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

Jae Hee Cho*, Sung Ill Jang, and Dong Ki Lee

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 Barrett’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.

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. Radiofrequency ablation (RFA) is an established minimally invasive therapeutic modality for various diseases including hepatocellular carcinoma, renal cell carcinoma, and Barrett’s esophagus. In pancreatobiliary disease, endoscopic retrograde cholangiopancreatography (ERCP)-guided intraductal RFA has also been increasingly performed in malignant biliary tract obstruction. 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. 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. RF may be delivered through mo-
An impedance of 1,000 Ω 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. However, segmental biliary strictures with cholangitis develop as a long-term result, so biliary stents should be placed to maintain biliary drainage after intraductal RFA.1

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).2 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

![Fig. 1. EUSRA RF electrode (STARmed, Goyang, Korea).](image)

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.

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.3 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.9 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.10 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>
<thead>
<tr>
<th>Reference</th>
<th>Author</th>
<th>No. patients</th>
<th>RFA devices</th>
<th>Mean tumor size (mm)</th>
<th>Settings</th>
<th>Efficacy</th>
<th>Overall survival (n)</th>
<th>RFA related adverse events (n)</th>
<th>Prophylaxis</th>
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<tbody>
<tr>
<td>Pancreatic neuroendocrine neoplasm</td>
<td>Lakhtakia et al⁴⁴</td>
<td>3 insulinomas</td>
<td>EUSRA</td>
<td>14–22</td>
<td>50 W</td>
<td>Symptoms relief (100%); persistent at 11 mo FU</td>
<td>All patients alive at 11 mo FU</td>
<td>0</td>
<td>NA</td>
</tr>
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<td></td>
<td>Choi et al⁴⁴</td>
<td>7 NF-NENs, 1 insulinoma</td>
<td>EUSRA</td>
<td>20 [8–28]</td>
<td>50 W (10 sec)</td>
<td>6 complete responses, 2 incomplete responses; remission of hypoglycemic symptoms in insulinoma patient</td>
<td>2 (25%): 1 abdominal pain, 1 pancreatitis</td>
<td>Broad-spectrum antibiotics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oleinikov et al⁴⁵</td>
<td>7 insulinomas, 11 NF-NENs (some multifocal; 2 with treatable metastasis); 27 total lesions</td>
<td>EUSRA</td>
<td>14.4 [4.5–30]</td>
<td>10–50 W, 5–12 sec</td>
<td>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</td>
<td>2 (11%) mild pancreatitis</td>
<td>Broad-spectrum antibiotics</td>
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<td></td>
<td>Barthet et al⁴⁵</td>
<td>14 NF-NENs (Grade 1)</td>
<td>EUSRA</td>
<td>12 [10–20]</td>
<td>50 W until bubbles or impedance 100–500 Ω</td>
<td>12 (86%) complete disappearance; 2 absence of Doppler at EUS</td>
<td>NA</td>
<td>2 (14%): 1 acute necrotizing pancreatitis (RF without suction of cystic fluid), 1 MPD stenosis; 20% postprocedural pain</td>
<td>After the first 2 patients: rectal NSAIDs + amoxicillin/clavulanate</td>
</tr>
<tr>
<td>Pancreatic ductal adenocarcinoma</td>
<td>Wang et al⁴⁵</td>
<td>3 LAPC</td>
<td>Habib</td>
<td>37.3</td>
<td>10–15 W, 2 min</td>
<td>Mean reduction in tumor size: 13.94%</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
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<tr>
<td></td>
<td>Song et al⁴⁶</td>
<td>4 LAPC + 2 MPC</td>
<td>EUSRA</td>
<td>38 [30–90]</td>
<td>20–50 W, 10 sec</td>
<td>NA</td>
<td>2 (31%) self-limiting pain</td>
<td>Broad-spectrum antibiotics</td>
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<tr>
<td></td>
<td>Scopelliti et al⁴⁷</td>
<td>10 LAPC</td>
<td>EUSRA</td>
<td>25–75</td>
<td>20 W (lesion &lt; 3 cm), 30 W until impedance 500 Ω</td>
<td>Mean diameter of necrosis at 30 day CT: 30 ± 13 mm</td>
<td>NA</td>
<td>4 (40%): 2 post-procedural self limiting pain, 2 asymptomatic ascite</td>
<td>Broad-spectrum antibiotics + octreotide + LMWH</td>
</tr>
<tr>
<td></td>
<td>Grinò et al⁴⁸</td>
<td>8 LAPC + 1 metastatic rectal cancer</td>
<td>EUSRA</td>
<td>36 [22–67]</td>
<td>30 W</td>
<td>Ablated area in all patients at 30 day CT: mean diameter 3.75 cm³ [0.72–12.6 cm³], 30% of tumor mass</td>
<td>NA</td>
<td>3 (33%): 3 mild abdominal pain</td>
<td>NA</td>
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<tr>
<td></td>
<td>Yang and Zhang⁴⁹</td>
<td>8 unresectable pancreatic cancer</td>
<td>Habib</td>
<td>NA</td>
<td>NA</td>
<td>Ablated area inside the tumor in 100%</td>
<td>8.3 mo</td>
<td>0</td>
<td>NA</td>
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</table>
### Table 1 Continued

<table>
<thead>
<tr>
<th>Reference</th>
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<th>RFA devices</th>
<th>RFA related adverse events</th>
<th>Prophylaxis</th>
<th>Efficacy</th>
<th>Overall survival (mo)</th>
<th>Mean tumor size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arcidiacono et al</td>
<td>22 LAPC</td>
<td>HybridTherm 35.7 (23–54)</td>
<td>18 W, cooling pressure 650 psi</td>
<td>NA</td>
<td>2 (33%): self-limiting pain</td>
<td>6 mo (13 patients)</td>
<td>8 (50%): 3 mild postprocedural bleeding; 1 hemorragic cyst; 1 postprocedural fluid collection</td>
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<td>Ceftriaxone + gabexate mesylate; Cyst aspiration before RFA</td>
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<td></td>
<td>Habib</td>
<td>36.5 (20–70)</td>
<td></td>
<td>5–25 W</td>
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<td></td>
<td>EU3RA</td>
<td>28 (0–60)</td>
<td></td>
<td>50 W until bubbling or until all lesions were coagulated</td>
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<tr>
<td></td>
<td>Pers et al</td>
<td>4 MCN; 1 IPMN; 1 microcytic adenoma</td>
<td>EUS-RFA</td>
<td>400–500 G</td>
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<tr>
<td></td>
<td>Barbut et al</td>
<td>14 IPMN; 1 MCN</td>
<td>EUS-RFA</td>
<td>120 (100–120)</td>
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<td>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; UC, computed tomography; LMWH, low-molecular-weight heparin; MRK, mucinous cystic neoplasm.</td>
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#### 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. 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. To date, clinical efficacy and safety of EUS-RFA have been

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**Note:** Values are presented as median [range] or mean ± SD only.
evaluated. EUS-RFA allows both reduced invasiveness and a real-
time control of the treatment. Furthermore, it is an easily repeat-
able procedure, if necessary. Available experiments of EUS-RFA of PDAC include a few small cohorts and focus mainly on techni-
cal feasibility and safety (Table 1).\textsuperscript{11,14-23} From these researches, EUS-RFA is technically feasible and has no major procedure-re-
lated adverse events such as mortality. Most RFA related adverse
events were minor, such as self-limiting postprocedural abdomi-
nal pain. As for efficacy, when a 30-day CT was executed,\textsuperscript{18,19}
an ablative necrotic area was identified compared to the original
tumor volume (between 5.7% and 73.5%).\textsuperscript{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 lo-
cal 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 rel-
atively few (Table 1).\textsuperscript{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
cyst 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 includ-
ing NETs, only 6 (20%) experienced minor events such as mild
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) comparing EUS-guided ethanol injection versus RFA for the celiac plexus/ganglia neurolysis using 1Fr 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 ablation 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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References

22. Yang J, Zhang X. Tu1357 feasibility and safety of EUS-guided radiofrequency