

Endoscopic ultrasound guided radiofrequency ablation for pancreatic tumors: A critical review focusing on safety, efficacy and controversies

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Abstract

The role of endoscopic ultrasound (EUS) in the last two decades has shifted from a diagnostic tool to an important therapeutic tool treating mainly pancreatobiliary disorders. In recent years, its applications for treating pancreatic diseases have broadened, including the implementation of radiofrequency ablation (RFA), which has been traditionally used for treating solid tumors. In this critical in-depth review, we summarized all the papers throughout the literature regarding EUS-RFA for pancreatic neuroendocrine neoplasms, adenocarcinoma, and pancreatic cystic lesions. Overall, for pancreatic neuroendocrine neoplasms we identified 16 papers that reported 96 patients who underwent EUS-RFA, with acceptable adverse events that were rated mild to moderate and a high complete radiological resolution rate of 90%. For pancreatic adenocarcinoma, we identified 8 papers with 121 patients. Adverse events occurred in 13% of patients, mostly rated mild. However, no clear survival benefit was demonstrated. For pancreatic cystic lesions, we identified 4 papers with 38 patients. The adverse events were mostly mild and occurred in 9.1% of patients, and complete or partial radiological resolution of the cysts was reported in 36.8%. Notably, the procedure was technically feasible for most of the patients. Nevertheless, a long road remains before this technique finds its definite place in guidelines due to several controversies. EUS-RFA for pancreatic tumors seems to be safe and effective, especially for pancreatic neuroendocrine neoplasms, but multicenter prospective trials are needed to consider this treatment as a gold standard.

Key Words: Endoscopic ultrasound; Radiofrequency ablation; Efficacy; Safety; Pancreas; Tumors

Core Tip: Endoscopic ultrasound guided radiofrequency ablation has been increasingly implemented in the treatment of pancreatic neoplasms. We reviewed the role of endoscopic ultrasound guided radiofrequency ablation in the treatment of pancreatic neuroendocrine tumors, unresectable pancreatic adenocarcinoma, and pancreatic cystic lesions, focusing on efficacy, safety, and controversies. We found that endoscopic ultrasound guided radiofrequency ablation was feasible with an excellent technical success, acceptable adverse events, and a beneficial effect for pancreatic neuroendocrine tumors, mainly on insulinoma. While its effect on pancreatic adenocarcinoma and cystic lesions is promising, more studies are needed to better explore its role.

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INTRODUCTION

In the recent years, endoscopic ultrasound (EUS) transformed from a diagnostic tool to an important therapeutic tool, especially for pancreato-biliary diseases[1]. Among the therapeutic options is radiofrequency ablation (RFA). RFA is a low-risk minimally invasive procedure that delivers heat waves (in the range of 350-500 kHz), with a high temperature ranging between 60 °C-100 °C that subsequently causes burning of the tumorous tissue. The effect is mediated *via* coagulation necrosis, leading to irreversible cellular damage and apoptosis, without significantly affecting the normal surrounding tissue[2]. Safety and effectiveness of EUS-RFA of the pancreatic tissue were evaluated in porcine models, which showed beneficial effects[3-6]. Moreover, RFA should have an anti-cancer effect induced by immunomodulatory activity[7]. RFA was shown previously to be a feasible and safe ablative therapeutic option for liver tumors[8]. With the invention of dedicated needles, RFA has recently been used more under EUS for the treatment of pancreatic neuroendocrine neoplasms (pNENs), pancreatic adenocarcinoma or pancreatic cystic lesions (PCL). However, the data in this field is still emerging. In this current review, we provided a critical in-depth overview of the most updated data of EUS-RFA for pancreatic tumors with a focus on safety, efficacy and controversies.

Literature search

A search for studies published before September 2022 was performed in the PubMed databases with the keywords EUS or endoscopic ultrasound with radiofrequency ablation and any of the following: Pancreatic neuroendocrine tumor or neoplasm, pancreatic functional neuroendocrine tumor or neoplasm, pancreatic non-functional neuroendocrine tumor or neoplasm, insulinoma, carcinoma or adenocarcinoma of pancreas, pancreatic tumor or neoplasm, pancreatic cystic lesions or neoplasms, pancreatic cysts, cysts of the pancreas, mucinous pancreatic cysts, pancreatic serous cystadenoma, intraductal papillary mucinous neoplasm, mucinous cyst, treatment or therapeutic and intervention. The search was restricted to articles in the English language and included prospective, retrospective, randomized controlled studies, case series and case reports. Moreover, the bibliographic section of the selected articles as well as the systematic and narrative articles on the topic were manually searched for further relevant articles. Review articles, presented abstracts and posters, position papers and guidelines were not included. Subsequently, we reviewed and summarized all the data on EUS-guided intervention for solid and cystic pancreatic neoplasms focusing on technical success, safety and efficacy.

Study definitions

Technical success was defined by the successful completion of the procedure (introduction of the RFA probe through EUS channel and induction of thermal current to the pancreatic lesions). Safety was defined by any adverse event (AE) that appeared during the procedure or after and that should be secondary to the EUS-RFA. Efficacy was defined as the complete or partial radiological resolution of the pancreatic tumor. Complete response was defined by total destruction of the lesion, while partial response was defined by 75%-90% destruction of the lesion. The longest follow-up period was used to report efficacy in studies that reported more than one follow-up time point. Pooled data for AE was calculated by the overall number of AE divided by the total number of EUS-RFA sessions. Procedure related AE was defined according to the American Society of Gastrointestinal Endoscopy classification [9] as follow: (1) Mild AE: Post-procedure medical consultation, unplanned hospitalization or hospital

stay prolongation for less than 3 nights; (2) Moderate AE: Unplanned anesthesia, unplanned hospitalization or hospital stay prolongation for 4-10 nights, admission to intensive care unit for 1 night, blood transfusion, interventional radiology or endoscopic treatment for AE secondary to the procedure; and (3) Severe AE: Unplanned admission or hospital stay prolongation for > 10 nights, intensive care stay for > 1 night, surgery needed for an AE related to the procedure, permanent disability and death related to the procedure[9]. The more recent AGREE classification was not used in these trials, and it was not possible retrospectively to find the data that would have been necessary to grade the AE. Pooled radiological response was calculated by the overall number of complete or partial radiological response divided by the total number of patients included. In cases where RFA session numbers were not provided by the original manuscript, we consider it the same as the number of patients included in the study[10-20].

EUS-RFA IN PNENS

To date, most of the studies assessed the role of RFA in the treatment of pNENs, in the form of case reports and case series. The first study was reported by Rossi *et al*[10] on 10 patients with pNENs. RFA was performed by the EUS route in 1 patient with non-functional pNEN. Lakhtakia *et al*[12] reported the first case series of 3 patients with functional pNENs (insulinoma), with rapid hypoglycemia relief in the same day. Similarly, Waung *et al*[21] and Bas-Cutrina *et al*[22] reported 2 successful cases of EUS-RFA for insulinoma. Pai *et al*[23] reported a study including 8 patients with complete resolution at 3-6 mo post-treatment and no procedure-related AEs.

Barthet *et al*[13] reported the first multicenter prospective study including 12 patients with 14 pNENs who underwent RFA. Two patients developed complications (16.7%), including acute pancreatitis with early infected necrosis and main pancreatic duct stenosis. Notably, the patient who developed infected necrosis had a cystic pNEN, and the cystic component was not aspirated before performing the RFA. Therefore, this AE was presumed to be secondary to the lack of cystic component suction. After this AE, the independent safety committee decided to administer antibioprohylaxis (2 g of intravenous amoxicillin and clavulanic acid intravenously) and to aspirate the main part of the fluid content prior to RFA in cystic pNEN in order to avoid excessive application of radiofrequency current into the liquid component[13]. The long-term follow-up data of the study by Barthet *et al*[24] was published recently; among the 12 patients with the 14 pNENs lesions, there was a complete disappearance in 12 pNENs lesions (85.7%) and 2 failures (14.3%) at a mean follow-up of 45.6 mo. The two failures were pNEN recurrence after disappearance at 1 year and a metastatic evolution at 3 years follow-up in a patient that had a persistence of the initial pancreatic tumor after two RFA sessions.

Another study by Choi *et al*[25] reported 8 patients with pNENs. Notably, the proliferative index Ki67% was reported in only 2 patients (1 patient with G1 and one patient with G2). Similarly, a prospective study by de Nucci *et al*[26] reported a complete radiological resolution rate at 6 and 12 mo following treatment among 10 patients with 11 pNEN lesions of G1 grading (< 5%), with only 2 mild AEs. Oleinikov *et al*[14] reported a retrospective study that included 18 patients with pNENs. Two patients with non-functional pNEN and one patient with insulinoma had multiple endocrine neoplasia syndrome type 1. Most of the lesions were G1 grading. Complete relief of hypoglycemia-related symptoms was achieved in the 7 patients with insulinoma within 1 h following the EUS-RFA[14].

Furthermore, recent case reports and prospective case series were published in patients with insulinoma who underwent EUS-RFA, with a complete clinical resolution of the hypoglycemic symptoms up to 1 d after the EUS-RFA and complete radiological resolution[27-29], with 1 case of acute necrotizing pancreatitis[28] and 2 cases of mild pancreatitis occurring 1 d after the procedure and 3 mo after[29]. Rossi *et al*[30] treated 3 elderly patients with insulinomas with one intraprocedural bleeding treated endoscopically.

Additionally, Marx *et al*[31] reported two recent trials. The first study included 7 patients with insulinoma, with a complete resolution rate reported in 6 patients (85.7%). Clinical success in terms of symptom relief was achieved immediately in all patients (100%). Notably, this study was associated with a safety signal, as 3 patients had mild to moderate AEs and 1 patient (aged 97 years) had a severe AE with retrogastric collection. He refused drainage, was symptomatically treated and died 2 wk later [15]. The second study retrospectively reported 27 patients with G1 non-functional pNENs. Nine out of the 27 lesions (33.3%) were cystic. Twenty-five patients (92.6%) had a complete radiological resolution at a mean follow-up time of 15.7 mo (range 2-41). Notably, procedure-related AEs occurred in 9 patients [31] (Table 1).

Pooling the available data, EUS-RFA was performed on 100 patients with 112 pNEN lesions that underwent 114 EUS-RFA sessions. Most of the data were published as case reports and small case series. The mean lesion size was 14.8 mm, ranging mostly from 10-20 mm. The procedure was technically feasible in all patients, and the AE rate was almost 21.9%, occurring in 25 of the 114 EUS-RFA sessions. Notably, most of the AE were mild and moderate according to the American Society of Gastrointestinal Endoscopy guideline[9] except for one fatal AE in a recent paper published by Marx *et al*[15]. Interestingly, the complete radiological resolution rate was approximately 90% during a follow-up

Table 1 Studies reporting endoscopic ultrasound-radiofrequency ablation for pancreatic neuroendocrine neoplasms

Ref.	Type of study (pNEN type)	Patients/lesions/RFA sessions, n	Location, n	Mean size (range) in mm	Histological grade (KI67%)	Technical success, n (%)	Adverse events, n (%)	Complete radiological/clinical ¹ resolution, n (%)	Mean follow-up in mo
Rossi <i>et al</i> [10]	Case report (nonfunctional)	1/1/1	Head (1)	10	NR	1 (100)	0	1 (100)	34
Armellini <i>et al</i> [11]	Case report (nonfunctional)	1/1/1	Tail (1)	20	G2 (> 5)	1 (100)	0	1 (100)	1
Lakhtakia <i>et al</i> [12]	Case series (insulinoma)	3/3/3	Body (2), diffuse (1)	17.7 (14-22)	NR	3 (100)	0	3 (100)/3 (100)	4.2
Waung <i>et al</i> [21]	Case report (insulinoma)	1/1/3	Uncinate (1)	18	NR	1 (100)	0	1 (100)/1 (100)	10
Bas-Cutrina <i>et al</i> [22]	Case report (insulinoma)	1/1/1	Body (1)	10	NR	1 (100)	0	1 (100)/1 (100)	10
Pai <i>et al</i> [23]	Prospective (nonfunctional)	2/2/3	Head (1)	27.5 (15-40)	NR	2 (100)	0	2 (100)	6
Barthet <i>et al</i> [13]	Prospective (nonfunctional)	12/14/12	Head (3), body (6), tail (5)	13.1 (10-20)	G1	12 (100)	2 (16.7) ²	9 (75)	12
Choi <i>et al</i> [25]	Prospective (nonfunctional-7), (insulinoma-1)	8/8/14	Head (3), body (5)	19.25 (8-28)	Reported in 2 patients (G1 and G2)	8 (100)	2 (14.3) ³	6 (75)/1 (100)	13
de Nucci <i>et al</i> [26]	Prospective (nonfunctional)	10/11/10	Head (3), body (8), tail (2)	14.5 (9-20)	G1 (< 4)	10 (100)	2 (20) ⁴	10 (100)	12
Oleinikov <i>et al</i> [14]	Retrospective (nonfunctional-11), (insulinoma-7)	18/27/18	Head (10), body (8), tail (2), uncinate (5), metastasis (2)	14.8 (12-19)	G1 (< 5) in 15 patients, G3 (34-40) in 2 patients	18 (100)	2 (11.1) ⁵	17 (94.4)/7 (100)	8.7
Rossi <i>et al</i> [30]	Case series (insulinoma)	3/3/4	NR	11.5 (9-14)	NR	3 (100)	1 (25) ⁶	3 (100)/3 (100)	8.5
Chang <i>et al</i> [27]	Case report (insulinoma)	1/1/1	Head (1)	12	NR	1 (100)	0	1 (100)/1 (100)	18
Kluz <i>et al</i> [28]	Case report (insulinoma)	1/1/1	Head (1)	9	NR	1 (100)	1 (100) ⁷	NR/1 (100)	NR
Furnica <i>et al</i> [29]	Case series (insulinoma)	4/4/4	Head (2), neck (1), tail (1)	12.9 (6.5-22.0)	G1 in 3 patients and G2 in 1 patient	4 (100)	2 (50) ⁸	4 (100)/4 (100)	22
Marx <i>et al</i> [15]	Retrospective (insulinoma)	7/7/7	Head (1), body (1), neck (3), body-tail junction (2)	13.3 (8-20)	G1 (< 3) in 4 patient, G2 (4) in 1 patient	7 (100)	4 (57.1) ⁹	6 (85.7)/7 (100)	20.3
Marx <i>et al</i> [31]	Retrospective (non-functional)	27/27/31	Head (6), body (3), tail (11), uncinate (2), body-tail junction (5)	14 (7-25)	G1 (< 3) in 25 patients, NR in 2 patients	27 (100)	9 (29) ¹⁰	25 (92.6)	15.7
Pooled data	Case reports: 9. Prospective: 4. Retrospective: 3	100/112/114	Head and neck (33), body (34), tail (22), uncinate (8), metastasis and diffuse (3), junction (7)	14.8	Unable to pool due to data lacking	96 (100)	25 (21.9)	90 (90)/21 (100)	13

¹Insulinoma.

²Infected pancreatic necrosis (1 patient, moderate), pancreatic duct stenosis (1 patient, moderate).

³Pancreatitis (1 patient, moderate), transient abdominal pain (1 patient, mild).

⁴Transient abdominal pain (2 patients, mild).

⁵Pancreatitis (2 patients, mild).

⁶Intraprocedural bleeding treated endoscopically (1 patient, moderate).

⁷Acute necrotizing pancreatitis (1 patient, moderate).

⁸Pancreatitis (2 patients, mild).

⁹Transient abdominal pain (1 patient, mild), pancreatitis (1 patient, moderate), coagulation necrosis (1 patient, moderate), retrogastric collection (1 patient, refused drainage, died 2 wk later, severe).

¹⁰Transient abdominal pain (3 patients, mild), pancreatitis (1 patient, moderate), periprocedural bleeding (2 patients, moderate), pancreatitis complicated by retrogastric or perisplenic collection managed by endoscopic drainage and antibiotic treatment (2 patients, moderate), pancreatitis with pancreatic fistula and paragastric collection drained by endoscopic cystgastrostomy (1 patient, moderate).

pNEN: Pancreatic neuroendocrine neoplasms; NR: Not reported; RFA: Radiofrequency ablation.

period of 13 mo (Table 1).

EUS-RFA IN PANCREATIC ADENOCARCINOMA

Recently, EUS-RFA was increasingly implemented in the treatment of pancreatic adenocarcinoma among patients who were not candidates for surgical resection. The first study was a feasibility study conducted by Arcidiacono *et al*[16] who reported 22 patients with locally advanced pancreatic adenocarcinoma who underwent EUS-RFA. Before the EUS-RFA treatment, all patients had received gemcitabine-based chemotherapy, and 6 patients had chemoradiation. Data regarding chemotherapeutic and radiation-induced response were available in 16 patients (3 patients had a partial response, whereas 13 had stable disease). The procedure was technically successfully completed in 16 patients (72.7%). For 6 patients, there was a failure to penetrate the gastric wall and the tumor. The number of procedure-related AEs was relatively high and noted in 8 patients (36.4%). However, most of them were mild. Neither clear survival benefit nor significant effect on tumor size was evidenced[16].

Later, Song *et al*[32] reported the safety among 6 patients with pancreatic adenocarcinoma (4 patients with locally advanced disease and 2 patients with metastatic disease). Three patients were on adjuvant chemotherapy with gemcitabine, whereas the other 3 patients did not receive concomitant chemotherapy. The procedure was successfully completed in all patients with only 2 mild procedure-related AEs (mild abdominal pain)[32]. Scopelliti *et al*[17] reported 10 patients with locally advanced pancreatic adenocarcinoma. All patients underwent systemic chemotherapy (4 patient received FOLFIRINOX, 2 patients received gemcitabine, 2 patients received GemOx and 2 patients received combined gemcitabine/nab-paclitaxel), and 5 patients underwent additional external radiation therapy. All patients had complete technical success, and mild pancreatitis occurred in 4 patients, with no major AEs[17].

Similarly, Crinò *et al*[18] reported 7 patients with locally advanced pancreatic adenocarcinoma that were previously treated with FOLFIRINOX + radiotherapy (3 patients), gemcitabine (2 patients), FOLFIRINOX (1 patient) and radiotherapy (1 patient) who underwent EUS-RFA with an excellent technical success rate and minor AE of mild abdominal pain in 3 patients. Mean tumor ablation was approximately 30% (5.8%-73.5%) at 30 d following the procedure. However, data regarding survival benefit were not reported[18]. Paiella *et al*[19] reported a genetic study of 30 patients with locally advanced adenocarcinoma. Thirteen patients received EUS-RFA before the chemotherapy, while 17 patients had EUS-RFA after treatment (FOLFIRINOX in 6 patients, gemcitabine/oxaliplatin in 4 patients, nab paclitaxel/gemcitabine in 2 patients and data not available in 5 patients, with additional radiotherapy in 4 patients). The overall median disease specific survival for all patients was 15 mo. *SMAD4* mutation was diagnosed in 18 patients (60%). The estimated post-RFA disease specific survival of patients without and with *SMAD4* mutation was 22 mo and 12 mo, respectively, with complete technical success of EUS-RFA and only 1 AE of bleeding from a duodenal ulcer[19].

Moreover, a recent prospective randomized study by Bang *et al*[20] reported the yield of EUS-guided RFA (12 patients) *vs* celiac plexus neurolysis (14 patients) for palliation of pain in pancreatic adenocarcinoma. EUS-RFA guided treatment was associated with a significant improvement in pain associated with pancreatic cancer ($P < 0.05$). Procedure-related AE occurred in 10 out of 12 included patients (83.3%) but were always mild[20]. Another recent study by Wang *et al*[33] reported 11 patients with pancreatic adenocarcinoma (only 1 patient was on chemotherapy), with complete technical success and only 2 patients with minor AEs of abdominal pain. A decrease in tumor size was only notable in 2 patients (18.2%), without a significant benefit on survival[33]. A recent study by Oh *et al*[34] reported 22 patients with pancreatic adenocarcinoma (19 patients received systemic gemcitabine-based chemotherapy before, and 3 patients received chemotherapy) who underwent 107 EUS-RFA sessions. The overall survival rate was 24 mo, with 4 procedure-related AEs (3 patients had transient abdominal pain, and 1 had peritonitis)[34].

Overall, the pooled analysis showed that EUS-RFA was applied to date in 120 patients with pancreatic adenocarcinoma who underwent 222 EUS fine needle aspiration sessions, most of them with locally advanced disease. The mean lesion size was 37.4 mm. The procedure was successfully completed in 95% of the patients, and AE occurred in 29 EUS-RFA sessions (13%), most of them were mild in severity, including transient abdominal pain and gastrointestinal symptoms. Notably, any decrease in tumor size was reported in 4 studies, as it was recorded in 25 among 50 patients (50%). However, only 4 studies provided data regarding the post EUS-RFA survival. Two studies did not show a clear survival benefit[16,33], and the other two studies showed a potential survival benefit[19,34] (Table 2).

RFA IN PCL

In the last few years, EUS fine needle aspiration was also implemented in the treatment of PCL in a few human case series. The first case was reported by Wiersema *et al*[35] in a patient with bleeding remnant intraductal papillary mucinous neoplasm that was successfully treated with endoscopic intraductal RFA. Pai *et al*[23] prospectively reported 6 patients with PCL [4 mucinous cystic neoplasm, 1 intraductal papillary mucinous neoplasm and 1 serous cystadenoma (SCA)]. Two (33.3%) and four (66.7%) patients had complete and partial cyst resolution at 3-6 mo follow-up, respectively. Among the 4 patients with partial resolution, 2 patients (50%) had > 50% ablation of the cyst size. Only 2 patients (33.3%) had mild transient abdominal pain. Notably, no long follow-up data were provided to assess recurrence. Furthermore, Choi *et al*[25] reported 2 patients with solid pseudopapillary tumors who underwent EUS-RFA because they refused surgery. The procedure was successfully completed in both patients, without procedure-related AEs. At a median follow-up of 13 mo, 1 patient (50%) had complete radiological response, while the other patient had no response with a decrease of approximately 20% from its pre-ablation size[25].

Additionally, Barthet *et al*[13] reported the yield of EUS-RFA among 17 patients with PCL (16 patients with intraductal papillary mucinous neoplasm and 1 patient with mucinous cystic neoplasm), notably 12 patients (70.6%) and 4 patients (23.5%) had mural nodules and thick cystic walls, respectively. The follow-up was assessed at two time-points. At 6-mo, 8 patients (47.1%) had a complete disappearance and necrosis of the cysts, and 3 patients (17.6%) had > 50% decrease in cyst diameter. However, there were 6 patients (35.3%) with failure of the procedure. At 12-mo follow-up, 11 patients (64.7%) had a complete disappearance and necrosis of the cysts, and 1 patient (5.9%) had > 50% decrease in cyst diameter. However, there were 5 patients (29.4%) with procedure failure. Only 1 procedure-related AE was noted with fever and pneumoperitoneum due to a perforation of the jejunal loop surgically corrected[13]. The long-term follow-up in 15 patients was recently reported. At 42.6-mo follow-up, complete cyst disappearance was noticed in 6 patients (40%). Four patients (26.6%) had a partial radiological response (decrease > 50% of the initial cyst diameter). Failure was seen in 5 patients, as the cyst lesion decreased < 50%[24].

A recent study by Oh *et al*[36] reported 13 patients with SCA who underwent 19 EUS-RFA sessions. One patient (5.3%) had peri-procedural transient mild abdominal pain. Notably, none of the patients had complete radiological response at 9.2 mo of follow-up, while 8 patients (61.5%) had partial radiological response (more than 30% in the longest diameter with an estimated volume reduction more than 66%)[36].

Pooling the data, 4 studies assessed EUS-RFA for PCL, with 38 patients included who underwent 44 EUS-RFA sessions. The mean cyst size was 32.1 mm, and worrisome features were only reported in one study. The procedure was feasible in all patients, with mild AEs of transient abdominal pain in most studies. Notably, complete radiological cyst resolution was achieved in 14 patients (36.8%) at a follow-up of 10.2 mo (Table 3).

SAFETY AND EFFICACY OF EUS-RFA IN PANCREATIC TUMORS

Overall, 377 EUS-RFA sessions were performed in 255 patients. The rate of mild, moderate and severe AEs according to American Society of Gastrointestinal Endoscopy guidelines[9] were 10.1%, 4.2% and 0.5%, respectively. For pNENs, the rate of mild and moderate AEs was 8.2% and 11.8%, respectively. For pancreatic adenocarcinoma and pancreatic cystic tumors, most of the AE were mild in severity. Notably, the rate of severe AEs and mortality were extremely low in all pancreatic tumor categories (Table 4). Finally, the EUS-RFA treatment is technically feasible, with high clinical and radiological success rates for pNENs and PCL and an acceptable AE rate (Table 5). Nevertheless, some limitations and controversies must be underlined as those limitations might impact the interpretation of the published literature and should be considered when planning future studies.

Technical considerations

The studies reported different power setting and application number used (Table 6). Moreover, in

Table 2 Studies reporting endoscopic ultrasound-radiofrequency ablation for pancreatic adenocarcinoma

Ref.	Study type	Patients/RFA session, n	Tumor location (n)	Cancer stage (n)	Mean size (range) in mm	Any decrease in tumor size, n (%)	Technical success, n (%)	Adverse events, n (%)	Mean follow-up in mo	Survival after RFA in mo
Arcidiacono <i>et al</i> [16]	Prospective	22/22	Head (16), uncinata (2), body (4)	Locally advanced (22)	35.7 (23-54)	6 (37.5)	16 (72.7)	8 (36.4) ¹	3	5.6 (1-12)
Song <i>et al</i> [32]	Prospective	6/8	Head (4), body (2)	Locally advanced (4), metastasis (2)	48 (30-90)	NR	6 (100)	2 (25) ²	4.2	NR
Scopelliti <i>et al</i> [17]	Prospective	10/10	Head (4), body (6)	Locally advanced (10)	49.2 (25-75)	10 (100)	10 (100)	4 (40) ³	1	NR
Crinò <i>et al</i> [18]	Retrospective	7/7	Head (2), body (3), uncinata (2)	Locally advanced (7)	36 (22-67)	7 (100)	7 (100)	3 (42.8) ⁴	6.1	NR
Paiella <i>et al</i> [19]	Retrospective	30/30	Head (23), body and tail (7)	Locally advanced (30)	35 (20-60)	NR	30 (100)	1 (3.3) ⁵	15	15
Bang <i>et al</i> [20]	Prospective	12/12	Head and uncinata (8), body and tail (4)	Locally advanced (5), metastasis (7)	29.6 (22.5-35.0)	NR	12 (100)	5 (41.6) ⁶	1	NR
Wang <i>et al</i> [33]	Retrospective	11/26	Head (4), neck (3), body (3), tail (1)	Locally advanced (7), metastasis (4)	28 (17.2-38)	2 (18.2)	11 (100)	2 (7.7) ⁷	5.2	5.2
Oh <i>et al</i> [34]	Prospective	22/107	Head (14), body (4), tail (3), metastasis (1)	Locally advanced (14), metastatic (8)	38 (32.8-45.0)	NR	22 (100)	4 (3.7) ⁸	21.2	24
Pooled data	Prospective: 5, Retrospective: 3	120/222	Head and uncinata (79), Body and tail (37), neck (3)	Locally advanced (100), metastasis (21)	37.4	Unable to pool due to data lacking	114 (95)	29 (13)	7.1	Unable to pool due to data lacking

¹Transient abdominal pain (3 patients, mild), minor duodenal bleeding endoscopically treated (1 patient, moderate), transient amylase elevation (3 patients, mild), transient cystic fluid collection between pancreas and left hepatic lobe (1 patient, mild).

²Transient abdominal pain (2 patients, mild).

³Mild pancreatitis (4 patients, mild).

⁴Transient abdominal pain (3 patients, mild).

⁵Duodenal bleeding (1 patient, moderate).

⁶Nausea and vomiting (4 patients, mild), transient abdominal pain (1 patient, mild).

⁷Transient abdominal pain (2 patients, mild).

⁸Transient abdominal pain (3 patients, mild), peritonitis (1 patient, moderate).

NR: Not reported; RFA: Radiofrequency ablation.

several studies, the size of the tip of the needle was not considered or not detailed. Power setting, size of the active type, duration of the irradiation, size of the needle (18 G *vs* 19 G) can interfere in the final destruction. Therefore, uniform studies with similar technical aspects should be performed to better assess the treatment efficacy and safety.

Optimal size of the pNENs and PCL

To date, no data are available regarding the optimal size of the pNENs and cystic lesions that are amenable to EUS-RFA. Predictably, the RFA probe can induce a 3 cm ablation area with a single deployment, thus it is postulated that lesions up to 3 cm will achieve the best ablative results with a single application, and larger lesions may need more needle applications during the same session[6]. In fact, a lot of lesions had more than one needle application during the same session even in lesions < 2

Table 3 Studies reporting endoscopic ultrasound-radiofrequency ablation for pancreatic cystic tumors

Ref.	Type of study	Patients/RFA sessions, n	Type of cyst	Mean size (range) in mm	Worrisome features	Technical success, n (%)	Adverse events, n (%)	Complete/partial resolution, n (%)	Mean follow-up in mo
Pai <i>et al</i> [23]	Prospective	6/6	MCN (4), IPMN (1), MCA (1)	41 (24-70), 35, 20	NR	6 (100)	2 (33.3) ¹	2 (33.3)/4 (66.7)	6
Choi <i>et al</i> [25]	Prospective	2/2	SPT (2)	21.5 (20-23)	NR	2 (100)	0	1 (50)/1 (50)	13
Barthet <i>et al</i> [13]	Prospective	17/17	MCN (1), IPMN (16)	28 (9-60)	16 (94.1)	17 (100)	1 (5.9) ²	11 (64.7)/1 (5.9)	12
Oh <i>et al</i> [36]	Retrospective	13/19	SCN (13)	50 (34-52.5)	NR	13 (100)	1 (5.3) ³	0/8 (61.5)	9.2
Pooled data	Prospective: 3, Retrospective: 1	38/44	MCN (5), IPMN (17), MCA (1), SPT (2), SCN (13)	32.1	Unable to pool due to data lacking	38 (100)	4 (9.1)	14 (36.8)/14 (36.8)	10.2

¹Transient abdominal pain (2 patients, mild).

²Fever and pneumoperitoneum with fluid collection and jejunal loop perforation needed surgery (1 patient, severe).

³Transient abdominal pain (1 patient, mild).

IPMN: Intraductal papillary mucinous neoplasm; MCA: Microcystic adenoma; MCN: Mucinous cystic neoplasm; NR: Not reported; RFA: Radiofrequency ablation; SPT: Solid pseudopapillary tumor; SCN: Serous cystic neoplasm.

Table 4 Pooled analysis of the adverse events

EUS-guided RFA for	Procedure-related adverse events according to ASGE[9] ¹			
	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Mortality, n (%)
Neuroendocrine neoplasms EUS-RFA sessions = 114	11 (9.6)	13 (11.4)	1 (0.9)	1 (0.9)
Adenocarcinoma EUS-RFA sessions = 223	26 (11.6)	3 (1.3)	0	0
Cystic tumors EUS-RFA sessions = 44	3 (6.8)	0	1 (2.3)	0
Pooled data	40 (10.5)	16 (4.2)	2 (0.5)	1 (0.26)

¹Overall, 380 EUS-RFA sessions performed for all pancreatic tumors.

ASGE: American Society of Gastrointestinal Endoscopy; EUS-RFA: Endoscopic ultrasound-radiofrequency ablation.

cm.

Heterogeneity of reporting the histological grading and mitotic activity for the pNENs

EUS-RFA for pNENs should be reserved for patients with G1 (Ki67 < 3%) or low G2 (Ki67 < 5%). However, most of the reported studies did not address the histological and mitotic activity of the pNENs, and in one study by Oleinikov *et al*[14], 2 patients with G3 (Ki67% of 34%-40%) were included in their series. Therefore, identification of the optimal histological grading that will most benefit from EUS-RFA is needed.

Technical success

In the published papers, the technical success was almost complete. However, the data did not state how many patients failed to undergo the procedure due to technical difficulties. Thus, the pooled technical success rate should be carefully interpreted. Further prospective studies are warranted with inclusion of all patients referred for an EUS-RFA procedure in intention-to-treat.

AE rate

Most of the AEs that were reported in the literature were intra- and periprocedural AEs, mainly reported from retrospective and small series with scarce data on long-term AEs (follow-up of only 1 mo for some trials). Moreover, there was one death in an elderly patient who refused endoscopic intervention, which might bias the severity of AEs as well. Therefore, larger studies are needed with

Table 5 Summary of efficacy and safety of endoscopic ultrasound-guided radiofrequency ablation for pancreatic tumors

Procedure	EUS-guided RFA for pancreatic		
	Neuroendocrine tumors	Adenocarcinoma	Cystic tumors
Technical success	High	High	High
Safety, complications	Mild-moderate ¹	Mild	Mild
Efficacy			
Clinical improvement	Significant for insulinomas	None	-
Radiological partial/complete resolution	High	Modest	Encouraging
Palliation	-	Encouraging	-
Mortality	None	None	None

¹When taking prophylactic measures (antibioprophylaxis, fluid component suction before radiofrequency ablation).
EUS-RFA: Endoscopic ultrasound-radiofrequency ablation.

Table 6 Technical considerations and imaging studies used in follow-up among patients with pancreatic neuroendocrine neoplasms

Ref.	Number of patients/sessions	Power setting in Watts	RFA application number in all sessions	Imaging study used in radiological follow-up
Rossi <i>et al</i> [10]	1/1	10-15	1	CECT or MRI
Armellini <i>et al</i> [11]	1/1	NR	2	CT and CE-EUS
Lakhtakia <i>et al</i> [12]	3/3	50	9	CECT (1 patient), CECT and EUS (2 patients)
Waung <i>et al</i> [21]	1/3	10	25	CT and gallium dotatate positron emission tomography
Bas-Cutrina <i>et al</i> [22]	1/1	10	3	NR
Pai <i>et al</i> [23]	2/3	20	10	Cross sectional imaging not stated which
Barthet <i>et al</i> [13]	12/12	50	NR	CT and EUS
Choi <i>et al</i> [25]	8/14	50	65	CECT and CE-EUS
de Nucci <i>et al</i> [26]	10/10	20	23	CT
Oleinikov <i>et al</i> [14]	18/18	50	3-10 in each EUS-RFA session	CECT (9 patients), NA (5 patients), CECT and somatostatin receptor imaging (3 patients)
Rossi <i>et al</i> [30]	3/4	30	14	EUS (1 patient), MRI (1 patient), refused follow-up (1 patient)
Chang <i>et al</i> [27]	1/1	50	2	CECT
Kluz <i>et al</i> [28]	1/1	50	3	NR
Furnica <i>et al</i> [29]	4/4	50	1-3 per each EUS-RFA	CT
Marx <i>et al</i> [15]	7/7	50	1-5 for each EUS-RFA session	CE-EUS or MRI
Marx <i>et al</i> [31]	27/31	50	1-5 for each EUS-RFA session	CT or MRI

CE-EUS: Contrast enhanced endoscopic ultrasound; CECT: Contrast enhanced computed tomography; CT: Computed tomography; EUS-RFA: Endoscopic ultrasound-radiofrequency ablation; MRI: Magnetic resonance imaging; NA: Not available; NR: Not reported.

longer follow-up to better define the AEs in these procedures.

Antibioprophylaxis in cystic lesions

Antibioprophylaxis and liquid component suction of all the fluid composition of the lesions before performing the RFA procedure is a controversy that should be addressed for cystic pNENs and for PCL. In their study, Barthet *et al*[13] revised their prophylaxis protocol after an AE of infection, so they administered antibioprophylaxis and aspirated the major cystic liquid component in their subsequent patients. Antibioprophylaxis in a PCL patient who underwent EUS-guided fine needle aspiration has

been a long debated clinical indication, as there were conflicting results regarding this condition[35,37-39]. A recent meta-analysis showed no significant difference in the rate of pancreatic cyst infection rate after puncture irrespective of the administration of antibioprophylaxis[40]. Moreover, the advantage of emptying the cyst might be a double pitfall. It will be less evident to see the thickening or the mural nodule within the PCL undergoing EUS-RFA, and it will need two punctures (one for emptying the fluid, and one for the EUS-RFA procedure), which might increase the procedure-related AE.

Association between complete clinical and radiological resolution in insulinomas

The complete disappearance of the clinical symptoms of insulinoma occurred in all patients (100%) throughout the reported studies. However, it does not mean that the tumor was totally destroyed, as some patients with insulinoma will have normal insulin levels[41,42]. Among the nine studies that included patients with insulinoma, only three studies had almost similar clinical and radiological follow-up periods after EUS-RFA, while the other studies had a longer clinical than radiological follow-up (Table 7). Further prospective studies are needed with uniform clinical, biochemical and radiological long-term follow-up periods.

Radiological efficacy

According to the literature, a high complete radiological resolution rate was demonstrated after EUS-RFA. However, the studies reported different imaging modalities or combined imaging tools. Moreover, some studies did not specify which imaging tool was used. Notably, only three studies used a combination of contrast enhanced computed tomography (CT) and contrast enhanced EUS, while most of the other studies used only single imaging modality. Furthermore, in some studies, CT and EUS were used for follow-up. However; it was not stated whether contrast enhancement was implemented (Table 6).

Previous studies have shown that contrast enhanced magnetic resonance imaging including diffusion-weighted imaging is preferred over contrast enhanced CT for examination of the pancreas and the liver[43,44]. On the other hand, EUS has an important role in the diagnosis of small pNENs of < 2 cm and is now considered as the imaging study of choice to be performed where other non-invasive studies failed to diagnose the pNENs[45,46]. Previous systematic review and meta-analysis showed that EUS consistently increased the detection of pNENs by over 25% after performing CT scan[47]. PET-Dotatoc should also be proposed for the follow-up of non-functional pNENs. Therefore, a prospective study with uniform imaging study to be used at follow-up is mandatory to precisely assess the efficacy of EUS-RFA in pNENs.

Patient number and study designs

The small number of patients reported and the study designs, which were primarily case reports and small case series, with the lack of uniform and long-term follow-up should urge careful interpretation of the current literature. The follow-up is too short (only one trial has a follow-up longer than 3 years) to know the long-term result on the tumor and on the possible metastatic evolution.

RFA in PCL

The indication of RFA in cystic lesions remains debated. Oh *et al*[36] reported a study on 13 patients with SCA. However, the interest in this indication is debatable due to its very rare malignant potential [48]. Excluding SCA, only 25 patients with PCL were treated by EUS-RFA, which is too small of a sample size to enable good and precise data interpretation. Therefore, more studies are needed in patients with high-risk PCL.

RFA in pancreatic adenocarcinoma

Most of the studies did not report the additional survival benefit of EUS-RFA when added to standard chemotherapeutic regimens. Moreover, some studies included patients with metastatic disease. It is difficult to justify this treatment for metastatic disease. Prospective randomized trials with uniform disease stage and standard chemotherapeutic regimens are necessary to draw conclusions of the efficacy.

CONCLUSION

High and promising expectations are held for EUS-RFA. Taking advantage of the EUS transducer proximity to the pancreatic parenchyma, coupled with its excellent imaging resolution and the capability of avoiding major internal organs and vascular structures, makes this procedure safe. The current evidence of efficacy is weak, as most studies were case reports and series that included a small number and heterogenous groups of patients. Prospective and randomized studies are needed to establish the potential therapeutic role of EUS-RFA in pancreatic tumors. The available literature suggests a beneficial impact mainly on functional pNENs where RFA should replace surgery. In nonfunctional pNENs the data are encouraging. Its role for PCL treatment is still to be elucidated. For

Table 7 Clinical and radiological follow-up in pancreatic insulinomas studies

Ref.	Patients with insulinoma, n	Mean time (range) of clinical follow-up in mo	Mean time (range) of radiological follow-up in mo
Lakhtakia <i>et al</i> [12]	3	11.7 (11-12)	4.2 (1.5-8)
Waung <i>et al</i> [21]	1	10	3 d
Bas-Cutrina <i>et al</i> [22]	1	10	10
Choi <i>et al</i> [25]	1	NR	NR
Oleinikov <i>et al</i> [14]	7	9.7 (3-21)	8.7 (2-21)
Rossi <i>et al</i> [30]	3	22 (14-27)	5.7 (3-14)
Chang <i>et al</i> [27]	1	18	18
Kluz <i>et al</i> [28]	1	NR	NR
Furnica <i>et al</i> [29]	4	22 (13-28)	8 (3-14)
Marx <i>et al</i> [15]	7	21 (3-38)	20.3 (3-38)

NR: Not reported.

pancreatic adenocarcinoma, the data are lacking especially on the survival rate. Finally, EUS-RFA for pancreatic tumors is far from being adopted as a first-line treatment except for insulinomas. For grade 1 nonfunctional pNENs < 2 cm, EUS-RFA should be discussed as an alternative to surgery or follow-up. For PCL with worrisome features, EUS-RFA could be considered among patients who are not candidates or refuse surgical intervention. For pancreatic adenocarcinoma, randomized controlled trials are required to determine if EUS-RFA adds a survival benefit to chemotherapy in locally advanced pancreatic adenocarcinoma.

FOOTNOTES

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