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Review Article

Recent developments in endoscopic ultrasound-guided radiofrequency ablation for pancreatic lesions

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A B S T R A C T

Radiofrequency ablation (RFA) has been regarded as an established technique to treat various diseases such as hepatocellular carcinoma, renal cell carcinoma and Barret's esophagus. Although the application of RFA in the pancreas has been limited due to increased risk of adverse events, endoscopic ultrasound-guided RFA (EUS-RFA) has generated interest as a novel minimally invasive treatment modality which combines real-time visualization with a precise localization of the treatment procedure. For over a decade, the optimization of RFA devices have made EUS-RFA relatively safe, and several studies have supported its feasibility. However, there is insufficient evidence to suggest the appropriate indications and to describe long-term outcomes of EUS-RFA for various pancreatic neoplasms such as pancreatic neuroendocrine tumor, ductal adenocarcinoma, and cystic lesions. Therefore, this review focuses on the technical aspects and clinical applications of EUS-RFA for each pancreatic disease.

Keywords: Endoscopic ultrasound; Pancreatic cystic lesions; Pancreatic neopla; Pancreatic neuroendocrine tumor; Radiofrequency ablation

Introduction

Surgery is the only potentially successful treatment option for various pancreatic neoplasms; however, a minority of these have a surgical indication. In pancreatic ductal adenocarcinoma (PDAC), only 20% of patients have the opportunity to undergo a surgical resection because most patients are diagnosed with unresectable disease at presentation. More so, surgery-related morbidity and mortality are not negligible. In pancreatic neuroendocrine neoplasm (PNEN) and pancreatic cystic lesion (PCL), patients with a low malignant potential require life-long surveillance rather than extensive surgical resection. Therefore, if some favorable results are verified, minimally invasive therapy is very attractive, due to safety, reproducibility, and affordability.[1] Radiofrequency ablation (RFA) is an established minimally invasive therapeutic modality for various diseases including hepatocellular carcinoma, renal cell carcinoma, and Barret's esophagus. In pancreatobiliary disease, endoscopic retrograde cholangiopancreatography (ERCP)-guided intraductal RFA has also been increasingly performed in malignant biliary tract obstruction.[2-5] However, the RFA for the pancreas is under investigation due to the increased risk of adverse events. Because the pancreas is a thermosensitive organ with more complex vascular systems, pancreatic neoplasms could infiltrate the bile duct or the duodenal wall, encase major vessels, or occlude the main pancreatic duct (MPD) by proximity.[1] With the recent widespread use of endoscopic ultrasound (EUS) which has the advantage of real-time visualization and precise localization of pancreatic neoplasms, the interest of local ablation through EUS is increasing. Therefore, even though several studies have showed non-negligible complication rates of EUS-RFA, it is necessary to verify the applicability of EUS-RFA in the management algorithms for various pancreatic neoplasms. This review will focus on the technical aspects of EUS-RFA and clinical applications of EUS-RFA for each pancreatic disease.

Technical Aspects

RFA is a technique in which a needle inserted inside a lesion causes a hyperthermal injury. The radiofrequency (RF) energy circuit delivers high-frequency alternating current to produce ionic agitation in the cell, resulting in hyperthermia and coagulation necrosis in the target tissue.[6] RF may be delivered through mo-

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nopolar or bipolar probes. In monopolar probes, a grounding pad must be used to close the electrical circuit. In the bipolar mode, the circuit is closed inside the probe and current is concentrated between the anode and the cathode. Although RFA has already been actively applied in pancreatobiliary disease, there have been several concerns about possible RFA related adverse events in pancreatobiliary disease. For example, ERCP-guided intraductal bipolar RFA can ablate the intraluminal biliary tumor with comparable safety; however, segmental biliary stricture with cholangitis develops as a long-term result, so biliary stents should be placed to maintain biliary drainage after intraductal RFA.[7]

In terms of technical aspects of EUS-RFA, the fine needle is passed through the shortest possible pathway into the normal pancreatic parenchyma and avoiding the bile duct, pancreatic duct, and major vessels. When RFA energy is applied, the real-time EUS visualization of bubbles can be seen on the pancreatic neoplasm, and these results in a hyperechoic lesion at the end of the treatment. After this, RFA electrodes should be repositioned during the same session to ablate the untreated area, and this can be repeated several times. However, during EUS-RFA, it is difficult to accurately estimate the effective area of RFA. Until now, available EUS probes are the Habib EUS-RFA probe (Boston, Marlborough, MA, USA), the EUSRA RF electrode (STARmed, Goyang, Korea) (Fig. 1) and the HybridTherm (ERBE Elektromedizin GmBH, Tübingen, Germany).[1] When RFA energy is applied, the amount of thermal injury depends on different parameters including power (in watts), duration, electrode length, and target temperature. Moreover, a heat sink effect that decreases the efficacy of RFA may occur in the area near the blood vessel. Therefore, each safe and effective RFA setting according to the various RFA probes should be presented.

Radiofrequency Ablation Probe

Habib EUS-RFA and EUSRA are monopolar RFA catheters. Habib is a through-the-needle probe and EUSRA is a needle-type catheter. The Habib device is a 1 Fr wire monopolar electrode that can be inserted into a standard 22G needle and connected to a standard electrosurgical unit (ERBE). The EUSRA electrode is an 19G needle connected to a specific VIVA RF generator (STARmed). Typically, this has a pump to cool the EUSRA needle through a chilled saline solution. RFA was stopped when automatically measured impedance exceeded 1,000 Ω. The performances of the two available monopolar EUS-RFA devices have been tested recently in the same animal models.[8] The technical success was 100%, and both the devices and the echogenic cloud during the application of RF were clearly visible. At histopathologic analysis, the extent of tissue necrosis was tissue damage ranging from 3.1 ± 0.4 mm (power = 8 W, effect 4, time = 120 sec) to 2.3 ± 0.1 mm (12 W, effect 4, 120 sec) in depth for the Habib probe. Moreover, the ablation depth ranged from 3.6 ± 0.5 mm (power = 30 W, time = 15 sec) to 3.8 ± 0.4 mm (power = 70 W, time = 11 sec) for the EUSRA probe. They showed an effective ablation of pancreatic tissue about 2.5 mm around the RFA electrode with both devices and suggested use of 10 W, 120-second ablation settings for the Habib EUS-RFA probe and 30 W, 15-second settings for the EUSRA when performing EUS-RFA for pancreatic lesions of 5 to 6 mm. Importantly, the ablation of larger lesions should probably require repeated procedures. Interestingly, due to the mechanical properties, each device has its own preferences. Since Habib is a thin device that is used by putting it inside a needle, it is difficult to use repeatedly due to its low durability. On the other hand, EUSRA is stiffer and technically difficult to handle in some challenging areas of the pancreas.[8]

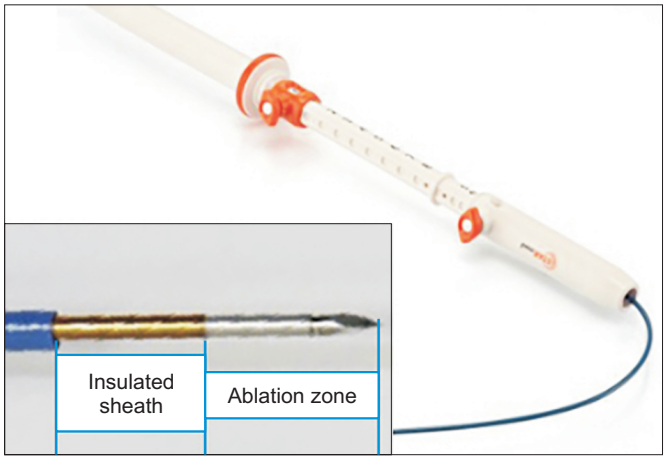

Fig. 1. EUSRA RF electrode (STARmed, Goyang, Korea).

Different from the aforementioned pure RFA probes, HybridTherm is a hybrid bipolar needle type probe that is also available with cryogenic cooling using carbon dioxide. The probe has a sharp distal tip with an active part (1.8 mm in diameter and 20 mm in length). The bipolar system has the theoretical advantage of reducing thermal injury; however, its RFA efficacy is limited. In order to overcome the shortcomings, the RFA effect of HybridTherm is augmented by a cryogenic gas, which increases interstitial devitalization.[9] Indirect comparisons with pure RFA indicate that a larger ablation zone can be obtained with reduced energy and reduced application time. Preclinical studies have shown the feasibility of the technique and demonstrated a linear correlation between the application time and the size of the ablated tissue, when the risk of necrotizing pancreatitis and other adverse events increased.[10] Complication rates were 43% for minor events and a single case of necrotizing pancreatitis, and all complications occurred when applications lasted > 300 seconds. HybridTherm has not been actively used yet, so further research is needed for appropriate treatment methods as well as the delivery protocol.

In summary, the limited available clinical experience makes it difficult to draw firm conclusions on the standard protocols for various EUS-RFA methods. Routine antibiotic prophylaxis and administration of rectal nonsteroidal anti-inflammatory drugs are now recommended to reduce the EUS-RFA related morbidity and mortality.[11] Furthermore, the proximity to the MPD has raised some doubts on the possibility of safe ablation of these lesions, and has led to theoretical advocacy for the possibility of prophylactic pancreatic stenting in these patients.

Clinical Applications

Pancreatic neuroendocrine neoplasm

PNENs are rare neoplasms that account for approximately 2% to 3% of primary pancreatic malignancies. The incidence of those has increased over the last three decades due to the advancement of diagnostic imaging studies as well as widespread awareness by physicians. The World Health Organization (WHO) 2010 grading system has been proposed to define a new pathologic grade stratification, and the system categorized neuroendocrine tumors (NETs) into low-grade (G1), intermediate grade (G2), and high-grade (G3) based on their proliferative rate using the mitotic activity and/or

Table 1 Published Data of EUS Guided RFA Treatments in Pancreatic Disease

Reference	Author	No. patients	RFA devices	Mean tumor size (mm)	Settings	Efficacy	Overall survival (*n*)	RFA related adverse events (*n*)	Prophylaxis
Pancreatic neuroendocrine neoplasm	Lakhtakia et al[15]	3 insulinomas	EUSRA	14–22	50 W	Symptoms relief (100%), persistent at 11 mo FU	All patients alive at 11 mo FU	0	NA
	Choi et al[14]	7 NF-NENs, 1 insulinoma	EUSRA	20 (8–28)		50 W (10 sec)	6 complete responses, 2 incomplete responses; remission of hypoglycemic symptoms in insulinoma patient	2 (25%): 1 abdominal pain, 1 pancreatitis	Broad-spectrum antibiotics
	Oleinikov et al[16]	7 insulinomas, 11 NF-NENs (some multifocal; 2 with treatable metastasis); 27 total lesions	EUSRA	14.4 (4.5–30)		10–50 W, 5–12 sec	26/27 lesions with typical post-ablative changes at CE-EUS; 7 (100%) symptoms resolution in insulinomas; no recurrence after mean 8.7 mo FU	2 (11%) mild pancreatitis	Broad-spectrum antibiotics
	Barthet et al[11]	14 NF-NENs (Grade 1)	EUSRA	12 (10–20)	50 W until bubbles or impedance 100–500 Ω	12 (86%) complete disappearance; 2 absence of Doppler at EUS	NA	2 (14%): 1 acute necrotizing pancreatitis (RF without suction of cystic fluid), 1 MPD stenosis; 20% postprocedural pain	After the first 2 patients: rectal NSAIDs + amoxicillin/clavulanate
Pancreatic ductal adenocarcinoma	Wang et al[21]	3 LAPC	Habib	37.3	10–15 W, 2 min	Mean reduction in tumor size: 13.94%	NA	0	NA
	Song et al[20]	4 LAPC + 2 MPC	EUSRA	38 (30–90)	20–50 W, 10 sec		NA	2 (33%) self-limiting pain	Broad-spectrum antibiotics
	Scopelliti et al[19]	10 LAPC	EUSRA	25–75	20 W (lesion < 3 cm), 30 W until impedeance 500 Ω	Mean diameter of necrosis at 30 day CT: 30 ± 13 mm	NA	4 (40%): 2 postprocedural self limiting pain, 2 asymptomatic ascite	Broad-spectrum antibiotics + octreotide + LMWH
	Crinò et al[18]	8 LAPC + 1 metastatic rectal cancer	EUSRA	36 (22–67)	30 W	Ablated area in all patients at 30 day CT: mean diameter 3.75 cm^3 (0.72–12.6 cm^3), 30% of tumor mass	NA	3 (33%): 3 mild abdominal pain	NA
	Yang and Zhang[22]	8 unresectable pancreatic cancer	Habib	NA	NA	Ablated area inside the tumor in 100%	8.3 mo	0	NA

Table 1 Continued

Reference	Author	No. patients	RFA devices	Mean tumor size (mm)	Settings	Efficacy	Overall survival (*n*)	RFA related adverse events (*n*)	Prophylaxis
	Arcidiacono et al[17]	22 LAPC	HybridTherm	335.7 (23–54)	18 W, cooling pressure 650 psi.		6 mo (13 patients)	8 (50%): 3 mild postprocedural pain, 1 duodenal bleeding; 1 hemobilia and jaundice‡, 1 jaundice‡, 1 duodenal stricture‡, 1 peripancreatic fluid collection	Ceftriaxone + gabexate mesylate
Pancreatic cystic lesiosns	Pai et al[23]	4 MCN, 1 IPMN, 1 microcystic adenoma	Habib	36.5 (20–70)	5–25 W, 90–120 sec	2 complete resolution; 4 reduction (mean: 50%)	NA	2 (33%): self-limiting pain	Cyst aspiration before RFA
	Barthet et al[11]	16 IPMN, 1 MCN	EUSRA	28 (9–60)	50 W until bubbles or impedance 100–500 Ω	12 (70.6%) significant response: 11 disappearance and 1 > 50% decrease; 12/12 (100%) disappearance of mural nodules	NA	1 (6%): 1 perforation of jejunal loop (RF without suction of cystic fluid); 20% postprocedural pain	After the first patient, aspiration of the cyst before RF After the first 2 patients: rectal NSAIDs + amoxicillin/clavulanate

EUS, endoscopic ultrasound; RFA, Radiofrequency ablation; FU, follow-up; NF-NEN, non-functioning neuroendocrine neoplasms; CE-EUS, contrast enhanced EUS; MPD, main pancreatic duct; NSAIDs, non-steroidal anti-inflammatory drugs; LAPC, locally advanced pancreatic cancer; MPC, metastatic pancreatic cancer; CT, computed tomography; LMWH, low-molecular-weight heparin; MCN, mucinous cystic neoplasm; IPMN, intraductal papillary mucinous neoplasm.
Values are presented as median (range) or mean only.

a Ki-67 labeling index.[12,13] PNEN G3 has a similar prognosis as PDAC, but PNEN G1/2 has a better prognosis than PDAC. Therefore, in PNEN G1/2, debulking surgery is considered as a primary therapeutic modality as well as a systemic treatment with a somatostatin analog or a molecular targeted agent. In particular, since PNEN G1/2 < 2 cm seems to harbor relatively low progressive potential, surveillance is a contemplated strategy to be balanced with surgical resection, whose morbidity and mortality seem unjustified in most cases. For this reason, there have been several studies attempting the local ablative treatment instead of simple observation in PNENs that are cumbersome to operate. Besides, since hyperhormonal symptoms evoked by functional PNENs can be controlled through local ablation therapy, the usefulness of local treatment can be more justified. Previous experiments of 1 to 8 patients have been published showing the feasibility of EUS-RFA in this setting (Table 1).[11,14-23]

One recent prospective study[11] including 14 PNENs (G1, <2 cm) demonstrated a 6-months success rate of 71%, whereas 85.7% of tumors completely disappeared at 12 months, possibly due to the late response related to RFA related immunomodulation. Two RFA related adverse events of acute necrotic pancreatitis and pancreatic duct stricture developed. Another recent study[16] also evaluated the efficacy of EUS-RFA in 18 patients with PNENs of heterogenous prognostic significance (symptomatic insulinomas, nonfunctioning G1, small NETs unwilling surveillance, and PNEN G3 unfit for surgery). The mean tumor size was 14 mm, with five cases having tumors sized between 2 cm and 3 cm. The post-RFA ablation area was found in 96% of lesions with one incomplete ablation due to its proximity to the MPD on postprocedural EUS and computed tomography (CT). Only two cases (11%) of mild acute pancreatitis occurred. In another study[15] for symptomatic PNENs, the complete resolution of hypoglycemia was obtained in all seven insulinomas within 1 hour from the RFA, which represents a valuable and long-lasting treatment for functioning PNENs that are not operable.

Based on the previous results, the appropriate indication for EUS-RFA in PNEN can be presented as follows: (1) PNEN patients required for surgery but unfit (Fig. 2); (2) hyperhormonal symptom control in small functioning NETs; and (3) small nonfunctioning, G1/2 NETs as an alternative for surveillance.

Pancreatic ductal adenocarcinoma

PDAC is one of the most aggressive malignancies, and a leading cause of cancer related mortality. Surgical resection is the only curative option; however, only 15% to 20% of patients have resectable tumors at initial diagnosis and most patients with locally advanced or metastatic PDAC require systemic chemotherapy.[2] Local ablative therapy including cryotherapy, irreversible electroporation, stereotactic body radiation therapy, and RFA might become potentially relevant in two major indications. One is palliation of cancer related symptoms and the other is local disease control. Although, local ablative therapy has not been helpful in improving the outcomes in PDAC, those administrable by EUS offer the best combination of excellent real-time visualization and precise localization with minimal invasiveness for selective ablation of the pancreatic lesions. Therefore, EUS-guided RFA has been increasingly employed in experimental and clinical settings in PDAC. Moreover, the role of RFA may go beyond local effects to the immunomodulation of PDAC that has low immunogenicity. RFA can alter the stroma and the permeability of vessels, and activate the adaptive immune response.[24]

To date, clinical efficacy and safety of EUS-RFA have been

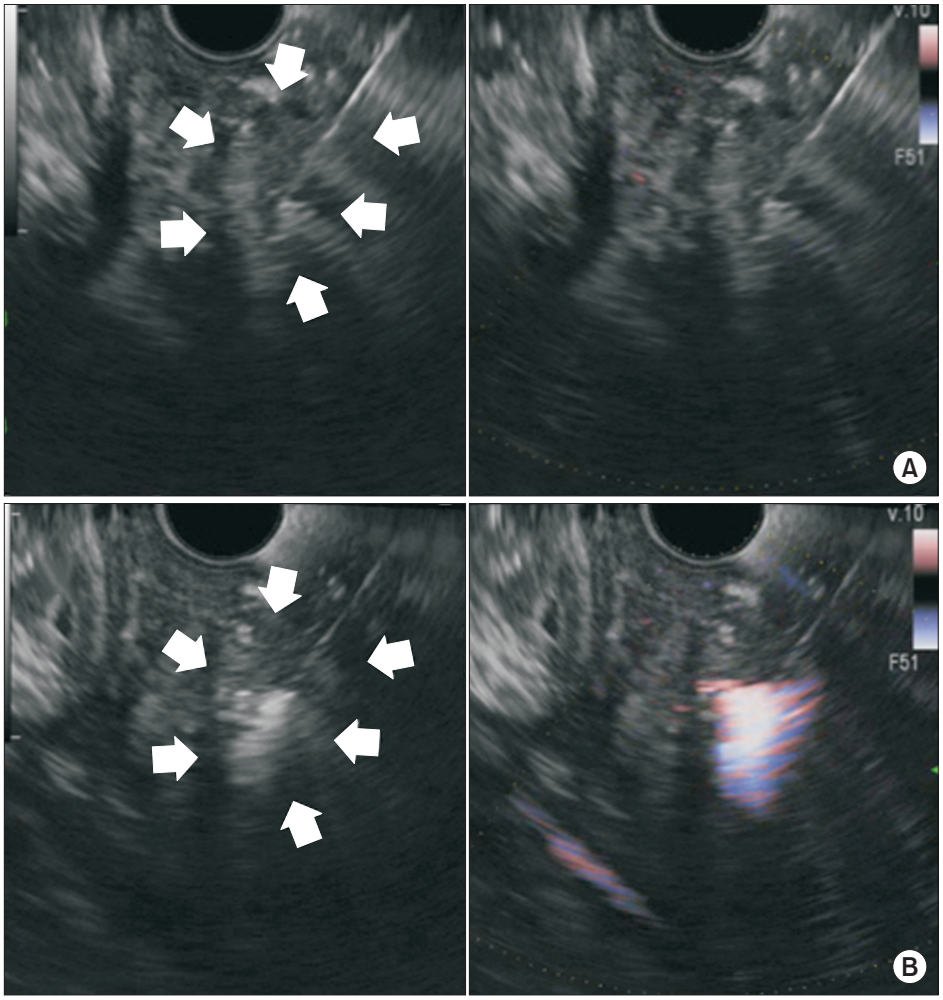

Fig. 2. Endoscopic ultrasound and Doppler flow images. (A) The tip of EUSRA needle was placed into the pancreatic neuroendocrine neoplasm (arrows) in head, (B) echogenic cloud around the needle during radiofrequency ablation (19 gauge EUSRA with 10 mm electrode, power 30 W, duration 15 seconds) (arrows).

evaluated. EUS-RFA allows both reduced invasiveness and a real-time control of the treatment. Furthermore, it is an easily repeatable procedure, if necessary. Available experiments of EUS-RFA of PDAC include a few small cohorts and focus mainly on technical feasibility and safety (Table 1).[11,14-23] From these researches, EUS-RFA is technically feasible and has no major procedure-related adverse events such as mortality. Most RFA related adverse events were minor, such as self-limiting postprocedural abdominal pain. As for efficacy, when a 30-day CT was executed,[18,19] an ablative necrotic area was identified compared to the original tumor volume (between 5.7% and 73.5%).[18] However, there are several problems in the interpretation of these results. There is a lack of data on long-term survival, and the differences between the three RFA catheters were not evaluated.

In PDAC, the efficacy of the local treatment has not been demonstrated, except for systemic anti-cancer treatment. For this reason, even if EUS-RFA is minimally invasive and technically feasible, its efficacy must be additionally verified to the validity of this procedure. In order to allow the correct positioning of the local treatment of EUS-RFA, further efforts should be made to find typical molecular characteristics of PDAC in which local ablation may be effective. In addition, prospective and controlled studies are required in parallel, to compare with systemic chemotherapy for the verification of the efficacy of EUS-RFA in PDAC.

Pancreatic cystic lesions

The PCLs are diagnosed with increasing frequency because of the widespread use of cross-sectional imaging. Although most patients undergo follow-up, in selected cases such as intraductal papillary mucinous neoplasms and mucinous neoplasms, serial morphologic changes pose an indication for surgery. EUS-guided cystic ablation using ethanol and/or an injection of paclitaxel has been suggested as an alternative for unfit for surgery patients with high risk of a malignant transformation. To date, EUS-RFA for PCLs has been proposed, and could provide a better control of the ablative area without the risk of fluid spread.

Unlike PDAC and PNEN, previous experiments on PCL are relatively few (Table 1).[11,14-23] A prospective study including 17 PCLs (mean size, 28 mm; range, 9–60 mm) of 16 intraductal papillary mucinous neoplasms with worrisome features and one mucinous cystic adenoma unfit for surgery demonstrated a 71% significant response rate at 12 months. (11 complete disappearances and one partial response in which the diameter was decreased by > 50%). In terms of the EUS-RFA technique, they experienced one case of jejunal perforation adjacent to a cyst treated without aspirating the fluid. EUS-RFA was applied after suction of the liquid from the cyst until a thin layer of film remained, to reduce damage to collateral structures. After this measure, no further complication was experienced. In the entire cohort of 30 patients, also including NETs, only 6 (20%) experienced minor events such as mild

abdominal pain.

Although the possibility of an effective treatment with EUS in PCL has been reported, consensus has not been reached. Since Intraductal pancreatic mucinous neoplasm, irrespective of who underwent cystic ablation, or required surveillance of the remaining pancreas, there has been a fundamental question of whether the treatment of PCLs is necessary. However, in some high-risk groups where surgery is difficult, EUS-RFA may be possibly used as an alternative solution; more well-designed studies to evaluate the safety and long-term efficacy are necessary.

Celiac ganglia neurolysis

Because pancreatic cancer is commonly associated with intense and refractory pain, non-pharmacologic therapies are administered with the aim of improving pain control and quality of life, while reducing the risks of opioid-induced side effects. Celiac plexus neurolysis and block can be performed percutaneously, surgically, or under EUS guidance. Among them, EUS-guided celiac plexus/ganglia neurolysis using bupivacaine, followed by alcohol injection is one of the most established; however, there is a possibility of severe adverse effects such as arterial embolism or spinal cord infarction due to the migration of ethanol. Recently, EUS-RFA has been proposed as a palliative treatment option, which allows the accurate control of the ablation zone and therefore produces more specific results without severe adverse events. A recent randomized controlled trial (RCT)[25] comparing EUS-guided ethanol injection versus RFA for the celiac plexus/ganglia neurolysis using 1 Fr monopolar probe passed via a 19G FNA needle. They concluded that EUS-RFA provided more pain relief and less severe GI symptoms in patients with pancreatic cancer. However, some doubts have arisen on the problem of small sample size and risk of the procedures.

Conclusions and Future Perspectives

RF ablation has been regarded as an established technique in various disease. Although the application of RFA in the pancreas has been limited due to the increased risk of adverse events, EUS-RFA has generated interest as a novel minimally invasive treatment that combines real-time visualization with precise localization of the treatment procedure. For over a decade, several experiments which support the safety and feasibility regarding EUS-RFA have been reported, but the evidence to suggest the appropriate indications and to describe the long-term therapeutic effects is still lacking. For this reason, various multicenter prospective studies (NCT0234369262, NCT0369032349, NCT0233667250) are being conducted in order to involve EUS-RFA as a part of multimodal treatments for the cure of pancreatic malignant and premalignant lesions.

In conclusion, EUS-RFA is a technically feasible, safe and minimally invasive ablation treatment in selected patients with PNEN, PDAC, and PCL. For the verification of each indication of EUS-RFA according to various pancreatic neoplasms, future prospective and well-designed controlled studies with longer follow-up are warranted. Furthermore, while evidence-based answers are generated, EUS-RFA should be included within research protocols, and centralized in high-volume EUS-centers which have multidisciplinary support.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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