

Percutaneous ablation therapies of inoperable pancreatic cancer: a systematic review

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Abstract

Initial studies about ablation therapies of the pancreas were associated with significant morbidity and mortality, which limited widespread adoption. Development of techniques with high quality imaging used as guidance improve outcomes reducing complications. Moreover, only few experiences of percutaneous pancreatic ablations are reported. They are performed by very skilled operators in highly specialized centers. This review presents the current status of percutaneous local ablative therapies in the treatment of advanced pancreatic cancer.

Keywords Percutaneous ablation, inoperable pancreatic cancer, review

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Introduction

Pancreatic cancer is one of the most aggressive human malignancies. Because of the insidious course and rapid growth, tumors are diagnosed at an advanced stage and therefore only the minority of these patients, about 20%, can benefit from surgical resection [1]. Nearly half of the patients are diagnosed with stage III disease [2,3]. Typically, involvement of the celiac axis, hepatic artery, or superior mesenteric artery (SMA) (>180° of the circumference of the vessel wall) is a contraindication to surgical resection. Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis, is considered a borderline factor for resection. Involvement of the portal vein or superior mesenteric vein (SMV) is not a contraindication nor does it preclude negative-margin resection, but may alter the sequence of multimodal treatment [4]. An additional 20% of patients have localized disease but it is unresectable [4].

Surgical procedures are sometimes excluded based on general considerations, such as advanced age, comorbidities,

or patient refusal [4,5]. In patients with unresectable or locally advanced pancreatic cancer several palliative therapeutic modalities have been applied for tumor regression, local control, slowing of growth, and relief of pain/symptoms, such as chemoradiation, intraoperative electron beam irradiation, interstitial or intraluminal brachytherapy [6-8].

Over the last decade, image-guided tumor ablation with both thermal and nonthermal sources has received substantial attention for the treatment of many focal malignancies, in particular liver tumors [9]. Increasing interest has been accompanied by continual advances in energy delivery, application technique, and therapeutic combinations with the intent to improve the efficacy and/or specificity of ablative therapies [10]. However, in contrast to the liver, where tumor-bearing tissue is surrounded by normal hepatic parenchyma, the pancreas is surrounded by structures such as the duodenum and common bile duct; the risk of thermal injury to these structures has limited the application of thermal ablation to pancreatic tumors [9]. Moreover, locally advanced pancreatic cancer often encases the vessels and extends retroperitoneally or proximally, making direct ablation of the entire tumor impossible [11]. However, recently there has been a growing interest in the use of ablation also for pancreatic tumors; inoperable cases of pancreatic adenocarcinomas, and also some cases of neuroendocrine symptomatic tumors and metastases, have been treated by various ablation techniques with promising results [12-14].

Pancreatic neuroendocrine tumors (P-NETs) are comparatively rare neoplasms, and account for only 1-2% of all pancreatic neoplasms [15]. P-NETs include benign neoplasms without metastasis or invasion, as well as high-grade malignant neoplasms [15]. The latter may be staged using the AJCC staging system for pancreatic adenocarcinoma [15,16]. To date, however, there have been only sporadic reports of percutaneous thermal ablation to treat P-NETs in humans [14].

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Image-guided minimally invasive ablative therapies delivered by using needlelike applicators include both thermal (i.e., radiofrequency [RF], microwave [MW], laser and cryoablation) and nonthermal (i.e., chemical ablation and irreversible electroporation [IRE]) techniques [10]. High intensity focused ultrasound (HIFU), conversely, does not require percutaneous placement of needles [11].

Percutaneous thermal therapies are limited, however, by the quality of imaging guidance and, in some cases, by complex anatomy and difficult access [10]. Sometimes, palliative treatment of unresectable pancreatic cancers has the only purpose to improve quality of life by reducing pain [17]. Pain management for patients with local advanced pancreatic cancer is an ongoing challenge. Pain can be both neuropathic and inflammatory, resulting from both tumor expansion and tumor invasion of the celiac and mesenteric plexus [18]. At disease progression, however, nonsteroidal anti-inflammatory drugs and narcotic analgesics may not be sufficient. Therefore, anesthetic blocking of the celiac plexus was used to palliate pain, but the duration of pain relief is limited [18].

Use of percutaneous ablation in the pancreas is related to well-founded fear of adverse effects, including thermal injury induced pancreatitis and thermal damage to structures in and around the pancreas (e.g. the duodenal wall, nearby viscera, and blood vessels), and to technical limitations of the real-time imaging modalities used to visualize target lesions and needles/electrodes used to ablate them [5]. Thermal ablation has been used only sporadically to treat P-NETs, because the Whipple procedure and other types of pancreatic resection are considered the treatment of choice of these tumors throughout the world, even though it is associated with high rates of major complications, including death [15]. Local control of the disease not suitable for surgery is often the first indication for ablation. Unfortunately, locally advanced pancreatic tumors usually bear a dismal prognosis and pain relief may be another aim of the ablation. Nowadays, very few P-NETS were treated percutaneously with ablation. At the moment it is difficult to establish inclusion criteria for ablation [5].

To date, treatment of the pancreas with ablative techniques has been mostly performed in the operating room by surgeons. The most important advantage of the ablative therapies performed percutaneously is to be mini-invasive, permitting to treat a lot of patients with comorbidities that contraindicate surgical approach [13,19]. The purpose of this review is to present the current status of local ablative therapies in the treatment of pancreatic tumors with a percutaneous approach.

Materials and methods

A systematic literature search was performed using the PubMed databases for studies published in the English language up to October 2014, with the following keywords; RF ablation (RFA), cryoablation, MW ablation (MWA), irreversible electroporation (IRE), high intensity focused ultrasound (HIFU) and (pancreas OR pancreatic). Only articles which described percutaneous ablation in pancreatic tumor were

included. In cryoablation and HIFU, many of the largest case-series are published in non-English language medical journals and were excluded from this systematic review. All references were screened for potentially relevant studies not identified in the initial literature search.

The following variables were extracted for each report when available: number of patients, demographic data (sex and age); tumor histology diameter of the lesion; disease extent; device used and settings; distance of probe from surrounding structures; duration of therapy and number of ablations applied; complications; mean follow up and survival; and treatment response.

All patients underwent radiologic investigations (ultrasound, contrast-enhanced CT and/or MRI) which revealed lesions suspicious of pancreatic tumors, confirmed by histological examination in almost all studies.

RFA

Five studies (Table 1) involving 11 patients with pancreatic tumor treated with percutaneous RFA were analyzed [5,12 14,20]. There were 3 case reports [12-14], 1 prospective study [20], and 1 pilot study [5]. All patients were treated percutaneously with CT (4 pts) or US (7 pts) guidance. The mean age of patients was 70 years old. Specifically, there were 4 non secretory neuroendocrine tumors, 3 insulinomas, 2 gastrinomas, 1 metastasis from renal cell carcinoma, and 1 locally advanced adenocarcinoma. The tumor size ranged from 13 to 40 mm, and in one study it was not described. Tumor was located in the pancreatic body-tail in 5 patients and in another 5 it was located in the head. Singh *et al* [20] did not specify the location of the tumor. Complications related to procedure included: diffuse abdominal pain, self-limiting form of pancreatitis associated with thermal injury, minimal peripancreatic inflammatory reaction, slight and transient increase in serum amylase and lipase, and a fluid peripancreatic collection (completely disappeared at CT scan at 1 year follow up [12]). There were no deaths related to the procedure. In all 5 studies a significant level of pain relief was observed in the patients.

Data regarding the follow up and survival were not available in all the studies. There was a mean follow-up of 17 months.

MWA

Although there are no pre-clinical studies published about MWA of pancreatic lesions and only two articles about the use of MWA in pancreatic cancer are available, this technique is considered an emerging option for the treatment of a variety of tumors and, when compared with RFA, offers several advantages. The largest case series of MWA in locally advanced pancreatic cancer reported in the literature includes 15 patients, but the ablation was performed intraoperatively at the time of palliative bypass surgery [21]. Carrafiello *et al* [17] (Table 2)

Table 1 Use of percutaneous radiofrequency ablation (RFA) in the treatment of advanced pancreatic tumor (articles; number; histology; dimension and location of the tumor; complications; survival and follow up and response)

Author Year	N° PT	Histology	Dimension (mm) and location (H/B/T)	Complications	Survival (months) or f.u.	Response
Carrafiello 2008 [12]	1	Mts from renal cell Carcinoma	20 B/T: 1	Abdominal pain Amylase serum increase Little peripancreatic fluid collection	f.u. 12	Patient free of symptoms; no recurrence
Limmer 2009 [14]	1	Insulinoma	15 B/T: 1	Minimal peripancreatic inflammatory reaction	f.u. 1.5	Patient free of symptoms
Wu 2010 [13]	1	Gastrinoma	30×40 B/T: 1	No complications	f.u. 20	Patient free of symptoms; no recurrence
Singh 2011 [20]	1/11	Ductal adenocarcinoma				RFA safe and feasible technique of cytoreduction
Rossi 2014 [5]	7/10	5 non functional P-NET, 2 insulinomas, 1 gastrinoma	13×16 H: 5 B/T: 2	Serum amylase and lipase increase pancreatitis	f.u. 34	After a median follow up of 34 months all patients are alive and well

Pt, patients; Mts, metastasis; H, head; B, body; T, tail; B/T, body/tail; P-NET, pancreatic neuroendocrine tumor; f.u., follow up

Table 2 Percutaneous microwave ablation of advanced pancreatic tumor (article; number; histology; dimension and location; complications, survival or follow up; and response)

Author Year	N° PT	Histology	Dimension (mm) and location	Complications	Survival (months) or follow up (f.u.)	Response
Carrafiello 2013 [17]	5/10	Ductal AdenoCa	32	2 mild pancreatitis 1 pseudocyst 1 PSA of GDA (minor 20%, major 10%)	9 f.u.	QOL improvement All complication resolved over the course of hospital stay

AdenoCa, adenocarcinoma; H, head; B/T, body/tail; PSA, pseudoaneurysm; GDA, gastroduodenal artery; QOL, quality of life; f.u., follow up

evaluated the safety and efficacy of percutaneous MWA treatment in locally advanced, non resectable, non metastatic pancreatic head cancer [17]. Ten patients were treated, with percutaneous (n=5) or laparotomic (n=5) approach. In all patients treated with the percutaneous approach, MWA was performed under moderate sedation. The path of the antenna was carefully evaluated on the basis of a preliminary US examination; a path was chosen such that the vessels, stomach, and bowel were far from the antenna (Fig. 1 A, B). The most important evaluation involved the prediction of the ablation area on the basis of the position of the antenna; in some cases, cone-beam CT acquisition provided a correct and safe position for the antenna with respect to the adjacent structures [17].

The procedure was feasible in all patients (100%). One late major complication was observed in one patient, a pseudoaneurysm of the gastroduodenal artery, treated with endovascular approach. Two patients presented with mild pancreatitis after 1 month; one case resulted in a pseudocyst that was managed with a drain [22]. No patients had further surgery, and all minor complications resolved during the hospital stay. An improvement in the quality of life was observed in all patients. No repeat treatment was performed. Despite the small number of patients, Carrafiello *et al* concluded that MWA is a feasible approach in the palliative treatment of pancreatic tumors [17].

Cryoablation

There are few reports about the use of cryoablation alone or in combination with other therapies for the treatment of pancreatic cancer, but many of the largest case series are published in non-English language medical journals [23]. Three studies involving a total of 105 patients with pancreatic lesions treated with percutaneous cryoablation fulfilled the eligibility criteria of this review (Table 3) [24-26]. All patients were treated percutaneously under CT or US guidance. The mean age of patients was 55 years old.

Specifically, there were 103 adenocarcinomas and 2 neuroendocrine tumors in multiple endocrine neoplasia type 1 (MEN1) syndrome (insulinomas). The tumor size ranged from 50 to 70 mm. Complications related to the procedure included: abdominal pain and distension, transient increase of amylases, fever, ascites, abdominal bleeding, mild decrease in platelet (in patients that underwent also immunotherapy), delayed gastric emptying, acute pancreatitis, increase in fasting blood glucose levels, pulmonary infection, myocardial infarction, and cerebral infarction. There were no deaths related to the procedure. In all studies, a significant level of pain relief was observed after procedure. Average survival after cryoablation ranged from 3 to 48 months.

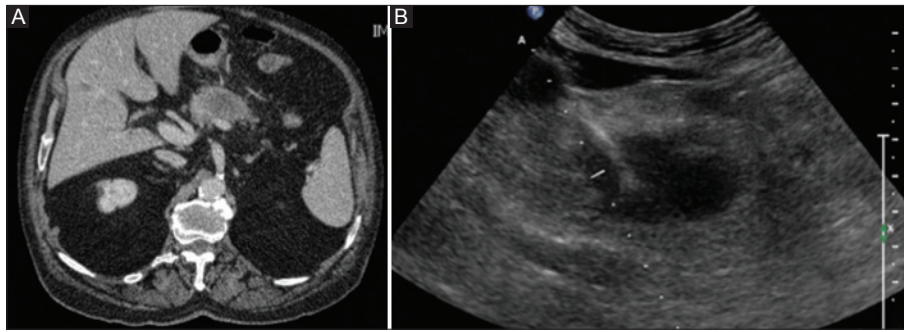


Figure 1 (A) Contrast-enhanced computed tomography reveals the presence of the pancreatic tumor. (B) Antenna for microwave ablation within the lesion, positioned under ultrasound guidance

Table 3 Percutaneous cryoablation of advanced pancreatic tumor (articles; number; histology; dimension and location; complications; survival or follow up; and response)

Author Year	N° PT	Histology	Dimension (mm) and location (H/B/T)	Complications	Survival (months) or follow up	Response
Xu 2008 [24]	36/49 +iodine seeds implantation	Ductal adenoCa	50	34: Abdominal pain 69% 26: Fever 53% 6: Acute pancreatitis 12% 25: Increased amylase 51% 3: Abdominal bleeding 6% 3: Pulmonary infection 6% 1: Myocardial infarction 2% 1: Cerebral infarction 2%	16 CR: 20.4% PR: 38.8% SD: 30.6% PD: 10.2% 18 f.u.	Iodine seed implantation can destroy residual cancer cells after cryoablation. A combination of modalities has a complementary effect
Niu 2013 [25]	67/106 31: cryoimmunotherapy 36: cryotherapy 17: immunotherapy 22: chemotherapy	Ductal adenoCa	NA	21: Abdominal distension and nausea 31% 19: Increased amylase 28% 17: Ascites 25% 14: Abdominal bleeding 21% 13: Fever 20% 12: Mild decrease in platelet 18% 7: Increase of fasting blood glucose levels 10%	13 in cryoimmunotherapy 7 in cryotherapy (higher than other groups) 4 years f.u.	Median OS was higher after multiple cryoablations than after a single cryoablation. Pain score decreased
Li 2013 [36]	2	Neuroendocrine (MEN1)	70 H:1 B/T:1		3 f.u.	Reduction of blood glucose levels and necrosis at CT scans. QOL improvement

AdenoCa, adenocarcinoma; H, head; B/T, body/tail; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; f.u., follow up; OS, overall survival; CT, computed tomography; QOL, quality of life; NA, not available; MEN1, multiple endocrine neoplasia 1; f.u., follow up

IRE

Four studies (Table 4), involving a total of 21 patients with locally advanced ductal adenocarcinoma treated with percutaneous IRE were analyzed [19,27-29] (Fig. 2 A, B). There were 1 prospective study, 2 retrospective studies, and 1 case report. Narayanan [30] added another 4 patients reported in a very recent study which contained data related to vascular patency post IRE in different organs and in particular 18 pancreatic carcinomas (14 published in 2012 [19] and 4 performed in the last years and reported in this recent study). Efficacy was not among the aims of his recent study, and dimensions, locations, histology, complications, follow up,

and response were not reported. Recently, Scheffer *et al* [31] reported a case of percutaneous pancreatic IRE: they reported the feasibility and the safety of the dorsal approach. They did not report data on the follow up and we excluded this case from our study.

We recently described the onset of asymptomatic multiple little splenic perfusion defects after the treatment of a locally advanced body-tail pancreatic cancer with the application of five percutaneous probes for IRE, in a 79-year-old man (Fig. 2 A, B). To the best of our knowledge, until now, no experience concerning percutaneous IRE of pancreatic cancer described that consequence of the treatment. This case report has not been included in the review because it was focused

Table 4 Use of percutaneous irreversible electroporation (IRE) for the treatment of locally advanced pancreatic tumor (articles; number; histology; dimension and location of the tumor; complications; survival or follow up; and response)

Author Year	N° PT	Histology	Dimension (mm) and location (H/B/T)	Complications	Survival (months) or follow up	Response
Bagla 2012 [27]	1	Ductal AdenoCa	41 B/T: 1	No complications	6 f.u.	No recurrence at 6 months
Martin II 2012 [28]	1/27	Ductal AdenoCa	30 H: 15/ B/T: 12			1 death at 3 months 1 recurrence at 3 months
Narayanan 2012/2014 [19]	14+4	Ductal AdenoCa	33 H: 7/ B/T: 7	1/14 pancreatitis 1/14 pneumothorax during anesthesia	Events free survival: 6.7	3 patients with metastatic disease died from progression of disease
Mansson 2014 [29]	5	Ductal AdenoCa	NA	No complications	6 f.u.	NA

AdenoCa, adenocarcinoma; H, head; B/T, body/tail; f.u., follow up

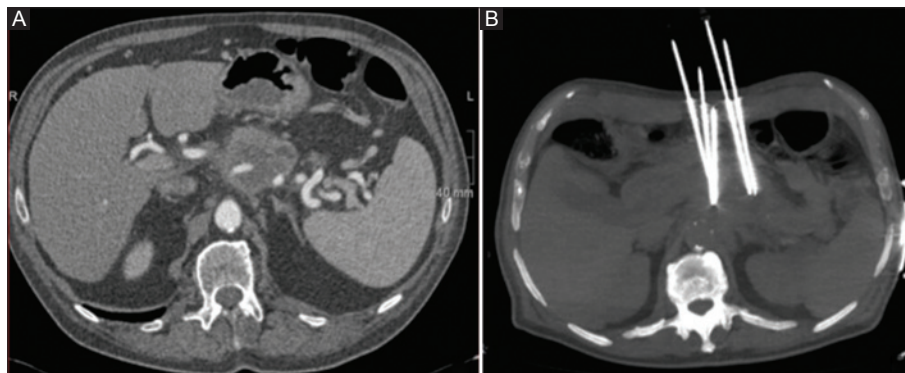


Figure 2 (A) Contrast-enhanced computed tomography reveals the presence of the pancreatic tumor. (B) maximum intensity projection (MIP) reconstruction demonstrates the presence of 5-needle for irreversible electroporation

on the description of vascular lock, with few data on the follow up [32]. The mean size of the tumors was 34.5 mm. Mansson *et al* [29] did not specify the diameter and location of the treated lesions. Tumor was located in the pancreatic head in 7 patients and in the body-tail in 8 patients. Martin II *et al* [28] treated 26 patients with an open approach and one patient percutaneously because of her multiple earlier surgical procedures unrelated to her disease. Therefore, it was not possible to accurately recover the data about tumor localization and complications.

Complications occurred only in the series of Narayanan and were 1 transient pancreatitis and 1 spontaneous pneumothorax during anesthesia [19]. There were no cases of vessel thrombosis after the procedure and a significant level of pain relief was observed in most of patients. There were no deaths related to the procedure.

HIFU

There are many reports about the use of HIFU alone or in combination with other therapies for the treatment of pancreatic tumors. Eleven studies involving a total of 500 patients with pancreatic lesions treated with HIFU fulfilled the eligibility criteria of this review (Table 5) [33-43]. Specifically, they

were all advanced pancreatic adenocarcinomas except for 3 neuroendocrine tumors and 1 metastasis from renal cell carcinoma. The tumor size ranged from 4 to 58 mm. Complications related to the procedure included: abdominal pain, transient pancreatitis, subcutaneous sclerosis, skin burns, transient fever, cytopenia (in patients that underwent also chemotherapy), subcutaneous fat callus, pancreatic-duodenal fistula, portal vein thrombosis, pseudocyst, and bleeding due to gastric ulcer. There were no deaths related to the procedure. In almost all studies, a significant level of pain relief was observed after the procedure. The average survival after cryoablation ranged from 5.4 to 26 months.

Discussion

Over the last decade, RF energy has become increasingly accepted for the ablation of solid parenchymal tumors [12]. There are mainly three different ways that an ablative procedure may be performed: laparotomic or laparoscopic ablation and image-guided percutaneous ablation. Due to the special anatomical location of the pancreas, currently, RFA via laparotomy is mainly used and in literature there are only a few studies referring to the percutaneous approach [13].

Table 5 Use of high intensity focused ultrasound (HIFU) for the treatment of locally advanced pancreatic tumor (articles; number; histology; dimension and location of the tumor; complications; survival or follow up; and response)

Author Year	N° PT	Histology	Dimension (mm) and location (H/B/T)	Complications	Survival (months) or follow up	Response
Wu 2005 [33]	8	Ductal AdenoCa (+1 mucinous adenoCa)	58 H:2 / B/T:6	No complication	f.u. 11	8/8 pain relief
Xiong 2009 [34]	89	Ductal AdenoCa	x H:34/B/T:55	3 Skin burns 2nd degree 3,4% 6 subcutaneous sclerosis 6,7% 1 pseudocyst 1%	stage II=26 stage III=11,2 stage IV=5,4 OS=8,6	80.6% pain relief 33.7 % partial necrosis 28.1% progression
Zhao 2010 [35]	39	Ductal AdenoCa	34 H:27/ B/T:12	Cht related (cytopenia, nausea)	12,6	Gemcitabine and concurrent HIFU was active and well tolerated 94.9% response 22/39 pain relief
Orsi 2010 [36]	7	6 Ductal AdenoCa 1 neuroendocrine	4.6	1 Portal vein thrombosis 1 bad response to treatment for gas bubbles in the stomach and duodenum during treatment	7	
Orgera 2011 [37]	2	Insulinoma	50 B/T: 2	No complication	f.u. 10	Good local tumor and symptoms control in symptomatic P-NETs
Orgera 2012 [38]	1	RCC metastases	9 H:1	No complication	f.u. 9	Satisfactory control of disease without evidence of recurrence
Sung 2011 [39]	46	Ductal AdenoCa	42	No complication 16/49 (32.7%) 5/49 Major complication (10.2%) 2 Pancreaticoduodenal fistula 1 Skin burn 2nd degree 1 1 Skin burn 3rd degree 1 bleeding due to gastric ulcer Mild complication 28/49 (57.1%) 16 Mild abdominal pain 7 Transient pancreatitis 3 Transient fever 2 Several abdominal pain with vomiting	12	24/46 pain relief
Li 2012 [40]	25	Ductal AdenoCa	x H:7/B/T:18	3 skin burns 1st degree	10	23/25 pain relief Significant reduction of CA19-9
Wang 2013 [41]	224	Ductal AdenoCa	110>5 cm 114<5 cm H:47/B/T:177	16 Transient amylase increase 10 abdominal distension and nausea 2 asymptomatic vertebral injury 1 obstructive jaundice	8	HIFU is safe, but requires careful preoperative preparation and exact operative performance
Gao 2013 [42]	39	Ductal AdenoCa	H:7 B/T:32	No severe complications	11	Pain relief in 79.5% of patients
Ge 2014 [43]	20	Ductal AdenoCa	4.5 B/T:20	5 Mild abdominal pain 4 subcutaneous fat callus 1 2 nd degree skin burn 1 pancreatic effusion		Tumors with posterior depths <7 cm may effectively be treated with HIFU-induced ablation with minimal adverse events

AdenoCa, adenocarcinoma; H, head; B/T, body/tail; LA, locally advanced; Mts, metastasis; OS, overall survival; RCC, colon – rectal carcinoma; cht, chemotherapy; f.u., follow up

The largest series analyzed in this review was the study of Rossi *et al* that performed RFA on 10 patients with histologically diagnosed P-NETs [5]. Seven of the 10 patients underwent percutaneous RFA. Tumors were potentially resectable but conventional surgery had been refused by patients or contraindicated by the anesthesiology team on the basis of patient's age and/or comorbidities. Patients treated with the percutaneous approach did not have major complications

in a shorter hospital stay period (7 days) compared to those who underwent laparotomy (mean, 22 days) [5]. Rossi *et al* [5] suggested that only skilled operators with substantial experience in interventional US-guided procedures can overcome the technical difficulties related to the deployment of the electrode very close to arteries of the celiac trunk, venous branches of the portal system, the wall of the duodenum, and the main pancreatic duct. Unfortunately, there are no

series in the literature on the use of RFA for treating ductal adenocarcinomas.

Limmer *et al* [14] and Wu *et al* [13], like Rossi [5], reported successful data on the use of RFA for the treatment of functioning neuroendocrine tumors; with the advantages of less trauma and pain, rapid recovery, curative effect and repeatability, the image-guided minimally invasive interventional treatment can accurately target tumor, destroy it and improve patients' quality of life [13,14].

Carrafiello *et al* [12] confirmed that RFA is feasible for the treatment of metastatic lesion located in the body-tail of the pancreas; as the lesion was located at the body-tail portion of the pancreas, we were quite confident that the risk of a biliary injury was reduced at a minimum.

Improved electrodes for percutaneous approaches could probably solve many of the problems related to difficult encounter during percutaneous RFA of pancreatic tumors; the goal should be to reduce the caliber of the needle while increasing (or at least without decreasing) the volume of the thermal lesions they produce. Electrode tips would also benefit from higher sonographic visibility [5].

MWA appears to have several advantages compared with RFA: at first, considering anatomic relationship of the pancreas with adjacent organs and vessels, MWA can decrease heat-sink effect [44]. MW can guarantee optimal heating of cystic masses and tumors close to the vessels, it takes shorter intraoperative time and, using multiple antennae simultaneously, it reduces the need of multiple treatment sessions decreasing the rate of incomplete treatments of larger tumors [45,46]. Additionally, MWA is associated with a lower amount of intra-procedural pain [44].

Cryosurgery has provided a novel therapeutic approach to the treatment of benign and malignant tumors, especially unresectable tumors [47]. Theories and *in vivo* and *in vitro* studies explained the effect of low-temperature exposure on the tissues. Studies showed that the pancreatic tissue may be locally damaged if the temperature is set in the range -80°C to -180°C, which results in aseptic necrosis and apoptosis, local capillary vessel circulation failure, and antiangiogenesis [48]. Niu *et al* [25] reported the largest retrospective series (67 pts). In this study, combined cryotherapy and immunotherapy were found to significantly improve the treatment of metastatic pancreatic cancer more than conventional chemotherapy. Median overall survival (OS) was higher in the cryoimmunotherapy (13 months) and cryotherapy groups (7 months) than in the chemotherapy group (3.5 months;). In both cryoimmunotherapy and cryotherapy groups, median OS was higher after multiple cryoablations than after a single cryoablation.

Xu *et al* [24] decided to use the combination of cryosurgery with ¹²⁵iodine seed implantation that provided γ radiation for a short distance, resulting in the death of the targeted cells. They found that the approach of cryosurgery (intraoperative vs percutaneous), tumor size (≤ 4 cm vs >4 cm), and location (head vs body or tail) were not independent risk factors affecting prognosis.

Li *et al* [26] described the efficacy of percutaneous cryoablation for the treatment of neuroendocrine pancreatic tumors in familial MEN1: after treatment, the physical status

of patients improved significantly; the preliminary results of blood glucose levels and CT scans have demonstrated the potential curative effects of cryosurgery in a short-term observation period.

Unresectable tumors can be treated with percutaneous cryosurgery, with similar efficacy as intraoperative cryosurgery and much less invasiveness for the patient. During percutaneous cryosurgery, other modalities, such as ¹²⁵iodine seed implantation, can be used simultaneously and also metastases could be treated simultaneously.

IRE is a relatively new non-thermal modality for ablation of soft-tissue tumors that uses very short pulses of high-voltage, low-energy direct current to induce cellular death by creating cellular membrane disruption [49]. Because of its mechanism of action, IRE is hypothesized to have wider indications than other ablation technologies. Tumors in contact with vessels can be treated with IRE without heat-sink effect [50]. The preservation of vascular and ductal structures within the treatment field of IRE is hypothesized to result from the supporting connective tissue matrix, which is unaffected by this modality as a result of the lack of thermal effects [50]. This makes IRE a very attractive option in patients with local advanced pancreatic cancer (LAPC), as the reason for unresectability is usually vascular encasement. However, IRE is very expensive at the moment and not available in many centers.

One of the most innovative and revolutionary techniques in the field of ablation is HIFU, completely extracorporeal, through the use of nonionizing energy. The first success of HIFU ablation for advanced pancreatic cancer was conducted in Chongqing China in 2000 [33]. It was a phase I-II prospective clinical trial, and both survival benefit and pain control were observed during follow-up period. After HIFU, pre-existing severe back pain of presumed malignant origin disappeared in each patient. Follow-up images showed reduction or absence of tumor blood supply in the treated region with significant shrinkage of the ablated tumor. Subsequently, several clinical studies were performed to investigate the safety and feasibility of HIFU for the treatment of patients with advanced-stage pancreatic cancer [34-43]. The largest clinical experience of using HIFU treatment was reported by Wang *et al* [41]. A total of 224 patients were enrolled in this study for safety analysis of HIFU treatment. One case developed obstructive jaundice 2 weeks after HIFU treatment. Vertebral injury, identified by MRI, occurred in 2 cases, although no symptoms were reported. No severe complications were observed in all enrolled patients.

Two methods have been developed in HIFU treatment: continuous and pulsed HIFU. They differ in both technical parameters and therapeutic approach [51]. Using high intensities ranging from 5-20 kW/cm², each continuous HIFU shot can induce coagulation necrosis of a targeted tumor. In contrast, pulsed HIFU uses lower ultrasound intensities, usually <3 kW/cm². In the first case, the it is a one-session treatment; either sedation or general anesthesia is required for patients during treatment procedure due to discomfort and pain. After treatment, the patients require hospitalization for several days. Pulsed HIFU is a multiple-session treatment, and needs to be repeated for many times

(5-10 sessions) if the patients are suitable. Most of the patients do not need sedation performed on an outpatient basis [51].

Xiong *et al* [34] reported the largest retrospective study of using pulsed HIFU treatment for advanced pancreatic cancer. Eighty-nine patients with pancreatic cancer were analyzed after HIFU. The authors concluded that the clinical application of HIFU for pancreatic cancer appeared to be safe and was a promising modality of treatment for palliation of pain related to pancreatic cancer. Recent studies indicated that pulsed HIFU can significantly enhance chemotherapeutic agents against tumor cells, suggesting that pulsed HIFU may be a treatment approach using focused ultrasound for hyperthermia, instead of HIFU for inducing coagulation necrosis: hyperthermia could make some cancer cells more sensitive to radiation and chemotherapy [52,53]. Up to now, HIFU has been largely reported mostly as a palliation option to treat patients with locally advanced pancreatic cancer. Although the mechanism is still unclear, HIFU might be an effective treatment option for pain control, particularly in patients with tumors infiltrating the celiac plexus and in whom conventional pain treatments are not considered an effective option [54]. Orsi and Orgera treated also inoperable patients with P-NET (insulinomas) with HIFU [36,37]. The patients suffered from episodes of severe night hypoglycemia, which was not efficiently controlled by medication. Symptom relief and local disease control were achieved also in these patients, without any complications.

In conclusion, the main advantages of HIFU therapy are: less invasive with no incision, no percutaneous placement of needles, no scarring, less pain, and short recovery time. These results are associated with a reduction in mortality, morbidity, hospital stay, cost, and improved quality of life for cancer patients.

In the future, lower energy treatments may play a significant role in mediating targeted drug and gene delivery for cancer treatment [55].

Concluding remarks

All studies demonstrated that percutaneous ablation of pancreatic tumors is feasible and reproducible. Difficulties related to the choice of the approach can be overcome by accurate selection of patients on the basis of pre-procedural images, and by the experience of the operator. The choice of a percutaneous approach must be carried out by evaluating the possibility of positioning the devices without risking damage to adjacent structures by a multidisciplinary team and with the right equipment. The involvement of vessels is one of the most important factors; some of the techniques considered in our review seem to overcome this limit. But more studies, particularly prospective randomized, with more patients are necessary to define the best treatment for the percutaneous management of locally advanced pancreatic cancer.

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