Title: Endoscopic ablation therapy for the pancreatic neoplasms

Running Head: Endoscopic ablation therapy for pancreas

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Authors' contributions

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Conflict of interest

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ABSTRACT

Recently, endoscopic ultrasound-guided ablation therapy has been reported as a less invasive therapy for patients with pancreatic neoplasms. Some ablation techniques, including injective ablation (using ethanol or other ablative agents), radiofrequency ablation (RFA), photodynamic therapy, and laser ablation, have been described in literature. Among these, injective ablation and RFA are more frequently used for treating pancreatic neoplasms. Few studies have evaluated the effectiveness of EUS-guided ethanol ablation (EUS-EA) for potentially malignant solid neoplasms (neuroendocrine neoplasms or solid pseudopapillary neoplasms) and have reported a complete response (CR) rate of 60%–80%. In addition, the CR rate after EUS-RFA for these lesions has been reported to be 55%–100%, with no additional procedure-related adverse events (AEs). Regarding the amelioration of the symptoms of an insulinoma, the success rates of both the therapies were found to be excellent. Regarding complete tumor ablation, EUS-RFA appeared to be superior than EUS-EA. Although EUS-RFA has been reported as a safe treatment for pancreatic cancers, its effectiveness remains inadequate. Some studies have examined the effectiveness of EUS-guided injection ablation therapy for pancreatic cystic neoplasms (PCNs) and have reported CR rates that range from 35% to 79%. Alcohol-free chemotherapeutic agent ablation appears to be effective, with a low risk of AEs. However, studies on the effectiveness of EUS-RFA for PCNs are limited. In the future, EUS-guided ablation therapy could become a more widely used approach for potentially malignant and malignant pancreatic lesions.

Key words: Endoscopic ultrasonography, pancreatic neoplasms, ablation techniques, ethanol, radiofrequency ablation

INTRODUCTION

Recently, endoscopic ultrasound (EUS)-guided ablation therapy has been reported as a less invasive therapy for patients with pancreatic neoplasms[1-3]. The potential advantages of EUS-guided antitumor therapy are real-time imaging and the ability to treat poor surgical candidates. EUS-guided ablation procedures have undergone various phases of experimentation for safety and efficacy, using either conventional EUS-fine needle aspiration (FNA) needle or its modifications. Many alternative ablation techniques have been described, including injective ablation (using ethanol or other ablative agents), radiofrequency ablation (RFA), photodynamic therapy, and laser ablation[1]. Among these, injective ablation and RFA are widely performed for pancreatic neoplasms. In this review, we evaluated the reports on solid and cystic pancreatic neoplasms treated with the two aforementioned ablation methods. Pancreatic solid neoplasms include malignancies (i.e., pancreatic cancer [PC] and metastatic lesions from other organs) and potentially malignant lesions (i.e., neuroendocrine neoplasm [NEN] and solid pseudopapillary neoplasm [SPN]). Pancreatic cystic neoplasms (PCNs) include benign serous cyst neoplasms (SCNs), potentially malignant lesions (including mucinous cystic neoplasms [MCNs] and intraductal papillary mucinous neoplasms [IPMNs]), and other uncategorized cystic lesions (neither serous nor mucinous).

Here, we have compiled our findings on EUS-guided ablation therapy for pancreatic neoplasms. Between April 2005 and October 2022, PubMed, MEDLINE, and Google Scholar databases were searched using the terms “EUS,” “Endoscopic,” “Ultrasound,” “neoplasm,” “cyst,” “pancreatic,” “ethanol,” “ablation,” and “radiofrequency ablation.” Articles were scrutinized by their titles and abstracts by two independent reviewers (KM and HK) and duplicates were eliminated. After excluding case reports and non-English manuscripts, a single reviewer (KM) finally selected the relevant articles after reading them.

Indications and definitions

1. Indications for EUS-guided ablation therapy

According to the reviewed studies, major indications for EUS-guided ablation therapy for pancreatic solid neoplasms were as follows: tumor size ≤ 2 cm in diameter, presence of hormone-related symptoms, and patients who were either unfit for or had rejected surgery[6,8,9,36-39,41-43]. Of the reviewed studies, two study on EUS-RFA had included patients with tumor size < 3 cm in diameter[35,44]. Next, mainly feasibility and safety in PC were evaluated, and in patients with advanced PCs and in those resistant to previous treatments, EUS-guided ablation therapy was indicated[32-34,40,45,46]. Major indications for EUS-guided ablation therapy for PCNs were as follows: patients with unilocular or oligolocular cysts with a suspected or confirmed diagnosis of a mucinous pancreatic cyst, those with enlarged pancreatic cysts >2 cm or >3 cm in diameter, poor candidates for surgery, and those who refused to undergo surgery despite reasonable life expectancy[10]. Some studies had also treated PCNs with a diameter of <2 cm if the patients had expressed a strong desire for treatment[11-18,22-24]. PCNs with six or fewer locules and measuring 2-6 cm in diameter were deemed to be the most responsive to ablation[10].

2. Diagnosis of PCNs

A presumed diagnosis of a cystic tumor was made based on the carcinoembryonic antigen (CEA) level and amylase concentration in the aspirated fluid. The specific type of cystic tumor was defined according to the following cutoff values: SCN or pseudo cyst if CEA < 5 ng/mL and MCN or IPMN if CEA > 200 ng/mL. An amylase value of > 800 U/L was used as a cutoff for diagnosing IPMN and pseudo cysts. Pancreatic cysts that did not meet these criteria were categorized as "other cysts"[11,12,19].

3. Evaluation of treatment response

Complete ablation of pancreatic solid neoplasms was defined as the lack of hormone-related symptoms in patients with functional tumors[4-8]. In patients with nonfunctional tumors, complete ablation was defined as the absence of enhancement within tumors in contrast-enhanced computed tomography (CE-CT) or CE-EUS images[6-9].

In patients with PCN, various methods can be used to assess response to treatment, including a decrease in cystic surface area[13,14], volume[12,15,17,18,20,21-24], or diameter[11,19] (response evaluation criteria in solid tumors). In most reports, baseline cyst size is measured as volume ($4/3 \times \pi \times r3$, where r is the cyst radius), and response to treatment is defined as complete (95% reduction in cyst volume), partial (95%–75% reduction) or nonresponse (<75% reduction) at follow-up[10].

Summary of reviewed studies

1. EUS-guided-ethanol ablation (EUS-EA) for pancreatic solid neoplasms

Hepatocellular carcinoma is commonly treated using ethanol ablation, which causes coagulation necrosis due to cellular dehydration and vascular occlusion[25]. For ablation, a 19–25-gauge FNA filled with ethanol was advanced into the tumor under EUS. Ethanol (95%–100%) was injected until a hyperechoic blush extended to the tumor's entire margin, and the needle was maintained inside the tumor for at least 1 min to avoid back flow of ethanol[4]. If ethanol did not adequately extend to the tumor margin after injection at one site, multiple injections at different sites were performed to cover the entire tumor, and repeated sessions were scheduled for incompletely ablated tumors[4,6,8,9].

Reviewed reports on EUS-EA for pancreatic solid neoplasms are summarized in Table 1. The first report of EUS-EA in humans was published in 2006 by Jurgensen et al.[2] They treated a 78-year-old woman with typical hypoglycemic symptoms of an insulinoma, which had a poor response to diazoxide. Overall, 8 mL of 95% alcohol was injected into a 13-mm symptomatic insulinoma under EUS guidance, and complete resolution was reported based on clinical, morphological, and biochemical data. The second report of EUS-EA for an insulinoma was published in 2008 by Deprez et al.[3] They treated a 78-year-old woman with hypoglycemic symptoms. The tumor was located in pancreatic head near the Wirsung's duct, thus endoscopic stenting of the biliary and pancreatic ducts was performed before EUS-EA. Overall, 3.5 mL of 98% alcohol was injected into a 17-mm tumor using 21-25 gauge needles, and complete resolution was reported based on clinical, morphological, and biochemical data. However a 50mm large hematoma and ulceration (Forrest 2a) of the duodenal wall due to back follow of the injected ethanol occurred at 14 days after procedure. Levy et al.[4] reported the first EUS-EA case series for insulinoma. Five patients were treated using EUS-EA; the mean diameter of the lesions treated was 17 mm. They performed repeated sessions with small amount of ethanol for incompletely ablated tumors. The mean number of sessions was 2.2, and the mean volume of ethanol injected per session was 0.8 mL (range, 0.1–3.0 mL). Among the five patients, hypoglycemic symptoms were resolved in three patients, and the remaining two patients had improved hypoglycemic symptoms. No adverse events (AEs) were observed. Subsequently, four reports involving ten patients with insulinoma were published, and in these patients, all hypoglycemic symptoms disappeared[5-8].

Park et al.[6] reported the use of EUS-EA in nine patients with nonfunctional-NEN (NF-NEN). The mean diameter of the lesions treated using EUS-EA was 11 mm, and the mean volume of ethanol injected per session was 2.1 mL (range, 0.5–7.0 mL). The complete ablation rate was 67% (6/9), and mild pancreatitis occurred in three of the nine patients (one patient had

pancreatic duct stricture as a late AE). They reported that the risk of pancreatitis was associated with the total amount of ethanol injected during the treatment session because all procedure-associated cases of pancreatitis occurred when >2 mL of ethanol was administered in a session. Considering these problems, Choi et al.[8] reported the efficacy and safety of ethanol–lipiodol ablation. Lipiodol, which is iodized poppy seed oil, plays a unique role in chemoembolization [26]. Overall, 33 patients with 40 lesions were treated with a mixture of 99% ethanol and lipiodol in a 1:1 ratio. The mean diameter of the lesions treated was 11 mm, and the mean volume of ethanol–lipiodol injected per session was 1.1 mL (range, 0.8–1.9 mL). The complete ablation rate was 60% (24/40), and mild pancreatitis occurred in only two of the 63 procedures (3.2%). We have reported the efficacy and safety of scheduled early EUS-guided ethanol reinjection therapy. Of the five treated patients, three underwent an additional session after 3 days of the first treatment. The mean volume of ethanol injected per session was 0.7 mL (range, 0.3–1.0 mL), and the mean total volume was 1.0 mL (range, 0.9–1.8 mL). Complete ablation was achieved in four of the five tumors (80%) without any procedure-related AEs[9].

As mentioned above, a sufficient therapeutic effect can be expected in terms of improving symptoms for functional tumors. Particularly, for controlling the symptoms of the elderly, it may be an alternative treatment to surgical resection. However, for nonfunctional tumors, the complete ablation rate was inadequate. Rimbas et al.[27] reviewed 83 patients with 96 lesions treated with EUS-EA, and the success rate was 94.7% for functional NEN and 50%–62.5% for NF-NEN. AEs were reported in 20% cases (i.e., abdominal pain, acute pancreatitis, pancreatic duct stricture, bleeding, pancreatic localized necrosis, and transient fever) and were more commonly associated with the injection of >3.5 mL of ethanol. Theoretically, increasing the amount of ethanol injected increases the tumor cautery rate; however, of course, the risk of AEs increases[28]. Moreover, achieving complete ablation in patients with tumor sizes ≥ 1 cm or those with the residual parts at the periphery of the tumor after EUS-EA were still challenging[8,9].

2. EUS-guided injective ablation of PCNs

Briefly, a 19- or 22-gauge FNA needle is introduced into the center of the cyst to carefully aspirate most of the cyst contents. A 19-gauge needle is advantageous in that it allows the aspiration of more viscous material than that achieved using a 22-gauge needle; howver, a larger diameter of the needle might also increase the possibility of procedure-related complications, such as bleeding or pancreatitis. Moyer et al[20, 23] reported that 22- and 19-gauge needles were utilized for cysts of diameter 1.5-2.5 cm and 2.6-5.0 cm, respectively. If ethanol lavage is used, then the cyst will be alternately filled and aspirated with ethanol for 3–5 min using an amount equal to the mucinous fluid originally aspirated[11]. If an ethanol-free approach is used, the lavage step of the procedure may be eliminated, and instead, after the initial cyst collapse, the ablative agent (i.e., paclitaxel, gemcitabine, etc.) is then infused into the cyst using an amount equal to the volume of the cyst fluid originally aspirated to refill the cyst to its original dimensions[20,23].

Reviewed reports on EUS-guided injective ablation for PCNs are summarized in Table 2. In the first study on EUS-guided cyst ablation with ethanol, Gan et al.[11] enrolled 25 patients with cysts with a mean diameter of 19 mm to be treated with 5%–80% ethanol. CR was achieved in eight (35%) of the 23 patients who completed a follow-up period of 12 months without AEs. Although the efficacy of ethanol ablation was different among the studies, the CR rate following treatment ranged from 9% to 41% after a follow-up duration of 3–40 months in the published prospective studies[11,13,18]. The main AEs were abdominal pain and pancreatitis, and the incidence was 0%–23%[11,13,14,16,19,20].

To improve treatment responses, paclitaxel, a widely used chemotherapeutic agent, has been used as an agent following ethanol lavage to treat PCNs. Oh et al.[12] conducted the first prospective study on ethanol and paclitaxel lavage for treating PCNs. They treated 14 patients with PCNs, and CR was achieved in 11 (79%) of the 14 patients who were followed up for 9

months. The CR rates for this treatment ranged from 50% to 79% after a follow-up duration of 9–69 months, and the incidence of abdominal pain and pancreatitis as AEs was 3.7%–24%[12,15,17,21,22]. The CR rate in most studies using ethanol lavage with paclitaxel injection was higher than that in studies using ethanol ablation without increasing AEs.

To evaluate whether ethanol is required for effective PCN ablation and is related to complication rates, Moyer et al.[23] conducted a prospective, double-blind trial involving 39 patients with MCNs and compared the effects of 80% ethanol (control group) with those of normal saline (ethanol-free group). All enrolled patients in the two groups were then infused with an admixture of paclitaxel and gemcitabine. The authors concluded that ethanol was not required for effective EUS-guided pancreatic cyst ablation because the CR rates in the two groups were similar (ethanol group: 61% vs. ethanol-free group: 67%), and the removal of ethanol decreased the complication rate (ethanol group: 28% vs. ethanol-free group: 0%). Their results also demonstrated that the paclitaxel–gemcitabine cocktail provided no advantages over the current standard consisting of alcohol lavage, followed by paclitaxel alone.

Lauromacrogol is a sclerosant with a mild anesthetic effect that was initially reported as a treatment for PCNs by Linghu et al.[24] They treated 29 patients using Lauromacrogol. Among them, 11 (38%) patients achieved CR within a 9-month follow-up period. The CR rate for Lauromacrogol was similar to that of ethanol and slightly lower than that of ethanol lavage with paclitaxel injection.

DiMaio et al.[14] evaluated the effectiveness of multiple ethanol lavage sessions and found that the size and surface area of the PCNs treated decreased more following two ethanol lavage treatment sessions than following only one ethanol lavage treatment session. Park et al.[19] reported the treatment outcomes of various patients (n = 91), and the rates of CR and PR were 45% and 41%, respectively; however, the success rate was significantly different according to cystic fluid analysis (SCN, 58%; MCN, 50%; IPMN, 11%; uncategorized cysts, 39%; $p <$

0.0001). They found that patients with IPMNs were less likely to achieve CR than those with other tumors.

Some studies examined EUS-guided injective ablation for PCNs, including a prospective randomized controlled trial, which reported that it is a promising and minimally invasive method for treating PCNs. Alcohol-free chemotherapeutic agent ablation seemed to be an effective method, demonstrating a low risk of AEs. However, the treatment effectiveness for PCNs with a multilocular form, such as IPMN, was inadequate. Further development of endoscopic equipment and research on new agents will be required.

3. EUS-RFA for pancreatic solid neoplasms

The mechanism of action of RFA is high-frequency alternating current, generating high local temperatures that induce coagulative necrosis of the tissues[29]. This treatment approach has been proposed for pancreatic solid lesions, such as PC, NEN, SPN, and other malignant metastatic lesions[30-46]; however, only the feasibility and safety for treating for PC were assessed. Two ablation devices specifically designed for EUS are mainly used. One device was STARmed RFA needles (STARmed, Koyang, South Korea). The needle sizes were 18 G, 19 G, and 22 G. This operative needle is cooled using chilled saline, which prevents the charring of the tip and improves ablation accuracy[31-39, 41-44, 46]. The other device was the Habib catheter (EMcision Ltd., Boston Scientific). This is a monopolar electrode without a cooling system, which is inserted inside a standard EUS-FNA needle and attached to an electrosurgical generator[30,40,45]. Different RFA needles/catheters and ablative energy settings were used in each study. The generator is activated to release certain wattage for a set amount of time that varies according to each RFA model. Usually, 20–50 wattage is selected for the STARmed system, and 5–20 wattage is selected for RITA (connected to Habib catheter) systems.

Reviewed reports on EUS-RFA for pancreatic solid neoplasms are summarized in Table 3. The first case series was reported by Pai et al[30]. They treated two patients with NF-NEN in their case series. The tumor sizes were 15 and 40 mm, respectively, and they were treated with a Habib RFA device. No AEs were observed, and changes in vascularity and central necrosis after EUS-RFA were demonstrated on cross-sectional images. Oleinikov et al.[37] treated 18 patients (seven patients with insulinomas and 11 patients with NF-NEN) with 27 lesions. The 27 lesions with a mean diameter of 14.3 mm were treated using a STARmed RFA device. Radiological CR was achieved in 17 of the 18 patients (94%) and 26 of the 27 lesions. A clinical response with normalization of glucose levels was observed in all seven patients with insulinoma within 24 h of treatment. Mild pancreatitis occurred in two patients, who were treated conservatively. No clinically significant recurrences were observed during a mean follow-up period of 8.7 months. Barthet et al[36] treated 12 patients with 14 NEN lesions (mean size: 13.1 mm), and complete tumor ablation was reported in 12 (86%) lesions at a 1-year follow-up. AEs occurred in two (17%) patients (pancreatic necrosis and main pancreatic duct [MPD] stenosis). One patient with pancreatic necrosis had a 15-mm cystic NEN, which was treated without fluid aspiration during the first attempt. However, because of the lack of increase in impedance, a second attempt was made after removing the fluid. The patient developed pancreatic necrosis on the following day but improved with conservative treatment. Another patient with MPD stenosis had a 12-mm NEN located at the head of pancreas and close to the MPD (1 mm away). One week later, the patient presented again with post-prandial pancreatic pain. CT revealed slight dilation of the MPD upstream, and the patient was treated with pancreatic stenting for 6 months. The authors recommend to keep a 2-mm distance between any critical surrounding structures (i.e., common bile duct and MPD) and the tip of the active part. Moreover, Choi et al[35] recommended to keep a 5-mm margin from the pancreatic duct to avoid pancreatitis. Marx et al[41] tread 27 patients with NF-NEN lesions (mean

size: 14.0 mm) using EUS-RFA. Complete treatment response was confirmed in 25 (93%) patients with mean follow-up 15.7 months. Acute pancreatitis occurred in 4 (14.8%), and three of them were treated by endoscopic cystogastrostomy for pseudocyst formation or retrogastric fluid collections complicated with pancreatitis. These patients had lesion diameter of 10, 10, and 9 mm and age ranging from 58-66 years old. The used needle tip size was 10 mm. Further evaluations are needed to decide proper patient selection and needle tip size for small tumors[47]. Nicola et al.[48] conducted a systematic review of EUS-RFA for pancreatic NENs. Sixty-one patients with 73 tumors (mean size: 16 mm, insulinomas: 30.1%) were included in 12 studies. The overall effectiveness of EUS-RFA was 96% (range, 75%–100%) without significant differences in effectiveness between functional NENs and NF-NENs (p = 0.3) and without relevant issues about safety (the rate of mild AEs was 13.7%).

A preliminary study involving six patients with unresectable PC was conducted by Song et al.[32] Four and two patients had locally advanced and metastatic diseases, respectively, and were resistant to previous treatments. The median diameter of the tumors was 38 mm, and a STARmed RFA device was used for the procedure. EUS-RFA was technically successful in all cases. No major procedure-related complications occurred; only two patients experienced mild abdominal pain. Oh et al.[46] treated 22 patients (n=14, locally advanced; n=8, metastatic) with unresectable PC underwent EUS-RFA combined with subsequent chemotherapy. The procedure was successful in all patients and median number of RFA sessions was 5. Early AE occurred in only 4 out of 107 sessions (3.74%), including pancreatitis (n=1) and abdominal pain (n=3). Overall survival (OS) and progression free survival were 24.03 months (95% confidence interval [CI], 16-35.8) and 16.37 months (95% CI, 8.87-19), respectively. EUS-RFA could be a technically feasible and safe treatment method for patients with unresectable PC; however, the efficacy of EUS-RFA in preventing disease progression and increasing the OS was not adequately evaluated. Overall, EUS-RFA was safe

and effective for treating potentially malignant solid neoplasms. The effectiveness of EUS-RFA for treating patients with PC has not been examined, which is a topic for the future.

4. EUS-RFA for PCNs

Before performing RFA, cyst fluid was aspirated using a 22-gauge regular needle to suck the fluid content until a thin layer of fluid remained, thereby allowing the targeting of the remaining cystic lesion[36,43,49]. In the literature, 50 wattage is selected for the STARmed system, and 5–25 wattage is selected for RITA systems.

Reviewed reports on EUS-RFA for PCNs are summarized in Table 4. Pai et al.[30] first reported a case series of EUS-RFA for PCNs. Six patients with PCNs (one with IPMN, four with MCN, and one with SCN) were treated. Among them, two (33%) patients had achieved CR. Two patients experienced abdominal pain as an AE; however, they improved following conservative treatment. Barthet et al.[36] reported that 17 patients with PCNs (16 with IPMNs and one with MCN) were treated with EUS-RFA. Among them, 11 (65%) patients had achieved CR within a 12-month follow-up period. Perforation of the jejunum occurred in one patient with IPMN. The patient had a high-grade IPMN located in the uncinated process with a diameter of 18 mm, and one RFA shot was applied without suction. The patient experienced pain and fever 12 h later, and CT showed pneumoperitoneum with a fluid collection. The patient underwent surgical exploration, and a perforation of an adjacent jejunal loop was found and surgically treated. Oh et al.[49] reported the outcomes of RFA for treating SCN. In their report, although a volume reduction of more than PR was observed in eight (62%) patients, CR was not observed in any patients. AEs occurred in 13 patients, including 3 patients with pancreatitis. They mentioned that all patients had microcystic SCNs with a honeycomb appearance; thus, several needle punctures were performed to ablate the SCNs. Multiseptation of cystic lesions may restrict heat delivery during ablation into multiple locules.

Therefore, these morphological differences may affect the treatment response. Studies on using EUS-RFA for the treatment of PCN are limited, and more studies are needed to confirm the effectiveness of the same.

Advantages and disadvantages of EUS-guided ablation therapy

The advantages of EUS-guided therapy over surgical resection are as follows: reduction in complications and preservation of pancreatic exocrine and endocrine functions. EUS-guided therapy is acceptable for patients with poor tolerance for surgery. However, EUS-guided therapy has some disadvantages. First, complete ablation may not be obtained in all patients, and because tumor ablation is determined based on CE-CT findings, it may sometimes be difficult to demonstrate complete tumor elimination. Thus, long-term follow up is required to prove the efficacy of EUS-guided therapy. Second, while most of the AEs seen after EUS-guided ablation therapy are manageable, severe AEs, such as pancreatic necrosis and perforation, can occur. Finally, the safety of ablation treatment for tumors close to the MPD has not yet been established.

Most importantly, treatment effects differ between the two approaches, and lymph node dissection cannot be performed under EUS guidance. Thus, EUS-guided treatment should be limited to patients with a potentially malignant lesion and low risk of lymph node metastasis

Conclusions

In this review, we assessed available reports on injective ablation and RFA treatments for solid and cystic pancreatic neoplasms. The use of EUS-guided ablation therapy for the treatment of potentially malignant and malignant pancreatic lesions can potentially increase in the future once data from long-term multicenter prospective studies are available and new devices and ablation drugs are developed.

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Figure legends

Figure 1

A: Contrast-enhanced computed tomography (CE-CT) image showing a hypervascular tumor, 10 mm in diameter, in the pancreatic body (arrow).

B: Endoscopic ultrasonography (EUS) image showing a low echoic tumor in the pancreatic body (arrow)

C: EUS-guided puncture of the tumor with a 25-G needle (arrow) and injections of pure ethanol into the tumor.

D: CE-CT image 1 month after the procedure. The previously enhanced areas of the tumor could not be detected on CE-CT (arrow), and the tumor was completely treated with ethanol ablation.

E: CE-CT image 1 year after the procedure. There are no enhanced areas in the ablated area.

F: EUS image 1 year after the procedure. There are no low echoic areas in the ablated area.