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REVIEW

Value of Endoscopic Ultrasound-Guided Through-the-Needle Biopsy in Pancreatic Cystic Lesions. A Systematic Review and Meta-Analysis

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Abstract

Background and Aim Endoscopic ultrasound-guided through-the-needle biopsy (EUS-TTNB) has been used over the past few years to increase diagnostic accuracy for pancreatic cystic lesions (PCLs). However, many concerns remain regarding its widespread use. This systematic review and meta-analysis aimed to pool the data from high-quality studies to evaluate the utility of EUS-TTNB in diagnosing PCLs.

Methods Electronic databases (PubMed, Embase, and Cochrane Library) from January 2010 through October 2022 were searched for publications addressing the diagnostic performance of EUS-TTNB in the diagnosis of pancreatic cystic lesions. Pooled proportions were calculated using fixed (inverse variance) and random-effects (DerSimonian-Laird) models.

Results The initial search identified 635 studies, of which 35 relevant articles were reviewed. We extracted data from 11 studies that met the inclusion criterion, comprising a total of 575 patients. Mean patient age was 62.25 years ± 6.12 with females constituting 61.39% of the study population. Pooled sensitivity of EUS-TTNB in differentiating a PCL as neoplastic or non-neoplastic was 76.60% (95% CI = 72.60–80. 30). For the same indication, EUS TTNB had a pooled specificity of 98.90% (95% CI = 93.80–100.00). The positive likelihood ratio was 10.28 (95% CI = 4.77–22.15), and the negative likelihood ratio was 0.26 (95% CI = 0.22–0.31). The pooled diagnostic odds ratio for EUS-TTNB in diagnosing PCLs as malignant/pre-malignant vs. non-malignant was 41.34 (95% CI = 17.42–98.08). Pooled adverse event rates were 3.04% (95% CI = 1.83–4.54) for pancreatitis, 4.02% (95% CI = 2.61–5.72) for intra-cystic bleeding, 0.94% (95% CI = 0.33–1.86) for fever, and 1.73% (95% CI = 0.85–2.91) for other minor events.

Conclusions EUS-TTNB has good sensitivity with excellent specificity in accurately classifying PCLs as neoplastic or non-neoplastic. Adding EUS-TTNB to EUS-FNA increases the accuracy of EUS-guided approach in diagnosing PCLs. However, it could significantly increase the risk of post-procedural pancreatitis.

Keywords Endoscopic ultrasound · Through-the-needle biopsy · EUS-TTNB · Pancreatic cystic lesion(s) · Cystic pancreatic lesion(s) · PCLs

Introduction

Pancreatic cystic lesions (PCLs) are being discovered with increasing frequency with the growing availability and use of cross-sectional imaging [1]. These are known precursors of pancreatic adenocarcinomas; however, most are non-neoplastic. Neoplastic PCLs include intraductal papillary mucinous neoplasms (IPMN), mucinous cystic neoplasms (MCN), and certain pancreatic tumors with cystic components like solid-pseudopapillary neoplasms, cystic neuroendocrine tumors, and cystic degeneration of pancreatic adenocarcinomas [2]. Although neoplastic, serous cystadenoma (SCN) has an extremely low malignant potential and can be considered benign. In their retrospective cohort study of the Veterans Administration database, Munigala et al. estimated the risk of overall malignant transformation of incidentally discovered pancreatic cysts (after excluding potential benign PCLs like pseudocysts and inflammatory fluid collections) over a 5- to 10-year follow-up to be about 5 to 8% [3]. The overall risk of malignancy in a patient who undergoes surgery for a pancreatic cyst has been estimated to be approximately 15% [4].

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The risk for malignant transformation varies in neoplastic PCLs depending on their type and characteristics. Less than 0.4% of MCNs smaller than 3 cm without a nodule harbor high-grade dysplasia or invasive cancer [5]. A recent retrospective study of a prospectively maintained database of individuals with branch duct IPMNs (BD-IPMNs) found that the risk of malignant transformation in small (< 15 mm) presumed or suspected IPMNs over a median follow-up of 58 months was 1.7% [6]. However, larger BD-IPMNs can have a higher risk of malignant transformation, with reported malignant rates ranging between 3 and 26% [4, 7]. Main duct IPMNs have the greatest risk of malignant transformation [7]. Size > 3 cm, dilated main pancreatic duct, presence of solid components on imaging, and a growth rate ≥ 2.5 mm per year have been recognized as the features most predictive of malignancy [4]. Given the potential for malignancy, PCLs are a frequent cause of anxiety for patients, their caregivers, and healthcare providers. An accurate diagnosis of a malignant lesion or one with potential for malignant transformation is of utmost importance given that most pancreatic cancers are invariably fatal with the lowest 5-year survival rate compared to any cancer [8, 9]. Only about 10 to 15% of patients are candidates for curative resection; hence, early diagnosis is critical [9, 10]. Conversely, the failure to recognize a benign lesion can result in significant morbidity, lowered quality of life, and increased healthcare costs associated with major surgeries and surveillance that may not be warranted. Multiple diagnostic modalities have been used, with varying and often less-than-ideal performance. These include MRI and EUS morphology, cyst fluid aspiration with fluid analysis (glucose, tumor markers, cytology, cyst fluid DNA, and molecular analysis), real-time in vivo microscopic imaging using needle-based confocal laser endomicroscopy (nCLE), and ERCP [2]. Currently, available guidelines recommend fine-needle aspiration with fluid analysis as the preferred initial diagnostic procedure [2, 7, 11–14]. However, there is wide variability in its reported accuracy, and it is often unsatisfactory [4]. EUS-TTNB has been a relatively recent addition to an endoscopist's armamentarium. The process involves obtaining a histological sample from the cyst wall, septations, or mural nodules using a microforceps passed through the FNA needle under EUS guidance [15]. Multiple studies have reported improved diagnostic accuracy with TTNB in diagnosing PCLs [16–32]. However, this enhanced diagnostic accuracy can come with an increased risk of complications like acute pancreatitis. In addition, for surgically operable PCLs with high-risk features, it is unlikely that a negative result on EUS-TTNB will alter the management.

This study aimed to analyze the results of high-quality studies evaluating the diagnostic accuracy of EUS-TTNB in diagnosing PCLs and calculating the pooled sensitivity, specificity, and positive and negative likelihood ratios. The other outcomes evaluated were the technical success rate, feasibility, and adverse-event rate.

Methods

Search Methodology

A literature search was conducted using the electronic database engines MEDLINE through PubMed, Ovid, Cochrane Library (Cochrane Central Register of Controlled Trials and Cochrane Database of Meta-Analysis), EMBASE, ACP Journal Club, and Database of Abstracts of Reviews of Effects (DARE) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines from January 2010 through October 2022 to identify studies addressing the diagnostic performance of EUS-TTNB in the diagnosis of PCLs.

Study Eligibility

Published studies were eligible if they reported using a EUS-guided through-the-needle micro-forceps in diagnosing PCLs. Articles were excluded if they were not in the English language. Animal model studies, editorials, abstracts with incomplete data, and comments were excluded. Case reports, reviews, and prospective and retrospective studies with less than 25 patients were also excluded. Eleven studies matched the study criterion, and two authors reviewed full-text articles independently (HG, SP). The agreement was evaluated using Cohen's κ.

Data Extraction and Quality Assessment

The following data were independently abstracted by two authors (HG, SP) into a standardized form: study characteristics (primary author, period of study, year of publication, and country of the population studied), study design, baseline characteristics of the study population (number of patients enrolled and participant demographics), and intervention details (number of forceps passes, technical success, use of prophylactic antibiotics, and adverse events). The quality of included studies was assessed using a modified version of the Newcastle–Ottawa scale based on three broad components. Quality was graded as high if the total score was ≥ 7 from a maximum possible score of 8. All included studies were of high quality. Discrepancies were resolved by discussion and review.

Outcomes Evaluated

Primary outcomes evaluated were pooled sensitivity, specificity, and positive and negative predictive value of EUS

TTNB in diagnosing pancreatic cysts as neoplastic or non-neoplastic. A combination of surgical pathology, when available, and clinical outcomes on long-term follow-up were used as the criterion to define PCLs as malignant/pre-malignant or non-malignant. The secondary outcomes evaluated were technical success, tissue acquisition failure, and adverse-event rates. Technical success was defined when the FNA needle followed by through-the-needle microforceps could be successfully passed into the pancreatic cyst under ultrasound guidance and aspiration followed by biopsy bites could be performed. Tissue acquisition failure was defined as cases where an adequate sample to perform the intended histopathological analysis was not obtained.

Statistical Analysis

This meta-analysis evaluating the diagnostic accuracy of EUS-TTNB in diagnosing PCLs was performed by calculating pooled estimates of sensitivity, specificity, likelihood ratios, and diagnostic odds ratio. Individual study proportions were transformed into a quantity using the Freeman-Turkey variant of the arcsine square-root transformed proportion. The pooled proportion is calculated as the back-transform of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed effects model and DerSimonian-Laird method for the random-effects model. Forest plots were drawn to show the point estimates in each study in relation to the summary of pooled estimate. The width of point estimates in the forest plots indicates the assigned weight to that study. The heterogeneity of the sensitivities and specificities was tested by applying the chi-squared test. The heterogeneity of likelihood ratios and diagnostic odds ratios was tested using the Cochran Q test based on inverse variance weights. Summary receiver operating characteristic curves (SROC) were also used to test the heterogeneity among studies. The effects of publication and selection bias on the summary estimates were tested by the Egger bias indicator and Begg-Mazumdar bias indicator. Funnel plots were constructed to assess potential publication bias using the standard error and diagnostic odds ratio. Statistical analysis was performed using the software Microsoft Excel 19.

Results

The initial search identified 635 studies, of which 35 relevant articles were reviewed. We extracted data from 11 studies that met the inclusion criterion, comprising a total of 575 patients. Of these 575 patients, 108 underwent surgical resection and had pathology results available. Table 1 shows the studies included in this meta-analysis. Table 2 shows the classification on PCLs into neoplastic, non-neoplastic, pre-malignant/malignant,

Table 1 Characteristics of studies included in this meta-analysis

Author (year)	Study design	Patients (*n*)	Females (%)	Cyst size (mm) ± SD	Microforceps used	Technical success	Clinical success	Surgical pathology available (*n*)
Mittal et al. [26]	Single center retrospective	27	59.25	37.80 ± 16.90	Moray	27	24	4
Kovacevic et al. [24]	Multicenter retrospective	28	53.57	30.00 ± 6.37	Moray	24	23	5
Yang et al. [30]	Multicenter retrospective	47	55.31	30.80 ± 24.60	Moray	46	40	8
Zhang et al. [32]	Single center retrospective	48	52.08	31.00 ± 1.10	Moray	48	36	10
Barresi et al. [17]	Multicenter retrospective	56	69.64	38.60 ± 9.75	Moray	56	47	15
Cheesman et al. [19]	Single center retrospective	44	63.63	33.50 ± 18.50	Moray	44	33	6
Hashimoto et al. [23]	Single center retrospective	56	53.57	28.80 ± 18.25	Moray	56	45	4
Crinò et al. [21]	Single center retrospective	61	77.04	40.70 ± 14.20	Moray	61	51	20
Yang et al. [31]	Multicenter prospective	114	56.14	35.10 ± 25.20	Moray	111	95	23
Stigliano et al. [27]	Single center retrospective	49	75.51	38.00 ± 16.00	Moray and MicroBite	49	33	4
Cho et al. [20]	Single center prospective	45	57.77	45.08 ± 1.97	Moray	45	37	9

Table 2 Classification of PCLs as neoplastic, non-neoplastic, malignant, pre-malignant, or non-malignant

Neoplastic PCLs	Non-neoplastic PCLs
Intraductal papillary mucinous neoplasms (IPMN) Mucinous cystic neoplasms (MCN) Serous cystadenoma (SCN) Pancreatic tumors with cystic components - Solid-pseudopapillary neoplasms - Cystic neuroendocrine tumors - Cystic degeneration of pancreatic adenocarcinomas	Pseudocysts Inflammatory cysts
Malignant/pre-malignant	**Non-malignant**
Pancreatic tumors with cystic components - Solid-pseudopapillary neoplasms - Cystic neuroendocrine tumors - Cystic degeneration of pancreatic adenocarcinomas IPMN, MCN, SCN with pathology showing high-grade dysplasia Diagnosis of malignancy on clinical follow-up in a cyst previously classified as non-malignant	Any non-neoplastic PCL and those neoplastic PCLs not meeting definition of malignant or premalignant

and non-malignant. The agreement between reviewers was 1.0, as measured by Cohen's κ. Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) describing the review process are shown in Fig. 1. Mean patient age was 62.25 years ± 6.12 with females constituting 61.39% of the study population. The mean cyst size was 35.51 mm ± 4.85 with 38.68% (95% CI = 34.76–42.68) of PCLs located in the head or uncinate process and 61.31% (95% CI = 57.31–65.23) located in the body or tail of the pancreas.

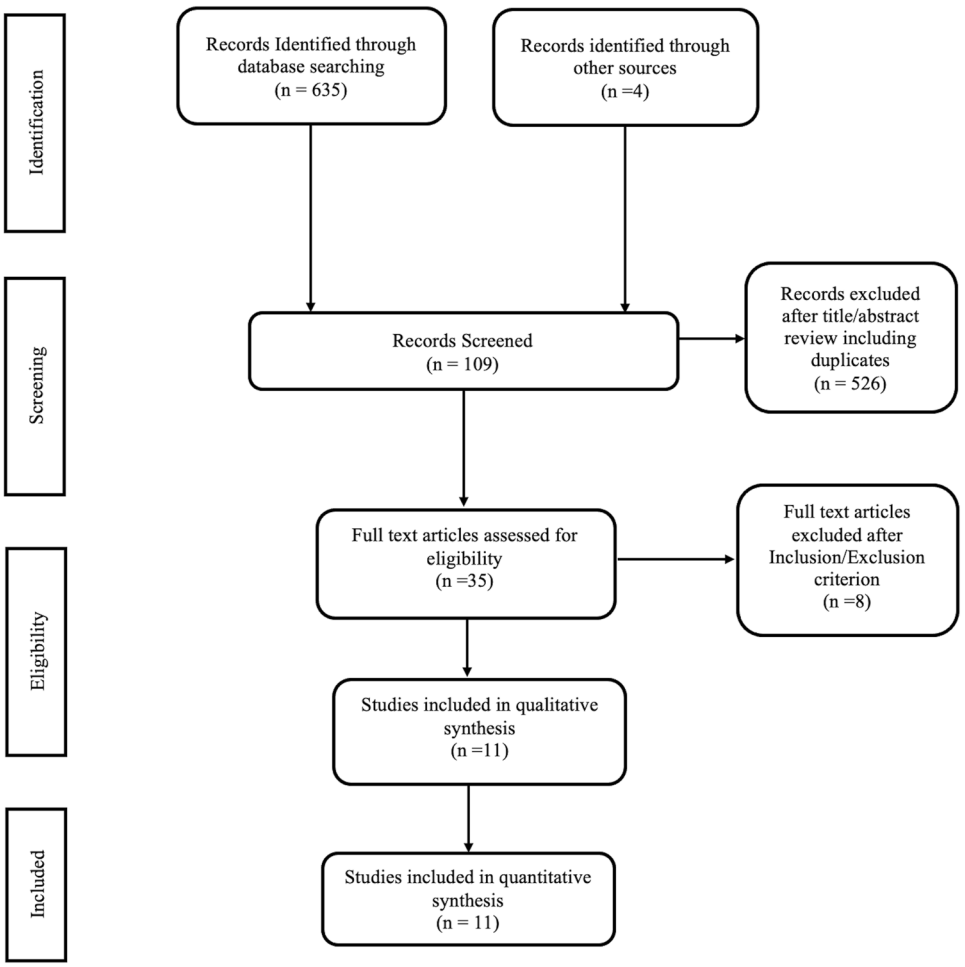

Fig. 1 Flow chart showing the review process following PRISMA guidelines

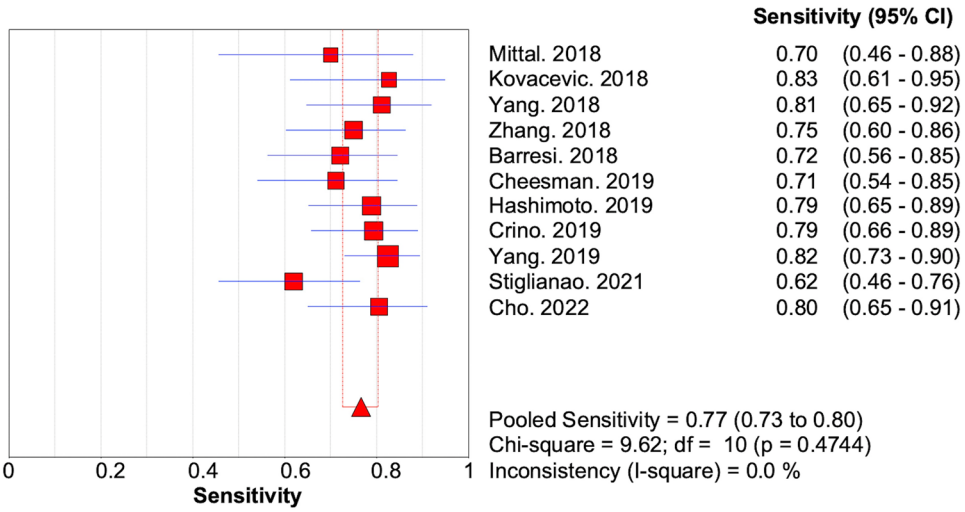

Fig. 2 Forest plot showing the individual and pooled sensitivity of EUS-TTNB in the diagnosis of PCLs

The pooled sensitivity and specificity of EUS-TTNB in diagnosing a PCL as neoplastic or non-neoplastic were 76.60% (95% CI = 72.60–80.30) and 98.90% (95% CI = 93.80–100.00), respectively. Figure 2 shows the pooled sensitivity, and Fig. 3 shows the pooled specificity. The heterogeneity of the sensitivities and specificities using the chi-squared test was calculated as 9.62, *p*-value = 0.47, indicating no heterogeneity. Inconsistency calculated using I [2] test was 0. The positive and negative likelihood ratios were 10.28 (95% CI = 4.77–22.15) and 0.26 (95% CI = 0.22–0.31), respectively. The pooled diagnostic odds ratio for EUS-TTNB in diagnosing PCLs as malignant/pre-malignant vs. non-malignant was 41.34 (95% CI = 17.42–98.08). The summary receiver operating characteristics curve showed an area under the curve of 0.88. Figure 4 shows the SROC plot. The pooled technical success rate of EUS-TTNB was 98.65% (95% CI = 97.55–99.42), while the pooled clinical success rate was 80.35% (95% CI = 77.03–83.48). Forest plot showing the pooled clinical success is shown in Fig. 5. Funnel plot showing no publication bias is shown in Fig. 6. The tissue acquisition failure rate of EUS-TTNB, despite the technical success, was 17.02% (95% CI = 14.08–20.19). The pooled mean number of microforceps passes was 3.22 (95% CI = 2.99–3.45). Pooled adverse event rates were 3.04% (95% CI = 1.83–4.54) for pancreatitis, 4.02% (95% CI = 2.61–5.72) for intra-cystic bleeding, 0.94% (95% CI = 0.33–1.86) for fever, and 1.73% (95% CI = 0.85–2.91) for other minor events. There was no publication bias calculated using the Egger or Begg-Mazumdar bias indicators.

Discussion

PCLs continue to pose a diagnostic and therapeutic challenge despite advancements in imaging, endoscopic, and genetic investigative modalities [1]. With an increasing incidence of PCLs, mostly from improved quality and growing use of cross-sectional imaging, the need to define these

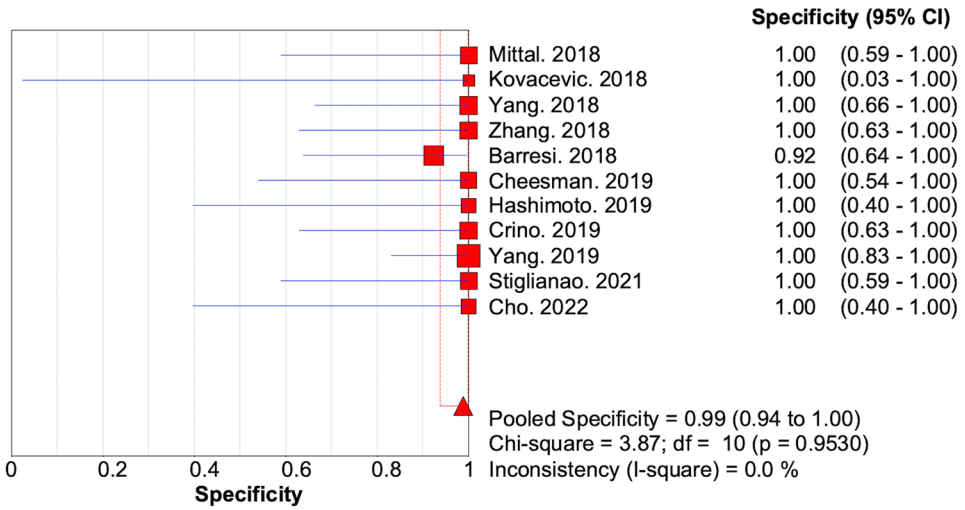

Fig. 3 Forest plot showing the individual and pooled specificity of EUS-TTNB in the diagnosis of PCLs

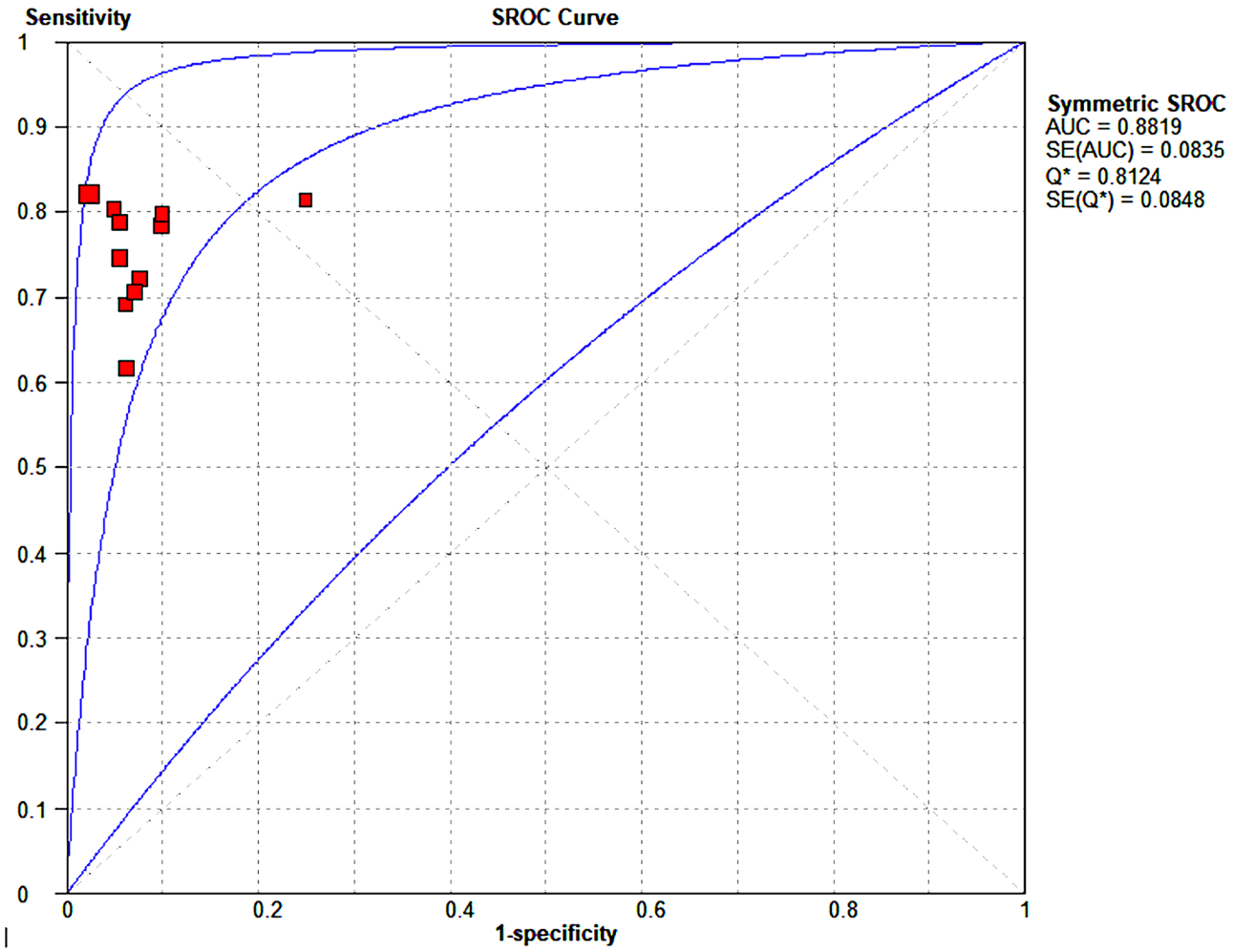

Fig. 4 Summary receiver operating curves showing EUS-TTNB to diagnose PCLs

lesions is a mounting pressure on the medical community given the malignant potential, although a vast majority are benign. The perils of misdiagnosing a potentially malignant lesion are apparent, but considering the significant direct financial burden and potential adverse patient outcomes associated with unwarranted monitoring is equally important. It is vital to consider the indirect cost of lost productivity and the emotional cost of living with a constant threat of possible underlying malignancy. EUS-TTNB was introduced to the endoscopist's armamentarium to tackle the varied and often low sensitivity and specificity of other diagnostic modalities. In keeping with the oncologic principles of diagnosing any suspected malignant lesion, obtaining a tissue sample for histopathological analysis is the gold standard. Of all the non-surgical methods in evaluating PCLs, only cyst fluid cytology and EUS-TTNB can offer tissue samples for analysis. However, cyst fluid cytology is often limited by the inadequacy of cellular yield [33]. Initial studies evaluating the performance of modified biopsy needles in obtaining histological samples from the cyst wall were disappointing, especially in cystic lesions without a solid component [34, 35]. Previous studies have evaluated the performance of EUS-TTNB in diagnosing PCLs since the first pilot study by Aparicio et al. [36] in 2010 and the first more extensive case series by Mittal et al. in 2017 [26]. However, wider adoption of this technique is still lagging, and the multiple guidelines are yet to endorse this modality fully.

We thoroughly analyzed high-quality, comparable studies, and the data from each selected study was reviewed independently by two reviewers to ensure accuracy. A particular strength of this study was that comparison of the data from two reviewers showed excellent agreement. Of the 11 studies, nine were retrospective, and two were prospective. All the studies reported using the microforces, Moray [Moray™, US Endoscopy, Mentor, OH, USA], except the study by Stigliano et al. [27] where both Moray and Microbite [Micro Bite, MTW Endoskopie Manufakture] were used. The location of pancreatic cysts was reported in all

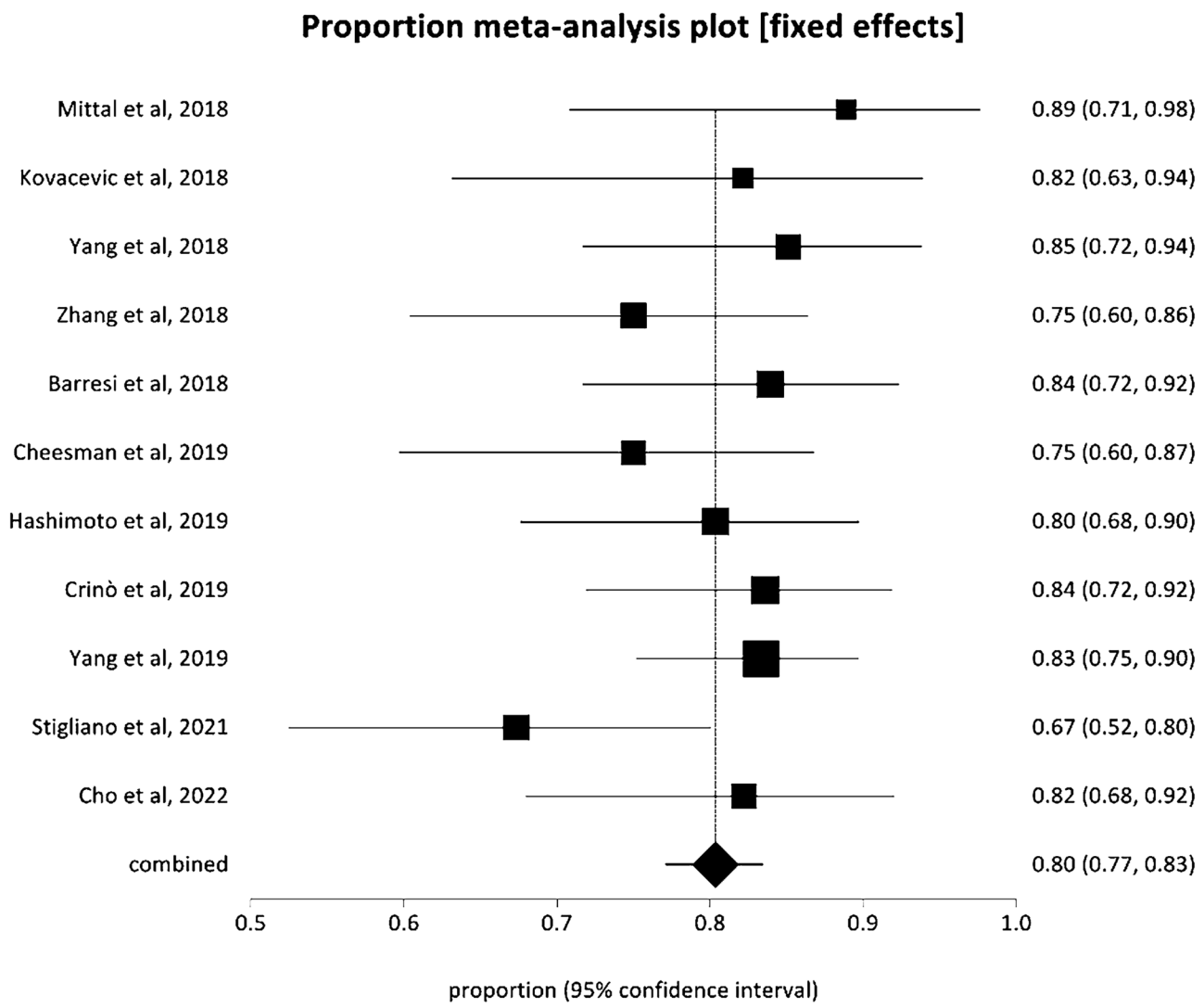

Fig. 5 Forest plot showing the clinical success rate of EUS-TTNB in the diagnosis of PCLs

the studies, with 61% in the body or tail and 39% in the head or uncinate process.

The primary finding from our study is that the pooled specificity of EUS TTNB in classifying PCLs as neoplastic versus non-neoplastic was 99%, with an acceptable pooled sensitivity of 77%. Heterogeneity, assessed using SROC curves and the Cochran Q test, shows that these results are robust. Another key finding of this study is that EUS-TTNB is highly feasible, with a pooled technical success rate of almost 99%. In two studies where a technical failure was reported, it was observed to be secondary to loss of flexibility of the echoendoscope once the FNA needle and biopsy forceps were inserted [24] or lack of finding a safe window due to interposing blood vessels [31]. The mean number of microforceps passes required for adequate sampling was 3.22 based on evaluating ten studies where this data was available. Zhang et al. reported microforceps passes until a visible sample was obtained [32]. Interestingly, in this study, there was no report of significant improvement in tissue yield despite this approach. A previous meta-analysis by Facciorusso et al. that evaluated sample adequacy with EUS-TTNB had reported an optimal histologic core procurement rate of about 80%, corresponding to the clinical success rate of 80% observed in our study [37].

EUS-TTNB also has the advantage of consistently providing adequate tissue samples for an accurate histopathological diagnosis compared to only classifying a lesion as mucinous versus non-mucinous using conventional methods. Another significant finding from this analysis is a high odds ratio of EUS-TTNB-derived histological diagnosis in diagnosing PCLs as malignant/pre-malignant or non-malignant. Cyst fluid obtained using EUS-FNA can be analyzed for chemical, cytological, and molecular studies to provide diagnostic information on PCLs. Chemical analysis primarily includes

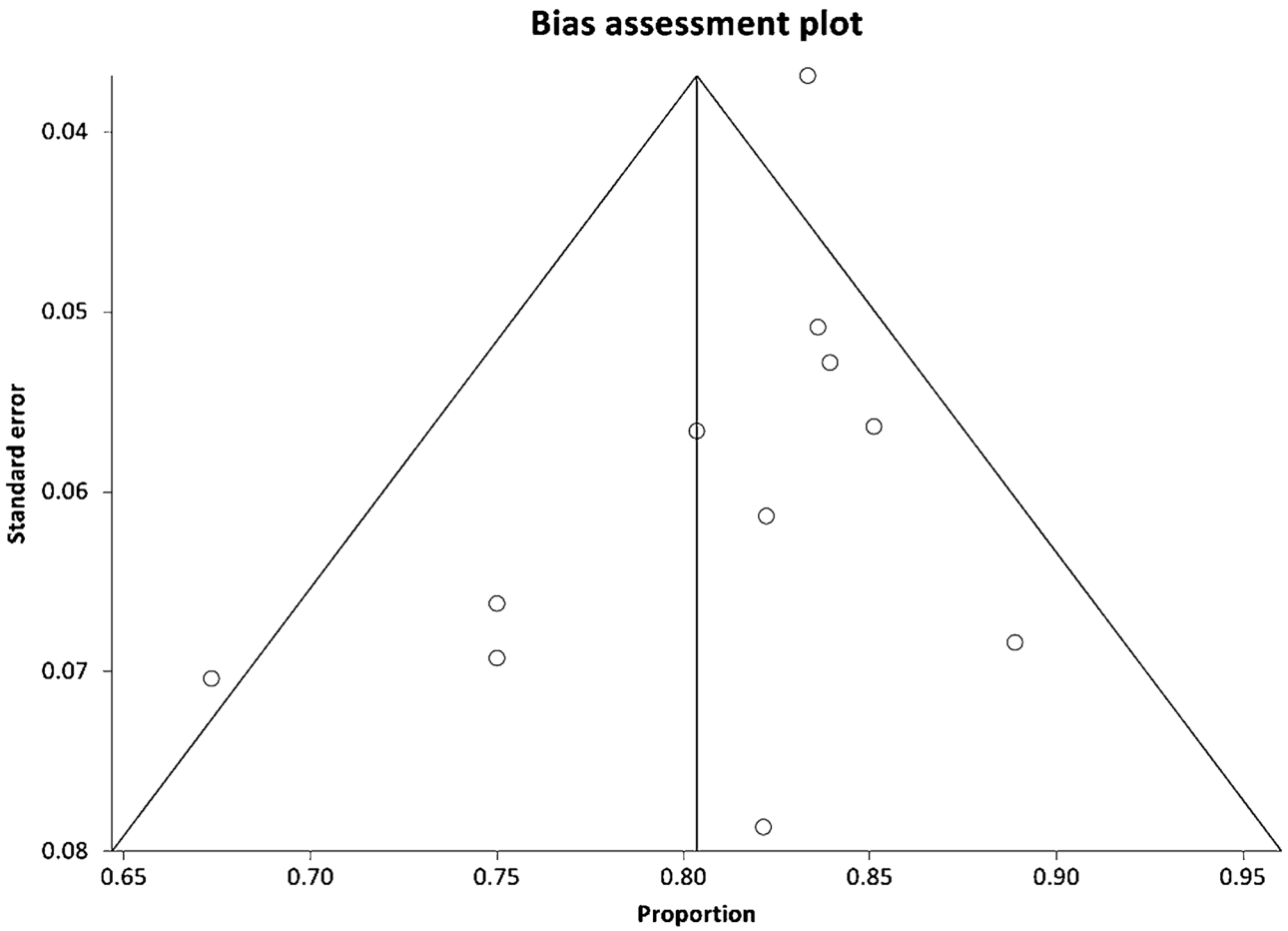

Fig. 6 Funnel plot showing no publication bias for included studies evaluating EUS-TTNB in diagnosis of PCLs

levels of glucose, amylase, and tumor markers like CEA. However, these methods have variable and often unsatisfactory diagnostic accuracy. A meta-analysis of eighteen studies found the sensitivity and specificity of CEA (at a cut-off of 192 ng/mL) to be about 63% and 88% for identifying mucinous cystic tumors [38]. Intra-cystic low glucose levels have recently been shown to have good overall diagnostic utility in classifying PCLs as mucinous at a cut-off of 50 mg/dL on fluid samples collected by endoscopic ultrasound-guided fine-needle aspiration showing a sensitivity of 90% and specificity of 85% [39]. False negative rates can be challenging in tests using cut-off values for a continuous variable. For example, Brugge et al. described CEA levels < 5 ng/mL in 7% of mucinous cystic neoplasms [40]. Other tumor markers like CA 19–9, CA 125, CA 72–4, and CA 15–3 have not been found to be helpful in the routine evaluation of PCLs [40].

Inadequate cytology samples and the availability of expert pancreatic cytologists often limit the availability of cytological diagnosis in most cases of EUS-FNA performed for PCLs. Barresi et al. described using EUS-guided fine-needle biopsy (FNB) for diagnosing PCLs. They showed that in cysts without solid components, samples were adequate for histological diagnosis in less than 40% of cases [34]. Molecular analysis also suffers from a lack of widespread availability and limited diagnostic accuracy. K-ras mutational analysis used as an individual screening test was shown to have poor diagnostic accuracy for PCLs with a sensitivity of 39% in a meta-analysis of twelve studies [41]. GNAS mutations detected on analysis of secretin-stimulated pancreatic juice samples showed a sensitivity of 64% for IPMNs [42]. Needle-based confocal laser endomicroscopy (nCLE) is a real-time in vivo endoscopic, microscopic imaging technique. nCLE has been reported to have excellent specificity of 100% in diagnosing IPMN, MCN, and adenocarcinoma, however, with a low sensitivity of around 60%. Again, this technology is also unavailable in most centers, and operators with experience are extremely limited [43, 44].

In a majority of clinical scenarios, due to the various reasons discussed above, cytology and molecular analysis are not available. In these cases, a combination of cyst fluid analysis, including glucose, CEA, and amylase, is primarily

used to differentiate PCLs as mucinous vs. non-mucinous, but this suffers from overall low sensitivity and specificity. Although all mucinous PCLs are neoplastic, most have a benign course, and diagnosing those with increased potential for malignant transformation can be critical. EUS-TTNB offers the ability to obtain adequate samples for histological evaluation consistently. Pancreaticobiliary and intestinal subtypes of IPMNs have been known to have a higher predilection for transformation to high-grade dysplasia and invasive carcinoma compared to gastric and oncocytic subtypes [45]. The prognosis of pancreatic cancers can also vary based on the subtypes of IPMN from which they are derived [46]. Nakata et al. showed that invasive carcinoma derived from intestinal-type IMPN of the pancreas is associated with minimal invasion, colloid carcinoma, and less invasive behavior, leading to a better prognosis [47]. Histologic subtyping of IPMNs, which can be more readily done with samples from EUS-TTNB, could potentially alter the diagnostic algorithm for managing IPMNs. In cases of a negative result, the availability of a histological sample could increase confidence in a diagnosis, especially in benign PCLs. Although there are several such theoretical advantages of accurate histopathological diagnosis, there is no evidence to support that this will change surgical management decisions, especially in high-risk PCLs.

It is also crucial to appreciate the high risk of acute pancreatitis following EUS-TTNB, with a pooled rate of about 3%. This is much higher than the reported rate of < 1% pancreatitis following other EUS-TA methods like EUS-FNA for diagnosing PCLS or EUS-FNA or FNB in diagnosing solid PCLs [48, 49]. Our finding of pooled rate of 3% for EUS-TTNB-related acute pancreatitis is more than the rate of 2% reported in a prior study [37]. It is essential to recognize that this 3% risk for post-procedural pancreatitis following EUS-TTNB is comparable to the rate of post-ERCP pancreatitis, a dreaded post-ERCP complication with significant morbidity and mortality [50, 51]. If the addition of EUS-TTNB to FNA can increase the risk for post-procedural pancreatitis to rates seen with ERCP, then this has to be given significant consideration before EUS-TTNB is adopted as a standard for evaluating PCLs. Future studies should determine the ideal indications for EUS-TTNB in the evaluation of PCLs.

There are a few limitations of this study. In most cases of benign cysts, further evaluation, including biopsy or resection with histopathology, was not available. Hence, a combination of surgical pathology and clinical outcomes was used as the criterion to define the standard of diagnosis as malignant or non-malignant. The length of follow-up can limit data on clinical outcomes, which could affect the interpretation of the results. There was also variability in how the studies reported follow-up. Mean, median, range, and narrative description were used. For example, Barresi et al. and Crinò et al. gave mean follow-up (16.6 and 15 months, respectively), while Kovacevic et al. provided a median (8.4 months) [17, 21, 24]. Follow-up duration was descriptive in the studies by Zhang et al., Cheesman et al., and Hashimoto et al. [19, 23, 32]. However, given the high morbidity of pancreatic surgeries and as a large proportion of PCLs are benign, this combination of pathology, when available, and long-term follow-up is possibly the best metric to evaluate the outcome. Another limitation was that experts in high-volume centers performed most of these studies. Whether the technical success demonstrated by the experts can be replicated in the community is a question that needs further research.

Conclusions

EUS-TTNB has good sensitivity with excellent specificity in diagnosing PCLs and an overall good safety profile. However, there was a higher post-procedural acute pancreatitis rate than in other EUS-TA modalities. The addition of EUS-TTNB, when available, to EUS-FNA with fluid analysis could increase the accuracy of EUS-guided approach in diagnosing PCLs. However, it significantly increases the risk of pancreatitis. Further prospective studies are needed to estimate the post-EUS-TTNB pancreatitis rate and evaluate potential techniques to mitigate this risk.

Author Contribution Harishankar Gopakumar, MD, contributed to the study's conception, design, review of literature, data collection, manuscript writing, and submission. Srinivas R. Puli, MD, conducted the data analysis, interpretation of results, and review of the manuscript with expert input. The manuscript has been read and approved by all the authors, and the requirements for authorship have been met. Each author believes that the manuscript represents honest work.

Data Availability The data that support the findings of this study are available on request from the corresponding author.

Declarations

Ethics Approval and Consent to Participate The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its subsequent amendments. This study does not contain identifying information about the patients.

Conflict of Interest The authors declare no competing interests.

References

1. Kromrey ML, Bülow R, Hübner J, et al. Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study. Gut. 2018;67(1):138–45.
2. Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG clinical guideline: diagnosis and management of pancreatic cysts. Am J Gastroenterol. 2018;113(4):464–79.

3. Munigala S, Gelrud A, Agarwal B. Risk of pancreatic cancer in patients with pancreatic cyst. Gastrointest Endosc. 2016;84(1):81–6.
4. Scheiman JM, Hwang JH, Moayyedi P. American gastroenterological association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015;148(4):824-848.e822.
5. Nguyen D, Dawson DW, Hines OJ, Reber HA, Donahue TR. Mucinous cystic neoplasms of the pancreas: are we overestimating malignant potential? Am Surg. 2014;80(10):915–9.
6. Ciprani D, Weniger M, Qadan M, et al. Risk of malignancy in small pancreatic cysts decreases over time. Pancreatology. 2020;20(6):1213–7.
7. Tanaka M, Fernández-Del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology. 2017;17(5):738–53.
8. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7–33.
9. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med. 2014;371(11):1039–49.
10. Sohal DP, Mangu PB, Khorana AA, et al. Metastatic pancreatic cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016;34(23):2784–96.
11. European evidence-based guidelines on pancreatic cystic neoplasms. Gut. 2018;67(5):789–804.
12. Aziz H, Acher AW, Krishna SG, Cloyd JM, Pawlik TM. Comparison of society guidelines for the management and surveillance of pancreatic cysts: a review. JAMA Surg. 2022;157(8):723–30.
13. Megibow AJ, Baker ME, Morgan DE, et al. Management of incidental pancreatic cysts: a white paper of the ACR Incidental Findings Committee. J Am Coll Radiol. 2017;14(7):911–23.
14. Vege SS, Ziring B, Jain R, Moayyedi P, Adams MA, Dorn SD, Dudley-Brown SL, Flamm SL, Gellad ZF, Gruss CB, Kosinski LR. American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015;148(4):819-22.
15. Kovacevic B, Kalaitzakis E, Klausen P, et al. EUS-guided through-the-needle microbiopsy of pancreatic cysts: Technical aspects (with video). Endosc Ultrasound. 2020;9(4):220–4.
16. Balaban VD, Cazacu IM, Pinte L, Jinga M, Bhutani MS, Saftoiu A. EUS-through-the-needle microbiopsy forceps in pancreatic cystic lesions: a systematic review. Endosc Ultrasound. 2021;10(1):19–24.
17. Barresi L, Crinò SF, Fabbri C, et al. Endoscopic ultrasound-through-the-needle biopsy in pancreatic cystic lesions: a multicenter study. Dig Endosc. 2018;30(6):760–70.
18. Basar O, Yuksel O, Yang DJ, et al. Feasibility and safety of microforceps biopsy in the diagnosis of pancreatic cysts. Gastrointest Endosc. 2018;88(1):79–86.
19. Cheesman AR, Zhu H, Liao X, et al. Impact of EUS-guided microforceps biopsy sampling and needle-based confocal laser endomicroscopy on the diagnostic yield and clinical management of pancreatic cystic lesions. Gastrointest Endosc. 2020;91(5):1095–104.
20. Cho SH, Song TJ, Seo DW, et al. Efficacy and safety of EUS-guided through-the-needle microforceps biopsy sampling in categorizing the type of pancreatic cystic lesions. Gastrointest Endosc. 2022;95(2):299–309.
21. Crinò SF, Bernardoni L, Brozzi L, et al. Association between macroscopically visible tissue samples and diagnostic accuracy of EUS-guided through-the-needle microforceps biopsy sampling of pancreatic cystic lesions. Gastrointest Endosc. 2019;90(6):933–43.
22. Guzmán-Calderón E, Martinez-Moreno B, Casellas JA, de Madaria E, Aparicio JR. Endoscopic ultrasound-guided, through-the-needle forceps biopsy for diagnosis of pancreatic cystic lesions: a systematic review. Endosc Int Open. 2020;8(9):E1123-e1133.
23. Hashimoto R, Lee JG, Chang KJ, Chehade NEH, Samarasena JB. Endoscopic ultrasound-through-the-needle biopsy in pancreatic cystic lesions: a large single center experience. World J Gastrointest Endosc. 2019;11(11):531–40.
24. Kovacevic B, Klausen P, Hasselby JP, et al. A novel endoscopic ultrasound-guided through-the-needle microbiopsy procedure improves diagnosis of pancreatic cystic lesions. Endoscopy. 2018;50(11):1105–11.
25. McCarty T, Rustagi T. Endoscopic ultrasound-guided through-the-needle microforceps biopsy improves diagnostic yield for pancreatic cystic lesions: a systematic review and meta-analysis. Endosc Int Open. 2020;8(10):E1280-e1290.
26. Mittal C, Obuch JC, Hammad H, et al. Technical feasibility, diagnostic yield, and safety of microforceps biopsies during EUS evaluation of pancreatic cystic lesions (with video). Gastrointest Endosc. 2018;87(5):1263–9.
27. Stigliano S, Covotta F, Di Matteo FM. A new micro-forceps for endoscopic ultrasound-guided through-the-needle biopsy in the diagnosis of pancreatic cystic lesions: single center experience. JGH Open. 2021;5(9):1004–8.
28. Tacelli M, Celsa C, Magro B, et al. Diagnostic performance of endoscopic ultrasound through-the-needle microforceps biopsy of pancreatic cystic lesions: systematic review with meta-analysis. Dig Endosc. 2020;32(7):1018–30.
29. Westerveld DR, Ponniah SA, Draganov PV, Yang D. Diagnostic yield of EUS-guided through-the-needle microforceps biopsy versus EUS-FNA of pancreatic cystic lesions: a systematic review and meta-analysis. Endosc Int Open. 2020;8(5):E656-e667.
30. Yang D, Samarasena JB, Jamil LH, et al. Endoscopic ultrasound-guided through-the-needle microforceps biopsy in the evaluation of pancreatic cystic lesions: a multicenter study. Endosc Int Open. 2018;6(12):E1423-e1430.
31. Yang D, Trindade AJ, Yachimski P, et al. Histologic analysis of endoscopic ultrasound-guided through the needle microforceps biopsies accurately identifies mucinous pancreas cysts. Clin Gastroenterol Hepatol. 2019;17(8):1587–96.
32. Zhang ML, Arpin RN, Brugge WR, Forcione DG, Basar O, Pitman MB. Moray micro forceps biopsy improves the diagnosis of specific pancreatic cysts. Cancer Cytopathol. 2018;126(6):414–20.
33. de Jong K, Poley JW, van Hooft JE, Visser M, Bruno MJ, Fockens P. Endoscopic ultrasound-guided fine-needle aspiration of pancreatic cystic lesions provides inadequate material for cytology and laboratory analysis: initial results from a prospective study. Endoscopy. 2011;43(7):585–90.
34. Barresi L, Tarantino I, Traina M, et al. Endoscopic ultrasound-guided fine needle aspiration and biopsy using a 22-gauge needle with side fenestration in pancreatic cystic lesions. Dig Liver Dis. 2014;46(1):45–50.
35. Levy MJ, Smyrk TC, Reddy RP, et al. Endoscopic ultrasound-guided trucut biopsy of the cyst wall for diagnosing cystic pancreatic tumors. Clin Gastroenterol Hepatol. 2005;3(10):974–9.
36. Aparicio JR, Martínez J, Niveiro M, et al. Direct intracystic biopsy and pancreatic cystoscopy through a 19-gauge needle EUS (with videos). Gastrointest Endosc. 2010;72(6):1285–8.
37. Facciorusso A, Del Prete V, Antonino M, Buccino VR, Wani S. Diagnostic yield of EUS-guided through-the-needle biopsy in pancreatic cysts: a meta-analysis. Gastrointest Endosc. 2020;92(1):1-8.e3.
38. Thornton GD, McPhail MJW, Nayagam S, Hewitt MJ, Vlavianos P, Monahan KJ. Endoscopic ultrasound guided fine needle aspiration for the diagnosis of pancreatic cystic neoplasms: a meta-analysis. Pancreatology. 2013;13(1):48–57.
39. Mohan BP, Madhu D, Khan SR, et al. Intracystic glucose levels in differentiating mucinous from nonmucinous pancreatic cysts: a systematic review and meta-analysis. J Clin Gastroenterol. 2022;56(2):e131–6.

40. Brugge WR, Lewandrowski K, Lee-Lewandrowski E, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. Gastroenterology. 2004;126(5):1330–6.
41. Gillis A, Cipollone I, Cousins G, Conlon K. Does EUS-FNA molecular analysis carry additional value when compared to cytology in the diagnosis of pancreatic cystic neoplasm? A systematic review HPB (Oxford). 2015;17(5):377–86.
42. Kanda M, Knight S, Topazian M, et al. Mutant *GNAS* detected in duodenal collections of secretin-stimulated pancreatic juice indicates the presence or emergence of pancreatic cysts. Gut. 2013;62(7):1024–33.
43. Konda VJ, Meining A, Jamil LH, et al. A pilot study of in vivo identification of pancreatic cystic neoplasms with needle-based confocal laser endomicroscopy under endosonographic guidance. Endoscopy. 2013;45(12):1006–13.
44. Nakai Y, Iwashita T, Park DH, Samarasena JB, Lee JG, Chang KJ. Diagnosis of pancreatic cysts: EUS-guided, through-the-needle confocal laser-induced endomicroscopy and cystoscopy trial: DETECT study. Gastrointest Endosc. 2015;81(5):1204–14.
45. Adsay NV, Merati K, Basturk O, et al. Pathologically and biologically distinct types of epithelium in intraductal papillary mucinous neoplasms: delineation of an "intestinal" pathway of carcinogenesis in the pancreas. Am J Surg Pathol. 2004;28(7):839–48.
46. Kim J, Jang KT, Mo Park S, et al. Prognostic relevance of pathologic subtypes and minimal invasion in intraductal papillary mucinous neoplasms of the pancreas. Tumour Biol. 2011;32(3):535–42.
47. Nakata K, Ohuchida K, Aishima S, et al. Invasive carcinoma derived from intestinal-type intraductal papillary mucinous neoplasm is associated with minimal invasion, colloid carcinoma, and less invasive behavior, leading to a better prognosis. Pancreas. 2011;40(4):581–7.
48. Ramai D, Singh J, Kani T, et al. Wet- versus dry-suction techniques for EUS-FNA of solid lesions: a systematic review and meta-analysis. Endosc Ultrasound. 2021;10(5):319–24.
49. Zhu H, Jiang F, Zhu J, Du Y, Jin Z, Li Z. Assessment of morbidity and mortality associated with endoscopic ultrasound-guided fine-needle aspiration for pancreatic cystic lesions: a systematic review and meta-analysis. Dig Endosc. 2017;29(6):667–75.
50. Andriulli A, Loperfido S, Napolitano G, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. Am J Gastroenterol. 2007;102(8):1781–8.
51. Mutneja HR, Vohra I, Go A, et al. Temporal trends and mortality of post-ERCP pancreatitis in the United States: a nationwide analysis. Endoscopy. 2021;53(4):357–66.