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REVIEW

Endoscopic Radiofrequency Ablation of the Pancreas

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Abstract Radiofrequency ablation (RFA) is a well-established technique to ablate dysplastic and neoplastic tissue via local thermal coagulative necrosis. Despite the widespread use in management of several cancers, the application of RFA in pancreas has been limited due to the increased risks of complications from the increased sensitivity of pancreatic tissue to thermal injury and proximity to vascular and biliary structures. RFA has been successfully used during laparotomy for locally advanced pancreatic carcinoma but requires an invasive approach. Endoscopic ultrasound-guided RFA offers the best combination of excellent visualization, real-time imaging guidance, and precise localization with minimal invasiveness. Several animal and human studies have demonstrated the technical feasibility and safety of endoscopic RFA in the pancreas. This article provides a comprehensive review of endoscopic RFA in the management of pancreatic lesions.

Keywords RFA · EUS · Endoscopic ultrasound · CTP · Cryotherm · Pancreatic cysts · Insulinoma · Pancreatic cancer · Habib · Pancreatic cystic lesion

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Introduction

Radiofrequency ablation (RFA) therapy has been found to be safe and effective in several gastrointestinal disorders. RFA has been available for over a decade and has an expanding list of indications including the treatment of benign and malignant gastrointestinal disease. Benign indications generally involve the application of RFA for mucosal ablation to achieve hemorrhagic control such as in gastric antral vascular ectasia (GAVE) [1, 2] and chronic radiation proctitis [3, 4]. Application of RFA for eradication of premalignant lesions is best exemplified by its use in Barrett's esophagus with dysplasia [5–8]. RFA has a potential role in the management of several malignancies such as hepatocellular carcinoma [9–12], hepatic metastatic lesions [13–16], unresectable pancreatic cancers [17–20], and cholangiocarcinoma [21–26].

Recently, RFA has been increasingly employed in experimental and clinical setting in the management of solid and cystic pancreatic lesions. RFA can be applied percutaneously, intraoperatively, or endoscopically. Endoscopic RFA of pancreatic lesions is performed using an endoscopic ultrasound (EUS)-guided RFA probe which offers the best combination of excellent real-time visualization and precise localization with minimal invasiveness for selective ablation of the lesion. In this review, we have evaluated the technical feasibility, safety, and efficacy of endoscopic RFA for pancreatic lesions.

Animal Studies

It was in 2009 when Goldberg et al. [27] first conducted RFA on 13 porcine models under EUS guidance. The pancreatic lesions were localized under EUS guidance and

approached through a transgastric approach. RF current (285 ± 120 mA) was delivered for 6 min. Pathological examination demonstrated a discrete histological progression of coagulation necrosis followed by fibrotic capsule contraction. The complications included mild hyperlipasemia with a focal zone of pancreatitis (<1 cm) followed by a pancreatic fluid collection in 1 pig and 4 visceral burns from improper probe placement. This study was the first to establish the potential of discrete coagulation necrosis in pancreatic lesions via endoscopic approach and its potential use in locally advanced malignancy, neuroendocrine tumors, and other focal pancreatic lesions.

Kim and colleagues also reported the technical feasibility, efficacy, and safety of EUS-guided RFA application in pancreas in an experimental animal model [28]. They used an 18-gauge endoscopic RFA electrode to puncture the body and tail of the pancreas in 10 adult mini pigs, with an output power of 50 W for 5 min. A spherical necrotic lesion surrounded by fibrous tissue localized in the pancreatic parenchyma was observed on histopathologic examination. The mean diameter of the ablated tissue was 23.0 ± 6.9 mm. No major procedure-related complications were noted, and all pigs survived without any distress behavioral pattern for 7 days until autopsy. Apart from small sample size with short-term observation, the study lacked evaluation of technique in head of the pancreas.

Subsequently, EUS-guided RFA of the head of the pancreas was evaluated by Gaidhaine et al. [29] in 5 pigs via transduodenal approach using the pilot Habib EUS RFA probe (EMcision Ltd., London, UK). This is a 1 Fr wire (0.33 mm, 0.013 in.) with a working length of 190 cm, which can be inserted through the biopsy channel of an echoendoscope [29] (Fig. 1). The RFA probe was applied with 6 mm of the probe exposed at 4 W for 300 s (5 min), 5 W for 54 s (0.9 min), and 6 W for 12 s (0.2 min). Then with 10 mm of the probe exposed in the pancreas, RFA was applied at 4 W for 258 s (4.3 min), 5 W for 84 s (1.4 min), and 6 W for 48 s (0.8 min). Of the 5 pigs, only 1 pig developed moderate pancreatitis. Minimal fat necrosis was noted in intrapancreatic and/or extrapancreatic adipose tissue.

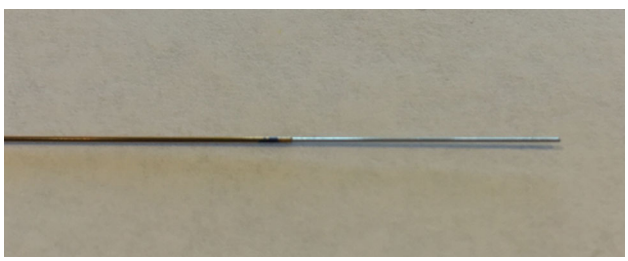

Fig. 1 Habib EUS-RFA probe

Silviu and colleagues performed another feasibility study of EUS RFA using the 0.33-mm RFA probe (EMcision Ltd., London, UK) through a 19G EUS-FNA needle on 10 pigs [30]. Four sessions of consecutive ablations were performed in the head of the pancreas with 4–6 mm of the catheter exposed at 5, 10, 15, and 20 W for 120 s each. A hyperechogenic elliptic lesion, with a median diameter of 2.65 cm (interquartile range 0.5 cm), was noted surrounding the inserted RFA probe. Necropsy was performed a week after the EUS-guided RFA procedures. The complications included iatrogenic gastric wall injury ($n = 1$) and moderate ascites of 100 ml ($n = 1$). Histopathologic examination showed a central area of coagulative necrosis demarcated by a peripheral rim of fibrinous exudate and inflammatory response. There was no evidence of focal pancreatitis at 2–3-cm distance from the lesions [30].

Yoon et al. [31] evaluated radiofrequency ablation using the 1-Fr wire electrode in the porcine pancreas accessed via a midline laparotomy. Manual monopolar RFA was performed over a 90-s period using a wide range of power settings (3, 4, 5, 10, 15, and 25 W). The maximum diameter of coagulative necrosis (8.0 ± 1.7 mm) was achieved at 5 W with higher power settings resulting in relatively homogeneous necrosis [31]. While RFA was not performed through the needle under EUS guidance in this study, the data provide initial settings to be considered when performing EUS RFA for pancreatic lesions.

More recently, a new innovation has coupled conventional RFA with cryotherapy. This new hybrid ablation system [cryotherm probe (CTP), ERBE Elektromedizin GmbH, Tübingen, Germany] combines the advantages of these two ablation methods with better efficacy and safety. Cryotherapy using liquefied CO_2 (650 psi) provides effective cooling which allows lower power (15–20 W) RFA to achieve similar tissue ablation effects compared to higher power (30–60 W) used by conventional RF ablation systems but with less collateral damage [32]. The CTP has an active electrical part with a diameter of 1.8 mm. The entire CTP is covered by a protection tube that can be safely passed through the operative channel of the echoendoscope without any risk for the instrument.

Carrara et al. [33] evaluated this hybrid cryotherm probe for delivery of transluminal RFA in 14 pigs. Under real-time EUS-guidance, the CTP was clearly visualized as a hyperechoic line moving out of the working channel until it reached its place in the pancreatic parenchyma. During the application, a hyperechoic elliptic area appeared around the distal tip of the probe, surrounded by a hypoechoic border from tissue edema. On histological examination, a sharp demarcation was visible between the ablated area and the untreated pancreatic parenchyma. Coagulative necrosis was evident in the center of the lesion 1 week after the

ablation; after 2 weeks, the lesions showed less edema and more fibrotic transformation. A significant correlation was observed between the size of the ablated area and application time. The complications were also related to the ablation time: All but histochemical pancreatitis occurred with ablations longer than 300 s.

Another ex vivo study evaluating the efficacy of CTP in destroying neoplastic tissue of explanted pancreas from patients with resectable pancreatic adenocarcinoma also found a positive correlation between the size of the ablated area and the application time [34]. This study also demonstrated the benefit of cooling from liquid CO_2 by reduction of desiccation zone, an area causing increased electrical impedance. The cryotherm by maintaining the temperature of RFA needle ensured a time-dependent (linear correlation) ablation area [34] (Table 1).

Human Studies

Pai et al. [35] performed a multicenter prospective trial including 8 patients with a median age of 65 (range 27–82) years; (7 female:1 male). The pancreatic pathology comprised pancreatic cystic neoplasm in 6 patients (4 mucinous cyst, 1 intraductal papillary mucinous neoplasm and 1 microcystic adenoma) and 2 had neuroendocrine tumors (NET) in the head of pancreas. The mean size of the cystic neoplasm and NET were 36.5 mm (SD ± 17.9 mm) and 27.5 mm (SD ± 17.7 mm), respectively. These patients underwent RFA for 90–120 s with fixed wattage (5–25 W) using the Habib EUS-RFA probe placed through a 19 or 22 gauge fine needle aspiration (FNA) needle after aspiration in patients with a tumor in the head of the pancreas. Among the 6 patients with a cystic neoplasm, there was complete resolution of the cysts in 2 cases, and in 3 more there was a 48.4% reduction [mean pre-RF 38.8 mm (SD ± 21.7 mm) vs. mean post-RF 20 mm (SD ± 17.1 mm)] in size. In 2 patients with NET, cross-sectional imaging demonstrated a change in vascularity and central necrosis after EUS-RFA. There were no immediate or early major post-procedural complications such as pancreatitis, perforation, or bleeding. Two patients reported a mild abdominal pain that resolved in 3 days.

In another pilot study, RFA was applied in 10 patients with histologically diagnosed pancreatic NETs via percutaneous ($n = 7$), intraoperative ($n = 2$), and endoscopic ($n = 1$) approach [36]. For the one patient (72-year-old male) who underwent EUS-guided RFA, they used active electrode comprising of a flexible 22G insulated steel wire, 200 cm in length and exposed tip measuring 1 cm in length. The tip was positioned in the center of the tumor in the head of pancreas, and a power of 10–15 W was delivered for 6 min. The secreting tumors underwent rapid and complete normalization of serum hormone levels with no recurrences observed during median follow-up of 34 months (range 12–60 months). This study had no mortality although acute pancreatitis developed in 3 patients treated with non-endoscopic RFA; 2 of whom developed pancreatic fluid collections requiring drainage. A higher complication rate in RFA of lesions with proximity to pancreatic duct was observed. Also the relative safety of endoscopic and intraoperative approaches over percutaneous approach and the need for electrodes with higher sonographic visibility was highlighted in the study.

A recent study by Song et al. [37] reported use of EUS-guided RFA in 6 patients with unresectable pancreatic cancer [head (4) and body (2); locally advanced (4) and metastatic (2)]. In this study, an 18-gauge RFA electrode was inserted into the pancreatic mass (median diameter—3.8 cm) to deliver 20–50 W ablation power for 10 s. Post-RFA follow-up with contrast-enhanced EUS (CE-EUS) revealed increased blood flow around the RFA site. Therefore, gemcitabine-based systemic chemotherapy was administered on the same day in 3 patients to enhance the effect of chemotherapy. Patients experienced mild post-procedural pain managed with analgesics without any bleeding, infection, vascular or viscus injury [37].

A small case series by Lakhtakia et al. [38] recently described insulinoma ablation in 3 symptomatic patients who were either unfit for surgery or refused it. Patients achieved symptomatic relief within 24 h of ablation and remained euglycemic during median follow-up of 12 months. Authors used a novel EUS-RFA system (STARmed, Seoul, Korea) consisting of a prototype 19G needle electrode (140 cm long, covered with a sheath except for the terminal 1 cm with a sharp conical tip for energy delivery), a RF generator, and an internal cooling system which circulates chilled saline solution through the needle electrode during the RFA procedure to prevent charring of the surface of the electrode and improve accuracy of ablation [38]. Echogenic bubbles were noted to appear around the needle tip indicating completeness of RFA, producing a coagulation necrosis area of about 10–12 mm by 5 mm at a power of 50 W for 10–15 s.

Arcidiacono and group demonstrated the feasibility and safety of an EUS-guided cryotherapy–RFA hybrid application using the cryotherm probe (CTP) in a prospective study enrolling 22 (mean age 61.9 years) patients with locally advanced, unresectable stage III, pancreatic adenocarcinoma [39]. CTP is a flexible bipolar device that combines bipolar RF heating (18 W) with cryogenic cooling (650 psi). CTP was successfully applied in 16 (72.8%) patients with a mean application time of 107 ± 86 s; in remaining 6, it was not feasible because of stiffness of the GI wall and of the tumor. The probe was clearly visible throughout the procedure. No severe

Table 1 Pancreatic EUS-RFA: animal studies

Study	*N*	RFA devices	Power settings	Generator	RFA to analysis duration	Area of ablation	Complications
Goldberg et al. [27]	13	19G Vilmann-type needle (GIP/MediGlobe, Grassau, Germany)	285 ± 120 mA for 300 s	Radionics Series 3	Immediate ($n = 5$) 1–2 days ($n = 2$) 14 days ($n = 6$)	8–10 mm	Gastric burn ($n = 3$) Intestinal burn ($n = 1$) Raised amylase levels ($n = 1$)
Carrara et al. [33]	14	Cryotherm Probe (ERBE, Tübingen, Germany)	Heating: 16 W Cooling: 650 psi for 107 ± 86 s (mean) 120–900 s (range)	Heating: VIO 300D Cooling: ERBO-KRYO CA	7 days ($n = 7$) 14 days ($n = 7$)	–	Pancreatitis ($n = 2$) Gastric wall burn ($n = 1$) Adhesions ($n = 4$)
Kim et al. [28]	10	18G RFA electrode (STARmed, Koyang, Korea)	50 W for 300 s	VIVA	7 days	23 ± 6.9 mm	Retroperitoneal fibrosis ($n = 1$) Adhesions ($n = 2$)
Gaidhane et al. [29]	5	Habib EUS-RFA probe (EMcision Ltd., London, UK)	6 mm probe exposure: 4 W–300 s 5 W–54 s 6 W–12 s 10 mm probe exposure: 4 W–258 s 5 W–84 s 6 W–48 s	RITA	5 days	8–10 mm	Pancreatitis (not clinically apparent but histology showed moderate (20%) acinar involvement)
Silviu et al. [30]	10	Habib RF DUO 13 needle (EMcision Ltd., London, UK)	5, 10, 15, 20 W for 120 s each	RITA 1500 RF	7 days	Median 26.5 mm (IQR 5 mm; Range 20–30 mm)	Gastric wall injury and adhesions ($n = 1$) Moderate Ascites-100 ml ($n = 1$)

complications arose during or immediately after the ablation. The early complications included abdominal pain with mild hyperamylasemia responding to analgesics ($n = 3$) and minor duodenal bleeding ($n = 1$) treated with endoclip placement. Four patients experienced late complications including jaundice ($n = 2$; hemobilia in 1) and duodenal stricture ($n = 1$) related mainly to tumor progression and asymptomatic cystic fluid collection ($n = 1$). The study demonstrated linear correlation between application time and ablated area. CT scan was done in all patients but only in 6/16 was it possible to clearly define the tumor margins after ablation. In these patients, the tumor seemed smaller than the initial mass ($P = 0.07$). The mean survival was 6 months after the procedure. Small sample size and difficulty of objectifying the size of the ablated zone by CT scan were noted as limitations by authors (Table 2).

Discussion

RFA is a well-established technique to ablate dysplastic and neoplastic tissue via local thermal-induced coagulative necrosis. An additional antitumor mechanism of action through release of tumor antigen within the blood stream to stimulate the T cell immunity has also been described [40–43]. Despite the wide use in management of several cancers, its use in pancreas has been limited due to the high risks of complication from the increased sensitivity of pancreatic tissue to thermal injury and proximity to vascular and biliary structures. RFA has been successfully used during laparotomy for locally advanced pancreatic cancer but requires an invasive approach [18–20]. Transabdominal ultrasound-guided percutaneous RFA offers a less invasive alternative but has been restricted because of poor visualization of the retroperitoneal pancreas. EUS-guided RFA offers the best combination of excellent visualization, real-time imaging guidance, and precise localization with minimal invasiveness. EUS coupled with Doppler enables further visualization of vascular elements in relation to the pancreas to minimize the risk of vascular injury. In addition, EUS-guided RFA is associated with less morbidity and lower costs than laparotomy.

Several small animal studies and case series as described above have demonstrated the technical feasibility, safety, and to some extent the efficacy of endoscopic RFA for pancreatic lesions. The clinical indications for EUS-RFA mostly included solid neoplasms and some cystic lesions. Although limited by small sample size and lack of comparative data, current studies show benefit in selected patients with adenocarcinoma and neuroendocrine tumors in whom surgery is not an option or who refuse surgery. Combination of EUS-guided RFA as adjunct cytoreductive therapy for local control of the disease along with systemic control with chemotherapy can potentially improve survival and quality of life [37, 44, 45]. Increased blood flow around the RFA site might also enhance the penetration and effect of systematic chemotherapy [37]. For borderline resectable tumors, targeted tumor ablation might improve the efficacy of neoadjuvant treatment with increased conversion to resectable disease [44, 45]. Small cystic and neoplastic lesions such as neuroendocrine tumors may be effectively cured with EUS-guided RFA. Lastly, EUS-guided RFA of premalignant pancreatic cystic lesions might provide a minimally invasive alternative to surgery or surveillance.

Despite growing interests in pancreatic RFA, few theoretical concerns and limitations still exist. Studies have used different RFA probes with markedly varying energy settings, ranging from 5 to 50 W applied for 10 s to 6 min. There is currently lack of standardization and lack of dose–effect dosimetry studies to evaluate the relationship between energy and duration of application and the zone of ablation produced to safely and effectively ablate the pancreatic lesion [46]. Another important limitation is follow-up after RFA to evaluate the success and completion of ablation and the potential need for retreatment. Appearance of a non-enhancing area at the site of ablation surrounded by a thin enhancing rim has been described on contrast-enhanced imaging studies including CE-EUS performed shortly after the RFA [36]. Arcidiacono and colleagues reported difficulty in CT follow-up of the ablation in the first 4 weeks given the inability to distinguish inflammatory reactions of the tumor tissue from tumor growth or necrosis [39]. Magnetic resonance imaging has been suggested as an alternative to better delineate the poorly perfused pancreatic areas and assess the presence and degree of necrosis after RFA [39, 47, 48].

Procedure-related mortality or severe complications such as major bleeding, perforation, severe pancreatitis, or pancreatic fistula/leak have not been reported with endoscopic RFA of pancreatic lesions. Most studies report only transient increases in serum amylase and lipase levels, which are often asymptomatic or associated with mild abdominal discomfort. This is in contrast to the major complications described during non-endoscopic RFA application [36, 40, 41, 49–51]. Thermal injury to the proximal main pancreatic duct during percutaneous and intraoperative RFA has been associated with mild to severe pancreatitis and pancreatic fluid collection requiring drainage [36]. Whether endoscopic stenting of main pancreatic duct prophylactically would reduce the risk of post-RFA pancreatitis in lesions close to main pancreatic duct needs to be evaluated.

In conclusion, endoscopic RFA is a technically feasible, minimally invasive, and a safe modality of ablation for

Table 2 Pancreatic EUS-RFA: clinical studies

Study	*N*	RFA device	Power settings	Generator	Indications	Complications	Follow-up period	Median survival
Arcidiacono et al. [39]	22	Cryotherm Probe (ERBE, Tübingen, Germany)	Heating: 18 W Cooling: 650 psi for variable time per tumor size (mean 107 ± 86, range 10–360 s)	Heating: VIO 300D Cooling: ERBOKRYO CA	Locally advanced unresectable adenocarcinoma	Abdominal pain and raised amylase levels ($n = 3$), Minor duodenal bleeding ($n = 1$) Jaundice ($n = 2$; one had hemobilia and anemia), Duodenal stricture ($n = 1$), Cystic fluid collection ($n = 1$)	12 months	6 months
Rossi et al. [36]	1	22G EUS-RFA needle (EMcision Ltd., London, UK)	10–15 W for 6 min	Model TAG 100 or Model RF 3000	Pancreatic neuroendocrine tumor	None	12–60 months	–
Pai M et al. [35]	8	Habib EUS-RFA needle (EMcision Ltd., London, UK)	5 W ($n = 3$) 15 W ($n = 2$) 20 W ($n = 2$) 25 W ($n = 1$) for 90 s each	Rita (×1500) or ERBE (ICC200)	Pancreatic cystic neoplasm ($n = 6$) Pancreatic neuroendocrine tumors ($n = 2$)	Mild abdominal pain ($n = 2$)	3–6 months	–
Song et al. [37]	6	18G RFA needle (STARmed, Koyang, Korea)	20–50 W for 10 s	VIVA	Unresectable locally advanced or metastatic pancreatic cancer	Mild abdominal pain ($n = 2$)	2–6 months	–

management of pancreatic solid and cystic lesions in select patients. Future prospective and controlled studies with larger sample size and longer follow-up are warranted to further establish the safety and long-term efficacy of RFA in premalignant and malignant lesions with potential survival and quality of life benefit among patients with pancreatic neoplasm.

Compliance with ethical standards

Conflict of interest None.

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