—Original Article—

EUS-guided biopsy *versus* confocal laser endomicroscopy in patients with pancreatic cystic lesions: A systematic review and meta-analysis

Bojan Kovacevic[1], Giulio Antonelli[2], Pia Klausen[1], Cesare Hassan[2], Alberto Larghi[3], Peter Vilmann[1], John Gásdal Karstensen[4,5]

[1]Gastro Unit, Division of Endoscopy, Herlev Hospital, Herlev, Denmark; [2]Digestive Endoscopy Unit, Nuovo Regina Margherita Hospital, Rome, Italy; [3]Digestive Endoscopy Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [4]Gastro Unit, Pancreatitis Centre East, Hvidovre Hospital, Hvidovre, Denmark; [5]Department of Clinical Medicine, University of Copenhagen, København, Denmark

ABSTRACT

Background and Objectives: Pancreatic cystic lesions (PCLs) are frequent incidental findings on cross-sectional imaging and represent a diagnostic challenge as different kinds of PCLs harbor a dissimilar risk of malignancy. Two diagnostic tools have recently been developed and introduced: through-the-needle biopsy (TTNB) and needle-based confocal laser endomicroscopy (nCLE). The aim of this meta-analysis was to compare the diagnostic yield and performance, as well as the safety profile of the two methods. **Methods:** This meta-analysis was performed in accordance with the PRISMA statement. Medline, Embase, Web of Science, and Cochrane Library databases were searched for studies with five or more patients undergoing either endoscopic ultrasound (EUS)-TTNB or EUS-nCLE for a PCL. Reviews, case reports, editorials, conference abstracts, and studies on exclusively solid pancreatic lesions were excluded. Outcomes of interest were diagnostic yield and performance, safety, and technical success. **Results:** Twenty studies with 1023 patients were included in the meta-analysis. Pooled diagnostic yield of EUS-nCLE was higher compared to EUS-TTNB (85% *vs.* 74%, $P < 0.0001$), while diagnostic performance was high and comparable for both methods (pooled sensitivity: 80% *vs.* 86% and pooled specificity: 80% *vs.* 83% for TTNB and nCLE, respectively, $P > 0.05$). Pooled estimate of total adverse event (AE) rate was 5% in the TTNB group and 3% in the nCLE group, $P = 0.302$. Technical success rates were high and comparable (94% and 99% for EUS-TTNB and nCLE, respectively; $P = 0.07$). **Conclusion:** EUS-TTNB and EUS-nCLE have a similar safety profile with a relatively low number of AEs. Technical success, sensitivity, and specificity are comparable; however, EUS-nCLE seems to have a slightly higher diagnostic yield.

Key words: EUS-through-the-needle biopsy, intraductal papillary mucinous neoplasm, moray, needle-based confocal laser endomicroscopy, pancreatic cyst

Access this article online

Quick Response Code:

Website: www.eusjournal.com

DOI: 10.4103/EUS-D-20-00172

How to cite this article: Kovacevic B, Antonelli G, Klausen P, Hassan C, Larghi A, Vilmann P, *et al*. EUS-guided biopsy versus confocal laser endomicroscopy in patients with pancreatic cystic lesions: A systematic review and meta-analysis. Endosc Ultrasound 2021;10:270-9.

Address for correspondence

Dr. Bojan Kovacevic, Gastro Unit, Division of Endoscopy, Herlev Hospital, Borgmester Ib Juuls Vej 1, 2730 - Herlev, Denmark.
E-mail: bojan.k@dadlnet.dk

Received: 2020-08-16; **Accepted:** 2021-02-11; **Published online:** 2021-07-19

INTRODUCTION

Pancreatic cystic lesions (PCLs) are frequent incidental findings on cross-sectional imaging performed for other reasons, and the prevalence increases with age.[1] There are many different types of PCLs, some of which have malignant potential. Distinction between mucinous (intraductal papillary mucinous neoplasm [IPMN] and mucinous cystic neoplasm [MCN]) and nonmucinous lesions (pseudocysts and serous cystic neoplasm [SCN]) is clinically relevant, as the former are considered premalignant lesions. Current guidelines recommend risk stratification based on a composite of variables, such as patient history, cross-sectional imaging, and in selected cases, EUS-FNA.[2] However, FNA cytology has only a moderate accuracy for distinguishing mucinous from nonmucinous lesions (pooled sensitivity 54%) mostly because of the low cellularity of the cyst fluid.[3] Carcinoembryonic antigen (CEA) in the cyst fluid is another diagnostic test but it performs rather modestly with a pooled sensitivity of 63% and a specificity of 88%.[3] In recent years, several other diagnostic tools have been introduced in an effort to improve the diagnostic process.

EUS-guided needle-based confocal laser endomicroscopy (EUS-nCLE) utilizes a laser beam to obtain *in vivo* microscopic images of the cyst wall epithelium, following injection of a contrast solution (2.5–5 mL 10% fluorescein sodium).[4] The probe (Cellvizio, Mauna Kea Technologies, Paris, France) is advanced into the cyst lumen following access by a 19G needle and is used for image acquisition of the cyst wall. Several different image features have been described and validated, such as papillary projections (consistent with IPMN) and a superficial vascular network (indicative of an SCN) to name a few.[5] The second novel method for the evaluation of PCLs is EUS-guided through-the-needle biopsy (EUS-TTNB) which uses a specifically developed microforceps (also inserted through a 19G needle) to obtain tissue samples from the cyst wall or suspected intracystic nodules/masses, overcoming the previously described issue of low cellularity.[6] Both methods are reported to have high technical success and a superior diagnostic yield compared to standard cytology,[7-9] but there is currently only a single, inconclusive comparison of the two methods.[10] Furthermore, concerns have been raised about the adverse event (AE) rate of EUS-TTNB, as several severe cases of pancreatitis have been reported.[11] The aim of this meta-analysis was to compare the diagnostic yield and performance, as well as the safety profile of EUS-TTNB and EUS-nCLE.

METHODS

Search strategy and study selection

A study protocol was developed and uploaded to PROSPERO (protocol no: 156867). Two authors (B.K. and G.A.) independently performed a systematic search of Medline, Embase, Web of Science, and Cochrane Library databases using a predefined search string (Supplementary Material). Inclusion criteria were studies with five or more patients undergoing either EUS-TTNB or EUS-nCLE for a PCL. Reviews, case reports, editorials, conference abstracts, and studies on exclusively solid pancreatic lesions were excluded. Additional papers were identified through backward snowballing. An online database (clinicaltrials.gov) was queried for any ongoing studies. In case of disagreement, a third author was consulted (J.G.K).

Outcomes and data extraction

Primary outcomes were diagnostic yield, defined as a proportion of lesions where a diagnosis was obtained, and safety (AEs were classified as mild, moderate, and severe according to the American Society for Gastrointestinal Endoscopy lexicon).[12] Secondary outcomes included technical success, defined as successful acquirement of a macroscopically visible histological sample in case of EUS-TTNB or obtainment of recognizable images in case of EUS-nCLE, total procedural time, and diagnostic performance (concordance with final diagnosis in surgical subgroup and ability to discriminate between mucinous and nonmucinous lesions). Furthermore, following data were extracted: name of first author, year of publication, study characteristics (design, location, and study length), patient characteristics (age, gender, lesion size, and location), and procedural characteristics (indication, type of sedation, and use of antibiotics). Data extraction was performed independently by two authors (B.K. and G.A.), and any disagreements were solved by consensus or by consulting a third author (J.G.K.). Quality was similarly assessed using the first eight items of Methodological Index for Nonrandomized Studies tool.[13] Mean score was calculated, and the studies were graded as having low (≤8) or high quality (>8).

Statistical analysis

As primary and secondary outcomes were expected to deviate considerably from a proportion of 0.5, double arcsine transformation of the proportions was employed to obtain unbiased effect size estimates.[14] The effect sizes were weighted by the inverse of the study variance and forest plots were constructed. The results were pooled using DerSimonian-Laird method (random-effect model), as a high level of heterogeneity was expected *a priori*. Heterogeneity was assessed by visual inspection of the plots and corresponding statistics (Higgins I^2, τ^2, and Cochran's Q test) and was considered low, moderate, and substantial in case of I^2 of <25%, 25%–75%, and >75%, respectively. A leave-one-out sensitivity analysis was performed to identify any influential studies.

In the surgical subgroup, the test diagnosis was compared to reference histology in an intention-to-diagnose approach. Discrimination between mucinous and nonmucinous lesions was evaluated by constructing 2 × 2 tables and calculating pooled sensitivity and specificity using the bivariate model. Furthermore, summary receiver operating characteristic (sROC) curves were plotted, and corresponding areas under the curve (AUC) were calculated for each method and compared. While an accuracy of a test is highly influenced by the distribution of classifiers and may be an inaccurate measure of test precision in case of an imbalanced classification (as often is the case with PCLs), AUC values give a more reliable estimate of a test performance.

Meta-regression was performed examining the effects of intervention, study design and quality, patient age, and lesion size on effect size estimates. Potential publication bias was evaluated by examining funnel plots, rank correlation test, and Egger's regression test for plot asymmetry. All statistical analyses were performed using *R* version 3.6.2 and R studio version 1.1.423 RStudio PBC, Boston, MA, US. Statistical significance was set at $P < 0.05$ for all calculations. All authors had access to the study data and had reviewed and approved the final manuscript.

RESULTS

Literature search yielded 848 articles, of which 20 studies with 1023 patients were included in the meta-analysis [Figure 1]. The majority of the studies were single center (n = 12, 60%) and retrospective by design (n = 11, 55%). Mean lesion size ranged from 25.0 to 43.7 mm with an overweight of the lesions (61%) located in the body/tail portion of the pancreas [Table 1]. Only a few studies reported on procedural time without clear definitions: in case of EUS-TTNB, the total procedural time ranged from 23 to 34 min;[18,19] whereas only image acquisition time was reported (mean 5–7 min) for nCLE.[5,24,26,30] All but five studies reported on prophylactic use of antibiotics. A single dose of intravenous quinolones, cephalosporins, or a combination of penicillin and β-lactamase was usually administered periprocedurally. Some centers continued antibiotic therapy for 3–5 days either routinely[5,15,20,27] or at the discretion of an endoscopist.[10]

Diagnostic yield and safety

Pooled diagnostic yield of EUS-nCLE was higher compared to EUS-TTNB (85%, 95% confidence interval [CI]: 82%–88% and 74%, 95% CI: 69%–78%; $P < 0.0001$). Heterogeneity was low in the nCLE group and moderate in the TTNB group [Figure 2]. Meta-regression did not reveal any other variables associated with diagnostic yield [Supplementary Table S1]. Pooled estimate of total AE rate was 5% (95% CI: 2%–8%) in the TTNB group and 3% (95% CI: 1%–5%) in the nCLE group, $P = 0.302$ [Figure 3]. AEs were mainly mild; but moderate (nCLE: 1.5%, TTNB: 1.3%) and severe AEs (nCLE: 0.0%, TTNB: 0.7%) were also reported. Most common AE was pancreatitis (nCLE: 2.1%, TTNB: 3.9%), followed by intracystic hemorrhage (nCLE: 0.4%, TTNB: 2.4%) and infection (nCLE: 0.4%, TTNB: 0.4%). Meta-regression did not show any association between study design and quality, patient age or lesion size, and AE rate [Supplementary Table S1]. Funnel plots and statistical tests did not reveal any publication bias [Supplementary Figure S1].

Diagnostic performance and technical success

In case of classification into mucinous and nonmucinous lesions, the pooled sensitivity was 80% (95% CI: 65%–89%) and 86% (95% CI: 69%–94%) for EUS-TTNB and nCLE, respectively. Pooled specificity was 80% (95% CI: 53%–94%) for EUS-TTNB and 83% (95% CI: 62%–94%) for nCLE [Figure 4]. There was no difference in diagnostic performance between the two modalities ($P > 0.05$). A leave-one-out sensitivity analysis failed to identify any influential studies. Estimated AUC of

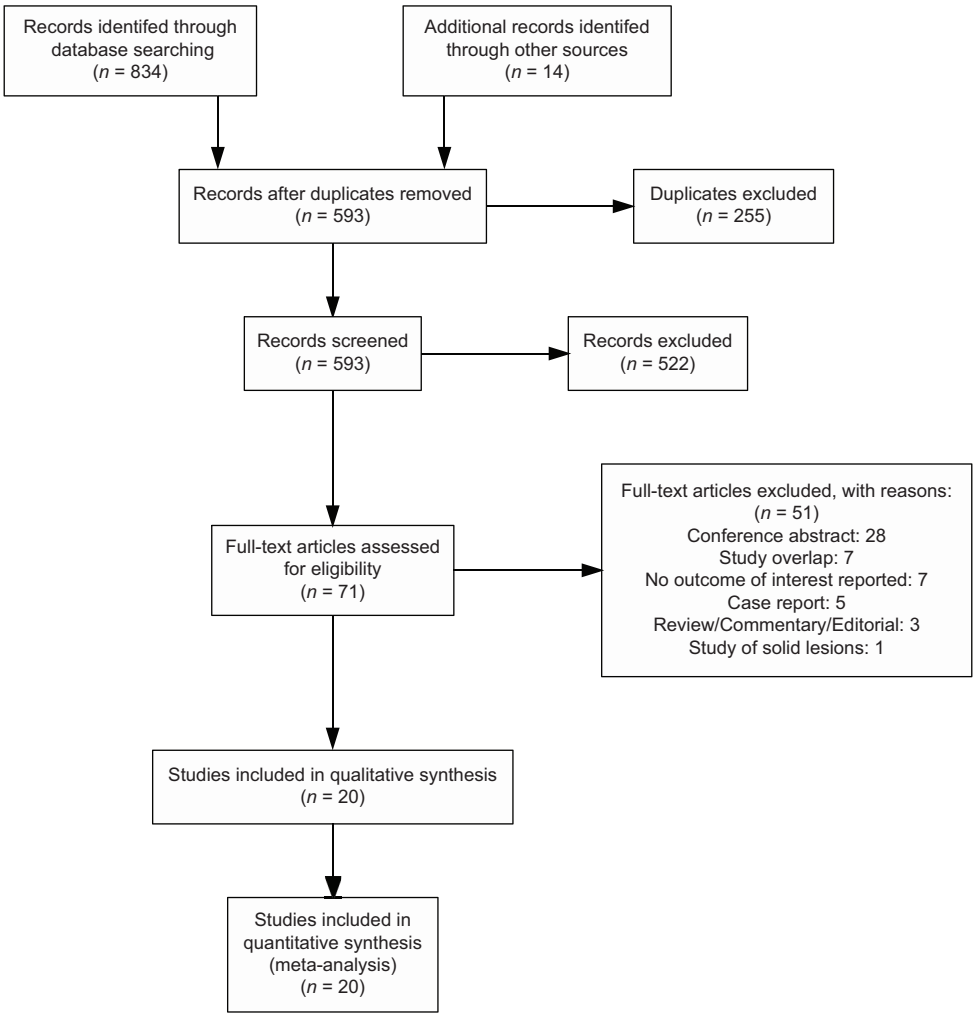

Figure 1. PRISMA flowchart

sROC was comparable: 0.86 for EUS-TTNB and 0.91 for EUS-nCLE ($P > 0.05$). Pooled estimate for concordance with final diagnosis in the surgical subgroup was 82% (95% CI: 72%–91%) and 65% (95% CI: 36%–91%) for the TTNB and nCLE groups, respectively. However, small sample size in the latter resulted in wide CIs, and the difference was statistically insignificant ($P = 0.21$). Technical success was high and comparable for both methods [Figure 5], but the heterogeneity was substantial ($I^2 = 78\%$ and 52%).

DISCUSSION

This meta-analysis provides a first comparison between EUS-TTNB and EUS-nCLE in the evaluation of PCLs. The study included 20 studies with 1023 patients and employed meticulous assessment and high methodological standards. However, no randomized controlled studies were identified, and half of the included studies were retrospective by design, which is a lower level of evidence. Conversely, we did not find any evidence of publication bias. The major limitation of this meta-analysis is an indirect comparison of the two methods due to the lack of comparative studies, which is why the results must be interpreted with caution. Study population in the EUS-TTNB and EUS-nCLE studies may be heterogeneous, as well as the technical setup and overall workflow, which must also be taken into consideration when interpreting the results. Furthermore, gold standard reference test (surgical histology) was only available in a small proportion of cases ($n = 104$, 10.2%), why estimates of diagnostic performance may be inaccurate [Figure 6].

The results of this study show that EUS-TTNB and EUS-nCLE seem to have a similar technical success rate, diagnostic performance, and safety profile, but the diagnostic yield of nCLE appears significantly higher than that of TTNB. Confocal endomicroscopy is an older technique with the first human pilot study for pancreatic

Table 1. Overview of the included studies

First author	Year	Design	Single/multicenter	Country	Intervention	Number of patients	Female, *n* (%)	Mean age (range)	Mean cyst size, mm (range)	Mean quality score
Barresi[15]	2018	Retrospective	Multicenter	IT, NL	TTNB	56	39 (70)	57.5 (27-80)	38.6 (16-55)	8.0 (low)
Basar[16]	2018	Retrospective	Multicenter	USA	TTNB	42	23 (55)	69.9 (27-91)	28.2 (12-60)	6.5 (low)
Cheesman[10]	2020	Retrospective	Single center	USA	TTNB	44	28 (64)	66.0	33.5 (19-90)	7.0 (low)
Hashimoto[17]	2019	Retrospective	Single center	USA	TTNB	56	30 (54)	66.9 (SD 11.7)	28.8 (12-85)	7.5 (low)
Kovacevic[18]	2018	Retrospective	Multicenter	DK, NO, FR, IT, ES, IL	TTNB	15*	7 (47)	65.0 (SD 10.3)	34.0	7.0 (low)
Kovacevic[19]	2018	Retrospective	Single center	DK	TTNB	31	15 (48)	69.9 (40-87)	33.6 (12-130)	8.5 (high)
Kovacevic[11]	2021	Prospective	Single center	DK	TTNB	101	54 (53)	67.9 (37-85)	25.0 (15-93)	16.0 (high)
Mittal[20]	2018	Retrospective	Single center	USA	TTNB	27	16 (59)	65.0 (32-87)	37.8 (SD 16.9)	7.0 (low)
Yang[21]	2018	Retrospective	Multicenter	USA	TTNB	47	26 (55)	64.2	30.8 (12-110)	10.0 (high)
Yang[22]	2019	Prospective	Multicenter	USA	TTNB	114	64 (56)	65.0	35.1	10.5 (high)
Zhang[23]	2018	Retrospective	Single center	USA	TTNB	48	25 (52)	69.6 (27-90)	31.0 (12-60)	6.0 (low)
Chin[24]	2018	Prospective	Single-center	SG	nCLE	12	6 (50)	66.5	33.9 (19-62)	10.5 (high)
Kadayifci[25]	2017	Prospective	Single center	USA	nCLE	20	10 (50)	65.4 (SD 17.1)	34.2 (SD 9.6)	9.5 (high)
Keane[9]	2019	Prospective	Multicenter	UK	nCLE	56	26 (46)	68.0 (28-80)	25.0 (10-70)	14.0 (high)
Konda[26]	2013	Prospective	Multicenter	USA, FR, DE	nCLE	66	30 (45)	63.1 (27-89)	28.0 (7-90)	10.0 (high)
Krishna[5]	2020	Prospective	Single center	USA	nCLE	144	76 (53)	60.2 (SD 14.3)	36.4 (SD 15.7)	13.5 (high)
Nakai[27]	2015	Prospective	Single center	USA	nCLE	30	21 (70)	72.0 (37-86)	31.0 (5-64)	10.0 (high)
Napoleon[28]	2019	Prospective	Multicenter	FR	nCLE	78†	52 (67)	57.0 (28-81)	40.0 (20-110)	8.0 (high)
Cheesman[10]	2020	Retrospective	Single center	USA	nCLE	44	28 (64)	66.0	33.5 (16-90)	6.5 (low)
Haghighi[29]	2019	Retrospective	Single center	USA	nCLE	32	20 (63)	65.6 (26-83)	43.7 (9-136)	7.0 (low)

*After exclusion of overlapping patients; †A part of a larger cohort; technical success and diagnostic yield is hence reported on 209 patients. TTNB: Through-the-needle biopsy; nCLE: Needle-based confocal laser endomicroscopy; SD: Standard deviation

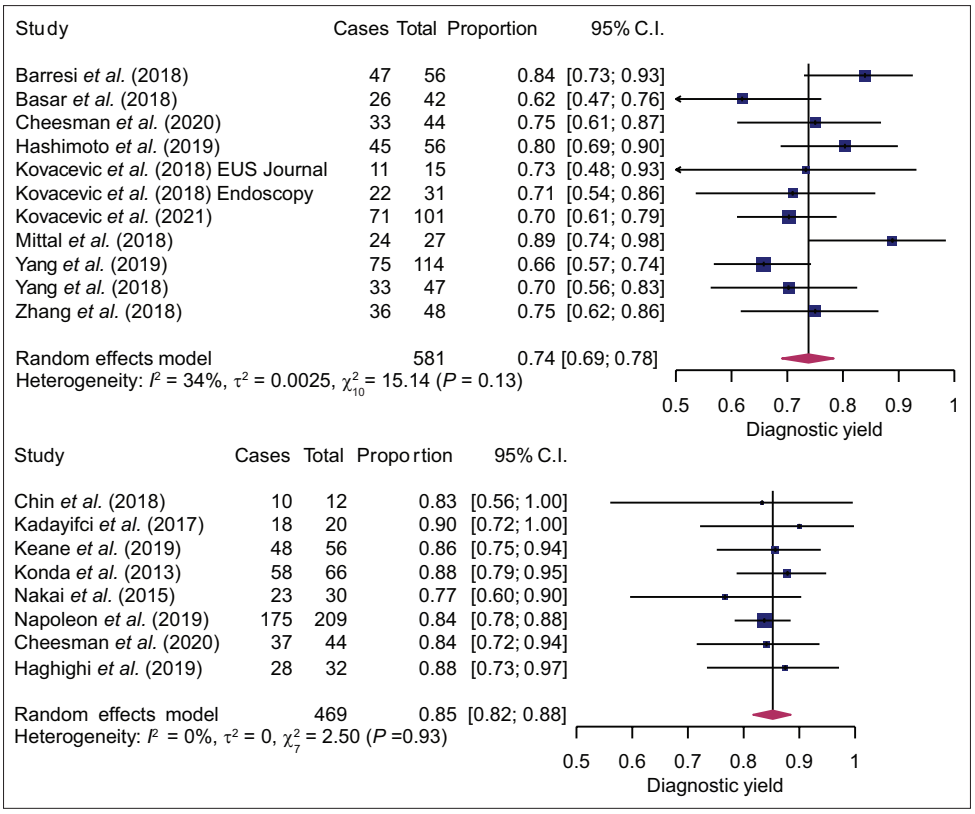

Figure 2. Forest plots of diagnostic yield of EUS-through-the-needle biopsy (top) and EUS-needle-based confocal laser endomicroscopy (bottom)

pathology published in 2011,[31] whereas TTNB was first introduced in 2016.[6] This difference can explain not only the lower heterogeneity in nCLE studies but possibly also the higher diagnostic yield observed, as it may well be the result of the high level of experience in image acquisition and interpretation in the high-volume centers performing EUS-nCLE. Several studies have confirmed this learning curve effect and showed an increased accuracy and levels of agreement following training period.[32-34] Similarly, EUS-TTNB yields very small tissue samples that require not only delicate processing but also an experienced pathologist to ensure a correct interpretation and diagnosis. Same learning curve effects seem to be present, hence the larger heterogeneity observed in EUS-TTNB studies.[11,35] Economical consideration must also be taken into account as the price of nCLE system is higher compared to TTNB (approximately $100,000 as the initial cost for the CLE system followed by $400 per examination compared to $500 for the TTNB forceps).[36]

AEs following EUS-FNA of PCLs are well known and include hemorrhage, pancreatitis, abdominal pain, and infection. A meta-analysis by Zhu *et al.* with >5000 patients estimated AE rate of EUS-FNA to be 2.7% (95% CI: 1.8%–3.6%), which does not seem to deviate significantly the results of this meta-analysis.[37] However, although mild and moderate AEs were similarly distributed in both groups, severe AEs due to pancreatitis were only observed in the EUS-TTNB group (n = 4, 0.7%). A single study reported a reduction in AEs following the use of high-volume perioperative resuscitation and prophylactic nonsteroid anti-inflammatory drugs; however, the difference was not statistically significant.[11] To determine whether this approach will reduce the occurrence of acute pancreatitis, a large number of patients is needed due to the low rate of this AE. However, it would be most relevant to identify high-risk patients who would benefit the most from this treatment.

Both diagnostic methods have high sensitivity and specificity, and the diagnostic performance is comparable. Moderate heterogeneity and low sample size when determining specificity are inherent to a naturally unbalanced distribution of PCLs, explaining why we decided to additionally calculate sROC curves with corresponding AUC values. Both methods had high and comparable AUC values. However, as surgical confirmation was only available in a small proportion of patients and the reference diagnosis was in most cases based on a combination of cytology, cyst fluid CEA, and cross-sectional imaging, the results must be interpreted carefully. Furthermore, when determining

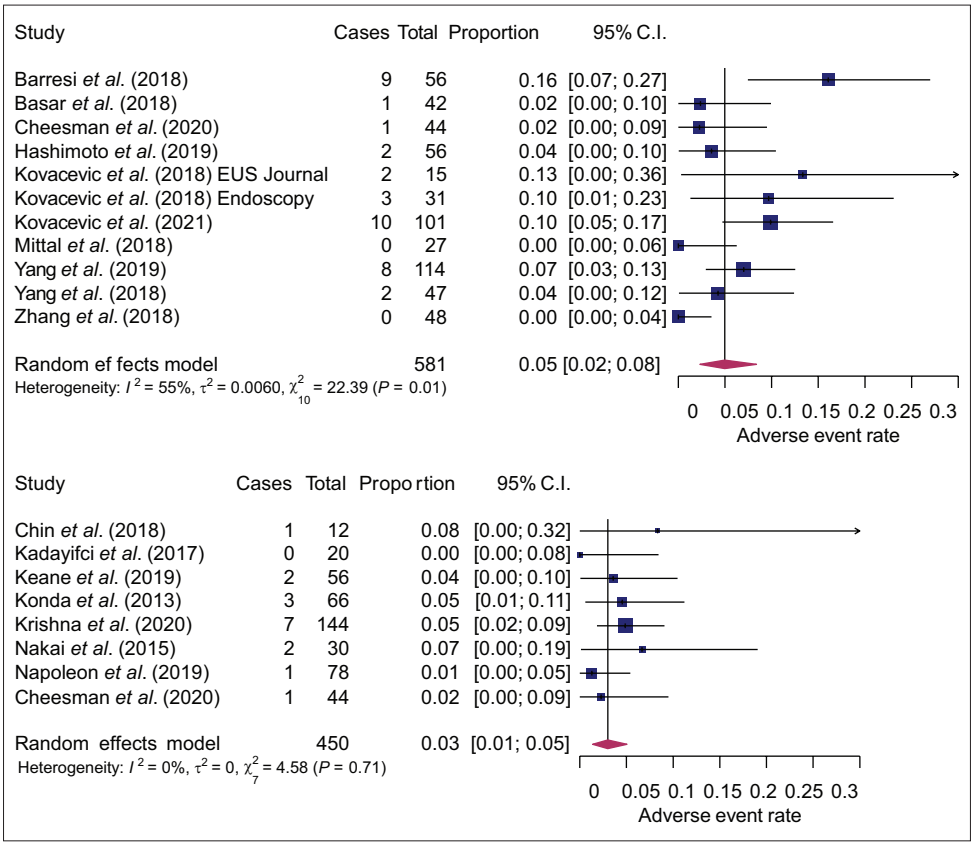

Figure 3. Forest plots of adverse event rate of EUS-through-the-needle biopsy (top) and EUS-needle-based confocal laser endomicroscopy (bottom)

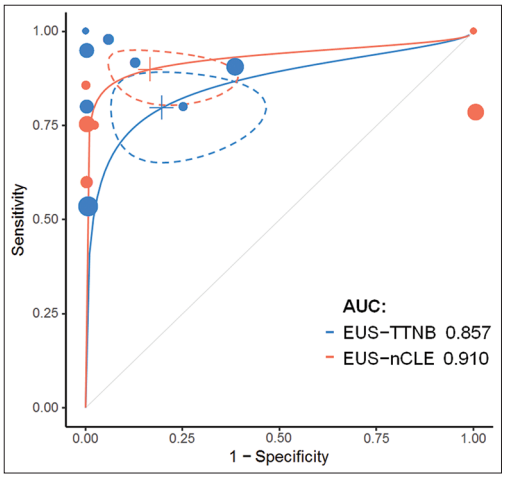

Figure 4. Receiver operating characteristics curves of the two methods with 95% confidence intervals (dashed lines) and individual studies plotted

concordance with the histological diagnosis in the surgical subgroup, a very small sample of 14 patients was encountered in the nCLE group. Although TTNB seemed to have a higher overall concordance rate (82% *vs.* 65%), any conclusions regarding nCLE may be unreliable due to previously mentioned limitations.

Extracting tissue samples provides the possibility of performing additional analyses, such as immunohistochemistry or even molecular sequencing, which is not feasible in case of EUS-nCLE. Specifically, IPMNs can be subdivided into three subtypes: gastric, intestinal, and pancreatobiliary, and the subtype seems to be associated with risk of malignancy and recurrence in case of resected lesions. Current guidelines recommend different follow-up based on the subtype of resected IPMNs, but the role of preoperative subtyping is currently unknown.[2] Furthermore, discerning IPMNs from MCNs is difficult and requires detection of an ovarian-type stroma, which is pathognomonic for MCN. Immunohistochemistry is useful in these cases, as different subtypes of IPMN show dissimilar expression of different MUC-proteins, whereas ovarian-type stroma stains positive for estrogen and progesterone receptor. Molecular analysis of the cyst fluid has shown promising results, as detection of certain mutations can reliably discern mucinous from nonmucinous lesions but also predict the grade of dysplasia.[38] Molecular sequencing of TTNBs may play a similar role in the future, but the current data are scarce.

CONCLUSION

This is the first systematic review and meta-analysis comparing EUS-TTNB and EUS-nCLE. Both methods

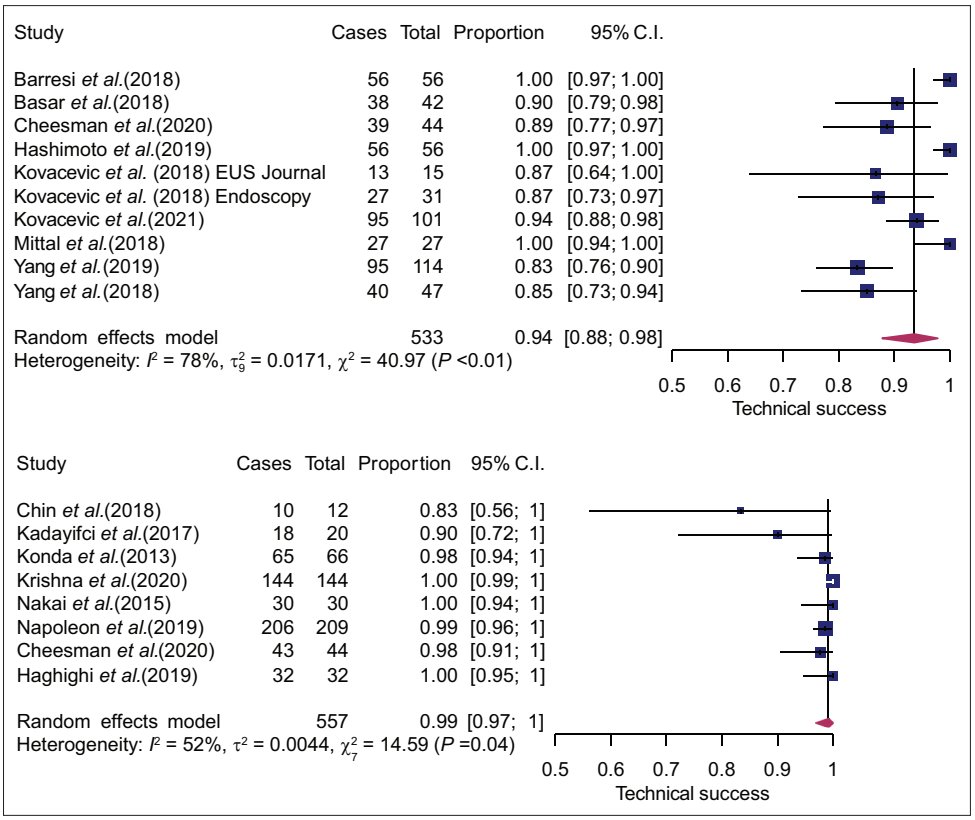

Figure 5. Forest plots of technical success of EUS-through-the-needle biopsy (top) and EUS-needle-based confocal laser endomicroscopy (bottom)

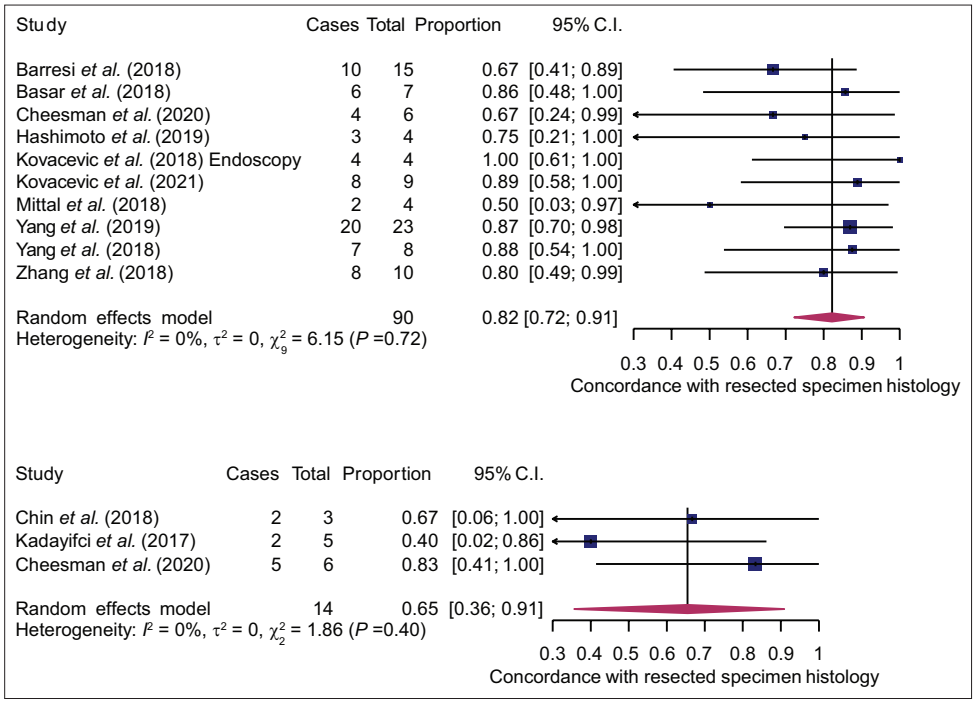

Figure 6. Forest plots of concordance rates of EUS-through-the-needle biopsy (top) and EUS-needle-based confocal laser endomicroscopy (bottom) with surgical histology

have a similar safety profile with a relatively low number of AEs. Diagnostic performance is comparable although EUS-nCLE seems to have a significantly higher diagnostic yield. While additional diagnostic possibilities of EUS-TTNB such as molecular analyses and IPMN subclassification will outweigh EUS-nCLE, remains to be seen.

Financial support and sponsorship

The authors wish to thank Danish Cancer Society, Arvid Nilsson Foundation, Ingrid Munkholm Foundation, Toyota Foundation, Novo Nordisk Foundation, Harboefonden, Tømrermester Jørgen Holm og hustru Elisa f. Hansens Mindelegat, and Herlev Hospital for their financial support.

Conflicts of interest

There are no conflicts of interest.

Supplementary Materials

Supplementary information is linked to the online version of the paper on the *Endoscopic Ultrasound* website.

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;67:138-45.
2. 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;17:738-53.
3. Thornton GD, McPhail MJ, Nayagam S, *et al*. Endoscopic ultrasound guided fine needle aspiration for the diagnosis of pancreatic cystic neoplasms: A meta-analysis. *Pancreatology* 2013;13:48-57.
4. Anand K, Kahaleh M, Tyberg A. Use of needle-based confocal laser endomicroscopy in the diagnosis and management of pancreatic cyst lesions. *Endosc Ultrasound* 2018;7:306-9.
5. Krishna SG, Hart PA, Malli A, *et al*. Endoscopic ultrasound-guided confocal laser endomicroscopy increases accuracy of differentiation of pancreatic cystic lesions. *Clin Gastroenterol Hepatol* 2020;18:432-40.e436.
6. Pham KD, Engjom T, Gjelberg Kollesete H, *et al*. Diagnosis of a mucinous pancreatic cyst and resection of an intracystic nodule using a novel through-the-needle micro forceps. *Endoscopy* 2016;48 Suppl 1:E125-6.
7. 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;32:1018-30.
8. Facciorusso A, Del Prete V, Antonino M, *et al*. Diagnostic yield of EUS-guided through-the-needle biopsy in pancreatic cysts: A meta-analysis. *Gastrointest Endosc* 2020;92:1-8.e3.
9. Keane MG, Wehnert N, Perez-Machado M, *et al*. A prospective trial of CONfocal endomicroscopy in CYSTic lesions of the pancreas: CONCYST-01. *Endosc Int Open* 2019;7:E1117-22.
10. 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;91:1095-104.
11. Kovacevic B, Klausen P, Rift CV, *et al*. Clinical impact of endoscopic ultrasound-guided through-the-needle microbiopsy in patients with pancreatic cysts. *Endoscopy* 2021;53:44-52.
12. Cotton PB, Eisen GM, Aabakken L, *et al*. A lexicon for endoscopic adverse events: Report of an ASGE workshop. *Gastrointest Endosc* 2010;71:446-54.
13. Slim K, Nini E, Forestier D, *et al*. Methodological index for non-randomized studies (minors): Development and validation of a new instrument. *ANZ J Surg* 2003;73:712-6.
14. Freeman M, Tukey J. Transformations related to the angular and the square root. *Ann Math Statist* 1950;21:607-11.
15. Barresi L, Crinò SF, Fabbri C, *et al*. Endoscopic ultrasound-through-the-needle biopsy in pancreatic cystic lesions: A multicenter study. *Dig Endosc* 2018;30:760-70.
16. Basar O, Yuksel O, Yang DJ, *et al*. Feasibility and safety of microforceps biopsy in the diagnosis of pancreatic cysts. *Gastrointest Endosc* 2018;88:79-86.
17. Hashimoto R, Lee JG, Chang KJ, *et al*. Endoscopic ultrasound-through-the-needle biopsy in pancreatic cystic lesions: A large single center experience. *World J Gastrointest Endosc* 2019;11:531-40.
18. Kovacevic B, Karstensen JG, Havre RF, *et al*. Initial experience with EUS-guided microbiopsy forceps in diagnosing pancreatic cystic lesions: A multicenter feasibility study (with video). *Endosc Ultrasound* 2018;7:383-8.
19. 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;50:1105-11.
20. 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;87:1263-9.
21. 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:E1423-30.
22. 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;17:1587-96.
23. Zhang ML, Arpin RN, Brugge WR, *et al*. Moray micro forceps biopsy improves the diagnosis of specific pancreatic cysts. *Cancer Cytopathol* 2018;126:414-20.
24. Chin YK, Khor CJ, Goh BK, *et al*. The clinical evaluation of needle-based confocal laser endomicroscopy in the assessment of pancreatic cystic lesion: A pilot study. *Proc Singapore Healthc* 2018;27:96-102.
25. Kadayifci A, Atar M, Basar O, *et al*. Needle-based confocal laser endomicroscopy for evaluation of cystic neoplasms of the pancreas. *Dig Dis Sci* 2017;62:1346-53.
26. 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;45:1006-13.
27. Nakai Y, Iwashita T, Park DH, *et al*. Diagnosis of pancreatic cysts: EUS-guided, through-the-needle confocal laser-induced endomicroscopy and cystoscopy trial: DETECT study. *Gastrointest Endosc* 2015;81:1204-14.
28. Napoleon B, Palazzo M, Lemaistre AI, *et al*. Needle-based confocal laser endomicroscopy of pancreatic cystic lesions: A prospective multicenter validation study in patients with definite diagnosis. *Endoscopy* 2019;51:825-35.
29. Haghighi M, Sethi A, Tavassoly I, *et al*. Diagnosis of pancreatic cystic lesions by virtual slicing: Comparison of diagnostic potential of needle-based confocal laser endomicroscopy versus endoscopic ultrasound-guided fine-needle aspiration. *J Pathol Inform* 2019;10:34.
30. Keane MG, Wehnert N, Perez-Machado M, *et al*. A prospective trial of CONfocal endomicroscopy in CYSTic lesions of the pancreas: CONCYST-01. *Endosc Int Open* 2019;7:E1117-22.
31. Konda VJ, Aslanian HR, Wallace MB, *et al*. First assessment of needle-based confocal laser endomicroscopy during EUS-FNA procedures of the pancreas (with videos). *Gastrointest Endosc* 2011;74:1049-60.
32. Chang J, Ip M, Yang M, *et al*. The learning curve, interobserver, and intraobserver agreement of endoscopic confocal laser endomicroscopy in the assessment of mucosal barrier defects. *Gastrointest Endosc* 2016;83:785-910.
33. Krishna SG, Brugge WR, Dewitt JM, *et al*. Needle-based confocal laser endomicroscopy for the diagnosis of pancreatic cystic lesions: An international external interobserver and intraobserver study (with videos). *Gastrointest Endosc* 2017;86:644-54.e642.

34. Liu J, Li M, Li Z, *et al*. Learning curve and interobserver agreement of confocal laser endomicroscopy for detecting precancerous or early-stage esophageal squamous cancer. *PLoS One* 2014;9:E99089.
35. Larghi A, Manfrin E, Fabbri C, *et al*. Interobserver agreement among expert pathologists on through-the-needle microforceps biopsy samples for evaluation of pancreatic cystic lesions. *Gastrointest Endosc* 2019;90:784-92.e784.
36. Karia K, Kahaleh M. A review of probe-based confocal laser endomicroscopy for pancreaticobiliary disease. *Clin Endosc* 2016;49:462-6.
37. Zhu H, Jiang F, Zhu J, *et al*. 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;29:667-75.
38. Singhi AD, McGrath K, Brand RE, *et al*. Preoperative next-generation sequencing of pancreatic cyst fluid is highly accurate in cyst classification and detection of advanced neoplasia. *Gut* 2018;67:2131-41.

SUPPLEMENTARY MATERIAL

Search string

- For EUS-TTNB: ("Moray" OR "microbiops*" OR "TTNF" OR "TTNB" OR "microforceps" OR "micro-biops*" OR "micro-forceps" OR "*through-the-needle*") AND ("pancrea*" OR "IPMN" OR "cyst*")
- For EUS-nCLE: ("*CLE" OR "confocal laser endomicroscop*") AND ("pancrea*" OR "IPMN" OR "cyst*").

Table S1. Meta-regression of intervention, study design and quality, patient age and lesion size on effect size estimates

	Effect size estimate	Lower 95% CI	Upper 95% CI	*P*
Diagnostic yield				
Intervention	0.1393	0.0740	0.2047	<0.0001
Study design	−0.0249	−0.1209	0.0711	0.6110
Quality	−0.0117	−0.1078	0.0845	0.8119
Lesion size	0.0059	−0.0032	0.0150	0.2053
Safety				
Intervention	−0.0426	−0.1235	0.0383	0.3022
Study design	−0.0131	−0.0969	0.0707	0.7586
Quality	0.0310	−0.0542	0.1162	0.4756
Patient age	−0.0019	−0.0122	0.0084	0.7221
Lesion size	−0.0009	−0.0103	0.0084	0.8462
Concordance with surgical histology				
Intervention	−0.1721	−0.4406	0.0963	0.2089
Study design	−0.0518	−0.2438	0.1403	0.5973
Quality	0.1224	−0.0641	0.3088	0.1983
Patient age	0.0152	−0.0102	0.0406	0.2409
Lesion size	−0.0150	−0.0391	0.0091	0.2229
Technical success				
Intervention	0.1173	−0.0079	0.2424	0.0664
Study design	−0.0120	−0.1527	0.1287	0.8675
Quality	−0.0628	−0.2021	0.0765	0.3769
Lesion size	0.0084	−0.0060	0.0228	0.2518

CI: Confidence interval

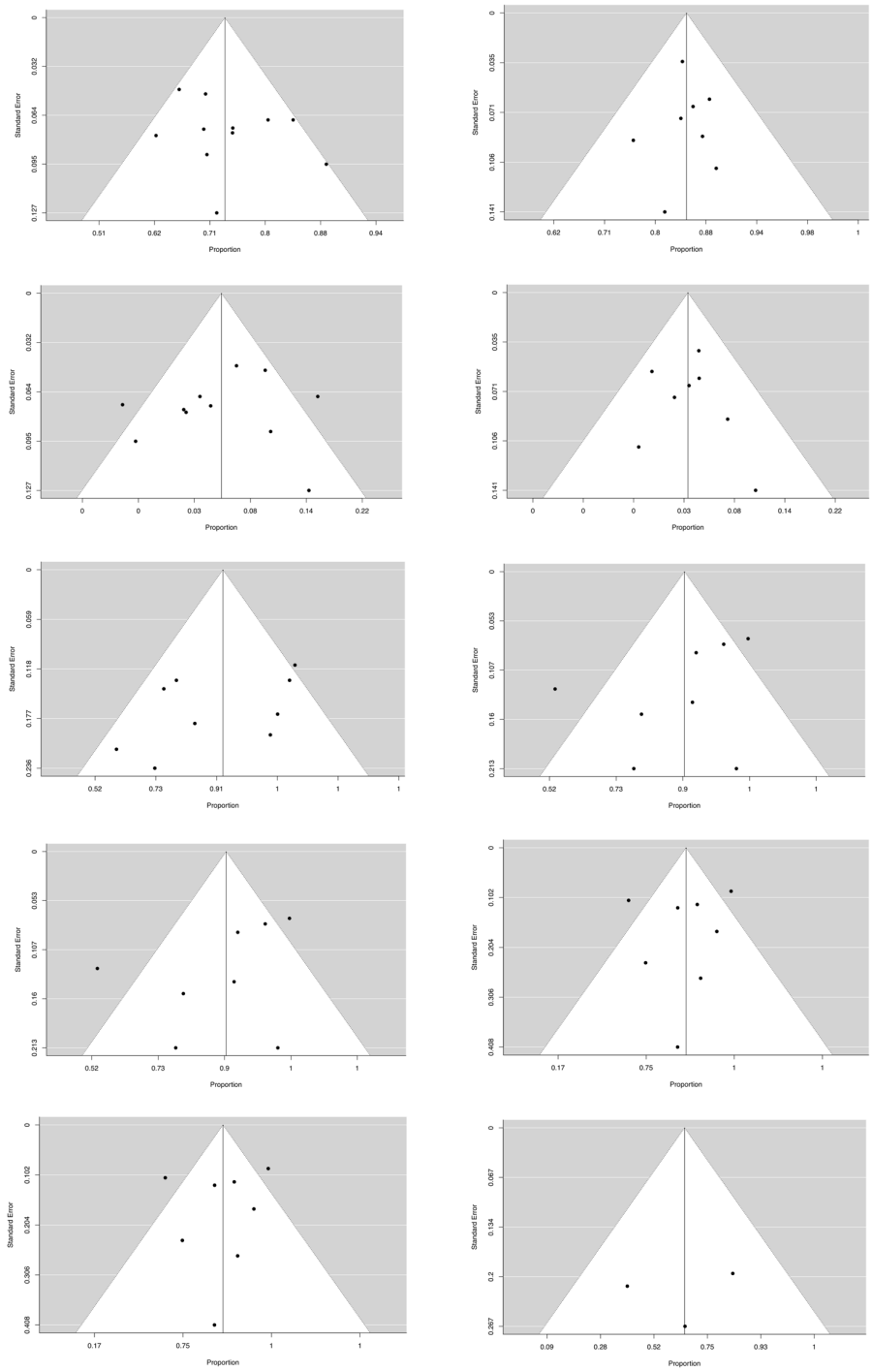

Figure S1. Funnel plots of effect size estimates for diagnostic yield, adverse event rate, sensitivity for mucinous lesions, specificity for mucinous lesions, and concordance with surgical histology respectively for each row. Left column corresponds to EUS-through-the-needle biopsy, whereas the right column depicts EUS-needle-based confocal laser endomicroscopy