Pancreatology 24 (2024) 649–660

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Contrast-enhanced endoscopic ultrasound likely does not improve diagnostic adequacy during endoscopic ultrasound guided tissue acquisition: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 10 September 2023
Received in revised form
16 April 2024
Accepted 23 April 2024
Available online 24 April 2024

Keywords:
Endoscopic ultrasonography
Pancreatic neoplasms
Endoscopic ultrasound-guided fine needle aspiration
Fine needle biopsy

ABSTRACT

Background and aims: Solid pancreatic masses are sampled through tissue acquisition by endoscopic ultrasound (EUS). Inadequate samples may significantly delay diagnosis, increasing costs and carrying risks to the patients. Aim: assess the diagnostic adequacy of tissue acquisition using contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS) compared to conventional EUS.

Methods: Five databases (PubMed, Embase, CENTRAL, Scopus and Web of Science) were searched in November 2023. Studies comparing diagnostic adequacy, accuracy and safety using CEH-EUS versus conventional EUS for tissue acquisition of solid pancreatic masses were included. Risk of bias was assessed using the Risk of Bias tool for randomized controlled trials (RoB2) and the Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool for non-randomized studies, level of evidence using the GRADE approach, Odds Ratios (RR) with 95 % Confidence Intervals (CI) calculated and pooled using a random-effects model. I^2 quantified heterogeneity.

Results: The search identified 3858 records; nine studies (1160 patients) were included. OR for achieving an adequate sample was 1.467 (CI: 0.850–2.533), for randomized trials 0.902 (CI: 0.541–1.505), for non-randomized 2.396 (CI: 0.916–6.264), with significant subgroup difference. OR for diagnostic accuracy was 1.326 (CI: 0.890–1977), for randomized trials 0.997 (CI: 0.593–1.977) and for non-randomized studies 1.928 (CI: 1.096–3.393), significant subgroup difference ($p = 0.0467$). No differences were observed for technical failures or adverse events. Heterogeneity was low, risk of bias "low" to "some concerns" for most outcomes, mostly moderate for non-randomized studies.

Conclusion: Non-randomized studies indicated differences in favor of contrast-enhanced EUS, randomized studies showed no difference in diagnostic adequacy, accuracy or sensitivity when using CEH-EUS.

1. Introduction

Pancreatic cancer is a leading cause of cancer death worldwide [1,2], with cases usually detected late and treatment options being scarce. One commonly used diagnostic tool for solid pancreatic masses is endoscopic ultrasound (EUS) guided tissue acquisition – aspiration or biopsy [3–5]. The sampling is an invasive procedure that requires sedation, clinical resources, and risks side effects, including pancreatitis and bleeding. Fourteen percent of samples are not adequate for histology and eight percent not adequate for cytology after up to two needle passes [6], as pancreatic masses may be difficult to target and are often surrounded by scar tissue or necrotic areas, which may decrease diagnostic sensitivity [3,7,8]. Improving the efficacy of EUS-guided tissue acquisition (EUS-TA) is important for a few reasons. A higher number of needle passes in one session may prolong the procedure and the need for sedation.

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https://doi.org/10.1016/j.pan.2024.04.007

List of abbreviations

CEH-EUS	Contrast enhanced harmonic endoscopic ultrasound
CI	Confidence Interval
EUS	Endoscopic Ultrasound
FNA	Fine needle aspiration
FNB	Fine needle biopsy
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
OR	Odds Ratio
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RR	Risk Ratio
TA	Tissue acquisition

It may also lead to higher costs due to greater equipment use [9].

Several strategies have been tested to decrease the rate of inadequate sampling and to protect patients from unnecessary re-intervention or re-puncture. Among the suggested strategies are the use of different needle tip designs, different types of suction, and variations of other technologies used.

Contrast-enhanced ultrasound allows better visualization of vessels in tissue, thereby allowing more precise discrimination of scar tissue from biologically active tissues [3,10]. This ability may allow better targeting of the mass for sampling, and studies have been carried out to determine whether this may increase diagnostic sensitivity and decrease the rate of inadequate samples. Contrast-enhanced EUS during the puncture has previously been shown to be cost-effective in a retrospective study that suggested that reducing the number of needles used off-set the cost of using contrast during the EUS [9]. CEH-EUS is discussed in the most recent European Society of Gastrointestinal Endoscopy (ESGE) guidelines for sampling of solid masses as a potential method to improve the sampling rate of solid pancreatic masses in patients with chronic pancreatitis. Here, guidelines highlight the inconclusive results in recent studies [5,11,12]. Recent ESGE guidelines on technical aspects of EUS-guided sampling specifically chose to not give recommendations due to the lack of evidence on the subject [13].

In this systematic review and meta-analysis, we aimed to assess the published evidence of the impact of contrast-enhanced ultrasound on sampling efficacy and safety during EUS-guided tissue acquisition of pancreatic solid masses.

2. Methods

2.1. Reporting and protocol

We report this systematic review and meta-analysis according to the recommendations of the PRISMA 2020 guideline (see Supplementary Table S1), and during the process, we followed the methodological guidance of the Cochrane Handbook [14]. The protocol of this review was registered on PROSPERO (CRD42022285023). The following protocol deviations occurred: Search and selection was expanded to include non-randomized studies during peer-review, diagnostic parameters from the included studies were pooled for added information on the clinical importance of any potential differences.

2.2. Inclusion criteria

Studies reporting on patients undergoing EUS-guided tissue acquisition (EUS-TA) for a solid pancreatic mass were included if they compared the use of contrast-enhanced EUS to that of conventional EUS and investigated the diagnostic adequacy, rate of adverse events and technical failures, number of needle passes or tissue yield. Randomized controlled trials, non-randomized interventional studies and prospective and retrospective cohort studies were eligible for inclusion. In cases where studies reported having assessed an outcome but did not publish results for that outcome, the corresponding author was contacted, and the relevant data were requested.

2.3. Outcomes

1.) Diagnostic adequacy

Diagnostic adequacy was chosen as the primary outcome, as EUS-TA is a sampling method, not a diagnostic method – and the diagnosis is made by a histopathologist following the sampling. Diagnostic adequacy was defined using the definition used in the papers, or where unavailable, as the inverse of inadequate or non-diagnostic samples.

2.) Diagnostic test parameters

The included studies and a previous meta-analysis [15] reported diagnostic test parameters. However, in most studies these comparisons were not reported in a way appropriate for diagnostic test meta-analysis, as diagnostic test meta-analysis requires sensitivity and specificity reported together, to analyze these as mutually dependent [16].

To assess diagnostic test parameters, the following outcome measures were used:

Sensitivity, Specificity and Accuracy for malignant versus benign cases were treated as regular dichotomous outcomes and used both for individual quantification of efficacy of both types of ultrasound (as proportions), and to compare the two using ratios (Risk or Odds Ratios). True negatives (TN), false positives (FP), true positives (TP) and false negatives (FN) were extracted or calculated from sensitivity or specificity and case numbers where available. Sensitivity was calculated as the proportion of TP to all malignant cases, specificity was calculated as the proportion of TN to all benign cases, and accuracy was calculated as the proportion of all correctly identified patients (benign or malignant) to all cases. Further, these numbers were used to conduct a regular, bivariate diagnostic meta-analysis as well.

3.) Adverse events

Adverse events were included as a safety outcome where available, using the definitions of the included papers.

4.) Needle passes needed

The number of needle passes needed to achieve an adequate sample were extracted from papers and pooled as a continuous outcome.

2.4. Eligibility for synthesis

As the papers differed in number of needle passes performed and this was considered an important confounding factor, this was considered when deciding which articles to pool. The data was

tabulated, and an analysis was performed for each needle pass for which basic requirements for analysis were satisfied (minimum of 3 eligible articles for the outcome). For studies which only gave a mean number of passes, this was the number considered. An additional analysis was performed including the final pass from each study.

2.5. Search and selection

The systematic search was performed on November 19th, 2023, in five major databases (Medline – via PubMed, Embase, CENTRAL, Scopus, and Web of Science). The search key consisted of domains representing pancreatic masses, tissue acquisition, and contrast-enhanced ultrasound (see supplementary material).

After automatic and subsequent manual duplicate removal, the selection was performed by two independent review authors (MAE, ASW) in two stages (by title and abstract, then by full text), with any disagreements resolved by a discussion. The degree of agreement was quantified using Cohen's kappa [17].

References of the included articles were systematically searched using an online tool [18].

2.6. Data extraction

Data extraction was performed by two reviewers independently (YH, OA) and compared by a third author (MAE). It was done in a pre-designed Excel sheet, and data were extracted on basic data of the study (author, year, location, number of centers), population data (age, sex, location of pancreatic mass), procedure data (details of sampling, the experience of the endoscopist and pathologist), outcomes (diagnostic adequacy, adverse events, technical failures, number of needle passes, tissue yield, rates of accurate diagnoses, rates of diagnostic sensitivity, diagnostic data (TP, FP, TN, FN) and their definitions.

2.7. Risk of bias and quality of evidence assessment

For randomized controlled trials (RCTs), the risk of bias was assessed using version 2 of the Cochrane Risk of Bias tool [19]. This assessment was performed by two independent reviewers (YH, OA), with disagreements resolved by a third reviewer (ME). For non-randomized studies of interventions, the Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool [20] was used and the assessments were performed by two independent reviewers (MAE, ASW) with disagreements resolved by discussion.

The strength of evidence was assessed with the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach [21] with the help of the GradePRO software [22].

2.8. Synthesis methods

Risk ratios (RRs) with a 95 % confidence interval (CI) were used for the effect size measure for the results from RCTs, as it is easier to interpret and RCTs have a higher level of evidence. When including non-randomized studies, odds ratios (ORs) were used instead. To calculate these ratios, the total number of patients and those with the event of interest (in each group separately) was extracted from each study. The results are reported as risk or odds of event of interest in the CEH-EUS group, versus the risk or odds of event of interest in the conventional group. For continuous outcomes, mean differences (MDs) with 95 % confidence interval (CI) were used and reported as the mean in the CEH-EUS group minus the mean in the conventional group. For diagnostic outcomes, different effect sizes were used: RRs or ORs for direct comparison, proportions for sensitivity, specificity and accuracy, As we anticipated considerable between-study heterogeneity, a random-effects model was used to pool effect sizes. Pooled RR and OR based on raw data was calculated by the Mantel-Haenszel method [23–25]. The exact Mantel-Haenszel method (without continuity correction) was used to handle zero cell counts. We used Hartung-Knapp adjustments for CIs. To estimate the heterogeneity variance measure $\tau 2$, the Paule-Mandel method [26] with the Q profile for confidence interval was applied [27]. Forest plots were used to graphically summarize the results. However, due to the small number of studies, assessing publication bias or performing outlier and influential analyses were not possible. All statistical analyses were made with R (R Core Team 2022, v4.2.1) using the meta (v5.5.0) package [28] and dmetar [29] for meta-analysis calculations. More detailed descriptions of analysis can be found in the supplementary material.

3. Results

3.1. Search and selection

Our search identified 7200 studies, of which 3852 remained after duplicate removal. Cohen's kappa of title abstract selection was 0.79 (substantial agreement), while that of full-text selection was 1.0 (perfect agreement). Nine studies [9,11,12,30–35] were included for synthesis, reporting on 1160 patients. Our search also identified two protocols of ongoing randomized trials [36,37]. The exact progression of selection is detailed in the PRISMA flowchart (Fig. 1).

The baseline characteristics of included studies are detailed in Table 1. Supplementary Table S2 lists the identified protocols of ongoing trials not already published and their details.

3.2. Diagnostic adequacy

3.2.1. Final pass

Seven studies total reported adequacy, four randomized trials [11,12,32,33] (three [11,32,33] reported the outcome in the text, data for the fourth [12] was provided by the corresponding author at our request), and three non-randomized studies [9,31,35]. The pooled OR for achieving an adequate sample was 1.467 (CI: 0.850–2.533), with subgroup totals of 0.902 (CI: 0.541–1.505) for randomized trials and 2.396 (CI: 0.916–6.264) for observational studies(Fig. 2). The test for subgroup differences was significant ($p = 0.0045$). For the analysis of randomized trials only, the pooled RR for achieving an adequate sample was 1.002 (95 % CI: 0.81–1.39), i^2 was 0 % (Fig. S1).

3.2.2. 1st pass

Four studies reported the diagnostic adequacy after the first pass, three RCTs [11,12,32] and one non-randomized study [35]. The pooled OR for adequacy was 2.263 (CI: 0.960–5.334) (Fig. S2). Two studies appeared to indicate no difference [12,32], while two studies [11,35] were significantly in favor of CEH-EUS. Pooling only randomized trials, RR was 1.171 (CI: 0.433–3.170), see Fig. S3.

3.3. Diagnostic accuracy

3.3.1. Final pass

Seven studies in total reported data necessary to calculate the accuracy, four randomized trials [11,12,32,33] and three non-randomized studies [9,30,31]. The pooled OR for diagnostic accuracy was 1.326 (CI: 0.890–1977), with subgroup totals of 0.997 (CI: 0.593–1.977) for randomized trials and 1.928 (CI: 1.096–3.393) for observational studies. The test for subgroup difference was significant ($p = 0.0467$), heterogeneity was low ($i^2 = 0$ %) (Fig. 3). The RR

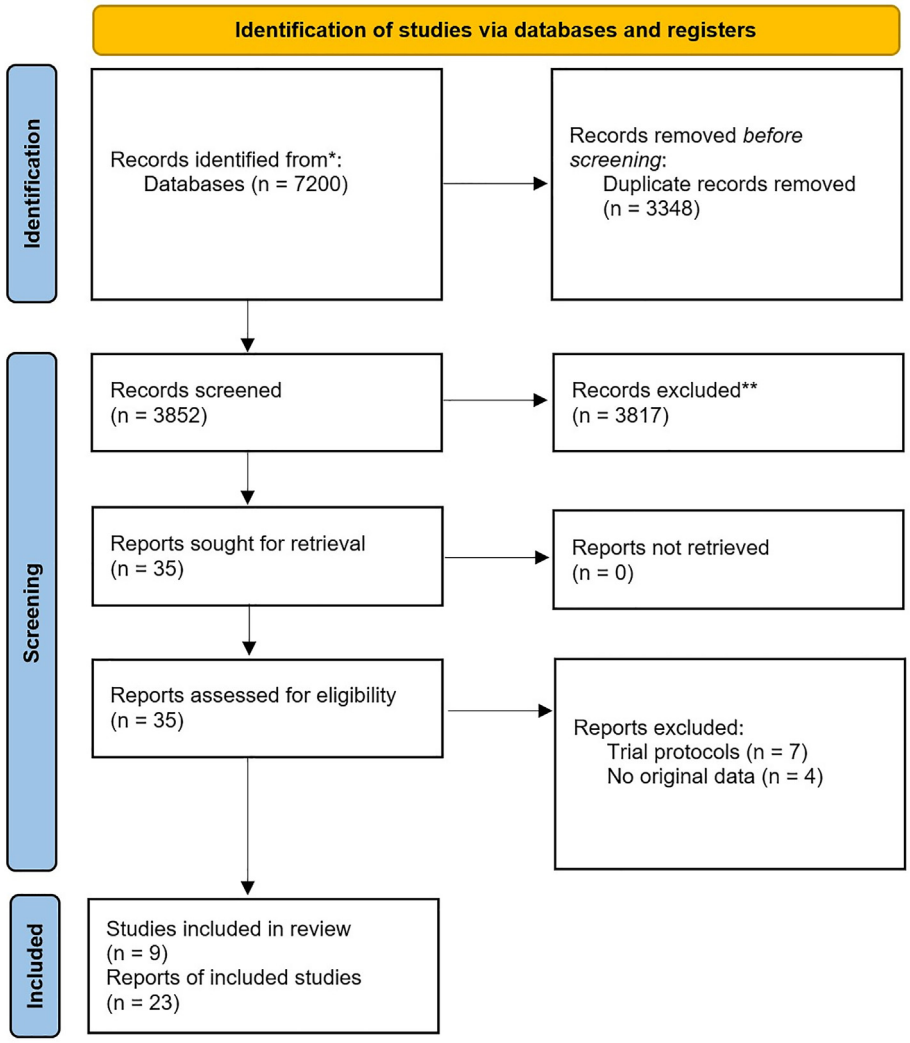

Fig. 1. PRISMA Flowchart detailing the selection process.

analysis including only randomized trials was 0.988 (CI: 0.959–1.017), heterogeneity was low ($i^2 = 0$ %) (Fig. S4).

3.3.2. 1st pass

Three studies [12,32,33] reported the accuracy after the first pass. The pooled OR for diagnostic accuracy was 1.182 (CI: 0.806–1.733). Heterogeneity was low ($i^2 = 0$ %). The forest plot of this analysis may be found in the supplementary material (Fig. S5).

3.3.3. 2. pass

Three studies [12,32,33] reported the accuracy after the second pass. The pooled OR for diagnostic accuracy after the second pass was 1.123 (CI: 0.340–3.706). The forest plot of this analysis may be found in the supplementary material (Fig. S6).

3.4. Sensitivity and specificity

1.) Ratios

Sensitivity: Nine studies reported data necessary to calculate sensitivity ratios, the pooled OR was 1.494 (CI: 1.052–2.121). In the subgroup for RCTs, the pooled OR was 0.968 (0.535–1.753), in that for non-randomized studies it was 1.950 (1.294–2.940). The test for subgroup differences was significant ($p = 0.0125$), heterogeneity was low ($i^2 = 0$ %). Including only RCTs, the pooled RR was 0.998 (CI: 0.965–1.033). Heterogeneity was low ($i^2 = 0$ %) (Fig. 4).

Specificity: Six studies [9,30–32,35] reported data necessary to calculate specificity ratios, however, due to a 100 % specificity rate in all but 1 study [32], pooling was not feasible.

2.) Proportions

Sensitivity: All studies reported data necessary to calculate sensitivity proportions. The pooled proportion in the case of CEH-EUS was 0.887 (CI: 0.826–0.928), with RCTS at 0.923 (0.694–0.985) and non-randomized studies at 0.858 (CI: 0.766–0.918). Heterogeneity was low ($i^2 = 7$ %), test for subgroup differences not significant ($p = 0.2281$) (Fig. S6). For conventional EUS the proportion was 0.854 (CI:0.740–0.924), in the subgroup of randomized trials 0.923 (CI: 0.696–0.985), in the subgroup of non-randomized studies 0.780 (CI: 0.620–0.885). Heterogeneity was substantial ($i^2 = 79$ %), the test for subgroup differences was significant ($p = 0.0384$) (Fig. S7).

Specificity: Six studies [9,30–32,35] reported data necessary to calculate specificity proportions, however, due to a 100 % specificity rate in all but 1 study [32], pooling was not feasible.

Table 1
Baseline characteristics of included studies. RCT: Randomized controlled trial, EUS-FNA: Endoscopic Ultrasound-guided Fine Needle Aspiration, CEH-EUS: contrast-enhanced harmonic endoscopic ultrasound, mm: millimeter.

Author (Year)	Country	Enrollment Period	Number of patients (female %)	Age (years)	Size of lesion (mm)	Study design	Endoscopist experience	Sampling technique	Ultrasound technique	Needle	Reference for diagnostic test parameters	Malignant NET Benign
Cho (2021)	South Korea	March 2016 −September 2019	240 (47.1 %)	67.3 (±11.85) EUS: 68.28 (±11.90), CEH-EUS: 66.31 (±11.78)[a]	32.03 (±14.41) EUS: 33.09 (±16.39), CEH-EUS: 30.96 (±12.09)[a]	Parallel RCT	"Experienced endosonographers"	10 mL negative pressure 20 to-and-fro movements	GF-UCT 260; Olympus. CEH-EUS: 2.4 mL SonoVue, 10 mL saline flush	19-25G FNA or FNB	Pathology results of FNA/FNB sampling or the surgical specimen. If unavailable, imaging studies 6 months after the endoscopic procedure. Malignancy where lesion progression or metastasis was observed on follow-up imaging, benign disease with a stable lesion without an increasing size or metastasis.	90.8 % 3.8 % 5.4 %
Facciorusso (2020)	Italy	January 2008 −December 2019	362 (40.6 %), 206 (45.1 %) after propensity score matching	Matched population: EUS: 66 ± 8 CEH-EUS ±6	Matched population: EUS: 32 ± 1, CEH-EUS: 32 ± 1.1	Propensity-score matched analysis, prospective	"Board certified gastroenterologist with 20 years' experience"	10 mL negative pressure "more than 10 to-and-fro movements"	Pentax FG-36UA CEH-EUS: 4.8 mL SonoVue followed by 20 mL saline flush	22G FNA (EchoTip Ultra, Cook Medical)	Surgical pathology or clinical course (progression or death, clinical changes indicative of diagnosis of benign disease) during follow-up of 12 months	73.9 % 6.7 % 19.4 %
Hou (2015)	China	October 2010−July 2013	163, CEH-EUS: 59 (38 %), Conventional: 105 (40 %)	CEH-EUS: 55.1 (±11.7)[a] Conventional: 56.2 (±12.5)[a]	Ceh-EUS: 38 (±12)[a] Conventional: 39 (±8) [a]	Post-hoc analysis of prospectively collected data	"Experienced Endosonographer"	NA	GFUCT2000(Olympus) CEH-EUS: GFUC-30p (Olympus) 4.8 mL SonoVue, 20 mL saline flush	22G needle (Wilson Cook Medical)	Surgical pathology, malignant cytology with clinical progression compatible with the diagnosis, or death from malignancy. In the absence of surgical confirmation, 12 month follow-up for disease progression or resolution of imaging or clinical changes.	61.3 % 6.13 % 32.5 %
Itonaga (2020)	Japan	October 2016 −October 2017	93 (46.3 %)	72.5 (34−89) [c]	25.2 (12−56) [c]	Prospective cohort with crossover	>300 EUS-FNA procedures	Negative pressure with 20 mL syringe, 20 to-and-fro movements	GF-UCT260 (Olympus) CEH-EUS: No information regarding contrast agent.	22G FNA (EZ shot 3, Olympus)	Surgical pathology result or 12 month follow-up with US, CT, MRI and/or EUS every 2−6 months or until death.	90.3 % 4.3 % 5.4 %
Kuo (2023)	Taiwan	February 2019 −January 2021	118 (39 %)	64.4 (±12.1) [a]	37.5 (30−46) [b]	Parallel RCT	"Experienced Endosonographers"	No suction. Conventional: 4x4 to-and-fro movement, fanning technique. CEH-EUS: 16 to-and-fro movements	GF-UCT260, (Olympus) CEH-EUS: 0.015 mL/kg body weight Sonazoid, 10 mL saline flush	22G FNB (Acquire, Boston Scientific)	Histopathological diagnosis surgical specimen, EUS-FNB with a compatible clinical course, or negative FNB diagnosis with no deterioration on imaging studies for follow-up time of 6 months	89 % 2.5 % 3.4 %
Lai (2022)	Taiwan	January 2019 −March 2021	155 (53.5 %)	63.64 (±12.58)	31.8 (±16.0) CEH-EUS: 29.5 (±11.5) Conventional: 34.8 (±18.2)	Retrospective chart review, CEH-EUS patients volunteered to self-pay procedure	"Two endoscopists who achieved the FNA learning curve"	Fanning method from at least 4 areas, slow-pull or low-negative suction	GF-UCT260, (Olympus) CEH-EUS: 0.015 mg/kg Sonazoid	22G FNB (Acquire, Boston Scientific)	Successful FNB diagnosis (suspicious or positive), surgical direct biopsy or transabdominal echo-guided metastatic lesion biopsy. In benign diagnosis: Imaging follow-up for at least 6 months.	74.2 % 11.6 % 12.2 %

(*continued on next page*)

Table 1 (*continued*)

Author (Year)	Country	Enrollment Period	Number of patients (female %)	Age (years)	Size of lesion (mm)	Study design	Endoscopist experience	Sampling technique	Ultrasound technique	Needle	Reference for diagnostic test parameters	Malignant NET Benign
Seicean (2015)	Romania	November 2012−March 2013	51 (41.2 %)	54 (30−83) [b]	35	Prospective cohort with crossover	No information	No suction, fanning technique used where possible.	GF-UCT180-AL5 (Olympus). CEH-EUS: 2.4 mL SonoVue followed by 5 mL saline flush-	22G FNA (Olympus)	FNA results in 38 patients, FNA + Surgical pathology in 13, in case of negative FNA findings 12-month clinical follow up, transabdominal ultrasound at 3-month intervals, repeated spiral CT/EUS if needed.	78.4 % 1.9 % 19.6 %
Seicean (2020)	Romania	January 2017 −October 2019	150 (43.2 %)	64.5 (±11.3) [a]	30 (20.8−35) [b]	Crossover RCT	>7000 EUS-FNA and >500 CEH-EUS	Slow-pull, 10 to-and-fro movements	GF-UCT 180 AL5 (Olympus) CEH-EUS: 2.4 ml SonoVue, 5 mL saline flush	22G FNA (Expect, Boston Scientific)	FNA results or post-surgical histopathological examination. Negative FNA findings: 12 month clinical follow up, CT at 3 months, subsequent transabdominal ultrasound at 3-month intervals.	78.3 % 8.8 % 12.8 %
Sugimoto (2015)	Japan	September 2013−June 2014	40 (62.5 %)	CEH-EUS: 69.5 (±10.5) [a] Conventional: 67.1 (±9.9) [a]	CEH-EUS: 25.0 (±8.0) [a] Conventional: 26.5 (±9.2) [a]	Parallel RCT	1st pass <100 EUS-FNA, 2nd pass >300 EUS-FNA	Negative pressure with 10 ml syringe, 20 to-and-fro movements	GF-UCT 260, GF-UCT24-AL5 (Olympus) CEH-EUS: 0.015 ml/kg Sonazoid	CEH-EUS: 22G FNB (Expect, Boston Scientific), Conventional: 22G or 25G Expect (Boston Scientific), 25G Echotip (Cook Medical), 22G EZ shot2 (Olympus Medical Systems)	Surgical specimens, if unresectable then based on EUS-FNA and imaging. Cytology class IV/V was deemed malignant	100 % 0 % 0 %

[a] Mean + SD.
[b] Median and range.
[c] Mean and range.

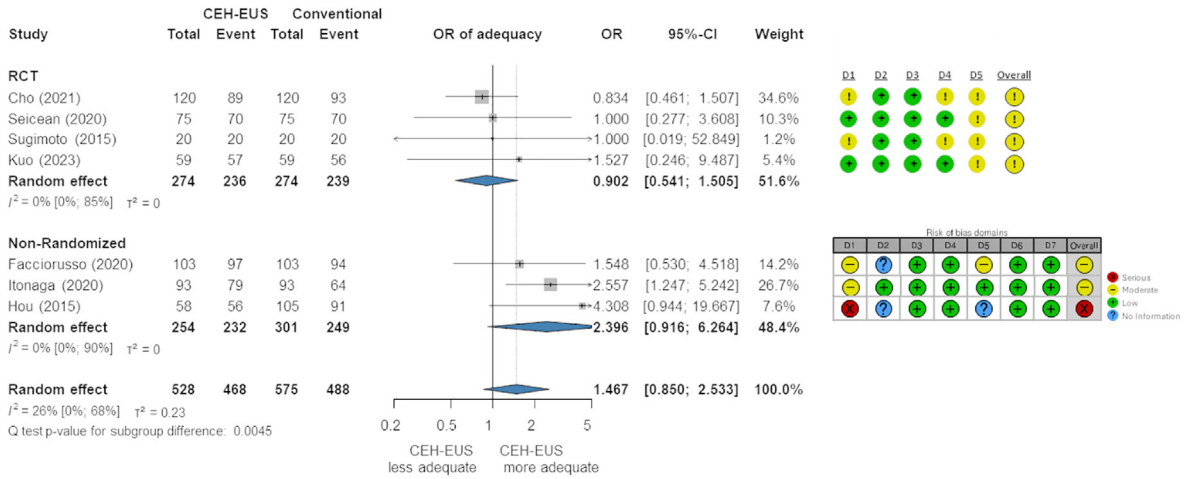

Fig. 2. Forest plot of pooled odds ratios for an adequate sample following tissue acquisition (FNA/FNB) using contrast-enhanced versus conventional ultrasound. Data for final needle pass used in each study. Results of the are summarized on the right by study, domain and overall. For Cochrane risk-of-bias tool v.2 (RoB2): Domains: D1: Risk arising from the randomization process, D2: Bias due to deviations from intended intervention, D3: Bias due to missing outcome data, D4: Bias in the measurement of the outcome, D5: Bias in the selection of the reported result. For Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool: D1: Bias due to confounding, D2: Bias due to selection of participants, D3: Bias in classification of interventions, D4: Bias due to deviations from intended interventions, D5: Bias due to missing data, D6: Bias in measurement of outcomes, D7: Bias in selection of the reported results
CEH-EUS: Contrast-enhanced harmonic endoscopic ultrasound, OR: Odds Ratio.

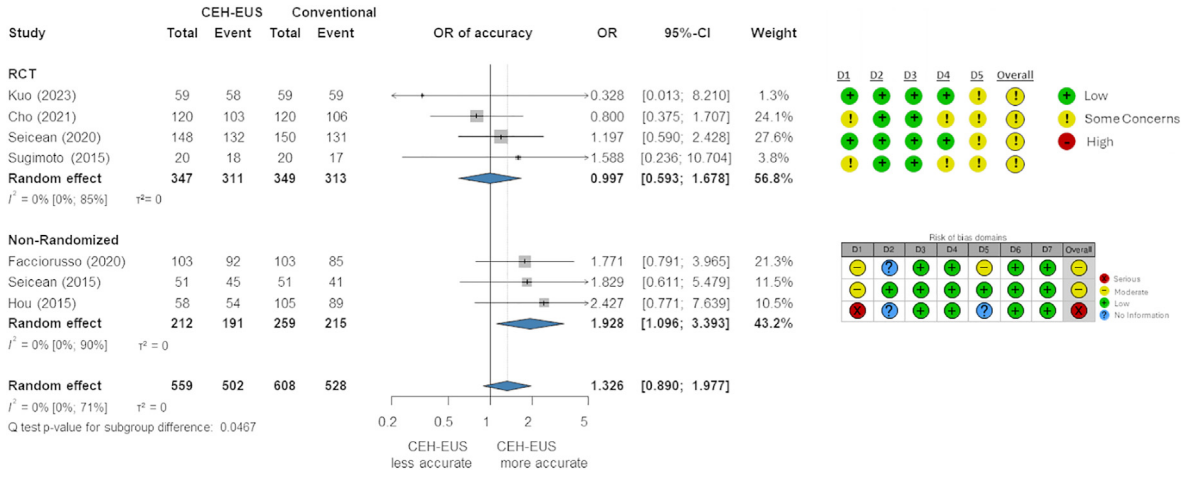

Fig. 3. Forest plot of pooled odds ratios for accurately diagnosing both negative and positive cases (diagnostic accuracy). Results of the Risk of Bias assessment are summarized on the right by study, domain and overall. For Cochrane risk-of-bias tool v.2 (RoB2): Domains: D1: Risk arising from the randomization process, D2: Bias due to deviations from intended intervention, D3: Bias due to missing outcome data, D4: Bias in the measurement of the outcome, D5: Bias in the selection of the reported result. For Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool: D1: Bias due to confounding, D2: Bias due to selection of participants, D3: Bias in classification of interventions, D4: Bias due to deviations from intended interventions, D5: Bias due to missing data, D6: Bias in measurement of outcomes, D7: Bias in selection of the reported results
CEH-EUS: Contrast-enhanced harmonic endoscopic ultrasound, OR: Odds Ratio.

3.) Bivariate Diagnostic Meta-Analysis

Conventional EUS: Six studies [9,12,30–32,35] reported data to calculate diagnostic test parameters in a bivariate basis. Bivariate analysis showed a sensitivity of 0.835 (CI: 0.673–0.926) for conventional EUS. Subgroup analysis for study type was not feasible. Heterogeneity was substantial ($i^2 = 75$ %). Pooled specificity with bivariate analysis was 1.000 (CI: 0.000–1.000), heterogeneity was low ($i^2 = 0$ %) (Fig. S8).

CEH-EUS: Six studies [9,12,30–32,35] reported data to calculate diagnostic test parameters in a bivariate basis. Bivariate analysis showed a sensitivity of 0.892 (CI: 0.807–0.942) for conventional EUS. Subgroup analysis for study type was not feasible. Heterogeneity was low ($i^2 = 22$ %). Pooled specificity with bivariate analysis was 0.998 (CI: 0.476–1.000), heterogeneity was low ($i^2 = 0$ %) (Fig. S8).

3.5. Adverse events

Adverse events were reported in all randomized trials, however two studies [11,12] reported zero event rates, while the other two [32,33] observed equal events in both arms. The RR for adverse events was 1.00 (95 % CI: 0.29–3.41), shown in Fig. 5.

3.6. Technical failures

No article reported the rate of technical failures, however Seicean et al. provided data on the rate of technical failures upon our request for their randomized trial. No technical failures were observed in either treatment arm.

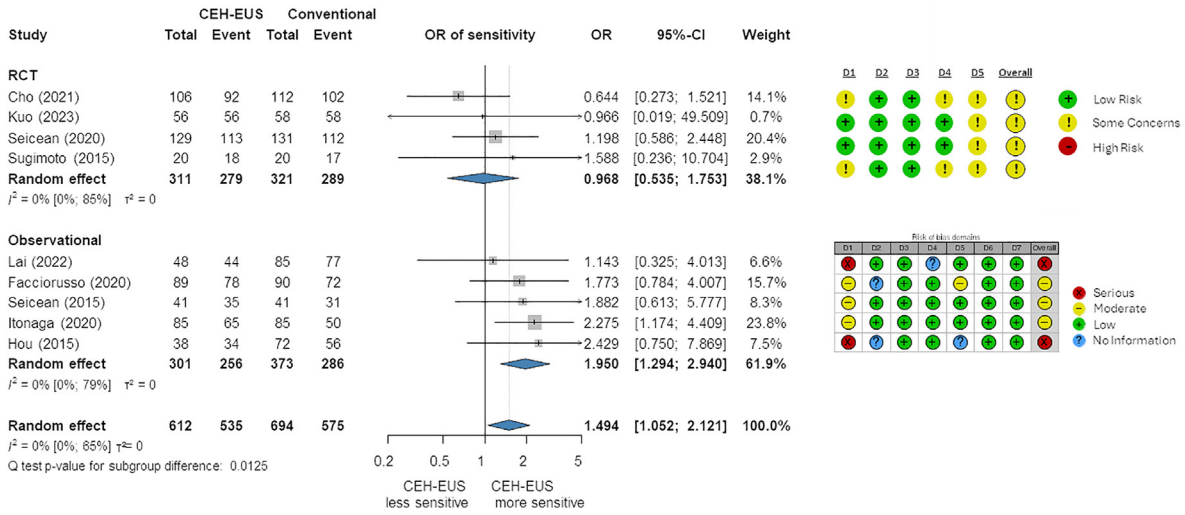

Fig. 4. Forest plot of pooled odds ratios for accurately identifying positive cases (diagnostic sensitivity). Results of the Risk of Bias assessment are summarized on the right by study, domain and overall. For Cochrane risk-of-bias tool v.2 (RoB2): Domains: D1: Risk arising from the randomization process, D2: Bias due to deviations from intended intervention, D3: Bias due to missing outcome data, D4: Bias in the measurement of the outcome, D5: Bias in the selection of the reported result. For Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool: D1: Bias due to confounding, D2: Bias due to selection of participants, D3: Bias in classification of interventions, D4: Bias due to deviations from intended interventions, D5: Bias due to missing data, D6: Bias in measurement of outcomes, D7: Bias in selection of the reported results
CEH-EUS: Contrast-enhanced harmonic endoscopic ultrasound, OR: Odds Ratio.

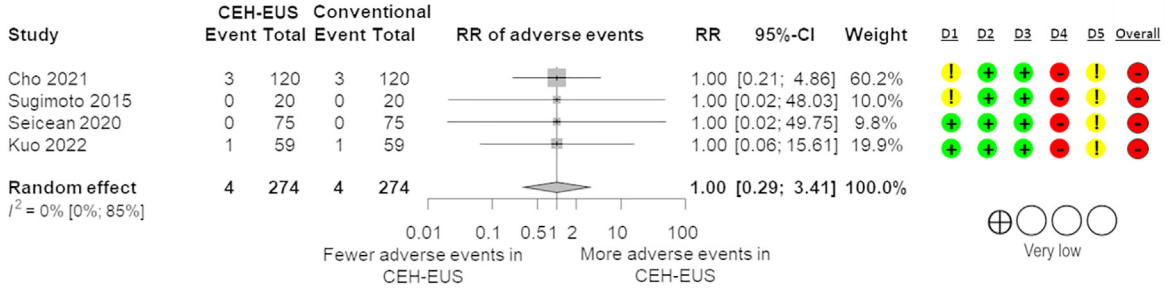

Fig. 5. Forest plot of pooled odds ratios for adverse events. Results of the Risk of Bias assessment are summarized on the right by study, domain and overall. For Cochrane risk-of-bias tool v.2 (RoB2): Domains: D1: Risk arising from the randomization process, D2: Bias due to deviations from intended intervention, D3: Bias due to missing outcome data, D4: Bias in the measurement of the outcome, D5: Bias in the selection of the reported result. For Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool: D1: Bias due to confounding, D2: Bias due to selection of participants, D3: Bias in classification of interventions, D4: Bias due to deviations from intended interventions, D5: Bias due to missing data, D6: Bias in measurement of outcomes, D7: Bias in selection of the reported results
CEH-EUS: Contrast-enhanced harmonic endoscopic ultrasound, OR: Odds Ratio.

3.7. Number of needle passes

Three studies [9,31,34] (all non-randomized) reported the mean number of needle passes to achieve an adequate sample. The mean difference was −0.54 (CI: 2.50-1.42), heterogeneity was substantial ($i^2 = 90$ %) (Fig. 6).

Kuo et al. reported the number of needle passes in terms of cumulative diagnostic accuracy after each needle pass, all given with 95 % Cis. They found that while the first needle pass yielded 76.3 % (CI: 63.4–86.4) accuracy in the CEH-EUS group and 72.9 % (CI: 59.7–83.6) accuracy in the conventional group (p-value: 0.833), this improved to 91.5 % (CI: 81.3–97.2) and 86.4 % (CI: 75.0–94.0) with the second pass (p-value: 0.558) and 93.2 % (CI: 88.3–99.6) and 94.9 % (CI: 85.9–98.9) with the third pass (p-value: 1). The fourth pass (CEH-EUS: 96.6 %, CI: 88.3–99.6 versus Conventional: 94.9 %, CI: 85.9–98.9), fifth pass (CEH-EUS: 96.6 %, CI: 88.3–99.6, Conventional: 96.6 %, CI: 88.3–99.6) and sixth pass (CEH-EUS: 98.3 %, CI: 90.9–100; Conventional: 100 %) also showed no difference (p-value: 1).

Sugimoto et al. reported adequacy after each needle passes up to 5 passes. They found that while the first needle pass yielded 60 % adequacy in the CEH-EUS group, and 25 % adequacy in the conventional group, this improved to 75 % and 65 % with the second pass and 90 % and 95 % with the third pass. In the CEH-EUS group, 100 % adequacy was achieved already on the fourth pass, while the conventional EUS group reached 95 % and finally 100 % on the fifth pass.

Cho et al. reported the number of needle passes in terms of diagnostic sensitivity after each needle pass, with 95 % Cis. They found that while the first needle pass yielded 70.0 % (CI: 61.2–77.5) sensitivity in the CEH-EUS group and 66.7 % (CI: 57.8–74.5) sensitivity in the conventional group, this improved to 80.0 % (CI: 71.9–86.2) and 83.3 % (CI: 75.6–89.0) with the second pass and 85.0 % (CI: 77.4–90.3) and 88.3 % (CI: 81.3–93.0) with the third pass. Further passes yielded limited improvement, at 85.8 % (CI: 78.4–91.0) and 88.3 % (CI: 81.3–93.0) for both the fourth and fifth needle passes.

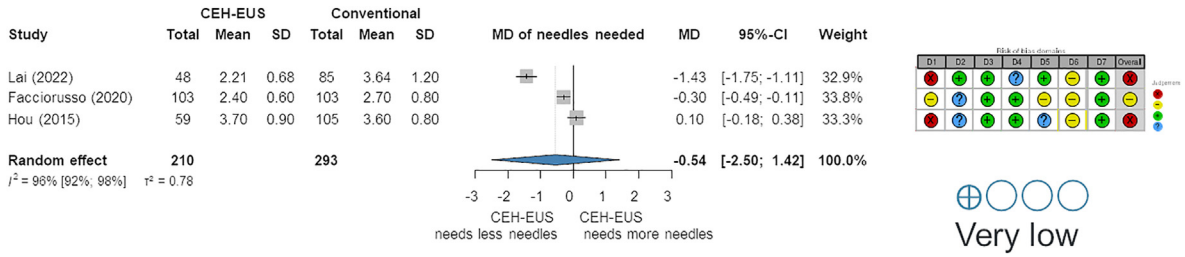

Fig. 6. Forest plot of mean differences of number of needle passes until adequacy. Results of the Risk of Bias assessment are summarized on the right by study, domain and overall. For Cochrane risk-of-bias tool v.2 (RoB2): Domains: D1: Risk arising from the randomization process, D2: Bias due to deviations from intended intervention, D3: Bias due to missing outcome data, D4: Bias in the measurement of the outcome, D5: Bias in the selection of the reported result. For Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool: D1: Bias due to confounding, D2: Bias due to selection of participants, D3: Bias in classification of interventions, D4: Bias due to deviations from intended interventions, D5: Bias due to missing data, D6: Bias in measurement of outcomes, D7: Bias in selection of the reported results
CEH-EUS: Contrast-enhanced harmonic endoscopic ultrasound.

3.8. Tissue yield

Only Kuo et al. reported sample size based on modality. In the contrast-enhanced group the median macroscopic visible core was 18 mm (IQR: 10–26), while the conventional/fanning group had a median macroscopic visible core of 18 mm (IQR: 11–30). There was no difference (p-value: 0.598).

3.9. Risk of bias assessment

Results of the Risk of Bias assessment are detailed on forest plots (Figs. 2–6). Some concerns were noted in Cho and Sugimoto regarding the randomization process, as there was no information about allocation concealment leading up to enrollment, as well as regarding the measurement of adequacy (no information/no blinding). The assessment of the selection of reported results also caused some concerns for the outcome of adequacy in all studies (lack of information in the pre-registered study plan), and for diagnostic test parameters in Kuo et al. and Sugimoto et al. (lack of information in the pre-registered study plan). Finally, for the outcome of adverse events, the risk of bias was high in all studies due to the measurement of outcome (no information regarding blinding, the definitions or measurement in any paper).

In the non-randomized studies, most domains were low or moderate, with not enough information for an assessment for domain 2 in two studies [9,31], for domain 4 in one [34] and for domain 5 in one study [9]. Most studies managed to mitigate the intrinsic bias of non-randomized studies through matching or crossover and received a rating of moderate for confounding, except for two: In one, patients who received the intervention were those who were willing to pay for it [34], in another [9], the reason for giving each intervention was not elaborated on and only patient charts were retrospectively reviewed. Both these papers received a rating of serious risk for domain 1 (confounding), and an overall rating of serious. All other studies received an overall rating of moderate.

3.10. Strength of evidence

Where results for randomized trials were pooled, GRADE assessment was performed only on that sub-analysis, as level of evidence is higher. For diagnostic adequacy, level of evidence was moderate. For diagnostic accuracy and sensitivity, level of evidence was low. For adverse events, number of needle passes and the not pooled evidence for technical failures the level of evidence was rated as very low. For details of reasons for downgrading and the complete table of the GRADE assessment, see Supplementary Table S3.

4. Discussion

While this review found a significant difference for sensitivity, favoring CEH-EUS, and strong trends for the outcomes of adequacy, accuracy and specificity, this difference was driven solely by differences in non-randomized studies, and the test for subgroup differences between randomized and non-randomized studies was significant in all cases. Individual analyses including only randomized controlled trials were all indicative of no difference in efficacy or safety between the two.

The difference in results between subgroups based on study type is strongly indicative of some baseline factors that may be at play, potentially contributing to better outcomes when using contrast-enhanced EUS: In the study by Facciorusso et al., patients were matched using propensity score matching, this was the observational study most closely aligned to the results of the randomized controlled trials. Both Seicean et al. and Itonaga et al. performed a crossover to match the patients, however always performing conventional EUS first. It stands to reason that, when performing these two passes consecutively in one intervention, the experience of performing the first pass may disproportionately benefit the success of the second. The study by Hou was a retrospective study and the criteria for receiving the different interventions were not clear. In the study by Lai et al., patients receiving CEH-EUS were those who were willing to pay for it out of pocket – however, this study was the exception among non-randomized studies, and showed no difference between conventional or contrast-enhanced EUS.

Interestingly, when proportions were pooled for diagnostic test parameters, significant subgroup differences were found between study types in the case of conventional EUS, but not in the case of CEH-EUS. This could potentially indicate that somehow, conventional EUS is performing worse in non-randomized studies than in the randomized trials.

All randomized trials reported adverse events/complications; however, two reported zero events, while the other two reported an equal but low (2.5 %, 1.7 %) rate of adverse events. While the meta-analysis of this outcome is weak, the individual results of studies still suggest that complications are rare and do not differ depending on the type of EUS used. Studies on EUS-guided tissue acquisition are commonly underpowered when assessing adverse events due to their rare nature [13].

The analysis of mean number of needle passes until adequacy showed a tendency towards fewer needle passes needed when using CEH-EUS, albeit an insignificant one. The point estimate showed a mean difference of half a needle pass less with the use of CEH-EUS, which – if a genuine difference – might mean that half the patients would need one fewer needle pass. While half a needle

pass may not be a clinically significant difference for an individual patient, one pass fewer for every second patient may still represent a beneficial effect on a population level. This difference however was largely driven by Lai et al., a retrospective study that was judged at serious risk of bias due to the way the treatments were assigned. The more well-designed, lower risk of bias paper by Facciorusso et al., which applied propensity score matching, showed a much smaller – albeit still statistically significant difference in favor of CEH-EUS. All these results should be considered with the caveat that they are based on non-randomized studies.

An additional three randomized trials [11,32,33] which could not be pooled for mean number of passes due to having a predetermined number of passes performed, reported data for separate needle passes. In these studies, CEH-EUS performed better for the first needle pass, albeit for diagnostic sensitivity or accuracy instead of adequacy in two studies, and for inexperienced endoscopists in the third. This difference quickly disappeared with repeated needle passes, even reversing non-significantly by the third needle pass in all three studies. The difference was only statistically significant in the study by Sugimoto et al., which will be further addressed.

On the topic of needle passes, another interesting trend was seen. In both the conventional and the CEH-EUS group, there was a clear tendency that the additional benefit after further needle passes plateaued after 3 needle passes. Although this does not answer the question of whether CEH-EUS may give an added benefit during tissue acquisition, it may be valuable knowledge for clinicians performing endoscopy procedures.

Attempts to improve the successful sampling rate from solid pancreatic masses have been ongoing for the past years, and multiple variables have been implicated as influencing factors. Among the factors discussed, the type and size of needles are most frequently highlighted, alongside suction techniques and differences between FNA and FNB [13]. Particularly needle size and design have been potential confounding factors in this review, as the choice of the needle was left up to the endoscopist in two of the four included randomized trials. Cho et al. [33], however, listed this as a potential factor in their baseline characteristics table and found that the groups did not differ significantly for either needle size or type (FNA or FNB). Sugimoto [11] used only 22G FNA needles in the CEH-FNA group and 22G and 25G needles in the conventional FNA group, unfortunately introducing an imbalance between the two groups. It has previously been suggested that 25G needles may be more effective for sampling than other sizes of needles [38], which may have disproportionately skewed the results in the direction of conventional EUS, especially due to their application for 5/20 patients in this study arm. Seicean et al. [12] [[,30], Hou et al. [9], Facciorusso et al. [31] and Itonaga et al. [35] performed all procedures using 22G FNA needles. Kuo et al. [32] and Lai et al. [34] performed all procedures using 22G Franseen type FNB needles.

Analyzing confounding factors that may affect the difference between the two modalities, Seicean [12] performed an association analysis between the relative risk of successful sampling and different features of pancreatic disease. The factors assessed were portal hypertension, biliary stent, tumor necrosis, tumor site, and chronic pancreatitis. Although some trends were visible, none were statistically significant. The authors particularly highlighted the importance of chronic pancreatitis, a disorder characterized by a high level of fibrosis of the pancreas. They found that although CEH-EUS performed better for diagnostic sensitivity than conventional EUS in the context of chronic pancreatitis, this difference was not significant (82.8 % vs. 75.8 %, $p = 0.47$). The authors suggested that this may have been due to the relatively small number of patients. Other factors which were assessed as potentially influencing the results across the papers included the mass location, presence of necrosis, mass size, size of core histology and presence of portal hypertension or biliary stents. None of these factors were found to significantly affect results, although Seicean et al. [12] also found a slight trend favoring CEH-EUS in the presence of biliary stents. None of the papers factored in the final pathology and whether the two methodologies differed in the context of adenocarcinoma from that of neuroendocrine tumors, and we were also unable to subgroup based on pathology. However, the relative distribution of pathology is included in the baseline characteristics table for context.

As has already been established, RCTs showed no difference overall between the two EUS methods in the meta-analysis. In the analysis of diagnostic adequacy after the first needle pass a slight, statistically non-significant tendency favoring CEH-EUS (RR 1.171, 95%CI: 0.433–3.170) was visible. This tendency was largely driven by the trial by Sugimoto et al. [11], which included only 20 patients in each arm and was the first of the randomized trials to complete patient enrollment (2014 vs 2019). This study found a 2.4 times higher risk for inadequate samples in the conventional EUS group, with 75 % of samples taken using conventional EUS inadequate for analysis on the first pass, compared to only 40 % in the CEH-EUS group. Interestingly, in this study, the first pass was performed by endoscopists with an experience of <100 performed EUS-FNAs, albeit in the presence of an expert, while any subsequent pass was performed in the same session by an expert endoscopist (>300 performed EUS-FNA), and authors themselves suggested repeating the research with experienced endosonographers. In comparison, the endoscopists in the study performed by Seicean et al. [12] had a minimum of 7000 EUS-FNA, including 500 CEH-EUS-FNA, performed, and this study found no difference between the groups (RR 1.00, 95 % CI: 0.92–1.09). Cho et al. [28] did not specify the experience beyond that “experienced endoscopists” performed the intervention and found no difference (RR 0.96, 95 % CI: 0.83–1.10).

As Sugimoto et al. [11] individually found a large, statistically and clinically significant difference in diagnostic adequacy favoring CEH-EUS when inexperienced endosonographers performed one single pass, it could potentially suggest that CEH-EUS may benefit less experienced endoscopists, allowing them to achieve a higher rate of adequate samples. Unfortunately, this suggestion is weakened by the potential bias introduced by different needle designs in the two arms. All other results of this review and meta-analysis indicate no or little difference between the diagnostic adequacies and sensitivities of tissue acquisition performed using contrast-enhanced or conventional EUS.

4.1. Strengths and limitation

This systematic review and meta-analysis summarized all available studies in five major databases on this topic and thus presented the highest level of evidence on the topic to date. Level of evidence for several outcomes was moderate, and the risk of bias for most outcomes was Low to Some concerns. We strictly followed the most up-to-date methodology as suggested by the Cochrane Collaboration, including pre-registering a protocol and reporting all deviations from the protocol.

However, the study is limited by the slightly different definitions of adequacy across studies and clinical and methodological heterogeneity among the different studies. Furthermore, only four published RCTs were eligible for inclusion.

4.2. Implication for practice and research

Translating scientific results to community benefits and implementing them into the patient care are of major importance [39,40]. Based on the results of our analysis, we suggest that CEH-

EUS likely shows no benefit over conventional EUS for tissue acquisition of solid pancreatic masses, and further research is only warranted to assess its applicability in a setting of chronic pancreatitis, alongside potential benefits for inexperienced endoscopists – e.g. in a training or educational setting. Any further trials should be carefully designed to avoid the obvious confounding factors highlighted in our study, and trials investigating the benefit in chronic pancreatitis should ensure using appropriate inclusion criteria. Unknown factors appear to affect the outcome of conventional EUS in non-randomized settings, detecting their nature may help better select patients that could benefit from CEH-EUS.

5. Conclusion

The use of CEH-EUS likely does not improve diagnostic adequacy during sampling from solid pancreatic masses. However, it may show a benefit for inexperienced endoscopists, and its use in a setting of chronic pancreatitis remains to be explored.

Data availability statement

All data in this study is publicly available in previously published studies.

Funding

Funding was provided by the Ministry for Innovation and Technology from the source of the National Research, Development and Innovation Fund through the ÚNKP-22-3 New National Excellence Program (to BT - ÚNKP-22-3-I-PTE-1693) and the Thematic Excellence Programme (TKP) (TKP2021-EGA-23).

The sponsors had no role in the design, data collection, analysis, interpretation, and manuscript preparation.

Ethical approval

No ethical approval was required for this systematic review with meta-analysis, as all data were already published in peer-reviewed journals. No patients were involved in the design, conduct, or interpretation of our study.

The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis.

CRediT author contribution

MAE: conceptualization, project administration, methodology, formal analysis, writing – original draft; YH: conceptualization, investigation, data curation, writing - review & editing; OA: conceptualization, investigation, data curation, writing - review & editing; ASW: validation, investigation, writing – review & editing, BT: conceptualization, methodology, writing - review & editing; DSV: conceptualization, formal analysis, visualization, writing – review & editing; PH: conceptualization, funding acquisition, writing - review & editing; BE: conceptualization; supervision; writing – original draft.

All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

Declaration of competing interest

None to declare.

Acknowledgment

None to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2024.04.007.

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