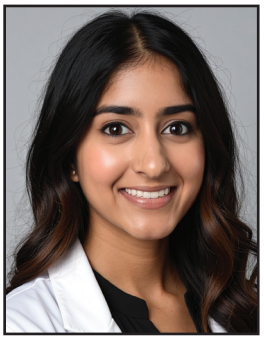
Douglas G. Adler MD, FACG, AGAF, FASGE, Series Editor

EUS-Guided Ablation Techniques for Pancreatic Lesions: A Review of Current Practices and Future Directions



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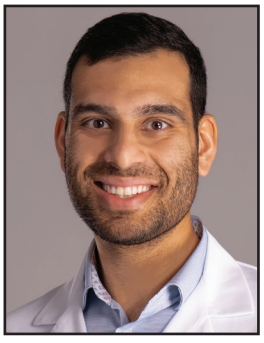

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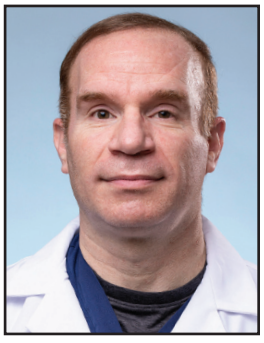

Douglas G. Adler

INTRODUCTION

Endoscopic ultrasound (EUS) has undergone a significant transformation, from a primarily diagnostic tool to an increasingly therapeutic one, in the evaluation and management of many benign and malignant conditions, most notably pancreaticobiliary diseases. EUS-guided ablation procedures, including chemoablation and radiofrequency ablation (RFA), are novel minimally invasive techniques that are emerging as potential therapeutic modalities in the management of focal pancreatic lesions.

Both solid and cystic pancreatic lesions present significant clinical challenges due to their potential for malignancy and the complexities involved in their management, often requiring a multidisciplinary and multimodal approach. In pancreatic adenocarcinoma, for instance, long term 5-year survival rates remain dismal at only 13%, despite neoadjuvant chemotherapy, as many patients are not candidates for curative surgery.[1] EUS-guided radiofrequency ablation provides a promising therapeutic option that, although not yet included in standard treatment paradigms, may potentially enhance outcomes while introducing minimal risk.

EUS-guided chemoablation involves the injection of destructive/cytotoxic agents using a fine needle aspiration (FNA) needle directly into a focal lesion. EUS-guided RFA involves delivering thermal energy directly into a target lesion via a monopolar electrode to induce cell death.[2,3]

Although the adoption of EUS-guided chemoablation and radiofrequency ablation in clinical practice is variable, primarily used in tertiary care centers with multidisciplinary expertise, there continues to be a growing amount of evidence evaluating these exploratory techniques. This review aims to summarize current practices and future directions of EUS-guided ablation for both pancreatic cysts and tumors.

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Radiofrequency Ablation Technology and Safety

RFA Technology

RFA delivery systems are designed to induce necrosis on the target lesion in contact with a radiofrequency energy delivery probe. A specialized catheter with a distal electrode is used and an alternating current of 400-500 kHz is passed from the electrode to the target tissue.[4,5] Radiofrequency waves cause vibration of water molecules adjacent to the probe, generating heat that is transferred to the target tissue.[6] Ideally, the target tissue is heated to at least 50 degrees Celsius, leading to irreversible cell damage and death, through coagulative necrosis and protein denaturation.[2,3,7] In the United States, the only EUS-RFA device currently approved for pancreatic use by the Food and Drug Administration is the EUSRA™ RF Electrode (TaeWoong Medical, Gimpso-si, South Korea). This needle connects to their VIVA RF generator (STARmed, Koyang, Korea), which cools the electrode tip by circulating saline to reduce tissue charring.[8]

EUS-RFA Technique

With EUS-guided RFA, a 19- or 22- gauge FNA needle is introduced into the target lesion under direct endosonographic guidance. The stylet is then removed and the RFA catheter is advanced within the needle. Finally, the FNA needle is gradually withdrawn, exposing the electrode tip [Figure 1]. Radiofrequency energy is then applied for 90 to 120 seconds, until complete ablation is achieved at the impedance value of 800 ohms with the electrosurgical generator set at 10 W.[9] The power output automatically cuts off once this impedance level is reached to prevent further tissue damage.[8]

EUS-RFA Safety

The most common adverse events (AEs), specifically for pancreatic EUS-guided RFA, include development of post-procedural pain and pancreatitis.[10-15] Less frequently, RFA also runs the risk of thermal damage to surrounding vessels, which may result in pseudoaneurysm formation.[16] A French study evaluating 100 patients undergoing 116 EUS-RFA sessions reported no procedure-related mortality but the authors noted an AE rate of 19%. Of these AEs, all but one were pancreatic in nature (abdominal pain, pancreatitis, or main pancreatic duct leak). The majority (86%) of the AEs required no interventions. The proximity of pancreatic neoplasms to the main pancreatic duct (≤1mm) was identified as an independent risk factor for AEs.[11] In a study of 377 EUS-RFA sessions performed in 252 patients, Khoury et al. found rates of mild, moderate, and severe AEs, were 10.1%, 4.2% and 0.5%, respectively.[14]

EUS-guided Chemoablation

Choice of Agents

The most common agents used in EUS-guided chemoablation of pancreatic lesions include ethanol, gemcitabine, and paclitaxel. Ethanol, most commonly used at 80% and 99% concentrations, was the first solution used as a chemoablative agent for pancreatic lesions.[17] Ethanol induces cell death by causing cell membrane lysis, protein denaturation, and vascular occlusion.[18] Paclitaxel is a chemotherapy agent that inhibits cell replication by binding to microtubules.[19,20] Paclitaxel is a highly viscous agent requiring a specialized infusion apparatus, such as a syringe strapped to a high-pressure "gun" or a specialized infusion device, to efficiently infuse the admixture through an FNA needle.[21] Gemcitabine, another chemotherapeutic agent, is an antimetabolite that works by interfering with DNA synthesis.[22] Ethanol is often used when treating pancreatic cysts and pancreatic neuroendocrine tumors, either alone or in combination with these other chemotherapeutic agents.[18,19] More recently, alcohol-free protocols have shown promise in treating both cysts and neuroendocrine tumors.[23]

Chemoablation Technique

For pancreatic cysts, a 19- or 22- gauge FNA needle is used, depending on the size of the cyst. First, a transgastric or transduodenal puncture of the cyst is performed under EUS guidance.[17] Fluid is then aspirated from the cyst, leaving just a small rim of fluid around the needle tip to ensure the needle is not introduced into surrounding pancreatic parenchyma. Next, the selected agent is infused [Figure 2]. The total volume infused generally equals the volume that was just aspirated from the cyst cavity.[24] The ablation procedure differs slightly based on which agent is being used. When

using ethanol, the cyst cavity is lavaged, where the agent is aspirated and reinjected for 3 to 5 minutes, in order to maximize the ablative effect on the cyst epithelium, improve distribution, and remove obstructive debris or dilute viscous cyst fluid.[17,25-27] Chemotherapeutic agents on the other hand, are generally injected and left in the cyst cavity permanently to potentiate their cytotoxic effect.[28]

For solid pancreatic tumors, generally a 22- or 25- gauge FNA needle is advanced into the lesion under direct EUS-visualization.[29] The needle tip is placed 0.5 to 1.0 cm from the distal tumor edge and the agent of choice is incrementally injected at the same site until a hyperechoic blush is visibly expanding within the tumor. Further injections at one site are discontinued when the hyperechoic blush extends up to the tumor margin.[30] For larger lesions, additional injections are given in the same path as the needle is retracted towards the proximal tumor border.[31] Additional passes can be made avoiding the same needle track, if needed, based on tumor size and pattern of spread after initial injection.[30] The goal is to inject just enough ethanol to permeate the tumor and terminate the injection as the injectate appears to extravasate outside the lesion.[30]

Chemoablation Safety

The most common AEs for EUS-guided chemoablation therapy includes abdominal pain and pancreatitis.[32,33] In a study of 207 patients undergoing pancreatic cyst ablation with ethanol, 21.2% experienced AEs, including abdominal pain, fever, pancreatitis, and intracystic bleeding. When looking at 347 patients who underwent cyst ablation with paclitaxel-based regimens (with or without ethanol), 15% of patients experienced AEs, the majority of which were pancreatitis and abdominal pain.[34] For solid pancreatic tumors, AE rates of chemoablation have also been reported as high as 21.2%.[33]

Pancreatic Cysts

Pancreatic cysts, largely incidentally identified on cross-sectional imaging performed for unrelated purposes, have increasing incidence with age.[35-37] Pancreatic cystic lesions (PCLs) include various entities with differing malignant potential.

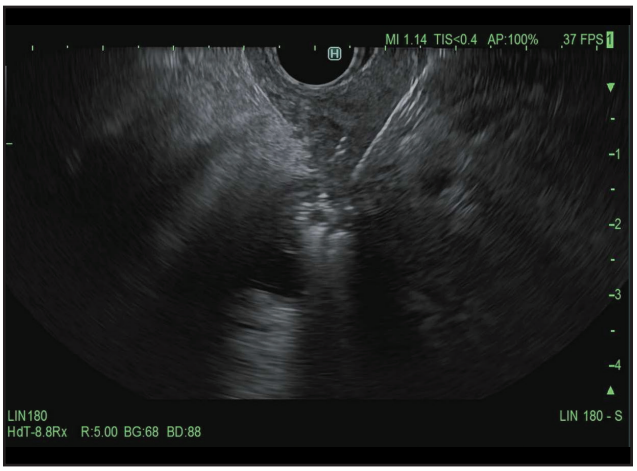

Figure 1a. EUS image of pancreatic mass with RFA catheter at first treatment

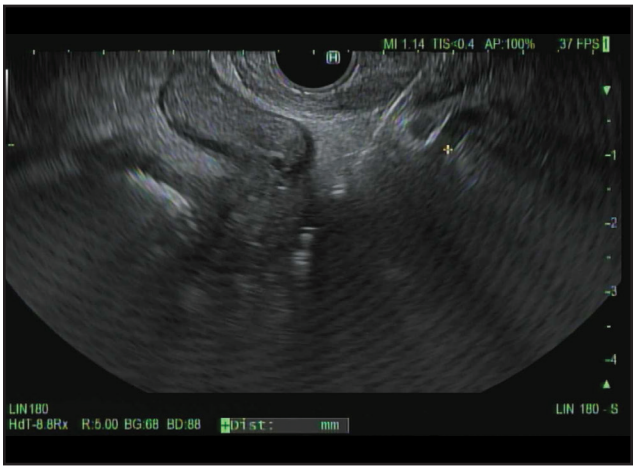

Figure 1b. EUS image of pancreatic mass with RFA catheter at third treatment

Types of PCLs include intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs), serous cystadenomas (SCAs), pseudocysts, and solid pseudopapillary neoplasms (SPNs).[38-41] Of these types, IPMNs and MCNs are categorized as mucinous pancreatic cysts, and have the greatest risk for malignant transformation. Certain characteristics for IPMNs, such as size greater than 3 centimeters, the presence of mural nodules, as well as communication with and/or dilation of the main pancreatic duct, increase their malignant potential.[42-44] The reported risk of malignancy for patients with main duct IMPN ranges from 38-68%, whereas the risk of malignancy for MCNs ranges from 10-17%.[40] EUS-guided ablation is generally only considered

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in non-surgical patients with either an enlarging/symptomatic MCN or IPMN, with cyst diameter of at least 1 cm and high-risk features.[17]

RFA of Pancreatic Cysts

The use of EUS-guided RFA for management of PCLs was first described in a pilot prospective study in 2015 by Pai et al. Of the six patients reported, two achieved complete response, defined as at least 95% reduction in cyst size. [45] A recent review pooling this pilot study with three others, 2 prospective and one retrospective, demonstrated that EUS-guided RFA for PCLs resulted in at least partial, if not complete, radiologic resolution in only 36.8% of cases at a follow up of 10.2 months. The total number of patients in this pooled review, however, was only 44, highlighting the paucity of data on this topic.[14]

Chemoablation of Pancreatic Cysts

EUS-guided chemoablation for pancreatic cysts has been studied for the last two decades. In that time, although the technique has not substantially changed, the agents used have evolved significantly. Initially, chemoablation of pancreatic cysts started with ethanol in 2005.[46] Soon after, paclitaxel injection was combined with ethanol lavage therapy.[20] A review by Papaefthymiou et al. evaluating 15 studies found that ethanol alone resulted in cyst resolution in 32% of cases, while the combination of ethanol and paclitaxel yielded complete cyst resolution in 70% of cases.[47]

To address safety concerns, newer protocols have explored alcohol-free chemoablation regimens.

The CHARM trial demonstrated that in patients with mucinous-type pancreatic cysts, 67% of those who underwent alcohol-free chemoablation with saline lavage and infusion of an admixture of paclitaxel and gemcitabine had complete ablation of their cysts at 12 months which was comparable to 61% of patients in the ethanol lavage group.[48] Recent long-term follow up of the same patient population found that 87% of those who had complete response at 12 months maintained resolution at a mean follow up of 36.5 months, demonstrating durability of EUS-guided chemoablation of pancreatic cysts.[23] Higher efficacy has been observed with chemoablation of cysts which are unilocular and less than 35 mm in size.[49,50] Despite this data, chemoablation of pancreatic cysts has still not been widely adopted. This is likely due to the paucity of long term/guideline-driven data, difficulty in ordering chemoablative medications outside of the oncologic space, and ultimately endoscopist reluctance to inject these cytotoxic medications into cysts without a defined treatment paradigm.

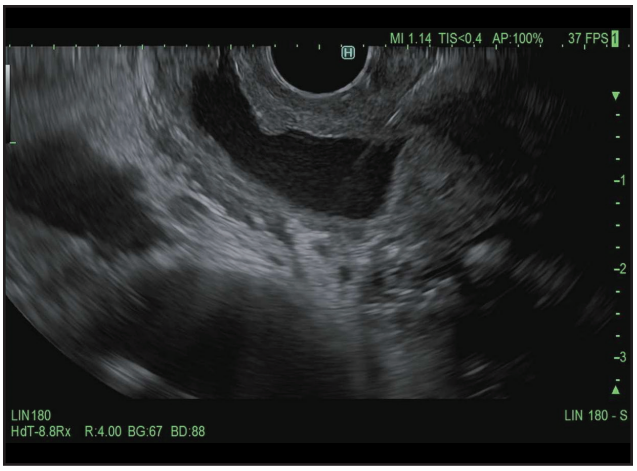

Figure 2. EUS image of pancreatic cyst with FNA needle prior to chemoablation

Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors (pNETs) represent 1-2% of pancreatic cancers and can be classified as nonfunctioning or functioning.[51] Nonfunctioning pNETs typically present as advanced disease or as localized disease found incidentally on cross-sectional imaging, whereas functioning pNETs often present earlier due to hormone-related symptoms.[52-55]

pNETs are further categorized by differentiation and grade; Well-differentiated pNETs are graded 0 to 3 based on mitotic count and Ki67 index, while poorly differentiated neuroendocrine carcinomas are classified as grade 3 and tend to be more aggressive.[56,57] EUS-RFA is not usually employed for poorly differentiated cases, as these generally

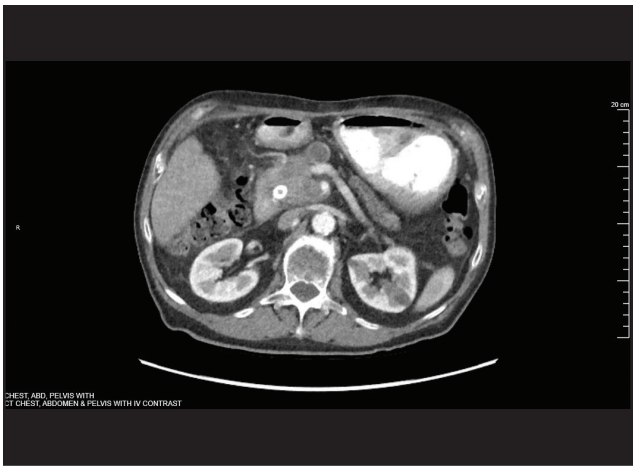

Figure 3a. CT image of pancreatic mass prior to first RFA treatment

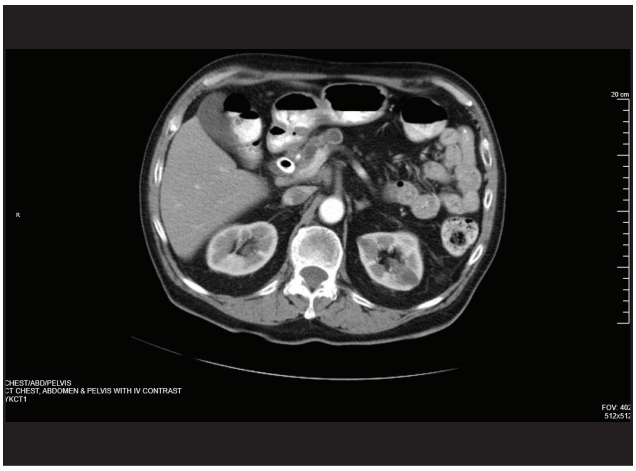

Figure 3b. CT image of pancreatic mass after third RFA treatment

necessitate more aggressive treatment approaches such as systemic chemotherapy.[58]

RFA of Pancreatic Neuroendocrine Tumors

For pNETs that require treatment, surgery is considered the gold standard. However, patients who are at high risk for surgery due to severe comorbidities or an unfavorable tumor location may require alternative treatment options. Additionally, there is a need for minimally invasive palliative options for symptomatic unresectable or recurrent pNETs.[7] EUS-RFA has been evaluated for both functional and nonfunctional pNETS. Data has shown that EUS-RFA is particularly useful for patients with small (< 2 cm) and localized tumors, offering a viable option for non-surgical candidates who require treatment due to advanced WHO grade or symptoms. A recent review of eleven studies involving 292 patients found a pooled complete radiologic response of 87.1% and pooled technical success rate of 99.2%. Of these, 134 patients had functional pNETs, for which the pooled clinical response rate was 94.9%.[59] Another review of 61 patients found the overall effectiveness of EUS-RFA to be 96% without differences between functional vs. non-functional pNETs. While tumor location was not predictive of response to EUS-RFA, a pNET size cut-off value of ≤18 mm was associated with better treatment response, with a sensitivity of 80% and specificity of 78.6%.[60] Of note, several studies and case series have described rapid hypoglycemia relief within the same day for patients with insulinomas after EUS-RFA.[61-64] However, since most insulinomas are typical treated surgically, EUS-RFA is only considered an alternative option for select patients.

Chemoablation of Pancreatic Neuroendocrine Tumors

In patients with low-grade pNETs < 2 cm in size who are not surgical candidates, EUS-guided ablation with ethanol (EUS-EA) may be considered as another alternative treatment option. EUS-guided ablation of an insulinoma was first described in 2006, with rapid improvement in symptoms after EUS-EA in a patient who could not undergo surgical resection due to comorbidities.[65] Another study found that of 5/9 patients (55.5%) with insulinomas who initially experienced symptom relief after EUS-EA later relapsed, with symptoms returning after a median of 128 days following the first ablation.[66] A propensity score-matching study by So et al. comparing EUS-guided ethanol ablation to surgery for management of nonfunctioning small pNETs found comparable 10-year overall (OS) and disease-specific survival (DSS) rates. Of the EUS-EA cohort, 65% showed complete ablation, but 46% had local recurrence after a median follow-up of 34.5 months.[67] A recent study evaluating the efficacy of EUS-guided ethanol injection of pNETs found that 88% (22/25) of patients achieved complete ablation at 1 and 6 months.[68] While EUS-EA may offer potential alternative for a select group of patients who are not suitable for surgical resection and are treated at expert centers, its application remains limited, and

careful monitoring is essential due to the relatively high rates of recurrence.

RFA of Pancreatic Adenocarcinoma

Given the aggressive nature of pancreatic ductal adenocarcinoma (PDAC) and the low percentage of patients that present with resectable disease, there has always been interest in exploring additional therapeutic options to treat this malignancy.[69-72] EUS-RFA is being studied as a potential palliative option for non-surgical candidates. Technical feasibility was first demonstrated in 2012 by Arcidiacono et al., though they used an experimental combination RFA and cryogenic cooling probe that is no longer on the market.[73] In 2016 Song et al. also demonstrated that EUS-RFA could be performed successfully in a pilot study of six patients with unresectable PDAC with minimal adverse events.[74]

Furthermore, several small, non-randomized, single-center studies have suggested that EUS-RFA may offer some benefit in terms of tumor reduction or survival in select patients with locally advanced or unresectable disease, though results remain mixed and generally modest [Figure 3]. Scopelliti et al. reported successful EUS-RFA in 10 patients and observed a reduction in tumor size in 50% on follow-up imaging.[75] In another small cohort of 10 patients with unresectable disease, Thosani et al. reported a median survival of 20.5 months for patients receiving 1-4 EUS-RFA sessions in combination with chemotherapy, compared to published averages of 9-12 months for those treated with chemotherapy alone.[12] In this cohort, tumor regression was observed in 7 out of 10 patients, with >50% reduction in size in 3 of those 12.[12] However, these results should be interpreted with caution, given the small sample size and lack of control groups. In another observational prospective study by Oh et al., 22 patients with both locally advanced and metastatic disease, who underwent a median of five EUS-RFA sessions and subsequent chemotherapy, had a median overall survival of 24 months, but this was not directly compared to outcomes in patients receiving chemotherapy alone.[76] A more recent study with 15 patients with locally advanced PDAC and 11 with metastatic disease demonstrated only a 42.3% overall survival of six months post EUS-RFA, but did show improvements in performance status and reduction in tumor size.[77] Notably, a post-treatment hypodense necrotic area was observed in the 11 patients who were still alive at the 6-month follow-up, suggesting effective tumor ablation.

While this technology, which is still in early stages of development, has generated interest, data have been obtained from very small, carefully selected groups of patients. Further large scale, controlled studies are essential to determine the long-term survival benefits, identify optimal treatment protocols, and fully assess the role of EUS-RFA in multimodal therapy for pancreatic cancer. Currently, there are two clinical trials underway that are exploring the combination of EUS-RFA and chemotherapy in patients with PDAC (NCT 05723107 and NCT 04990609). However, it is important to note that both are single arm studies, and the evidence from these trials is still limited in terms of establishing clear survival benefits and treatment efficacy.

Chemoablation of Pancreatic Adenocarcinoma

EUS-guided chemoablation of pancreatic adenocarcinoma has not been thoroughly studied, is rarely performed, and remains experimental. Only one study to date has investigated the feasibility of EUS-guided fine-needle injection of gemcitabine for locally advanced and metastatic pancreatic cancer.[31] This approach involves delivering chemotherapy directly to the tumor, potentially improving local drug concentrations while minimizing systemic side effects. In the study by Levy et al., the technique was found to be feasible and safe, with minimal adverse effects. Further studies are required to assess its clinical benefits.

CONCLUSION

EUS-guided ablation techniques, including RFA and chemoablation, offer a minimally invasive option for managing pancreatic lesions, particularly for patients who are not candidates for surgical resection. While the available data suggest that these approaches may improve local control and quality of life, they have not yet become mainstream therapies incorporated into the management of pancreatic disease and must be considered

exploratory at this time. One of the key limitations to the widespread adoption of EUS-guided ablation is the lack of large, randomized controlled trials that clearly establish long-term survival benefits, particularly in the neoadjuvant setting. Most studies to date have been small, single-center, and non-randomized, limiting data analysis and making it difficult to draw definitive conclusions about their effectiveness. Additionally, these techniques are not included in current treatment paradigms, further limiting their use in clinical practice.

Despite these challenges, the potential of EUS-guided ablation therapies remains optimistic, and ongoing studies will be crucial in addressing these gaps. Until larger trials are completed, it is unlikely that these techniques will gain widespread adoption, but they may become a valuable tool for a select group of patients, particularly those with advanced or unresectable pancreatic lesions who lack other therapeutic options. ■

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