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REVIEW

Endoscopy-guided ablation of pancreatic lesions: Technical possibilities and clinical outlook

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Abstract

Endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP)-guided ablation procedures are emerging as a minimally invasive therapeutic alternative to radiological and surgical treatments for locally advanced pancreatic cancer (LAPC), pancreatic neuroendocrine tumours (PNETs), and pancreatic cystic lesions (PCLs). The advantages of treatment under endoscopic control are the real-time imaging guidance and the possibility to reach a deep target like the pancreas. Currently, radiofrequency probes specifically designed for ERCP or EUS ablation are available as well as hybrid cryotherm probe combining radiofrequency with cryotechnology. To date, many reports and case series have confirmed the safety and feasibility of that kind of ablation technique in the pancreatic setting. Moreover, EUS-guided fine-needle injection is emerging as a method to deliver ablative and anti-tumoral agents inside the tumuor. Ethanol injection has been proposed mostly for the treatment of PCLs and for symptomatic functioning PNETs, and the use of gemcitabine and paclitaxel is also interesting in this setting. EUS-guided injection of chemical or biological agents including mixed lymphocyte culture, oncolytic viruses, and immature dendritic cells has been investigated for the treatment of LAPC. Data on the long-term efficacy of these approaches, and large prospective randomized studies are needed to confirm the real clinical benefits of these techniques for the management of pancreatic lesions.

Key words: Endoscopic ablation; Radiofrequency ablation; Cryoablation; Endoscopic ultrasound-guided ablation; Ethanol; Alcohol ablation; Chemoablation; Endoscopic ultrasound; Pancreatic cancer; Endoscopic

retrograde cholagiopancreatography; Pancreatic cystic neoplasm; Pancreatic endocrine tumours

Core tip: Endoscopic ablation is a procedure with interesting potential for the treatment of locally advanced pancreatic ductal adenocarcinoma, functioning pancreatic endocrine tumours, and pancreatic cystic neoplasms in patients unfit for surgery. There is limited evidence regarding the feasibility, safety, and efficacy of such treatments. Both endoscopic ultrasound and endoscopic retrograde cholangiopancreatography have been employed to guide ablation with several chemo-physical agents (including alcohol-chemo ablation, radiofrequency ablation, and cryo-therm-ablation). However, evidence regarding the best treatment and the ideal clinical setting for ablation strategies is still lacking. In the multidisciplinary approach to pancreatic cancers, these emerging local ablation techniques will probably be the future for individualized patient treatments.

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INTRODUCTION

The technical possibilities for treating pancreatic tumours under endoscopic retrograde colangiopancreatography (ERCP) and endosonographic (EUS) guidance have been evolving thanks to the development of biotechnologies applied to endoscopy. During the last 15 years, EUS has expanded more and more into a therapeutic tool and many studies have tested new probes and devices, especially in porcine models. The EUS-guided delivery of anti-tumour agents has been proposed as an alternative method to treat pancreatic cancer[1]. The concept is that if you can get in with a needle to acquire tissue, you can also insert a needle to release drugs or you can insert a probe to ablate tissues by using physical agents. Among the techniques proposed, the most promising are delivery of antitumoural drugs like TNF-erade[2], local immunotherapy with Cytoimplant[3], modified viruses[4], alcohol[5,6], and physical agents like monopolar or bipolar radiofrequency probes[7,8], cryotherm probes[9,10], and Nd:YAG laser[11,12]. All the studies carried out in *in vivo* animal models have demonstrated that the EUS-guided ablation of the pancreas is feasible, efficient and safe, but they all concluded that its clinical application in humans requires further evaluation in future studies. However, while a number of technologies for the local treatment of pancreatic masses are available, the real clinical indications and the outcomes of treatment still need to be elucidated. The current review will present different kinds of technologies, how they work, and their possible present and future applications in the treatment of different types of pancreatic lesions.

Locally advanced pancreatic cancer

Pancreatic cancer has a poor prognosis, with a 5-years survival rate < 10% for all stages[13]. Radical resection is the only treatment for resectable disease, but, unfortunately, at diagnosis only 15%-20% of patients are candidates for surgery[14]. About 40% of pancreatic cancer patients have locally advanced unresectable disease[15]. An autopsy series identified 30% of patients with pancreatic cancer who died because of locally destructive disease, without evidence of distant progression. The authors of this study concluded that the determination of *DPC4* gene status at diagnosis might play a role in the choice of patient's treatment: Systemic *vs* loco-regional[16].

Several studies have shown improved outcomes and survival when a multidisciplinary team evaluates patients[17]. In this context, EUS plays a role as a diagnostic and staging tool, but it becomes also an alternative/additional therapeutic approach to pancreatic cancer, and the gastroenterologist can join the oncology team in the treatment of patients with pancreatic cancer by administering anticancer drugs.

Patients who would benefit more from loco-regional treatment are those with unresectable locally advanced pancreatic cancer (LAPC). LAPC is defined by the National Comprehensive Cancer Network as a local disease, with no distant metastasis, with a 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)[18]. This vascular involvement makes the surgery ineffective and impossible even in case of small solid masses. Usually, LAPC is classified into borderline resectable (< 10% of pancreatic cancers) and unresectable disease (20%-30%)[19]. The American Society of Clinical Oncology Clinical Practice Guidelines suggest that "for patients who have tumours that are anatomically resectable but are characterized by a high likelihood of metastatic disease or margin-positive resection, a preoperative strategy is appealing because the results of an initial surgical strategy are particularly poor"[20].

A local ablative treatment that allows selective destruction of the tumour might improve the efficacy of chemo-radiation therapy in patients with vascular involvement that precludes resection as a first treatment (Table 1). EUS-guided ablation allows a minimally invasive approach to target pancreatic lesions that are extremely difficult to reach by a percutaneous approach by obtaining real-time imaging.

Pancreatic neuroendocrine tumours

Pancreatic neuroendocrine tumours (PNETs) are usually

Table 1 Characteristics and findings of studies of endoscopy-guided ablation for locally advanced pancreatic adenocarcinoma

Ref.	Year	No.	Endoscopy technique	Type of ablation	Stage of PDAC *n* (%)	Median survival (mo)	Complications *n* (%)	Response rate *n* (%)
Chang *et al*[3]	2000	8	EUS-FNI	EUS-FNI Cytoimplant	4 (50) Ⅱ 3 (37) Ⅲ 1 (12.5) Ⅳ	13.2	8 (86) fever, 3 (37.5) GI toxicities, 3 (37.5) hyperbilirubinemia	3 (37) PR
Irisawa *et al*[85]	2007	7	EUS-FNI	EUS-FNI DCs	7 (100) Ⅳ	9.9	None	1 (14) CR 3 (43) PR
Hirooka *et al*[86]	2009	5	EUS-FNI	EUS-FNI DCs plus systemic GEM	5 (100) Ⅲ	15.9	None	1 (20) PR
Hecht *et al*[4]	2003	21	EUS-FNI	ONYX-015 plus systemic GEM	3 (48) Ⅲ 2 (52) Ⅳ	7.5	2 (10) sepsis, 2 (10) duodenal perforation, 2 (10) cystic fluid collection, 1 (5) fever	2 (10) PR
Hecht *et al*[87]	2012	50	EUS-FNI or percutaneous	TNFerade plus radiation and 5-FU	(100) Ⅲ	13.2	6 (12) GI bleeding, 6 (12) deep vein thrombosis, 2 (4) pulmonary embolism, 9 (18) abdominal pain, 2 (4) pancreatitis, 1 (2) cholangitis	1 (2) CR 3 (6) PR
Herman *et al*[88]	2013	304	EUS-FNI or percutaneous	TNFerade plus radiation (180 pts) and 5-FU *vs* radiation and 5-FU (90 pts)	NR (Unresectable PDAC)	10 (the same in two groups) NR (7 pts alive at 6 mo and 2 at 12 mo)	34 (20) *vs* 10 (11) GI toxicities grade 3-4, 60 (33) *vs* 32 (35) hematologic toxicities grade 3-4, 22 (12) *vs* 7 (10), non-GI/ nonhematologic toxicities (*e.g.*, fever, fatigue) grade 3-4	8 (8.2) *vs* 6 (12) PR 3 PR
Hanna *et al*[89]	2012	9	EUS-FNI or percutaneous (TC-guided)	BC-819	8 (88.9) Ⅲ 1 (10.1) Ⅳ		4 (44) gastrointestinal disorders, 2 (22) abdominal pain, 1 (11) influenza like illness, 1 (11) fatigue, 2 (22) back pain, 2 (22) hypertension 2 (22) metabolic disorders, 1 (11) syncope	
Facciorusso *et al*[81]	2016	123	EUS-FNI	CPN plus ethanol (65 pts) *vs* CPN alone (58 pts)	25 (20.4) Ⅳ 98 (79.6) Ⅲ	8.3 *vs* 6.5	16 (25) *vs* 14 (24) diarrhoea 31 (48) *vs* 11 (19) fever	NR
Waung *et al*[51]	2016	3	EUS-guided	RFA	3 (100) Ⅲ	NR	30 (46) *vs* 20 (34) abdominal pain None	NR (14% mean reduction in size)
Song *et al*[48]	2016	6	EUS-guided	RFA	4 (67) Ⅲ 2 (33) Ⅳ	NR	2 (33) abdominal pain	NR
Figueroa-Barojas *et al*[44]	2013	22	ERCP-guided	RFA	7 Ⅲ plus 16 CHR 1 HGD IPMN	NR	5 (23) (1 pancreatitis post ERCP with cholecystitis, 5 abdominal pain)	NR
Kallis *et al*[45]	2015	69	ERCP-guided	RFA plus SEMS stenting (23 pts) *vs* SEMS stenting alone (46 pts)	100% Ⅲ	7.5 *vs* 4.1	1 (1.4) cholangitis, 1 (1.4) asymptomatic hyperamylasaemia	NR

PDAC: Pancreatic ductal adenocarcinoma; EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholagiopancreatography; EUS-FNI: Endoscopic ultrasound fine-needle injection; RFA: Radiofrequency ablation; CHR: Cholangiocarcinoma; DCs: Dendritics cells; GEM: Gemcitabine; IPMN: Intraductal papillary mucinous neoplasia; SEMS: Self-expandable metal stent; NR: Not reported; CR: Complete response; PR: Partial response; 5-FU: 5-fluorouracil; CPN: Celiac plexus neurolysis; GI: Gastrointestinal; HGD: High grade dysplasia.

considered rare neoplasms, but their incidence has steadily increased over the past decades[21]. Furthermore, as the prognosis of PNETs is good even in the advanced disease setting, they represent about 10% of all pancreatic neoplasms by prevalence[22]. PNETs are categorized according to their diagnosis as sporadic or as genetically determined in the setting of inherited syndromes. They are further classified depending on the disease stage and histological grade, which depends on ki67 immunostaining, and, from a clinical viewpoint, based on the presence or absence of symptoms due to the secretion of hormones. Functioning PNETs produce hormones such as insulin, gastrin, and glucagon that can determine specific syndromes[23]. However, the majority of PNETs are non-functioning. All the above-mentioned features of PNETs are important to plan the most appropriate therapeutic strategy[24]. Most functioning PNETs present with a resectable disease and therefore have an indication for surgery. Given the high risks related with pancreatic surgery, however, some patients might benefit from alternative treatments able to reduce the symptoms due to hormone hypersecretion. Endoscopic-guided ablative techniques might therefore have a role in this setting, although limited data are available so far (Table 2).

Pancreatic cystic lesions

Pancreatic cystic lesions (PCLs) are extremely common,

Table 2 Characteristics and findings of studies of endoscopic ultrasound-guided ablation of pancreatic neuroendocrine tumours

Ref.	Year	No.	Endoscopy technique	Type of ablation	Tumour type *n* (%)	Clinical response (mo)	Complications *n* (%)	Morphological response *n* (%)
Pai *et al*[8]	2015	2	EUS guided	RFA	2 NF-PNET	NR	2 abdominal pain	Complete necrosis of NF-PNET
Armellini *et al*[49]	2015	1	EUS guided	RFA	NF-PNET G2 (the patient refused surgery)	NR	No complications	CA on CT scan (one month later)
Lakhatia *et al*[50]	2016	3	EUS guided	RFA	Symptomatic insulinomas in patients unfit for surgery	All patients asymptomatic 12 mo after the procedure	No complications	1 disease free at 8 mo, 1 residual asymptomatic disease at 12 mo, 1 CA and asymptomatic at 11 mo
Waung *et al*[51]	2016	1	EUS-guided	3 consecutive RFA sessions	Symptomatic insulinoma (resistant to medical therapy)	Asymptomatic at 10 mo FU	No complications	NR
Levy *et al*[82]	2012	8	EUS-guided or intraoperative US (IOUS) guided	Ethanol	8 (100) insulinomas	5 patients asymptomatic, 3 clinical improvement	1 minor peritumoural bleeding (IOUS)	NR
Park *et al*[83]	2015	10 (13 tumours)	EUS-guided	Ethanol	10 NF-PNETs 4 insulinomas	2 asymptomatic pts with insulinomas	3 mild pancreatitis, 1 abdominal pain	13 (61.5) CA
Paik *et al*[84]	2016	8	EUS-guided	Ethanol	2 NF-PNETs, 3 insulinomas, 1 gastrinoma, 2 SPN	4 patients asymptomatic	1 severe acute pancreatitis, 2 abdominal pain, 1 fever	6 CA
Deprez *et al*[90]	2008	1	EUS-guided	Ethanol	1 insulinoma	Asynmptomatic	Ulceration of duodenal wall	CA
Jürgensen *et al*[6]	2006	1	EUS-guided	Ethanol	1 insulinoma	Asynmptomatic	1 mild acute pancreatitis	CA
Muscatiello *et al*[91]	2008	1	EUS-guided	Ethanol	1 insulinoma		1 pancreatic necroting lesion	CA

EUS: Endoscopic ultrasound; RFA: Radiofrequency ablation; MCN: Mucinous cystic lesions; IPMN: Intraductal papillary mucinous neoplasia; SPN: Solid pseudopapillary tumours; NET: Pancreatic endocrine tumour; NF-PNET: Non-functioning pancreatic neuroendocrine tumour; FU: Follow-up; NR: Not reported; CT: Computed tomography; CA: Complete ablation.

being incidentally diagnosed in about 10% of subjects undergoing abdominal imaging[25]. EUS imaging is an important method to evaluate PCLs and to determine the internal structure such as the presence of septa, wall thickness, and mural nodules or masses[26]. The epithelium of mucinous cystic lesions of the pancreas, which include intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs), can undergo dysplastic changes ranging from benign to borderline or malignant. Others cystic lesions such as serous cystadenomas (SCA) instead have a negligible malignant potential and surgery is required only in case of mass-related symptoms[27]. As a large part of patients diagnosed with PCLs are elderly and/or not good surgical candidates, the interest in a minimally invasive approach such as an endoscopic-guided one to treat such lesions has increased considerably in the past few years (Table 3).

RADIOFREQUENCY ABLATION

Physical and biological considerations

Radiofrequency ablation (RFA) works at high local temperatures to induce irreversible cellular damage, cellular apoptosis, and the coagulative necrosis of the tissue[28]. The technical advantages of loco-regional thermo-ablative techniques, when compared to surgical procedures, are lower rates of morbidity, the preservation of healthy surrounding tissues, shorter hospital stay and overall lower costs. In addition to that, evidence supports a possible immuno-modulation with an additional overall anti-cancer effect[29]. Radiofrequencies cause hyper-thermal damage through the delivery of high energies eventually resulting in a destruction of the tumour micro-environment, damages to the cell membrane, and sub-cellular injuries[30].

It is noteworthy that cancer cells are more heat-sensitive when compared to normal tissue probably due to a higher metabolic stress, a lower thermal conductance, and a lower cancer microenvironment pH[31].

Inside the ablated field, three areas can be easily recognised: (1) a zone of coagulative necrosis in direct contact with the probe; (2) a surrounding peripheral zone with a sub-lethal injury (whose final destiny is either apoptosis or complete "*restitutio ad integrum*"); and (3)

Table 3 Characteristics and findings of studies of endoscopic ultrasound-guided alcohol ablation in pancreatic cystic lesions

Ref.	Year	No.	Ablative agent	Clinical diagnosis (%)	Size mm (range)	Septated cysts *n* (%)	Follow-up months (range)	Complications	Percentage of ablated cysts
Gan *et al*[5]	2005	25	Ethanol	MCN 56%, IPMN 12%, SCA 12%, PCs 4%, unknown 8%	19.4 mean (6-37)	7 (28)	6-12	0%	35%
Oh *et al*[72]	2008	14	Ethanol and paclitaxel	MCN 14%, SCA 2%, lymphangioma 21%, unknown 43%	25.5 median (17-52)	3 (21.4)	9 median (6-23)	AP (7%)	79%
Oh *et al*[73]	2009	10	Ethanol and paclitaxel	MCN 30%, SCA 40%, unknown 30%	29.5 median (20-68)	10 (100)	8.5 median (6-18)	AP (10%)	60%
DeWitt *et al*[75]	2009	42	Ethanol *vs* saline	MCN 40%, IPMN 40%, SCA 12%, PCs 7%	20.5 (10-40)	17 (40.5)	3-4 mo after 2nd lavage	AP (2.4%), intracystic bleeding (2.4%), abdominal pain (24%), major complications, (24%)	33% (ethanol) 0% (saline)
Oh *et al*[74]	2011	52	Ethanol and paclitaxel	MCN 17%, SCA 29% PCs 4%, unknown 50%	31.8 (17-68)	20 (38.5)	21.7 mean (2-44)	Fever (2%), AP (2%), abdominal pain (2%), splenic vein obliteration (2%)	62%
DiMaio *et al*[76]	2011	13	Ethanol	IPMN 100%	20.1 mean (13-27.2)	7 (54)	3-6 mo after 2nd lavage	Abdominal pain (15%)	38%
Park *et al*[77]	2016	91	Ethanol	Indeterminate	30 (20-50)	64 (70)	40 median (13-117)	Fever (9%), abdominal pain (20%) AP (3%)	45%
Moyer *et al*[78]	2016	10	Ethanol or saline plus paclitaxel and gemcitabine	MCN 70%, IPMN 30%, unknown 10%	30	Unilocular predominantly	12	AP (10 %)	75% (ethanol plus paclitaxel and gemcitabine) 67% (alcohol free harm)

MCN: Mucinous cystic neoplasm; IPMN: Intraductal papillary mucinous neoplasm; SCA: Serous cystadenoma; PC: Pseudocyst; AP: Acute pancreatitis.

a healthy, surrounding, non-ablated zone. The process that leads to tumoural destruction takes place in two phases: One direct and the other indirect. In fact, cellular damages occur in parallel at multiple levels, either sub-cellular and tissutal. In general, the thermal-mediated toxicity varies according to the amount of energy delivered and to the thermal sensitivity of the treated tissue. In addition, other processes, such as the loss of membrane integrity, the occurrence of mitochondrial dysfunction, and the inhibition of the replication, play also a role in the killing process[30]. Finally, indirect hits such as oxidative stress and inflammatory processes also occur. The former is due to ischemia-reperfusion injury, while the latter is due to the strong infiltration of the marginal zone by neutrophils, macrophages, dendritic cells, natural killer lymphocytes, T and B lymphocyte[32].

These inflammatory cells have been also highlighted in the blood stream at a distance from the tumour, reflecting a possible systemic, autoimmune reaction triggered by RFA and mediated by the interplay of various interleukins. The levels of heat shock proteins (particularly HSP70) seem also to be increased after RFA, being recognised as a potential early marker of good therapeutic response.

From a physical point of view, temperatures ranging between 60 ℃ and 100 ℃ are generated by high frequency alternating currents that induce frictional heating, which is also known as resistive heating.

Interestingly, temperatures above 100 ℃ are less efficient in local ablation, probably due to a process of the immediate vaporization and drying of the tissue surrounding the probe, which finally leads to a higher thermal impedance and ultimately a lower ablative efficiency.

Another limitation of RFA is the heat-shrink effect, a phenomenon occurring when the heat is absorbed by the blood stream of an adjacent vessel, dissipating hyperthermia and thus limiting the effectiveness of treatment[33].

From a technical point of view, two different types of radiofrequency probes are available on the market: Monopolar and bipolar. Monopolar probes include a generator, a delivering electrode, and a dispersive electrode (ground pad). The delivering electrode releases high-density current providing localized heating. The ground pad disperses energy in order to avoid possible thermal injury on the skin. Bipolar probes include two interstitial electrodes (in the middle of which, the electrical pulses oscillate) and the ground pad. In bipolar probes, energy delivering is confined between the two electrodes with the advantage of a more rapid and focal heating, overall

with less perfusion conductance, potentially less injuries to the surrounding tissue but an overall minor ablative capacity[34].

Previous applications

RFA is a polyhedral technique, interestingly applied in many different oncological setting. Particularly it has been described for obtaining local control of lesions potentially evolving into high grade, as in cases of Barrett's oesophagus for which RFA is considered the ablative procedure of choice[35].

RFA has also been widely studied with curative intent in hepatocellular carcinoma (HCC). Currently, clinical practice guidelines for the management of HCC support the use of loco-regional ablation with RFA as a standard of care in patients with Barcelona Clinic Liver Cancer stage 0 unsuitable for surgery. Particularly, the treatment is recommended in most instances, as the ablation of masses < 5 cm leads to a significant better control of the disease[36].

RFAs have been employed elsewhere, with palliative aims, in case of lung and bone metastasis, breast, adrenal cancer, head and neck lesions, and cholangiocarcinoma[37,38].

Pancreatic applications

Despite numerous applications in different settings, pancreatic RFA *per se* has always been regarded with reluctance by clinicians, for the fear of adverse events such as thermal induced pancreatitis, thermal injury to adjacent structures (*e.g.,* the duodenum, stomach, mesenteric artery and vein, and bile duct), as well as for technical limitations, due to the fact that pancreatic cancer has generally poorly defined margins, making it difficult to ablate all the tumoural mass in a single session[39].

Although most of the clinical experiences with thermo-ablative procedures on the pancreas continue to be confined to a surgical setting[40], the potential use of an endoscopic guided approach provides undoubted advantages, such as the possibility of real-time imaging during the procedure, the ability to monitor the evolution of the treated lesion, and the possibility, compared to percutaneous approaches, to reach extremely distant and inaccessible anatomical areas[41].

On the other hand, the pancreas is a highly thermo-sensitive organ, with a potential susceptibility to iatrogenic injury leading to pancreatitis, peripancreatic fluid collections, stomach or intestinal perforation, and peritonitis, as suggested by some studies conducted on animal models[7].

In fact, initial clinical studies on animal models showed a high rate of mortality (25%). Anyway, it is noteworthy that all these preliminary studies were performed by applying high temperatures above 90 ℃ and treating large tumours[42].

Interestingly, the previous surgical experiences suggest that the iatrogenic injuries might be limited by applying some technical precautions, such as the reduction of the ablation temperature (< 90 ℃), the maintenance of a safety margin from major vessels or from the duodenum (which can also be irrigated by cold saline), and the use of a step-up approach in case of large size lesions[28,38].

So far, some studies on animal models or in small surgical human series have been performed to assess the feasibility and safety profile of the procedure.

Goldberg *et al*[7] conducted preliminary studies on the effect of RFA on normal pancreatic tissue on Yorkshire pigs (500 kHz for 6 min in order to obtain a temperature of 90 ℃). Histological examination was performed immediately after the procedure or 15 d later, showing respectively a bleeding zone surrounding the central coagulative necrotic area that after 2 wk was organized in fibrotic scar tissue.

Gaidhane *et al*[43] performed EUS-guided RFA in the normal pancreas of 5 Yucatan pigs by testing different powers (4, 5, 6 Watt), different exposure times (12-300 s) and application lengths (6 mm *vs* 10 mm). They reported no mortality and a mild pancreatitis rate of 25%, without other major complications.

For pancreatic applications, the currently available commercial probes have been designed to be used during either ERCP or EUS. ERCP probe (Habib EndoHBP catheter, EMcision London United Kingdom) has a catheter compatible with standard Duodenoscopes (3.2 mm working reeds) and can be passed over a 0.035 inch guidewire and connected to an RFA generator which delivers energy at 400 kHz (1500 RF generator; RITA Medical Systems, Inc., Fremont, CA, United States).

The clinical experience with this kind of probe comes mostly from the palliative treatment of inoperable cholangiocarcinomas, while "pure" pancreatic applications have been less extensively studied and pancreatic duct treatment has not been described so far.

Figueroa-Barojas *et al*[44] reported the palliation of obstructive jaundice, in a small series of pancreatic cancers and cholangiocarcinomas. They treated 22 patients with obstructive jaundice, including 16 with cholagiocarcinomas, 7 with stage Ⅲ pancreatic cancer and 1 with high-grade dysplasia IPMN, with RFA of the bile duct. The outcome of the study was the assessment of efficacy and safety profile. The procedure was effective in 100% of cases. Overall complications have been reported in 5 patients, 1 of whom required a surgical drainage. In contrast to what described in animal studies, no major complications on the surrounding organs were observed.

Kallis *et al*[45] performed a retrospective case-control analysis on 23 patients with malignant biliary obstruction and unresectable pancreatic carcinoma and undergoing endoscopic SEMS positioning and RFA and 46 controls (matched for sex, age, metastases, ASA score, and comorbidities). The median survival was 226 d in the RFA group *vs* 123.5 d in controls (P = 0.010). RFA was found to be an independent predictor of survival at 90 d and 180 d (respectively OR = 21.07, 95%CI: 1.45-306.64, and OR = 4.48, 95%CI: 1.04-19.30), potentially conferring a concrete early survival benefit.

Currently, three commercial probes specifically designed for EUS are available on the market[46]: (1) EUS RFA System (STARMED, Koyang, South Korea), which consists of a prototype 19 g, 140 cm long needle electrode, with an inner internal part, isolated in all its length except for the distal centimetre which delivers energy. It is provided with an internal cooling system and can be connected to a RF generator (VIVA, STARMED, Seoul, South Korea); (2) habib EUS-monopolar RFA catheter (EMcision Ltd, London, United Kingdom), which is a 1 Fr wire (0.33 mm, with a working length of 190 cm) which can be connected to RITA (Electrosurgical RF Generator). The catheter is placed through EUS control through a 19-gauge biopsy needle with a stylet and RF energy is then generally applied for 90-120 s; and (3) mixed radio-cryoablation probes, which are a flexible bipolar hybrid ablation device (ERBE Elektromedizin, Tübingen, Germany) combining bipolar RF ablation with cryotechnology.

EUS guided pancreatic RFA has been applied in small human case series (mostly stage Ⅲ pancreatic cancer or neuroendocrine tumours).

Wang *et al*[47] reported a series of three patients with stage Ⅲ pancreatic cancers treated by EUS guided RFA through a 22 gauge needle, delivering a 10 watts to 15 watts current for 2 min. Multiple EUS-RFA procedures were performed when needed, according to the size of tumour with a mean reduction in tumour size of 13.94%, a significant reduction in CA19-9 and without any complications.

Song *et al*[48] performed an ablation procedure by applying radiofrequency 20-50 W, for 10 s on a total of six patients with pancreatic cancer, either locally advanced (four patients) or metastatic (two patients). The procedure was successfully performed in 100% of the patients without major complications such as pancreatitis, bleeding, duodenal lesions, portal vein thrombosis, or splenoportal vein. Even in this small series, mortality was 0%.

Interestingly a preliminary application of RFA to treat pancreatic cystic neoplasms has also been recently described.

Pai *et al*[8] performed a multi-center, pilot safety and feasibility study describing RFA in eight patients, including six with cystic lesions (four mucinous cysts, one intraductal papillary mucinous neoplasm, and one microcystic adenoma) and two with neuroendocrine tumours of the pancreatic head. EUS-RFA was successfully completed in 100% of cases, with a complete resolution in 2/6 patients and a 50% size reduction in 3/6 patients with pancreatic cystic neoplasms. PNET also displayed a change in vascularity, with central necrosis after EUS-RFA. No major complications occurred. Two patients developed mild, self-limiting abdominal pain.

In addition to that, other clinical experiences with RFA of neuroendocrine tumours have been reported so far. Armellini *et al*[49] successfully treated a 20 mm G2 endocrine tumour by EUS-guided RFA in an asymptomatic 76-year-old patient who had refused surgery. The lesion was completely ablated without complications and one month computed tomography (CT) scan confirmed the efficacy of treatment.

A small series of three patients, unfit for surgery, with symptomatic neuroendocrine tumours successfully treated by EUS guided RFA has also been described by Lakhtakia *et al*[50]. No procedure related complications occurred. Similarly, Waung *et al*[51] reported the successful treatment of a symptomatic 18 mm insulinoma in a patient unfit for surgery (due to comorbidity) in which other medical treatments had failed. The patient underwent three consecutive treatments and eventually the full control of hypoglicaemic symptoms was obtained.

With a similar purpose, radiofrequency treatment has also recently been proposed as an additional treatment to endoscopic resection margins after ampullectomy, in case of recurring intraductal growing ampullary adenoma[52].

RFA for locally advanced or metastatic pancreatic cancer, functional neuroendocrine tumours and potentially in the future, pancreatic cystic tumours, through a mini-invasive ERCP or EUS-guided approach, can reasonably be an effective, not curative, cytoreductive treatment. In a multidisciplinary setting, those approaches might confer a better response to therapy, palliation of symptoms, and survival improvement in patients unfit for surgery.

CRYO-THERM ABLATION

Previous applications

A hybrid bipolar cryotherm probe (CTP) has been developed (ERBE Elektromedizin, Tübingen, Germany). The choice to create a bipolar device was sustained by the fact that bipolar systems ablate with less collateral thermal damage than monopolar systems but with the trade-off of less efficiency overall[53,54].

By combining the effects of the two technologies (RFA and cryotechnology), this flexible ablation device increases the effects of the two approaches and overcomes the disadvantage of less efficiency. It is known that the interstitial devitalization of tissues induced by radiofrequency is increased by the cooling effect of cryogenic gas[55].

Cryoablation has been used successfully for many years for the local treatment of many cancers (kidney, prostate, breast, and skin).

Besides the local tissue ablation, a systemic inflammatory response to cryoablation has been postulated as a reaction that can lead to an antitumour response, not only in the treated area, but also, in distant metastasis.

Most of these effects have been studied in mouse tumour models. Joosten *et al*[56] implanted subcutaneously two fragments of colon 26-B tumours into the thigh and flank of BALB/c mice. The thigh tumours were treated by either cryoablation or resection. Cryoablation clearly induced the inhibition of adjacent tumour growth, compared to the mere excision of the primary tumour. Plasma levels of TNF and IL-1 were significantly elevated after cryoablation. The authors concluded that cryosurgery leads to a systemic inflammatory response that can lead

to the inhibition of tumour growth. Another experiment in mice with MT-901 mammary adenocarcinoma demonstrated that cryoablation prior to surgical resection of breast cancer generated tumour specific T-cells. This immune response could be used for adjuvant adoptive cellular immunotherapy[57].

The CTP developed by ERBE is a hybrid RFA probe that is internally cooled with carbon dioxide, which allows efficient cooling because of the Joule-Thomson effect. The probe has been created on the model of a 19G needle for EUS-fine needle aspiration, with the distal tip that is sharp and stiff enough to penetrate the gastric and duodenal wall and pancreatic parenchyma with no need to apply current. The electrically active part of the CTP has a diameter of 1.8 mm.

A protective tube covers the entire probe so that it can be safely passed through the operative channel of the echoendoscope without the risk of damaging the instrument. The commercially available generator VIO 300D (ERBE) is used for power delivery, together with the ERBOKRYO CA system (ERBE) which is used for cooling. The pressure of the gas exiting through the expansion vessel, the power setting of the generator, and the duration of application can be varied independently. In the initial study in an *in vivo* animal model, the power and pressure settings were standardized according to previous laboratory experiments (respectively 16 W and 650 psi) and the application time ranged from 120 to 900 s[9]. The probe was applied under real-time EUS guidance in the pancreas of 14 pigs. Some of them received more than one application. The CTP was easily recognized during the ablation as a hyperchoic line. During the power delivery, a hyperechoic elliptic area was visualized around the distal tip of the probe, surrounded by a hypoechoic margin. The study demonstrated the ability of EUS to guide the placement of the probe and to measure the ablated area. There was a positive correlation between the size of the ablated area and the duration of application. The procedure was safe and the mortality was zero, while the morbidity was significant due to gastric wall burns and gut adhesions. There was one major complication (7%), while the overall rate for minor complications was 43%. The complications were clearly dose-dependent: The pig with the major complication (necrotic pancreatitis with peritonitis) was treated for more than 900 s.

At histological evaluation two weeks after ablation, the ablated area was clearly demarcated from the surrounding pancreatic parenchyma. An inflammatory wall with a remarkable number of lymphocytes and polymorphonucleated neutrophil granulocytes, and granulation tissue with fibroblastic reaction and new blood vessels surrounded a central necrosis (cellular debris and amorphous material).

The CTP was applied also in the liver and spleen of the pigs with no complications and with a good correlation between the application time and the size of the ablated area[58].

Pancreatic applications

Based on the results of the preliminary study in pigs, the CTP was used for the first time under EUS guidance in a pilot compassionate study in patients with LAPC with disease progression after standard chemotherapy ± radiotherapy[10].

Twenty-two patients were enrolled. The cryotherm ablation was feasible in 16 patients, but in six, it was not possible to apply the probe because of the stiffness of the gastro-duodenal wall and of the tumour due to desmoplastic reaction or fibrosis after radiation. The power (heating) was set at 18 W; the pressure (cooling) was set at 650 psi; the mean application time was 107 ± 86 s (range 10-360 s). Before the calculated application time, a computer connected to the energy delivery system automatically stopped the power when a rapid increase of electric resistance induced by fast desiccation and devitalization of the tumour tissue occurred. The probe was well visible inside the tumour and the effect of the ablation was followed under real-time EUS guidance.

There were no complications during or immediately after the ablation. Late complications were mostly related to tumour progression. One major limitation of this study is the difficulty of objectifying the size of the ablated area by CT scan. The low specificity of imaging techniques like B-mode EUS cannot distinguish between reactive oedema and the persistence of tumour. Some studies have demonstrated the role of contrast-enhanced ultrasonography (CEUS) in the surveillance of radiofrequency-ablated renal tumours[59]. Other studies have focused on the image fusion, demonstrating that the CEUS-CT/RM image fusion is feasible also intraoperatively during ablation of HCC and can improve the ablated margins by guiding supplementary ablation of margins[60]. Such good results are expected by the use of contrast-enhanced endoscopic ultrasound in the evaluation of devitalized tissues, but more studies are required.

ALCOHOL/CHEMO ABLATION

Previous applications

Ethanol is a low viscosity, cost effective chemical agent that induces coagulative necrosis, and subsequent fibrosis, small vessel thrombosis and granulomatous tissue formation[61]. It can be easily injectable through a small gauge needle. Percutaneous ethanol injection therapy, indeed, has been used for the ablation of several solid and cystic lesions.

Ethanol is the most common sclerosing material used for cyst ablation. After the initial success in the sclerosis of renal cysts[62], ethanol has been also used for the percutaneous ablation of hepatic cysts. US-guided aspiration with ethanol sclerosis is a relatively non-invasive, safe and effective procedure with low complication rates (that potentially can range from mild fever and loco-regional pain to systematic reactions

such as shock and intoxication)[61]. The 95%, 96% and 99% alcohol solutions are equally safe and effective without a dose-related adverse event[63].

Ethanol has been administered percutaneously as a safe therapeutic modality for patients with solid neoplastic lesions such as small HCC[64] and adrenal tumours[65]. In HCCs, the toxic effect of ethanol is facilitated by the hypervascularity and soft consistency of the tumour (softer compared to surrounding cirrhotic liver) that permit a selectively diffusion of alcohol within the nodule. EUS-guided fine needle injection (EIUS-FNI) is a safe and minimally invasive therapeutic EUS technique. It has been used for precise delivery of antitumour agents into target lesion. However, to date, there are few data regarding the use of chemotherapeutic and biologic agents, limited to animal feasibility studies, human case series, and phase Ⅰ/Ⅱ studies (see pancreatic application). As regards EUS-guided ethanol injection, it has been previously reported for celiac necrolysis[66] and more recently it has also been used for ablation of abdominal tumour such as gastrointestinal stromal tumour of the stomach[67], solid hepatic metastasis[68], metastatic pelvic lymph nodes[69], and adrenal metastatic carcinoma[70].

Pancreatic applications

EUS-guided ethanol ablation therapy: Some clinical trials of PCL ablation have been published so far (Table 3). To date, all studies about EUS-guided pancreatic cyst ablation have used a 22-gauge needle under EUS guidance to aspirate the cystic fluid. Through the needle, ethanol is injected in the collapsed cyst using a volume equal to the aspirate. The cavity can be alternately filled and emptied for 5 min[71].

Gan *et al*[5] first showed that EUS-guided ethanol injection for the ablation of pancreatic cysts is a feasible and safe procedure. They treated 25 patients with pancreatic cysts (13 MCN, 4 IPMN, 3 SCA, 3 pseudocysts, and 2 of unknown origin) and cyst resolution was achieved in 35% of patients during the follow-up (6-12 mo). Five patients (33%) underwent surgical resection and a variable degree of epithelial ablation (up to complete) was described on pathology.

Oh *et al*[72] evaluated the results of EUS-guided pancreatic cyst ablation after injection of ethanol and paclitaxel that was injected into the cyst after alcohol lavage and left in place. Paclitaxel is chemotherapeutic agent (viscous and hydrophobic) which interferes with G2 mitotic-phase cell replication by the arrest of cellular microtubule assembly.

An initial study[72] on 14 patients found that complete resolution of pancreatic cystic tumours was achieved in 11 out of 14 patients followed for more than 6 mo. After treatment, minor complications were observed in one patient (including hyperamylasemia and abdominal pain). The same authors reported the results of 10 patients with septated cysts[73]. They observed a 60% rate of complete radiological cyst resolution, proving that the presence of septations within the cyst is not an absolute contraindication to injection therapy. The same group published a subsequent study in 2011 involving a larger population (n = 52)[74], reporting a complete resolution in 62% of the patients without any major complications.

DeWitt *et al*[75] conducted a randomized double-blind trial comparing ethanol with saline lavage in 42 patients. The study showed that EUS-guided lavage with 80% ethanol achieved a greater reduction in cystic size compared with saline solution injection, providing further evidence for pancreatic cyst ablation efficacy. As demonstrated by a CT scan, complete resolution was obtained in 33% of patients. Epithelial ablation was observed from 0% (with saline solution injection) to 50% or 100% (with one or two ethanol lavages, respectively) in the four patients who underwent surgery.

In 2011 the same group[76] analyzed retrospectively the efficacy of multiple EUS-guided lavages with ethanol for the treatment of pancreatic cystic tumours. The authors concluded that a complete cyst resolution was achieved in 38% of 13 patients who underwent two EUS-ethanol lavage sequential treatments.

Recently, Park *at al*[77] presented data on the longest follow-up and the largest number of patients with clinically indeterminate PCLs treated by EUS injection with 99% ethanol. They showed that the success rate of EUS-guided ethanol ablation therapy was significantly dependent upon findings of cystic fluid analyses (SCN, 58%; MCN, 50%; IPMN, 11%; uncategorized cyst, 39%; $P < 0.0001$). Another prognostic factor determining success rate of EUS-guided ethanol ablation therapy was the size of the cyst (smaller diameters had a significantly higher treatment success rate after EUS-guided ethanol ablation therapy).

Since complete ablation rates of 60%-79% have been reached in studies that added paclitaxel to ethanol, Moyer *et al*[78] recently published a prospective randomized trial pilot study (CHARM). The authors compared the efficacy of either an ablation with saline plus a chemotherapy cocktail of gemcitabine and paclitaxel or of an alcohol-free regimen with saline and the same chemotherapeutic agents in 10 patients with PLCs. Similar ablation rates were found in the two groups (a 67% complete ablation rate in the alcohol-free arm compared to 75% in the ethanol group), showing the efficacy of EUS-FNI of chemotherapeutic agents alone in treating PCLs.

Heterotopic pancreatic tissue and pancreatic tumours also have been directly injected with absolute ethanol without reported major complication as showed by porcine animal studies[79,80]. The role of contrast-enhanced EUS has been also described in a porcine model showing that this procedure can be used not only in the detection of small pancreatic lesions but also for monitoring necrosis after pancreatic tissue ablation[80]. Phase Ⅰ and Ⅱ studies will be necessary on this topic.

Facciorusso *et al*[81] prospectively enrolled 123 patients with advanced PDAC to compare the efficacy and safety of EUS-FNI ethanol ablation combined with EUS-guided celiac plexus neurolysis (EUS-CPN) with respect to EUS-CPN alone for pain management. They also reported data

about ablation rate of the tumour and the overall survival. At 48-h CT-scan imaging, ablation was confirmed in 55 patients (84.6%) treated with the combined approach and, at 3 mo, the response was maintained in 13 patients (20%). Moreover, a significantly longer median overall survival was observed after the combined therapy (8.3 mo *vs* 6.5 mo; $P = 0.05$).

In patients with a small endocrine tumour, EUS-guided ethanol injection could also be an alternative to surgery (Table 2). A retrospective study was conducted by Levy *et al*[82] that reported the data of eight patients with symptomatic insulinomas who received EUS and intraoperative US ethanol ablation after incomplete surgical resection. In five patients who underwent EUS-guided ethanol injection, hypoglycemia-related symptoms completely disappeared without complications.

Ethanol ablation was also successfully performed in a South Korean pilot study performed in 14 neuroendocrine tumours[83] (4 insulinomas) with a response rate of 53.8%, and three cases of mild pancreatitis were observed after treatment. After multiple treatment sessions performed in other three patients with residual enhancing tumours, the successful rate increased to 61.5%.

A recent study[84] reported a success rate of 75% in a cohort of six PNETs less than 2 cm (2 cases of non-functioning NETs, 3 cases of insulinomas, and 1 case of gastrinoma). Complete remission was obtained in five patients (the median follow-up period was 16.5 mo). Moreover, four patients with functioning NETs reported complete relief from tumour-related symptoms. Three mild adverse events were reported after the procedure: One case of abdominal pain, self-limiting fever, and acute pancreatitis each.

EUS-guided injection of anti-tumoural agents: Various anti-tumoural agents have been considered for the treatment of pancreatic adenocarcinoma trough EUS injection such as mixed lymphocyte culture, oncolytic viruses, and immature dendritic cells.

Allogenic Mixed Lymphocyte Culture (Cytoimplant): The first phase I trial was published in 2000 by Chang *et al*[3] who used EUS-FNI to deliver allogenic mixed lymphocyte culture (Cytoimplant) in eight patients with advanced pancreatic adenocarcinoma to induce cytokine production and activate the host immune effector mechanism. They reported no adverse events and a median survival of 13.2 mo, with 2 partial responses (> 50% reduction in tumour size measured on imaging) and 1 minor response (< 50%).

Immunotherapy/dendritic cells: To date two pilot trials evaluated EUS injection of immature dendritics cells to stimulate primary T-cell response against tumour antigens in 7 and 5 patients with unresectable pancreatic cancer[85,86], respectively. The first study reported a median survival of 9.9 mo with one complete response, three partial remissions while 3 out of 5 patients demonstrated effective response (1 partial response and 2 stable disease over 6 mo) in the later trial that combined systemic gemcitabine with EUS injection.

Adenovirus ONYX-015: Intravenous gemcitabine and EUS-guided ONYX-015[4] injection was observed in 21 patients with unresectable pancreatic cancers. ONYX-015 is a modified adenovirus (deletion in the E1B gene) which replicates preferentially in tumour cells, leading to cell death. In this phase Ⅰ/Ⅱ trial, no patients showed tumour regression with the injection alone after five weeks while two partial responses were described when administrated in combination with gemcitabine. Two patients had sepsis and two others duodenal perforation.

Tumour necrosis factor erade: Hecht *et al*[87] published a phase Ⅰ/Ⅱ study about the efficacy of TNFerade (replication-deficient adenovirus vector that expresses human TNF-alpha gene, which is inducible by chemotherapy and radiation) EUS injected in 50 patients with locally advanced PDAC. They reported three cases of partial response, one case of complete response and 12 cases of stable disease (median survival of 297 d). Dose-limiting toxicities were observed in three patients (pancreatitis and cholangitis). Although one case of complete pathologic response and six clear margins were observed among the seven patients surgically treated after treatment, the subsequent large randomized multi-center phase Ⅲ study[88] involving 304 patients reported no survival benefit of adding intratumoural TNFerade injection to 5-fluorouracil and radiotherapy compared with chemotherapy alone.

BC-819: A phase Ⅰ/Ⅱa trial[89-91] assessed the safety and tolerability and preliminary efficacy of a DNA plasmid that targets the expression of diphtheria-toxin gene under the control of H19 regulatory sequences that can potentially treat pancreatic adenocarcinoma overexpressing the H19 gene. It was injected into unresectable non-metastatic PDAC under EUS (six patients) or TC guidance (three patients). No serious major complications occurred. Two patients were successfully down-staged for surgery and three achieved partial response.

CONCLUSION

The rapid improvement in the development of devices for pancreaticobiliary endoscopy, particularly for EUS, has led to an increasing number of indications for endoscopically guided pancreatic lesions ablation. As regards pancreatic adenocarcinoma, the recent improvement of survival obtained thanks to more efficient chemotherapy regimens will most likely lead to a more widespread use of different ablative techniques, with EUS presenting the advantage of a minimally invasive technique with low risk and direct imaging of the lesions. The most efficient treatment has yet to be identified and there is a need of well-designed randomized controlled trials. Pancreatic cystic lesions are epidemic, and most of them require follow-up as potential preneoplastic lesions[25,27]. The use of cyst ablation in incidentally identified lesions or those that may not meet the criteria for surgical resection is controversial, while it could be proposed to those patients with high-risk stigmata or symptomatic pancreatic cysts who either refuse or are not fit for surgery.

In this setting, although EUS-guided ethanol injection has proved to be a safe and minimally invasive procedure, the total ablation of cystic epithelium was not always reached and it seemed less effective in IPMNs that are the most common lesions and those with a preneoplastic potential. The intracystic treatment with paclitaxel and gemcitabine is an interesting option that requires further evaluation.

EUS-guided ethanol ablation therapy for PNETs seems to be a promising technique for patients with functioning tumours who refuse or are unfit for surgery. Nevertheless one should notice that all the above-mentioned local ablative techniques are not completely free from complications. The decision to treat a pancreatic lesion by a loco-regional ablation technique can sometimes represent a very difficult task, particularly in cases of cystic lesions, demanding the need of well-trained operators and high volume centers. Clinical trials enrolling more patients with longer follow-up are required in order to better understand the complete ablation rate as well as the risk of metastasis after ablation.

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