarcinoma. Patients with obstructive jaundice had biliary stents placed prior to the study.

EUS-guided interstitial brachytherapy

All eligible patients underwent implantation of iodine-125 seeds and chemotherapeutic implants. The operator wore a lead apron. A linear-array echo-endoscope (EG3830UT; Pentax Precision Instruments, Orangeburg, New York, USA) was inserted into the proximal stomach. EUS was performed to show the conformation of the pancreatic tumor and nearby metastatic lymph nodes. EUS images were captured by computer. The tumor and lymph node volumes were calculated using EUS and CT images, and the 3D diameters of the tumors were determined by a treatment plan system software (Zhiye Medical Software Co., Shenyang, China). The minimum peripheral dose was then set to 100 Gy, and the dose of every seed was entered into the software. The number of seeds required was calculated by the software. The total number of the chemotherapeutic implants was twice as many as the number of seeds. The distribution plan maps were then drawn. The operator determined the distance and direction of every target site from the center of the tumor.

Iodine-125 radioactive seeds (China Institute of Atomic Energy, Beijing, China) can be easily inserted through the channel of a 19-gauge needle (Wilson. Cook Medical Inc., Winston-Salem, North Carolina, USA). When the needle was inserted into the target site under EUS guidance, the stylet was removed. A seed or a chemotherapeutic implant was inserted into the needle. The stylet of the needle was then advanced to push the implant forward. The implant was released from the needle and implanted into the tissue (**Figure 1**). This implantation procedure was repeated, and one radioactive seed and two chemotherapeutic implants were implanted at one site until all the seeds and chemotherapeutic implants were implanted into the target sites as planned.

Evaluation

Patients were monitored for adverse effects and for abnormalities in laboratory indices, including hematological parameters, lipase, amylase, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and liver function indicators. The patients were assessed by physical examination (including weight, Karnofsky performance status, and visual analog scale pain score), and the tumor size was monitored by CT scan or EUS. The response of the tumor to the treatment was evaluated using standard World Health Organization (WHO) criteria. According to WHO criteria for efficacy, objective tumor responses were classified into five grades, namely, 'complete response', 'partial response', 'minor response', 'stable disease' and 'progressive disease'.

Follow-up CT or EUS examinations were performed within 4 weeks after the operation and every 2 months thereafter whenever possible. The size of the implanted area was evaluated by measuring two perpendicular diameters.

The clinical benefit response assessment in patients with locally advanced pancreatic cancer was derived from the measurement of pain levels, functional impairment (assessed by the Karnofsky performance status score), and weight loss. For patients to achieve an overall positive rating for their clinical benefit response, they had to be positive for at least one parameter (pain, performance status, or weight) without being negative for any of the others. This improvement had to last for at least four weeks.

Patient survivals, tumor responses, and clinical benefit responses were recorded. A Kaplan-Meier survival curve was plotted for all the patients.

Results

Patient characteristics

Between April 2009 and April 2011, a total of 8 eligible patients were enrolled from 18 patients with

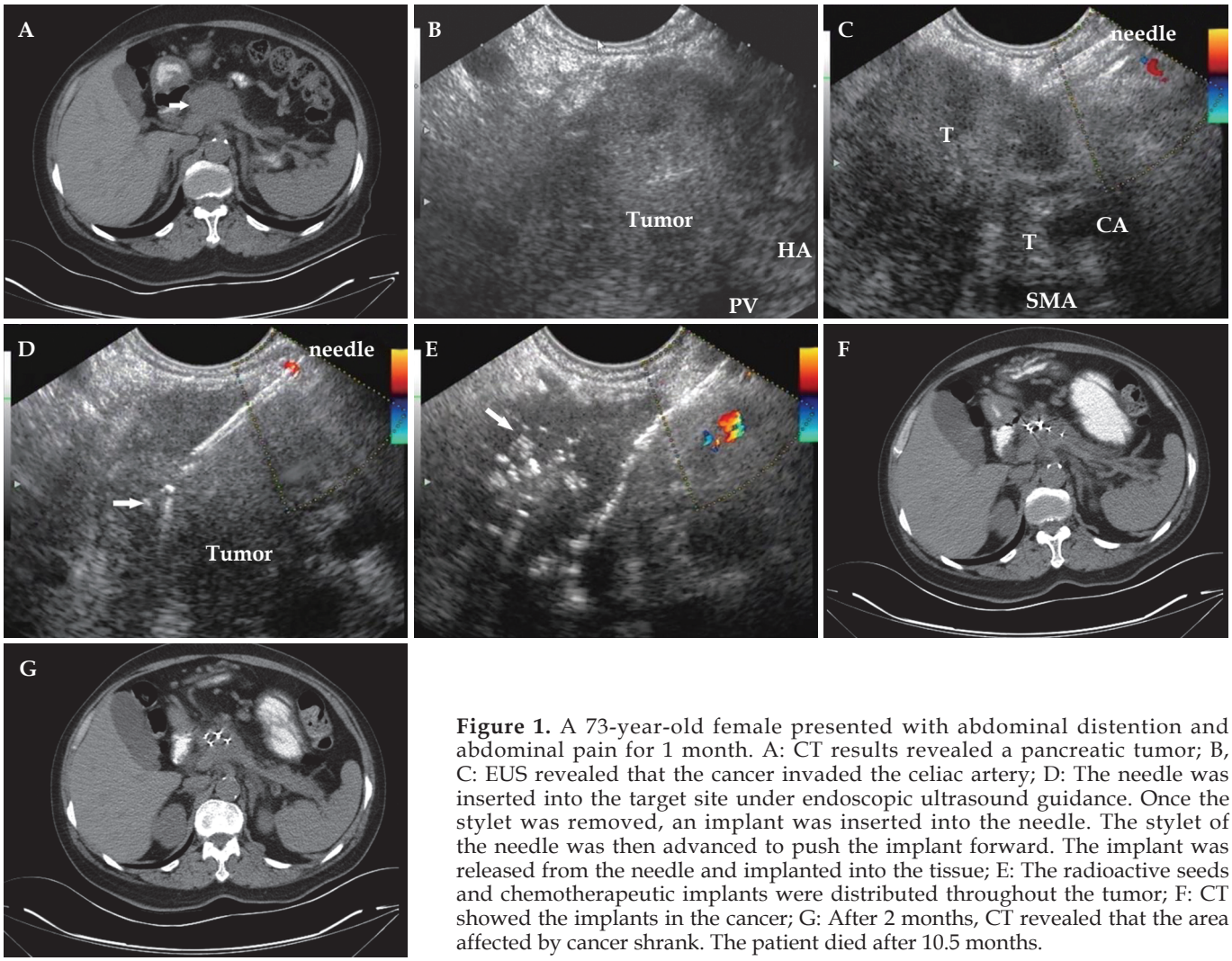

Figure 1. A 73-year-old female presented with abdominal distention and abdominal pain for 1 month. A: CT results revealed a pancreatic tumor; B, C: EUS revealed that the cancer invaded the celiac artery; D: The needle was inserted into the target site under endoscopic ultrasound guidance. Once the stylet was removed, an implant was inserted into the needle. The stylet of the needle was then advanced to push the implant forward. The implant was released from the needle and implanted into the tissue; E: The radioactive seeds and chemotherapeutic implants were distributed throughout the tumor; F: CT showed the implants in the cancer; G: After 2 months, CT revealed that the area affected by cancer shrank. The patient died after 10.5 months.

unresectable, locally advanced pancreatic cancers. The characteristics of these eight patients are summarized in **Table 1**. There were 3 males and 5 females with a median age of 69 years (range of 61 to 84 years). The median Karnofsky performance status score was 70 (range of 60 to 100). Six of the tumors were located in the pancreatic head, and two were in the pancreatic body and tail. Two patients with obstructive jaundice had biliary stents inserted prior to the study.

All patients underwent implantation of iodine-125 seeds. The average time taken to complete the implantation was 35 min. The mean number of passes required per operation was 13 (range of 8 to 16). The average number of seeds implanted was 19 per patient (range of 16 to 28 per patient) with a mean radioactivity of 0.72 mCi per seed and a mean total implanted activity of 13.68 mCi. The mean volume of implants was 28 cm^3 (range of 21 cm^3 to 33 cm^3).

Toxicity and complications

No severe toxic or adverse effects were observed (**Table 2**). No therapy complication occurred.

Response to treatment

The tumor responses demonstrated by CT and EUS are summarized in **Table 3**. Out of the eight patients, there was one partial response, two minor responses, three described as "no change" (i.e., stable disease), and two classified as showing progressive disease. The overall rate for a positive response or having a stable disease was 75% (6/8). The tumor classified as partial response showed a decrease of more than 50% in the largest cross-sectional area of the pancreatic tumor after 2 months. The median duration of the partial responses was 3 months.

Four of the patients experienced clinical benefits as assessed by the primary measures (pain and Karnofsky performance status score) (**Table 4**). Two patients experienced improvement in pain with stabilization of performance status, and two patients showed improvement in both pain and Karnofsky performance status.

The median time to achieve clinical benefit was 3.5 months. The level of CA19-9 and/or CEA decreased in 4 patients 1 month after the therapy (**Table 5**). A return to the normal levels of CEA and CA19-9 was observed among patients who achieved partial responses.

Table 1. Demographic and clinical characteristics of the 8 patients with advanced unresectable pancreatic cancer who were enrolled into the study

Demographic and clinical characteristics	
Age	
Median (range), years	69 (61-84)
<70 years, n	4
70-80 years, n	2
>80 years, n	2
Gender, Male/Female	3/5
Tumor location, n	
Pancreatic head	6
Pancreatic body and tail	2
Karnofsky performance status score	
Median (range)	70 (60-100)
<70	2
70-80	4
>80	2
Mean visual analog scale pain score (range)	4 (1-9)
Prior therapy, n	
None	6
Radiation	0
Chemotherapy	1
Biliary stent placement	2

Survival

The follow-up period ranged from 5.2 to 11.4 months. Survival was measured from the time of EUS-guided interstitial therapy to the time of death. The Kaplan-Meier survival analysis curve is shown in **Figure 2**. The overall median survival was 8.3 months (range 5.2±11.4 months). The 3-, 6-, 9-, and 12-month survival rates were 100%, 87.5%, 37.5%, and 0%, respectively.

Discussion

Local complications of advanced pancreatic carcinoma result in significant morbidity and mortality. Although systemic therapy is needed in finding a cure for pancreatic cancer, an effective locoregional therapy for treating pancreatic primary and/or regional metastases

Table 3. Objective tumor responses in the 8 study patients

Tumor responses	n (%)
Complete response	0 (0)
Partial response	1 (12.5)
Minor response	2 (25)
Stable disease	3 (37.5)
Progressive disease	2 (25)

Table 2. The number of toxic and adverse effects that occurred in the 8 study patients, classified according to the maximum World Health Organization (WHO) grades for laboratory and symptomatic toxicity

Toxic effect	Maximum WHO grade, n			
	I	II	III	IV
Neutropenia	1	0	0	0
Anemia	0	0	0	0
Thrombocytopenia	0	0	0	0
Raised alanine aminotransferase	0	0	0	0
Raised alkaline phosphatase	0	0	0	0
Nausea/vomiting	0	0	0	0
Rash	0	0	0	0
Fever	0	0	0	0
Hair loss	0	0	0	0
Infection	0	0	0	0
Loss of appetite	1	1	0	0
Constipation	1	0	0	0
Diarrhea	1	0	0	0

Table 4. The primary measures of clinical benefit in the four patients who showed a clinical benefit response (CBR)

Patient No.	Karnofsky performance status score		Pain score		Duration of CBR, months
	Baseline	When CBR was achieved	Baseline	When CBR was achieved	
1	70	70	6	1	1.2
3	80	80	5	0	3.2
4	70	90	4	1	4
7	70	80	4	0	3.8

Table 5. Tumor marker responses in the 8 study patients

Patient No.	CA19-9, u/ml		CEA, ng/ml	
	Baseline	1 month later	Baseline	1 month later
1	301	180	33.1	21.3
2	32	35	21.2	23.5
3	162	89	8.9	8.9
4	187	11	17.3	2.5
5	283	320	12.7	13.1
6	106	41	7.8	8.1
7	12	18	11.2	13.5
8	145	155	2.1	3.5

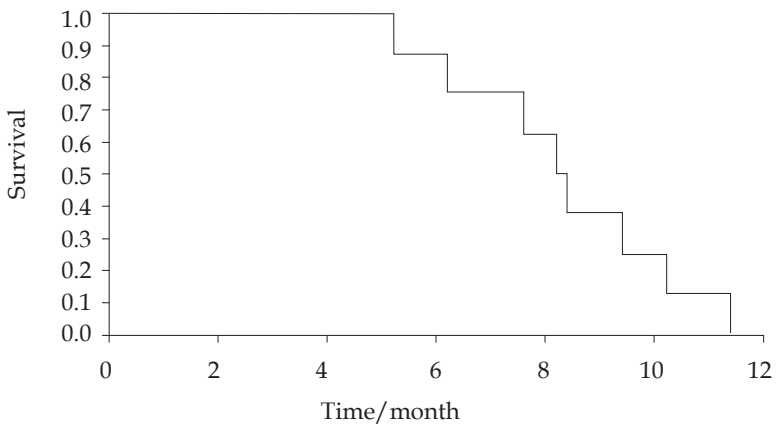

Figure 2. The Kaplan-Meier survival analysis curve for the 8 patients with unresectable pancreatic cancer enrolled in the study

in the liver is beneficial for patients who do not have extensive extrahepatic disease at the time of presentation. Current therapies, however, provide limited benefits for most patients. The high incidence of complications associated with resection of advanced pancreatic cancer and the significant gastrointestinal toxicity of external beam radiation or systemic chemotherapy limit their usefulness.[16] As an effective alternative, two kinds of interstitial therapy, namely, interstitial brachytherapy and interstitial chemotherapy, have been used to treat various cancers, such as prostate, breast, pancreas, and brain cancers.[1-8] If "nuclear weapon" and "chemical weapon" could be implanted in a minimally invasive method, they might replace systemic radiation therapy and chemotherapy, either partially or entirely. Although ultrasound-guided percutaneous implantation of interstitial implants for cancer therapy has been reported, the difficulty and accuracy of percutaneous implantation in pancreatic lesions are under dispute. Over the past few years, there have been reports of pancreatic cancer treatments using EUS-guided gene therapy, EUS-guided immunotherapy, EUS-guided radiofrequency therapy, and EUS-guided photodynamic therapy.[9-14] Previous studies have shown that EUS-guided interstitial brachytherapy has a moderate effect and does not reduce the quality of life.[3] EUS-guided interstitial therapy on canine pancreas has been reported.[4] The present study show that EUS-guided interstitial chemoradiation allow precise and safe implantation of chemotherapeutic implants and may provide a new minimally invasive

method for interstitial chemotherapy of pancreatic cancer.

Both response rates of interstitial brachytherapy and chemotherapy for pancreatic cancer are limited. In many cases, radiation and chemotherapy are combined to treat pancreatic cancer in an attempt to keep the cancer under control as much as possible. This method is also known as chemoradiation because a synergy between external radiation and systematic chemotherapy is possible. The general mechanisms of chemotherapy and radiotherapy interaction involve the induction of DNA damage by both chemotherapy and radiotherapy and inhibition of post-radiation damage repair by chemotherapy.[17] We investigated the possibility of combining chemotherapy and radiotherapy as sensitizers for each other because not all pancreatic cancer cells are sensitive to brachytherapy or chemotherapy. EUS was used in the present study to guide the simultaneous implantation of radioactive seeds and chemotherapeutic implants with a 19-gauge needle to assess the feasibility and safety of EUS-ICR in human pancreatic cancer. Experienced endosonographers encountered no technical difficulties in puncturing and releasing the two kinds of implants into the solid pancreatic tissues.

Other series of intraoperative iodine-125 implantation and systematic chemotherapy have been associated with mortalities ranging from 0% to 16% with a major morbidity of 18%.[18] Complications include fistula formation, gastrointestinal bleeding, ascending cholangitis, and intrahepatic cyst formation. Jin *et al*[19] reported a clinical trial of EUS-guided brachytherapy combined with routine gemcitabine-based 5-fluorouracil chemotherapy for unresectable pancreatic cancer. The results showed pain alleviation and no obvious complications. In the present study, although there was no obvious long-term survival benefit, some patients who achieved clinical benefit showed a decrease in tumor markers. A decrease or return to normal in tumor marker levels may indicate that the cancer has favorably responded to therapy.[20] The result of EUS-ICR was similar to the previous result of EUS-guided interstitial brachytherapy.[3] However, the radioactivities of radioactive seeds in EUS-ICR were reduced when radiotherapy was combined with chemotherapy. This result explained the absence of complications or adverse events in this study.

Although the objective response rate in patients with locally advanced pancreatic cancer was moderate, four patients experienced clinical benefit, and one patient showed a partial tumor response. This study demonstrated the technical feasibility of EUS-ICR in pancreatic tumors. Moreover, the patients showed more tolerance to the technique. The technique did not significantly reduce the quality of life either. Therefore, EUS-ICR may ultimately be used in the palliation of unresectable malignant tumors of the pancreas, which is an important part of systematic management. Other potential clinical uses of this technique include the management of recurrent abdominal lesions or mediastinal lesions. The present study is limited. A multimodality approach, with EUS-interstitial brachytherapy or interstitial chemotherapy combined with other interstitial therapy, such as EUS-guided gene therapy, EUS-guided immunotherapy, EUS-guided radiofrequency therapy, or EUS-guided photodynamic therapy, may be used and should be tested in further studies.

Acknowledgements

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References

1. Takácsi-Nagy Z, Varga J, Poller I, *et al*. Successful treatment of a T1 cancer of the pancreatic head with high dose rate brachytherapy and external radiotherapy. *Hepatogastroenterology* 2002; 49:844-6.
2. Bodner WR, Hilaris BS, Mastoras DA. Radiation therapy in pancreatic cancer: current practice and future trends. *J Clin Gastroenterol* 2000; 30:230-3.
3. Sun S, Xu H, Xin J, *et al*. Endoscopic ultrasound-guided interstitial brachytherapy of unresectable pancreatic cancer: results of a pilot trial. *Endoscopy* 2006; 38:399-403.
4. Sun S, Wang S, Ge N, *et al*. Endoscopic ultrasound-guided interstitial chemotherapy in the pancreas: results in a canine model. *Endoscopy* 2007; 39:530-4.
5. Berrada M, Yang Z, Lehnert S. Tumor treatment by sustained intratumoral release of 5-fluorouracil: effects of drug alone and in combined treatments. *J Radiat Oncol Biol Phys* 2002; 54:1550-7.
6. Fournier C, Hecquet B, Bouffard P, *et al*. Experimental studies and preliminary clinical trial of vinorelbine-loaded polymeric bioresorbable implants for the local treatment of solid tumors. *Cancer Res* 1991; 51:5384-91.
7. Arica B, Calis S, Kas H, *et al*. 5-Fluorouracil encapsulated alginate beads for the treatment of breast cancer. *Int J Pharm* 2002; 242:267-9.
8. Brem H, Piantadosi S, Burger PC, *et al*. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. *Lancet* 1995; 345:1008-12.
9. Soetikno RM, Chang K. Endoscopic ultrasound-guided diagnosis and therapy in pancreatic disease. *Gastrointest Endosc Clin N Am* 1998; 8:237-47.
10. Chang KJ, Nguyen PT, Thompson JA. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. *Cancer* 2000; 88:1325-35.
11. Hecht JR, Bedford R, Abbruzzese JL, *et al*. A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma. *Clin Cancer Res* 2003; 9:555-61.
12. Chan HH, Nishioka NS, Mino M, *et al*. EUS-guided photodynamic therapy of the pancreas: a pilot study. *Gastrointest Endosc* 2004; 59:95-9.
13. Goldberg SN, Mallery S, Gazelle GS, *et al*. EUS-guided radiofrequency ablation in the pancreas: results in a porcine

model. *Gastrointest Endosc* 1999; 50:392-401.
14. Bhutani MS. Endoscopic ultrasonography: new developments and interesting trends. *Endoscopy* 2004; 36:950-6.
15. Sun S, Qingjie L, Qiyong G, *et al*. EUS-guided interstitial brachytherapy of the pancreas: a feasibility study. *Gastrointest Endosc* 2005; 62:775-9.
16. Yeo CJ, Cameron JL, Lillemoe KD, *et al*. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lympha. Denectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. *Ann Surg* 2002; 236:355-68.
17. Seiwert TY, Salama JK, Vokes EE. The concurrent chemoradiation paradigm—general principles. *Nat Clin Pract Oncol* 2007; 4:86-100.
18. Order SE, Siegel JA, Principato R, *et al*. Selective tumor irradiation by infusional brachytherapy in nonresectable pancreatic cancer: a phase I study. *Int J Radiat Oncol Biol Phys* 1996; 36:1117-26.
19. Jin Z, Du Y, Li Z, *et al*. Endoscopic ultrasonography-guided interstitial implantation of iodine 125-seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study. *Endoscopy* 2008; 40:314-20.
20. Szajda SD, Waszkiewicz N, Chojnowska S, *et al*. Carbohydrate markers of pancreatic cancer. *Biochem Soc Trans* 2011; 39: 340-3.