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

Khoury T *et al*. EUS-RFA for pancreatic tumors

Abstract

The role of endoscopic ultrasound (EUS) in the last two decades has shifted from a diagnostic to an important therapeutic tool treating mainly pancreato-biliary disorders. In the 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 that dealt with EUS-RFA for pancreatic neuroendocrine neoplasms (pNENs), adenocarcinoma and pancreatic cystic lesions (PCL). Overall, for pNENs we could identify 16 papers that reported 96 patients who underwent EUS-RFA, with an acceptable adverse event (AE) rate mainly mild to moderate and a high complete radiological resolution rate of 90%. For pancreatic adenocarcinoma, we could identify 8 papers with 121 patients. AE occurred in 13% of patients, mostly were mild. However, no clear survival benefit was demonstrated. For PCL, we could identify 4 papers with 38 patients. The AE were mostly mild and occurred in 9.1% of patients, and complete or partial radiological resolution of the cysts was reported in 36.8% for each. Notably, the procedure was technically feasible in most of the patients. Nevertheless, a long road remains before this technique finds its definite place in guidelines. The different points requiring studies are detailed in controversies. EUS-RFA for pancreatic tumors seems to be safe and effective, especially for pNENs, but multicenter prospective trials are needed to consider this treatment as a gold standard.

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

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Core Tip: Endoscopic ultrasound guided radiofrequency ablation (EUS-RFA) has been increasingly implemented in the treatment of pancreatic neoplasms, mainly for pancreatic neuroendocrine tumors (pNENs). Herein, we provided a comprehensive review on the role of EUS-RFA in the treatment of pNENs, unresectable pancreatic adenocarcinoma and pancreatic cystic lesions, focusing on efficacy, safety and controversies. We found that EUS-RFA were feasible with an excellent technical success, with an acceptable adverse events, and beneficial effect pNENs, mainly on insulinoma. While its effect on pancreatic adenocarcinoma and cystic lesions is promising, as more studies are needed to better explore its role. Nevertheless, a long road remains before this technique finds its definite place in guidelines.

INTRODUCTION

In the recent years, endoscopic ultrasound (EUS) transformed from a diagnostic tool to an important therapeutic tool especially for biliopancreatic diseases[1]. Among the therapeutic options, is radiofrequency ablation (RFA). RFA is a low-risk minimally invasive procedure acting by delivering heat waves (in the range of 350-500 kHz), with a high temperature ranging between 60-100 □C, that subsequently causes burning of the tumorous tissue, an effect that 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 a beneficial effects[3-6]. Moreover, RFA should have an anti-cancer effect induced by an immunomodulatory activity[7]. RFA was shown previously to be a feasible and safe ablative therapeutic option for liver tumors[8]. With the apparition 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 provide a critical in-depth overview on the most updated data of EUS-RFA for pancreatic tumors with 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 (ASGE) 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; (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 sessions 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 had 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 only in 1 patient with non-functional pNENs. 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; among them, with complete resolution at 3-6 mo post treatment and no procedure related AE. Barthet *et al*[13] has reported the first multicenter prospective study including 12 patients with 14 pNENs who underwent RFA. Two patients had 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 sucked 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 antibioprophylaxis (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 pNENs 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 2 RFA sessions. Another study by Choi *et al*[25] reported 8 patients with pNENs. Notably, the proliferative index Ki67% was reported only in 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 two mild AE. Oleinikov *et al*[14]. reported a retrospective study which included 18 patients with pNENs. Two patients with NF-pNENs 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 obtained 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 one case of acute necrotizing pancreatitis[28], and two cases of mild pancreatitis occurring 1 d after the procedure, and 3 mo after[29]. Rossi *et al*[30] treated 3 old 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 AE and 1 patient (aged 97 years) had severe AE with retrogastric collection. He refused drainage, was symptomatically treated, and died two weeks 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 AE occurred in 9 patients[31], see Table 1. Pooling the available data, overall, EUS-RFA was performed on 100 patients with 112 pNENs lesions that underwent 114 EUS-RFA sessions. Most of the data were published as case report 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 114 EUS-RFA sessions. Notably, most of the AE were mild and moderate according to the ASGE guideline[9] except one fatal AE in a recent paper published by Marx *et al*[15]. Interestingly, the complete radiological resolution rate was high of approximately 90% during a follow-up 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 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 (three 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 AE was

relatively high, 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 didn't receive concomitant chemotherapy. The procedure was successfully completed in all patients with only 2 mild procedure related AE (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 five underwent additional external radiation therapy. All patients had complete technical success and mild pancreatitis occurred in 4 patients, with no major AE[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 the EUS-RFA upfront the chemotherapy, while 17 patients had EUS-RFA after treatment (folfirinox in 6 patients, gemcitabine/oxaliplatinum 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 and 12 mo, respectively, with complete technical success of EUS-RFA, and only 1 AE of bleeding from duodenal ulcer[19]. Moreover, a recent prospective randomized study by Bang *et al*[20] had 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 AE 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 AE (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-FNA 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 PANCREATIC CYSTIC TUMORS

In the last few years, EUS-FNA was also implemented in the treatment of PCL in a few human case series. The first case was reported by Wiersema *et al*[36] in a patient with bleeding remnant intraductal papillary mucinous neoplasm (IPMN) that was successfully treated with endoscopic intraductal RFA. Pai *et al*[23] prospectively reported 6 patients with PCL [4 mucinous cystic neoplasm (MCN), 1 IPMN, and 1 serous cystadenoma (SCA)]. Two (33.3%) and 4 (66.7%) patients had complete and partial cyst

resolution at 3-6 mo follow-up respectively. Among the 4 patients with partial resolution, two 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 AE. 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 IPMN and 1 patient with MCN), notably 12 patients (70.6%) and 4 patients (23.5%) had mural nodules and thick cystic wall 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 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*[35] 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 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%)[35]. Pooling the data, overall, 4 studies have assessed EUS-RFA for PCL, with 38 patients included who underwent 44 EUS-RFA sessions. The mean cyst size was 32.1 mm, worrisome features

was only reported in 1 study. The procedure was feasible in all patients, with mild AE of transient abdominal pain in most studies. Notably, complete radiological cyst resolution was achieved in 14 patients (36.8%), at 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 AE according to ASGE guidelines[9], were 10.1%, 4.2% and 0.5%, respectively. For pNENs, the rate of mild and moderate AE 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 AE and mortality were extremely low in all pancreatic tumors categories (Table 4). Finally, the EUS-RFA treatment is technically feasible, with high clinical and radiological success rate 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 several studies, 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), should 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 lesion that are amenable to EUS-RFA. Predictably, 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 sessions[6]. In fact, a lot of lesions had more than one needle application during the same session even in lesions < 2 cm.

Heterogenicity 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], two 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 is 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 EUS-RFA procedure in intention-to-treat.

AEs rate

Most of the AE that were reported in the literature were intra and peri-procedural AE, mainly reported from retrospective and small series with scarce data on long term AE (follow-up of only one month for some trials). Moreover, there was one death in a very old patient who refused endoscopic intervention that might biased the severity of AE as well. Therefore, larger studies are needed with longer follow-up to better define the AE 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 antibioprophylaxix and sucked the major cystic liquid component in their subsequent patients. Antibioprophylaxis in PCL that underwent EUS-guide fine needle aspiration has been long time a debated clinical indication, as there were conflicting results regarding this condition[36-39], and 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, 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 is totally destroyed, as some patients with insulinoma will have normal insulin levels[41,42]. Among the 9 studies that included patients with insulinoma, only 3 studies had almost similar clinical and radiological follow-up period 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 follow-up period.

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 didn't specify which imaging tool was used. Notably, only 3 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 is 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 NF NET. 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.

Patients' number and study designs

The small number of patients reported and the study designs which mostly are 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*[35] reported a study on 13 patients with SCA, however, the interest in this indication seems onable due to its very rare malignant potential[48]. Excluding SCA only 25 patients with PCL were treated by EUS-RFA. A too small number 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 didn't report the additional survival benefit of EUS-RFA when added to standard therapeutic chemotherapeutic regimen. Moreover, some studies included patients with metastatic disease, which is difficult to justify this treatment in

metastatic disease. Prospective randomized trials with uniform disease stage and standard chemotherapeutic regimen are necessary to be able to conclude about the efficacy.

CONCLUSION

High and promising expectations are held for EUS-RFA. Taking advantage from the EUS transducer proximity to the pancreatic parenchyma, coupled with its excellent imaging resolution and the capability of avoiding major internal organs, mainly vascular structures, makes this procedure safe. The current evidence of efficacy is weak, as most studies were case report and series that included a small number and heterogenous group 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 on PCL is still to be elucidated. For pancreatic adenocarcinoma, the data are lacking especially on the survival rate. Finally, EUS-RFA for pancreatic tumors are yet 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 something to chemotherapy in locally advanced pancreatic adenocarcinoma.

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