Review

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EUS–guided radiofrequency ablation of solid pancreatic lesions: An updated review

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ABSTRACT

Recent years have brought to light newly developed therapeutic modalities for the treatment of premalignant and malignant pancreatic lesions. The role of EUS–guided radiofrequency ablation (EUS-RFA) as a treatment modality for malignant pancreatic lesions is still under evaluation. Several animal studies and human studies have demonstrated the safety and efficacy of EUS-RFA in the management of premalignant and malignant pancreatic lesions.

EUS-RFA therapy can potentially ablate these lesions safely and with minimally invasive techniques. In this article, we provide an updated review of the application of EUS-RFA of pancreatic lesions. We also review the clinical efficacy and safety of this technique and future directions.

Key words: EUS; Radiofrequency ablation; Pancreatic neoplasm ablation; Celiac plexus neurolysis

INTRODUCTION

EUS continues to evolve as a reliable diagnostic and therapeutic endoscopic modality. The potential benefits of EUS-guided radiofrequency ablation (EUS-RFA) for therapy of premalignant/malignant pancreatic lesions are the provision of a viable minimally invasive alternative to traditional approaches such as surgery particularly in patients who are not surgical candidates.[1]

EUS-RFA uses alternating current and high frequency (460–500 kHz) to deliver therapy to affected areas. This form of energy leads to coagulative necrosis, irreversible cell damage, and cell death.[2] The current of RFA is delivered using monopolar or bipolar probes. The monopolar probe applies high-current energy through an electrode that heats the target tissue. The bipolar system functions with the flow of current between 2 electrodes. Although the monopolar requires grounding, the bipolar system does not. Bipolar probes, although providing lesser ablative effect to the target tissue, are regarded as safer with less damage to surrounding healthy tissue.[1] In addition, anticancer immunomodulation effect has been noted following the application of RFA.[3]

The clinical application of RFA has been effective as a therapeutic modality for treating hepatocellular carcinoma (HCC), Barrett's esophagus, and malignant biliary strictures, most commonly from cholangiocarcinoma.[4–6] However, the efficacy and safety of EUS-RFA have been limited to few animal studies and limited human studies.

In this review article, we appraise the current literature regarding the use of EUS-RFA for the therapy and/or palliation of pancreatic lesions.

CYSTIC PANCREATIC NEOPLASMS

To date, limited studies have been conducted evaluating the outcomes and overall effect of EUS-RFA in cystic pancreatic tumors (intraductal papillary mucinous neoplasms or mucinous cystic pancreatic neoplasm). One of the initial studies analyzing the safety and efficacy of this procedure in humans was a multicenter study by Pai et al.[7] The study evaluated 8 patients, 6 of which had confirmed pancreatic cystic neoplasms, who underwent EUS-RFA of the pancreatic cystic neoplasm using a 19- or 22-gauge fine needle biopsy needle. The power applied during each application varied per patient, with 5 W administered for 3 patients, 15 W administered for 2 patients, and 25 W administered for 1 patient. All patients had only one session of EUS-RFA (3–7 applications during the session). Overall, Pai et al. noted a complete reduction in the pancreatic cysts in 2 patients, whereas a 48.4% reduction was seen in 3 patients on postprocedure imaging. Mild adverse events occurred in 2 patients who experienced abdominal pain, which resolved within 3 days.

Barthet et al.[8] reported a multicenter study that analyzed 17 patients with cystic tumors and 12 patients with a neuroendocrine tumor (NET) of the pancreas. EUS-RFA was performed using an 18-gauge RFA cooling needle. Fifty watts was applied, and a 2-mm distance was kept between the needle and surrounding structures. After the first 2 patients, the study was modified to include preprocedure antibiotic prophylaxis. Before this study modification, one patient developed pancreatitis and fever. The other patient, premodification, was revealed to have pneumoperitoneum with fluid collection after the onset of pain and fever for 12 hours. After these changes were made, no additional patient with a cystic pancreatic neoplasm experienced an adverse event. During the 12-month follow-up, the cystic neoplasms were completely eradicated in 11 patients. One patient had a cystic neoplasm that decreased in diameter by greater than 50%. The remaining 5 patients experienced less than a 50% reduction or no

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tumor change—the results of the study exemplified an overall response rate of 71% using EUS-RFA.

These 2 studies established that EUS-RFA is potentially a safe and effective treatment of targeting cystic pancreatic neoplasms. However, larger prospective studies are needed to explore the long-term efficacy of EUS-RFA further.

NETs OF THE PANCREAS

EUS-RFA has been studied for its ability to treat pancreatic NETs, specifically tumors that are ineligible for surgical intervention. The initial studies were first conducted using animal models, but human studies have taken precedence in the last 5 years. Barthet et al.[8] conducted a prospective multicenter study focused on both cystic neoplasms and NETs. As described previously, this study included 12 patients who had 14 NETs. An 18-gauge needle with 50 W was also used for patients with NETs. At the 6-month follow-up, 9 of the 14 tumors had disappeared or showed complete necrosis. By 1 year, 12 of 14 tumors (85.7%) had disappeared on cross-sectional abdominal imaging; no tumor was observed at a 1-year follow-up. Only 2 tumors did not show any improvement after initial treatment. Of the 2 tumors that did not respond to RFA, 1 had increased in size. The only adverse event reported was stenosis of the main pancreatic duct. The patient was treated with Endoscopic retrograde cholangiopancreatography (ERCP) with pancreatic stenting.

Oleinikov et al.[9] evaluated 11 patients diagnosed with a nonfunctional pancreatic NET (NF-pNET) and 7 patients with insulinomas. Two of the patients diagnosed with an NF-pNET had an association with multiple endocrine neoplasia type 1 (MEN1) syndrome. Ten of the 11 patients were asymptomatic, and the tumor diagnosis was incidental. In this study, a 19-gauge needle was used with a power of 10 to 50 W. Each application lasted between 5 and 12 seconds. Of the 11 patients with NF-pNET, 10 patients were recorded to have a complete response to RFA therapy as indicated by a hyperechoic area seen on EUS after the procedure. One patient was unable to have complete ablation because of the location of the tumor, which was near the main pancreatic duct. However, this patient showed residual tissue after postprocedural imaging. Mild pancreatitis were reported in 2 patients with NF-pNET, appearing on day 10 and day 7, respectively. Both were conservatively managed with good recovery.

Similarly, De Nucci et al.[10] reported a series of 10 patients, of which 5 had symptomatic insulinomas. A 19-gauge needle with 20 W was used to ablate tumor areas for 10 to 25 seconds. A distance of at least 2 mm was maintained from the pancreatic and bile ducts to avoid endoscopic injury. Complete ablation was reported in all patients and was confirmed at 6- and 12-month follow-ups. Two patients experienced mild abdominal pain, whereas 3 patients had minimally elevated amylase levels without abdominal pain.

These preliminary reports provide some evidence that EUS-RFA may be effective in treating NETs. However, among studies, there is a lack of consensus on the optimal power and the number of sessions required for treatment.

PANCREATIC INSULINOMAS

Pancreatic insulinomas are uncommon NETs that may be amenable to endoscopic therapy with EUS-RFA.[9] Recent human studies have demonstrated the benefits and risks associated with using this treatment as opposed to traditional methods such as surgery. Lakhtakia et al.[11] reported a small case series involving 3 patients who opted for nonsurgical interventions and elected for EUS-RFA. A 19-gauge, 140-cm-long needle electrode was used to administer 50 W for 10 to 15 seconds to the pancreatic lesion. All 3 patients experienced hypoglycemia before treatment, which resolved within 48 hours of EUS-RFA as indicated by normal C-peptide levels and serum insulin levels. At 11 to 12 months of follow-up, all patients remained asymptomatic. No adverse events were reported.

Similarly, Furnica et al.[12] reported a case series of 4 patients with benign pancreatic insulinomas treated with EUS-RFA. The tumors were multifocal within the pancreas, including the head, neck, and tail. Using an approach akin to Lakhtakia et al., all patients experienced resolution of hypoglycemic symptoms after ablation. Patients remained asymptomatic at 22-month follow-up. Two patients experienced pancreatitis, which resolved after conservative management.[12]

Various case reports have also reported successful outcomes after EUS-RFA for treating pancreatic insulinoma.[13–15] These early case series indicate that EUS-RFA offers a resolution of symptomatic pancreatic insulinomas. However, to our knowledge, no large clinical trials exist to confirm these initial experiences. Further studies are needed to determine the long-term efficacy of EUS-RFA. Although adverse events appear to be mild, future studies should attempt to determine means for reducing these effects, including the use of prophylactic nonsteroidal anti-inflammatory drugs for postoperative pancreatitis.

PANCREATIC ADENOCARCINOMAS

Because of the poor prognosis of pancreatic adenocarcinomas, EUS-RFA has been evaluated for its capability to offer adjuvant therapy. Song et al.[16] prospectively assessed 6 patients with unresectable pancreatic cancer. An 18-gauge RFA needle was used to deliver 20 to 50 W of power to the tumor site. The ablation continued until a demarcated hyperechoic zone on EUS was identified, thus covering the entire tumor. After the procedure, 2 patients experienced mild abdominal pain, which resolved with analgesics. Some of the patients simultaneously underwent chemotherapy after the EUS-RFA. Long-term data were not reported on these patients; therefore, the effectiveness of this treatment cannot be evaluated from this study.

Crinò et al.[17] looked at the feasibility of EUS-RFA for patients with solid pancreatic neoplasms. Nine patients (pancreatic adenocarcinoma, 8; renal cancer metastasis, 1) were treated with EUS-RFA using an 18-gauge needle at 30 W of power. One patient was excluded because of the discovery of a large necrotic portion inside the tumor while performing EUS. EUS-RFA was successfully completed in the other 8 patients. After the procedure, 3 patients reported mild abdominal pain but were treated successfully with NSAIDs. Serum analysis after the procedure revealed normal amylase and lipase levels in most patients; one asymptomatic patient was found to have elevated amylase and lipase levels 24 hours after the procedure. In this patient, amylase and lipase levels returned to a normal range by day 2. Overall, a mean of 30% tumor ablation was achieved in this study cohort.

Similarly, Wang et al.[18] retrospectively studied 11 patients with unresectable pancreatic cancer. An EUS-RFA catheter was used to deliver 5 to 10 W of power, less power when compared with prior studies. Patients were evaluated after the procedure through computed tomography, magnetic resonance imaging, and serum CA19-9. Seven patients in the study had locally advanced disease, and the remaining 4 had metastatic cancer. In this trial, there was variability in the number of times RFA was applied and the

number of weeks in which RFA was performed. For example, 1 patient had 8 sessions of RFA with a subsequent decrease in tumor size; at 12 months after the procedure, the patient was still alive. CA19-9 levels decreased in 5 of the patients, and tumor size decreased in 2 of the patients. Excluding the patient who underwent 8 sessions of RFA, all other patients were deceased by 9 months after the procedure. This study illustrated that there were limited long-term survival benefits of RFA for treatment of advanced pancreatic cancer. Case reports on the use of EUS-RFA in pancreatic adenocarcinoma have shown similar findings.[19,20]

Pancreatic adenocarcinomas are notoriously challenging to treat, with a median survival of 6 months.[21] The current literature indicates some potential therapeutic benefits in reducing tumor burden, although with less mortality benefit. However, these conclusions are drawn from very small sizes. Further studies are warranted to determine the long-term outcomes and mortality benefits of EUS-RFA in patients with pancreatic adenocarcinoma.

CELIAC PLEXUS NEUROLYSIS

EUS-RFA has been used to cause celiac plexus neurolysis (CPN) for palliation of pain in patients with pancreatic cancer. However, data on its effectiveness for palliation of pain are limited.

Jin et al.[22] performed an EUS-RFA of the celiac nerve plexus in a 57-year-old man diagnosed with metastatic pancreatic cancer. EUS-RFA using the EMcision Company, Montreal, Canada, was performed after EUS-guided puncture of the celiac ganglion using a 19-gauge EUS needle. Ablation parameters were set as follows: fixed RF power (heating) was 10 W for 120 seconds and 15 W for 120 seconds; after the procedure, the patient's visual analog pain score decreased from 8 to 2, eliminating the need for opioid medications. There were no postprocedure adverse events.

Given the potential benefits of EUS-guided CPN (EUS-CPN) with dehydrated alcohol, Bang et al.[23] performed a single-blind, randomized trial to compare the effectiveness of EUS-CPN and EUS-RFA of the celiac nerve node for palliation of pain in pancreatic cancer. In this study, patients with abdominal pain because of locally advanced or metastatic pancreatic cancer were randomized to EUS-CPN (n = 14) or EUS-RFA (n = 12). Their primary outcome was pain severity as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire pancreatic cancer module (PAN26). The primary outcome was evaluated before treatment and at 2 and 4 weeks after treatment. The secondary outcome was a comparison of quality of life as determined by the PAN26 and EORTC Quality of Life Questionnaire core questionnaire (C30) and opioid analgesia use between the 2 groups.[23] Results revealed that 21.4% of patients with persistent pain after undergoing EUS-CPN were treated by EUS-RFA; however, none of the patients treated by EUS-RFA required rescue therapy using CPN. In addition, both the PAN26 (49.0 *vs.* 57.0, $P < 0.001$) and C30 (51.9 *vs.* 64.4, $P = 0.032$) revealed less pain for EUS-RFA than for EUS-CPN. There was also a significant difference in several quality-of-life components observed between the 2 groups, likely associated with the lower severity of pain in the EUS-RFA cohort. However, there was no significant difference in the opioid analgesia use between the 2 groups at the end of follow-up (105.4 mg for CPN *vs.* 112.7 mg for RFA, $P = 0.583$). There were no intraprocedural adverse events encountered in any patient. There was no significant difference in the incidence of postprocedural adverse events between the 2 groups (35.7% for CPN *vs.* 41.7% for RFA, $P = 0.999$), and all these symptoms had resolved with conservative management at the 2-week follow-up.

The results of the studies mentioned previously highlight the potential role of EUS-CPN in the palliation of pain in patients with pancreatic cancer. Despite the preliminary evidence that EUS-RFA may be superior to EUS-CPN for pain palliation, there are unanswered questions on the size of the probe, type of RFA probe, length of the exposed tip, power settings, and short duration of follow-up. More importantly, it is still debated if EUS-RFA is cost-effective compared with EUS-CPN. Large-scale standardized studies with long-term follow-up are needed to evaluate the safety, long-term efficacy, and cost-effectiveness of EUS-RFA of the celiac plexus in patients with unresectable pancreatic cancer.

HEPATIC LESIONS

Percutaneous and intraoperative RFAs of HCC are widely used treatment methods. More recently, there has been growing interest in using EUS-RFA in the ablation of hepatic lesions, a technique that induces thermal necrosis of tumor mass as a potentially curative technique with low periprocedural risk.

The initial application of EUS-RFA of hepatic lesions was based on animal studies. Carrara et al.[24] evaluated the efficacy and safety in the use of an EUS-guided internally gas-cooled RFA probe in the liver and spleen of an animal model. Their study demonstrated the ability to create a well-defined area of coagulative necrosis as revealed by histopathologic examination without adverse events.[22]

Similarly, Varadarajulu et al.[25] evaluated the feasibility and safety of EUS-RFA with a retractable umbrella-shaped needle electrode array for inducing coagulation necrosis in the liver. Their study performed EUS-RFA of the liver by using a 19-gauge EUS-FNA needle with a retractable echogenic umbrella-shaped monopolar electrode array at its tip in 5 Yorkshire pigs. Histopathology revealed a well-demarcated area of complete coagulative necrosis without damage to the surrounding liver parenchyma or vasculature.

More recently, the efficacy and safety of EUS-RFA of hepatic lesions have been evaluated in human studies, albeit limited to case reports. Attili et al.[26] performed an EUS-RFA using a 19-gauge 10-mm-long needle (Starmed-Taewoong Medical, Seoul, South Korea) in a 75-year-old man with hepatitis C cirrhosis with a 25 × 20-mm hypovascular lesion of the III liver segment. The lesion was deemed inaccessible by a percutaneous approach; hence, an EUS-guided approach was performed. The lesion was punctured with the RFA needle, and a 30-W monopolar electric current was delivered for 3 to 8 seconds under direct EUS control directly into the principal lesion and into the satellite lesions. There were no immediate adverse events after the procedure. On 1-month follow-up, the abdominal magnetic resonance imaging showed complete disappearance of the lesion in segment III.

Likewise, de Nucci et al.[27] performed an EUS-RFA treatment of a 30 × 45-mm HCC lesion localized to the II–III and IVb liver segments in a 70-year-old man who presented with HCV-related liver cirrhosis (Child-Pugh A6, Model for End-Stage Liver Disease [MELD] 9). After 2 sessions, about 70% of the neoplastic tissue was destroyed, with downstaging the lesion on follow-up imaging, which eventually led to a successful resection of the lesion. The procedure was well tolerated with mild fever and an increase in C-reactive protein after the procedure.[27] These cases highlight the potential efficacy and safety of EUS-RFA of hepatic lesions

when percutaneous or surgical treatments are potentially technically challenging or prohibitive. Another potential benefit of an EUS-RFA approach is the ability to identify better the vascular structures surrounding the lesion to reduce the risk of thermal energy dispersion. Nonetheless, the safety and efficacy of EUS-RFA of hepatic lesions are limited by small human studies and should be evaluated in a larger series and prospective studies because of potential major adverse events such as liver abscess, bile leaks, and bleeding that might occur.

CONCLUSION AND FUTURE DIRECTIONS

In conclusion, EUS-RFA of pancreatic lesions has gained interest as a potential novel minimally invasive therapeutic option that provides real-time visualization with precise localization of the treatment procedure. However, most of the publications on EUS-guided pancreatic tumor therapy are mainly experienced in small study populations. Multiple studies support the safety and feasibility regarding EUS-RFA; however, the evidence is based on animal studies and small study populations. Studies to determine the appropriate indications and the long-term therapeutic effects are still lacking. Large prospective and well-designed controlled studies with longer follow-up are warranted to determine the safety, long-term efficacy of EUS-RFA, and outcomes, including survival for these newer indications. Until such time, based on the limited data as presented earlier, endoscopic RFA seems to be a viable, innovative, and emerging modality with expanding indications. In addition, while evidence-based efficacy is being determined, EUS-RFA should be included in research protocols, multidisciplinary treatment, and experimental therapy.

Author Contributions

Andrew Ofosu contributed to the writing and editing of the manuscript and read and approved the final manuscript. Daryl Ramai edited the manuscript and read and approved the final manuscript. Amanda Morga edited the manuscript and read and approved the final manuscript. Christina Chan edited the manuscript and read and approved the final manuscript. Douglas G. Adler contributed to the writing and editing of the manuscript and read and approved the final manuscript. Ali Siddiqui contributed to the writing and editing of the manuscript and read and approved the final manuscript.

Conflict of Interest

Douglas G. Adler is an Co-Editor-in-Chief of the journal, and Ali Siddiqui is an Associate Editor. This article was subject to the journal's standard procedures, with peer review handled independently of the editors and their research group.

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