Cryobiology 65 (2012) 301–307

Contents lists available at SciVerse ScienceDirect

Cryobiology

journal homepage: www.elsevier.com/locate/ycryo

Percutaneous ultrasonography and computed tomography guided pancreatic cryoablation: Feasibility and safety assessment ☆

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ARTICLE INFO

Article history:
Received 2 August 2012
Accepted 22 August 2012
Available online 31 August 2012

Keywords:
Pancreatic cancer
Cryoablation
Percutaneous

ABSTRACT

Objective: To assess the safety and feasibility of percutaneous cryoablation on pancreatic cancer via ultrasonography (US) and computed tomography (CT) guidance.
Materials and methods: This retrospective review was approved by the institutional review board and of informed consent. Thirty-two patients (18 men and 14 women; median age 62; age range, 30–77 years) with pancreatic cancer (stage II/III/IV, 3/11/18) treated with percutaneous US and CT guided cryoablations between February 2009 and February 2010 were eligible for this review. Thirteen tumors in pancreatic head and 19 in pancreatic body and/or tail measuring 2–11 cm (mean, 5.2 cm ± 8 [standard deviation]) were ablated with 49 procedures in total. Feasibility was analyzed by enhanced CT 1–3 months post procedure and safety was assessed by clinical signs, symptoms and laboratory results.
Results: Neither procedural death nor serious complications occurred. Fifteen tumors (46.9%) smaller than 5 cm were successfully ablated by one session of cryoablation. Twenty-seven patients experienced a $\geqslant$50% reduction in pain score, 22 experienced a 50% decrease in analgesic consumption and 16 experienced a $\geqslant$20 increase in Karnofsky Performance Status (KPS) Score. Partial response (PR) and stable disease (SD) turned up in 9 and 21 patients, respectively, lesions in whom were identified controlled by none enhancement on enhanced CT. Mean and median survival was 15.9 and 12.6 months, respectively. The 6-, 12- and 24-month survival rates were 82.8%, 54.7% and 27.3%, respectively.
Conclusion: US and CT guided percutaneous cryoablation is a safe and promising local treatment for pancreatic cancer.

Introduction

Pancreatic cancer is one of the most lethal forms of digestive system cancer. In spite of recent advances in surgery, chemotherapy and radiotherapy, there has been little improvement in the survival [1], and pancreatic cancer continues to be the fourth leading cause of cancer mortality in both men and women. One year and five year survival rates are estimated at 24% and 4.3%, respectively [17]. Cryotherapy, which offers both instant and delayed destruction of cellular ultrastructure [2,9], has emerged as an alternative technique for the treatment of various tumors, and has been shown to prolong survival in patients with pancreatic cancer [13]. Recently, the development of thin probes used with argon–helium systems has led to the development of minimally invasive cryoablation techniques that can be performed percutaneously under cross-sectional imaging guidance. Percutaneous cryoablation has been shown to be safe and effective for the treatment of tumors of the kidney, liver, prostate, as well as uterine fibroids [6,14–16]. However, this approach has not been used in the treatment of pancreatic cancer, as a result of the particular anatomical location of the pancreas, which increases the difficulty of the percutaneous approach.

The purpose of this study was to introduce percutaneous cryoablation of pancreatic cancer using ultrasonography (US) and double row helical computed tomography (CT) guidance, and to determine its safety and feasibility.

☆ *Statement of funding*: Funding support for this programme of research was provided by the Guangdong Province medical research fund (No. WSTJJ2009040144010619660215475 6) "Comprehensive research of pancreatic cancer".

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http://dx.doi.org/10.1016/j.cryobiol.2012.08.004

Materials and methods

Patient selection

Patients were enrolled unblinded and independent with signing a study-specific consent form, and the study was approved by the institutional review board.

Eligibility for the study required a histological or cytological confirmation of exocrine pancreatic cancer. All patients were pathological or cytological diagnosed prior to the procedure. Thirty-two patients (18 men and 14 women; median age 62; age range, 30–77 years) with unresectable pancreatic cancer or resectable pancreatic cancer which are not amenable to surgery, staged from II to IV [12], treated with percutaneous US and CT guided cryoablations between February 2009 and February 2010 were analyzed. Patients included were required a Karnofsky Performance Status (KPS) score greater than 60, a blood leukocyte $>3 \times 10^9$/L, a platelet count $>5 \times 10^{10}$/L, a hemoglobin concentration >100 g/L, an absolute granulocyte count of 1500 cells/L, a serum albumin >30 g/L, a calculated creatinine clearance greater than 50/ml/min, a glutamic–oxaloacetic transaminase level no more than three times the upper limit of normal, and a serum bilirubin level less than 2.0 mg/dL [8]. Exclusion criteria are listed in Table 1. Thirteen tumors in pancreatic head and 19 in pancreatic body and/or tail measuring 2–11 cm (mean, 5.2 cm ± 8 [standard deviation]) were ablated with 49 procedures in total (Table 2). All patients received routine chemotherapy with GP (gemcitabine Gemzar 1000 mg/m^2, orally weekly, plus cisplatin 35 mg/m^2 for 3 days at the third week every 4 weeks; 2–4 courses were completed on each patients) as well.

Cryoablation procedure

Procedures were performed during localized anesthesia, then the patients were positioned supine (for transabdominal cryoablation) or prone (for transdorsal percutaneous cryoablation) on the CT docking table. US by color ultrasound device (ALOKA SSD-5500SA; Aloka, Japan) and CT images by double row helical CT (Somatom Emotion Duo; Siemens, Germany) were obtained before cryoablation in order to design the number, angle and depth of probes. The transabdominal approach was performed for tumors in the head, body or tail of the pancreas (Fig. 1), while the transdorsal approach was conducted for tumors in the pancreatic body or tail (Fig. 2) [18,19]. For the transabdominal approach, three optional pathways were considered, including transgastric, transhepatic, and between the stomach and the transverse colon (Fig. 3a and b). Gastrointestinal and pancreatic juice secretion inhibitors and gastric tube (preserved till 24 h after procedure) were delivered preoperatively. If necessary, abdominal cavity drainage was adopted when pronounced bleeding occurred. The transdorsal approach was performed as inserting cryoprobes between T12 and L1, 4–7 cm away from the spine on the left side (Fig. 3c and d). Approaching pathway was determined on principle of puncturing directly to tumor if possible, through liver as the second choice, and through stomach when you have to. Probes (CRYO-42; Endocare, US), of 1.7 mm in diameter, were advanced through the center of the mass until the tip was positioned along 0.5 cm to its distal inner border. To cover the tumor in all dimensions, 1–4 probes were used for masses that were 2–5 cm in diameter, and 5–8 probes for larger tumors [4,11]. Two or more sessions were performed for residual tumors in case of incomplete necrosis or large tumor. All metastatic tumors whose diameter was more than 3 cm were frozen simultaneously.

Cryosurgery system and guidance

The Cryocare surgical system (CRYO-20; Endocare, Inc., USA) with argon–helium was activated for 5–10 min freezing by argon of 100% output power, achieving a temperature of −160 °C in the center of ice ball within 2 min. Continuous US and CT imaging every 1–3 min were performed to monitor ice ball formation and tumor coverage. The ice ball was depicted as hypoecho and hypodense on US and CT, respectively. The ice ball size was increased until it completely enveloped the mass and the edge extended 5 mm beyond the mass, then rewarm at room temperature naturally, two cycles in all. The probes were removed after the second thaw cycle and elastic bandage with woven gauze was packed to facilitate hemostasis. All procedures were performed by three surgeons (L.Z.N., L.Z. and B.H.W) with 4–8 years of experience in image-guided tumor ablation.

Brachytherapy

Brachytherapy of ^{125}I seed (length 4.5 mm, diameter 0.8 mm, thickness 0.05 mm, activity of single seed 0.7 mCi, half life period 1–6 mCi) (FTTPS; Beijing Fei Tian Zhao Ye Scientific Ltd., Beijing) which was planned by 3D treatment planning system was conducted for the peripheral of frozen tumors in case the tumor adjacent to vital organs, such as stomach, duodenum, pancreatic duct or bile duct. The matched peripheral dose was 120 Gy.

Post procedure care

Patients was observed in the intensive care unit for at least 6 h and fasted for 24 h after the procedure. During this time, anti-infective therapy with cephalosporin, metronidazole or tinidazole, antacid treatment with omeprazole, inhibition of pancreatic juice secretion with octreotide acetate, and fluid replacement, were undertaken. For transhepatic pathway, oppressing hemostasis and bellyband were used after procedure.

Effects valuation

Imaging

Imaging evaluation was performed via contrast medium-enhanced CT 1–2 day(s) prior, and every month after cryoablation. Collimation of 1.5–2.5 mm was performed for demonstration on axial or reformatted sections. Intraprocedural CT images of ice balls were compared with post procedural estimates of cryonecrosis, which was defined as new (as compared with findings on pretreatment CT images) areas of decreased enhancement. All CT images were assessed by the same imaging specialist (Z.Z.Y.).

Clinical benefit response

A clinical response evaluation according to response evaluation criteria in solid tumor [3] was conducted 3 months after cryoablation. Clinical benefit response [7], including pain scores and analgesic consumption, was assessed before and 1 month after the procedure. The KPS score at discharge was assessed and compared with those observed on admission.

Follow up

Until December 2011, the follow-up of patients ended and all the 32 patients have died. The mean and median survival times were summed up. Meanwhile, the overall 6-, 12- and 24-month survival rates were obtained (Table 2).

Complications

Laboratory evaluation included serum amylase levels, blood glucose, white blood cell count were obtained at 6, 12, and 24 h and 1 week after the procedure, for the assessment of therapy-related complications.

Comparison of KPS scores pre- and post-cryoablation were performed using paired-sample *t*-tests (SPSS Statistics 17.0, SPSS Inc.,

Table 1
Exclusion criteria.

Evidence of bile ductal, pancreatic ductal or gastrointestinal obstuction on CT, MRI or endoscopy
Patients with high celiac pressure due to biliary tract or gastrointestinal obstuction, ascitis or aerenterectasia
Ambiguous or unclear appearance of structure of pancreas and intestine on imaging
Patients discovered to have _ 1_ proteinuria at baseline were required to have a 24-h urine protein _ 1000 mg
Patients with too thick abdominal and lumbar adipose

Abbreviation: CT, computed tomography; MRI, magnetic resonance imaging.

Chicago, IL). A P value of 0.05 or less was considered statistically significant.

Results

Imaging

The ice balls were seen as sharply marginated during the procedure, hypoecho on US (Figs. 1c and 2c) and ellipsoid regions of low density on CT (Figs. 1f and 2f). Fifteen tumors smaller than 5 cm were completely ablated with a single session of procedure (Fig. 5f) and others were controlled by the second session of cryoablation combined with or without brachytherapy. Residual enhanced nodules at the rim of the lesions were detected in 13 lesions 1–3 month(s) after the first ablative session, 11 of which did not show progression in situ at follow-up (Fig. 4c), while the remainder were controlled with brachytherapy.

Clinical benefit response

Partial response, stable disease and progressive disease were achieved in 9, 21 and 2 patients, respectively. Clinical benefit response was 84.4%, with 27 and 22 patients experiencing $\geqslant$50% reduction in pain scores and analgesic consumption after cryoablation, respectively. Sixteen patients experienced a $\geqslant$20 increasing in KPS score. Rate of clinical benefit response showed no significantly differentiation between large tumors (>5 cm) and small ones (>2 cm, $\leqslant$5 cm), on account of 13 and 11 patients with large tumors experienced $\geqslant$50% reduction in pain scores and analgesic consumption, respectively, and eight patients with large tumors experienced a $\geqslant$20 increasing in KPS score. CA 199, CA 242 and CA 125 were 31427.9 ± 10020.3, 117.2 ± 13.1 and 1368.6 ± 346.1 in patients prior procedure, respectively. Compared to that, a significant decline were manifested in CA 242 post procedure (88.6 ± 16.4 vs. 117.2 ± 13.1, $P < 0.05$), and a trend of decreasing were showed in CA 199 and CA 125 as well. The median hospital stay after cryosurgery was 8 days (range, 4–11 days).

Survival

The mean and median survival times were 15.9 months and 12.6 months, respectively. The overall 6-, 12- and 24-month survival rates were 82.8%, 54.7% and 27.3%, respectively. The maximum survival time was 32 months in a 55-year-old man with cancer of the pancreatic head and liver metastasis.

Complications

All percutaneous cryoablations of pancreatic cancer by US and CT monitoring were performed successfully without any serious complications, such as pancreatic fistula, bile leakage, and intestinal fistula. Serum amylase increased (upper limitation: 220 U/L) in three patients on the first day after the procedure, unaccompanied by acites or leukocytosis, and returned to normal levels the following day, after receiving omeprazole, octreotide acetate and symptomatic treatment. One of the seven patients with diabetes experienced a rise in fasting blood glucose levels to 25 mmol/L at the first day post cryoablation, which was well controlled with an insulin injection. A mild decrease in the platelet count developed after two cryoablative procedures in one patient (7.8×10^{10}/L and 8.1×10^{10}/L), which returned to normal within 10–13 days without any treatment. Abdominal distension and nausea occurred in one patient on the first day post cryoablation, and disappeared automatically the following day. Post procedural US did not reveal any acites or abdominal bleeding, which was believed to be due to the transient slowing down of gastric motility by

Table 2
Patients' characteristics.

Characteristics	*N*	Survival (%)		*P*-value
		6-months	12-months	
Age (years)				
Median	62 (range, 30–77)			
<62	15	12/14 (85.7)	7/14 (50.0)	0.857
$\geqslant$62	17	12/15 (80.0)	6/11 (63.6)	
Sex				
Male	18	13/15 (86.7)	8/13 (64.6)	0.272
Female	14	11/14 (78.6)	5/12 (44.2)	
Pancreas tumor location				
Head of pancreas	13	10/12 (83.3)	6/10 (64.3)	0.133
Body and/or tail of pancreas	19	14/17 (82.4)	7/15 (48.4)	
Max diameter of tumor (cm)				
Mean (mean ± SE)	5.2 ± 0.3 (range, 2.0–11.0)			
>2, $\leqslant$5	16	13/15 (86.7)	6/11 (60.5)	0.671
>5	16	11/14 (78.6)	7/14 (50.0)	
Stage				
II	3	2/2 (100.0)	1/1 (100.0)	
III	11	8/10 (80.0)	4/9 (46.7)	0.973
IV	18	14/17 (82.4)	8/15 (56.1)	

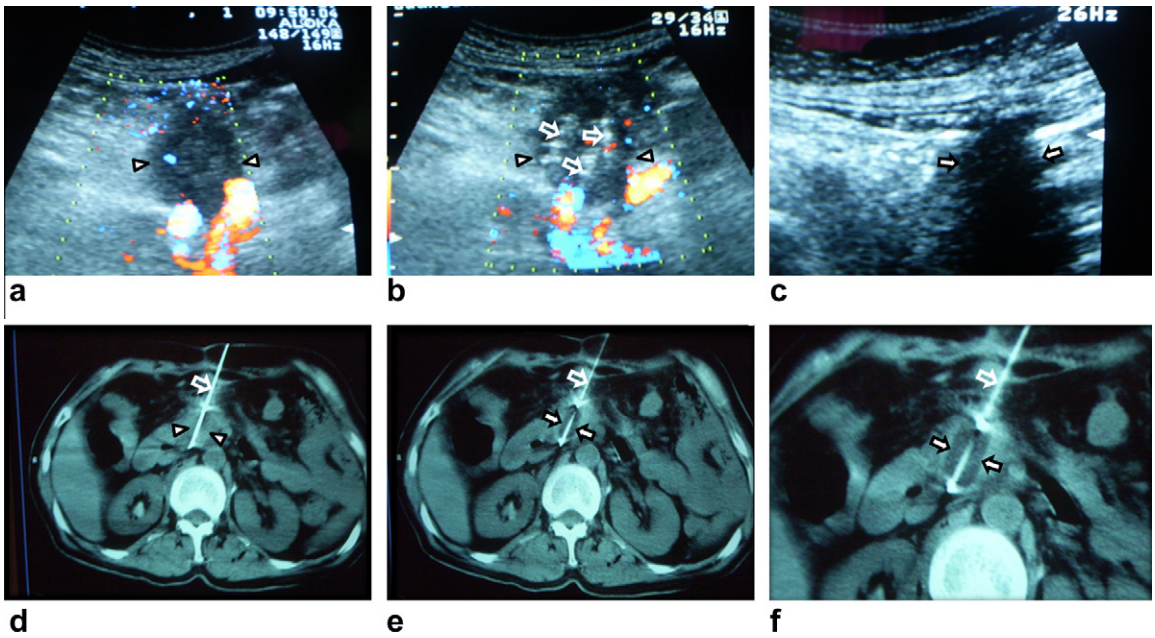

Fig. 1. Transabdominal percutaneous cryoablation guided and monitored by US and CT in a 59-year-old patient with tumor in the head of the pancreas (adenocarcinoma, 3.5 × 4.0 cm, stage IV). Under the guidance of US (a) the position of tumor (arrow head) and its adjacent vessels are depicted; (b) three cryoprobes (hollow arrow) were advanced through the stomach to the distal edge of the tumor and initiated freeze–thaw cycles; (c) ice ball (arrow) formation in the tumor. Under the guidance of CT, after the probe had been stuck into the tumor (d), ice ball area turned from small (e) to big (f).

freezing irritation of ice ball. One patient complained of a poor appetite after the cryosurgery and was found to have acites by US, and improved the following day without any treatment. Three further patients were found to have mild acites, one of whom developed a fever of 37.6 °C, a small pleural effusion, and a mild increase in white blood cells and neutrophil granulocytes. Fourteen hepatic metastases and four lung metastases were also cryoablated percutaneously without any serious complications.

Discussion

It has been a long time to treat cancer through freezing method, but only argon–helium knife technology makes it possible to freeze deep body tumors. Along with the development of imaging technology, we brought out several approaches of percutaneous cryosurgery. According to the characteristics of rapid healing of liver and stomach, we had invented three transabdominal approaches, and

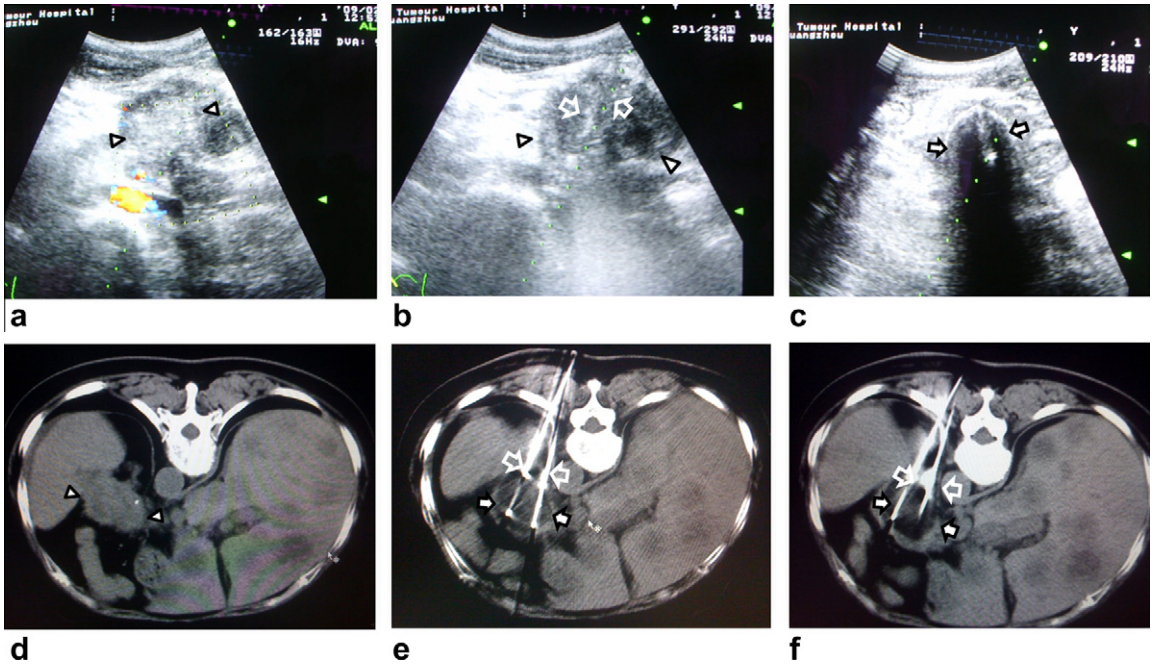

Fig. 2. Transdorsal percutaneous cryoablation guided and monitored by US and CT in a patient with cancer in the body and tail of pancreas (cystadenoma, 4.5 × 3.2 × 2.1 cm, stage IV). Under the guidance of US (a) the position of tumor (arrow head) and its adjacent vessels are depicted; (b) two cryoprobe (hollow arrow) was advanced between T12 and L1, 5 cm away from the spine on the left side to the distal inner border of the mass; (c) ice ball (arrow) formation in the tumor. Under the guidance of CT, after the probe had been stuck into the tumor (d), real-time plain CT scan shows ice-ball enlargement (e) and eventually covered more than 90% of the tumor (f).

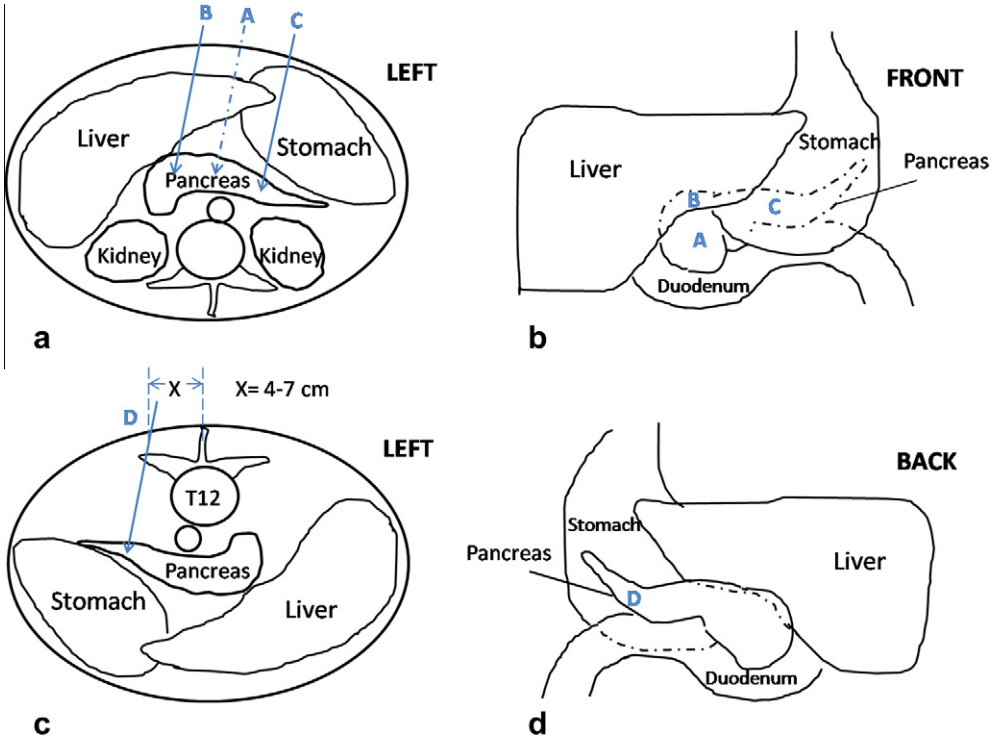

Fig. 3. Process illustration of percutaneous approach to pancreas. (a) Illustration of transabdominal percutaneous approach on abdominal cross section, including advancing between stomach and transverse colon (pathway A), transhepatic (pathway B) and transgastric (pathway C) pathways. (b) Front coronal plan of three transabdominal percutaneous pathways on pancreas. (c) Abdominal cross section of transdorsal percutaneous approach by inserting cryoprobe between T12 and L1, 4–7 cm away from the spine on the left side. (d) Back coronal plan of transdorsal percutaneous pathways on pancreas body or tail.

made it possible for percutaneous cryosurgery of pancreatic cancers, especially cancer in pancreatic head; as for cryosurgery of cancers on pancreatic body or tail, transdorsal approaches were invented and commonly used. In these treatments, the parts which are difficult to repair (e.g. transverse colon and main pancreatic duct) should be avoid for direct puncture by cryoprobes. Because of the flushing action of blood flow, 0.5 cm distance from cryoprobe is safe for protection of great blood vessels. After three years of exploration, these approaches appear feasible and safe in this study.

US is an optimal real-time guidance technique for cryoablation. Kovach et al. performed nine intraoperative US guided cryosurgeries on patients with pancreatic cancer, neither pancreatitis nor pancreatic fistulae were found during and after cryosurgery [10]. By US scanning, the margins of the tumor and the adjacent arteries are detected, allowing the visualization of its relationship with the adjacent organs and arteries. Nonetheless, posterior acoustic shadowing limits visualization with US. CT, a widespread technique in cryoablated tumors monitoring that allows morphologic imaging of various organs, can be used to complement US for the visualization of the entire ice ball (Fig. 5c and e). Compatible continuous-monitoring by CT scanning with a high spatial resolution can provide an assurance of accurate cryoprobe advancing and positioning. For the treatment of pancreatic cancer, percutaneous cryoablation has three advantages over the US and CT guided approach: firstly, it supplies real time and accurate monitoring of ice ball formation, vascular visualization, achieves an optimal design for cryoprobe positioning and varying during procedure; secondly, it protects adjacent vascular and organs during the process of cryoprobe positioning and freezing via a better combined visualization of US and CT imaging; thirdly, it associates with an easier procedure of shorter duration (approximately 1 h) and facilitates, improves recovery with a shorter length of hospital stay.

An analysis of eleven large serial studies on pancreatic resection was performed in 2002, showing an incidence of common

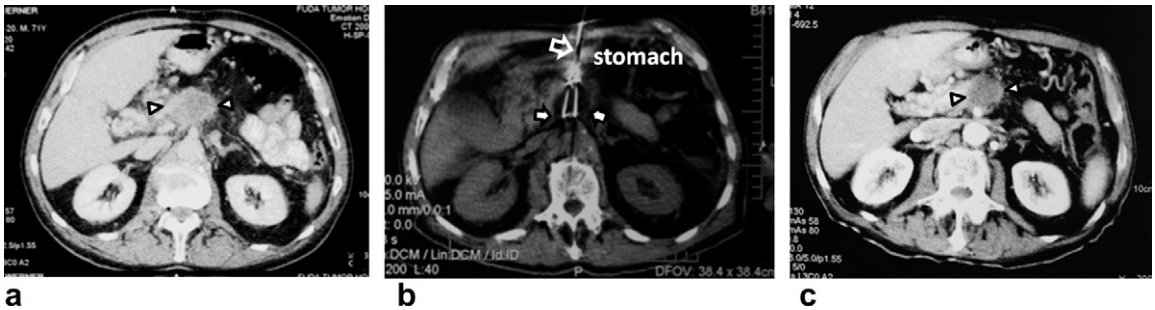

Fig. 4. CT imaging comparison of carcinoma before, during and 1.5 months post cryoablation. The patient was a 71 year old male, with adenocarcinoma of the pancreatic body and liver metastasis and has survived for 20 months. (a) The tumor was 4.5 × 4.6 × 3.8 cm, stage IV (arrow head); (b) cryoprobes were inserted through the stomach approaching the mass (hollow arrow), the cryoablative procedure was performed with complete coverage of pancreatic tumor by ice ball (arrow); (c) shrinkage and non-enhancement of the mass central (arrow head) 1.5 months post cryoablation. Comparatively enhancement at the lesion rim was proved to be stable in the follow up.

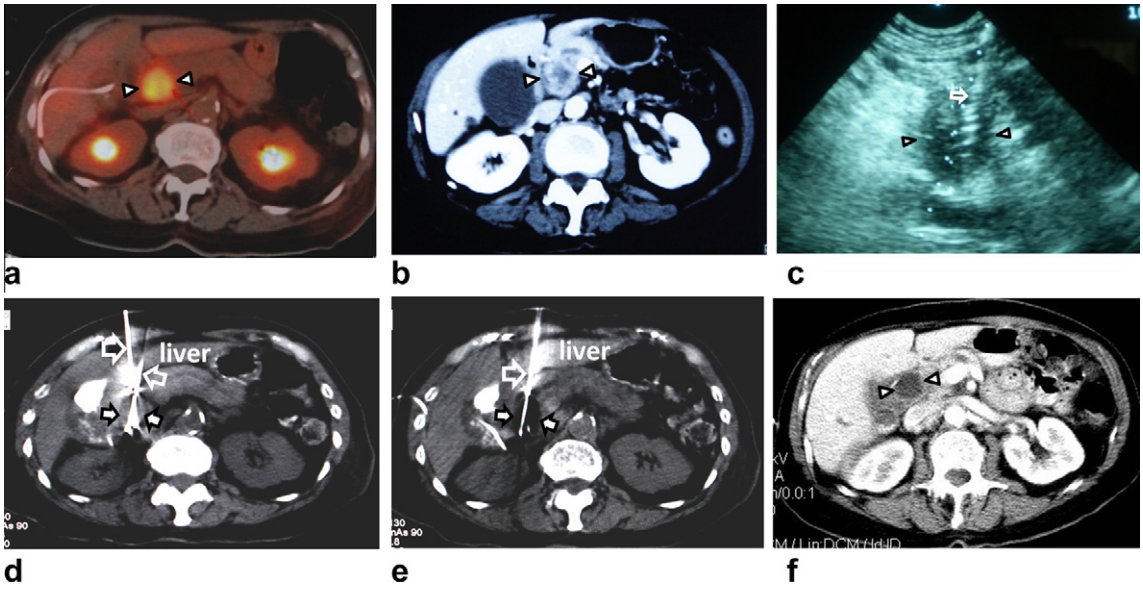

Fig. 5. Therapeutic data of a 55-year-old female patient who suffered from adenocarcinoma on pancreatic head and has survived for 32 months. The tumor (arrow head) was 3.7 × 3.6 × 3.1 cm, stage IIa, detected by PET-CT (a) or CT (b). The procedure was performed with a cryoprobe (hollow arrow) approaching through the left liver lobe (c) and the center of the mass to the inner border of the mass (d), and two freeze–thaw cycles gradually enlarged the ice ball (arrow) until it completely covered the mass (e). A contrast enhanced CT image 3 months after cryoablation (f) depicts non-enhancement in the site of the tumor (arrow head).

complications of 10.4% for fistula, 9.9% for delayed gastric emptying, 4.8% for bleeding, 4.8% for wound infection and 3.8% for intra-abdominal abscess [5]. The application of percutaneous cryoablation in this study, as well as the intraoperative cryoablation [10,13,18], was shown to be safe for the treatment of pancreatic cancer. None of those patients died as a result of cryoablation or experienced severe complications (e.g. pancreatic fistula, bile leakage, bleeding), despite the fact 31 patients with celiac artery, mesenteric artery and/or regional lymph nodes metastases.

As been demonstrated, 15 tumors less than 5 cm were successfully controlled by cryoablation with one session of procedure, tumor in mediate size [4] could be expected to be percutaneously completely ablated, and a prolonging life base on that was possible (Figs. 4 and 5). On the contrast, six tumors were under controlled until brachytherapy administered. Whether brachytherapy is better than cryoablation for local control, or is more useful as a supplement to cryoablation for the treatment of pancreatic cancer, requires further studies. However, percutaneous cryoablation is considerable therapy for treatment of tumor less than 5 cm, or contributional therapy for the comprehensive treatment for large pancreatic tumor.

In conclusion, the percutaneous approach appears safe in cryoablation for the treatment of PC. Percutaneous cryoablation via US and CT manifested advantages in less therapy-related complications, accurate ablation and prolong survival in the treatment of pancreatic cancer, which provides a potentially alternative therapy for independent or comprehensive treatment of pancreatic cancer.

Disclosures of potential conflicts of interest

All authors have no potential conflicts of interest to disclose.

Acknowledgments

We thank Dr. Jibing Chen, Fuda Hospital, Guangzhou 510000 for writing assistance.

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