Feasibility and safety of EUS-guided cryothermal ablation in patients with locally advanced pancreatic cancer

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Background: New therapies are needed for pancreatic cancer.

Objective: To determine the feasibility and safety of a new endoscopic treatment. Secondary endpoints were to determine effects on tumor growth measured with CT scan and to find the overall survival.

Design: A cohort study of patients with local progression of advanced pancreatic adenocarcinoma after neoadjuvant therapy. The cryotherm probe (CTP), a flexible bipolar device that combines radiofrequency with cryogenic cooling, was used under EUS guidance.

Setting: San Raffaele Hospital, Milan, Italy; University Medical Center, Hamburg-Eppendorf, Germany.

Patients: A total of 22 patients (male/female 11/11; mean age 61.9 years) were enrolled from September 2009 to May 2011.

Intervention: Radiofrequency heating: 18 W; pressure for cooling: 650 psi (Pounds per Square Inch); application time: depending on tumor size.

Main Outcome Measurements: Feasibility was evaluated during the procedure. A clinical and radiologic follow-up was planned.

Results: The CTP was successfully applied in 16 patients (72.8%); in 6 it was not possible because of stiffness of the GI wall and of the tumor. Amylase arose in 3 of 16 patients; none had clinical signs of pancreatitis. Late complications arose in 4 cases: 3 were mostly related to tumor progression. Median postablation survival time was 6 months. A CT scan was performed in all patients, but only in 6 of 16 was it possible to clearly define the tumor margins after ablation. In these patients, the tumor appeared smaller compared with the initial mass ($P = .07$).

Limitations: Small sample of patients, difficulty of objectifying the size of the ablated zone by CT scan.

Conclusion: EUS-guided CTP ablation is feasible and safe. Further investigations are needed to demonstrate progression-free survival and local control. (Gastrointest Endosc 2012;76:1142-51.)

Pancreatic cancer is one of the major causes of cancer death in Western countries, with a dismal 5-year survival rate of less than 5%. About 40% of patients have no metastases on diagnosis, but in half of them tumor resection is not feasible because of vascular invasion, poor general health, or lack of surgical skills.[1] The standard treatment for these patients is chemotherapy followed by chemoradiation therapy, giving a median survival of 8 to 12 months.[2]

Abbreviations: CTP, cryotherm probe; RF, radiofrequency; RFA, radiofrequency ablation.

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New therapeutic options for unresectable pancreatic cancer include radiofrequency (RF) and cryotherapy. These have been successful in solid cancers,[3] although few studies have examined radiofrequency ablation (RFA) in pancreatic cancer because of the risk of thermal injury to important structures such as the bile duct, the duodenum, and the vessels close to the pancreas.[4] Recently, a monopolar RF probe was used during laparotomy for locally advanced pancreatic cancer, demonstrating the feasibility and safety of this technique.[5]

EUS is currently the best procedure for real-time imaging of the pancreas, and it permits targeting lesions easily wherever they are located in the pancreas. An EUS-guided treatment could overcome several problems related to the laparotomy and/or laparoscopic or transcutaneous approach.

The cryotherm probe (CTP) (ERBE Elektromedizin GmbH, Tübingen, Germany) is a new, flexible device that combines bipolar RFA with cryogenic cooling. CTP characteristics have been extensively explained elsewhere.[6] In a previous study, the CTP was applied in an animal model (19 pigs) with the aim of demonstrating the feasibility of the transluminal EUS-guided RF-cryotherm-ablation and to evaluate the efficacy of the device in creating an area of tumor devitalization.

The treatment was feasible, and the probe was easily seen in all the applications. In order to evaluate the efficacy of the CTP, we assessed the size of the ablated tissue in relation to the duration of application because the power input (16 W) and the carbon dioxide cooling (650 psi-pounds per square inch) had been standardized and fixed in ex vivo experiments. Application times varied between 120 and 900 seconds. The reason for these time settings was that the ex vivo studies did not show larger ablation zones with ablation durations longer than 900 seconds.

The relationship between the size of the ablated area after necroscopy and the application time measured by means of robust regression analysis showed a fitted fixed ratio of 2.3 ($P < .0001$) in pigs that underwent euthanasia after 1 week and 0.2 ($P = .01$) after 2 weeks. These results reflect a linear correlation between application time and size of ablated tissue. The treatment for more than 900 seconds induced necrotic pancreatitis more often in healthy pancreas.[6,7] In a second ex vivo study, the CTP was tested under ultrasonographic guidance on human resected pancreatic carcinoma specimens[8] to study the ablative effect of CTP in neoplastic tissue. A modified Fibonacci dose escalation was used as a valid method to find the best application time. Study results confirmed the linear correlation between application time and size of the ablated tissue.

Based on the results of the two preliminary studies, we assumed that the EUS-guided CTP application could be feasible and safe in patients with pancreatic cancer. Here we report the results of the first in vivo study in patients with locally advanced and unresectable pancreatic cancer treated with the CTP under EUS guidance.

Take-home Message

- EUS-guided cryotherm ablation is a feasible, safe, and minimally invasive method for treating pancreatic cancer. It could be used to treat locally advanced pancreatic cancer in a multidisciplinary approach.

PATIENTS AND METHODS

Study design

This was a prospective case study in a series of consecutive patients with locally advanced pancreatic adenocarcinoma (confirmed by EUS-guided FNA and CT scan) with disease progression after standard chemotherapy ± radiotherapy. The ethics committees of the two institutions approved the study before it was started (first compassionate pilot study approved in August 2009; protocol CTP2010 approved on May 25, 2010, at San Raffaele Hospital, Milan, Italy, and protocol PV3241 approved on September 22, 2010, by the Ethik-Kommission der Ärztekammer Hamburg, Germany). Each patient gave informed consent for all procedures.

Inclusion and exclusion criteria

The inclusion and exclusion criteria are listed in Table 1. Only patients with pathologically proven, locally advanced, unresectable pancreatic adenocarcinoma were selected. The criteria for unresectability after neoadjuvant therapy were those set out in the guidelines used by our pancreatic surgery team and approved by the institutional review boards of the two institutions. Briefly, these were as follows: encasement or thrombosis of one or more large vessels surrounding the pancreas (celiac axis, portal vein, and/or superior mesenteric artery and/or vein, and/or hepatic artery, except the splenic vessels); infiltration of the vessel wall or contact >180° for more than 2 cm length, with initial stricture of the vessel or alteration of the Doppler signal. Each patient underwent thoracic and abdominal CT with contrast medium to check resectability and detect the absence of distant metastasis.

Primary endpoints

The primary endpoint was to assess the feasibility and safety of EUS-guided CTP treatment in patients with locally advanced pancreatic cancer.

Feasibility. The procedure was defined as feasible if the placement of the probe inside the tumor was successful and not feasible if it was not possible to place the probe inside the lesion because of difficulties such as hardness of the tumor, stiffness of the GI wall, or interposition of vessels.

TABLE 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age >18 y	Severe alteration of hemostasis
Gave consent	Could not give consent
Platelet count >100,000/mm^3	Pregnancy
International normalized ratio <1.5	Infection and/or severe leukopenia
Unresectable locally advanced pancreatic adenocarcinoma already treated with neoadjuvant chemotherapy	Acute pancreatitis Distant metastasis

Safety. According to our experimental and clinical experience, we expected the following potential major complications: necrotizing acute pancreatitis, pseudocysts, pancreatic fistulas, burns of the gastric or intestinal wall, adhesions, pain, bleeding. Therefore, laboratory and radiologic follow-up were used to detect these possible complications.

Early complications. Complications observed during the treatment or in the first week after the ablation were defined as early complications. In order to detect these we stated in the protocol that we would follow up all treated patients by close surveillance in an inpatient setting for 5 days, regardless of their clinical conditions, by evaluating the clinical status, blood tests at 6, 24, and 48 hours (hemochrome with white blood cell count, amylase, lipase, blood glucose, CRP_C reactive protein_), and contrast-enhanced multidetector CT scan, scheduled at 48 hours after CTP treatment.

Late complications. Any complications arising at the site of the primary tumor within 3 months from CTP were considered as late complications potentially related to the procedure.

Secondary endpoints

Secondary endpoints were the effects of the procedure on primary tumor growth and the overall survival. As radiologic follow-up, two CT scans were performed within the next 3 months after ablation. The images were discussed by all of the specialists, and a measure of the volume of the lesions was given by a radiologist with great expertise in pancreatic imaging.

EUS-guided CTP ablation: technical and clinical aspects

The CTP is an internally carbon dioxide–cooled bipolar RFA probe with a length of 1.5 m and is covered by a protection tube that can be safely passed through the operative channel of a therapeutic echoendoscope (3.8 mm). The distal tip of the probe is sharp-pointed and stiff in order to penetrate gut wall and pancreatic parenchyma. The electrically active part of the CTP has a diameter of 1.8 mm and a length of 20 mm. Power for RF-induced heating is delivered by the VIO 300D RF-surgery system, and the ERBOKRYO CA system is used for cooling (both ERBE Elektromedizin GmbH).

Ablation parameters were set as follows: fixed RF power (heating) of 18 W; fixed pressure (cooling) of 650 psi; the application time depended on the size of the lesion. Prior results of animal and ex vivo human studies showed that a range from 240 seconds for a 2-cm mass to 480 seconds for masses >3 cm is applicable.[6-8]

The EUS-guided CTP ablation was performed by using a convex linear-array echoendoscope with a 3.8-mm operative channel (EG3830UT Pentax Inc, Hamburg). The probe was passed through the operative channel of the echoendoscope and placed directly into the target lesion through either the stomach wall or the duodenal wall under real-time endosonographic guidance.

One endoscopist from each center performed all procedures. Both of the physicians were highly skilled endosonographers, and they had previous experience on the animal model with the CTP. The German endosonographer had been trained on pigs in Italy by the Italian endosonographer who had performed all the procedures in the animal study and who performed all the procedures in this human study (P.G.A.).

In the animal model, the puncture of the normal pancreas was very easy, and the use of color Doppler eliminated the risk of vascular damage. The firm position during the treatment was helpful in controlling the ablation area and avoiding sonographic artifacts.

According to the previous studies[6-8] and to the distance between the electrodes of the active part of the probe, a tumor size with a longitudinal axis ≥2 cm was eligible for inclusion into the study. There were no restrictions to location within the pancreas.

To prevent acute pancreatitis and infections, before the ablation all patients were given an infusion of antibiotic (ceftriaxone, 1 g × 2 daily, for 3 days) and antiprotease prophylaxis (gabexate mesylate 500 mg in saline solution 500 mL, starting 1 hour before the procedure and continuing for 6 hours). We chose to give antiprotease treatment to the patients in order to hypothetically decrease the risk of thermal-induced pancreatitis, which has a different etiology as compared with post-ERCP pancreatitis, and we thought that this prophylactic therapy would give us a potential protective effect.[9]

The tumors were treated under real-time EUS guidance (pancreatic body and tail through the stomach; head and uncinate process through the bulb or descending duodenum), with the patient in the endoscopy room, under deep sedation with propofol given by an anesthesiologist.

The procedures were performed in the endoscopy room according to the following scheme:

Step 1: Diagnostic EUS with FNA with a 22-gauge or 25-gauge needle to confirm the neoplastic nature of the tumor mass.

Step 2: EUS-guided CTP ablation: the probe was placed under real-time EUS into the tumor. The RF generator–cooling system interface was set to automatically stop the ablation in case of tissue desiccation, regardless of the scheduled time of application. In fact, an increase of desiccation of tissue leads to an increase of electrical impedance, thus resulting in a decrease of current flow that is detected by the RF generator, resulting in an automatic stop of the RF generator in order to avoid additional effectless power delivery.[5,6]

Post-procedure follow-up

After discharge, patients were followed monthly by the oncology team on an outpatient basis. In case of complications such as bleeding or jaundice, the patients were readmitted.

Statistical analysis

Data were analyzed by using descriptive statistics (mean, standard deviation, and range). For independent, unpaired, and normally distributed samples, a *t* test was used. If samples were not normally distributed, the Mann-Whitney test was used. Groups of categorical variables were compared by the Fisher exact test. Correlation was done by using traditional linear least-squares regression. *P* values $< .05$ were considered significant. All statistical calculations were done by using PRISM 5.0 software (GraphPad Software Inc, La Jolla, Calif).

RESULTS

From September 2009 to May 2011, 22 patients (11 male and 11 female, mean age 61.9 years, range 35-84 years) with unresectable stage III pancreatic adenocarcinoma were enrolled. Table 2 shows their main characteristics. The tumor was in the pancreatic head and neck in 16 patients, in the uncinate process in 2, and in the body in 4. The mean length of the long axis of the tumor was 35.7 mm (range 23-54 mm). All patients had major vessels involved, and tumors were considered unresectable at CT and EUS staging. All the lesions had been confirmed by EUS-FNA as pancreatic adenocarcinoma. Before the CTP treatment, all patients had received gemcitabine-based chemotherapy, and 6 had chemoradiation therapy. Three patients had a partial response from standard therapies, whereas 13 had stable disease (Table 3). The follow-up of patients between first diagnosis and final CTP treatment is listed in Table 3.

Feasibility

CTP was feasible in 16 of 22 patients (72.8%). The probe was clearly visible throughout the procedure. The application time (Table 2) differed with the size of the tumor and was automatically stopped before the calculated application time due to rapid increase of electric resistance induced by fast desiccation and devitalization of the tumor tissue. The mean application time was 107 ± 86 seconds (range 10-360 seconds). At the end of the ablation, EUS showed a hyperechoic line along the path of the probe in the treated area surrounded by nonhomogeneous tissue with hyperechoic spots (Fig. 1).

Safety

Early complications. No severe complications arose during or immediately after the ablations. Vital parameters (blood pressure, heart rate, oxygenation) were stable in all of the patients during and after the procedures. Three patients reported postinterventional abdominal pain, well responsive to analgesic drugs. Only one patient experienced minor bleeding in the duodenal lumen after the procedure, which was treated by endoscopic placement of hemostatic clips and did not require blood transfusion therapy.

Table 4 shows the laboratory test results. Three patients had a postablation amylase level rise, accompanied by mild abdominal pain responsive to analgesic drugs, without any sign of severe acute pancreatitis, and returning to normal range within 2 days. In these patients, who also had the most severe morbidity status, the hospitalization was prolonged by 1 day compared with the 5 days scheduled in the protocol, in order to follow the clinical evolution accurately.

Late complications. Jaundice occurred in 2 patients within 1 month. One patient, previously treated with biliary stent placement because of obstructive jaundice, presented 3 weeks after the ablation with anemia and jaundice with hemobilia. The patient underwent ERCP for removal of clots from the biliary tract and placement of a new metal biliary stent. Another patient with pancreatic head tumor presented 1 month after the ablation with jaundice; he underwent ERCP with biliary stent placement, achieving a fast resolution of the symptoms. One patient presented with duodenal stricture 1 month after the treatment. Another had a cystic fluid collection between the pancreas and the left hepatic lobe. The cyst was not treated because of the otherwise healthy condition of the patient. On follow-up, the cyst could no longer be detected. Table 5 summarizes the early and late complications.

Radiologic 48-hour follow-up. All patients were examined by multidetector CT scan 48 hours after the ablation. The CT was reviewed by a radiologist skilled in pancreatic diagnostics. No patients had any signs of severe pancreatitis, necrosis of nonneoplastic pancreatic parenchyma, or peripancreatic fluid. At the site of ablation, the scan showed a devascularized, inhomogeneous, hypodense area, confirmed after intravenous injection of contrast medium, compatible with colliquative necrosis. It

TABLE 2. Characteristics of patients, tumors, and application time

Patient	Center	Age, y	Sex	Site	Size (mm)	Application time (sec)	Survival (mo)
1	HSR	68	M	Neck	26 × 16	120	4
2	HSR	84	M	Head	38 × 32	360	9
3	HSR	63	M	Neck	35 × 35	180	1
4	HSR	57	M	Head	23 × 17		–
5	HSR	55	F	Neck, body, tail	34 × 25	85	6
6	HSR	59	M	Neck	38 × 30	30	3
7	HSR	61	F	Unc pr	30 × 30	120	Lost to follow-up
8	HSR	53	F	Neck	30 × 30		—
9	HSR	62	M	Body		60	3
10	HSR	54	F	Unc pr	40 × 30	90	6
11	HSR	70	F	Body	40 × 40	40	9
12	HSR	61	F	Head	20 × 20	38	3
13	HSR	71	F	Head	30 × 30		—
14	HSR	76	M	Head	27 × 24	85	8
15	HSR	66	M	Neck, body	30 × 30	38	Died after surgery
16	HSR	51	M	Head	50 × 30		—
17	HSR	45	F	Neck	40 × 40		—
18	UKE	74	F	Head	43 × 38	180	12
19	UKE	48	M	Head	44 × 36	150	6
20	UKE	35	F	Head	54 × 51		—
21	UKE	70	F	Head	44 × 30	10	Lost to follow-up
22	UKE	78	M	Head	44 × 42	120	3

HSR, Milan patients; *M,* male; *F,* female; *unc pr,* uncinate process; *UKE,* Hamburg patients. Dashes are for patients who could not be treated with the CTP ablation.

was difficult to assess the size of this area precisely because of the edema and the sonographic artifacts, but it was judged by the radiologist to be grossly similar to that of the primary tumor. The changes in density and vascularization were the only visible differences and were considered as important markers of necrosis.

Effect of CTP on primary tumor growth

Only in 6 patients was the CT scan clear enough to interpret the images in order to calculate the volumes leading to a statistical analysis. These 6 patients had no evidence of tumor growth for up to 78 days. Figure 2 shows the linear correlation of the variables change of tumor volume after the CT scan (cm^3) (denoted as post I) and the corresponding observation time (days). The CT scan in the post I phase was performed after 14.6 ± 15.8 days (range 0-37 days) after treatment with CTP. The linear regression coefficient is $r = 0.84$, which denotes an acceptable correlation between the variables and thus a strong relationship between the variables. The longer the observation time, the lower the change of tumor volume. This could mean that the tumor volume decreases in size during follow-up of the post I phase.

Figure 3 shows the linear correlation of the variables change of tumor volume after the CT scan (cm^3) (denoted as post II) and the corresponding observation time (days). The CT scan in the post II phase was performed after 38.8 ± 22.8 days (range 12-76 days) after treatment with CTP. In this case, we see a reduction of the tumor volume during the postoperative follow-up phase post II (linear regression coefficient $r = 0.84$).

Survival

Two of 16 patients who underwent the procedure were lost to follow-up. Another patient died during hospitalization after surgery. Median post-CTP survival of the other 13 patients was 6 months.

TABLE 3. Previous treatment, success rate of the pre-CTP treatment, and follow-up before CTP and follow-up after CTP

Patient	Center	Treatment type before CTP	Success of pretreatment	Time since first diagnosis (mo)	Time between first treatment and start of CTP (mo)
1	HSR	CRT	PR	24	15
2	HSR	CRT	SD	8	2
3	HSR	CRT	SD	19	9
4	HSR				
5	HSR	Chemotherapy	SD	6	1
6	HSR	Chemotherapy	SD	7	3
7	HSR	Chemotherapy	SD	8	5
8	HSR				
9	HSR	Chemotherapy	SD	7	1
10	HSR	Chemotherapy	SD	8	2
11	HSR	CRT	PR	10	1
12	HSR	CRT	SD	15	11
13	HSR				
14	HSR	Chemotherapy	SD	12	1
15	HSR	Chemotherapy	SD	4	1
16	HSR				
17	HSR				
18	UKE	Chemotherapy	PR	10	1
19	UKE	CRT	SD	12	6
20	UKE				
21	UKE	Chemotherapy	SD	8	4
22	UKE	Chemotherapy	SD	5	1

CTP, Cryotherm probe; *HSR,* Milan patients; *CRT,* chemoradiation therapy; *PR,* partial response; *SD,* stable disease; *UKE,* Hamburg patients.

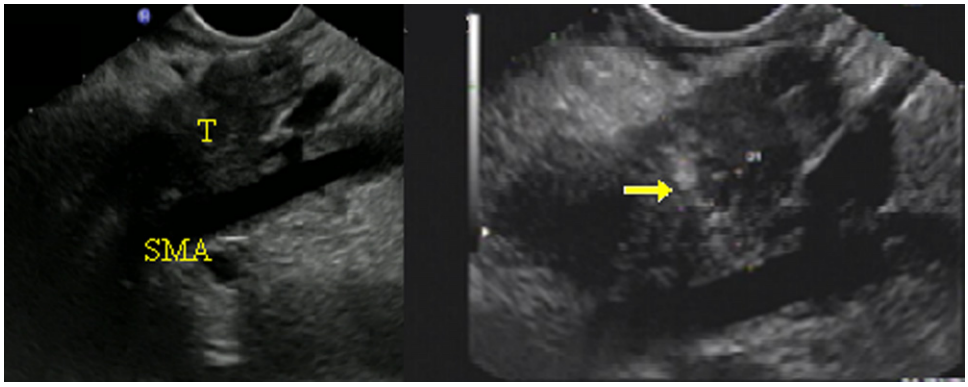

Figure 1. Hyperechoic line along the path of the probe surrounded by non-homogeneous tissue with hyperechoic spots. *T,* tumor; *SMA,* superior mesenteric artery.

TABLE 4. Laboratory test results (hemoglobin, white blood cells, amylase) before and 3 days after ablation

	Hemoglobin (g/dL)		WBC (10^9/L)		Amylase (U/L)		CRP (μg/L)	
Patient	Before	After	Before	After	Before	After	Before	After
1	11.7	11.8	3.5	3.1	24	28	<2.5	10.6
2	9.8	10.7	9.8	6.3	233	150	—	34
3	10.7	11.3	3.0	3.2	28	19	—	21
4	—	—	—	—	—	—	—	—
5	9.4	11	3.6	5.5	39	35	2.5	2.5
6	11	12.9	3.8	6.1	45	40	2.5	50
7	12.4	12.7	5.4	5.6	45	51	3	16.1
8	—	—	—	—	—	—	—	—
9	10	11	4.5	9.8	37	22	3	155
10	11	11	6.1	6.9	55	150	2.5	2.5
11	11	11	4.6	2.9	118	95	2.5	2.8
12	12.4	12.1	6.1	10.1	28	49	3.8	40.6
13	—	—	—	—	—	—	—	—
14	13.4	12.7	3.9	4.8	84	218	<2.5	
15	12.7	12.7	5	5.4	78	65		20.0
16	—	—	—	—	—	—	—	—
17	—	—	—	—	—	—	—	—
18	13.9	12.9	5.5	7.2	NA	NA	7	5
19	12.2	9.7	6.3	9	NA	19	<5	76
20	—	—	—	—	—	—	—	—
21	10.7	10.8	3.1	5.3	31	1964	20	28
22	11.1	11.7	10.1	10.7	NA	13	20	92

WBC, White blood cell count; *CRP,* C-reactive protein; *NA,* not available. Dashes are for patients who could not be treated with the CTP ablation.

Six patients died within 6 months: 1 patient, who previously had severe portal hypertension due to infiltration of the splenic vein, superior mesenteric vein, and portal vein, died 1 month after the ablation because of duodenal variceal bleeding. One patient died 3 months after the ablation because of tumor perforation into the duodenum, with massive bleeding and hemorrhagic shock; another died after 4 months while in the hospital for pneumonia. Three other patients died after disease progression to the lung and the liver.

In 1 patient, the CT scan after the CTP showed only minimal infiltration of the superior mesenteric vein due to an adenocarcinoma growing over a diffuse, intraductal, papillary mucinous neoplasm. The patient underwent total pancreatectomy 6 days after the procedure but died on the seventh postoperative day from operative complications (liver failure because of acute hepatic artery thrombosis with subsequent multiple organ failure).

In 7 patients, disease progression was clear at radiologic follow-up: 3 had liver metastasis, 2 peritoneal nodules, and 2 pulmonary metastasis. These patients also had a local progression of the primary tumor.

Histology of the resected specimen. The histologic specimen was made up of whitish tissue with microcystic spaces in correspondence to the primary tumor at the body of the pancreas, with a small area (nearly 1 cm) of colliquative necrosis and cell debris.

DISCUSSION

This is the first in vivo study of EUS-guided application of the CTP in patients with locally advanced pancreatic

TABLE 5. Early and late complications after the EUS-guided CTP ablation

Early complications			Late complications		
Complication	**No. patients**	**Treatment**	**Complication**	**No. patients**	**Treatment**
Postinterventional abdominal pain	3 (18%)	Intravenous paracetamol	Jaundice	2 (12%)	Biliary stent
Minor duodenal bleeding	1 (6%)	Endoscopic hemostatic clips	Duodenal stricture	1 (6%)	Duodenal stent
Amylase level rise	3 (18%)	Spontaneous resolution	Cystic fluid collection	1 (6%)	Self-limiting

CTP, Cryotherm probe.

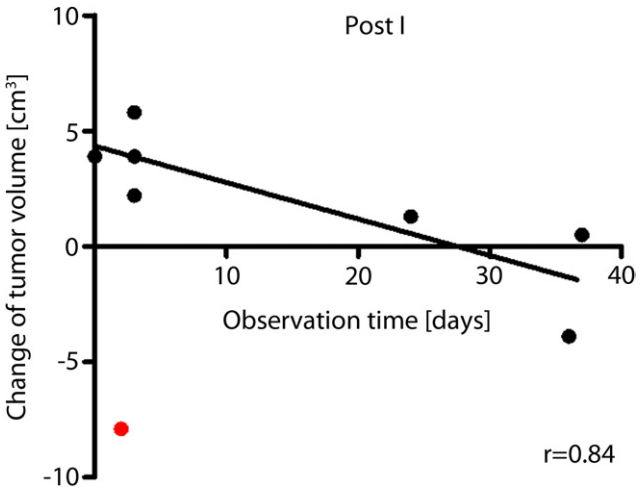

Figure 2. Linear regression statistics of changes in tumor volume on the first CT scan after the procedure in relation to observation time. Except for one sample (*marked red*) all samples follow a linear correlation with a correlation coefficient of $r = 0.84$. The × axis shows the days after the ablation.

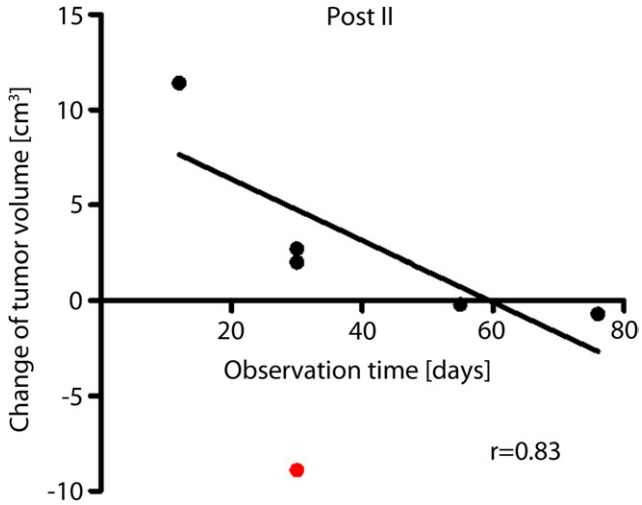

Figure 3. Linear regression analysis of change of tumor volume on the second CT scan after the procedure in relation to observation time. Except for one sample (*marked red*) all samples follow a linear correlation with a correlation coefficient of $r = 0.83$.

cancer after standard oncology therapy. Our primary aim was to assess the feasibility and safety of this new procedure that could potentially improve local control of this lethal cancer, giving patients either the possibility of becoming resectable or prolonging survival with an acceptable quality of life.

In our study, the CTP was successfully applied under EUS guidance in 72.8% of patients, with a minimally invasive technique, and there were no severe complications or deaths related to the procedure. The reason for the unsuccessful placement of the probe inside the tumor in 6 cases was stiffness of the GI wall and of the tumor due to desmoplastic reaction, tumor infiltration, and/or scar and fibrosis in patients who had already undergone radiation therapy.

The development of sharper probes and the possibility of applying a cutting current—similar to the needle-knife used for EUS-guided pseudocyst drainage[10,11]—probably could overcome this main technical limitation of the EUS-guided procedure. EUS guidance may increase the safety of application, and the use of color Doppler could reduce the risk of puncturing vascular structures between the gastric or duodenal walls and the target lesion. EUS also is minimally invasive, with less morbidity and lower costs than laparotomy.

Only a few studies have used RFA for pancreatic cancer,[3,12-18] as recently reported in a review,[19] and most of them were studies of feasibility and safety. No randomized, controlled trials have been published.

Many of the publications dealing with monopolar RFA report severe complications related to the treatment. Girelli et al[5] applied RFA during laparotomy in 50 patients with locally advanced pancreatic cancer and reported 17 complications, 9 directly related to the RFA (2 pancreatic fistulas, 4 portal vein thromboses, 2 duodenal bleedings, and 1 severe pancreatitis). In another 3 patients, the authors reported intra-abdominal bleeding of uncertain origin.

Wu et al[4] reported 25% of fatal hemorrhagic complications after intraoperative treatment of pancreatic head tumors by Cool-Tip RF probe (RFA generator, Radionics, Burlington,

Mass). In some isolated case reports, the RFA was used to treat renal metastasis to the pancreas[12] and primary neuroendocrine tumors of the pancreas.[13] Elias et al[12] used intraoperative RFA to treat pancreatic metastasis from renal cell carcinomas in two patients who received multiple ablations in the same session. The results were a pancreatic-cutaneous fistula and rupture of the splenic artery inside a pseudocyst in one case and severe necrotizing pancreatitis in the other.

Limmer et al[13] used CT scan guidance to ablate with success and without complications an insulinoma of the tail of the pancreas in a patient with high surgical risk. The authors concluded that surgery is still the first-line treatment for patients with insulinomas, and RFA should be reserved for those who are not candidates for surgery, with symptoms that cannot be controlled by medical therapy.

The risk of unintended thermal injury exists with RFA, and recent studies have confirmed that RFA in the pancreas is dangerous without additional cooling of adjacent tissue and real-time visualization.[11,13,15] The risk of thermal injury of the main vessels or the surrounding structures such as gastric or duodenal wall seems to be negligible with the CTP. This is mainly due to the extreme precision of targeting the lesion provided by the EUS guidance with color Doppler coupling and to the possibility of predetermining the ablation area to a certain extent. A minimally invasive technique that would allow selective ablation of tumor masses might improve the efficacy of neoadjuvant treatment procedures in patients not suitable for any other kind of treatment.

In our series, there were no cases of severe pancreatitis or major complications. Only 3 patients had mild increase of amylase levels or pain. One patient had mild bleeding into the duodenal lumen coming from the puncture site. The bleeding was treated early with endoscopic placement of hemostatic clips and did not require blood transfusion. There were no cases of hemoperitoneum, indicating that the use of color Doppler during the EUS-guided procedure might reduce the risk of puncturing vessels between the gastric and duodenal walls and the pancreas. None of the patients needed surgical intervention. The patients with jaundice were successfully treated with endoscopic biliary stent placement. Duodenal stricture also was treated endoscopically. In these cases it was impossible to distinguish complications related to the procedure from those due to tumor growth or stent obstruction. In cases of hemobilia, it can be supposed that microhemorrhages from the ablated tumor in the pancreatic head and necrotic debris might involve and occlude the biliary tract.

Future studies should assess the efficacy of the CTP procedure for local control of this lethal disease, ideally in a controlled design.

One major limitation in our study turned out to be the difficulty of measuring satisfactorily the size of the ablated zone by CT scan. Magnetic resonance imaging might be a more useful alternative method for assessing the presence and degree of necrosis after the ablation, because it probably would show better the poorly perfused pancreatic areas.[20,21] Also, radiologic follow-up of the ablation was not useful in the first 4 weeks, because it was impossible to distinguish inflammatory reactions of the tumor tissue from tumor growth or necrosis.

Conclusions

EUS-guided application of the CTP in patients with pancreatic cancer is feasible and safe, especially compared with other RFA methods described in the literature being used in pancreatic treatment to date. Its impact on tumor growth needs further research. In our study, the limited data seem to show a tendency toward tumor reduction. Some improvements to the probe and randomized, controlled trials are needed. Nevertheless, this minimally invasive treatment bears the potential to be proposed to patients who are not candidates for surgery (in association with chemotherapy and radiation) in order to limit local growth of the tumor.

EUS is the least invasive way to guide the probe inside the tumor and the best way to reduce the risk of damage to anatomical structures such as the duodenum, common bile duct, and vessels.

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