Review Article

Systematic review of endoscopy ultrasound-guided thermal ablation treatment for pancreatic cancer

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ABSTRACT

The development of curvilinear-array EUS and EUS-guided fine-needle aspiration (EUS-FNA) has led these approaches to become interventional procedures rather than purely diagnostic, as a minimally invasive antitumor therapeutic alternative to radiological and surgical treatments. The possibility to accurately position needle devices and to reach a deep target like the pancreas gland under real-time imaging guidance has expanded the use of EUS to ablate tumors. Currently, a variety of probes specifically designed for EUS ablation are available, including radiofrequency, hybrid cryothermal ablation (combining radiofrequency with cryotechnology), photodynamic therapy, and laser ablation. To date, several studies have demonstrated the safety and feasibility of these ablation techniques in the pancreatic setting, but only a few small series on pancreatic thermal ablation under EUS guidance are available. EUS-guided thermal ablation is primarily used for pancreatic cancer. It is well suited to this disease because of its superior anatomical access compared with other imaging modalities and the dismal prognosis despite improvements in chemoradiotherapy and surgery in the management of pancreatic cancer. Other targets are pancreatic neuroendocrine tumors and pancreatic cystic neoplasms, which are curable by surgical resection, but some patients are poor surgical candidates or prefer conservative management. This is a literature review of previously published clinical studies on EUS-guided thermal ablative therapies. Data on the long-term efficacy of EUS-guided antitumor thermal ablation therapy and large prospective randomized studies are still needed to confirm the real clinical benefits of these techniques for the management of pancreatic neoplasms.

Key words: Cryoablation, endoscopic ablation, EUS, EUS-guided ablation, laser ablation, pancreas, pancreatic cancer, pancreatic cystic neoplasm, pancreatic neuroendocrine tumor, photodynamic therapy, radiofrequency ablation, thermal ablation

INTRODUCTION

"Tumor thermal ablation" is the term used to define the direct application of thermal energy to a focal tumor, attempting to achieve a mass cytoreduction through the induction of tissual damage and cellular

Access this article online	
Quick Response Code:	Website: www.eusjournal.com
	DOI: 10.4103/eus.eus_74_19

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How to cite this article: Testoni SG, Healey AJ, Dietrich CF, Arcidiacono PG. Systematic review of endoscopy ultrasound-guided thermal ablation treatment for pancreatic cancer. Endosc Ultrasound 2020;9:83-100.

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Received: 2019-08-28; **Accepted:** 2019-11-18; **Published online:** 2020-04-15

necrosis. It has been found that cancer cells are more heat sensitive when compared to normal tissue, likely because of a higher metabolic stress, a lower thermal conductance and a lower cancer microenvironment pH.[1]

The most commonly used techniques for tumor thermal ablation in the current practice are radiofrequency ablation (RFA), photodynamic therapy (PDT), microwave ablation, high-intensity focused ultrasound, and cryoablation (CRYO). Neodymium-doped yttrium aluminum garnet (Nd:YAG) laser has also been used.

Over the last decade, thermal ablation has become increasingly accepted for the treatment of different solid parenchymal tumors, particularly in patients with inoperable disease or those unfit for surgery. However, the application of thermal ablation to pancreatic tumors has been limited by the risk of precipitating severe complications induced by thermal injury to the pancreatic parenchyma and surrounding structures (*e.g.*, duodenum and common bile duct). Moreover, in the case of pancreatic cancer, that often encases neighboring vasculature and extends retroperitoneally or proximally, the direct ablation of the entire tumor is impossible.

Recently, despite this limitation, there has been a growing interest in the use of thermal ablation techniques for pancreatic tumors. In the cases of inoperable pancreatic adenocarcinomas (PDACs), symptomatic pancreatic neuroendocrine tumors (PNETs) and pancreatic metastases, the results have been promising. Locoregional thermo-ablative techniques present lower rates of morbidity, better preservation of healthy surrounding tissues, shorter hospital stay, and overall lower cost, when compared to surgical intervention. Hence, the improvement of biotechnologies applied to endoscopy has allowed the development of this real-time targeted minimally invasive treatment modality.[2] Additional advantages of this technique are the possibility to use real-time Doppler imaging to avoid major vessel injury during the procedure and the capacity to monitor the change in the lesions in response to the treatment.[3,4]

New probes and devices have been studied, particularly in porcine models. All those studies carried out in *in vivo* animal models, demonstrate that EUS-guided ablation of the pancreas is feasible, efficient, and safe, but its clinical application in humans requires further evaluation.

EUS-guided tumor thermal ablation therapy has been mostly used for pancreatic tumors, mainly PDAC and pancreatic neuroendocrine tumors (PNETs). PDAC has a poor prognosis, with a 5-year survival rate <10% for all stages.[5] Radical resection is the only potentially curative treatment, but, unfortunately, only 15%–20% of patients are eligible for surgery at diagnosis.[6] About 40% of pancreatic cancer patients have locally advanced unresectable disease (LAPC),[7] without evidence of distant spread. LAPC is defined by the National Comprehensive Cancer Network as a local disease, without distant metastases, in which the tumor is in circumferential contact with the superior mesenteric artery (SMA) or the celiac artery (CA) >180° (head-uncinate process cancer), or a contact >180° with the SMA or CA, or CA and aortic involvement (body-and-tail cancer).[8] LAPC is classified into borderline resectable (<10% of pancreatic cancers) and unresectable disease (20%–30%).[9] Despite the new chemotherapy (ChT) and radiotherapy (RT) regimens, minimal survival benefits have been achieved in these patients.[10] The American Society of Clinical Oncology Clinical Practice Guidelines suggest that a preoperative strategy should be applied to patients who have tumors that are anatomically resectable, but are characterized by a high likelihood of metastatic disease or margin-positive resection.[11] In this context, a local ablative treatment under EUS guidance that precipitates minimally invasive tumor destruction, might improve the efficacy of chemoradiation therapy in selected patients. PNETs present a prevalence of about 10% of all pancreatic neoplasms.[12,13] PNETs are typically categorized into sporadic or genetically determined as part of inherited syndromes. They are further classified depending on the disease stage, histological grade, and on whether they cause patients to be symptomatic due to the secretion of hormones.[14] The majority of PNETs are nonfunctioning. Most functioning PNETs present with a resectable disease and therefore, surgical resection is the treatment of choice.[15] However, pancreatic surgery still presents high risks and patients who are poor surgical candidates or prefer less invasive management might benefit from EUS-guided ablative treatment to reduce the symptoms due to hormone hypersecretion. However, limited data on this approach is available thus far. In recent years, there has also been increasing interest in treating pancreatic cystic neoplasms (PCNs) by EUS-guided ablation. These are common and are incidentally diagnosed in about 10% of patients undergoing abdominal imaging.[16] The epithelium of mucinous cystic lesions

of the pancreas, including intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs), can undergo dysplastic changes ranging from benign to borderline or malignant, and again, many of these patients are elderly and/or not good surgical candidates.[17]

The current systematic review will present the different technologies available for EUS-guided thermal therapy of pancreatic neoplasms and the safety and efficacy of each ablative therapy.

RESEARCH METHODOLOGY

The primary end point of the current review was to assess the safety and efficacy of the different thermal ablation therapies under EUS guidance in the treatment of pancreatic cancer. The secondary end point was to assess improvement in overall survival, when available.

A systematic literature search was performed using PubMed and EMBASE databases and Cochrane library for studies published in the English language up to July 2017. A search in clinical trial registries, online journals, and conference proceedings was also performed. The following MeSH terms were also used: Ablation techniques OR pulsed radiofrequency treatment OR catheter ablation OR cryosurgery OR microwaves OR high intensity focused ultrasound ablation OR laser therapy OR photochemotherapy AND pancreas OR pancreatic diseases OR pancreatic neoplasms OR carcinoma, pancreatic ductal AND endoscopic ultrasound fine needle aspiration OR endosonography OR endoscopy OR endoscopy, digestive system OR endoscopy, gastrointestinal. MeSH terms were restricted to title, abstract, and keywords. Only articles describing EUS-guided thermal ablation in pancreatic cancer were included in the review. Articles describing nonthermal EUS-guided ablative therapies, those describing thermal ablative therapies in nonhuman clinical setting, those reporting on tumors that did not originate in the pancreas, and those published in non-English language were excluded from the systematic review. All references were screened for potentially relevant studies not identified in the initial literature search. For each study, the following data were extracted, when available: number of patients, pancreatic cancer's type and extent, device used and settings, feasibility of the procedure, duration of therapy, number of ablation sessions, complications related to procedure, additional safety methods applied, and outcomes.

From the literature search on PubMed, EMBASE, and Cochrane Library, a total of 424 articles were found. Excluding duplicate articles, review articles, and non-English publications and selecting articles that met the inclusion criteria, nine clinical human studies were found, with six entailing radiofrequency ablation, one on cryothermal ablation, one using photodynamic therapy, and one on YAG-laser ablation (LA). Moreover, three published abstracts, presented in conference proceedings (*i.e.*, not yet full text published), were found: two about EUS-guided radiofrequency ablation and one about EUS-guided cryothermal ablation. No studies were found about other EUS-guided pancreatic thermal ablative therapies, such as microwave ablation, cryoablation, and high-intensity focused ultrasound in the clinical setting.

EUS-GUIDED RADIOFREQUENCY ABLATION

RFA produces tissue thermal-induced damage through the induction of high local temperatures, ranging between 60°C and 100°C. These are generated by high-frequency alternating currents that induce frictional heating, resulting in irreversible cellular damage, apoptosis, and coagulative necrosis of the tissue.[18,19] Temperatures above 100°C are less efficient in inducing tissue ablation. This is felt to be because they induce a process of immediate vaporization and drying of the tissue surrounding the probe, leading to a higher thermal impedance and by proxy, a lower ablative efficiency. Another consequence of RFA is the heat-shrink effect. This occurs when the heat is absorbed by the bloodstream of adjacent vessels, causing the dissipation of hyperthermia and thus a reduction of the ablative effect.[20]

Two different types of RFA probes are currently available. Monopolar probes include a generator, a delivery electrode (that releases the high-density current providing localized heating), and a dispersive electrode as an earth pad. This disperses the energy in order to avoid possible thermal injury. Bipolar probes include two interstitial electrodes. These deliver energy confined between the two electrodes. The bipolar probes have the advantage of a more local and rapid heating, with potentially lower injury rate to the surrounding tissue and less perfusion conductance, when compared to monopolar probes. However, they have a lesser ablative capacity.[21]

RFA has been applied percutaneously or intraoperatively in many different oncological settings, either with curative intent as in hepatocellular carcinoma (HCC),[22] or as palliation in case of liver, lung, and bone metastasis; cholangiocarcinoma; and breast, adrenal, and head-and-neck cancers.[23,24] RFA is also thought to trigger an immunomodulatory activity, with an additional overall anticancer effect.[25]

However, the application of RFA in the pancreatic setting has found clinicians reluctant, due to the fear of possible complications related to thermal injury to adjacent structures (*e.g.*, stomach, duodenum, mesenteric artery and vein, and bile duct) and risk of thermal-induced pancreatitis, as reported by some initial studies conducted on animal models, showing a high rate of mortality (25%).[3,26] Preliminary surgical experiences showed that the iatrogenic injury might be reduced by applying some technical precautions, such as an ablation temperature lower than 90°C, the maintenance of a safety margin from major vessels and adjacent structures, and the use of a step-up approach in the case of large-sized lesions.[18,24] In truth, pancreatic cancer has generally poorly defined margins, making it difficult to ablate all the tumoral masses in a single session.[27]

Recently, there has been growing interest in investigating the role of RFA in EUS-guided treatment of pancreatic tumors, mostly in studies on animal models [Table 1].[3,28-34] Only a few small case series in patients exist, mostly with Stage III pancreatic cancer or neuroendocrine tumors [Table 2].

Currently available commercial probes specifically designed for EUS-guided treatment of pancreatic lesions are all monopolar and are:[35] (1) 19G EUS-FNA needle electrode (Radionics Inc., Burlington, MA, USA), which consists of a prototype 19G (1.1 mm) needle, with the active segment of 10–15 mm length and (2) Habib™ EUS-RFA catheter (EMcision Ltd, London, United Kingdom), which is a 1-Fr wire (0.33 mm, 0.013") with a working length of 220 cm and active segment length of 10–20 mm. It can be connected to a an electrosurgical RF generator (RITA Medical Systems Inc., Mountain View, CA, USA). The catheter is placed through a 19G needle with a stylet, and RF energy is generally applied for 90–120 s; EUSRA RFA electrode system (STARmed, Koyang, South Korea) consists of a prototype 19G (1.1 mm) or 18G, 140-cm-long needle electrode, with an inner part isolated in all its length except for the distal active segment (5, 10, 15, and 20 mm) and a sharp conical tip which delivers energy. It can be connected to a VIVA RF generator (STARmed, Seoul, South Korea). Only the EUSRA RF electrode is provided with an internal cooling system (cold saline), with two tubes connected to the needle electrode handle. This cooling system prevents charring of the electrode surface, enabling efficient transmission of heat. The Habib EUS-RFA probe is a "through-the-needle" device, whereas others are "EUS-FNA needle-type" devices.

The first human pilot study assessing the feasibility and safety of EUS-guided RFA in the pancreatic setting was published in 2015, using the Habib™ EUS-RFA probe.[36] In this prospective multicenter study, eight patients were enrolled: six with PCNs (4 MCNs, 1 IPMN, and 1 microcystic adenoma) and two with PNETs in the pancreatic head, who were poor surgical candidates. This study also represented the first published application of RFA to treat PCNs. The mean diameter of PCNs and PNETs was 36.5 mm and 27.5 mm, respectively. For RFA, the FNA needle with stylet was first placed in the deepest part of the tumor in case of PNETs and near the far end of the lesion in case of PCNs. Then, the stylet was removed, and the RFA probe was inserted into the needle until resistance was met. The FNA needle was then slowly withdrawn by 3 cm in order to be separated from the active part of the RFA catheter, which was visualized using fluoroscopy. RF (RITA, Model 1500x or ERBE Model ICC200) was applied at 5 W, 15 W, 20 W, and 25 W in 3, 2, 2, and 1 patients, respectively, over 90 s for each Watt setting. Repeated treatments were done in larger pancreatic lesions, in different needle axes. All the six patients with PCNs underwent one ablative session; the two patients with PNETs underwent one and two treatment sessions, respectively. EUS-RFA with Habib™ probe was feasible in all the patients. Among the patients with PCNs, complete resolution of the cysts and cyst reduction of 48.4% were observed at 3- and 6-month postprocedure imaging in two and three cases, respectively. In the patients with PNETs, a change in vascularity and a central necrotic area of 15 mm were observed. Overall, two patients developed mild and self-limiting abdominal pain, and there were no major complications in the 48-h postprocedural follow-up. All the patients were alive at the time of publication of the study.

Waung *et al.*[37] reported the successful treatment of a sporadic symptomatic 18-mm insulinoma by using

Table 1. Pancreatic EUS-guided thermal ablative therapy: Animal studies

Study	*n*	Procedure Device	Power settings	Generator	Time of application, mean seconds (range)	Sessions, *n*	Treatment to analysis duration, mean days (range)	Outcome	Complications
Goldberg *et al.*, 1999[3]	13	RFA 19G Vilmann-type needle (GIP/MediGlobe, Grassau, Germany)	285±120 mA	Radiomics Series 3	360	16 ablations	Immediate (*n*=5) 1-2 (*n*=2) 14 (*n*=6)	Well-demarcated coagulative necrotic area of 8-12 mm (*n*=7) Retraction of coagulated focus (*n*=4) 1-3 mm fibrotic capsule surrounding coagulated tissue (*n*=2)	Gastric burn (*n*=1) Intestinal burn (*n*=1) Mild hyperamylasemia with focal zone of pancreatitis and later pancreatic fluid collection (*n*=1)
Kim *et al.*, 2012[28]	10	RFA 18G RFA electrode (STARmed, Koyang, Korea)	50 W	VIVA (STARmed, Korea) Internal cooling system	300	NA	7	Technical success 100% Mean area of ablation: 23±6.9 mm	Retroperitoneal fibrosis (*n*=1) Adhesions of pancreas to stomach wall and bowel wall (*n*=2)
Gaidhane *et al.*, 2012[29]	5	RFA 19G Habib EUS-RFA probe (EMcision Ltd., London, UK)	6-mm probe exposed: 4 W 5 W 6 W 10-mm probe exposed: 4 W 5 W 6 W	RITA (Electrosurgical RF Generator)	6-mm probe exposed: 300 54 12 10-mm probe exposed: 258 84 48	26 ablations	6	Area of ablation: 8-10 mm	Moderate pancreatitis (*n*=1) Fat necrosis around pancreas (*n*=2)
Silviu *et al.*, 2015[30]	10	RFA 19G Habib RF DUO 0.33 mm, 0.013 needle (EMcision Ltd., London, UK)	5 W 10 W 15 W 20 W	RITA Medical System 1500 RF (Angiodynamics, New York, USA)	120	4	7	Median area of ablation: 26.5 mm (IQR 5 mm; range 20-30 mm)	Gastric wall injury, retrperitoneal fibrosis and adhesions on the bowel wall (*n*=1) Moderate ascites (*n*=1)
Carrara *et al.*, 2008[31]	14	Cryothermal ablation Cryotherm probe (ERBE Elektromedizin, Tubingen, Germany)	Heating: 16 W Cooling: 650 psi	Heating: VIO 300D (ERBE Elektromedizin, Tubingen, Germany) Cooling: ERBEKRYO CA (ERBE Elektromedizin, Tubingen, Germany)	107 (120-900)	NA	7 (*n*=7) 14 (*n*=7)	Positive correlation of the lesion area seen by EUS with macroscopic lesion area at necropsy (r=0.89; P=0.0006) Significant positive correlation between macroscopic lesion area and application time (P<0.0001 at 1 week, P=0.01 at 2 weeks)	Necrotic pancreatitis with peritonitis (*n*=1) Pancreatitis (*n*=1) Gastric wall burn (*n*=1) Gut adhesions (*n*=4)

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Table 1. Contd...

Study	*n*	Procedure Device	Power settings	Generator	Time of application, mean seconds (range)	Sessions, *n*	Treatment to analysis duration, mean days (range)	Outcome	Complications
Chan *et al.*, 2004[32]	3	PDT 19G EUS-FNA (Wilson-Cook Medical Inc, Winston-Salem, N.C.) Quartz optical fiber with 1.0 cm light diffuser (modified Optiguide; Laserscope, Fibersdirect.com, Kirkland, Wash)	0.4 W 50 J/per site	630-nm wavelength laser (Domed, Axcan Pharma, Inc., Mont-Saint-Hilaire, Quebec, Canada) Porfimer sodium (Photofrin; Axcan Pharma, Inc., Mont-Saint-Hilaire, Quebec, Canada)	125	9 ablations	2 (*n*=3)	Complete necrosis	None
Yusuf *et al.*, 2008[33]	6	PDT 19G EUS-FNA (Echotip, Cook Endoscopy, Wnton-Salem, NC) Quartz opitical fiber	400 mW×125 s 150J/cm^2	689-nm wavelength laser light Verteporfin (Visudyne; Novartis Ophthalmics, East Hanover, NJ)	600 900 1200	NA	7 (*n*=6)	Mean diameter of ablation area on CT scan: 6.6 mm for 600 s, 9.4 mm for 900 s, 26.3 mm for 1200 s Mean diameter of ablation area on gross pathology: 15 mm for 600 s, 24 mm for 900 s, 30.5 mm for 1200 s	Mild increase in serum amylase (*n*=1)
Di Matteo *et al.*, 2010[34]	8	Nd: YAG laser 19G EUS-FNA (Cook Medical Inc., Wnston-Salem, NC) Quartz optical fiber with tip 300 µm in diameter (Echolaser X4; Elesta srl, Florence, Italy)	2 W at 500 J (*n*=3) 3 W at 500 J (*n*=3) 2 W at 1000 J (*n*=3) 3 W at 1000 J (*n*=1)	1064 nm wavelength Nd:YAG laser (Echolaser X4, Elesta srl)	250 167 500 333	10 ablations	1 (*n*=8)	Ablation area/volume: 49 mm^2/314 mm^3 59 mm^2/428 mm^3 67 mm^2/460 mm^3 80 mm^2/483 mm^3 Technical failure (*n*=1)	Asymptomatic small peripancreatic fluid collection (*n*=6) Not clinically significant increase in serum amylase levels (*n*=7) and lipase levels (*n*=8)

RF: Radio frequency, RFA: RF ablation, PDT: Photodynamic therapy, Nd: YAG: Neodymium-doped Yttrium aluminum garnet, CT: Computed tomography, NA: Not available

Table 2. Pancreatic EUS-guided thermal ablative therapy: Clinical studies

Study	*n*	Procedure/ device	Power settings	Generator	Indications	Tumor size, mean mm (range)	Time of application, mean seconds (range)	Sessions, *n*	Outcome	Complications	Follow-up period, mean months (range)	Median survival, mean months (range)
Wang *et al.*, 2013[42]	3	RFA/22G Habib EUS-RFA needle (EMcision Ltd., London, UK)	10-15 W	NA	Stage III PC	37	120	1 (*n*=2) 3 (*n*=1) 2 RF applications per session	Technical success 100% 13.94% mean reduction in tumor size 46.53% mean reduction in CA19-9 levels	None	2 weeks	NA
Rossi *et al.*, 2014[38]	1	RFA/22G Habib EUS-RFA needle (EMcision Ltd., London, UK)	10-15 W	RF generator Model TAG 100 (Invatec S.r.l., Concesio, Italy) or Model RF 3000 (Boston Scientific Corp, Natick, Mass)	PNET	9	360	1	Complete ablation and no clinical recurrence	None	34	NA
Pai *et al.*, 2015[36]	8	RFA/19G Habib EUS-RFA catheter (EMcision Ltd., London, UK)	5 W (*n*=3) 15 W (*n*=2) 20 W (*n*=2) 25 W (*n*=1)	Rita (Model 1500X) or ERBE (Model ICC 200)	MCN (*n*=4) IPMN (*n*=1) Microcystic adenoma (*n*=1) PNET (*n*=2)	36.5 (20-70) 27.5 (15-40)	90-120	1 (*n*=7) 2 (*n*=1) RF application per session 4.5 (2-7)	Cyst resolution (*n*=2) 48.4% cyst reduction (*n*=3) Change in vascularity and central necrosis in PNETs (*n*=2)	Mild abdominal pain (*n*=2)	3-6	NA
Armellini *et al.*, 2015[40]	1	RFA/18G EUSRA RF needle electrode (STARmed, Koyang, Korea)	5 W	Heating: VIVA RF generator (STARmed) Internal cooling system	PNET	20	NA	1 2 RF applications per session	Complete morphological ablation and clinical remission	None	1	NA
Waung *et al.*, 2016[37]	1	RFA/Habib EUS-RFA probe (EMcision, Ltd., London, UK)	10 W	NA	Insulinoma	18	100 (90-120)	3 *n*=8.3 (3-14) total ablations	Morphological and clinical complete remission	None	10	NA
Lakhtakia *et al.*, 2016[39]	3	RFA/19G EUS-RFA needle electrode (STARmed, Seoul, South Korea)	50 W	Heating: VIVA RF generator (STARmed) Internal cooling system (2 tubes connected to the needle electrode)	Insulinoma (hypoglycemia)	19 (14-22)	10-15	1 Multiple applications per session	Clinical complete remission (*n*=3) Morphological complete remission (*n*=1)	None	11-12	NA
Song *et al.*, 2016[41]	6	RFA/18G EUS-RFA needle electrode (STARmed, Koyang, Korea)	20-50 W	Heating: VIVA RF generator (STARmed, Koyang, Korea) Internal cooling system	Locally advanced PDAC (*n*=4) Metastatic PC (*n*=2)	38 (30-90)	10-15	1.3 (1-2) Multiple applications per session	Necrosis with air bubbles at the ablation site (*n*=1)	Mild abdominal pain (*n*=2)	4.2 (3-6)	NA

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Table 2. Contd...

Study	*n*	Procedure/ device	Power settings	Generator	Indications	Tumor size, mean mm (range)	Time of application, mean seconds (range)	Sessions, *n*	Outcome	Complications	Follow-up period, mean months (range)	Median survival, mean months (range)
Goyal *et al.*, 2017[43]	5	RFA/22G Habib EUS-RFA needle (EMcision Ltd., London, UK)	Soft coagulation effect of 4 10 W	NA	PNET (*n*=1) MCNs (*n*=2) Locally advanced PDAC (*n*=2)	NA	120	3-5 cycles	Technical success 100% Clinical success and increase in EUS elastography strain ratio from 4.7 to 17 in PNET	None	NA	NA
Arcidiacono *et al.*, 2012[49]	22	Cryothermal ablation CryoTherm Probe (ERBE Elektromedizin, Tübingen. Germany)	Heating: 18 W Cooling: 650 psi	Heating: VIO 300D RF system (ERBE Elektromedizin, Tübingen. Germany) Cooling: ERBEKRYO CA system (ERBE Elektromedizin, Tübingen. Germany)	Locally advanced unresectable PDAC	36 (23-54)	107 (10-360)	1 (*n*=13) 2 (*n*=3)	Technical failure in 6 patients Volume reduction (*n*=6 patients; *P*=0.07)	Transient abdominal pain and raised serum amylase levels (*n*=3); minor duodenal bleeding (*n*=1); jaundice (*n*=2; 1 had hemobilia and anemia); duodenal stricture (*n*=1); cystic fluid collection (*n*=1)	-	6 (1-12)
Petrone *et al.*, 2017[52]	35	Cryothermal ablation/ HTP (ERBE Elektromedizin, Tübingen. Germany)	Heating: 18 W Cooling: 650 psi	Heating: VIO 300D RF system (ERBE Elektromedizin, Tübingen. Germany) Cooling: ERBECRYO2 system (ERBE Elektromedizin, Tübingen. Germany)	Locally advanced unresectable PDAC	37 (20-60)	126 (30-360)	1 (*n*=20) 2 (*n*=6) 4 (*n*=1)	Technical failure in nine patients Necrotic area of 35% (3%-65%) of tumoral mass Positive correlation: Ablation time *versus* necrosis volume (*r*=0.66; *P*=0.013); necrosis volume *versus* tumor volume (*r*=0.92; *P*<0.0001) Median survival time of patients threated >1 EUS-HTP increased from 5 to 9 months (*P*=0.066)	Early (*n*=11): 10 mild, 1 moderate Late: 1 procedure-related, 5 mostly related to tumor progression	-	6 (1-22)

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Table 2. Contd...

Study	*n*	Procedure/ device	Power settings	Generator	Indications	Tumor size, mean mm (range)	Time of application, mean seconds (range)	Sessions, *n*	Outcome	Complications	Follow-up period, mean months (range)	Median survival, mean months (range)
Choi *et al.*, 2015[59]	1	PDT/0.39 mm quartz core flexible laser probe (PhotoGlow, South Yarmouth, Massachusetts, USA) 19G EUS-FNA (Cook Endoscopy) Chlorine e6 derivative (Photolon, Belmedpreparaty, Minsk, Republic of Belarus)	300 mW/ cm 100 J/cm of 2 cm diffuser tip length	Photoactivation at 660 nm wavelength (UPL-FDT; LEMT Research and Development Private Unitary Enterprise, Misnk, Republic of Belarus)	Locally advanced PDAC with localized tumor progression following CRT	31	330	*n*=2 laser-light deliveries per session	Median radius of necrosis=0.85 cm Volume of necrosis on CT scan at 1 month=1.9 cm3 Disease stable	None	3	NA
Di Matteo *et al.*, 2014[64]	1	Nd:YAG laser/0.30 mm quartz optical fiber (Echolaser X4; Elesta Srl, Florence, Italy) 19G FNA (Cook Medical Inc, Winston-Salem, NC)	4.0 W	1.064 nm wavelength Nd:YAG laser (Echolaser X4; Elesta Srl, Florence, Italy)	Recurrent PNET (MEN I)	9	300	1	Well-defined coagulative necrotic area of 35 mm immediately after ablation, 18 mm at 1 month CT scan, 9 mm at 1 year CT scan No metabolic activity on 68Ga-DOTA-NOC-PET	None	12	NA

RF: Radiofrequency, RFA: RF ablation, PDT: Photodynamic therapy, Nd:YAG: Neodymium-doped Yttrium aluminum garnet, PC: Prostate cancer, PNETs: Pancreatic neuroendocrine symptomatic tumors, MCNs: Mucinous cystic neoplasms, IPMN: Intraductal papillary mucinous neoplasm, PDAC: Pancreatic adenocarcinoma, CRT: Chemoradiation therapy, MEN: Multiple endocrine neoplasia, HTP: HybridTherm probe, NA: Not available, CT: Computed tomography

the Habib™ RFA probe in a 70-year-old patient, who was unfit for surgery due to comorbidity and was not responsive to other medical treatments. The lesion was located in the uncinate process of the pancreas. The patient underwent three consecutive treatment sessions, each 1 week apart, with three applications lasting 120 s during the first procedure, into the central part of the tumor, eight applications lasting 90 s during the second treatment, within the tumor in two different planes, and 14 applications lasting 90 s during the third procedure, in other three planes and within the distal wall. The energy delivery was set at 10 W. After the last RFA treatment, there was biochemical and clinical remission, and glucose requirement and octreotide therapy were withdrawn. A postprocedural CT scan showed that the lesion had been almost completely replaced by necrotic tissue, and a 68 gallium dotatate positron emission tomography (PET)-CT scan showed absence of abnormal uptake within the uncinate process. The patient was still asymptomatic after 10-month follow-up.

Another clinical experience of EUS-RFA of a secreting PNET, by using the Habib™ probe, with the exposed tip measuring 10 mm in length, was reported by Rossi *et al.*[38] in a 72-year-old male patient with a PNET located in the pancreatic head, with a dimension of 0.5 cm × 0.9 cm. The RF catheter was advanced through a 22G needle (Cook Ireland Ltd, Limerick, Ireland), previously inserted into the tumoral lesion under EUS guidance, after removal of the stylet from the needle, until its tip reached the center of the tumor. The RF energy was delivered at 10–15 W of power for 6 min. Hospital stay for the patient was 7 days. No complications related to the procedure occurred. Twenty-four hours after the treatment, serum hormone levels returned within the normal limits and symptoms completely regressed. At 1-month imaging studies, the lesion was completely ablated, showing a nonenhancing area at the ablation site. The patient remained asymptomatic, with serum hormone levels within the normal ranges during the 12-month follow-up.

Lakhtakia *et al.* evaluated the feasibility of EUSRA RFA system for the treatment of symptomatic insulinoma in an observational human case series of three patients, not eligible for surgery.[39] Lesions larger than 1 cm were selected, in order to accommodate the 10-mm length active needle electrode and avoid complications related to thermal injury to normal pancreatic tissue. The needle electrode was passed under EUS guidance into the pancreatic tumor, at the far end of the lesion. The most technically challenging area of the tumor was ablated first as visual artifacts after RFA may hinder accurate targeting. The RF energy delivery was set at 50 W and applied for 10–15 s, creating an area of coagulative necrosis of 10–12 × 5 mm. Further ablation was done by withdrawal of the needle electrode to more proximal sites, through the same needle tract of the first application. Different areas of the same lesion were ablated through additional needle electrode passes by using a fanning technique. EUS-RFA was technically successful in all the patients. The completion of RF application was showed by the appearance of echogenic bubbles around the needle tip at the site of RFA. There were no procedure-related complications. During the 11/12-month follow-up, all the patients remained normoglycemic and symptom free with biochemical improvement.

Other clinical experience with RFA for the treatment of PNET using the EUSRA RF 18G water-cooled needle electrode has been reported by Armellini *et al.*[40] The authors successfully treated a 20-mm, G2 graded (Ki67 >5%), PNET in an asymptomatic 76-year-old patient, who had refused surgery. The length of the active tip of the probe was of 5–30 mm. The lesion was completely ablated in a single session, with two passes of the exposed-tip needle (10 mm long), without procedure-related complications. Computed tomography (CT) scan and contrast-enhanced EUS performed after 1 month confirmed a complete radiological ablation, and the patient remained free of disease.

The feasibility and safety of EUS-RFA was assessed also for the treatment of PDAC and reported in one published study and two abstracts presented in conference proceedings. A preliminary study involving six patients with unresectable pancreatic cancer was performed by Song *et al.*[41] The tumors were located in the pancreatic head and body in four and two cases, respectively. The median diameter of the pancreatic tumors was 3.8 cm (range: 3–9 cm). Four patients and two patients had Stage III and Stage IV PDAC, respectively, and were resistant to previous treatments. An EUSRA RFA 18G needle electrode, connected to a VIVA RF generator, was used for the procedure. The length of the exposed tip of the RFA electrode was 10 mm. The RFA needle electrode was inserted under EUS guidance into the mass, and the generator was activated to deliver energy of 20–50 W

ablation power for 10 s. During the procedure, the RF electrode was cooled and internally perfused with circulating chilled saline solution delivered through a pump. Depending on the tumor size, the ablation was repeated, in different sites of the tumor mass until the hyperechoic area around the electrode tip covered all the lesion. On contrast-enhanced EUS after RFA, the thermal-induced necrotic areas appeared nonenhancing, surrounding areas with increased blood flow. EUS-RFA was technically successful in all cases. No major procedure-related complications occurred; only two patients experienced mild abdominal pain. In this study, the overall survival of treated patients was not assessed.

Wang *et al.*[42] reported their experience with EUS-RFA using the Habib™ catheter in a series of three patients with Stage III pancreatic cancers. The mean tumor size was 37.3 mm. The RF probe was placed through a 22G needle infixed into the tumor. The energy was delivered at 10–15 W ablation power for 2 min. Depending on the size of the tumor, the procedure was repeated performing a second needle tract about 1–1.5 cm apart from the first needle tract. Three EUS-RFA procedures, each 2 weeks apart, were performed in one patient. Technical success was 100%. The 2-week follow-up showed a mean reduction in tumor size of 13.94% at US imaging, with vacuolar degeneration, and a mean reduction in CA19-9 levels of 46.53%. No complications were observed up to 49-day follow-up.

Goyal *et al.* used the Habib™ probe in five patients, two of them with unresectable locally advanced PDAC, two with high-risk MCNs, and one with a functional PNET.[43] The last three patients were poor surgical candidates. The lesions were located in the pancreatic head (one case), genu and tail (one case), and body (two cases). The RF probe was inserted into the lesions through a 22G needle, after removal of the stylet. RF energy was applied in 3–5 cycles, each lasting 2 min, with the following settings; soft coagulation effect of 4 and power setting of 10 W. The ablation was feasible in all the cases. No procedure-related complications occurred. Immediate clinical success was achieved in the case of functional PNET (cessation of diarrhea). No follow-up data were available.

Based on these clinical experiences, EUS-guided RFA for locally advanced PDAC, functional PNETs, and, potentially in future, PCNs can be considered a safe and effective cytoreductive treatment. In a multidisciplinary setting, this treatment might help achieve a better response to the standard therapy, palliation of symptoms, better quality of life and improved survival nonsurgical patients. However, confirmation of EUS-RFA safety and efficacy should be warranted through prospective larger randomized studies.

EUS-GUIDED CRYO-THERM ABLATION

A flexible hybrid bipolar cryotherm probe that combines the effects of RFA and cryotechnology and can be inserted through the working channel of a linear echoendoscope, has recently been developed (HybridTherm, ERBE Elektromedizin GmbH, Tübingen, Germany). A bipolar system ablates with less collateral thermal damage than monopolar one, but appears to be less efficient.[44,45] CRYO has been used successfully for the local treatment of many cancers, such as kidney, prostate, breast, and skin cancers. Besides the local tissue ablation, it is supposed that CRYO induces a systemic inflammatory response that can stimulate an antitumor response, not only in the treated area, but also in distant metastasis.[46,47] Thus, by combining the effects of the two technologies (RFA and CRYO), the HybridTherm probe (HTP) utilizes the effects of the two approaches and overcomes the disadvantage of lower efficacy of bipolar RFA. In fact, the cooling effect of cryogenic gas increases the interstitial devitalization of tissues induced by RFA.[48]

The HTP is an internally carbon dioxide-cooled device, allowing efficient cooling based on the Joule-Thomson effect. It is a EUS-19G FNA needle-type device with a sharp and stiff distal tip, allowing the puncture of the gastric and duodenal wall and pancreatic parenchyma with no need to apply current. The probe has a length of 1.4 m. It is covered by a protective tube for all its length, so that it can be safely passed through the 3.8-mm operative channel of the echoendoscope. The electrically active part of the HTP has a diameter of 2.2 mm and a length of 25 mm and is easily identifiable as a hyperechoic line at EUS real-time imaging during the ablation. The probe is connected to the RF energy generator VIO 300D RF-surgery system and to the cooling system ERBECRYO2 (both ERBE, Elektromedizin GmbH, Tübingen, Germany). The pressure of the exiting gas, the power setting of the generator, and the duration of application can be varied independently.

HTP was used for the first time under EUS guidance by Arcidiacono *et al.* in a pilot study involving patients with unresectable locally advanced PDA, with disease progression after standard chemotherapy (ChT) ± RT or unfit for ChT regimens or surgery due to comorbidity.[49] This study was designed on the basis of results of preliminary *in vivo* animal and *ex vivo* human studies, performed by the same group.

The power and pressure settings were standardized in the initial *in vivo* animal study, according to previous *ex vivo* experiments on liver and spleen of an animal model (respectively, 16 W and 650 psi), with application time ranging from 120 to 900 s, depending on the size of the lesion.[31,50] The probe was applied under EUS guidance into the pancreas of 14 pigs. Some of the study animals underwent more than one application. During the power delivery, a hyperechoic elliptic area was visualized around the distal tip of the probe, surrounded by a hypoechoic margin. EUS was able to guide the placement of the probe into the pancreatic lesion and to measure the ablated area. After the ablation, a good correlation between EUS findings and macroscopic appearance and a significant positive correlation between the size of the ablated area and the application time were observed. None of the pigs died. However, there was one major complication (necrotic pancreatitis with peritonitis). Minor complications occurred in 43% of cases: two pigs showed histochemical pancreatitis and autopsy revealed gastric wall burn and gut adhesions in one and four pigs, respectively. The complications were clearly dose dependent in three out of four cases of gut adhesions, as well as the burn of the gastric wall and the clinically overt pancreatitis occurred after an ablation duration of about 900 s. The procedure showed to be technically feasible and safe. Histology, performed 2 weeks after ablation, showed a sharp demarcation between the ablated area and the surrounding pancreatic parenchyma. There was also a central necrotic area, containing amorphous material and cellular debris, surrounded by an inflammatory wall, consisting of granulation tissue with fibroblastic reaction, new blood vessels, and a significant presence of lymphocytes and polymorphonucleated neutrophil granulocytes.

In the subsequent *ex vivo* human study on 16 surgical specimens with pancreatic carcinoma (mean tumor size: 29 mm, range: 20–42 mm), the probe was tested under US guidance (7.5–10-MHz probe) in order to assess the ablative effect of HTP in the neoplastic tissue. Anatomic specimens were divided into four groups, each of them receiving a predefined HTP application time ranging from 120 to 480 s. A VIO 300D RF generator (ERBE Elektromedizin GmbH) and the ERBEKRYO CA system (ERBE Elektromedizin GmbH) were used to ablate the pancreatic tissue, with the RF power output set at 16 W and the cryogenic cooling set at 650 psi. During the application, a hyperechoic area appeared around the probe's distal tip. After the ablation, all the pancreatic specimens showed histological signs of coagulative necrosis, restricted within the tumor (mean short axis ranging from 10 to 20 mm), surrounded by a zone with edema and cellular damage (mean short axis ranging from 21 to 29 mm), but with no signs of cellular death. Again, a significant linear correlation between the application time and the extension of the necrotic tissue has been observed ($P = 0.009$), as well as between the application time and the extension of the area with edema and cellular damage ($P = 0.026$). These results showed that the probe was effective in destroying neoplastic pancreatic tissue and creating a necrotic area, the size of which extension was dependent on the duration of application.[51]

In the *in vivo* human study,[49] 22 patients were enrolled. The ablation using HTP was feasible in 16 patients (72.8%). It was performed by using a convex linear-array echoendoscope with a 3.8-mm operative channel (EG3830UT, Pentax Inc., Hamburg, Germany). In six patients, the treatment was not possible due to gastroduodenal wall stiffness and tumor hardness, likely secondary to postradiation desmoplastic reaction or fibrosis. The power (heating) was set at 18 W; the pressure (cooling) was set at 650 psi; and the mean application time was 107 ± 86 s (range 10–360 s). A computerized system connected to the energy delivery system automatically stopped the ablation before the calculated application time when the electric resistance, induced by desiccation and devitalization of the tumor tissue increased. The probe was well visible inside the tumor, and the effect of the ablation was followed under real-time EUS guidance. At the end of the ablation, EUS showed a hyperechoic line along the path of the probe in the treated area, surrounded by nonhomogenous tissue with hyperechoic spots. There were no major complications during or immediately after the ablation. Early minor complications occurred in 43.7% of patients: asymptomatic hyperamylasemia (three cases), abdominal pain (three cases), and minor duodenal

bleeding (one case) treated with endoscopic hemostatic clip placement. Late complications were mostly related to tumor progression (jaundice, duodenal stricture, and self-limiting cystic fluid collection in 2, 1, and 1 cases, respectively). One major limitation of this study was the difficulty in assessing correctly the size of the ablated area by CT scan during the follow-up, due to the difficulty in distinguishing between reactive edema and the persistence of the tumor. The median posttreatment survival was 6 months (range: 1–12 months).

The effectiveness of this treatment was thorough in a larger cohort of patients (n = 35), using the same inclusion criteria. EUS-HTP was feasible in 26 patients (74.3%). Six patients received two or more treatments. Evaluation through CT scans, by using a new semi-automated advanced visualization computer-aided detection system (IntelliSpace Portal 7.0, Philips Healthcare, Koninklijke Philips N.V., Netherlands), was able to measure the lesion volumes in 24/26 treated patients (92.3%) on posttreatment first CT scan evaluation and in 12/15 patients (80%) on posttreatment second CT-scan control. This found no significant changes in the lesion volume at the two posttreatment radiological evaluations (mean 15 days and mean 45 days, respectively), compared to the pretreatment lesion volume. Overall, HTP treatment results showed that the technique was able to ablate 34.9% (range 3%–65%) of the neoplastic tissue. There was a significant positive correlation between the ablation time and the necrotic volume (R = 0.66, P = 0.013) as well as between the lesion volume and the necrotic volume (R = 0.92, P = 0.0001). The median postablation survival time was 6 months (range: 1–22 months). An analysis of the median survival time revealed an increase of the survival time from 5 to 9 months (P = 0.066) for the patients treated by more than one HTP ablation session, compared to those treated by only one session.[52]

EUS-guided cryothermal ablation seems to be a feasible and safe cytoreductive therapy. However, technical improvement of the cryothermal probe and randomized, controlled trials are necessary to demonstrate the survival benefit of EUS-guided cryothermal ablation in patients with locally advanced PDAC.

EUS-GUIDED PHOTODYNAMIC THERAPY

PDT is a clinically accepted method of producing selective tissue necrosis or apoptosis in patients with malignant and benign tumors of epithelial-lined and solid organs, as in case of cholangiocarcinoma, esophageal and gastric cancers.[53,54] After intravenous (IV) injection of a photosensitizing drug, the target tissue is exposed to light with a determined wavelength that activates the drug to interact with oxygen, generating singlet oxygen that produces localized tissue necrosis. Different studies applying PDT in the pancreatic setting demonstrated that photosensitizing drugs are highly captured by the pancreatic tissue, with a 7-fold greater concentration in the malignant pancreatic tissue compared with the normal pancreatic tissue, without significant structural damage to the gastroduodenal musculature.[55-58]

Previous preliminary studies in animal models showed that EUS-guided PDT could be performed safely in the tail of the pancreas.[32,33] Chan *et al.* applied EUS-guided PDT in a porcine model (three healthy swine) to pancreas, liver, spleen, and kidney. After injection of porfimer sodium (Photofrin, Axcan Pharma, Inc. Mont-Saint-Hilaire, Quebec, Canada), a 19G needle was inserted into the organ under EUS guidance, and a small diameter quartz optical fiber with a 1.0-cm cylindrical light diffuser (modified Optiguide; Laserscope, Fibersdirect.com, Kirkland, Washington, USA) was passed through it and used to illuminate the tissue with a 630-nm laser light (total light dose of 50 J/cm, delivered at 0.4 W over 125 s) (Domed, Axcan Pharma Inc., Mont-Saint-Hilaire, Quebec, Canada). Localized tissue necrosis was achieved in all organs, without significant complications as well as significant difference in the degree of inflammation induced by PDT within the various organs.[32] Yusuf *et al.* assessed the effectiveness and safety of EUS-PDT by using Verteporfin (benzoporphyrin derivative monoacid A) (Visudyne; Novartis Ophthalmics, East Hanover, NJ, USA), a novel photosensitizer with a short drug-light interval (only 5 h) and associated with less photosensitivity, in six swines, that received 6 mg/m^2 of vertporfin through IV injection before EUS. The tail of the pancreas was located with EUS and was used to guide the placement of the light catheter through a 19G needle inserted into the pancreatic tail tissue. The pancreatic head was not accessible because of the stiffness of the laser light catheter due to the quartz optic fiber. The pancreatic tail was exposed for 10, 15, or 20 min with 689-nm wavelength laser light at a light dose of 150 J/cm^2 (400 mW × 125 s). Localized tissue necrosis within the pancreatic tail (range: 6.6–30.5 mm in diameter) was seen in all animals at autopsy 7 days

later. It was found that the diameter of the necrotic tissue was directly related to the dose of light. No postprocedural complications were observed; only one pig had a mild increase in serum amylase but no clinical evidence of pancreatitis.[33]

The first clinical experience with EUS-PDT in pancreatic cancer has been published in 2015 by Choi *et al*.[59] The authors reported the technical feasibility and safety of EUS-guided PDT by using a novel second-generation photosensitizer and a flexible laser probe, in four patients with locally advanced pancreatico-biliary cancers, one of them with pancreatic tail cancer 3.1 cm in size, who had localized tumor progression after chemoradiotherapy. This novel photosensitizing drug, compared with hematoporphyrin-type photosensitizers, has an intensive absorption band at a longer wavelength. This leads to a deeper effective penetration of light in biological tissue, faster excretion, and high accumulation rates, preventing damage to healthy tissues and reducing skin photosensitivity. For EUS-PDT, a chlorin e6 derivative (Photolon; Belmedpreparaty, Minsk, Republic of Belarus) and a flexible laser-light probe, composed of a quartz core with a diameter of 0.39 mm, a biocompatible polymer coating, and a cylindrical diffuser tip 1–2 cm-long (PhotoGlow; South Yarmouth, Massachusetts, USA) were used. The photosensitizer was administered intravenously at a dose of 2.5 mg/kg 3 h before the procedure. Before the procedure, the laser-light catheter was preloaded inside a 19G FNA needle (Cook Endoscopy, Winston-Salem, North Caroline, USA) that was then inserted into the tumor under EUS guidance. Then, the needle was withdrawn 2 cm while the catheter was advanced in order to be in direct contact with the tumor. Photoactivation at a 660-nm wavelength (UPLFDT; LEMT Research and Development Private Unitary Enterprise, Minsk, Republic of Belarus) for an irradiation time of 330s was performed, with a power density 300 mW/cm and energy dose of 100 J/cm of the 2-cm long diffuser length. The laser probe was easily visible on EUS images. The procedure was repeated to ensure complete coverage of the tumor, without overlapping the treatment fields. No significant procedure-related adverse events, including skin photosensitivity, occurred after PDT. In the patient with pancreatic tail cancer, two laser-light deliveries were done in a single session, with duration of procedure of 29 min. The median radius of pancreatic necrosis created by PDT was 0.85 cm. The volume of the pancreatic necrosis on CT scan performed 1 month after EUS-PDT was 1.9 cm^3. The patient showed stable disease during the follow-up period of 3 months.

The authors suggested that EUS-PDT could be applied as a salvage treatment for patients with locally advanced pancreatico-biliary cancers, who are poor surgical candidates and/or had progression despite chemoradiotherapy.

US-GUIDED NEODYMIUM-DOPED YTTRIUM ALUMINUM GARNET LASER

LA with a Nd:YAG laser represents a promising minimally invasive approach able to achieve a high rate of complete tissue necrosis. It works by delivering low-power laser light energy into the tissue. Promising results have been reported as a minimally invasive, palliative and potentially curative option for HCC, colorectal cancer liver metastasis, and malignant thyroid nodules.[60-62] The advantage of the laser compared to other techniques of energy delivery seems to be the great precision of laser-induced tissue necrosis. This method has been investigated under EUS-guidance by Di Matteo *et al.* in preliminary *in vivo* and *ex vivo* animal studies.[34,63]

In the *in vivo* animal study, a group of eight healthy farm pigs were treated by EUS-guided Nd:YAG laser (EUS-LA). A Hitachi EUB 8500 US system (Hitachi, Hamburg, Germany) and a Pentax FG-36UX linear-array echoendoscope (Pentax Precision Instruments, Hamburg, Germany) were used for the procedure. The treatment was applied to the body and tail of the pancreas which were easily visible. The puncture was performed with a 19 G FNA needle (Cook Medical Inc., Winston-Salem, NC, USA) under EUS guidance, and then withdrawn for few millimeters. After removal of the stylet, a quartz optical fiber with a tip 300 μm in diameter was passed through the fine needle (Echolaser X4; Elesta Srl, Florence, Italy). A Nd:YAG laser with a wavelength of 1.064 nm (Echolaser X4; Elesta Srl) was used with the two output powers (OPs) set at 2 and 3 W, the total energy delivered being 500 and 1000 J in continuous mode. In three pigs, two different power values were introduced at two different sites of the pancreas; in the others, only one lesion was created. The fiber was clearly visible as a hyperechoic line emerging from the tip of the needle. During laser application, a hyperechoic elliptical area

appeared around the distal tip of the probe, surrounded by a hypoechoic border. The area of lesions was monitored directly under EUS guidance. There was no procedure-related mortality nor major complications, 24 h after the procedure, before euthanasia. In six pigs, a small asymptomatic peripancreatic fluid collection was identified on pathological examination; serum amylase levels increased from 1.2 to 3.6 times in seven pigs, and serum lipase levels increased from 1 to 9 times in all pigs, but there were no clinically significant signs of pancreatitis. Histopathological examination revealed a central core of vaporized cells, a clear distinction between coagulated necrosis and untreated pancreas with a 1 mm to 2 mm watershed zone of early inflammatory response surrounding the coagulated tissue. The ablation area and volume, at histological examination 24 h after the procedure, were calculated with the formula $A = \pi ab$ (a and b = semi-axes of a hypothesized ellipse) and by using the sum of ablation areas measured on each slide multiplied by the thickness of the slide under consideration, respectively. Increasing the power energy was associated with an increased EUS ablation area and volume at EUS. At energy setting of 500 and 1000 J, with a set power of 2 W, mean ablation area was 49 mm^2 and 67 mm^2, and mean ablation volume (V_a) was 314 mm^3 and 460 mm^3, respectively, with a set power of 3 W, mean ablation area was 59 mm^2 and 80 mm^2, and the mean V_a was 428 mm^3 and 483 mm^3, respectively.[34]

The same group performed subsequently an *ex vivo* study applying US-guided Nd:YAG laser in sixty porcine healthy pancreatic tissue, in order to establish the best laser setting of Nd:YAG lasers for pancreatic tissue ablation and to create a mathematical model to predict the V_a based on the Pennes equation. US-guided Nd:YAG laser was applied immediately after pancreatic resection, previous puncture of the pancreas with a 22G cannula, through which was inserted a quartz optical fiber with a tip 300 μm in diameter (Echolaser X4, Elesta s.r.l.; Florence, Italy). Laser OP of 1.5, 3, 6, 10, 15, and 20 W were delivered, with a total energy of 1000 J in continuous mode. Ten applications for each OP were performed. Time of laser application ranged from 50 s for the higher OP to 667 s for the lower OP. The V_a and the central carbonization volume (V_c) were measured on histologic specimens as the sum of the lesion areas measured on each slide multiplied by the thickness of the slide under consideration. A circumscribed ablation zone was observed in all histologic specimens. V_a values grew with the increase of the OP up to 10 W and reached a plateau between 10 and 20 W. The trend of V_c values raised constantly until 20 W, with an increase of 46% between 3 and 6 W and of 58% between 10 and 20 W. The theoretical model showed a good agreement with the experimental V_a and V_c for OP between 1.5 and 10 W. The authors concluded that LA with Nd:YAG laser was a minimally invasive approach able to achieve a high rate of tissue necrosis. Hence, the best laser OP could be the lowest one to obtain a similar V_a with smaller V_c, in order to avoid the risk of thermal injury to the surrounding healthy tissue. Moreover, the developed theoretical model could be potentially used to predict the laser-induced ablation size at the different laser OPs.[63]

Di Matteo *et al.* reported the first clinical experience with EUS-guided Nd:YAG laser for the treatment of recurrent 9-mm PNET in residual pancreatic body in a 46-year-old woman who had previously undergone curative distal pancreatectomy for PNET in the setting of multiple endocrine neoplasia Type I. The patient declined total pancreatectomy. Ablation was performed at 4 W for 300 s. No complications occurred during the procedure. At CT scan evaluation performed immediately after the procedure, the ablated lesion appeared as a well-defined 35-mm coagulative necrotic area without peri-lesional parenchymal alteration nor vascular damage. The 2-month follow-up CT scan showed the ablated area to be 18 mm; at 1 year, the area was 9 mm, with no metabolic activity on 68Ga-DOTA-NOC PET.[64]

CONCLUSIONS AND FUTURE DIRECTIONS

The development of new devices for pancreatico-biliary endoscopy has led to an increasing number of potential applications in endoscopically guided ablation in pancreatic neoplasms, with EUS presenting the advantage of a minimally invasive technique with fewer risks compared to surgical approach, and direct real-time imaging for the target of the lesion. Pancreatic surgery still has a high perioperative morbidity, and an increasing number of patients are not suitable for surgery. However, while a number of technologies for the EUS-local thermal treatment of pancreatic masses are available, this procedure is not completely free from severe adverse events, and the real clinical indication and the outcomes of the treatment are still under investigation.

Functioning PNETs, as well as pancreatic lesions associated to MEN syndrome, seem to be the ideal target for EUS-guided thermal ablative therapy because of their hormone-related symptoms and potential of malignant evolution. Different clinical experiences show that EUS-guided ablation of functioning PNETs was effectively able to resolve these symptomatic hormonal syndromes. In case of nonfunctioning PNETs, this approach could be a good alternative therapeutic option in case of patients with high perioperative risk or those not amenable to surgery.[36-40,43,64]

In the case of pancreatic cancer, the recent improvement of survival (even if only marginal) obtained thanks to new chemotherapy regimens could lead to a more widespread use of a local thermal ablative technique as an adjunct to this standard multidisciplinary treatment.[24,41-43,49,52,59,65] An EUS-local thermal ablation with safe direct tumor targeting even into multiple sites in one session, may reduce the extension of pancreatic cancer through a cytoreductive effect and potentially increase the efficacy of neoadjuvant chemo/chemoradiation therapy. This stems from the thermal-induced change in the pancreatic cancer microenvironment and desmoplasia, that limits the delivery of chemotherapeutic drugs.[66] Moreover, postnecrotic infiltration of the marginal tumor zone by neutrophils, macrophages, dendritic cells, natural killer, T and B lymphocytes, and amplification of an anti-tumor systemic immune response, triggered by thermal-mediated subcellular and tissue damage and *in-situ* freezing of the malignant tissue, has been demonstrated in several studies using radiofrequency and CRYO in solid cancers.[25,67-71] However, further clinical studies should be warranted to validate this effect.

The use of cyst ablation in incidentally identified lesions or those that may not meet the criteria for surgical resection is controversial, but may yet have a role in those patients with high-risk stigmata or symptomatic pancreatic cysts, who either refuse surgery or are not fit for surgery.[36,43]

In conclusion, EUS-guided thermal ablation therapy seems to be a valid option for solid pancreatic tumors and alternative to surgical resection for functioning and multiple tumors. However, most of the publications on EUS-guided tumor thermal therapy are mainly experience on small study populations or case series. Moreover, no study has yet assessed survival and quality of life as primary end points. Thus, well-designed prospective randomized controlled trials comparing EUS-guided thermal ablative therapy with standard treatment and a comparison of the different thermal ablative therapy modalities, (enrolling more patients with longer follow-up), are required to evaluate the associated morbidity and better understand ablation efficacy and its role in cancer treatment.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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