

# SYSTEMATIC REVIEWS AND META-ANALYSIS

## Short-Term Outcomes of Endoscopic Ultrasound-Guided Pancreatic Cyst Ablation: A Systematic Review and Meta-Analysis



Ahmed Al Qady,<sup>1,2</sup> Kapil Dev Nayar,<sup>3</sup> Fatima Elmustafa,<sup>4</sup> Mohamed Salih,<sup>5</sup> Joseph Emran,<sup>2</sup> Amir Beirat,<sup>2</sup> Sasmith Menakuru,<sup>2</sup> Dana Harris,<sup>6</sup> Dan J. Echols,<sup>6</sup> Baoan Ji,<sup>7</sup> John M. DeWitt,<sup>8</sup> Zhen Wang,<sup>9</sup> Fernando F. Stancampiano,<sup>6</sup> and Yan Bi<sup>3</sup>

<sup>1</sup>Division of Gastroenterology, Hepatology and Nutrition, University of Florida, Gainesville, Florida; <sup>2</sup>Department of Medicine, Indiana University School of Medicine, Muncie, Indiana; <sup>3</sup>Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, Florida; <sup>4</sup>Department of Medicine, Ascension Macomb-Oakland Hospital, Warren, Michigan; <sup>5</sup>Department of Internal Medicine, Cairo University Faculty of Medicine, Cairo, Egypt; <sup>6</sup>Department of Medicine, Mayo Clinic, Jacksonville, Florida; <sup>7</sup>Department of Cancer Biology, Mayo Clinic, Jacksonville, Florida; <sup>8</sup>Department of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, Indiana; <sup>9</sup>Department of Health Care Delivery Research, Mayo Clinic, Rochester, Minnesota

**BACKGROUND AND AIMS:** Pancreatic cysts (PCs) are increasingly detected through abdominal imaging, prompting exploration of alternatives such as endoscopic ultrasound-guided PC ablation due to the risks and costs associated with surgery. This study conducts a systematic review and meta-analysis of endoscopic ultrasound-guided PC ablation's short-term efficacy and complications for PC management. **METHODS:** A systematic review and meta-analysis were carried out on PubMed, Ovid, Cochrane, and TRIP electronic databases. The primary outcome was cyst resolution (partial and complete) and persistence on imaging 12 months after ablation. The secondary outcome was procedure-related adverse events. **RESULTS:** Eight studies were eligible for analysis. Complete cyst resolution on imaging 12 months after endoscopic ultrasound ablation was 50% [95% CI 36–63, I<sup>2</sup> = 85.31%]. Partial cyst resolution was 27% [95% CI 15–41, I<sup>2</sup> = 87.07%], and cyst persistence was 17% [95% CI 11–24, I<sup>2</sup> = 62.11%]. The rate of complete resolution varied depending on the treatment agent (for ethanol 29% [95% CI 10–53]; laur-omacrogol 51% [95% CI 36–67]; ethanol and paclitaxel 63% [95% CI 48–76]; paclitaxel and gemcitabine 67% [95% CI 45–83]; and ethanol, paclitaxel, and gemcitabine 61% [95% CI 39–80]). Postprocedure adverse events included abdominal pain in 4% [95% CI 0–11], pancreatitis in 3% [95% CI 1–5], and fever in 1% [95% CI 0–3] of all patients. **CONCLUSION:** The treatment of pancreatic cysts with endoscopic ultrasound ablation results in acceptable levels of complete resolution, and low incidence of severe adverse events. The effectiveness of this treatment is further enhanced when chemoablative agents are employed.

**Keywords:** Pancreatic Cysts; Endoscopic Ultrasound; Cyst Ablation

techniques. This increase has led to a greater identification of incidental findings related to PCs. The incidence of PCs reported on computed tomography is 9% and 27% on magnetic resonance imaging.<sup>1,2</sup> In the United States, the prevalence of PCs in the elderly is estimated at 2.5%–6.6% and increases to 10% in persons over 70 years of age.<sup>1,3,4</sup> PCs reflect a diverse array of histopathology ranging from benign to malignant. Intraductal papillary mucinous neoplasms, the most common PCs, have the potential for malignant transformation. Although many guidelines have been developed, the optimal management of intraductal papillary mucinous neoplasms remains unclear. Current management for PCs is based on the potential of malignancy and symptomology. Surgery is the primary approach for managing symptomatic and high-risk pancreatic cysts; however, it carries perioperative risks of morbidity (such as infections, pancreatic leaks, and fistulae) and rare mortality.<sup>5–7</sup> Furthermore, surgical resection may cause long-term development of diabetes and exocrine insufficiency.<sup>4</sup> Most patients with PCs will undergo long-term surveillance until they are unfit for surgical management or the PCs develop high risk features but this approach is very expensive with an estimated annual cost of \$9 billion for life-long PC surveillance in patients ages 40 and 79 years.<sup>8</sup> Efficient and cost-effective management of pancreatic cysts is urgently needed.

**Abbreviations used in this paper:** EUS, endoscopic ultrasound; PC, pancreatic cyst; PCA, pancreatic cyst ablation.

Most current article

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### Introduction

In recent years, the prevalence of pancreatic cysts (PCs) has risen significantly, primarily attributed to the widespread use of cross-sectional abdominal imaging

Endoscopic ultrasound-guided pancreatic cyst ablation (EUS-PCA) has emerged as a possible alternative for cyst management. It offers several advantages including less postoperative pain and complications compared to surgery.<sup>9</sup> Currently, there are diverse technical variations in reagents for EUS-PCA, including alcohol, chemotherapeutic agents, or both. However, there is a paucity of research evaluating the effectiveness and safety profile of PCA. Despite the existence of published studies, there is no consensus on the role of EUS ablation in the management of PCs, due to the lack of a comprehensive assessment of its efficacy and safety. In 2019, an international position statement was published concerning EUS-PCA, which albeit based on weak evidence, supported the use of ethanol ablation for unilocular or oligolocular mucinous or enlarging PCLs in patients who opt to avoid surgery and in poor surgical candidates with reasonable life expectancy.<sup>10</sup>

We conducted a systematic review and meta-analysis of PCs management with EUS-PCA to evaluate the short-term treatment efficacy and complications, and identify different techniques utilized for PCA.

## Methods

This meta-analysis was reported following the recommendation of Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.<sup>11,12</sup> Two investigators (AS, JE) independently extracted the data, with any disagreements settled through discussion. Inclusion and exclusion criteria and analysis methods were discussed and agreed upon to ensure consistency, reduce bias, and enhance the validity and reliability of the meta-analysis findings.

### Inclusion and Exclusion

Inclusion criteria included prospective studies that met the following criteria: 1) Participants: patients >18 years of age with pancreatic cysts, 2) Intervention: EUS-guided cyst ablation comparing control and ablation reagents, and 3) Outcome: Primary outcome was cyst resolution (partial and complete) and persistence on imaging at 12 months after ablation. It is noteworthy that outcome definitions varied among the included studies. While most defined complete cyst resolution as <5% final volume in comparison to the original, partial cyst resolution as 5%–25% final volume, and cyst persistence as >25% final volume,<sup>13–17</sup> 3 studies differed: 1 defined complete cyst resolution as no visible PCs, partial cyst resolution as  $\leq 25\%$  final volume, and cyst persistence as >25% final volume<sup>18</sup>; another set complete cyst resolution as no visible PCs, partial cyst resolution as  $\leq 30\%$  final volume, and cyst persistence as >30% final volume.<sup>19</sup> The remaining study did not specify these criteria.<sup>20</sup> The secondary outcome was procedure-related adverse events, including fever, infections, acute pancreatitis, abdominal pain, and injury to adjacent structures. Exclusion criteria were retrospective observational studies, those that

included malignant or neuroendocrine cysts, and those that followed the patients for less than 12 months. There were no language, publication type, or comparison group restrictions.

### Literature Search

We systematically searched PubMed (3248), Ovid (2964), Cochrane (10), and Trip (52) electronic databases using the terms “Endoscopic,” “Endoscopy,” “Endoscopic Ultrasound,” “EUS,” “Ablation,” and “Pancreatic cysts.” The numbers reference the quantity of articles from each initial search. A manual search of relevant article’s references was also performed. The most recent search was conducted on November 11, 2022. The detailed search process is outlined in Figure 1. Titles and abstracts were screened by 2 authors independently (A.S and J.E). Any disagreement was resolved through consensus or, if required, by a discussion with a third author (A.B).

### Data Extraction

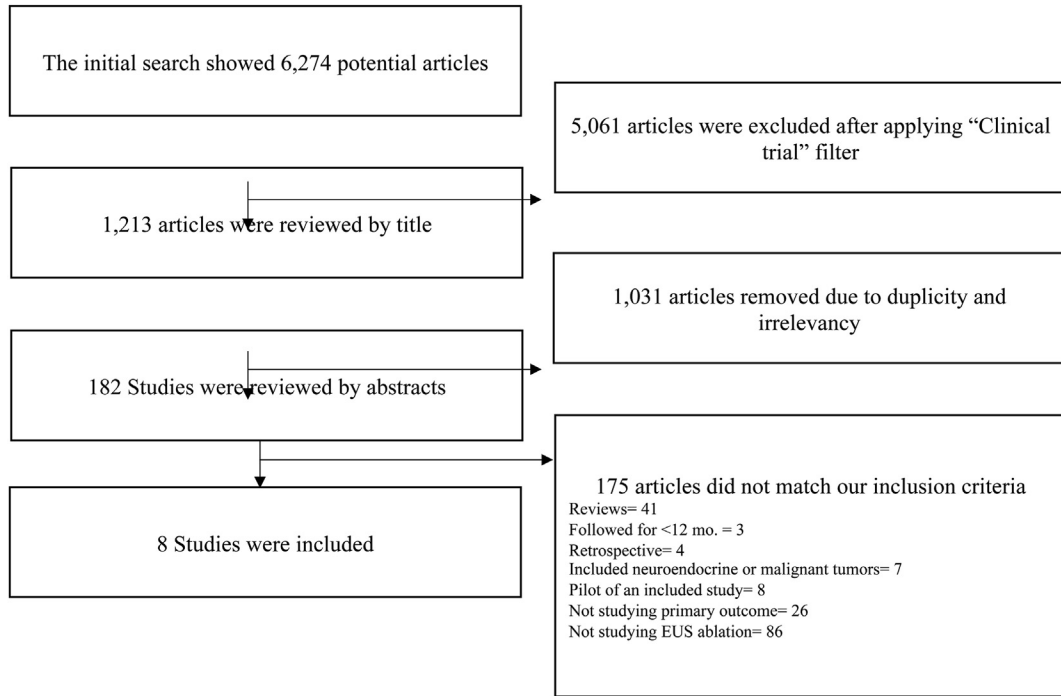
Two authors (A.S and J.E) assessed each article independently to determine eligibility based on the inclusion criteria. Any differences were resolved by mutual agreement. The following information was extracted from each included study: the first author’s name, year of publication, sample size, gender, cyst type, location and size, type of ablation, resolution, and procedure-related adverse events.

### Quality Assessment

Several criteria are widely used to assess quality in clinical trials with treatment and control cohorts.<sup>21–23</sup> We used the modified Downs and Black (D&B) checklist, which was designed to assess clinical trials with and without a control arm.<sup>24</sup> The quality assessment and risk of bias included 4 sections: reporting, external validity, internal validity (bias), and internal validity (confounding). We applied 1 modification to the D&B tool by excluding question 27 (Power calculation). Figure 2 presents how much each study scored in each category.

### Statistical Analysis

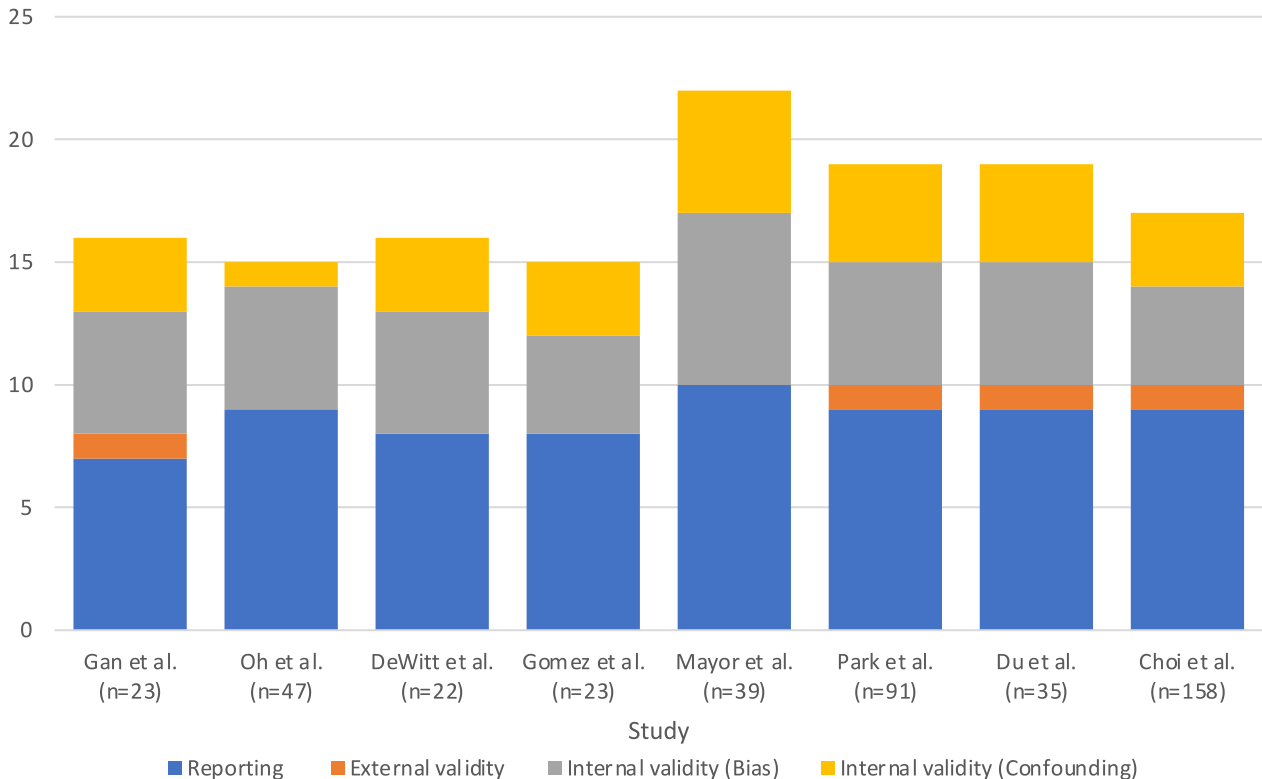
All statistical analyses were performed using Stata/SE v.17 (College Station, Texas, USA). The Metaprop command, invented by Nyaga et al.,<sup>25</sup> was used. First, the Freeman-Tukey double arcsine transformation method was used on the proportions of outcomes before pooling to stabilize the variance. The pooled estimates were then computed using the DerSimonian-Laird random-effects method based on the transformed values. Results are presented as pooled proportions with 95% CI. A subgroup analysis was conducted using Stata/SE to explore potential differences in the effect of cyst size and ablative agent on the complete resolution among different subgroups of studies. The subgroup analysis accounted for the correlation between effect estimates



**Figure 1.** Search process detailed based on PRISMA’s 2020 recommendations. PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis.

within each subgroup and estimated the between-study variance using the DerSimonian-Laird random-effects method.

Heterogeneity was assessed using I-squared statistics. We were unable to statistically evaluate publication bias due to the small number of studies included.<sup>26</sup>



**Figure 2.** Quality assessment and risk of bias using the modified D&B checklist.

## Results

The initial search identified 6274 reference studies, from which 182 articles were selected and reviewed. Eight studies<sup>13-20,27</sup> met our inclusion criteria (Figure 1). All the included studies were published as full-text articles. The characteristics of each individual study are shown in (Table).

The modified D&B checklist was utilized to assess the risk of bias in the included studies. The total scores of the studies ranged from 15 to 22, with a median score of 16 out of 26. The reporting domain was adequately addressed, with a median score of 8 out of 10. However, the domains of bias and confounding displayed certain weaknesses, with median scores of 5 out of 7 and 3 out of 6, respectively. It is worth noting that the studies often lacked or insufficiently addressed external validity, with a median score of 0 (Figure 2).

The total number of patients included in this meta-analysis is 438, with a predominantly female population of 68.9% (282). The clinical diagnosis included mucinous cysts in 42.1% (n = 170), serous cystadenomas in 9.4% (n = 38), and 46.8% (n = 189) were classified as indeterminate. The mean diameter of the cysts was 27.46 ± 4.89. A total of 145 cysts were located in the head of the pancreas, 175 in the body, and 94 in the tail. Ablation was performed with ethanol alone in 31.2% (n = 137); laur-omacrogol alone in 7.9% (n = 35); paclitaxel and alcohol in 51.8% (n = 227); paclitaxel and gemcitabine in 4.7% (n = 21); and paclitaxel, gemcitabine, and alcohol in 4.1% (n = 18).

The individual study proportions and the pooled estimate are shown in (Figure 3). The pooled proportion for complete cyst resolution on imaging after 12 months of EUS ablation was 50% [95% CI 36-63, I<sup>2</sup> = 85.31%]. Partial cyst resolution was 27% [95% CI 15-41, I<sup>2</sup> = 87.07%], and cyst persistence was 17% [95% CI 11-24, I<sup>2</sup> = 62.11%].

Three subgroups based on the mean cyst diameter were evaluated for resolution (Figure 4). For cysts <2 cm, between 2-3 cm and >3 cm, the proportion of complete resolution was 35% [95% CI 19-55], 44% [95% CI 17-72], and 60% [95% CI 42-77], respectively. Five subgroups based on the ablating agent were evaluated for resolution. The pooled proportion for complete resolution for ethanol alone was 29% [95% CI 10-53]; for laur-omacrogol alone was 51% [95% CI 36-67]; for ethanol and paclitaxel was 63% [95% CI 48-76]; for paclitaxel and gemcitabine was 67% [95% CI 45-83]; and for Ethanol, Paclitaxel, and Gemcitabine was 61% [95% CI 39-80] (Figure 5).

Postprocedure adverse events included abdominal pain in about 4% [95% CI 0-11], pancreatitis in 3% [95% CI 1-5], and fever in 1% [95% CI 0-3]. Additionally, 2 patients experienced pericystic spillage, leading to chemical peritonitis, and 1 patient developed small bowel perforation.

Loss to follow-up was inconsistently reported across studies. Gan et al. and Oh et al. reported 2 and 4 patients lost to follow-up, respectively, while Gómez et al. documented 5

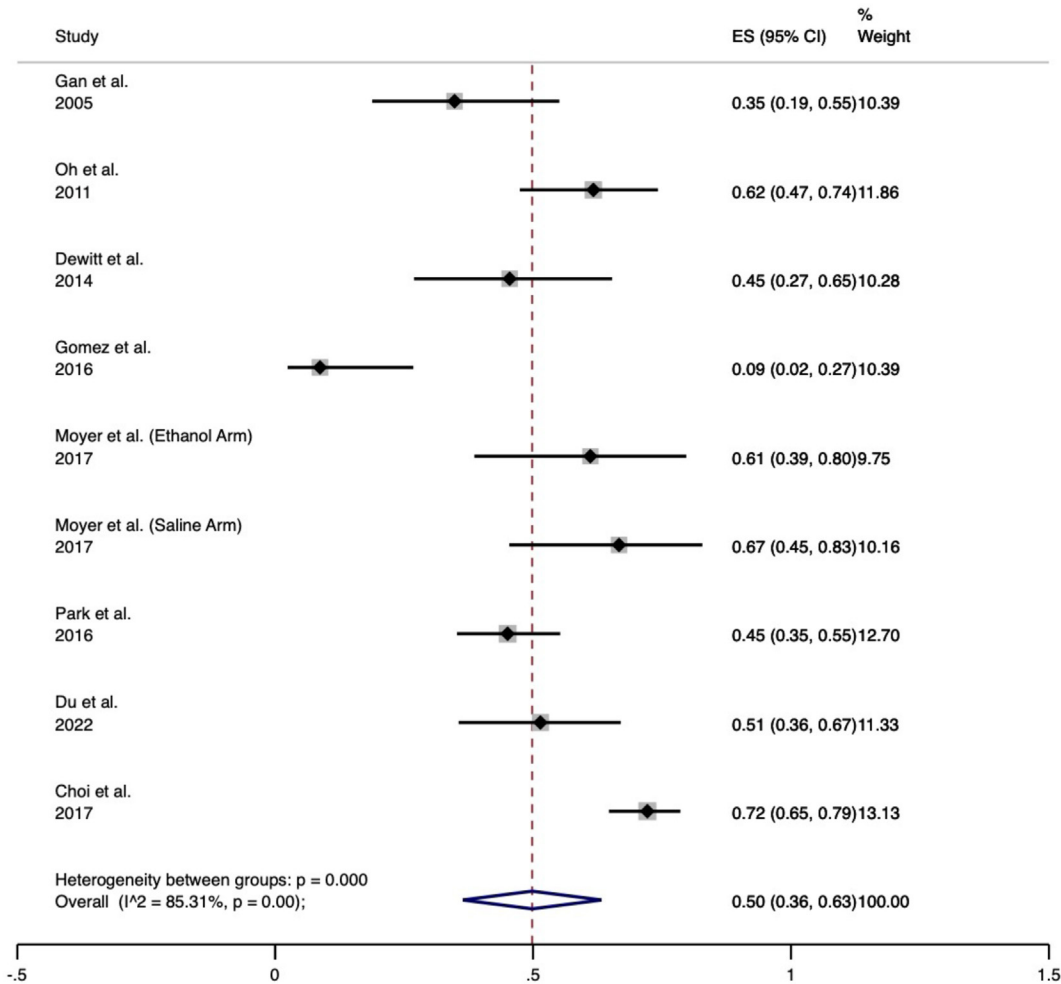
Table. Outcomes of EUS-Guided Pancreatic Cyst Ablation

Study	Year of publication	No. of patients	Sex: M/F	Type of cyst				Cyst location				Mean diameter (mm)	Technique
				Mucinous	Serous	Pseudo	Indeterminate	Head	Body	Tail			
Gan et al.	2005	23	5/18	17	3	1	2	8	7	8	18.33	ETOH	
Oh et al.	2011	47/52 <sup>a</sup>	13/34	9	15	2	26	16 <sup>b</sup>	17 <sup>b</sup>	19 <sup>b</sup>	31.8	ETOH + P	
DeWitt et al.	2014	22	7/15	18	4	0	0	10	8	4	25.73	ETOH + P	
Gómez et al.	2016	23	13/10	19	0	0	4	15	6	2	28.66	ETOH	
Moyer et al.	2017	39	16/23	36	0	0	3	19	19	1	25	ETOH + P + G	
Park et al.	2016	91	24/67	0	0	0	91	35	32	24	30.7	Saline + P + G	
Du et al.	2022	35	Na	Na	Na	Na	Na	Na	Na	Na	Na	ETOH	
Choi et al.	2017	158	49/115	71	16	3	63	42	86	36	32	EUS-LA	
Total	-	438	127/282	170	38	6	189	145	175	94	-	ETOH + P	

ETOH, alcohol; G, gemcitabine; EUS-LA, endoscopic ultrasound-laur-omacrogol; P, paclitaxel.

<sup>a</sup>Five patients lost to follow-up; 47 were the total completed follow-up for 12 mo.

<sup>b</sup>This categorization is from the total number of patients included in the trial, not considering the loss of follow-ups.



**Figure 3.** Forest plot of pooled proportions for complete cyst resolution on imaging after 12 Months of EUS.

deaths during follow-up. All other studies did not provide information on follow-up loss.

## Discussion

The management of PCs has been a topic of debate for many years. The management approach depends on many factors but mainly on the type and size of the cyst, as it may reflect its malignancy potential. The use of EUS to ablate these lesions has been an ongoing area of research. Our analysis showed that EUS-PCA is an effective and safe way of managing PCs.

Typical EUS-PCA includes careful assessment of the PCs, including location, size, and presence of high-risk stigmata or worrisome features, followed by cyst fluid aspiration, and injection of chemicals into the cyst.<sup>13</sup> The most used chemical is alcohol due to its ability to cause tissue necrosis from direct coagulation, sclerosis of the tissue in contact, denaturation of proteins, and dehydration of the epithelial cells.<sup>21,28</sup> Adding chemotherapeutic agents, such as paclitaxel and gemcitabine, to ethanol injection has improved cyst resolution.<sup>13,14,16</sup>

Lauromacrogol, a sclerosing agent, is an emerging alternative to alcohol and chemotherapeutic agents.<sup>15</sup>

In the present meta-analysis, we sought to determine the effectiveness of EUS-PCA in managing pancreatic cystic neoplasms. A total of 438 patients with pancreatic cysts were included in the study, with the majority classified as indeterminate ( $n = 189$ ) or mucinous ( $n = 170$ ). The anatomical distribution of cysts revealed a predominance in the pancreatic body, followed by the head and then the tail. The combined analysis of the studies included in our review revealed that EUS-PCA exhibits substantial effectiveness in the treatment of pancreatic cystic neoplasms, leading to cyst resolution in nearly 80% of cases (comprising 50% complete resolution and 27% partial resolution). Moreover, subgroup analysis suggests that EUS ablation permits a higher degree of complete resolution of pancreatic cysts larger than 2 cm, and when using a chemotherapeutic agent. These findings suggest that EUS-PCA represents a promising therapeutic option for patients with pancreatic cystic neoplasms, with potential benefits in reducing the risk of malignant transformation and improving patient outcomes.

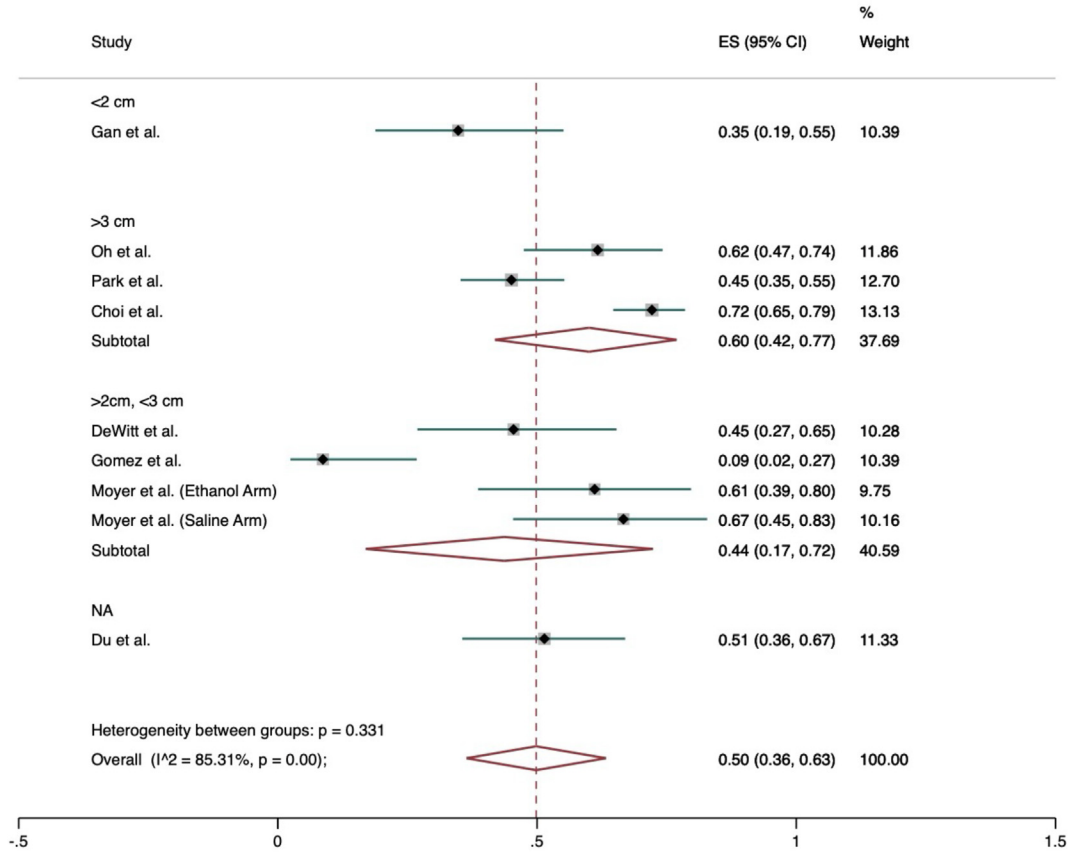


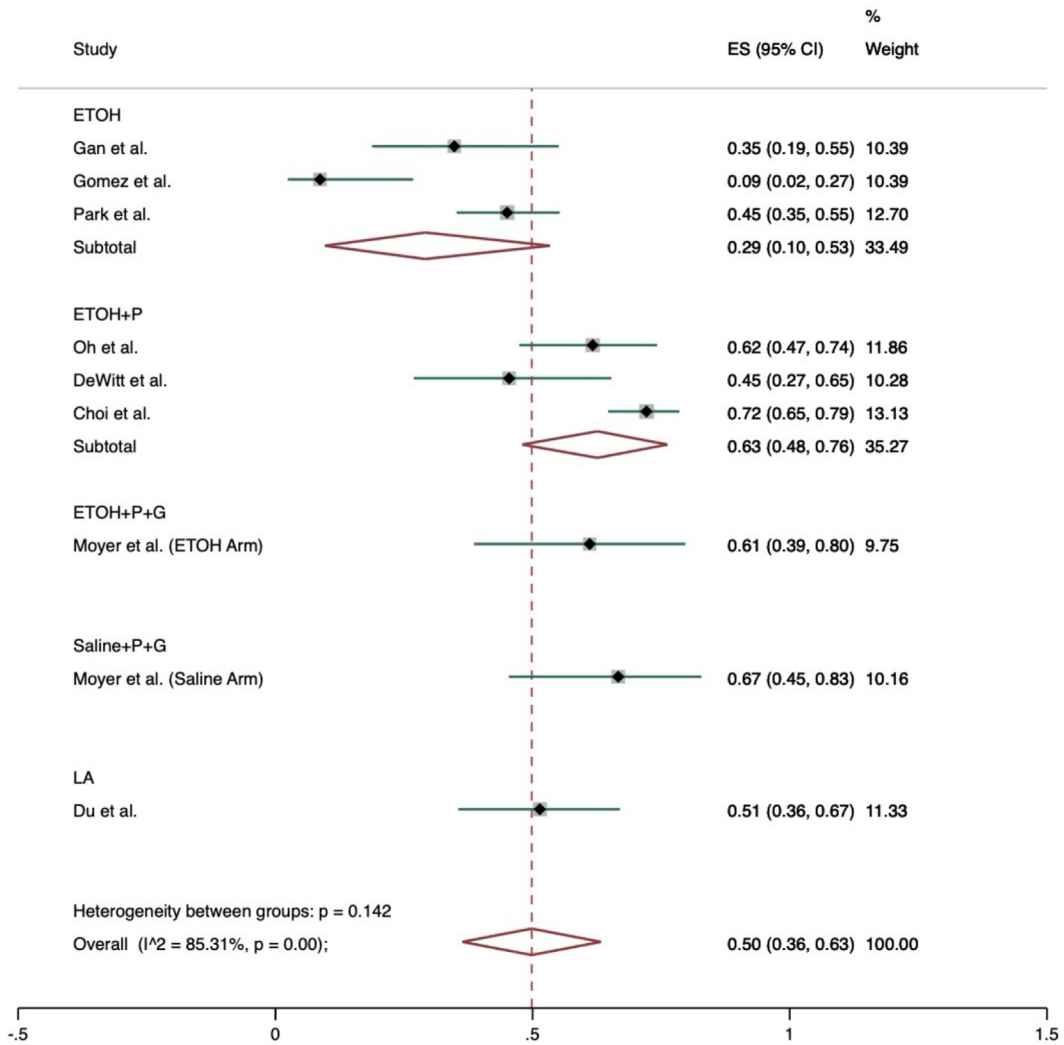
Figure 4. Subgroup analysis of the complete cyst resolution based on the mean diameter of cysts.

Our analysis also provided evidence supporting the safety of EUS-PCA, with only a few major complications observed among the included patients. Acute pancreatitis was reported in 3% of patients, while one patient experienced a small bowel perforation, and 2 patients exhibited pericystic spillage and chemical peritonitis. The occurrence of acute pancreatitis may be attributed to the activation of zymogens as a result of the cytotoxic effects of the chemicals employed during the procedure on the exposed main pancreatic duct.<sup>21,29</sup> The findings are in contrast to pancreatic surgery, which has a morbidity rate higher than 40% and a mortality rate reaching 20%.<sup>9,30</sup>

It is also noteworthy that our findings are consistent with those reported in a recent meta-analysis by Papaefthymiou et al.,<sup>31</sup> reflecting similar outcomes of EUS-PCA, particularly regarding resolution rates. Furthermore, both studies align in their assessment of the incidence of mild complications associated with the procedure. However, Papaefthymiou et al. identified rare adverse events, including pseudocysts, abscesses, portal vein thrombosis, splenic vein obliteration, duodenal stricture, and main pancreatic duct strictures, which were not observed in our review. This alignment in findings underscores the reliability of EUS-PCA as a therapeutic intervention for pancreatic cystic neoplasms, while also highlighting the need for continued vigilance regarding potential adverse events in clinical practice.

EUS-PCA is a valuable alternative for patients who are deemed unsuitable for surgical intervention. Nevertheless, it is imperative to note that EUS ablation is not a suitable treatment for all types of cysts.<sup>10,32,33</sup> In 2019, an international position statement on EUS-guided PC ablation recommended chemoablation for surgically fit patients with an anticipated reasonable life expectancy, confirmed diagnosis of a mucinous pancreatic cyst that is 2 cm and enlarging or at least 3 cm in diameter.<sup>10,33</sup> Nevertheless, the group did not reach a consensus on absolute indications or contraindications for EUS-PCA. Therefore, a patient-centered approach regarding EUS ablation should consider a multidisciplinary discussion of individual circumstances and thoroughly assess the potential risks and benefits of the procedure.

We utilized the modified D&B checklist to assess the risk of bias in the studies included in our analysis. The results indicated variations in the overall quality of the studies, with some demonstrating a higher degree of bias risk than others. While the reporting domain was generally well-addressed, certain aspects, such as bias and confounding, displayed weaknesses. Additionally, an important finding was the frequent lack of attention or insufficient consideration of external validity in the included studies. This aspect warrants particular attention in future research, as it may significantly impact the generalizability of findings in similar studies.



**Figure 5.** Subgroup analysis of the complete cyst resolution based on the ablating agent. ETOH, alcohol; G, gemcitabine; LA, lauromacrogol; P, paclitaxel.

A primary obstacle in the implementation of EUS-PCA is the accessibility and precision in targeting pancreatic cysts. This is especially pronounced when dealing with small or hard-to-reach cysts in the tail or inferior pancreatic head. Furthermore, the use of ethanol as an ablative agent may be difficult due to trouble achieving optimal intracystic ethanol concentration<sup>20</sup> and potentially less efficacious in cysts with thick septations, adjacent masses, and nodules.<sup>18</sup> Newer agents such as lauromacrogol, which is usually used as sclerotherapy for varicose veins, are being explored as a possible ablation agent and have shown promising results with fewer side effects.<sup>25</sup> These limitations underscore the importance of careful patient selection, as well as skilled technical expertise, when utilizing EUS-PCA as a therapeutic option for pancreatic cystic neoplasms.

All studies included in this meta-analysis were prospective where patients were followed for at least 12 months after the procedure. All studies reported positive outcomes except for Gómez et al.<sup>20</sup> They explained that the results could be due to low final ethanol concentrations;

however, final ethanol concentrations close to 80% were achieved in some participants, and no correlation with therapy response was found.<sup>20</sup>

This meta-analysis has several limitations that warrant consideration. Notably, there was significant heterogeneity in the techniques employed across the included studies, potentially introducing inconsistencies in treatment outcomes. Another limitation of our study is the variation in defining primary outcomes across included studies. While most used the same volume percentages, three studies had different criteria, such as the absence of visible cysts. Additionally, not all studies reported complications in a standardized manner, raising concerns about the accuracy of reported incidence rates, particularly due to the lack of an evidence-based adverse events grading system. Moreover, the emphasis on short-term outcomes, particularly due to the limited availability of long-term data, may lead to an overestimation of the treatment’s effectiveness, as negative outcomes from PCs are often seen over the long term. However, one study with a 69-month follow-up period

showed positive effects,<sup>17</sup> These promising results indicate the need for further studies assessing potential long-term benefits. Consequently, these limitations should be acknowledged when interpreting the meta-analytic findings and applying them in clinical practice.

Furthermore, several studies in our review included indeterminate cysts but provided limited detail of worrisome features beyond size. This lack of information leaves uncertainty about the malignancy risk of these cysts, making it unclear whether ablation or surveillance would have been the more appropriate treatment. Ultimately, the overall uncertainty surrounding the effectiveness of EUS-PCA in reducing the risk of malignant transformation is a notable limitation, warranting further investigation.

In light of the identified limitations, further research is required to fully assess the safety and efficacy of EUS-PCA and enhance its adoption for the treatment of pancreatic cysts. Specifically, prospective controlled randomized trials are needed to provide robust and conclusive evidence to support the use of this technique. Moreover, comparative studies evaluating the effectiveness of EUS-PCA against surgical excision of pancreatic cysts could offer valuable insights into the benefits and limitations of each approach. Such studies may elucidate the specific indications and optimal treatment strategies for each modality, facilitating the appropriate selection based on patient and lesion characteristics. Ultimately, these efforts may help to establish EUS-PCA as a widely accepted, safe, and effective therapeutic option for the management of pancreatic cystic lesions.

## Conclusion

Our meta-analysis demonstrated the efficacy of EUS pancreatic cyst ablation as a viable option for managing pancreatic cysts, while highlighting the acceptable level of procedure-related complications associated with this approach. Nonetheless, a tailored approach should be adopted when determining the optimal therapeutic intervention, taking into account key variables such as cyst type, size, and location. Further, randomized controlled trials comparing EUS-PCA to conventional surgical interventions are warranted to enhance the existing body of evidence in this field. Such investigations could help provide more robust data to inform clinical decision-making regarding the use of EUS-PCA in the management of pancreatic cystic neoplasms.

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**Correspondence:**

Address correspondence to: Ahmed Al Qady, MD, Division of Gastroenterology, Hepatology and Nutrition, University of Florida, 1329 SW 16th ST STE 5251, Gainesville, Florida 32608. e-mail: [Ahmed.Alqady@ufl.edu](mailto:Ahmed.Alqady@ufl.edu).

**Authors' Contributions:**

Ahmed Mourtada Al Qady: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft; Writing – review & editing. Kapil Dev Nayar: Writing – original draft; Writing – review & editing. Fatima Elmustafa: Writing – original draft; Writing – review & editing. Mohamed Salih: Literature review; Writing – review & editing. Joseph Emran: Data curation; Investigation. Amir Beirat: Investigation; Writing – review & editing. Sasmith Menakuru: Data curation; Writing – review & editing. Dana Harris: Supervision; Writing – original draft; Writing – review & editing. Dan J. Echols: Methodology; Writing – original draft; Writing – review & editing. Baoan Ji: Methodology; Writing – original draft. John M. DeWitt: Methodology; Supervision; Writing – original draft; Writing – review & editing. Zhen Wang: Formal analysis; Software; Supervision. Fernando F. Stancampiano: Supervision; Writing – original draft; Writing – review & editing. Yan Bi: Conceptualization; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing.

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**Ethical Statement:**

This study was conducted in accordance with ethical guidelines. As a systematic review and meta-analysis of previously published studies, it did not involve human subjects or new data collection. Therefore, institutional review board approval was not required.

**Data Transparency Statement:**

Data, analytic methods, and study materials will be made available to other researchers upon reasonable request. Interested researchers may contact the corresponding author at [Ahmed.Alqady@ufl.edu](mailto:Ahmed.Alqady@ufl.edu) for further details.

**Reporting Guidelines:**

PRISMA.