

Efficacy of EUS-RFA in pancreatic tumors: Is it ready for prime time? A systematic review and meta-analysis




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ABSTRACT

Background and study aims Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) can be used in patients with unresectable pancreatic ductal adenocarcinoma (PDAC). We performed a systematic review and meta-analysis to evaluate the efficacy of EUS-RFA in treatment of locally advanced unresectable PDAC and other pancreatic tumors.

Patients and methods A comprehensive search was done of multiple electronic databases and conference proceedings including PubMed, EMBASE, Web of Science databases, Google Scholar and manual search of references (from inception through May 2019) to identify the studies reporting use of EUS-RFA for pancreatic lesions. The primary outcome was to evaluate technical and clinical success of the procedure. The secondary outcome was to study overall adverse events (AEs).

Results Thirteen studies reporting 165 EUS-RFA procedures on 134 patients were included. Of 134 patients, 27.94% (38) had unresectable locally advanced PDAC, 40% (53) had PNETs, 3% (4) had metastasis to the pancreas and 30% (41) had other lesions. The pooled technical success rate calculated out of the total number of procedures was 100% (95% CI [99.18–100], I²=0%). The pooled clinical success rate calculated out of the total number of patients was 91.58% (95% CI [82.5–98.08], I²=21.5%). The pooled overall AE rates were 14.67% (95% CI [4.77–27.46], I²=56.19%) out of which abdominal pain was the most common with 9.82% (95% CI [3.34–18.24], I²=23.76%). Low to moderate heterogeneity was noted.

Conclusion EUS-RFA has high technical (100%) and clinical success (91.5%) rates. Further multicenter trials are needed to further validate our findings.

Introduction

Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) works by placing an RFA probe, inserted through an EUS

needle, under EUS color Doppler guidance, into a target pancreatic lesion, delivering various energy outputs directly related to the size of the lesion for a variable amount of time or until an

electrical impedance of >500 Ohms is detected, suggesting that coagulative necrosis has occurred within the lesion [1]. This is confirmed by postoperative imaging with a computed tomography (CT) scan.

Unfortunately, given current National Comprehensive Cancer Network (CCN) guidelines, approximately 80% of patients with pancreatic ductal adenocarcinoma (PDAC) will have disease deemed unresectable at the time of diagnosis. [2] This creates a potential opportunity for EUS-RFA to provide a palliative option in their treatment plan. In cases of unresectable or locally advanced PDAC, EUS-RFA is a developing option with the potential to reduce or downstage the tumor burden. EUS-RFA is potentially a valuable tool for reducing tumor size by inducing coagulative necrosis from direct thermal destruction and/or triggering immunostimulation and antitumor antigens [3,4].

Use of EUS-RFA in the pancreas also extends to treatment and ablation of small pancreatic neuroendocrine tumors (PNETs), pancreatic cystic neoplasms (PCN) which include mucinous pancreatic cystic neoplasms (MCN), and intraductal papillary mucinous neoplasms (IPMN) and other pancreatic tumors measuring <3 cm [1].

To date, several studies have evaluated use of EUS-RFA in the pancreas. The primary end point of this systematic review and meta-analysis is to evaluate technical and clinical success of EUS-RFA in locally advanced PDAC and other pancreatic tumors. Secondary endpoints were to recognize and study both early and late adverse events (AEs), given the thermosensitivity of pancreatic tissue.

Methods

Search strategy

We conducted a comprehensive search of several databases and conference proceedings including PubMed, EMBASE, MEDLINE, Google-Scholar, Cochrane, LILACS, SCOPUS, and Web of Science databases (earliest inception to May 2019). We followed the preferred reporting items for systematic reviews and meta-Analyses (PRISMA) guidelines to identify studies reporting on EUS RFA in pancreatic tumors [5]. An experienced medical librarian, using inputs from the study authors, helped with the literature search.

Key words used in the literature search included a combination of 'EUS, 'Endoscopic, and 'Ultrasound', 'radiofrequency, ablation', 'tumor and pancreatic. The search was restricted to studies in human subjects and published in English language in peer-reviewed journals. Two authors (BD, JC) independently reviewed the titles and abstracts of studies identified in the primary search and excluded studies that did not address the research question, based on prespecified exclusion and inclusion criteria. The full text of remaining articles was reviewed to determine whether they contained relevant information. Any discrepancies in article selection were resolved by consensus, and in discussion between the co-authors.

The bibliographic section of the selected articles, as well as the systematic and narrative articles on the topic were manually searched for additional relevant articles.

Study selection

We included studies that evaluated the efficacy of and AEs associated with EUS-RFA in pancreatic tumors. Studies were included as long as they provided data needed for the analysis. Exclusion criteria were as follows: (1) studies using EUS-RFA in tumors other than pancreas, (2) studies performed in the pediatric population (Age <18 years), and (3) studies not published in the English language.

In cases of multiple publications from the same cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were included.

Data abstraction and quality assessment

Data on study-related outcomes in the individual studies were abstracted onto a standardized form by at least three authors (BD, AD, JC), and two authors (BD, AD) performed the quality scoring independently.

The data collection was performed as number of reported events (n) out of the total number of patients (N) from each study. The collected data was treated akin to single group cohort studies and therefore we used the Newcastle-Ottawa scale for cohort and case-control studies to assess the quality of studies [6]. This quality score consisted of 8 questions, the details of which are provided in ► **Table 1**.

EUS-RFA technique

EUS-RFA is a procedure that requires a unipolar probe deployed under ultrasound guidance to the center of the tumor. A generator is activated to release a certain wattage for a set amount of time that varies and specific to each RFA model. The probe is

► **Table 1** Quality assessment of the study with Newcastle Ottawa Scale.

Author	Year	Newcastle-Ottawa Scale		
		Selection	Comparability	Outcome
Oleinikov [11]	2019	***	*	***
Barthet [1]	2018	***	*	**
Scopelliti [3]	2018	***	*	**
Crino [9]	2018	***	*	***
De la Serna [8]	2018	**	*	*
Choi [7]	2018	***	*	***
Thosani [12]	2018	**	*	**
Goyal [13]	2017	**	*	*
Malikowski [14]	2017	**	*	*
Wang [16]	2016	***	*	*
Song [4]	2016	***	*	*
Lakhtakia [10]	2016	***	*	***
Pai [15]	2015	**	*	**

then rotated, and the process is repeated from one to four times. An internal cooling system is sequentially employed to prevent thermogenic damage to surrounding tissue. Post-operative computed tomography (CT) scans were performed to compare the change in size of the enhanced tissue of the tumor to a preoperative CT, as well as to assess for any complications [3].

EUS-RFA needles and catheters

Two types of RFA probes were used in our meta-analysis. A STARmed needle of different sizes (18G/19G/22G) was most commonly used to deliver RFA energy [3, 4, 7–12]. This operative needle is associated with a pump cooling the needle with help of chilled saline which prevents charring of the tip and improves accuracy of ablation.

The rest of the studies used the Habib catheter for delivery of RFA energy [13–16]. This is a monopolar electrode without a cooling system which is inserted inside a standard EUS FNA needle and attached to an electrosurgical generator [17]. The different RFA needles/catheters and ablative energy settings used in our study population are listed in ► **Table 2**.

Outcomes assessed

Primary outcome

Technical success and clinical success of EUS-RFA in pancreatic tumors

► **Table 2** EUS-RFA Needle/catheter with RFA energy used in different studies.

Author	Catheter/Needle used	RFA Energy
Oleinikov [11]	STARmed 19G	50W
Barthet [1]	STARmed 18G	50W
Scopelliti [3]	STARmed 18G	lesions > 3 cm – 30W and Lesions < 3 cm-20W
Crino [9]	STARmed 18G	30W
De la Serna [8]	STARmed 18G and 19G	50W
Choi [7]	STARmed 18G and 19G	50W
Thosani [12]	STARmed 19G and 22G	–
Goyal [13]	Habib catheter (1Fr)/22G	10W
Malikowski [14]	Habib catheter	10W
Wang [16]	Habib catheter/22G	10W-15W
Song [4]	STARmed 18G	20W-50W
Lakhtakia [10]	STARmed 19G	50W
Pai [15]	Habib catheter (1Fr)/19 and 22G	5–25W

EUS-RFA, endoscopic ultrasound radiofrequency ablation.

Secondary outcomes

1. Total AEs
2. Analysis of individual AEs

Definitions

Technical success was defined as the successful placement of the needle within the pancreatic lesions with safe margins from the surrounding vital structures to avoid potential thermal injuries and application of radiofrequency ablation based on impedance.

Clinical success was defined as decrease in lesion size and presence of hypodense area (necrosis) on CT scan after the procedure in case of unresectable locally advanced pancreatic adenocarcinoma, metastatic pancreatic lesions, and other benign pancreatic tumors. In case of PNETs, it was defined as improvement in symptoms along with decrease in lesion size and presence of hypodense area on CT scan.

Overall, locally advanced unresectable pancreatic carcinoma was defined in two studies as per 2016 NCCN guidelines: in cases of tumor contact greater than 180° with major arteries such as the celiac trunk (CT), the superior mesenteric artery (SMA) and the first jejunal branch, involvement of the aorta, unreconstructable involvement of vessels such as the hepatic artery (HA), the superior mesenteric vein (SMV), and the portal vein (PV), and contact with the most proximal draining jejunal branch into SMV and SMV or PV occlusion (due to the tumor or bland thrombus).

AEs were divided into early (<7 days) and late (>7 days to 3 months). In the early group, subgroup analysis was then done to calculate the pooled rates of individual AEs.

Statistical analysis

We used meta-analysis techniques to calculate the pooled estimates for each outcome following the methods suggested by DerSimonian and Laird using the random-effects model [18]. When incidence of an outcome was zero in a study, a continuity correction of 0.5 was added to the number of incident cases before the study was entered into the statistical model [19]. We assessed heterogeneity between study-specific estimates by using Cochran Q statistical test for heterogeneity, and the I² statistics. [20,21] In this, values <30%, 30% to 60%, 61% to 75%, and >75% were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively [22].

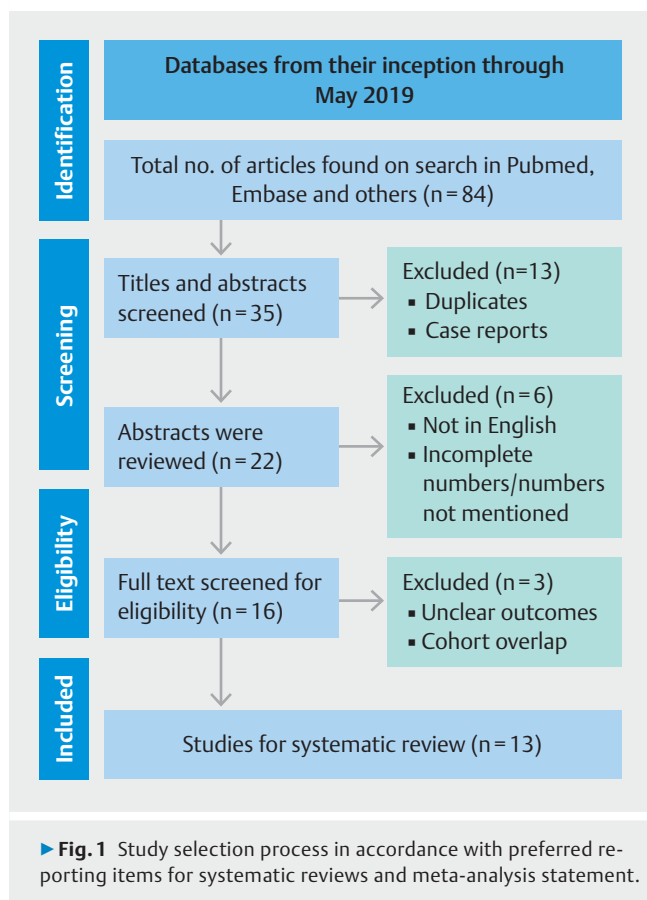
All analyses were performed using Comprehensive Meta-Analysis (CMA) software, version 3 (BioStat, Englewood, New Jersey, United States).

Results

Search results and population characteristics

From an initial pool of 84 studies, 13 studies reported use of EUS-RFA in pancreatic lesions [1, 3, 4, 7–16]. The schematic diagram of study selection as per PRISMA guidelines is illustrated in ► **Fig. 1**.

Mean age was 61.42 (range 45–69) years with a predominantly male population. The “mean” median lesion was 27.21 mm (range 9–49.2). Mean follow-up post-procedure



was 6.5 months (range 1–12). Four studies used Habib catheters and nine studies used STARmed needles. Patient demographics are described in ► **Table 3**.

Characteristics and quality of included studies

Twelve studies were prospective and one study was retrospective. Three studies were multicenter and the rest were single center. No studies were population based. All studies reported adequately on the technical success, adverse events, assessment, and factors were comparable between the study groups. Ten of 13 studies reported on location of pancreatic tumor and clinical success. Overall, five studies were considered of high quality, six were of medium quality and two were low-quality studies. A detailed assessment of study quality is given in ► **Table 1**.

Meta-analysis outcomes

A total of 134 patients were included in the analysis and 165 EUS-RFA procedures were performed on these patients. Of 134 patients, 27.94% (38) had unresectable locally advanced PDAC, 40% (53) had PNETs, 3% (4) had metastasis to the pancreas and 30% (41) had other lesions which included IPMNs, mucinous cysts, solid pseudopapillary neoplasm, and microcystic adenomas. The most common lesion location was the head (51.6%) followed by the body of the pancreas (39.5%).

The primary outcomes of the study were technical and clinical success of EUS-RFA. The pooled technical success rate cal-

culated out of the total number of procedures was 100% (95% CI [99.18–100], $I^2=0\%$). The pooled clinical success rate calculated out of the total number of patients was 91.58% (95% CI [82.5–98.08], $I^2=21.5\%$) (► **Fig. 2**, ► **Fig. 3**).

The secondary outcome was to assess AEs associated with EUS-RFA. The pooled overall AEs were 14.67% (95% CI [4.77–27.46], $I^2=56.19\%$) (► **Fig. 4**). In individual AE analysis, abdominal pain was the most common side effect 9.82% (95% CI [3.34–18.24], $I^2=23.76\%$). No bleeding was noted, and post-procedure pancreatitis was noted in two patients. Perforation and procedure-related infections were noted in one patient each (► **Table 4**).

Delayed AEs (>7 days) were reported in two studies including three patients [1, 11]. In the Oleinokov study, two patients developed mild pancreatitis between 7 and 10 days post-procedure, which resolved on the second or third day of the hospitalization. In the Barthet study, one patient developed stenosis of the main pancreatic duct 1 week after the procedure and underwent pancreatic duct stenting.

Validation of meta-analysis results

Sensitivity analysis

To assess whether any one study had a dominant effect on the meta-analysis, we excluded one study at a time and analyzed its effect on the main summary estimate. On this analysis, no single study significantly affected the outcome or the heterogeneity.

Heterogeneity

We assessed dispersion of the calculated rates using I^2 percentage values. The I^2 tells us what proportion of the dispersion is true versus chance [19]. The pooled rates of technical success and clinical success showed low heterogeneity and pooled overall early AE rates showed moderate heterogeneity.

Publication bias

Publication bias was difficult to estimate properly as we were evaluating one-arm studies with dichotomous outcomes and most of the studies were fairly small.

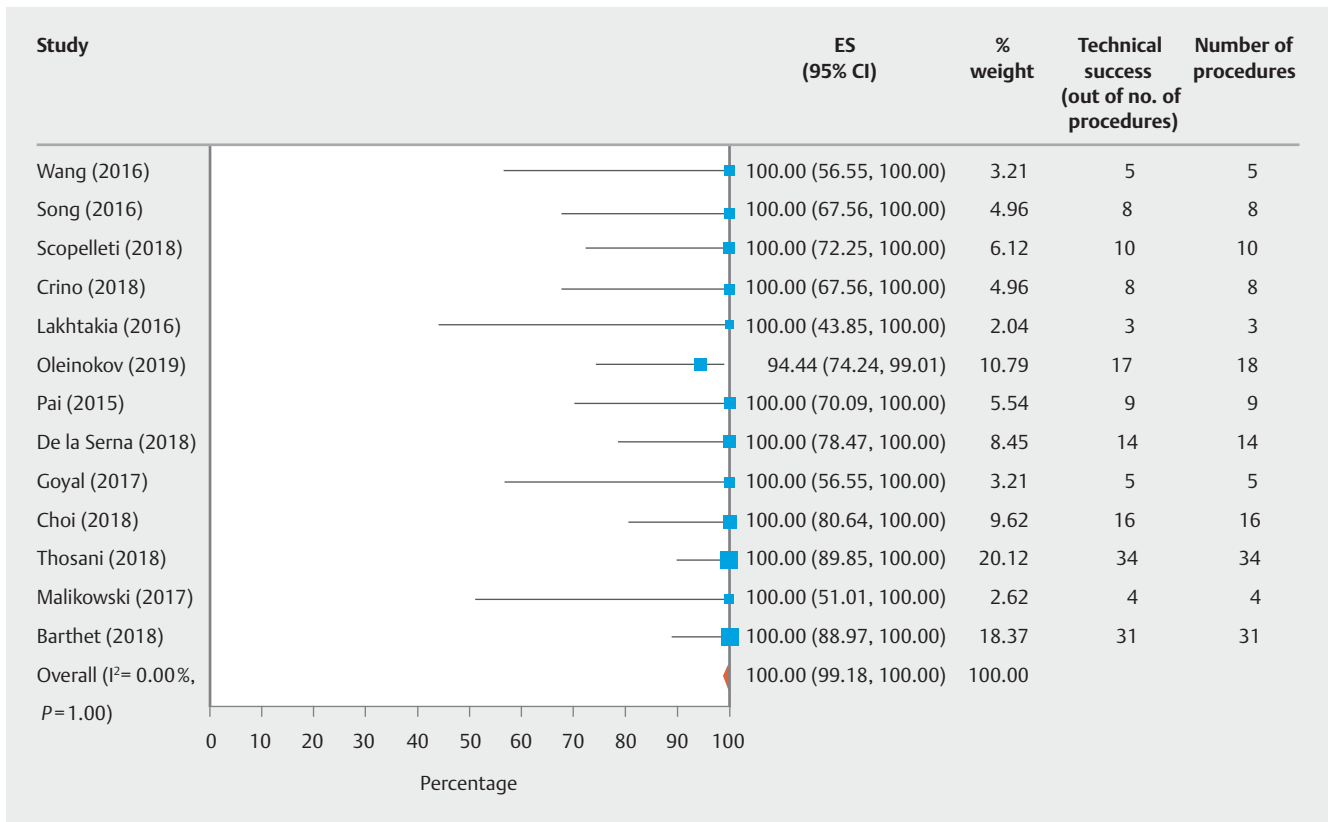
Discussion

The primary measured outcomes of the studies included in this meta-analysis were the technical and clinical success of EUS-RFA in treating pancreatic lesions, both malignant and potentially malignant. The pooled technical success rate was 100% (95% CI [99.18–100], $I^2=0\%$) for all types of pancreatic lesions. In the 13 studies we examined, 12 studies reached 100% technical success, including Barthet et al who examined the highest number of lesions at 31. The remaining one study had technical success of 94%. Scopelliti et al, who had a 100% technical success rate, pointed out logistical and anatomical limitations such as scarring from previous radiation or inability to maneuver the stiff probe to the target site [3].

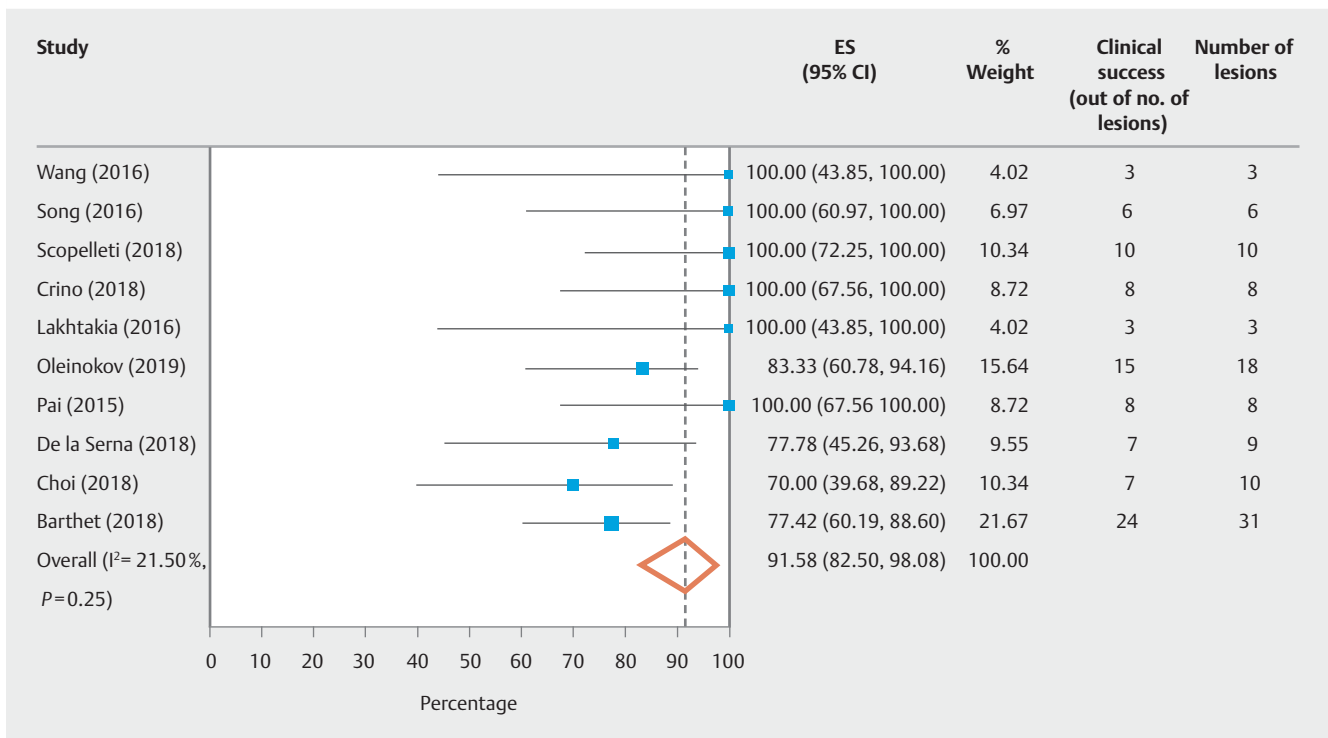
The pooled clinical success rate was 91.58% (95% CI [82.5–98.08], $I^2=21.5\%$). Given the wide range of pancreatic lesions being treated, the success rate was defined as decrease in tu-

► **Table 3** Description of 13 studies used in the final analysis.

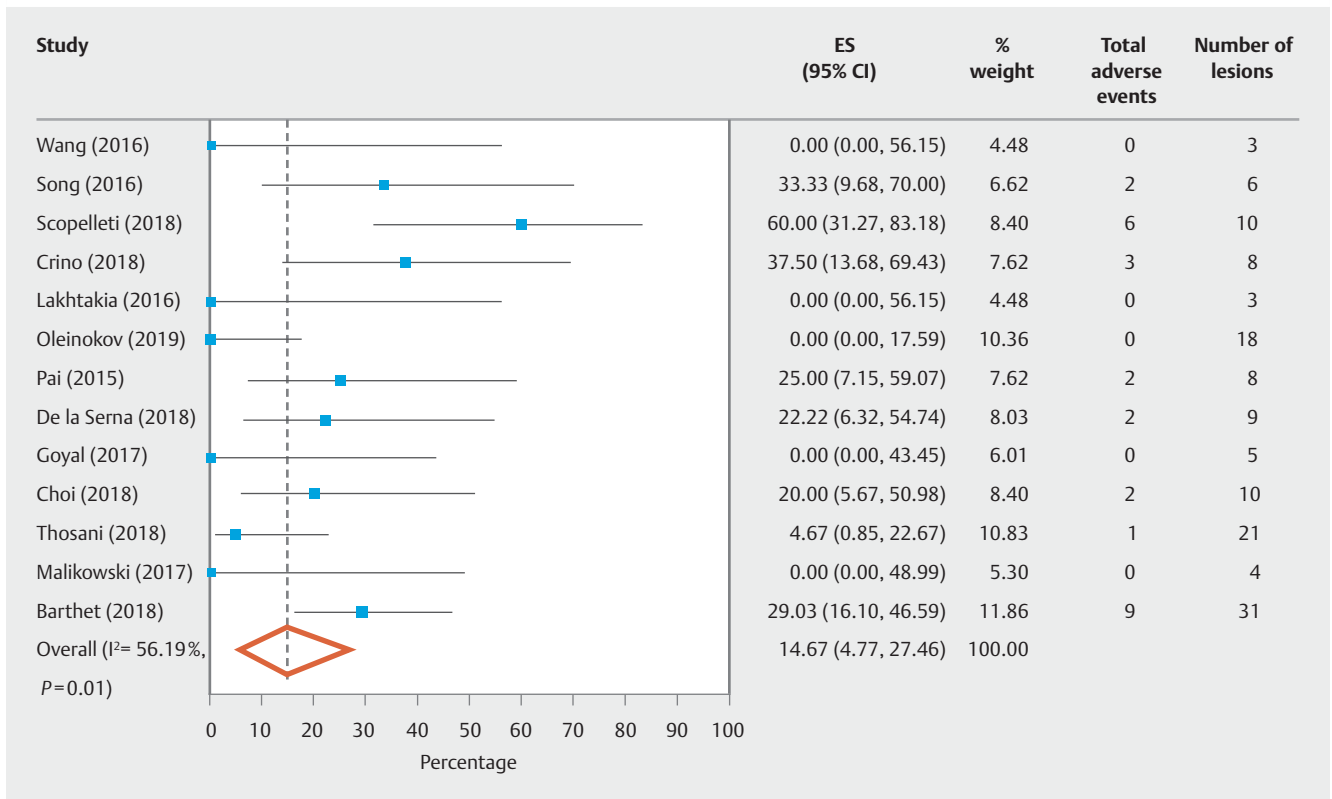
Author	Study year	Study type	No. of patients	Mean age	Males	Females	No. of procedures	Indication			Technical success		Clinical success
								Advanced pancreatic cancer	Neuro-endocrine	Metastatic to pancreas	Other		
Oleinikov [11]	2019	prospective	18	60.4	10	8	18	0	18	0	0	17	15
Barthel [1]	2018	prospective	29	62.4	14	15	31	0	14	0	17	31	24
Scopelliti [3]	2018	prospective	10	62	7	3	10	10	0	0	0	10	10
Crino [9]	2018	prospective	8	67	8	0	8	7	0	1	0	8	8
De la Serna [8]	2018	prospective	9	69	9	0	14	0	3	0	6	14	7
Choi [7]	2018	prospective	10	51.4	4	6	16	0	8	0	2	16	7
Thosani [12]	2018	retrospective	21	62	13	8	34	10	3	0	8	34	-
Goyal [13]	2017	prospective	5	63.6	4	1	5	2	1	0	2	5	-
Malikowski [14]	2017	prospective	4	66	-	-	4	0	1	3	0	4	-
Wang [16]	2016	prospective	3	62.7	-	-	5	3	0	0	0	5	3
Song [4]	2016	prospective	6	62	1	5	8	6	0	0	0	8	6
Lakhtakia [10]	2016	prospective	3	45	3	0	3	0	3	0	0	3	3
Pai [15]	2015	prospective	8	65	1	7	9	0	2	0	6	9	8



► Fig. 2 Overall pooled technical success rate of EUS-RFA in pancreatic tumors.



► Fig. 3 Overall pooled clinical success rate of EUS-RFA in pancreatic tumors.



► Fig. 4 Overall pooled total early adverse events.

► Table 4 Early and delayed adverse events in EUS-RFA.

Author	Total early adverse events	Pancreatitis	Bleeding	Perforation	Infection	Abdominal pain	Others	Late adverse events
Oleinikov [11]	0	0	0	0	0	0	0	2
Barthet [1]	9	1	0	1	1	6	0	1
Scopelleti [3]	6	0	0	0	0	2	4	0
Crino [9]	3	0	0	0	0	3	0	0
De la Serna [8]	2	0	0	0	0	2	0	0
Choi [7]	2	1	0	0	0	1	0	0
Thosani [12]	1	0	0	0	0	1	0	0
Goyal [13]	0	0	0	0	0	0	0	0
Malikowski [14]	0	0	0	0	0	0	0	0
Wang [16]	0	0	0	0	0	0	0	0
Song [4]	2	0	0	0	0	2	0	0
Lakhtakia [10]	0	0	0	0	0	0	0	0
Pai [15]	2	0	0	0	0	2	0	-

mor size, necrosis of tumor as evidenced by hypo-enhanced areas noted on post-intervention CTs, and/or decrease in symptoms caused by functioning pancreatic tumors. Ten of 13 studies noted the clinical success rate [1, 3–11, 15, 16]. Of these, six studies showed 100% pooled clinical success rates with the remaining four reporting clinical success rates ranging from 70% to 83%. Many noted a sustained linear regression of the tumor with time when comparing CTs from 7 days post-procedure to CTs at 30 days post-procedure [1, 3, 10, 11].

No significant correlation was found between ablation time, radiofrequency strength, and sustained reduction in tumor burden. For example, Crino et al used 30W to produce a 30% reduction in locally advanced PDAC, while Choi et al employed 20 to 50W to see a 58.9% reduction in tumor size [7, 9]. Multiple sessions of EUS-RFA were employed in all studies.

EUS-RFA can be used successfully to treat PNETs regulated to surveillance, or to ablate lesions in patients who refuse surveillance or decline surgery due to its invasiveness; individuals who are not surgical candidates because of comorbidities; and young patients with PNETs associated with MEN-1 in whom pancreas-sparing options are preferable [23]. In non-functional PNETs, Berthet et al noted 86% had diminished by at least 50% in size or completely by 12 months following ablation [1]. Functional PNETs exhibited a sustained attenuation of clinical symptoms such as hypoglycemia or diarrhea, rapid normalization of secreted hormone levels, and sustained significant decrease in size of the neoplasm. PNETs had a pooled clinical success rate ranging from 83% to 100% [10–13].

The secondary endpoint of this meta-analysis was to analyze AEs associated with EUS-RFA. The overall pooled incidence of AEs was 14.67% (95% CI [4.77–27.46], $I^2=56.19\%$). AEs were divided into early (<7 days) and late (>7 days). The most common early AE was self-resolving abdominal pain (9.82% (95% CI [3.34–18.24], $I^2=23.76\%$)). There was one report of self-resolving pancreatitis. In that instance, Choi et al. recommended a 5-mm margin from the pancreatic duct to avoid pancreatitis. Delayed AEs were reported in two studies [1, 3]. In all patients, no correlation was found between AEs and ablation time or energy settings.

Limitations of our meta-analysis include the fact that 10 of 13 studies were single-center studies with 10 or fewer patients [3, 4, 7, 9, 10, 13–16]. Our meta-analysis also showed moderate to substantial heterogeneity. The studies pertaining to pancreatic neuroendocrine tumors all had short follow-up periods under 1 year [7, 8, 10, 11, 14].

Conclusion

Overall, EUS-RFA has exhibited both high technical and clinical success with minimal AEs in addressing locally advanced unresectable PDAC and other pre-malignant pancreatic lesions where curative surgery is not an option. In the future, EUS-RFA may become a more widely used approach to treatment of a myriad of pancreatic lesions. Further long-term multicenter prospective studies are needed to correlate our findings.

Competing interests

The authors declare that they have no conflict of interest.

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