Communication from the ASGE Standards of Practice Committee

SOCIETY DOCUMENTS

ASGE American Society for Gastrointestinal Endoscopy

American Society for Gastrointestinal Endoscopy guideline on role of endoscopy in the diagnosis and management of solid pancreatic masses: methodology and review of evidence

Prepared by: THE ASGE STANDARDS OF PRACTICE COMMITTEE

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This guideline document was prepared by the Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy using the best available scientific evidence and considering a multitude of variables including but not limited to adverse events, patient values, and cost implications. The purpose of these guidelines is to provide the best practice recommendations that may help standardize patient care, improve patient outcomes, and reduce variability in practice. We recognize that clinical decision-making is complex. Guidelines therefore are not a substitute for a clinician's judgment. Such judgements may at times seem contradictory to our guidance because of many factors that are impossible to fully consider by guideline developers. Any clinical decisions should be based on the clinician's experience, local expertise, resource availability, and patient values and preferences. This document is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating for, mandating, or discouraging any particular treatment. Our guidelines should not be used in support of medical complaints, legal proceedings, and/or litigation, as they were not designed for this purpose.

Each year in the United States, pancreatic cancer is diagnosed in 62,200 individuals and causes the death of 48,800 people, positioning pancreatic cancer as the second most common GI malignancy and third leading cause of cancer-related deaths.[1] Endoscopists play an essential role in the diagnosis and management of patients with pancreatic cancer and other solid pancreatic masses. Thereby, the American Society for Gastrointestinal Endoscopy (ASGE) Standards of Practice Committee aimed to develop guidelines on the role of endoscopy in the diagnosis and management of pancreatic masses. These guidelines follow the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[2-4] In formulating these guidelines, we conducted extensive literature reviews, including a formal systematic review of the literature and meta-analyses. To make all information we collected and analyzed readily accessible, this guideline is presented in 2 documents: Methodology and Review of Evidence provided here and the accompanying document, Summary and Recommendations.

METHODS

The present document describes the methodology and provides a detailed review of the evidence used to inform this guideline. It details the formulation of clinical questions, literature searches, data analyses, panel composition, evidence profiles, and other considerations such as cost-effectiveness, patient preferences, and health equity. For each clinical question, the outcomes of interest, pooled-effects estimates, and evidence that was considered by the panel in making final recommendations are provided. A separate publication provides a summary of the main findings and final recommendations of the ASGE Standards of Practice Committee.

Formulation of clinical questions

Seven clinical questions were conceptualized by the authors of the documents and members of the ASGE Standards of Practice Committee, which were then approved by the

ASGE Governing Board. The questions followed the PICO format: P, population in question; I, intervention; C, comparator; and O, outcomes of interest. For all clinical questions, potentially relevant patient-important outcomes were identified a priori and rated from "critical" to "important" through a consensus process. A detailed list of PICO questions and outcomes is provided in Table 1.

Literature search and study selection criteria

To inform the guideline panel, we performed systematic reviews and meta-analyses to address each PICO question. A comprehensive literature search was designed and carried out by an experienced health science librarian using MEDLINE, EMBASE, and Cochrane Library from inception of each database through November 24, 2021. An updated search was made on February 17, 2022. Three separate searches were conducted in total, 1 for PICO questions 1 to 4, 1 for PICO questions 5 and 6, and 1 for PICO question 7. The full search strategy is provided in Appendix 1 (available online at www.giejournal.org). Citations were imported into EndNote (Thompson Reuters, Philadelphia, Pa, USA), and duplicates were removed. The library was uploaded into Covidence (Melbourne, Victoria, Australia).

We included studies if they were randomized controlled trials (RCTs; parallel or crossover), in human subjects, in the English language, and included ≥1 of the outcomes of interest. Observational studies, case reports, case series, editorials, review articles, letters to the editor, guidelines, or meta-analyses were excluded. For PICO questions 1 to 4, we excluded RCTs on pancreatic cystic lesions or extrapancreatic lesions that did not separately report outcomes on solid pancreas masses. For PICO questions 5 and 6, we excluded studies on benign biliary obstruction, hilar stricture, percutaneous or EUS-guided drainage, or with a malignant pancreatic mass in <50% of the study population. For PICO question 7, we included RCTs that administered celiac plexus neurolysis (CPN) by EUS, percutaneously, or surgically and excluded studies with benign indications.

Three reviewers (J.D.M., S.G.S., and J.M.C.) screened titles and abstracts for eligibility, with the first 2 independent assessments used to determine inclusion or exclusion in the next stage and with disagreements resolved by consensus. Full-text screening then took place in a similar fashion.

Data extraction and statistical analysis

Two or more independent reviewers (J.D.M., S.G.S., and J.M.C.) abstracted data using a standardized form created in Microsoft Excel (Microsoft Corporation, Redmond, Wash, USA). The primary estimate of effect was based on a priori–identified outcomes of interest. We reported odds ratios (ORs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, with their respective 95% confidence intervals (CIs). The meta-analysis was carried out with DerSimonian and Laird random-effects models, given the anticipation of heterogeneity among abstracted studies. Heterogeneity was quantified using the I^2 statistic, with significant heterogeneity defined at $I^2 > 50\%$ and significant P value (<.05) on the Q statistic. Other sources of heterogeneity were assessed with subgroup and sensitivity analyses. Studies were weighted based on sample size. Publication bias was assessed using funnel plots. Potential bias was assessed using the Cochrane risk of bias tool.[5] Statistical analyses were performed using RevMan version 5.0 (The Cochrane Collaboration, 2020, Copenhagen, Denmark) and STATA version 14.2 (StataCorp, College Station, Tex, USA).

Panel composition and conflict of interest management

We assembled a panel of stakeholders to review the evidence and make recommendations. The panel consisted of lead authors (J.D.M. and S.G.S.), content experts (G.I.P. [advanced endoscopist and pancreatologist], V.S. [medical oncologist], and I.N. [surgical oncologist]), and a GRADE methodologist (N.F.) and was led by the committee chair (B.J.Q.). A patient representative from the National Pancreas Foundation was also included. The lead authors presented the entire body of the evidence at a GRADE panel on January 21, 2023. All panel members were required to disclose potential financial and intellectual conflicts of interest, which were addressed according to ASGE policies set forth in the ASGE & Journal Policy for Managing Declared Conflicts of Interest found at https://www.asge.org/docs/default-source/default-document-library/coi-full-policy-for-asge-and-publications_edd_2-10-20.pdf. Panel members who received funding for any technologies or companies associated with any of the PICO questions or had other relevant conflicts of interest were asked to declare this before the discussion and did not vote on the final recommendation addressing that specific PICO question. Lead authors and methodologists were also excluded from voting.

Certainty in the evidence (quality of the evidence)

The certainty in the evidence was determined using the GRADE framework, beginning with study design and then assessing methodologic limitations, inconsistency, indirectness, imprecision, publication bias, potential large study effects, dose–response gradients, and plausible confounding, in addition to other sources of bias. The final quality of evidence ranged from very low to high (Table 2). We used the results of meta-analyses and the assessments above to prepare a GRADE evidence profile for each PICO question by a GRADE methodologist using the GRADEpro GDT application (http://gdt.guidelinedevelopment.org/app). Evidence profiles were presented during the panel meeting and discussed in detail with all stakeholders before voting on final recommendations. Approval of final recommendations was based on a simple majority.

Outcomes and definitions

For questions pertinent to EUS-guided tissue acquisition (EUS-TA) of solid pancreatic masses, standard definitions of

TABLE 1. Summary of population, intervention, comparator, and outcomes questions

Population	Intervention	Comparator	Outcomes	Rating
1. Solid pancreatic mass undergoing EUS-guided tissue acquisition	FNB sampling	FNA	1. Diagnostic accuracy 2. Sample adequacy 3. Diagnostic yield 4. Number of needle passes 5. Adverse events 6. DNA volume	Critical Critical Critical Critical Critical Important
2. Solid pancreatic mass undergoing EUS-guided tissue acquisition	22-gauge	25-gauge	1. Diagnostic accuracy 2. Sample adequacy 3. High-quality specimen 4. Number of needle passes 5. Adverse events	Critical Critical Critical Critical Critical
3. Solid pancreatic mass undergoing EUS-guided FNB sampling	Novel/contemporary FNB needles (Fork-tip or Franseen)	Alternative FNB needle designs	1. Diagnostic accuracy 2. Sample adequacy 3. Adverse events	Critical Critical Critical
4. Solid pancreatic mass undergoing EUS-guided tissue acquisition	Rapid on-site evaluation	No rapid on-site evaluation	1. Diagnostic accuracy 2. Diagnostic yield 3. Sample adequacy 4. Need for repeated biopsy sampling 5. Number of passes 6. Procedure duration 7. Adverse events	Critical Critical Critical Critical Critical Important Critical
5. Distal malignant biliary obstruction undergoing ERCP	SEMS	Plastic stents	1. Mean survival 2. Stent patency 3. Rate of stent failure 4. Cholangitis or sepsis 5. Unplanned reinterventions 6. Adverse events 7. Surgical resectability 8. Postoperative adverse events	Critical Critical Critical Critical Critical Critical Critical Critical
6. Distal malignant biliary obstruction undergoing ERCP with SEMS	Covered SEMS	Uncovered SEMS	1. Mean survival 2. Stent patency 3. Rate of stent failure 4. Cholangitis or sepsis 5. Unplanned reinterventions 6. Adverse events 7. Surgical resectability	Critical Critical Critical Critical Critical Critical Critical
7. Pancreatic cancer–related abdominal pain	Celiac plexus neurolysis	Medical analgesic therapy alone	1. Mean survival 2. Pain assessed by visual analog scale 3. Opioid use 4. Quality of life 5. Constipation 6. Diarrhea 7. Drowsiness	Critical Critical Critical Critical Important Important Important

FNB, Fine-needle biopsy; *SEMS*, self-expandable metal stents.

diagnostic outcomes were used.[6,7] Diagnostic accuracy was defined as the proportion of lesions sampled that corresponded to the final diagnosis at surgical histopathology and/or clinical follow-up. Sample adequacy was defined as the percentage of lesions sampled in which the obtained material was representative of the target area and sufficient for diagnosis. Diagnostic yield represented the proportion of lesions sampled for which a tissue diagnosis was obtained. A high-quality histologic specimen was defined as a total tissue sample more than 1 × 10 power field in length, according to the scoring system created by Gerke et al.[8] Other relevant outcomes to EUS-TA of pancreatic masses included the mean number of needle passes, proportion of adverse events, and total DNA volume obtained. When comparing fine-needle biopsy (FNB) needles, both the Franseen and Fork-tip designs were grouped into the novel or contemporary FNB group, whereas the alternative FNB needle group included the side-fenestrated, Menghini, and Tru-cut configurations. Rapid on-site evaluation (ROSE) was defined as immediate cytopathologic assessment during the procedure to

TABLE 2. GRADE categories of quality of evidence

GRADE quality of evidence	Meaning	Interpretation
High	We are confident that the true effect lies close to that of the estimate of the effect.	Further research is very unlikely to change our confidence in the estimate of the effect.
Moderate	We are moderately confident in the estimate of the effect; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Further research is likely to have an impact on our confidence in the estimate of the effect and may change the estimate.
Low	Our confidence in the estimate of the effect is limited; the true effect may be substantially different from the estimate of the effect.	Further research is very likely to have an impact on our confidence in the estimate of the effect and is likely to change the estimate.
Very low	We have very little confidence in the estimate of the effect; the true effect is likely to be substantially different from the estimate of the effect.	Any estimate of the effect is very uncertain.

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

provide real-time feedback regarding the content and quality of the specimen. Studies were stratified based on reported mean lesion size as <3 cm or ≥3 cm and based on the most frequent location of the mass as head, uncinated, and neck or body and tail locations.

When comparing biliary stent options during ERCP in patients with distal malignant biliary obstruction, we evaluated mean survival and 30-day mortality after the procedure. Stent patency was defined as the mean time until onset of cholangitis or jaundice after initial normalization of bilirubin after drainage. Other outcomes related to stent patency were rate of stent failure, rate of cholangitis or sepsis, and rate of unplanned reinterventions. The cause of stent failure was subdivided into blockage by sludge or stone, tumor ingrowth, tumor outgrowth, and stent migration. The rate of postprocedure adverse events was measured, including post-ERCP pancreatitis and acute cholecystitis. In patients with resectable pancreatic cancer, we evaluated the effect of stent type on surgical resectability and postoperative adverse events. Covered self-expandable metal stents (cSEMS) include both fully covered and partially covered SEMS.

To evaluate the benefits of CPN, we evaluated mean survival, pain severity using the 10-point visual analog scale (VAS), opioid use by morphine milligram equivalents, and quality of life measured on a scale from 0 to 10 at various time points. We measured adverse events including constipation, diarrhea, and drowsiness. The medical analgesic group included patients receiving medical therapy alone or sham CPN.

External review

The final guideline was reviewed by the *Gastrointestinal Endoscopy* Editorial Board and was made available for public comment on the ASGE website before final approval by the ASGE Governing Board.

RESULTS

For each clinical question, we have summarized the results for the a priori–identified outcomes of interest. Other considerations including cost-effectiveness, patient preferences and acceptability, and equity that are common to more than 1 question are also summarized.

Question 1: In patients with a solid pancreatic mass undergoing EUS-TA, are FNB needles superior to FNA needles?

Recommendation 1: For patients with a solid pancreatic mass undergoing EUS-TA, the ASGE recommends FNB over FNA needles.

(Strong recommendation/moderate quality of evidence)

We conducted a systematic review and meta-analysis of RCTs to inform this question. A literature search addressing PICO questions 1 to 4 was conducted through February 17, 2022. A Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) diagram detailing study screening and inclusion is provided in Figure 1. Of 2216 citations, we identified 25 RCTs that compared FNB with FNA needles among 2765 patients with pancreatic masses. All studies were full-text publications, of which 16 were crossover trials[9-24] and 9 were parallel RCTs.[25-33]

Fifteen studies included only patients with pancreatic masses,[9-12,15,16,18,19,24-26,28-30,32] whereas 10 RCTs included patients with different lesions that provided a separate subgroup analysis for pancreatic masses for any of the outcomes of interest.[13,14,17,20-23,27,31,33] The most used FNB needle design across studies was the side-fenestrated configuration (n = 18),[10,11,14,15,17,19-25,27-31,33] followed by the Franseen (n = 3),[12,13,26] Fork-tip (n = 3),[16,18,32] and

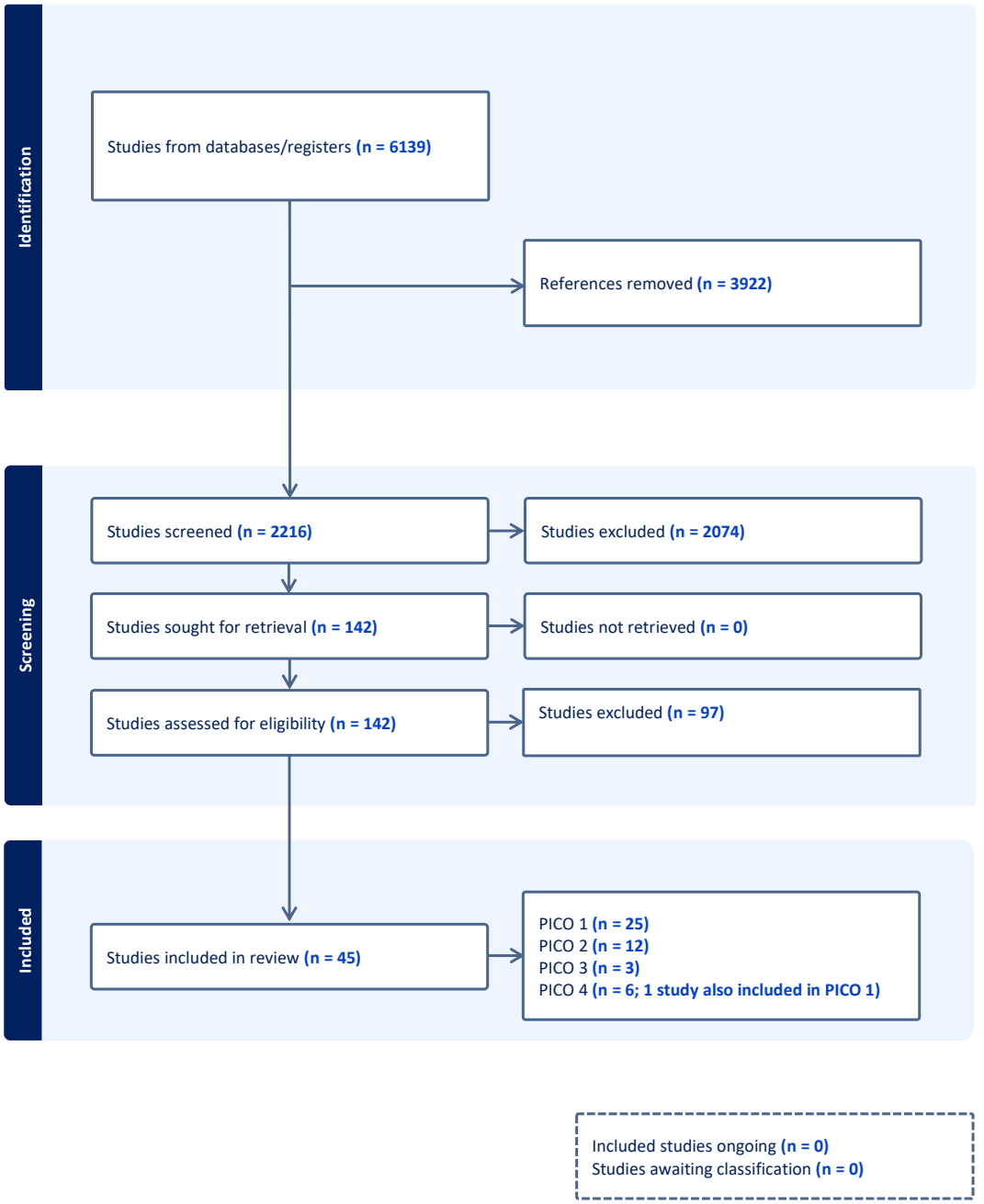


Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses diagram showing the studies included in the systematic review evaluating EUS-guided tissue acquisition of solid pancreatic masses (PICO questions 1-4). *PICO*, Population, intervention, comparator, and outcomes.

Menghini (n = 1).[9] A 22-gauge needle was used in 13 RCTs,[10-14,17,19,22-28,31] whereas the other studies used a 25-gauge needle (n = 2),[15,29] 19-gauge needle (n = 1),[20] or other gauges (n = 9). The most common sampling technique across studies was the use of suction (n = 13)[9,10,13,16,19,20,22-28,30] followed by stylet slow pull (n = 6),[11,14,17,18,24,29] both suction and stylet slow-pull techniques (n = 3),[31-33] or not specified (n = 3). An even distribution of studies used ROSE (n = 10)[9,10,12-16,18,27,30] or did not use ROSE (n =10),[11,17,21-23,25,26,28,29,31] with 5 studies not describing or using ROSE at the discretion of the endoscopist.[19,20,24,32,33]

Diagnostic accuracy, yield, and sample adequacy

Using data from 15 RCTs, we observed higher diagnostic accuracy with FNB needles (86.3%, 1130/1309) as compared with FNA needles (82.8%, 1091/1318) when sampling solid pancreatic masses (OR, 1.33; 95% CI, 1.07-1.67; I^2 = 0%)

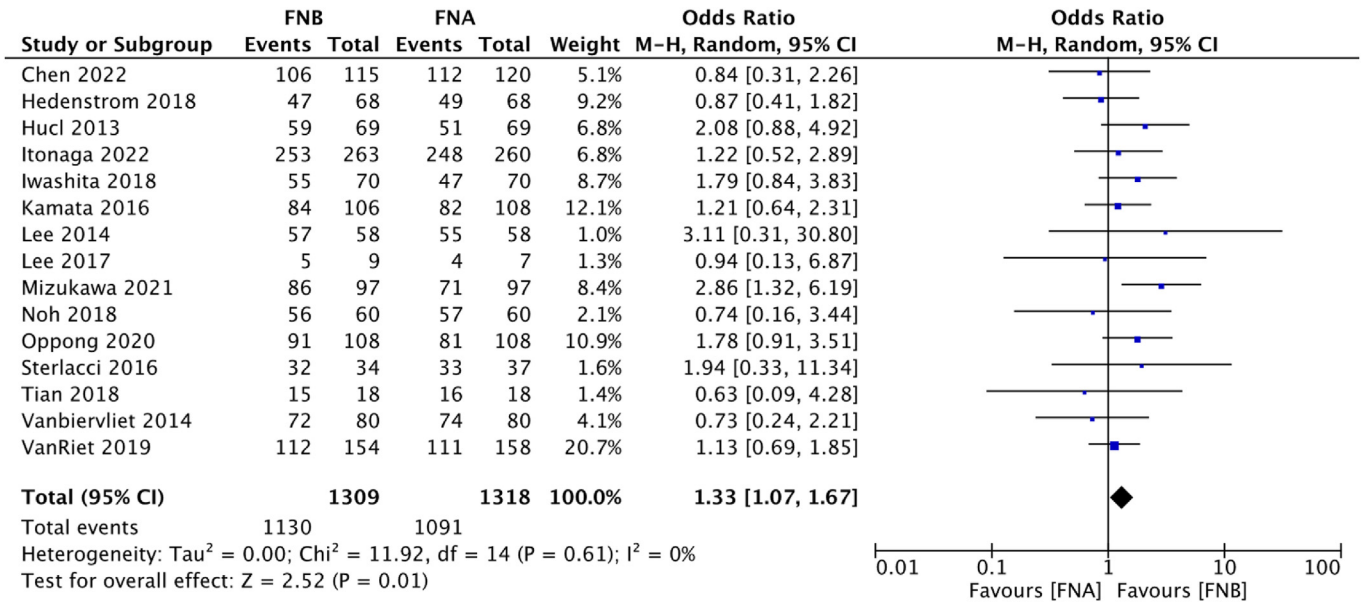


Figure 2. Forest plot comparing diagnostic accuracy of FNB versus FNA needles for EUS-guided tissue acquisition of solid pancreatic masses. *FNB*, Fine-needle biopsy; *CI*, confidence interval.

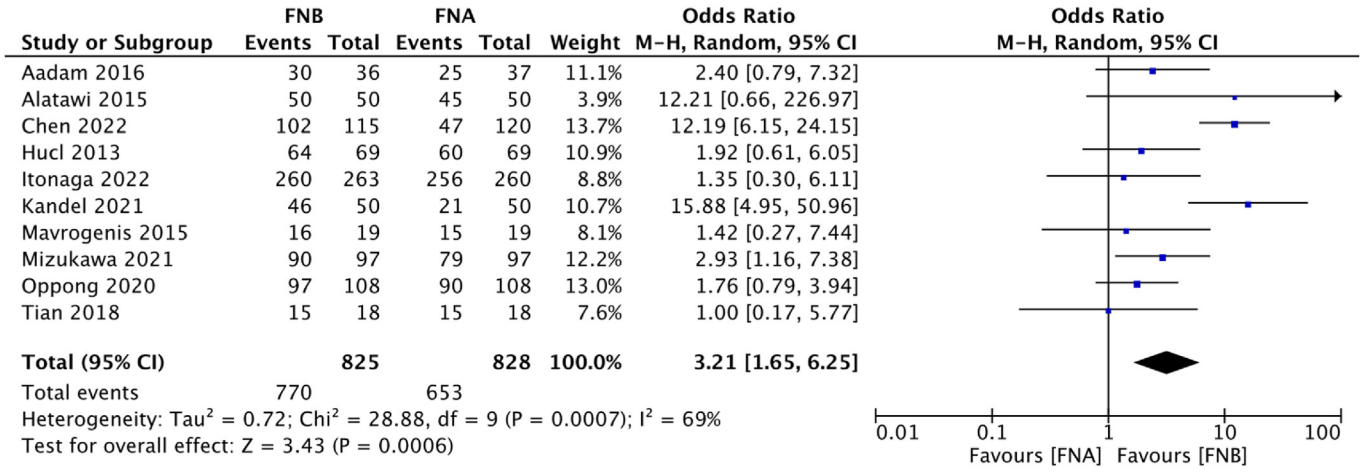


Figure 3. Forest plot comparing sample adequacy of FNB versus FNA needles for EUS-guided tissue acquisition of solid pancreatic masses. *FNB*, Fine-needle biopsy; *CI*, confidence interval.

(Fig. 2).[9,11,16,17,19,20,22-26,29,30,32,33] In 10 RCTs, the diagnostic yield was 84.8% (553/652) with FNB needles and 79.3% (520/656) with FNA needles; however, this difference was not statistically significant (OR, 1.53; 95% CI, .94-2.49; I^2 = 49%) (Supplementary Fig. 1A, available online at www.giejournal.org).[10,12-16,19,25,28,31] In 10 RCTs, sample adequacy of solid pancreatic masses was superior with FNB needles (93.3%, 770/825) as compared with FNA needles (78.9%, 653/828) (OR, 3.21; 95% CI, 1.65-6.25; I^2 = 69%) (Fig. 3).[9,14,16,18,21,22,25,26,28,32]

Needle passes

Fewer needle passes were required with FNB needles as compared with FNA needles in 9 RCTs evaluating EUS-TA of pancreatic masses (MD, –.65; 95% CI, –.96 to –.34; I^2 = 89%) (Fig. 4).[10,15,22,25-28,30,32] A diagnosis was reached with a single needle pass in 85.1% (462/543) of FNB samples and in 67.8% (389/574) of FNA samples in 7 RCTs (OR, 2.90; 95% CI, 1.78-4.70; I^2 = 39%) (Supplementary Fig. 1B).[13,25-30]

Adverse events

Adverse events with EUS-TA of pancreatic masses were low. In 16 RCTs, no significant differences were found in adverse events between FNB and FNA needles, with .7% (9/1202) with FNB needles and 1.3% (16/1241) with FNA needles (OR, .68; 95% CI, .29-1.57; I^2 = 0%) (Supplementary Fig. 1C).[9-11,13,18,19,23-32] In 15 RCTs,

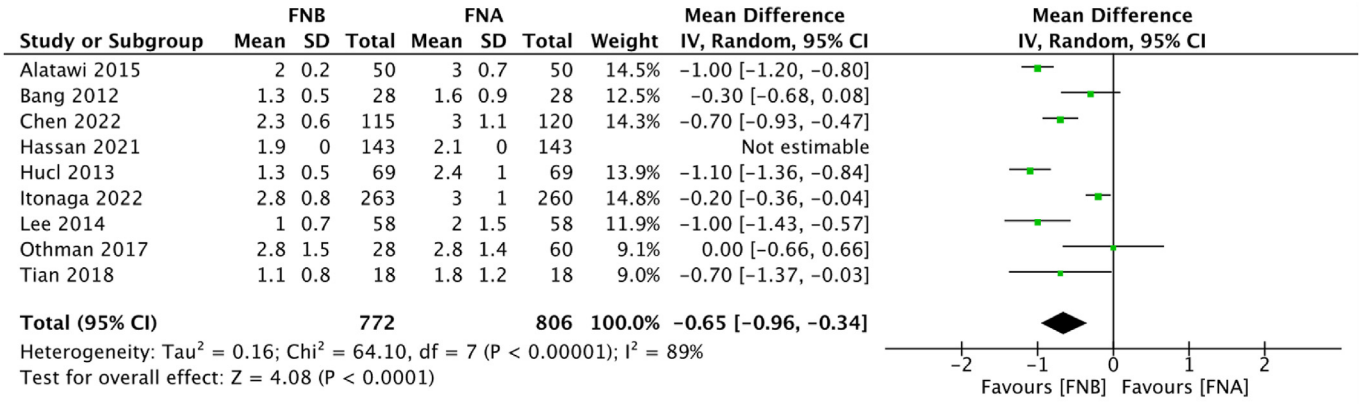


Figure 4. Forest plot comparing number of needle passes of FNB versus FNA needles for EUS-guided tissue acquisition of solid pancreatic masses. *FNB*, Fine-needle biopsy; *CI*, confidence interval; *SD*, standard deviation.

postprocedure pancreatitis occurred in .5% of patients (5/1088) after FNB sampling and in .4% of patients (5/1124) after FNA sampling (OR, 1.01; 95% CI, .31-3.24; I^2 = 0%) (Supplementary Fig. 1D).[9,10,13,18,19,22-30,32]

DNA volume

This outcome was reported in a single crossover RCT of 50 patients with a solid pancreatic mass. DNA material was greater in samples obtained with FNB needles as compared with FNA needles (MD, 2.57 μg/mL; 95% CI, 2.24-2.90).[18]

Subgroup analysis

The results of the outcomes of interest did not change by sampling technique (suction, stylet, or both), FNB type (novel or contemporary vs alternative), use of ROSE (ROSE vs no ROSE), trial design (crossover vs parallel RCT), study population (pancreatic mass alone vs heterogeneous), mass size (<3 cm vs ≥3 cm), or lesion location (head/uncinate/neck vs body/tail).

Certainty in the evidence

For most outcomes, the risk of bias was judged to be serious, as 8 RCTs had significant sources of potential bias and 10 provided limited information to judge their bias (Supplementary Fig. 2A and B, available online at www.giejournal.org). All studies lacked blinding among endosonographers. There were concerns with imprecision in studies reporting on diagnostic yield and adverse events because of wide CIs. Issues with inconsistency, indirectness, or publication bias were not found for any of the included studies (Supplementary Fig. 3A-E, available online at www.giejournal.org). For most outcomes, the quality of the evidence was moderate. A full evidence profile for this question is provided in Table 3.

Other considerations

Although the cost of FNB needles is higher than FNA needles, 1 RCT showed that for patients with pancreatic masses, 2 passes with FNB needles without ROSE was more cost-effective than FNA passes dictated by ROSE.[14] We used a Monte Carlo simulation of 1000 patients and found that EUS-guided FNB sampling (EUS-FNB) confirmed the diagnosis in 988 patients at an average cost of $2152 (95% CI, 2070-2162) per patient and EUS-guided FNA confirmed the diagnosis in 921 patients at an average cost of $2605 (95% CI, 2263-2664) per patient.[14] No data were found on patient values and preferences. However, our patient representative strongly favored FNB needles given their higher diagnostic accuracy, which can result in fewer repeated procedures and earlier treatment decisions.

Discussion

EUS-TA is the standard of care to establish a histologic diagnosis of solid pancreatic masses. Traditionally, FNA needles were used, which provide loose cells for a cytologic diagnosis. Over the last few decades, different FNB needles with various configurations have emerged and are able to obtain intact tissue fragments for histologic assessments in addition to offering the capability for more advanced tissue staining and molecular profiling if required. Despite the theoretical advantages of FNB needles, previous meta-analyses had revealed conflicting results on accuracy and sample adequacy when comparing FNA with FNB needles in sampling of solid pancreatic masses.[34,35] In our meta-analysis of 25 RCTs, we demonstrated that FNB needles are superior to FNA needles in yielding better diagnostic accuracy and sample adequacy, which is concordant with the findings of a recent meta-analysis of 18 RCTs.[35] The difference of our results with previous meta-analyses may be explained by the inclusion of more recent RCTs that used contemporary FNB needles.[16,26,32] We also noticed that the advantage of FNB needles over FNA needles was unchanged regardless of sampling technique, type of FNB needle, lesion characteristics, or use of ROSE.

In addition to improved diagnostic accuracy and sample adequacy, FNB needles also reduced the number of passes

TABLE 3. Evidence profile for population, intervention, comparator, and outcome question 1: in patients with solid pancreatic masses undergoing EUS-TA, are FNB needles better than FNA needles?

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FNB needles	FNA needles	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Diagnostic accuracy												
15	Randomized trials	Serious*	Not serious†	Not serious	Not serious	None	1130/1309 (86.3%)	1091/1318 (82.8%)	OR 1.33 (1.07-1.67)	37 more per 1000 (from 9 more to 61 more)	⨁⨁⨁◯ Moderate	CRITICAL
Diagnostic yield												
10	Randomized trials	Not serious‡	Not serious§	Not serious	Serious‖	None	553/652 (84.8%)	520/656 (79.3%)	OR 1.53 (.94-2.49)	61 more per 1000 (from 10 fewer to 112 more)	⨁⨁⨁◯ Moderate	CRITICAL
Sample adequacy												
10	Randomized trials	Serious¶	Not serious**	Not serious	Not serious	None	770/825 (93.3%)	653/828 (78.9%)	OR 3.21 (1.65-6.25)	134 more per 1000 (from 72 more to 170 more)	⨁⨁⨁◯ Moderate	CRITICAL
Mean number of needle passes												
9	Randomized trials	Serious††	Not serious‡‡	Not serious	Not serious	None	772	806	—	MD .65 fewer (.96 fewer to 0.34 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Diagnosis at first needle pass												
7	Randomized trials	Serious§§	Not serious‖‖	Not serious	Not serious	None	462/543 (85.1%)	389/574 (67.8%)	OR 2.90 (1.78-4.70)	181 more per 1000 (from 111 more to 230 more)	⨁⨁⨁◯ Moderate	IMPORTANT
DNA concentration												
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	50	50	—	MD 2.57 μg/mL higher (2.24 higher to 2.9 higher)	⨁⨁⨁⨁ High	IMPORTANT
Adverse events												
16	Randomized trials	Serious¶¶	Not serious†	Not serious	Very serious***	None	9/1202 (.7%)	16/1241 (1.3%)	OR .68 (.29-1.57)	4 fewer per 1000 (from 9 fewer to 7 more)	⨁◯◯◯ Very low	CRITICAL
Postprocedural pancreatitis												
15	Randomized trials	Serious†††	Not serious†	Not serious	Very serious***	none	5/1088 (.5%)	5/1124 (.4%)	OR 1.01 (.31-3.24)	0 fewer per 1000 (from 3 fewer to 10 more)	⨁◯◯◯ Very low	IMPORTANT

FNB, Fine-needle biopsy; *CI*, confidence interval; *OR*: odds ratio; *MD*, mean difference; —, unable to calculate the relative effect for this continuous outcome.
*Most trials (11/15) were at high risk of bias or had some concern because of risk of bias.
†I^2 = .0% and in most studies the point estimates and 95% CIs overlap considerably.
‡Not rated down for risk of bias because of an equal number of trials judged to be at high and low risk of bias, but *P* value for test of interaction showed no difference between 2 estimates.
§Considerable heterogeneity (I^2 = 49%). Not rated down because clinical inconsistency was deemed not important because all results of included studies have similar clinical implication.
‖Limits of CI suggest a small benefit in favor of FNB needles in 1 extreme and large benefit in favor of FNA needles on the other extreme. Because imprecision is linked to inconsistency and the use of a random-effects model, certainty of the evidence rated down by only 1 level.
¶All trials were at high risk of bias or had some concern because of risk of bias.
**Considerable heterogeneity (I^2 = 69%). Not rated down because clinical inconsistency was deemed not important because all results of the included studies have similar clinical implications.
††All trials except 1 (Bang et al, 2012[10]) were at high risk of bias or had some concern because of risk of bias.
‡‡Considerable heterogeneity (I^2 = 89%). Not rated down because clinical inconsistency was deemed not important because all results of the included studies have similar clinical implications.
§§All trials except 1 (Asokkumar et al, 2019[13]) were at high risk of bias or had some concern because of risk of bias.
‖‖I^2 = 39.0% and in most studies the 95% CIs overlap considerably.
¶¶Most trials (8/10 trials that contributed to the pooled estimate) were at high risk of bias or had some concern because of risk of bias.
***CI suggests that FNB needles increase the likelihood of events in 1 extreme but decrease the likelihood in the other extreme. This was based on small number of events not meeting the optimal information size.
†††Most trials (5/7 trials that contributed to the pooled estimate) were at high risk of bias or had some concern because of risk of bias.

required with FNA needles. Although adverse events did not seem to be affected, requiring a fewer number of passes may reduce procedure duration and improve efficiency of the endoscopy unit, as demonstrated in 1 RCT.[32] Another advantage is that FNB needles provide better material than FNA needles for personalized medicine platforms and genomic testing (eg, next-generation sequencing).[18] This is crucial in tailoring treatment regimens for patients with pancreatic adenocarcinoma.[36] Despite the increased costs of FNB compared with FNA

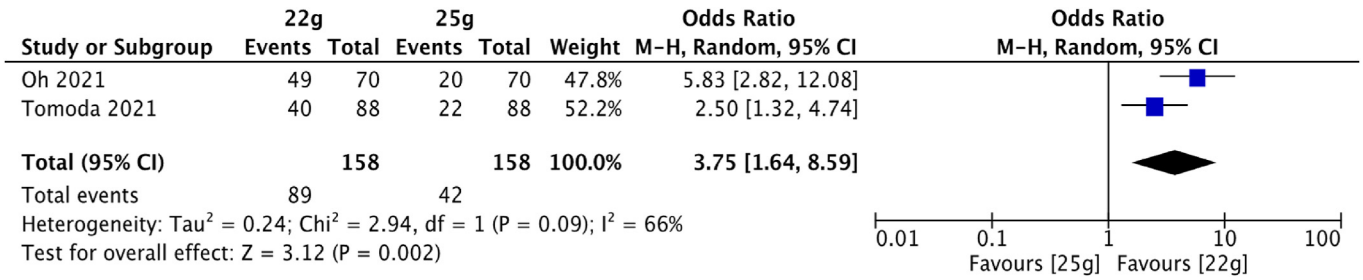


Figure 5. Forest plot comparing high-quality specimen between 22-gauge and 25-gauge needles for EUS-guided tissue acquisition of solid pancreatic masses. *CI*, Confidence interval.

needles, FNB needles appear to be more cost-effective.[14] The patient representative also expressed preference toward FNB needles.

Given the benefits of FNB over FNA needles, comparable adverse events with both needle types, and moderate quality of the evidence, the panel made a strong recommendation to use FNB needles for EUS-TA of solid pancreatic masses. The panel recognized that the source RCTs predominantly included patients with pancreatic adenocarcinoma, skilled endosonographers, and variable sampling techniques (eg, suction or stylet, number of actuations, number of passes). In addition, the studies excluded certain populations such as those with chronic pancreatitis, recent acute pancreatitis, coagulopathy, thrombocytopenia, and biliary stent in place. Thereby, future studies are needed to compare both needle types in these special circumstances.

Question 2: In patients with solid pancreatic masses undergoing EUS-TA, are 22-gauge needles superior to 25-gauge needles?

Recommendation 2: For patients with a solid pancreatic mass undergoing EUS-TA, the ASGE suggests 22-gauge over 25-gauge needles.

(Conditional recommendation/moderate quality of evidence)

Our search resulted in 2216 citations. We identified 12 RCTs that met our inclusion criteria and compared 22-gauge with 25-gauge needles in 1665 patients with pancreatic masses. All studies were full-text publications, including 7 crossover trials[37-43] and 5 parallel RCTs.[44-48] Eight studies included only subjects with a pancreatic mass.[39,41-47] Samples were obtained with an FNA needle in 8 RCTs[37-40,44,45,47,48] and an FNB needle in 4 RCTs (Franseen needle in 2 studies[42,46] and side-fenestrated needle in 2 studies[41,43]). ROSE was used in 6 studies.[37-40,42,44]

Diagnostic accuracy, sample adequacy, and histologic quality

In 7 RCTs, no significant differences in diagnostic accuracy were found between 22-gauge (91.5%, 561/613) and 25-gauge needles (93%, 570/613) when sampling solid pancreatic masses (OR, .81; 95% CI, .52-1.25; I^2 = 0%). No issues were seen with inconsistency, indirectness, or publication bias with any of the included studies (Supplementary Fig. 4A, available online at www.giejournal.org).[29,39-41,44-46] In 6 RCTs,[37,38,41,42,44,46] sample adequacy was similar with 22-gauge (81.8%, 392/479) and 25-gauge (78.9%, 382/484) needles (OR, 1.11; 95% CI, .65-1.88; I^2 = 46%) (Supplementary Fig. 4B).[37,38,41,42,44,46] A high-quality histologic specimen was more likely to be obtained with 22-gauge (56.3%, 89/158) as compared with 25-gauge needles (26.6%, 42/158) in 2 RCTs (OR, 3.75; 95% CI, 1.64-8.59; I^2 = 66%) (Fig. 5).[42,46] Both RCTs used FNB needles and measured tissue quality according to the scoring system created by Gerke et al,[8] which rates specimens from 0 (material insufficient for interpretation) to 5 (material sufficient for adequate histologic interpretation and of high quality). Diagnostic yield was not reported in the included RCTs.

Needle passes

A similar number of passes were required with the 22-gauge and 25-gauge needles in 4 RCTs (MD, .16; 95% CI, –.10 to .42; I^2 = 13%; Supplementary Fig. 4C).[37,38,44,47]

Adverse events

In 10 RCTs, adverse events occurred in 3.6% of cases (26/727) with 22-gauge needles and in 3% of cases (22/738) with 25-gauge needles (OR 1.94; 95% CI, .60-6.27; I^2 = 56%) (Supplementary Fig. 4D).[37,38,40,41,43-48] The risk of postprocedure pancreatitis was similar between the 22-gauge needles (1.4%, 7/505) and 25-gauge needles (.4%, 2/509) in 8 RCTs (OR, 2.53; 95% CI, .47-13.63; I^2 = 13%) (Supplementary Fig. 4E).[37,40,41,43,45-48]

Subgroup analysis

In a subgroup analysis by location of the pancreatic mass, a trend toward higher diagnostic accuracy was seen with the 25-gauge needle in masses located in the pancreatic head or uncinate process; however, this did not reach statistical significance (OR, .54; 95% CI, .29-1.00; I^2 = 69%) (Supplementary Fig. 4F). The results of other outcomes by location were similar to the overall results. Additional subgroup analyses by needle type (FNB vs FNA) (Supplementary Fig. 4G-J), use of ROSE (ROSE vs no ROSE), sampling technique (suction vs stylet), trial design

TABLE 4. Evidence profile for population, intervention, comparator, and outcome question 2: in patients with solid pancreatic masses undergoing EUS-guided tissue acquisition, are 22-gauge needles better than 25-gauge needles?

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	22-gauge needle	25-gauge needle	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Diagnostic accuracy												
7	Randomized trials	Not serious*	Not serious†	Not serious	Serious‡	None	561/613 (91.5%)	570/613 (93.0%)	OR .81 (.52-1.25)	15 fewer per 1000 (from 57 fewer to 13 more)	⨁⨁⨁◯ Moderate	CRITICAL
Sample adequacy												
6	Randomized trials	Not serious§	Serious‖	Not serious	Serious‡	None	392/479 (81.8%)	382/484 (78.9%)	OR 1.11 (.65-1.88)	17 more per 1000 (from 80 fewer to 86 more)	⨁⨁◯◯ Low	CRITICAL
High-quality specimen												
2	Randomized trials	Not serious	Serious¶	Not serious	Not serious	None	89/158 (56.3%)	42/158 (26.6%)	OR 3.75 (1.64-8.59)	310 more per 1000 (from 107 more to 491 more)	⨁⨁⨁◯ Moderate	CRITICAL
Mean number of needle passes												
4	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	329	337	—	MD .16 more (.1 fewer to .42 more)	⨁⨁⨁⨁ High	CRITICAL
Adverse events												
10	Randomized trials	Not serious*	Serious**	Not serious	Serious††	None	26/727 (3.6%)	22/738 (3.0%)	OR 1.94 (.60-6.27)	26 more per 1000 (from 12 fewer to 132 more)	⨁⨁◯◯ Low	CRITICAL
Postprocedural pancreatitis												
8	Randomized trials	Not serious	Serious‖	Not serious	Serious††	None	7/505 (1.4%)	2/509 (.4%)	OR 2.53 (.47-13.63)	6 more per 1000 (from 2 fewer to 47 more)	⨁⨁◯◯ Low	CRITICAL
Diagnostic accuracy subgroup: head/uncinate												
3	Randomized trials	Serious‡‡	Not serious	Serious§§	Not serious	None	275/305 (90.2%)	288/305 (94.4%)	OR .54 (.29-1.00)	43 fewer per 1000 (from 113 fewer to 0 fewer)	⨁⨁◯◯ Low	IMPORTANT

CI, Confidence interval; *MD*, mean difference; *OR*, odds ratio; —, unable to calculate the relative effect for this continuous outcome.
*Not rated down for risk of bias because an equal number of trials were judged to be at high and low risk of bias, but *P* value for test of interaction showed no difference between 2 estimates.
†I^2 = 0.0% and in most studies the point estimates and 95% CIs overlap considerably.
‡Limits of CI suggest a small benefit in 1 extreme and benefit important to patients in the other.
§Two studies were judged to have an overall high risk of bias (Park et al, 2016[41] and Tomoda et al, 2022[42]), but test of interaction showed no difference between estimates from low-risk studies and those at high risk of bias.
‖Despite partial overlap of 95% CIs, direction of effect varied across studies.
¶I^2 = 66%.
**The CIs of some of the studies do not overlap with those of the most included studies and/or the point estimate of some of the included studies. High I^2 and 4 studies did not contribute to the pooled estimate with zero events in both arms.
††Limits of CI suggest small harm was associated with using a 22-gauge needle in 1 extreme and large harms on the other extreme with a small number of events. Because imprecision is probably linked to inconsistency and use of the random-effects model, certainty of the evidence was rated down by only 1 level.
‡‡Three studies were judged to have an overall high risk of bias.[39-41]
§§Subgroups were created based on most masses being in the head/uncinate or body/tail of the pancreas.

(crossover vs parallel RCTs), study population (pancreatic mass alone vs heterogeneous lesions), and lesion size (<3 cm vs ≥3 cm) were not different compared with overall results.

Certainty in the evidence

The risk of bias was judged to be not serious for all analyzed outcomes (Supplementary Fig. 5A and B, available online at www.giejournal.org). We rated down for inconsistency because the direction of effect varied across studies for histologic adequacy and postprocedure pancreatitis. In addition, we rated down for inconsistency for adverse events (I^2 = 56%). There were concerns with imprecision for all outcomes except histologic quality and number of needle passes. No issues were seen with indirectness or publication bias with any of the included studies (Supplementary Fig. 6A-D, available online at www.giejournal.org). For most outcomes, the quality of the evidence was rated as moderate. A full evidence profile for this question is provided in Table 4.

Other considerations

There is no cost difference between 22- and 25-gauge needles. No cost-effectiveness studies have compared both interventions, and no data were available on patient values and preferences.

Discussion

Our systematic review compared 22- with 25-gauge needles for EUS-TA of solid pancreatic masses. Other needle calibers such as 19, 20, or 21 gauges were not included

in our analysis because these needles are uncommonly used by endosonographers for sampling solid pancreatic masses in clinical practice.[49] Our results indicate that 22-gauge needles provided higher tissue quality than 25-gauge needles. The 2 RCTs included for this outcome used Franseen FNB needles and defined high tissue quality according to the Gerke scale[8] (material sufficient for adequate histologic interpretation and of high quality).[42,46] The clinical implications of this difference are unclear. Better tissue architecture with 22-gauge needles may translate into better samples for personalized medicine and ancillary molecular testing of pancreatic adenocarcinoma (eg, next-generation sequencing to select chemotherapy). This was suggested in a retrospective study of 190 patients with pancreatic adenocarcinoma who had EUS-TA in which the use of 22- or 19-gauge needles provided greater DNA volume and was independently associated with more successful next-generation sequencing as compared with 25-gauge needles.[50]

Nevertheless, the panel recognized that the major advantage of 22- over 25-gauge needles is if the tissue sample would be used for personalized medicine. Otherwise, both needle calibers seemed to perform equally on relevant clinical endpoints such as diagnostic accuracy and sample adequacy, which are directly implicated in prompt patient care and treatment decisions. In addition, neither of the needle calibers reduced the number of passes performed or the rate of adverse events. Hence, if a sample is obtained for purely diagnostic purposes and molecular profiling is not anticipated, then either needle caliber may be appropriate. However, this is often not known at the time of EUS, and as the field of precision medicine in pancreatic cancer is growing to target treatments since the time of initial diagnosis,[51] obtaining the highest tissue quality possible is most appropriate even when the goal of EUS-TA is for diagnostic purposes. As the field of precision medicine in pancreatic cancer continues to grow, future RCTs comparing needle gauges should be adequately powered to detect differences in the capacity for molecular profiling.

An extensive subgroup analysis was performed in our meta-analysis, and no situation was found in which a 25-gauge needle would be significantly superior to a 22-gauge needle. However, 25-gauge needles had a nonsignificant trend toward higher diagnostic accuracy in masses located in the pancreatic head and uncinate. It is important to mention that this subgroup analysis was based on the most frequent location of the mass in each of the studies and not in individual patient data. Thereby, this analysis is exploratory and requires future evaluation.

Given the moderate quality of evidence on providing a better tissue architecture and similar adverse events, the panel made a conditional recommendation in favor of using 22-gauge needles for EUS-TA of solid pancreatic masses. The panel considered that this conditional recommendation would be acceptable because 22-gauge needles are already strongly preferred by most endosonographers for EUS-TA of pancreatic masses.[50] Although not included as an outcome in prior studies, endosonographers in the panel also pointed out that expelling the tissue from the needle was easier and less time-consuming with the larger diameter 22-gauge needle than with 25-gauge needles. The panel acknowledged that a 25-gauge needle should be selected when a 22-gauge needle is expected to have limited manipulability (eg, excessive endoscope torqueing) or cannot be advanced into a lesion.

Question 3: In patients with solid pancreatic masses undergoing EUS-FNB, are novel or contemporary FNB needles (Fork-tip and Franseen) superior to alternative FNB needles?

Recommendation 3: Among patients with a solid pancreatic mass undergoing EUS-FNB, the ASGE recommends using novel or contemporary FNB needles (Fork-tip or Franseen) over alternative designs.

(Strong recommendation/ moderate quality of evidence)

Our systematic review identified 3 RCTs comparing EUS-TA with novel or contemporary FNB needles and alternative FNB needle designs in 381 subjects with solid pancreatic masses.[52-54] Two were parallel RCTs[52,54] and 1 was a crossover trial.[53] One RCT compared Fork-tip needles with side-fenestrated needles,[52] 1 RCT compared the Franseen design with side-fenestrated FNB needles,[53] and 1 RCT evaluated 4 different FNB needle designs (Franseen, Fork-tip, side-fenestrated, and Menghini).[54] In the 3 studies, the tissue-sampling approach was performed using 2 to 3 passes without ROSE. One study used macroscopic on-site evaluation (MOSE).[52] An additional meta-analysis was performed by using 4 RCTs that compared the Fork-tip and Franseen needle designs among 243 patients with solid pancreatic masses undergoing EUS-TA.[54-57] Of these 4 RCTs, 3 were parallel RCTs[54,55,57] and 1 was a crossover trial.[56] Three of these RCTs used ROSE.[55-57]

Diagnostic accuracy

The diagnostic accuracy of novel or contemporary FNB needles (91.7%, 201/219) was significantly greater than alternative FNB needle designs (78.8%, 175/222) when performing EUS-TA of pancreatic masses in 3 RCTs (OR, 2.99; 95% CI, 1.07-8.36; $I^2 = 64\%$) (Fig. 6).[52-54]

Sample adequacy

Using data of 3 RCTs, we found that sample adequacy was significantly higher with novel or contemporary FNB needles (100%, 219/219) as compared with alternative FNB needle designs (83.8%, 186/222) when sampling pancreatic masses (OR, 25.90; 95% CI, 4.96-135.32; $I^2 = 0\%$) (Fig. 7).[52-54]

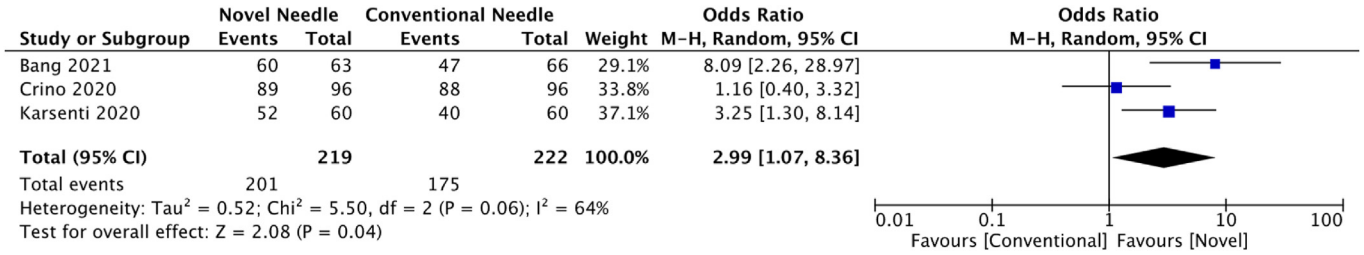


Figure 6. Forest plot comparing diagnostic accuracy of novel or contemporary versus alternative fine-needle biopsy needles for EUS-guided tissue acquisition of solid pancreatic masses. *CI*, Confidence interval.

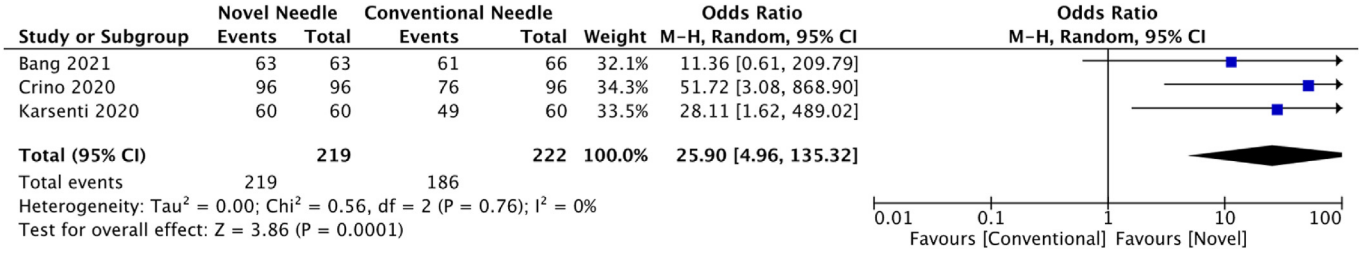


Figure 7. Forest plot comparing sample adequacy of novel or contemporary versus alternative fine-needle biopsy needles for EUS-guided tissue acquisition of solid pancreatic masses. *CI*, Confidence interval.

Adverse events

Adverse events occurred at a similar rate in patients with a pancreatic mass undergoing EUS-TA with novel or contemporary (2.7%, 6/219) and alternative (.9%, 2/222) FNB needle designs (OR, 2.41; 95% CI, .51-11.43; I^2 = 0%) (Supplementary Fig. 7A, available online at www.giejournal.org).[52-54]

Comparison of Franseen and Fork-tip FNB needles

In 2 RCTs, both the Fork-tip and Franseen designs provided similar diagnostic accuracy (OR, 1.61; 95% CI, .37-7.03; I^2 = 0%) (Supplementary Fig. 7B).[54,55] Sample adequacy was also similar with the Fork-tip and Franseen designs in 4 RCTs (OR, 1.65; 95% CI, .69-3.93; I^2 = 0%) (Supplementary Fig. 7C).[54-57] No difference in adverse events was found between the 2 novel or contemporary FNB designs (OR, .61; 95% CI, .14-2.66; I^2 = 0%) (Supplementary Fig. 7D).[54-57]

Certainty in the evidence

The risk of bias (Supplementary Fig. 8A and B, available online at www.giejournal.org), indirectness, and publication bias (Supplementary Fig. 9A-C, available online at www.giejournal.org) were judged to be not serious for all the analyzed outcomes. We rated down for inconsistency in diagnostic accuracy because the point estimates varied widely with a I^2 of 74%. There were concerns with imprecision for all outcomes given very wide CIs and small number of events. For most outcomes, the quality of evidence was rated as moderate. A full evidence profile for this question is provided in Table 5.

Other considerations

No data were available on costs, cost-effectiveness, and patient values and preferences when comparing the different FNB needle designs. The patient representative on the panel indicated a personal preference for using novel or contemporary needles because they were more accurate with similar adverse events.

Discussion

The first description of EUS-FNB, reported by Binmoeller et al in 1998,[58] used a Menghini-type core needle. FNB needle designs with different needle-tip alterations have evolved over the past 25 years. The first generation of needles was designed using a Tru-cut adaptation and a reverse-bevel needle configuration. The most contemporary end-cutting FNB needles are the Franseen needle, which is based on a 3-plane symmetric design of the tip, and the Fork-tip needle, which has 6 cutting surfaces in an asymmetric design. Our meta-analysis of 3 RCTs indicates that both the Franseen and Fork-tip needles provided greater diagnostic accuracy and sample adequacy than alternative FNB needle designs in solid pancreatic masses. These results align with a recent network meta-analysis of 16 RCTs that demonstrated the Franseen and Fork-tip needles are the highest performing needles for sampling of solid pancreatic masses.[59]

In addition, we conducted an additional meta-analysis of 4 RCTs comparing the Franseen and Fork-tip needles, which revealed that both novel or contemporary FNB needles offer similar diagnostic accuracy, sample adequacy, and adverse events. These novel or contemporary FNB needles are widely available in the United States, and their selection should be driven by costs and physician preferences. Future

TABLE 5. Evidence profile for population, intervention, comparator, and outcome question 3: in patients with solid pancreatic masses undergoing EUS-guided FNB sampling, are novel/contemporary FNB needles (Fork-tip and Franseen) better than alternative FNB needles?

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Contemporary FNB needles	Alternative FNB needles	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Diagnostic accuracy (diagnostic odds ratio)												
3	Randomized trials	Not serious	Serious*	Not serious	Serious†	None	201/219 (91.7%)	175/222 (78.8%)	OR 2.99 (1.07-8.36)	129 more per 1000 (from 11 more to 181 more)	⨁⨁◯◯ Low	CRITICAL
Sample adequacy												
3	Randomized trials	Not serious	Not serious	Not serious	Serious‡	None	219/219 (100.0%)	186/222 (83.8%)	OR 25.90 (4.96-135.32)	155 more per 1000 (from 125 more to 161 more)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse events												
3	Randomized trials	Not serious	Not serious	Not serious	Very serious§	None	6/219 (2.7%)	2/222 (.9%)	OR 2.41 (.51-11.43)	12 more per 1000 (from 4 fewer to 85 more)	⨁⨁◯◯ Low	CRITICAL
Diagnostic accuracy: Fork-tip vs Franseen FNB needles												
2	Randomized trials	Not serious	Not serious	Not serious	Serious†	None	64/67 (95.5%)	66/71 (93.0%)	OR 1.61 (.37-7.03)	25 more per 1000 (from 100 fewer to 60 more)	⨁⨁⨁◯ Moderate	
Sample adequacy: Fork-tip vs Franseen FNB needles												
4	Randomized trials	Not serious	Not serious	Not serious	Serious†	None	124/139 (89.2%)	127/154 (82.5%)	OR 1.65 (.69-3.93)	61 more per 1000 (from 60 fewer to 124 more)	⨁⨁⨁◯ Moderate	
Adverse events: Fork-tip vs Franseen FNB needles												
4	Randomized trials	Not serious	Not serious	Not serious	Serious‖	None	3/140 (2.1%)	5/153 (3.3%)	OR .61 (.14-2.66)	12 fewer per 1000 (from 28 fewer to 50 more)	⨁⨁⨁◯ Moderate	

FNB, Fine-needle biopsy; *CI*, confidence interval; *OR*, odds ratio.
*Point estimates vary widely with high I^2 (74%).
†Limits of CI suggest a small benefit in 1 extreme and a large benefit in the other extreme. Because imprecision is linked to inconsistency and use of a random-effects model, certainty of the evidence rated down by only 1 level.
‡Small number of events and very wide 95% CIs, but because of the large effect the certainty of evidence was rated down only 1 level.
§Limits of CI suggest small harm was associated with using novel needles in 1 extreme and large harms on the other extreme with a small number of events.
‖Limits of CI crosses 1.

needle designs should be compared with either the Franseen or Fork-tip needles to determine their noninferiority or superiority in EUS-TA of pancreatic masses. After considering all the desirable and undesirable effects with the different FNB needle types, in addition to the moderate quality of the evidence, the panel made a strong recommendation in favor of using novel or contemporary FNB needles.

Question 4: In patients with solid pancreatic masses undergoing EUS-TA, is ROSE beneficial as compared with no ROSE?

Recommendation 4: In patients with a solid pancreatic mass undergoing EUS-TA, the ASGE suggests against the routine use of ROSE.

(Conditional recommendation/low quality of evidence)

We found 6 RCTs that compared EUS-TA with and without ROSE among 1476 patients with solid pancreatic masses.[32,60-64] All studies were parallel RCTs. Five studies were published as full-text manuscripts[32,60-63] and 1 in abstract form only.[64] Four studies were multicenter RCTs.[32,60-62] Three studies used FNA needles,[60,62,63] 2 used FNB needles,[61,64] and 1 used both type of needles.[32] ROSE was performed by a cytopathologist in 5 studies[32,60-63] or a trained endoscopist in 1.[64] In the ROSE group, the number of passes was guided by the cytopathology evaluation until an adequate sample was obtained. The accuracy of a preliminary diagnosis with ROSE was not described in any of the RCTs. When an FNA needle was used without ROSE, 2 studies performed 7 passes[60,62] and 1 study performed 3 to 5 passes.[63] For studies using FNB needles in the absence of ROSE,[60,62] the number of passes ranged from 2 to 5.[32,61,64]

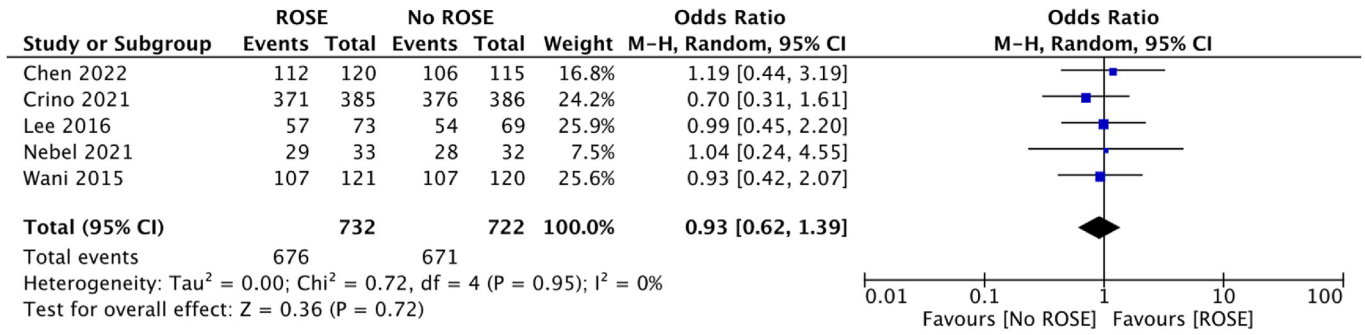


Figure 8. Forest plot comparing the diagnostic accuracy of EUS-guided tissue acquisition of solid pancreatic masses with and without ROSE. *ROSE*, Rapid on-site evaluation; *CI*, confidence interval.

Diagnostic accuracy, yield, and sample adequacy

Using data from 5 RCTs, we found no difference in the diagnostic accuracy when using ROSE (92.3%, 676/732) as compared with not using ROSE (92.9%, 671/722) during EUS-TA of solid pancreatic masses (OR, .93; 95% CI, .62-1.39; I^2 = 0%) (Fig. 8).[32,60-63] Diagnostic yield was not significantly different between ROSE (84.2%, 139/165) and no ROSE (79.8%, 130/163) in 3 RCTs (OR, 1.36; 95% CI, .77-2.41; I^2 = 0%) (Supplementary Fig. 10A, available online at www.giejournal.org).[60,63,64] No statistical difference was found in sample adequacy when ROSE was present (70.9%, 527/743) or absent (82.5%, 605/733) in 6 RCTs (OR, .56; 95% CI, .21-1.45; I^2 = 88%) (Supplementary Fig. 10B).[32,60-64]

Need for repeated biopsy sampling

Performing ROSE did not reduce the need for future repeated pancreatic mass biopsy sampling as compared with no ROSE in 3 RCTs (OR, .73; 95% CI, .30-1.80; I^2 = 0%) (Supplementary Fig. 10C).[61,62,64]

Needle passes and procedure duration

Six RCTs found no difference in the number of passes performed with and without ROSE (MD, −1.06 passes; 95% CI, −2.18 to .06; I^2 = 99%) (Supplementary Fig. 10D).[32,60-64] In 6 RCTs, the procedure duration was not different between ROSE and no ROSE (MD, 2.29 minutes; 95% CI, −1.84 to 6.42; I^2 = 99%) (Supplementary Fig. 10E).[32,60-64]

Adverse events

Adverse events occurred at a similar rate with ROSE (2.6%, 16/611) and without ROSE (1.8%, 11/602) in 4 RCTs (OR, 1.48; 95% CI, .46-4.80; I^2 = 36%) (Supplementary Fig. 10F).[32,61-63]

Subgroup analysis with FNB needles

In the 2 RCTs evaluating the role of ROSE with FNB needles, the addition of ROSE resulted in lower sample adequacy as compared with no ROSE (OR, .67; 95% CI, .49-.92; I^2 = 0%) (Fig. 9).[61,64] Moreover, the mean procedure duration of EUS-FNB in 2 RCTs was prolonged by 6.99 minutes when ROSE was used (95% CI, 3.97-10.02; I^2 = 38%) (Fig. 10).[61,64] In 1 RCT, .1 fewer FNB needle passes were needed with ROSE (95% CI, −.15 to −.05) (Fig. 11) as compared with 3 passes without ROSE; however, this difference was not clinically meaningful.[61] Other outcomes with FNB needles were not different from the overall results.

Subgroup analysis with FNA needles

With regard to the performance of ROSE when using FNA needles, 3 RCTs found that ROSE reduced the number of needle passes as compared with no ROSE (MD, −1.97 passes; 95% CI, −2.93 to −1.01; I^2 = 97%) (Fig. 11).[60,62,63] This was explained by the need to perform as many as 7 FNA passes in the absence of ROSE. All other outcome comparisons between ROSE and no ROSE with FNA needles were similar to the overall results.

Subgroup analysis comparing FNA with ROSE versus FNB sampling without ROSE

One study compared FNA with ROSE and FNB sampling without ROSE and showed that EUS-FNA with ROSE resulted in lower sample adequacy (OR, .08; 95% CI, .04-.16) (Fig. 9), extended the procedure duration by 3.4 minutes (95% CI, .96-5.84) (Fig. 10), and required .7 more needle passes (95% CI, .47-.93) (Fig. 11).[32]

Certainty in the evidence

The risk of bias was judged to be not serious for most outcomes (Supplementary Fig. 11A and B, available online at www.giejournal.org), except the need for repeated biopsy sampling, in which 2 of the 3 included RCTs had some concerns for risk of bias.[61,64] We rated down for inconsistency in sample adequacy (I^2 = 88%), number of needle passes (I^2 = 99%), and procedure duration (I^2 = 99%) because of considerable heterogeneity. There was concern with inconsistency in adverse events because 1 study had a different direction of effect as compared with the other

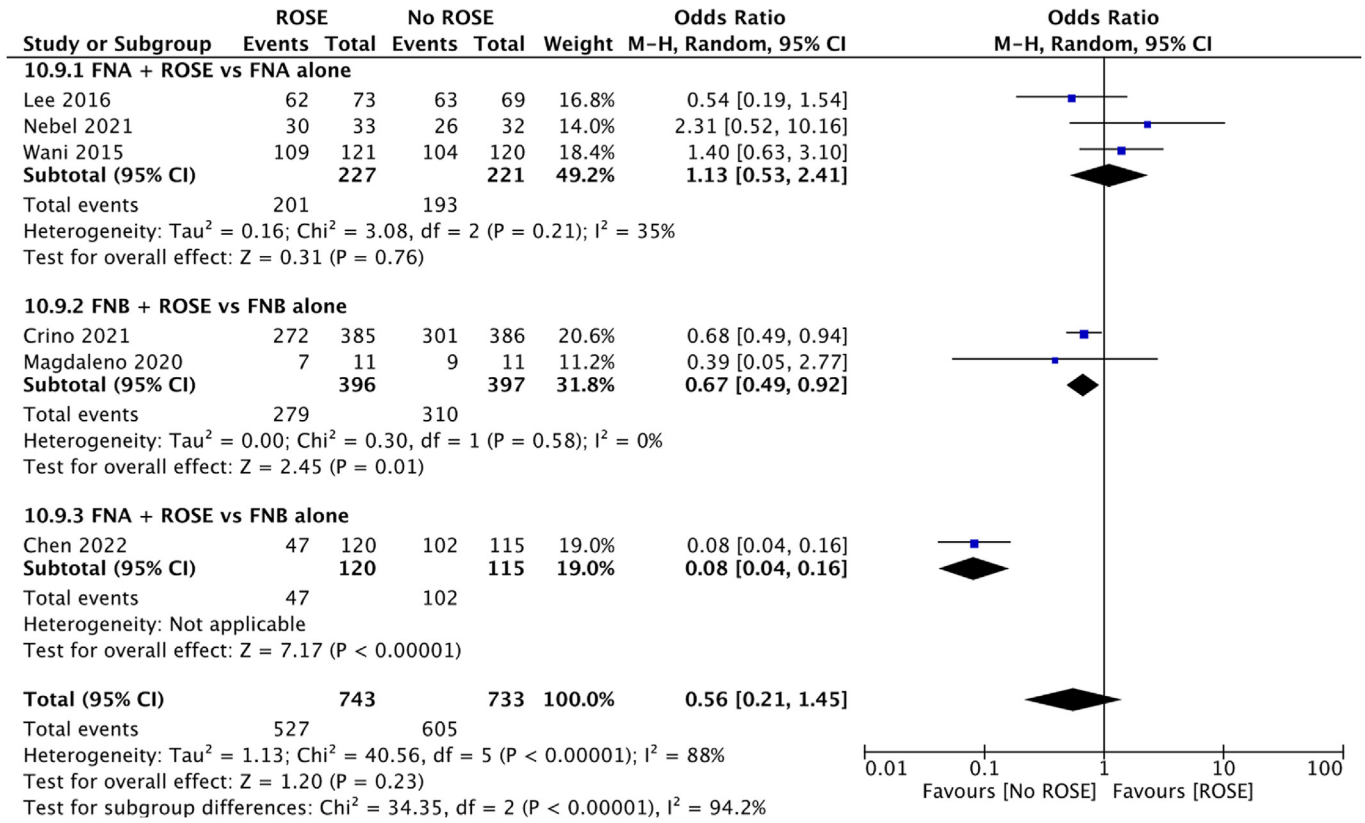


Figure 9. Forest plot comparing sample adequacy of EUS-guided tissue acquisition of solid pancreatic masses with and without ROSE by needle type. *ROSE*, Rapid on-site evaluation; *CI*, confidence interval; *FNB*, fine-needle biopsy.

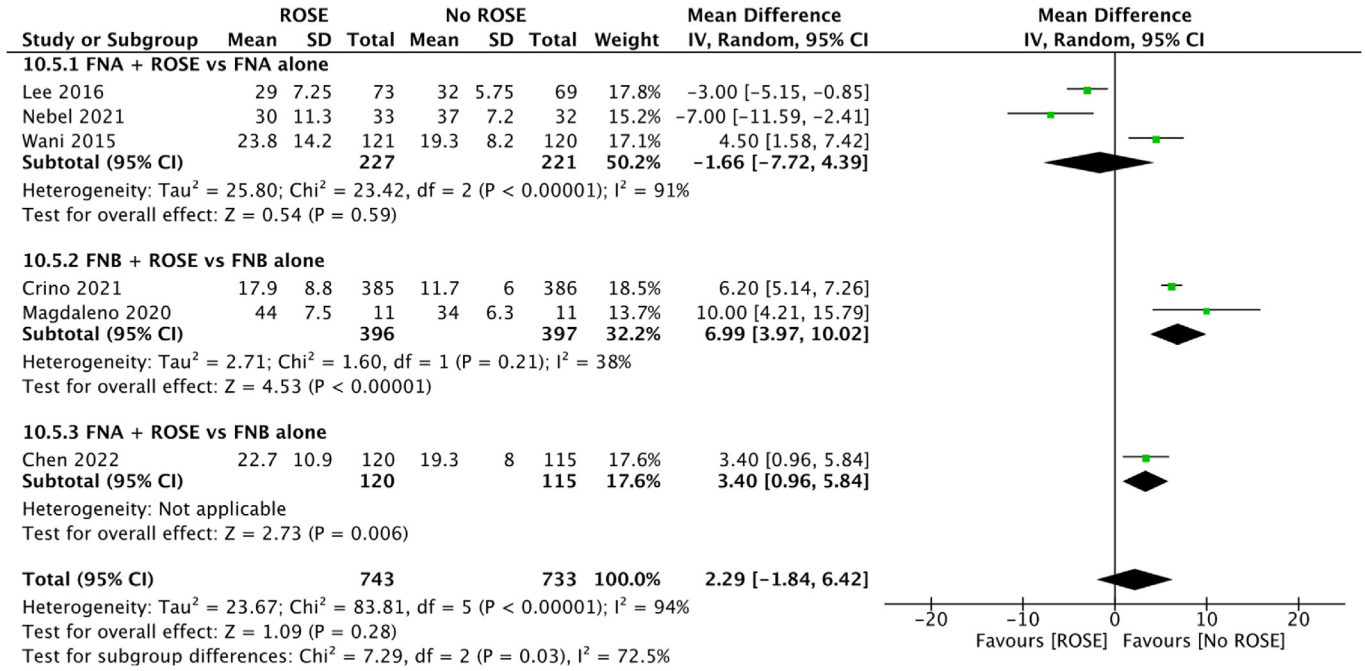


Figure 10. Subgroup analysis comparing procedure duration of EUS-guided tissue acquisition of solid pancreatic masses with and without ROSE by needle type. *ROSE*, Rapid on-site evaluation; *CI*, confidence interval; *FNB*, fine-needle biopsy; *SD*, standard deviation.

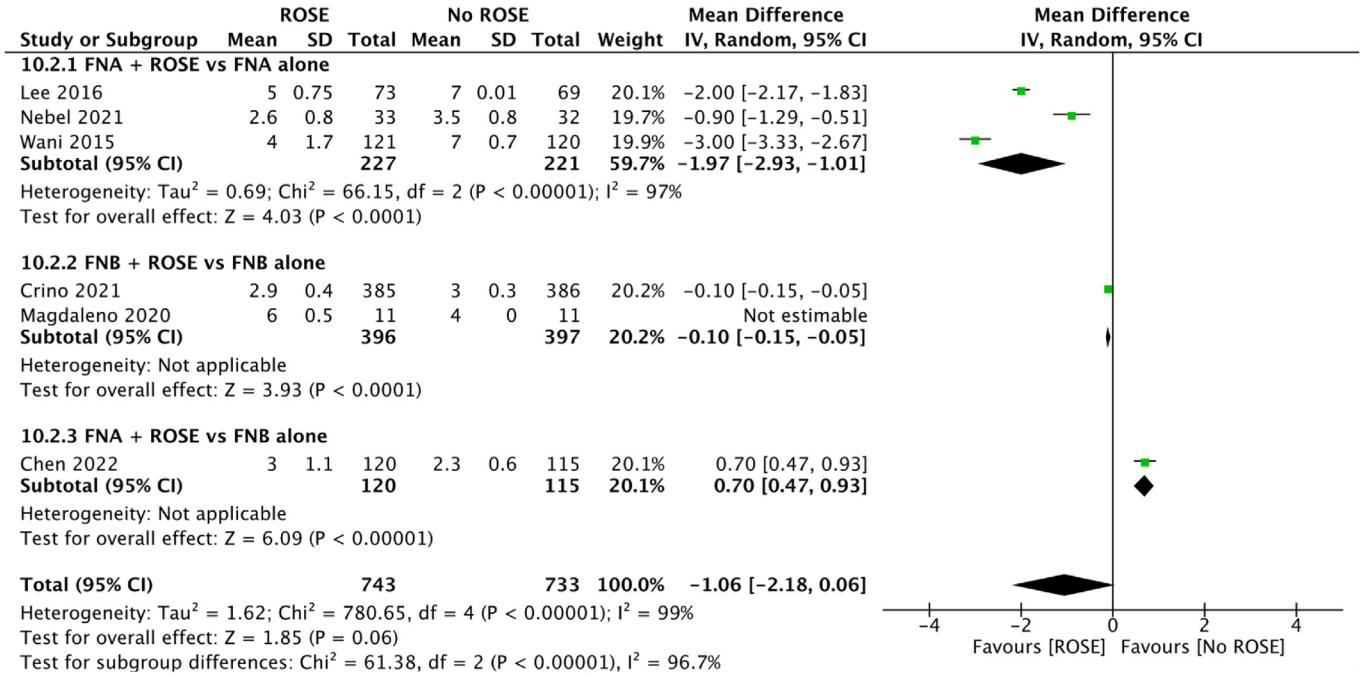


Figure 11. Subgroup analysis comparing number of passes of EUS-guided tissue acquisition of solid pancreatic masses with and without ROSE by needle type. *ROSE*, Rapid on-site evaluation; *CI*, confidence interval; *FNB*, fine-needle biopsy; *SD*, standard deviation.

studies. Issues occurred with imprecision for all outcomes except procedure duration, given the benefits of using ROSE in 1 extreme and benefit in favor of no ROSE in the other extreme. No issues were seen with indirectness or publication bias with any of the included studies (Supplementary Fig. 12A-G, available online at www.giejournal.org). The quality of evidence ranged from very low to moderate. A full evidence profile for this question is provided in Table 6.

Other considerations

Three RCTs evaluated the cost related to adding ROSE to EUS-TA of pancreatic masses. One RCT showed that the cost of FNA with ROSE was significantly higher compared with FNA without ROSE ($1058 vs $375, $P < .01$).[62] In contrast, another RCT showed comparable costs for EUS-FNA with and without ROSE ($2053 vs $2090).[60] In another RCT, the cost of FNB sampling without ROSE ($764) was also comparable with FNA with ROSE ($719).[32] No formal cost-effectiveness studies compared EUS-TA with and without ROSE. No data were found on patient values and preferences.

Discussion

ROSE is a method to obtain real-time evaluation and feedback of a sampled specimen, which theoretically should improve sample adequacy and diagnostic accuracy while reducing the number of needle passes during EUS-TA of solid pancreatic masses. Early observational studies suggested that use of ROSE was associated with better sample adequacy and diagnostic accuracy of pancreatic masses as compared with no ROSE.[65,66] Several subsequent RCTs comparing EUS-TA with and without ROSE have been conducted over the last decade and have failed to confirm the benefits of ROSE. In our systematic review and meta-analysis of 6 RCTs, we found that adding ROSE resulted in similar diagnostic accuracy, diagnostic yield, sample adequacy, need for repeated procedures, number of passes, procedure duration, and adverse events as compared with EUS-TA of pancreatic masses without ROSE. This is similar to the results of a meta-analysis of 7 studies (6 observational and 1 RCT) showing that ROSE did not increase diagnostic yield or sample adequacy and did not reduce the number of needle passes.[67]

Not only did ROSE results in a lack of differences in measurable outcomes, but ROSE required more resources and may be more costly compared with not performing ROSE, as demonstrated in 1 RCT.[62] The costs entailed in ROSE vary across institutions and include costs for a trained technician, trained cytopathologist, microscope, and longer anesthesia time. In addition, there are logistical and personnel challenges to performing ROSE in clinical practice, which makes this service not equally available or used in all institutions. ROSE using telecytology may offer a solution to staffing issues and unit efficiency by allowing the cytopathologist to perform ROSE remotely.[68] Novel artificial intelligence systems are being tested that may eliminate the need for a trained cytopathologist and may make ROSE more widely available in the future.[69]

In a subgroup analysis based on needle type, when an FNB needle was used, we found that adding ROSE required longer procedure duration, provided lower sample

TABLE 6. Evidence profile for population, intervention, comparator, and outcome question 4: in patients with solid pancreatic masses undergoing EUS-guided tissue acquisition, is ROSE beneficial as compared with no ROSE?

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ROSE	No ROSE	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Diagnostic accuracy (diagnostic odds ratio)												
5	Randomized trials	Not serious*	Not serious†	Not serious	Serious‡	None	676/732 (92.3%)	671/722 (92.9%)	OR .93 (.62-1.39)	5 fewer per 1000 (from 39 fewer to 19 more)	⨁⨁⨁◯ Moderate	CRITICAL
Diagnostic yield												
3	Randomized trials	Not serious	Not serious†	Not serious	Very serious§	None	139/165 (84.2%)	130/163 (79.8%)	OR 1.36 (.77-2.41)	45 more per 1000 (from 45 fewer to 107 more)	⨁⨁◯◯ Low	CRITICAL
Sample adequacy												
6	Randomized trials	Not serious‖	Serious¶	Not serious	Serious**	None	527/743 (70.9%)	605/733 (82.5%)	OR .56 (.21-1.45)	100 fewer per 1000 (from 327 fewer to 47 more)	⨁⨁◯◯ Low	CRITICAL
Sample adequacy: FNA with ROSE vs FNA without ROSE												
3	Randomized trials	Not serious	Not serious	Not serious	Serious††	None	201/227 (88.5%)	193/221 (87.3%)	OR 1.13 (.53-2.41)	13 more per 1000 (from 88 fewer to 70 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Sample adequacy: FNB sampling with ROSE vs FNB sampling without ROSE												
2	Randomized trials	Not serious	Not serious	Not serious	Serious††	None	279/396 (70.5%)	310/397 (78.1%)	OR .67 (.49-.92)	76 fewer per 1000 (from 145 fewer to 15 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT
Need for repeated biopsy sampling												
3	Randomized trials	serious‡‡	Not serious†	Not serious	Very serious§§	None	9/469 (1.9%)	12/466 (2.6%)	OR .73 (.30-1.80)	7 fewer per 1000 (from 18 fewer to 20 more)	⨁◯◯◯ Very low	CRITICAL
Mean number of needle passes												
5	Randomized trials	Not serious‖	Very serious‖‖	Not serious	Serious¶¶	None	743	733	—	MD 1.06 fewer (2.18 fewer to .06 more)	⨁◯◯◯ Very low	CRITICAL
Mean duration of the procedure												
6	Randomized trials	Not serious‖	Very serious‖‖	Not serious	Not serious***	None	743	733	—	MD 2.29 min more (1.84 fewer to 6.42 more)	⨁⨁◯◯ Low	IMPORTANT
Mean duration of the procedure: FNA with ROSE vs FNA without ROSE												
3	Randomized trials	Not serious	serious†††	Not serious	Serious‡‡‡	None	227	221	—	MD 1.66 min fewer (7.72 fewer to 4.39 more)	⨁⨁◯◯ Low	IMPORTANT
Mean duration of the procedure: FNB sampling with ROSE vs FNB sampling without ROSE												
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	396	397	—	MD 6.99 min more (3.97 more to 10.02 more)	⨁⨁⨁⨁ High	IMPORTANT
Adverse events												
4	Randomized trials	Not serious*	Serious§§§	Not serious	Very serious§§	None	16/611 (2.6%)	11/602 (1.8%)	OR 1.48 (.46-4.80)	9 more per 1000 (from 10 fewer to 64 more)	⨁◯◯◯ Very low	CRITICAL

ROSE, Rapid on-site evaluation; *CI*, confidence interval; *FNB*, fine-needle biopsy; *MD*, mean difference; *OR*, odds ratio; —, unable to calculate the relative effect for this continuous outcome.

*One study (Crino et al, 2021[61]) was judged to be at high risk bias, but there was no difference between estimates from low risk studies and this study.

†I^2 = .0% and in most studies the point estimates and 95% CIs overlap considerably.

‡Limits of CI suggest a better diagnostic accuracy associated with using ROSE in 1 extreme and worse diagnostic accuracy on the other extreme.

§A small number of events not meeting optimal information size criteria. Limits of CI suggest a small benefit in 1 extreme for ROSE and benefit important to patients in the other for not using ROSE.

‖Two studies were judged to have some concerns for overall risk of bias (Crino et al [2021][61] and Magdaleno et al [2020][64]), but a test of the interaction showed no difference between estimates from low-risk studies and those at high risk of bias.

¶Considerable heterogeneity (I^2 = 88%). The CI of some studies do not overlap with those of some studies and/or the point estimate of some of the included studies and the direction of the effect is not consistent between the included studies.

**Limits of CI suggest a large benefit in favor of using ROSE in 1 extreme and a large benefit in favor of not using ROSE on the other extreme. Because imprecision is linked to inconsistency and use of a random-effects model, certainty of the evidence was rated down by only 1 level.

††Limits of CI cross 1.

‡‡Two of 3 included studies (Crino et al [2021][61] and Magdaleno et al [2020][64]) were judged to have some concerns for an overall risk of bias.

§§Wide 95% CI with a small number of events not meeting optimal information size criteria.

‖‖Considerable heterogeneity (I^2 > 90%). The CIs of most studies do not overlap with those of some studies and the direction of the effect is not consistent between the included studies.

¶¶Wide 95% CI with its limits suggesting benefits in favor of ROSE in 1 extreme and trivial benefit in favor of no ROSE.

***The limits of the CI suggest trivial benefit on either extreme.

†††I^2 = 91%.

‡‡‡Limits of CI interval cross 0.

§§§One study (Nebel et al, 2021[63]) had a different direction of effect with some overlap of 95% CI.

adequacy, and was otherwise no different in other clinical outcomes as compared with no ROSE. The lower sample adequacy with ROSE was explained by the reduction of the overall histologic material and partial use for touch-imprint cytology required for ROSE.[61] These data highlight that ROSE carries some undesirable effects without advantages when FNB needles are used and can thereby be obviated with EUS-FNB of solid pancreatic masses. In contrast, when FNA needles are used, our results demonstrated that ROSE reduced the number of needle passes as compared with not using ROSE. However, without a difference in other outcomes, it is difficult to justify whether the 2 fewer passes with EUS-FNA with ROSE have any impact in patient care or unit efficiency.

The panel acknowledged that ROSE may provide some unmeasured benefits. Although not its primary objective, ROSE can provide a preliminary diagnosis of malignancy when performed by a cytopathologist. In clinical practice, this may aid same-session treatment decisions when considering placement of uncovered metal biliary or duodenal stents, application of CPN, and performing EUS-guided gastrojejunostomy or EUS-guided choledochoduodenostomy if ERCP fails. Formal cost-effectiveness analyses could be performed to elucidate the potential benefits of ROSE in these scenarios. A positive preliminary diagnosis may also allow endosonographers to start the discussion of pancreatic cancer diagnosis immediately after the procedure and to initiate prompt coordination of oncologic care. However, the panel expressed concern with the use of preliminary diagnosis with ROSE, because this is not a definitive diagnosis and may change on the final histopathologic report. The accuracy of preliminary diagnoses using ROSE was not reported in any of the RCTs of our systematic review and deserves future investigation.

This guideline did not specifically assess the optimal number of passes required with FNB needles when ROSE is not used. Emerging data, including a recent RCT and meta-analysis of RCTs,[70,71] suggested that a minimum of 2 passes with contemporary FNB needles are optimal to accurately diagnose solid pancreatic masses and to obtain an adequate sample in the absence of ROSE. In 1 RCT, the addition of MOSE to guide the number of passes seemed to reach a similar accuracy as FNB sampling without ROSE or MOSE; however, MOSE required fewer number of passes (1 with MOSE vs 3 without MOSE).[72] An adequate sample with MOSE is considered when the sample reveals several worm-like whitish or yellowish cores clearly longer than 10 mm on visual inspection. If adequacy with MOSE is doubtful with subjective inspection, the material is removed from the container, aligned on a slide, and the entire length measured using a ruler to ensure the sample is >10 mm. Future studies are needed to define if endosonographers should be performing MOSE routinely in the absence of ROSE; however, current data do not support the superiority of MOSE over FNB needle passes without ROSE or MOSE other than potentially reducing the number of passes.

In summary, based on the moderate to low quality of the evidence and after considering all desirable and undesirable effects, the panel made a conditional recommendation against the routine use of ROSE in patients undergoing initial EUS sampling of a solid pancreatic mass. This does not mean that ROSE should never be used; however, its use should not be a routine part of EUS-TA of pancreatic masses, especially when FNB needles are used. The panel discussed some circumstances in which ROSE may be considered when available:

1. Initial nondiagnostic EUS sampling
2. Lesion not clearly seen or obscured by artifact (eg, stent, pancreatitis changes)
3. Use of an FNA needle (although not recommended in this guideline, FNA needles may be used when FNB needles are unavailable)
4. A preliminary diagnosis is desired to guide immediate treatment decisions and a cytopathologist is willing to provide an on-site diagnosis

Question 5: In patients with distal malignant biliary obstruction undergoing ERCP, are SEMS superior to plastic stents?

Recommendation 5: For patients with distal malignant biliary obstruction undergoing ERCP, the ASGE suggests using SEMS over plastic stents.

(Conditional recommendation/low quality of evidence)

A systematic review and meta-analysis of RCTs was performed to address this question. A single literature search informing PICO questions 5 and 6 was conducted through February 17, 2022. A PRISMA diagram detailing study screening is provided in Figure 12. A total of 2814 citations were found, and 48 full-text manuscripts were reviewed for eligibility. We identified 15 RCTs that compared SEMS with plastic stents among 1253 patients with distal malignant biliary obstruction.[73-87] All studies were full-text publications and used a parallel RCT design. Eleven studies included variable causes of distal malignant biliary obstruction, with pancreatic cancer being the predominant etiology (range, 53%-88%).[73-76,79,80,82,83,85-87] The other 4 RCTs enrolled only patients with pancreatic cancer.[77,78,81,84] Ten studies included patients with unresectable malignancy,[73-76,82-87] whereas 4 studies included resectable or borderline resectable disease,[77,78,80,81] and 1 study included variable staging.[79] The type of SEMS more commonly used was uncovered in 6 studies[73,74,83,85-87] followed by fully covered in 4 studies[78,80,81,84] and partially covered in 1 study.[79] The remaining 4 studies either did not mention SEMS type or used variable types. Plastic stents were of 10F diameter in

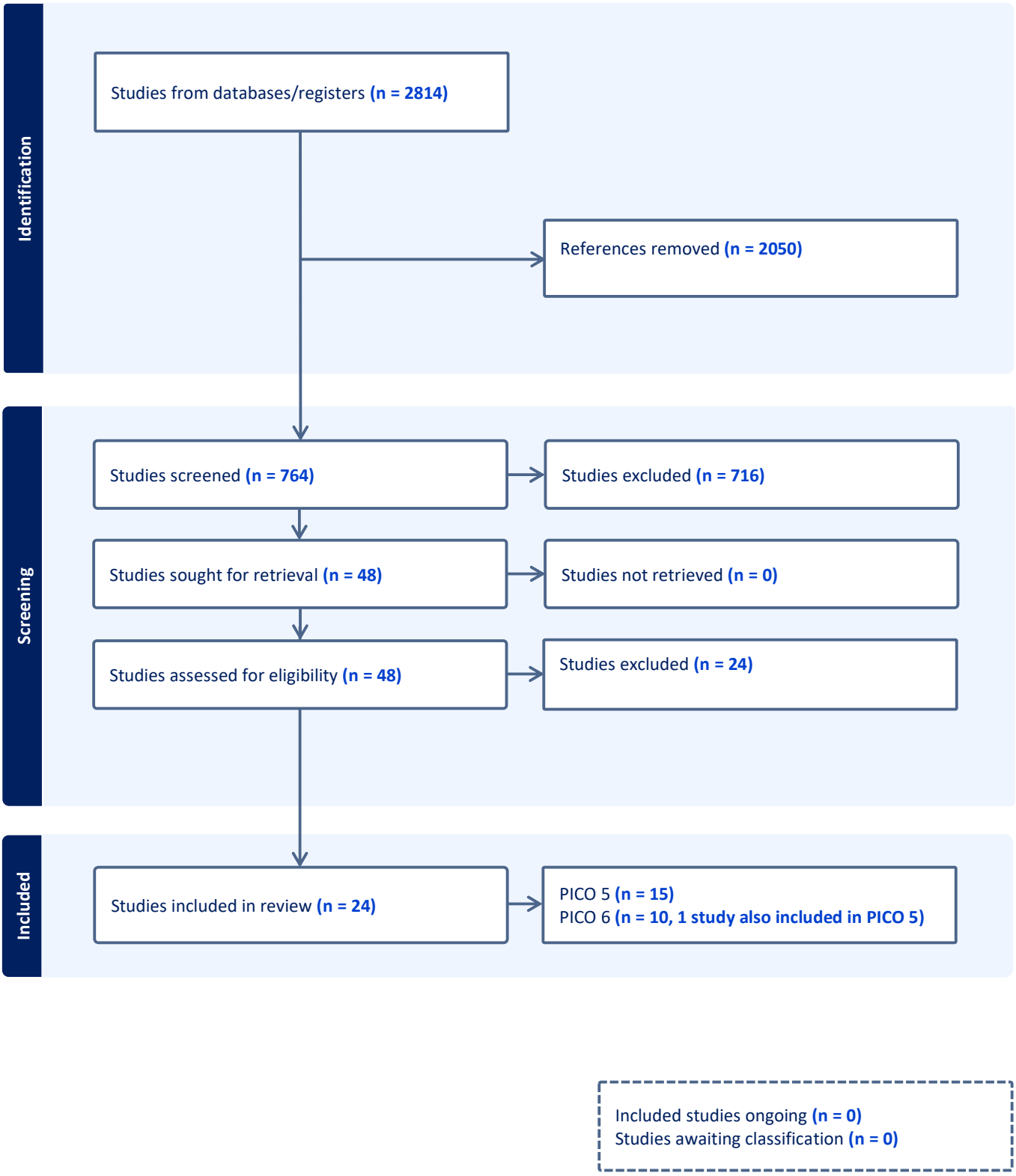


Figure 12. Preferred Reporting Items for Systematic reviews and Meta-Analyses diagram showing the studies included in the systematic review evaluating ERCP with stent placement of distal malignant biliary obstruction (PICO questions 5 and 6). *PICO*, Population, intervention, comparator, and outcomes.

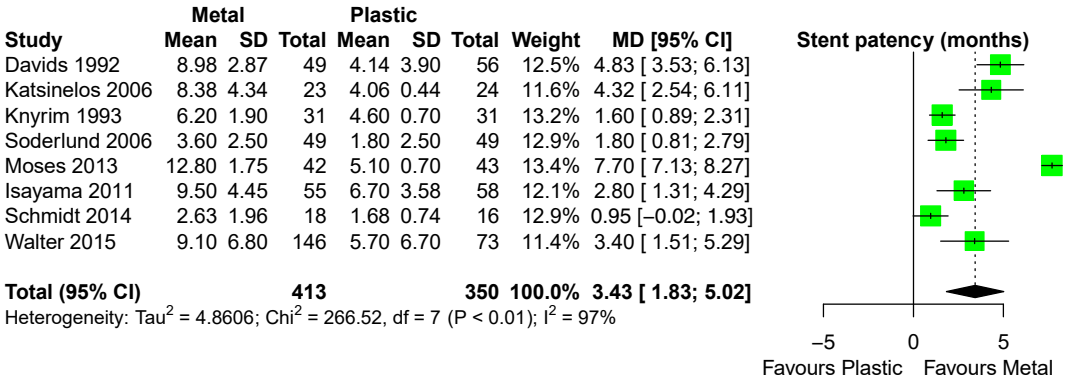


Figure 13. Forest plot comparing stent patency between metal and plastic biliary stents in patients with distal malignant biliary obstruction. *CI*, Confidence interval; *SD*, standard deviation.

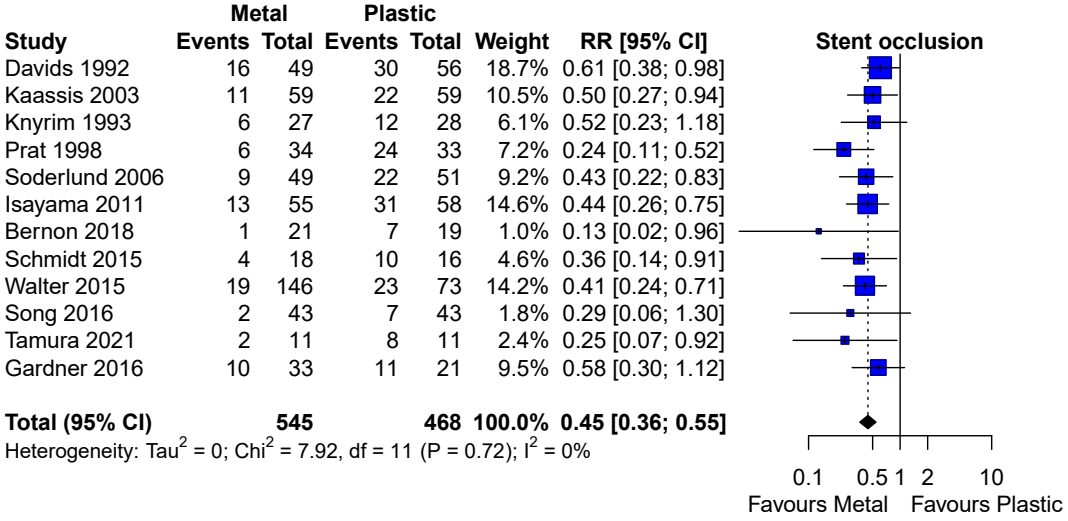


Figure 14. Forest plot comparing stent failure rate between metal and plastic biliary stents in patients with distal malignant biliary obstruction. *CI*, Confidence interval; *RR*, risk ratio.

11 studies,[74,76-81,83-85,87] whereas 2 studies used 11.5F plastic stents[73,86] and 2 studies did not mention stent diameter or used variable diameters. No planned stent exchange was conducted in any of the studies.

Survival

The mean survival in patients undergoing ERCP for drainage of distal malignant biliary obstruction was similar with either metal or plastic biliary stents in 6 RCTs (MD, .66 months; 95% CI, −.39 to 1.71; I^2 = 69%) (Supplementary Fig. 13A, available online at www.giejournal.org).[75,79,82,84,85,87] In a sensitivity analysis after removing 1 RCT with outlier results and a high risk of bias,[79] the mean survival was higher with SEMS as compared with plastic stents in the remaining 5 RCTs (MD, 1.12 months; 95% CI, .26-1.99; I^2 = 0%).[75,82,84,85,87] The rate of mortality at 30 days was not different between SEMS (9.8%, 18/184) and plastic stents (6.3%, 12/190) in 5 RCTs (OR, 1.65; 95% CI, .78-3.49; I^2 = 0%) (Supplementary Fig. 13B).[73,83,85-87]

Stent patency, cholangitis, and reinterventions

In patients with distal malignant biliary obstruction, SEMS had 3.4 months longer patency than plastic stents in 8 RCTs (95% CI, 1.83-5.02; I^2 = 97%) (Fig. 13).[75,76,79,82,84-87] In 12 RCTs, the rate of stent failure was lower with SEMS (18.2%, 99/545) as compared with plastic stents (44.2%, 207/468) (OR, .45; 95% CI, .36-.55; I^2 = 0%) (Fig. 14).[73,74,76-78,80,82-87] As a result, patients with SEMS were less likely to develop acute cholangitis (10.0%, 49/488) than patients with plastic stents (19.6%, 85/433) in 11 RCTs (OR, .53; 95% CI, .33-.87; I^2 = 44%) (Fig. 15).[74-76,78-80,82,83,85-87] In addition, SEMS also reduced the need for unplanned endoscopic reinterventions (19.0%, 28/147) as compared with plastic stents (37.3%, 59/158) in 4 RCTs (OR, .58; 95% CI, .40-.85; I^2 = 28%) (Fig. 16).[75,80,81,87]

When assessing the causes for stent failure, SEMS were less likely to get occluded by stones or sludge than plastic stents in 7 RCTs (OR, .14; 95% CI, .09-.23; I^2 = 0%) (Supplementary Fig. 13C).[76,78,82,84-87] As compared with

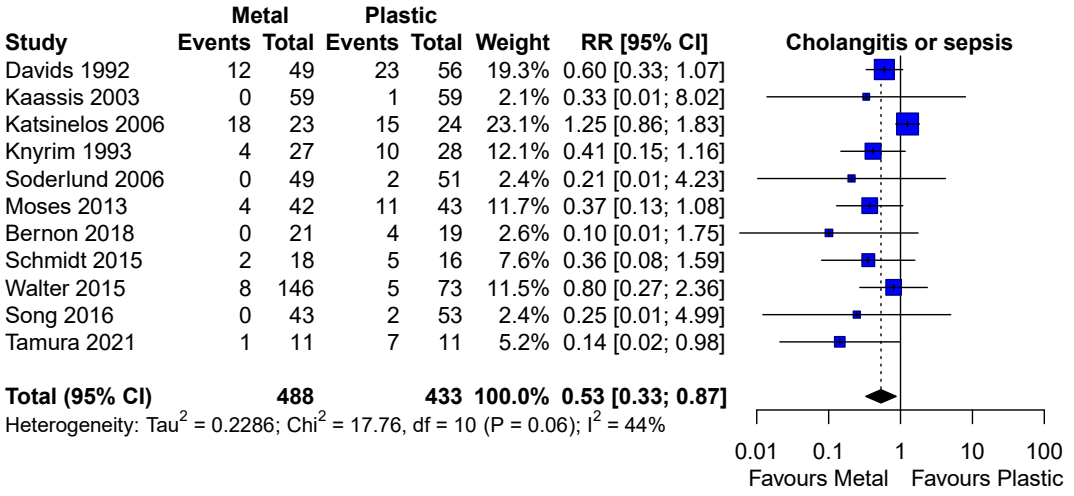


Figure 15. Forest plot comparing risk of cholangitis or sepsis between metal and plastic biliary stents in patients with distal malignant biliary obstruction. *CI*, Confidence interval; *RR*, risk ratio.

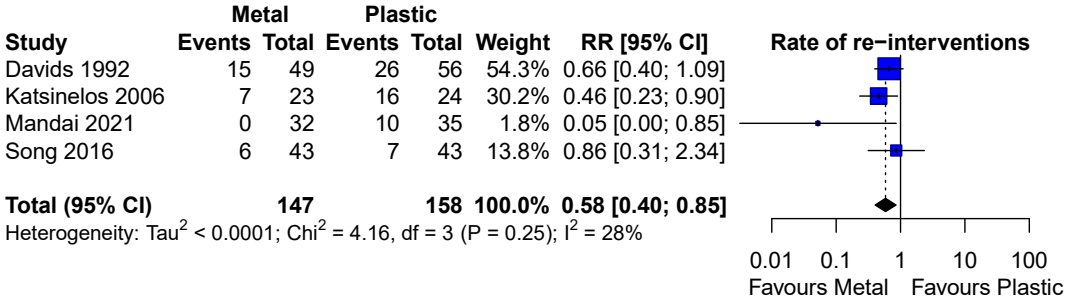


Figure 16. Forest plot comparing risk of reintervention rate between metal and plastic biliary stents in patients with distal malignant biliary obstruction. *CI*, Confidence interval; *RR*, risk ratio.

plastic stents, SEMS were more likely to fail because of tissue ingrowth (OR, 7.60; 95% CI, 2.05-28.23; I^2 = 0%) (Supplementary Fig. 13D).[76,82,84,86,87] The risk of migration was similar for SEMS and plastic stents (OR, .81; 95% CI, .21-3.13; I^2 = 44%) (Supplementary Fig. 13E).[76,78,82,84-87]

Post-ERCP adverse events

The rate of post-ERCP adverse events in distal malignant biliary obstruction was no different for SEMS (12.7%, 31/245) and plastic biliary stents (8.1%, 19/235) in 7 RCTs (OR, 1.21; 95% CI, .41-3.56; I^2 = 62%) (Supplementary Fig. 13F).[74,75,77,78,80,83,84] The rate of post-ERCP pancreatitis was similar for SEMS (3.1%, 15/481) and plastic stents (1.4%, 6/416) in 10 RCTs (OR, 1.91; 95% CI, .65-5.63; I^2 = 16%) (Supplementary Fig. 13G).[74-76,78-81,83-85] No difference in the rate of acute cholecystitis was found after SEMS (3.7%, 14/374) or plastic stents (1.9%, 6/310) in 8 RCTs (OR, 1.61; 95% CI, .62-4.16; I^2 = 0%) (Supplementary Fig. 13H).[76,78,79,81-84,87]

Surgical outcomes

Surgical resectability was comparable between patients who underwent SEMS (61.3%, 73/119) and plastic stent (67.3%, 74/110) placement in 4 RCTs (OR, .90; 95% CI, .77-1.05; I^2 = 20%) (Supplementary Fig. 13I).[77,78,80,81] No differences were found in the rates of postoperative adverse events between SEMS (38.1%, 24/63) and plastic stents (30.6%, 22/72) in 3 RCTs (OR, 1.38; 95% CI, .45-4.25; I^2 = 63%) (Supplementary Fig. 13J).[78,80,81]

Subgroup analysis

We found no differences in the overall results in subgroup analyses by etiology of malignant obstruction (studies with pancreatic cancer only vs variable etiology of distal malignant obstruction), malignancy staging (resectable vs unresectable), type of metal stent (covered vs uncovered), or plastic stent diameter (10F vs 11.5F).

Certainty in the evidence

The risk of bias (Supplementary Fig. 14A and B, available online at www.giejournal.org) was determined to be serious for most outcomes, except for 30-day mortality, stent failure rate, and etiology of stent failure. Inconsistency was concerning for mean survival, post-ERCP adverse events, and stent migration, because the direction of effect varied across studies for these outcomes. We also rated

TABLE 7. Evidence profile for population, intervention, comparator, and outcome question 5: in patients with distal malignant biliary obstruction undergoing ERCP, are SEMS better than plastic stents?

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS	Plastic stents	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Mean survival time (mo)												
6	Randomized trials	Serious*	Serious†	Not serious	Serious‡	None	236	248	—	MD .66 mo higher (.39 lower to 1.71 higher)	⨁◯◯◯ Very low	CRITICAL
30-day mortality												
5	Randomized trials	Not serious§	Not serious‖	Not serious	Very serious¶	None	18/184 (9.8%)	12/190 (6.3%)	RR 1.65 (.78-3.49)	41 more per 1000 (from 14 fewer to 157 more)	⨁⨁◯◯ Low	CRITICAL
Mean stent patency (mo)												
8	Randomized trials	Serious**	Serious††	Not serious	Not serious‡‡	None	413	350	—	MD 3.43 mo higher (1.83 higher to 5.02 higher)	⨁⨁◯◯ Low	CRITICAL
Stent failure rate												
12	Randomized trials	Not serious§§	Not serious‖	Not serious	Not serious	Publication bias strongly suspected	99/545 (18.2%)	207/468 (44.2%)	RR .45 (.36-.55)	243 fewer per 1000 (from 283 fewer to 199 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Cholangitis or sepsis												
11	Randomized trials	Serious‖‖	Not serious¶¶	Not serious	Serious***	Publication bias strongly suspected	49/488 (10.0%)	85/433 (19.6%)	RR .53 (.33-.87)	92 fewer per 1000 (from 132 fewer to 26 fewer)	⨁◯◯◯ Very low	CRITICAL
Need for reintervention												
4	Randomized trials	Serious†††	Not serious	Not serious	Serious***	None	28/147 (19.0%)	59/158 (37.3%)	RR .58 (.40-.85)	157 fewer per 1000 (from 224 fewer to 56 fewer)	⨁⨁◯◯ Low	CRITICAL
Postprocedure adverse events												
6	Randomized trials	Serious‡‡‡	Serious§§§	Not serious	Serious¶	None	31/245 (12.7%)	23/235 (9.8%)	RR 1.21 (.41-3.56)	21 more per 1000 (from 58 fewer to 251 more)	⨁◯◯◯ Very low	CRITICAL
Post-ERCP pancreatitis												
8	Randomized trials	Serious‖‖‖	Serious†	Not serious	Serious¶¶¶	None	15/481 (3.1%)	6/416 (1.4%)	RR 1.91 (.65-5.63)	13 more per 1000 (from 5 fewer to 67 more)	⨁◯◯◯ Very low	CRITICAL
Post-ERCP cholecystitis												
7	Randomized trials	Serious****	Not serious	Not serious	Serious¶¶¶	None	14/374 (3.7%)	6/310 (1.9%)	RR 1.61 (.62-4.16)	12 more per 1000 (from 7 fewer to 61 more)	⨁⨁◯◯ Low	CRITICAL
Surgical resectability												
4	Randomized trials	Serious††††	Not serious	Not serious	Serious¶	None	73/119 (61.3%)	74/110 (67.3%)	RR .90 (.77-1.05)	67 fewer per 1000 (from 155 fewer to 34 more)	⨁⨁◯◯ Low	CRITICAL
Postoperative adverse events after resection												
3	Randomized trials	Serious‡‡‡‡	Not serious§§§§	Not serious	Very serious‖‖‖‖	None	24/63 (38.1%)	22/72 (30.6%)	RR 1.38 (.45-4.25)	116 more per 1000 (from 168 fewer to 993 more)	⨁◯◯◯ Very low	CRITICAL
Stent blockade from sludge/stone												
7	Randomized trials	Not serious§§	Not serious‖	Not serious	Serious***	None	19/359 (5.3%)	120/293 (41.0%)	RR .14 (.09-.23)	352 fewer per 1000 (from 373 fewer to 315 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT
Stent tissue ingrowth												
5	Randomized trials	Not serious§§	Not serious‖	Not serious	Very Serious¶¶¶	None	23/299 (7.7%)	0.5/235 (.2%)	RR 7.60 (2.05-28.23)	14 more per 1000 (from 2 more to 58 more)	⨁⨁◯◯ Low	IMPORTANT

(*continued on the next page*)

TABLE 7. Continued

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS	Plastic stents	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Stent migration												
6	Randomized trials	Not serious§§	Serious§§§	Not serious	Serious¶¶¶¶	None	10/359 (2.8%)	11/296 (3.7%)	RR .81 (.21-3.13)	7 fewer per 1000 (from 29 fewer to 79 more)	⨁⨁◯◯ Low	IMPORTANT

SEMS, Self-expandable metal stents; *CI*, confidence interval; *MD*, mean difference; *mo*, months; *RR*, risk ratio; —, unable to calculate the relative effect for this continuous outcome.
*Most trials (4/6) had a high risk of bias or had some concern because of risk of bias.
†Despite a partial overlap of 95% CIs, the direction of effect varied across studies.
‡Limits of CI suggest a trivial benefit in favor of metal stents in 1 extreme and a small benefit in favor of plastic stents on the other extreme. Because imprecision is linked to inconsistency and use of a random-effects model, certainty of the evidence was rated down by only 1 level.
§Two studies were judged to have an overall high risk of bias or some concern because of risk of bias (Davids et al [1992][87] and Prat et al [1998][73]), but a test of the interaction showed no difference between estimates from low-risk studies and those at a high risk of bias.
‖I^2 = .0% and in most studies the point estimates and 95% CIs overlap considerably.
¶Limits of CI suggest a small benefit in favor of metal stents in 1 extreme and a large benefit in favor of plastic stents on the other extreme. A small number of events did not meet the optimal information size criteria.
**Most studies (5/8) were judged to have an overall high risk of bias or some concerns because of a risk of bias with >60% of weight.
††Considerable heterogeneity (I^2 = 97%). Certainty of the evidence was rated down by only 1 level because a risk of bias was potentially the source of inconsistency and clinical inconsistency is trivial because the results of most included studies have similar clinical implication.
‡‡The observed imprecision is most likely linked to inconsistency, risk of bias, and use of a random-effects model.
§§Not rated down for risk of bias because an equal number of trials was judged to be at high and low risk of bias, but *P* value for test of interaction showed no difference between the 2 estimates.
‖‖Most trials (7/11) were at high risk of bias or had some concern because of the risk of bias.
¶¶Considerable heterogeneity (I^2 = 44%). Not rated down because clinical inconsistency was deemed not important because all results of included studies have a similar clinical implication.
***A small number of events did not meet the optimal information size criteria.
†††Only 1 trial (Song et al, 2016[80]) was judged to be at low risk of bias with <15% of weight showing no difference between metal and plastic stents.
‡‡‡Most trials (4/6 contributing to pooled estimate) were at high risk of bias or had some concerns.
§§§Despite partial overlap of 95% CIs, the direction of effect varied across studies.
‖‖‖Most trials (6/9 contributing to pooled estimate) were at high risk of bias or had some concern because of risk of bias.
¶¶¶Limits of CI suggest a trivial benefit in 1 extreme and benefit important to patients in the other. This is based on a small number of events not meeting the optimal information size criteria.
****Only 1 of 7 contributing trials (Isayama et al, 2011[84]) was at a low risk of bias.
††††Most trials (3/4) were at a high risk of bias or had some concern because of risk of bias.
‡‡‡‡One study at an overall high risk of bias (Mandai et al, 2022[81]) and 1 study with some concern because of risk of bias (Tamura et al, 2021[78]) showed completely opposite effects.
§§§§Because the observed heterogeneity (I^2 = 63%) is largely linked to 2 studies with risk of bias problems, certainty of the evidence was not rated down any further.
‖‖‖‖Limits of CI suggest a large imprecise harm on both extremes based on a small sample size and small number of events. Because imprecision is likely linked to inconsistency, certainty of the evidence was rated down by only 2 levels.
¶¶¶¶Limits of CI suggest a benefit in favor of metal stents in 1 extreme and a benefit in favor of plastic stents in other. This is based on a small number of events, but because imprecision is linked to inconsistency and use of a random-effects model, certainty of the evidence was rated down by only 1 level.

down for inconsistency in mean stent patency because of significant heterogeneity (I^2 = 97%). Almost all outcomes were rated down for imprecision except stent patency and stent failure rate. The concern for imprecision in the outcomes of cholangitis and need for reinterventions was because of a small number of events not meeting the optimal information size criteria. Other outcomes were rated down for imprecision because the limits of the CI suggested benefit in favor of metal stents in 1 extreme and benefit in favor of plastic stents on the other extreme. Publication bias was suspected in the rates of stent failure and cholangitis (Supplementary Fig. 15A-C, available online at www.giejournal.org). There was no concern with indirectness of the evidence for any of the included studies. The quality of evidence ranged from very low to moderate. A complete evidence profile is shown in Table 7.

Other considerations

Metal stents are 10 to 15 times more expensive than plastic stents. Several RCTs have compared the cost-effectiveness between metal and plastic biliary stents. In 1 RCT, metal stents were more cost-effective than plastic stents; however, a survival time of 3 to 6 months showed no difference in cost-effectiveness, and if survival was <3 months, plastic stents were more cost-effective.[73] Another RCT showed that metal stents were more cost-effective in patients without liver metastasis, whereas plastic stents were more cost-effective in patients with liver metastasis (median survival, 2.7 months).[74] Another RCT found no difference in cost-effectiveness between both stents in the absence of liver metastasis, but plastic stents were more cost-effective in patients with liver metastasis.[75] Three other RCTs reported no difference in the cost-effectiveness of metal and plastic stents.[76-78] We found no studies reporting on patient values and preferences.

Discussion

Over half of patients with pancreatic cancer develop jaundice because of distal common bile duct obstruction.[88] This is associated with pruritus, fatigue, poor quality of life,

and rarely cholangitis, all of which can be improved with biliary decompression.[89] Although some patients with obstructive jaundice and resectable disease may not require preoperative biliary drainage when upfront surgery is planned within 2 weeks, many patients are not eligible for upfront surgery and warrant biliary decompression.[90,91] With increasing use of neoadjuvant therapy among most patients with borderline resectable and locally advanced pancreatic cancer, as well as in many patients with resectable disease, those with obstructive jaundice benefit from durable biliary drainage that allows for safe administration of the treatment regimen.[92-94] In patients with unresectable pancreatic cancer, biliary drainage facilitates palliative interventions and can improve survival as compared with no biliary interventions.[95] When biliary drainage is indicated, ERCP is the preferred modality because it has been demonstrated to increase survival, shorten hospital stay, reduce adverse events, and decrease costs as compared with percutaneous biliary drainage.[95] In patients with distal malignant biliary obstruction because of confirmed or presumed pancreatic cancer in whom an ERCP is performed for biliary drainage, there is still wide variability in the selection of plastic or metal biliary stents.[96]

Our systematic review and meta-analysis revealed that in patients with distal malignant biliary obstruction, SEMS have longer stent patency than plastic stents, which reduces the risk of stent failure, cholangitis, and endoscopic reinterventions. These results align with previous published meta-analyses in distal malignant biliary obstruction.[97,98] The shorter patency of plastic stents is because of biofilm formation and stent occlusion by sludge or stone. Despite the clinical benefits of SEMS, we found no difference in survival or surgical resectability between metal and plastic stents. Even though 11 of the 15 RCTs in our meta-analysis included patients with diverse causes of distal malignant biliary obstruction, with pancreatic cancer the most common, a subgroup analysis of the 4 RCTs that enrolled only patients with pancreatic cancer showed similar results to those with diverse malignancies. Thereby, our results are generalizable to distal malignant biliary obstruction with or without a pancreatic mass. Some outcomes such as rehospitalizations or chemotherapy interruptions were not measured by the included RCTs, but our results allow us to infer these are likely less common with SEMS.

Although SEMS are superior to plastic stents in important clinical outcomes, pancreatic masses often do not have a confirmatory tissue diagnosis at the time of ERCP. None of the RCTs included in our meta-analysis studied patients with this clinical situation, and data to guide stent selection in patients with a pancreatic mass without a final diagnosis are lacking. If the pretest probability of malignancy is high and simultaneous EUS-TA is performed, the panel favors the use of cSEMS. If the pretest probability of malignancy is high and EUS is not available, a plastic stent should be considered during ERCP, in addition to cytology brushings with intraductal biopsy sampling. In addition, because of the inferior accuracy of ERCP sampling methods as compared with EUS-FNB for solid pancreatic masses, patients undergoing ERCP often require repeated procedures for sampling to establish a diagnosis, which can be more difficult with a SEMS in place.[99]

The undesirable effects with SEMS and plastic stents were not significantly different, including similar risk of post-ERCP pancreatitis, post-ERCP cholecystitis, and post-surgical adverse events. However, a SEMS is more costly than a plastic stent and is less cost-effective when survival is shorter than 3 months. Prognostic factors that predict very poor survival in patients with pancreatic cancer include Karnofsky scores <80 or presence of liver metastases.[74,100] When these or other factors suggest life expectancy shorter than 3 months or when the anticipated timing of a surgical resection is within 3 months, a plastic stent might be reasonable. If this information is unknown, endoscopists can consider placing a cSEMS or initiate a multidisciplinary discussion with oncology and surgical oncology to guide stent selection.

Question 6: In patients with distal malignant biliary obstruction undergoing ERCP with SEMS, are covered SEMS (cSEMS) superior to uncovered SEMS (uSEMS)?

Recommendation 6: Among patients with distal malignant biliary obstruction undergoing ERCP with SEMS, the ASGE suggests using cSEMS over uSEMS.

(Conditional recommendation/low quality of evidence)

For patients with distal biliary obstruction from a pancreatic mass and unconfirmed malignancy, the ASGE recommends against uSEMS.

(Strong recommendation/low quality of evidence)

We identified 10 full-text parallel RCTs to address this question, encompassing 1337 patients with distal malignant biliary obstruction.[77,101-109] Of these, 3 RCTs enrolled only patients with pancreatic cancer,[77,102,109] whereas 7 RCTs were in patients with various malignant etiologies of distal biliary obstruction,[101,103-108] with pancreatic cancer the most common (range, 59%-92%). Eight RCTs were in patients with unresectable disease[101-108] and 2 were in resectable or borderline resectable malignancy.[77,109] With regard to the type of cSEMS, 6 RCTs used fully covered SEMS[77,102,103,105,107,109] and 4 used partially covered SEMS.[101,104,106,108]

Survival

Survival was similar after placement of cSEMS or uSEMS in 9 RCTs (MD, –27.1 days; 95% CI, –72.17 to 17.92; I^2 = 88%) (Supplementary Fig. 16A, available online at www.giejournal.org).[77,101-108]

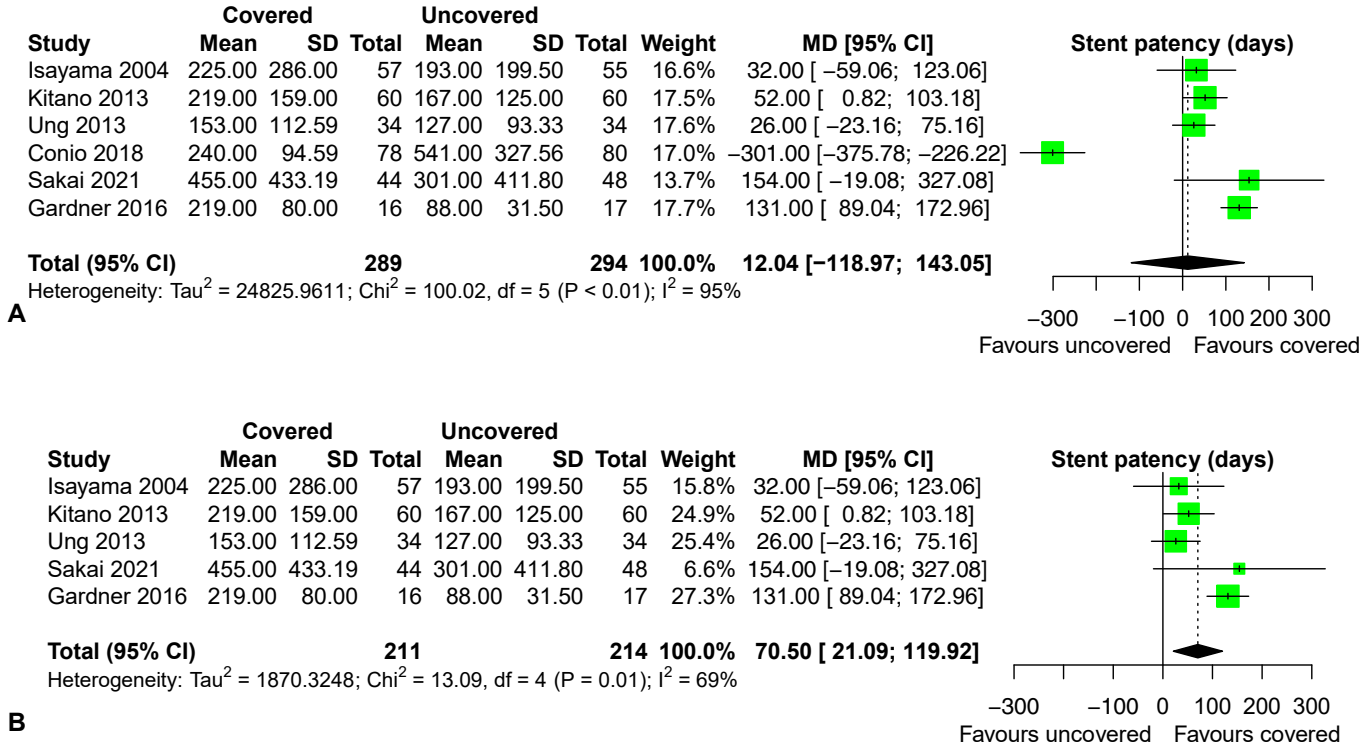


Figure 17. Forest plot comparing stent patency between covered metal and uncovered metal biliary stents in patients with distal malignant biliary obstruction. **A,** Overall results. **B,** Sensitivity analysis after removing outlier study of Conio et al[107] (high risk of bias). *CI*, Confidence interval; *SD*, standard deviation; *MD*, mean difference.

Stent patency, cholangitis, and reinterventions

Stent patency was not different between cSEMS and uSEMS in 6 RCTs (MD, 12.04 days; 95% CI, −118.97 to 143.05; I^2 = 95%) (Fig. 17A).[77,101,102,105,107,108] After excluding 1 outlier study with a high risk of bias,[107] cSEMS had a longer stent patency of 70.5 days compared with uSEMS in 5 RCTs (95% CI, 21.09-119.92; I^2 = 69%) (Fig. 17B).[77,101,102,105,108] We found no difference in the risk of stent failure between cSEMS (26.7%, 179/671) and uSEMS (28.5%, 190/667) in 10 RCTs (OR, .84; 95% CI, .55-1.27; I^2 = 60%) (Supplementary Fig. 16B).[77,101-109] The risk of cholangitis was no different between cSEMS (5.8%, 27/468) and uSEMS (6.3%, 30/474) in 6 RCTs (OR, .90; 95% CI, .52-1.56; I^2 = 0%) (Supplementary Fig. 16C).[103,105-109] The rate of reinterventions was similar for cSEMS (23.6%, 61/259) and uSEMS (20.4%, 53/260) in 2 RCTs (OR, 1.20; 95% CI, .79-1.83; I^2 = 0%) (Supplementary Fig. 16D).[103,109]

In 8 RCTs that evaluated the reasons for stent failure, cSEMS were more likely to get occluded by stones and sludge (OR, 2.70; 95% CI, 1.50-4.86; I^2 = 0%) (Supplementary Fig. 16E) and to migrate (OR, 8.31; 95% CI, 2.68-25.81; I^2 = 0%) (Supplementary Fig. 16F) than uSEMS.[101-104,106-109] Compared with uSEMS, cSEMS were less likely to fail because of tissue ingrowth (OR, .14; 95% CI, .05-.37; I^2 = 61%) (Supplementary Fig. 16G).[101-104,106-109] No significant difference was found between cSEMS and uSEMS in the risk of tissue outgrowth (OR, 1.77; 95% CI, .83-3.77; I^2 = 0%) (Supplementary Fig. 16H).[101-104,106-109]

Post-ERCP adverse events

Adverse events occurred at a similar rate after ERCP with cSEMS (17.7%, 78/442) and uSEMS (15.2%, 69/453) in 6 RCTs (OR, 1.22; 95% CI, .82-1.82; I^2 = 0%) (Supplementary Fig. 16I).[77,103,106-109] The incidence of post-ERCP pancreatitis was similar for cSEMS (2.2%, 14/651) and uSEMS (1.2%, 8/650) in 9 RCTs (OR, 1.47; 95% CI, .60-3.60; I^2 = 0%) (Supplementary Fig. 16J).[101-109] The risk of acute cholecystitis was no different for cSEMS (3.4%, 20/592) and uSEMS (2.0%, 12/614) in 9 RCTs (OR, 1.62; 95% CI, .78-3.36; I^2 = 0%) (Supplementary Fig. 16K).[101-109]

Surgical outcomes

The type of SEMS did not impact surgical resectability in 1 RCT (P = .99); however, the SEMS were placed at least 2 cm below the hepatic hilum in that study.[109] No RCTs have compared postsurgical adverse events between cSEMS and uSEMS.

Subgroup analysis

None of the results differed in subgroup analyses by etiology of malignant obstruction (studies with pancreatic

TABLE 8. Evidence profile for population, intervention, comparator, and outcome question 6: in patients with distal malignant biliary obstruction undergoing ERCP, are covered SEMS better than uncovered SEMS?

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Covered SEMS	Uncovered SEMS	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Mean survival time (days)												
9	Randomized trials	Serious*	Serious†	Not serious	Not serious‡	None	608	607	—	MD 27.1 days fewer (72.17 fewer to 17.92 more)	⨁⨁◯◯ Low	CRITICAL
Mean patency (days) after excluding outlier with high risk of bias												
5	Randomized trials	Serious§	Serious‖	Not serious	Not serious	None	211	214	—	MD 70.5 days more (21.09 more to 119.92 more)	⨁⨁◯◯ Low	CRITICAL
Stent failure												
10	Randomized trials	Serious¶	Not serious**	Not serious	Serious††‡‡	None	179/671 (26.7%)	190/667 (28.5%)	OR .84 (.55-1.27)	34 fewer per 1000 (from 105 fewer to 51 more)	⨁⨁◯◯ Low	CRITICAL
Cholangitis												
6	Randomized trials	Not serious§§	Not serious	Not serious	Serious‖‖	None	27/468 (5.8%)	30/474 (6.3%)	OR .90 (.52-1.56)	6 fewer per 1000 (from 29 fewer to 32 more)	⨁⨁⨁◯ Moderate	CRITICAL
Need for reintervention												
2	Randomized trials	Not serious¶¶	Not serious	Not serious	Very serious‖‖	None	61/259 (23.6%)	53/260 (20.4%)	OR 1.20 (.79-1.83)	31 more per 1000 (from 36 fewer to 115 more)	⨁⨁◯◯ Low	CRITICAL
Postprocedure adverse events												
6	Randomized trials	Serious***	Not serious	Not serious	Very serious‖‖	None	78/442 (17.6%)	69/453 (15.2%)	OR 1.22 (.82-1.82)	27 more per 1000 (from 24 fewer to 94 more)	⨁◯◯◯ Very low	CRITICAL
Post-ERCP pancreatitis												
9	Randomized trials	Serious*	Not serious	Not serious	Serious†††	None	14/651 (2.2%)	8/650 (1.2%)	OR 1.47 (.60-3.60)	6 more per 1000 (from 5 fewer to 31 more)	⨁⨁◯◯ Low	CRITICAL
Acute cholecystitis												
9	Randomized trials	Serious*	Not serious	Not serious	Serious‡‡‡	None	20/592 (3.4%)	12/614 (2.0%)	OR 1.62 (.78-3.36)	12 more per 1000 (from 4 fewer to 43 more)	⨁⨁◯◯ Low	CRITICAL
Surgical resectability												
1	Randomized trials	Serious§§§	Not serious	Not serious	Not serious		24/55 (43.6%)	25/59 (42.4%)	Not assessable		—	CRITICAL
Stent blockade from sludge or stone												
8	Randomized trials	Serious‖‖‖	Not serious	Not serious	Serious‡‡	None	50/617 (8.1%)	16/616 (2.6%)	OR 2.70 (1.50-4.86)	41 more per 1000 (from 12 more to 89 more)	⨁⨁◯◯ Low	IMPORTANT
Stent migration												
8	Randomized trials	Serious‖‖‖	Not serious	Not serious	Very serious‡‡‡	None	27/617 (4.4%)	.5/617 (.1%)	OR 8.31 (2.68-25.81)	6 more per 1000 (from 1 more to 20 more)	⨁◯◯◯ Very low	IMPORTANT
Stent tumor ingrowth												
8	Randomized trials	Serious‖‖‖	Not serious**	Not serious	Serious‡‡	None	19/617 (3.1%)	107/616 (17.4%)	OR .14 (.05-.37)	145 fewer per 1000 (from 163 fewer to 102 fewer)	⨁⨁◯◯ Low	IMPORTANT

(*continued on the next page*)

cancer only vs variable etiology of distal malignant obstruction), malignancy staging (resectable vs unresectable), or type of cSEMS (fully covered vs partially covered).

Certainty in the evidence

A serious risk of bias was found for most outcomes (Supplementary Fig. 17A and B, available online at www.giejournal.org), except for cholangitis and rate of reinterventions. We rated down for inconsistency in mean survival (I^2 = 88%) and mean stent patency (I^2 = 95%). Most outcomes were rated down for imprecision except for mean survival and mean stent patency. No concerns were found with indirectness of the evidence or publication bias for any of the included studies (Supplementary Fig. 18A-D,

TABLE 8. Continued

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Covered SEMS	Uncovered SEMS	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Stent tumor outgrowth												
8	Randomized trials	Serious|||||	Not serious	Not serious	Very serious†††	None	23/616 (3.7%)	11/616 (1.8%)	OR 1.77 (.83-3.77)	13 more per 1000 (from 3 fewer to 46 more)	⨁◯◯◯ Very low	IMPORTANT

SEMS, Self-expandable metal stents; *CI*, confidence interval; *MD*, mean difference; *OR*, odds ratio; —, unable to calculate the relative effect for this continuous outcome.
*Most trials (6/9) were at a high risk of bias or had some concern because of risk of bias.
†Considerable heterogeneity (I^2 > 80%). Certainty of the evidence was rated down by only 1 level because risk of bias is potentially the source of inconsistency and clinical inconsistency was trivial because the results of most included studies have similar clinical implication.
‡Limits of CI suggest a moderate-to-large benefit in favor of uncovered stents in 1 extreme and a small benefit in favor of covered stents on the other extreme. Because imprecision is linked to inconsistency and use of a random-effects model, certainty of the evidence was not rated down further.
§Only 1 trial (Ung et al, 2013[105]) was judged to be at a low risk of bias with <20% of weight showing no difference between covered and uncovered metal stents.
||I^2 = 69%.
¶Most trials (7/10) were at a high risk of bias or had some concern because of risk of bias.
**Considerable heterogeneity (I^2 = 60%). Not rated down because clinical inconsistency was deemed not important because all results of included studies have a similar clinical implication.
††Limits of CI suggest a small benefit in 1 extreme and a large benefit in the other extreme. Because imprecision is linked to inconsistency and use of a random-effects model, certainty of the evidence was rated down by only 1 level.
‡‡A small number of events did not meet the optimal information size criteria.
§§Not rated down for risk of bias because an equal number of trials were judged to be at high and low risk of bias, but *P* value for test of interaction showed no difference between the 2 estimates.
||||Limits of CI interval suggest a small imprecise benefit on both extremes based on a small number of events not meeting optimal information size criteria.
¶¶One study (Seo et al, 2019[109]) at a high risk of bias had <30% of the weight and results similar to the low risk of bias study.
***Most trials (4/6) were at a high risk of bias or had some concern because of risk of bias.
†††Limits of CI suggest a trivial benefit in favor of covered stents in 1 extreme and a small-to-moderate benefit in favor of uncovered stents on the other extreme based on a small number of events not meeting optimal information size criteria.
‡‡‡Limits of CI suggest a trivial benefit in 1 extreme and a benefit important to patients in the other. This is based on a small number of events not meeting optimal information size criteria.
§§§High risk of bias with the RoB-1 tool.
||||||Most trials (6/8) were at a high risk of bias or had some concern because of risk of bias.

available online at www.giejournal.org). The quality of the evidence ranged from very low to moderate. A complete evidence profile is shown in Table 8.

Other considerations

cSEMS are 25% to 40% more expensive than uSEMS. However, cSEMS were shown to be more cost-effective in 1 RCT of 112 patients with unresectable distal malignant biliary obstruction, in which the costs for the stent and reinterventions were significantly lower with cSEMS (U.S.$3901) as compared with uSEMS (U.S.$5129, $P = .0072$).[101] Another RCT showed equivalent cost-effectiveness between cSEMS and uSEMS in patients with pancreatic head cancer before neoadjuvant chemotherapy; however, patients assigned to the fully covered SEMS had fewer chemotherapy interruptions because of lower risk of stent occlusion.[77] No studies compared patient values and preferences regarding cSEMS and uSEMS.

Discussion

There has been debate on what type of metal stent provides better outcomes in patients with distal malignant biliary obstruction. The panel discussed the difficulties of removing a uSEMS after placement because of tissue ingrowth. This property is important to consider when the histologic diagnosis of malignancy has not yet been confirmed. As a result, the panel strongly emphasized that uSEMS should not be placed in patients with unconfirmed malignancy because the prosthesis could become permanently embedded in the bile duct, which may be detrimental in patients with a benign condition. This property is also relevant in patients with resectable or borderline resectable disease in whom deployment of uSEMS within 2 cm of the hepatic hilum may make surgical dissection and anastomosis creation more difficult.[109]

Our meta-analysis of RCTs showed that cSEMS and uSEMS performed similarly in patients with distal malignant biliary obstruction, except for a longer stent patency of 70.5 days with cSEMS. This difference between cSEMS and uSEMS was noticed after excluding 1 outlier study favoring uSEMS that was judged to have a high risk of bias because of a lack of an intention-to-treat analysis and unclear methods for blinding participants and outcome assessors.[107] Similar to our meta-analysis, a single-center observational study of 454 patients with distal malignant biliary obstruction recently reported longer stent patency of ~6 months with cSEMS, with associated lower rates of stent occlusion and reinterventions.[110] This advantage of cSEMS over uSEMS is likely explained by a lower risk of tissue ingrowth with cSEMS despite their higher rates for occlusion with stone and sludge and migration.

Previous observational studies had reported a higher risk of acute cholecystitis with cSEMS, suspected to be

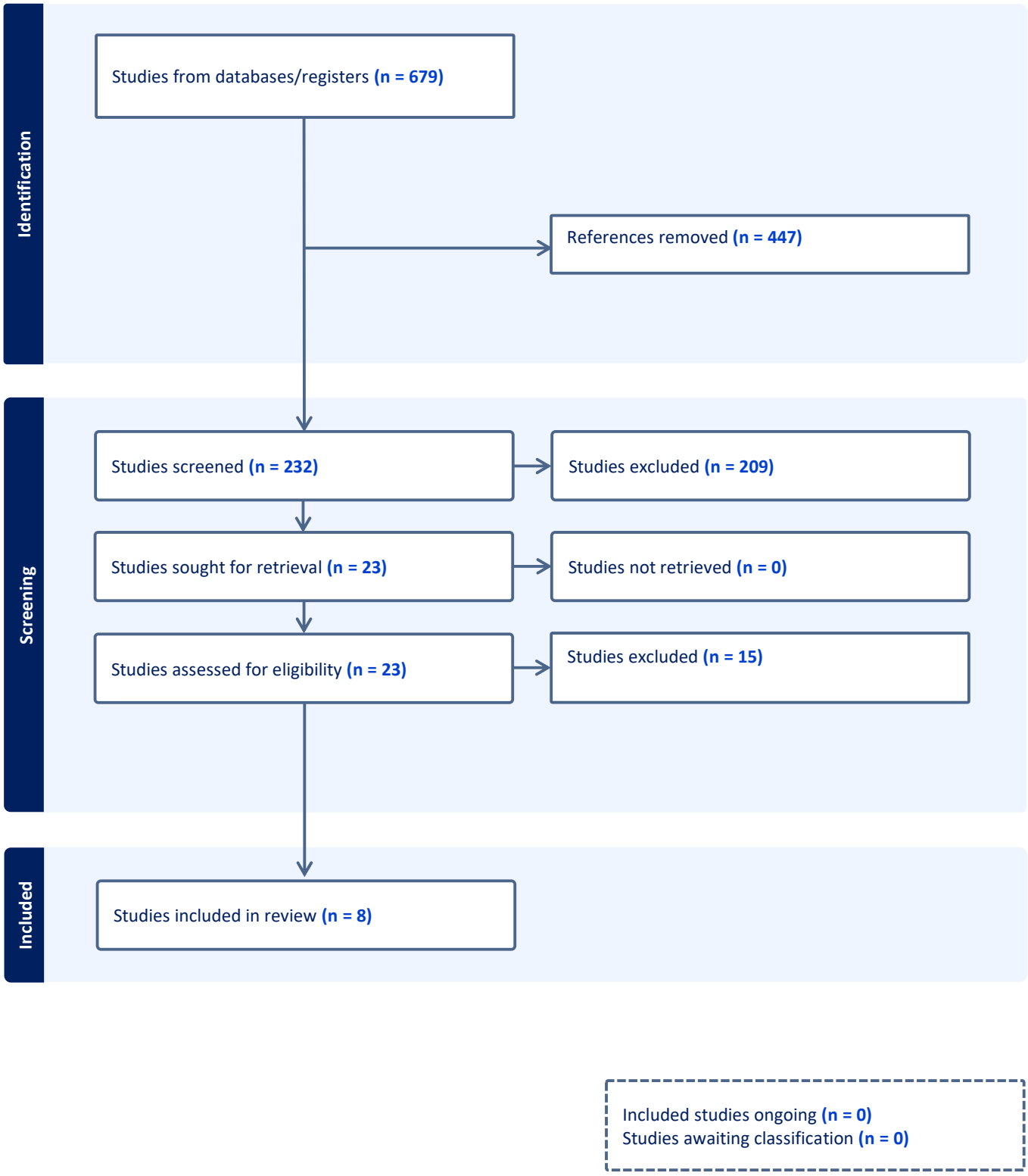


Figure 18. Preferred Reporting Items for Systematic reviews and Meta-Analyses diagram showing the studies included in the systematic review evaluating celiac plexus neurolysis for pancreatic cancer–related abdominal pain (population, intervention, comparator, and outcome question 7).

caused by mechanical occlusion of the cystic duct.[111,112] However, in our meta-analysis of RCTs, we found no difference between uSEMS and cSEMS in the development of acute cholecystitis. Because the risk for acute cholecystitis after SEMS placement is small (~2%), it is possible that the lack of difference between uSEMS and cSEMS in our meta-analysis of RCTs may be from insufficient power and that a larger sample size is needed to confirm our findings.

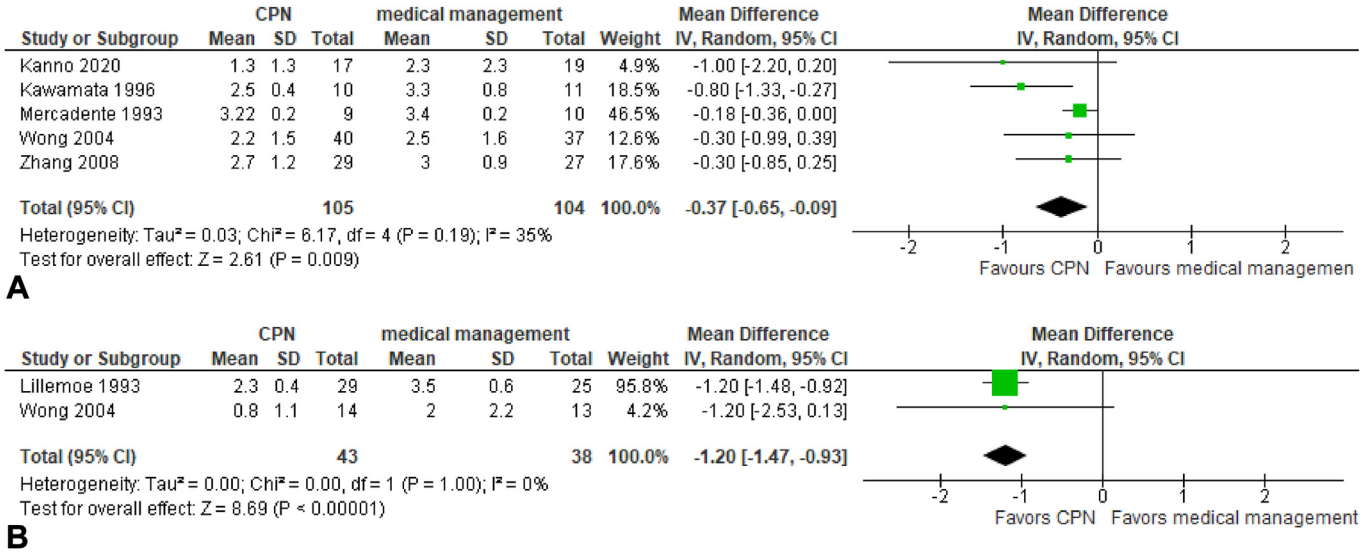


Figure 19. Forest plot comparing mean pain severity by the visual analog scale between medical analgesic therapy with and without CPN in patients with pancreatic cancer. **A,** At 4 weeks. **B,** At 6 months. *CPN*, Celiac plexus neurolysis; *CI*, confidence interval; *SD*, standard deviation

Considering all the body and quality of the evidence, the panel made a conditional recommendation in favor of using cSEMS in patients with distal malignant biliary obstruction undergoing ERCP. Moreover, the panel recommended against the use of uSEMS in patients with unconfirmed malignancy.

Question 7: In patients with pancreatic cancer–related abdominal pain, is celiac plexus neurolysis (CPN) better than medical analgesic therapy alone?

Recommendation 7: In patients with unresectable pancreatic cancer and abdominal pain, the ASGE suggests CPN as an adjunct to medical analgesic therapy.

(Conditional recommendation/low quality of evidence)

To address this question, a systematic review and meta-analysis of RCTs was conducted. A PRISMA diagram detailing study screening is provided in Figure 18. Our search yielded 679 citations, of which 23 studies were fully reviewed for eligibility. Eight RCTs in 504 patients that compared CPN with analgesic medical therapy were identified.[113-120] All enrolled participants had unresectable pancreatic cancer and abdominal pain. All studies used a parallel RCT design. CPN was delivered percutaneously in 5 studies,[113,115-118] endoscopically using EUS in 2 studies,[119,120] and surgically in 1 study.[114] A bilateral injection approach was used for CPN in all RCTs, using a range of 7 to 30 mL of 100% alcohol. In the medical therapy group, 4 studies used analgesics alone[113,115,118,120] and 4 studies used sham CPN followed by analgesics.[114,116,117,119] After CPN, patients were prescribed analgesics in a similar fashion to those assigned to medical therapy.

Survival

Three RCTs found no difference in survival on patients receiving CPN or medical analgesic therapy (MD, .11; 95% CI, –1.13 to 1.35; I^2 = 0%) (Supplementary Fig. 19A, available online at www.giejournal.org).[114,116,120]

Pain severity and opioid use

Using VAS scores, the group assigned to CPN had lower pain severity than the group assigned to medical analgesic therapy at 4 weeks in 5 RCTs (MD, –.37; 95% CI, –.65 to –.09; I^2 = 35%) (Fig. 19A)[113,115,117,118,120] and at 6 months in 2 RCTs (MD, –1.2; 95% CI, –1.47 to –.93; I^2 = 0%) (Fig. 19B).[114,117] At 8 weeks, no difference in pain severity was found between CPN and medical analgesic therapy in 7 RCTs (MD, –.7; 95% CI, –1.57 to .17; I^2 = 99%) (Supplementary Fig. 19B).[113-115,117-120] Patients receiving CPN and medical therapy had similar opioid needs by morphine milligram equivalents at 4 weeks in 5 RCTs (MD, –34.91; 95% CI, –79.01 to 9.19; I^2 = 99%) (Supplementary Fig. 19C)[113,114,116,118,120] and at 8 weeks in 5 RCTs (MD, –38.31; 95% CI, –93.57 to 16.95; I^2 = 99%) (Supplementary Fig. 19D).[113,115,116,118,120]

Quality of life

Quality of life was no different at 4 weeks in 2 RCTs (MD, .57; 95% CI, –.43 to 1.57; I^2 = 0%) (Supplementary Fig. 19E)[113,120] or at 8 weeks in 4 RCTs (MD, .57; 95% CI, –.45 to 1.6; I^2 = 0%) (Supplementary Fig. 19F).[113,117,119,120] Data on quality of life and opioid use at 6 months were not reported.

Adverse events

Constipation, which is a common side effect of opioids, occurred less often in patients receiving CPN (32.4%,

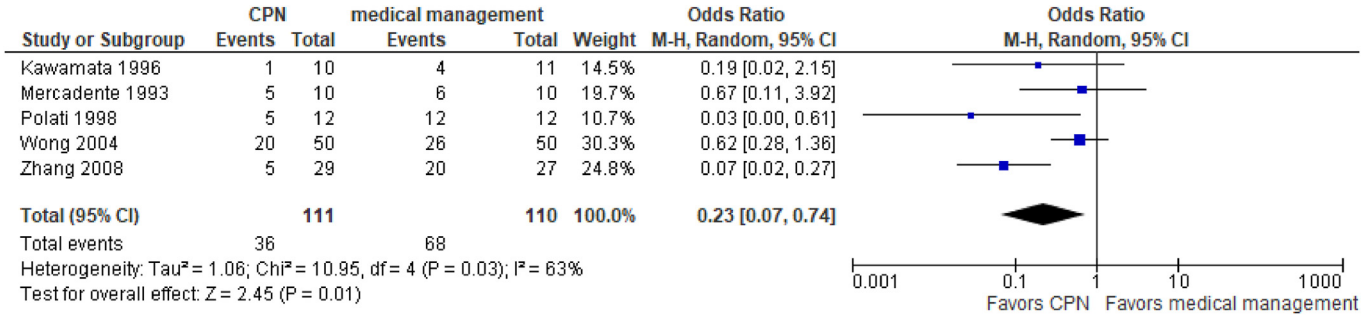


Figure 20. Forest plot comparing constipation between medical analgesic therapy with and without CPN in patients with pancreatic cancer. *CPN*, Celiac plexus neurolysis; *CI*, confidence interval.

36/111) than those assigned to medical therapy (61.8%, 68/110) in 5 RCTs (OR, .23; 95% CI, .07-.74; I^2 = 63%) (Fig. 20).[113,115-118] In 4 RCTs, transient diarrhea was more frequent after receiving CPN (16%, 12/75) compared with medical therapy (2.8%, 2/71); however, this difference was not statistically significant (OR, 3.73; 95% CI, .99-14.12; I^2 = 0%) (Supplementary Fig. 19G).[115,116,118,120] No significant difference in drowsiness was noticed between CPN (38.3%, 23/60) and medical therapy (28.3%, 17/60) in 2 RCTs (OR, .92; 95% CI, .09-9.03; I^2 = 56%) (Supplementary Fig. 19H).[115,117]

Subgroup analysis

Subgroup analyses by the CPN approach (EUS-guided vs percutaneous or surgical) and by type of control (analgesics alone vs sham CPN) showed similar effects of CPN on the overall results.

Certainty in the evidence

Risk of bias was rated as serious for most outcomes (Supplementary Fig. 20A and B, available online at www.giejournal.org), except for pain at 6 months and drowsiness. We rated down for inconsistency in pain severity at 8 weeks, opioid use at 4 weeks, opioid use at 8 weeks, and quality of life at 8 weeks (I^2 > 75%). All outcomes were rated down for imprecision. No concerns were found with indirectness of the evidence or publication bias for any of the included studies (Supplementary Fig. 21A-G, available online at www.giejournal.org). The quality of evidence ranged from very low to moderate. A complete evidence profile is shown in Table 9.

Other considerations

Data comparing CPN with medical therapy on costs and cost-effectiveness are lacking. The costs of CPN depend on the route of administration. Although all forms of CPN share the costs for alcohol at 100% concentration, EUS-guided CPN involves costs of EUS, FNA needles, and anesthesia time, whereas the percutaneous approach incurs costs of percutaneous needles, radiologic images, and administration of moderate sedation. It is unclear if these costs offset the costs of using medical analgesic therapy alone. However, because the need for opioids does not seem to differ for either group at follow-up, it is possible that the costs of CPN surpass the costs of medical therapy alone. Data on patient values and preferences are lacking for the comparison of CPN and medical analgesic therapy. Our patient representative considered CPN as an attractive intervention that seemed to reduce pain severity and constipation.

Discussion

Abdominal pain is reported by ~80% of patients with pancreatic cancer.[121] The pathophysiology of pain in pancreatic cancer is complex and multifactorial, involving mechanisms of tissue damage, inflammation, luminal or ductal obstruction, and/or perineural tumor invasion.[122,123] Cancer-related pain is often severe and linked to decreased survival, low performance status, impaired quality of life, poor tolerability to anticancer therapy, fatigue, anxiety, and depression.[124] As a result, interventions to reduce pain are essential in the multidisciplinary management of patients with pancreatic cancer. Curative surgical resection alleviates pain and increases patient survival; however, less than 20% of patients with pancreatic cancer are eligible for this.[122,125] As a result, most patients are managed with pharmacologic interventions, which mostly rely on opioids.[126] Unfortunately, opioid analgesia is sometimes ineffective and can lead to several adverse events (eg, tolerance, constipation, confusion), making alternative analgesic strategies necessary. CPN, which consists of irreversibly ablating the celiac plexus with a neurolytic agent, can be used as an alternative or adjunct to opioids in patients with pancreatic cancer. Traditionally, CPN was performed using a percutaneous posterior approach guided by fluoroscopy or CT. With the development of linear echoendoscopes, CPN became possible with EUS and has been used over the past 3 decades.[127] Thereby, endoscopy plays a crucial role in the management of pain in patients with pancreatic cancer.

Our meta-analysis of 8 RCTs showed that adding CPN was more effective than medical analgesic therapy alone in reducing pain severity at 4 weeks and 6 months, with comparable results in survival and quality of life and with

TABLE 9. Evidence profile for population, intervention, comparator, and outcome question 7: in patients with pancreatic cancer–related abdominal pain, is celiac plexus neurolysis better than medical analgesic therapy?

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Celiac plexus neurolysis	Medical therapy	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Mean survival time (mo)												
3	Randomized trials	Serious*	Not serious	Not serious	Serious†	None	104	107	—	MD .11 more (1.13 fewer to 1.35 more)	⨁⨁◯◯ Low	CRITICAL
Pain severity (follow-up: mean 4 wk; assessed with 10-point VAS)												
5	Randomized trials	Serious‡	Not serious§	Not serious	Serious‖	None	105	104	—	MD .37 lower (.65 lower to .09 lower)	⨁⨁◯◯ Low	CRITICAL
Pain severity (follow-up: mean 8 wk; assessed with 10-point VAS)												
7	Randomized trials	Serious‡	Serious¶	Not serious	Serious**	None	214	169	—	MD .7 lower (1.57 lower to .17 higher)	⨁◯◯◯ Very low	CRITICAL
Pain severity (follow-up: mean 6 mo; assessed with 10-cm VAS)												
2	Randomized trials	Not serious††	Not serious	Not serious	Serious**	None	43	38	—	MD 1.2 lower (1.47 lower to .93 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Opioid use (follow-up: mean 4 wk; assessed with morphine mg equivalent)												
5	Randomized trials	Serious*	Serious¶	Not serious	Serious**	None	78	79	—	MD 34.91 lower (79.01 lower to 9.19 higher)	⨁◯◯◯ Very low	CRITICAL
Opioid use (follow-up: mean 8 wk; assessed with morphine mg equivalent)												
5	Randomized trials	Serious*	Serious¶	Not serious	Very serious**	None	62	61	—	MD 38.31 lower (93.57 lower to 16.95 higher)	⨁◯◯◯ Very low	CRITICAL
Quality of life (follow-up: mean 4 wk; scale 0-10)												
2	Randomized trials	Serious*	Not serious	Not serious	Very serious‡‡	None	26	30	—	MD .57 higher (.43 lower to 1.57 higher)	⨁◯◯◯ Very low	CRITICAL
Quality of life (follow-up: mean 8 wk; scale 0-10)												
4	Randomized trials	Serious‡	Serious¶	Not serious	Very serious**	None	123	81	—	MD .57 higher (.45 lower to 1.6 higher)	⨁◯◯◯ Very low	CRITICAL
Constipation												
5	Randomized trials	Serious‡	Not serious§§	Not serious	Serious‖‖	None	36/111 (32.4%)	68/110 (61.8%)	OR .23 (.07-.74)	347 fewer per 1000 (from 516 fewer to 73 fewer)	⨁⨁◯◯ Low	IMPORTANT
Diarrhea												
4	Randomized trials	Serious*	Not serious	Not serious	Very serious¶¶	None	12/75 (16.0%)	2/71 (2.8%)	OR 3.73 (.99-14.12)	69 more per 1000 (from 0 fewer to 262 more)	⨁◯◯◯ Very low	IMPORTANT

(*continued on the next page*)

a lower risk of constipation. These results align with a Cochrane review from 2011 that included 6 of the 8 RCTs in our meta-analysis.[128] Although a meaningful clinical difference in the 11-point VAS is unknown among patients with pancreatic cancer, studies in chronic pain have shown that a difference of at least 1.7 points is needed to be meaningful.[129] The superiority of adding CPN to medical analgesic therapy in our meta-analysis was only 1.2 points in the VAS, which is likely not clinically relevant. This may explain the similar opioid requirements at 4 and 8 weeks between patients who did or did not receive CPN.

When considering the undesirable effects of adding CPN and medical analgesic therapy alone, we found that adding CPN significantly reduced the risk of constipation by 76%. However, several outcomes of interest were not captured by our meta-analysis given the intrinsic differences between CPN and medical therapy. In a systematic review of 16 studies (n = 817), CPN was associated with transient adverse events such as diarrhea (9%), pain exacerbation (8%), and hypotension (6%).[130] A rare, long-term, serious adverse event of CPN is spinal cord infarction and paralysis, which has been reported in .2% of

TABLE 9. Continued

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Celiac plexus neurolysis	Medical therapy	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Drowsiness												
2	Randomized trials	Not serious***	Not serious†††	Not serious	Very serious‡‡‡	None	23/60 (38.3%)	17/60 (28.3%)	OR .92 (.09-9.03)	17 fewer per 1000 (from 249 fewer to 498 more)	⨁⨁◯◯ Low	IMPORTANT

CI, Confidence interval; *MD*, mean difference; *OR*, odds ratio; *VAS*, visual analog scale; —, unable to calculate the relative effect for this continuous outcome.
*All studies were at high risk of bias or had some concern because of risk of bias.
†Limits of CI suggest a trivial effect at both extremes based on a small sample size and small number of events.
‡Only 1 study (Wong et al, 2004[117]) was judged to be at a low risk of bias.
§Considerable heterogeneity (I^2 = 35%). Not rated down because clinical inconsistency was deemed not important because all results of the included studies have similar clinical implication.
||Limits of CI suggest a trivial benefit (less than minimally clinical important difference of 1 cm on a 10-cm VAS) based on a small sample size not meeting optimal information size criteria.
¶Point estimates vary widely with CIs of some studies not overlapping with those of most included studies and a high I^2 (>75%).
**CI suggests a trivial unimportant benefit in 1 extreme and a large benefit that patients might consider important in other extreme. Because this imprecision was a result of inconsistency and small sample sizes of the included studies, certainty of the evidence was rated down by only 2 levels.
††One study (Lillemoe et al, 1993[114]) at a high risk of bias had <5% of the weight and results similar to the low risk of bias study.
‡‡Limits of CI suggest a trivial benefit in 1 extreme in favor of celiac plexus neurolysis and a small-to-moderate benefit on the other extreme in favor of medical management based on a small sample size.
§§Considerable heterogeneity (I^2 = 63%). Not rated down because clinical inconsistency was deemed not important as all results of the included studies have similar clinical implication.
||||Limits of CI suggest a trivial-to-small benefit in 1 extreme and a large benefit in the other extreme. Because imprecision is linked to inconsistency and use of a random-effects model, certainty of the evidence was rated down by only 1 level.
¶¶Limits of CI suggest no benefit in 1 extreme and a benefit important to some patients in the other based on a small number of events and small sample sizes of the included studies.
***One study (Mercadente, 1993[115]) at a high risk of bias had 31% of the weight and results clinically similar to the low risk of bias study.
†††Considerable heterogeneity (I^2 = 56%). Not rated down because clinical inconsistency was deemed not important as all results of the included studies have similar clinical implication given the considerable overlap of 95% CIs.
‡‡‡A small number of events and sample sizes and included studies with wide 95% CIs for pooled effect.

patients undergoing EUS-guided CPN.[130] Other undesirable outcomes inherent to the invasive nature of CPN are sedation adverse events and risk of bleeding with needle puncture. In addition, it is expected that the costs of CPN are higher than analgesic therapy alone, especially because the need for opioid requirements is not different after CPN. There is a potential risk of retroperitoneal fibrosis caused by neurolytic agents, which may make pancreatic surgery more difficult.[131] Thereby, only patients with unresectable disease have been enrolled in RCTs of CPN, and its effects in resectable pancreatic cancer are not well known. Finally, the analgesic effects of CPN appear to decrease over time and have not been demonstrated after 6 months of administration in any of the included RCTs.[132]

Given the modest benefits in pain severity and potential undesirable effects with CPN, the panel discussed that analgesic therapy alone should be preferred as the first-line strategy to alleviate abdominal pain in patients with pancreatic cancer. Data are also emerging showing that chemotherapy and/or radiation have an analgesic role in patients with pancreatic cancer, which may further enhance the effect of analgesics.[133,134] The additional reduction in pain severity with CPN may be relevant in patients with unresectable pancreatic cancer when medical therapy is not as effective or when its adverse events are not well tolerated.

No studies are available that directly compare percutaneous and EUS-guided CPN. In a subgroup analysis based on the method of CPN administration, we found no difference in results across RCTs using percutaneous or EUS-guided CPN. Therefore, the route of CPN administration should be driven by local availability and expertise. In situations when an EUS or other endoscopic procedure is warranted, the EUS-guided approach should be preferred. When CPN is done using EUS, 10 to 20 mL of 99% alcohol should be administered with a 22-gauge or larger gauge FNA needle using a central (anterior to the celiac artery) or bilateral (left and right of the celiac artery) approach. A recent systematic review demonstrated that both EUS approaches were equally effective, but the bilateral approach was linked to serious adverse events.[130] Compared with CPN, 1 RCT has shown that celiac ganglia neurolysis is associated with reduced survival and similar clinical outcomes, and as a result, celiac ganglia neurolysis should not be used for neurolysis.[135]

GUIDELINE UPDATE

ASGE guidelines are reviewed for updates approximately every 5 years or in the event that new data may influence a recommendation. Updates follow the same ASGE guideline development process.

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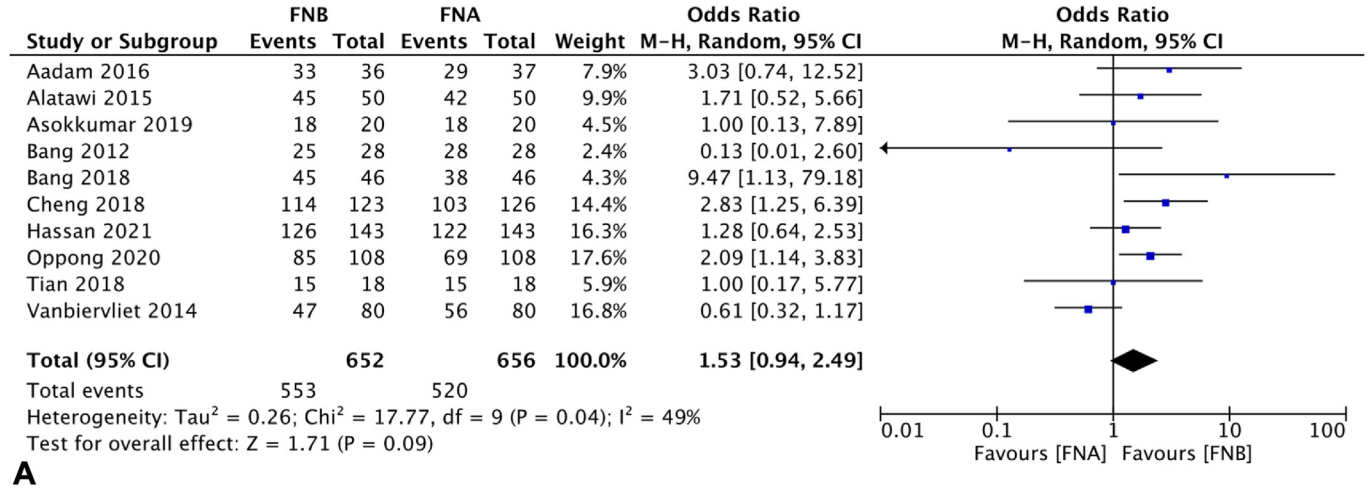
Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; CI, confidence interval; cSEMS, covered self-expandable metal stents; CPN, celiac plexus neurolysis; EUS-FNB, EUS-guided FNB sampling; EUS-TA, EUS-guided tissue acquisition; FNB, fine-needle biopsy; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio; MD, mean difference; MOSE, macroscopic on-site evaluation; PICO, population, intervention, control, and outcomes; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT, randomized controlled trial; ROSE, rapid on-site evaluation; SEMS, self-expandable metal stents; uSEMS, uncovered self-expandable metal stents; VAS, visual analog scale.

*Drs Machicado and Sheth contributed equally to this article.

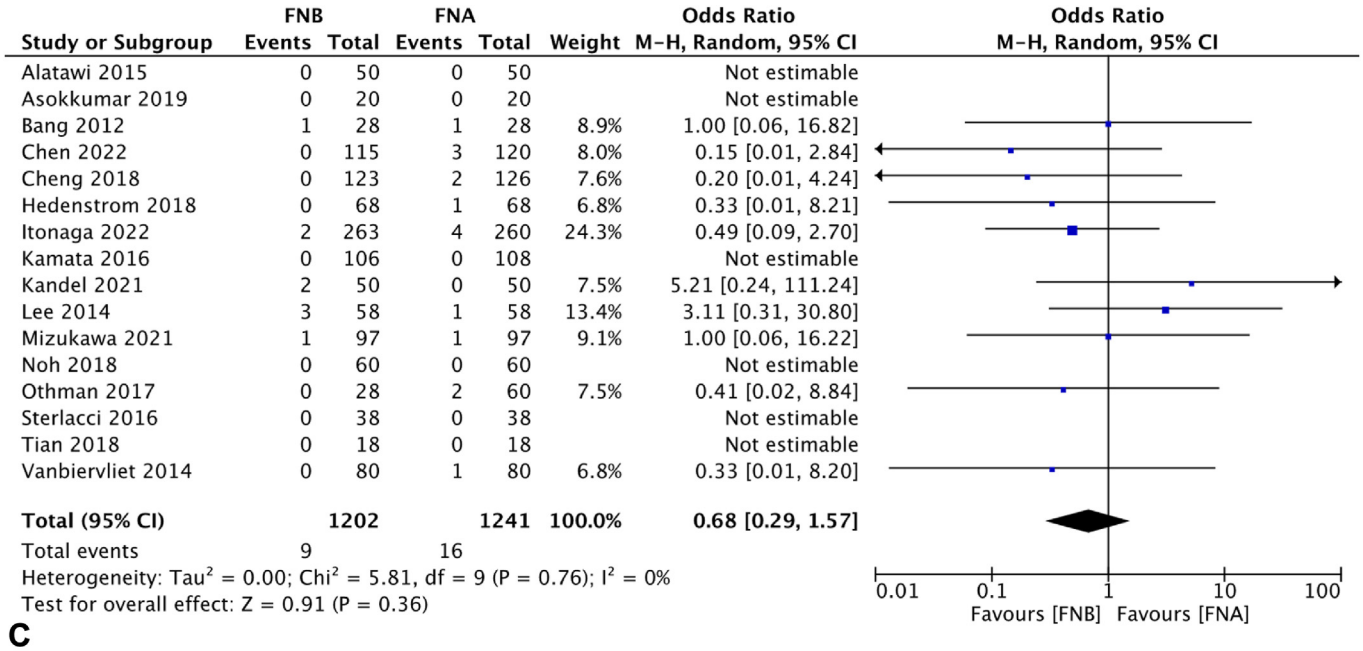
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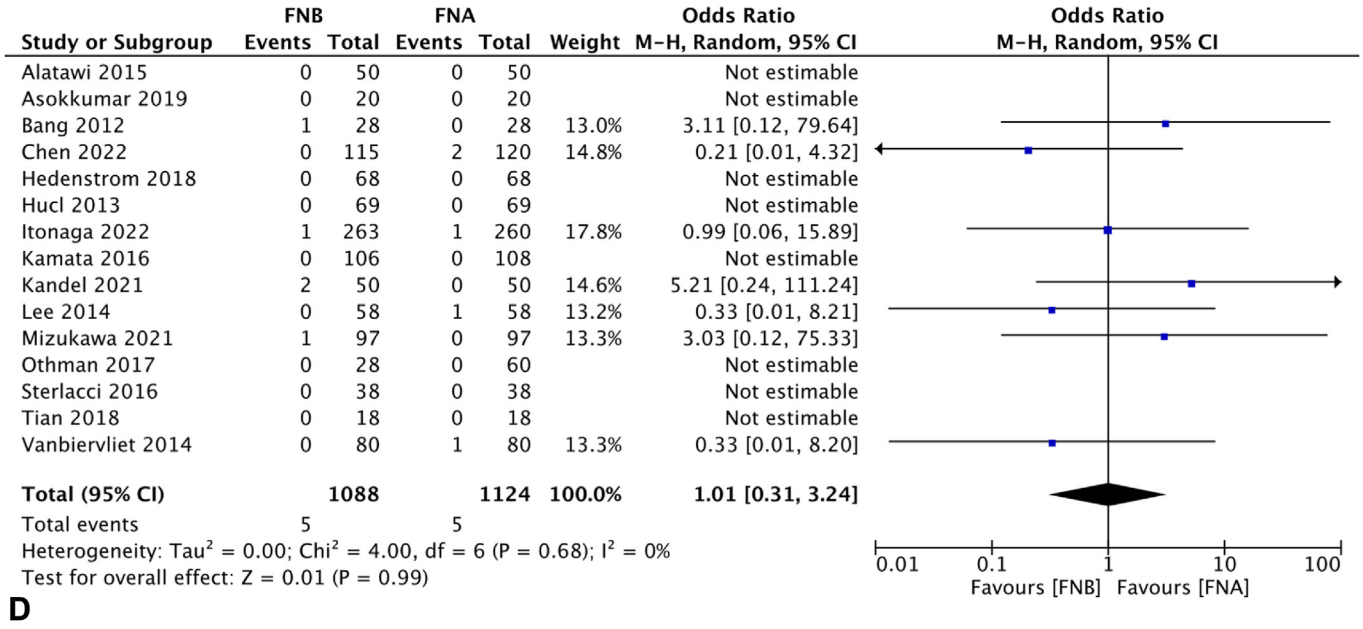
ROLE OF ENDOSCOPY IN THE DIAGNOSIS AND MANAGEMENT OF SOLID PANCREATIC MASSES SEARCH STRATEGIES



Supplementary Figure 1. Forest plot comparing (**A**) diagnostic yield, (**B**) diagnosis at first pass, (**C**) adverse events, and (**D**) risk of postprocedure pancreatitis of FNB versus FNA needles for EUS-guided tissue acquisition of solid pancreatic masses. *FNB*, Fine-needle biopsy; *CI*, confidence interval.

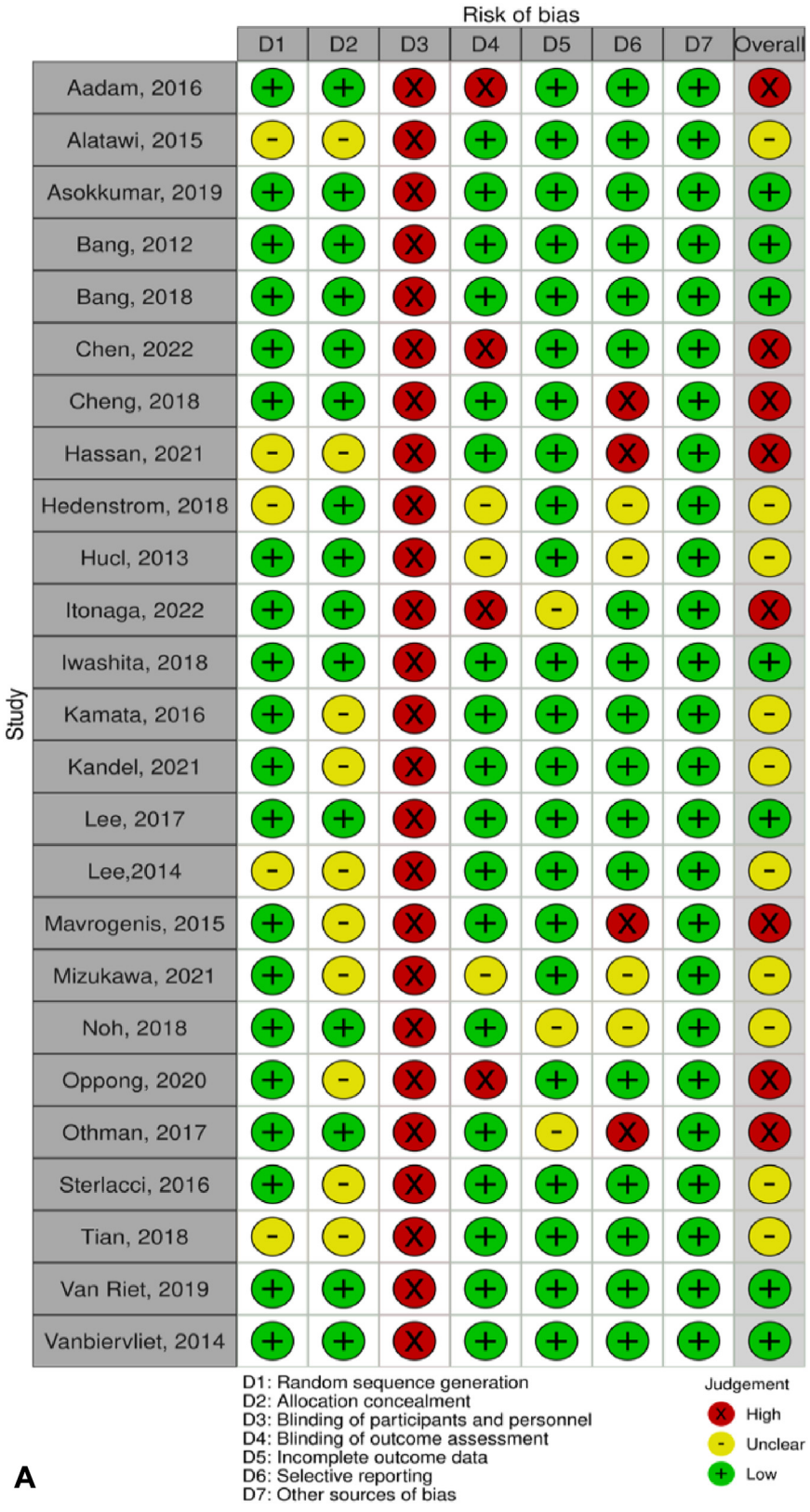


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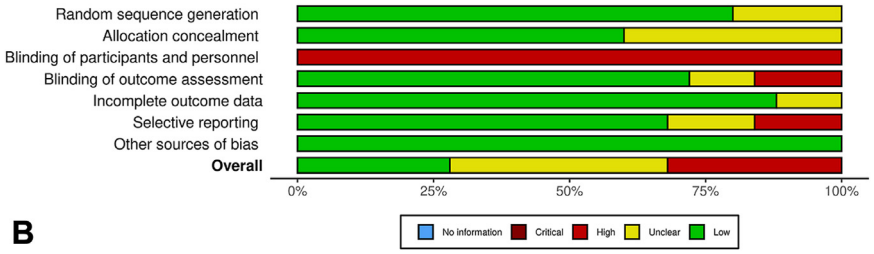


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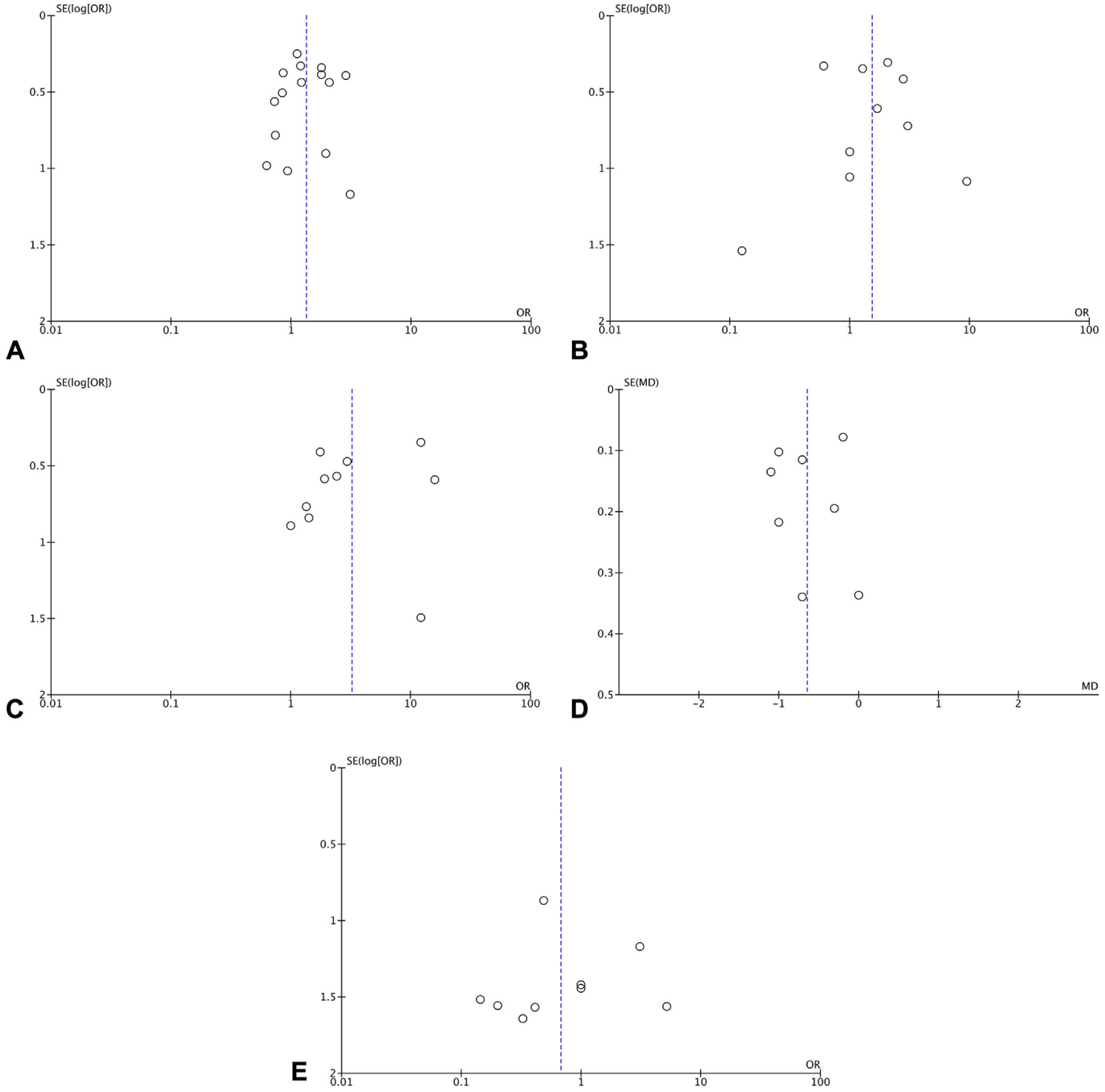


Supplementary Figure 2. (**A**) Risk of bias summary and (**B**) overall quality assessment of included randomized controlled trial comparing fine-needle biopsy needles versus FNA needles for EUS-guided tissue acquisition of solid pancreatic masses.

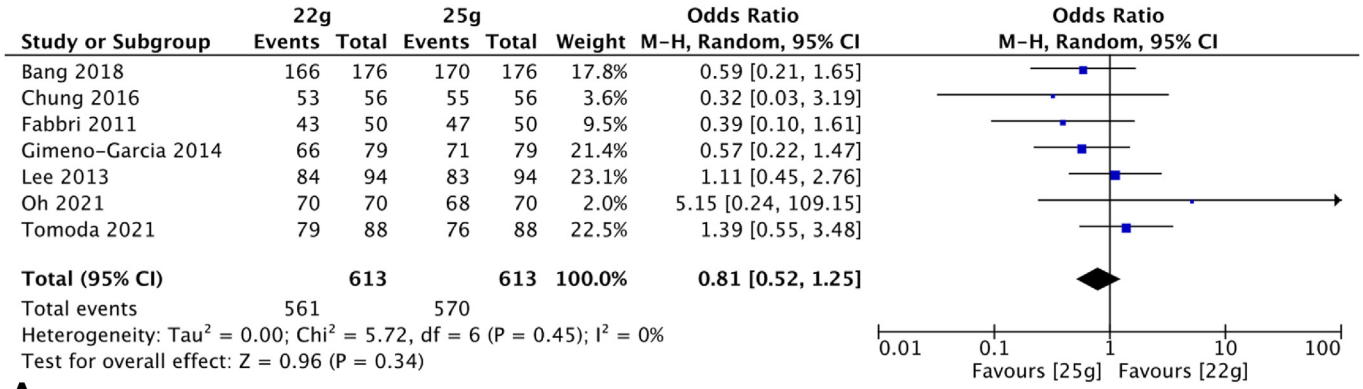


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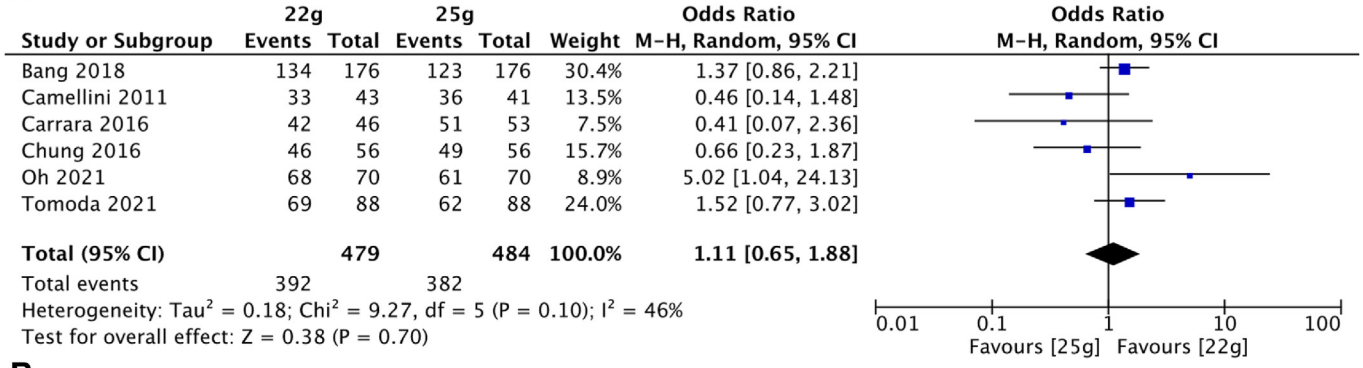
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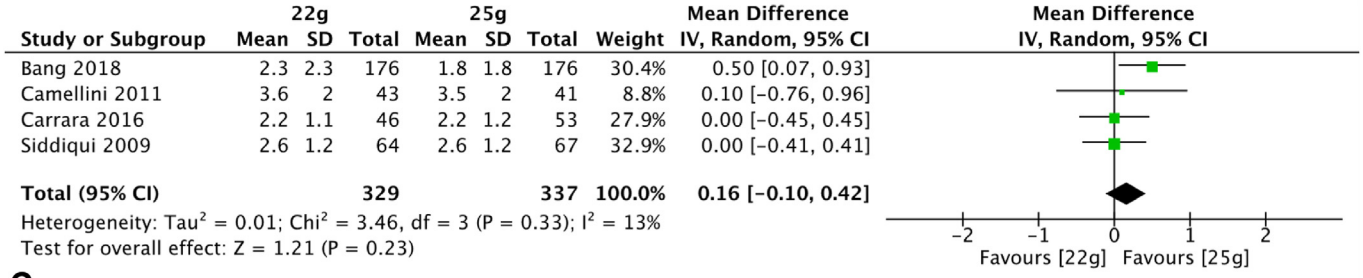
Supplementary Figure 3. Funnel plot comparing (**A**) diagnostic accuracy of, (**B**) diagnostic yield of, (**C**) sample adequacy of, (**D**) number of needle passes between, and (**E**) adverse events between fine-needle biopsy needles versus FNA needles for EUS-guided tissue acquisition of solid pancreatic masses. *SE*, Standard error; *OR*, odds ratio; *MD*, mean difference.



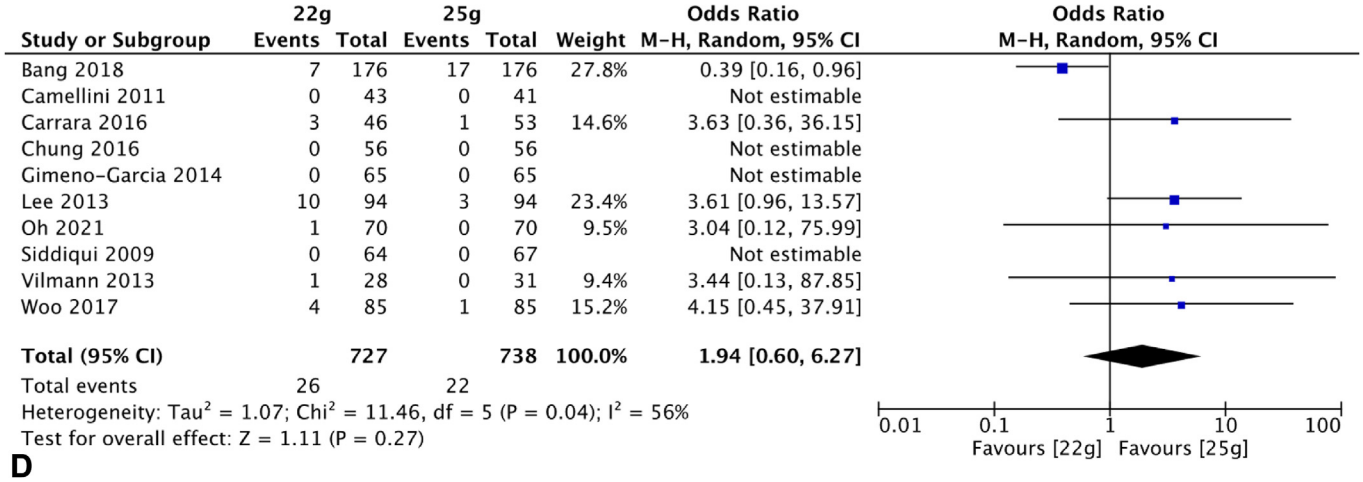
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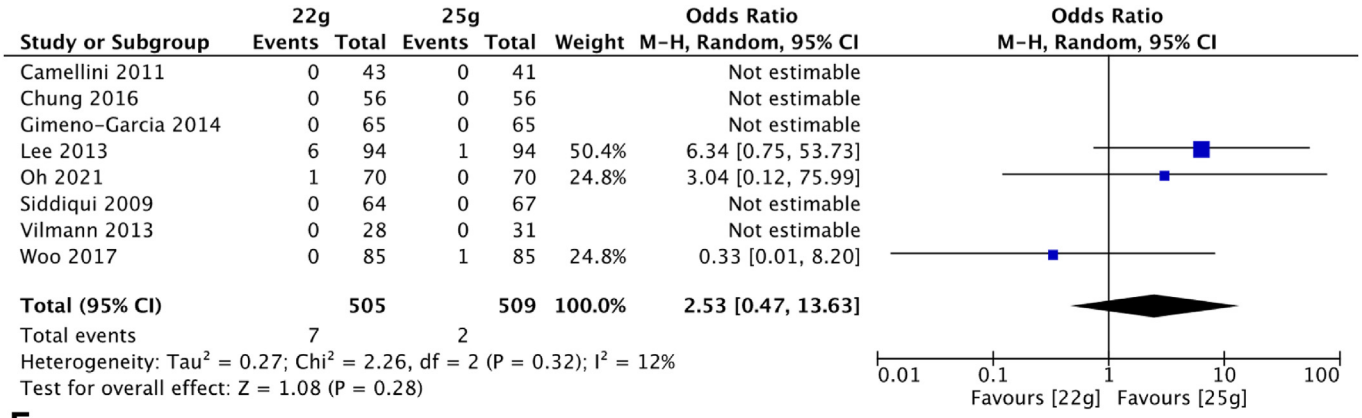


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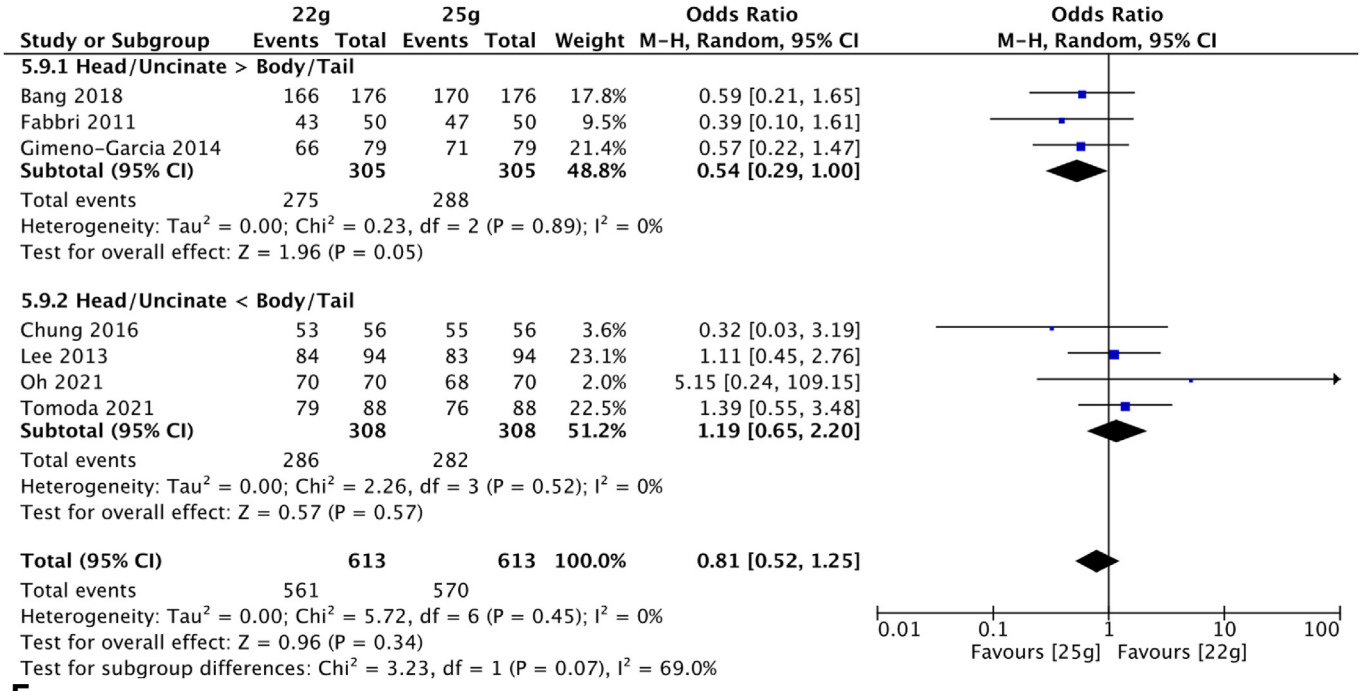


D

Supplementary Figure 4. Forest plot comparing (**A**) diagnostic accuracy of, (**B**) sample adequacy of, (**C**) number of needle passes between, (**D**) adverse events between, and (**E**) risk of postprocedure pancreatitis between 22-gauge versus 25-gauge needles for EUS-guided tissue acquisition of solid pancreatic masses. **F,** Subgroup analysis comparing diagnostic accuracy between 22-gauge and 25-gauge needles for EUS-guided tissue acquisition of solid pancreatic masses based on lesion location. Subgroup analysis comparing (**G**) diagnostic accuracy, (**H**) histologic adequacy, (**I**) adverse events, and (**J**) post-EUS pancreatitis between 22-gauge and 25-gauge needles for EUS-guided tissue acquisition of solid pancreatic masses based on needle type (FNB vs FNA). *CI*, Confidence interval; *SD*, standard deviation; *FNB*, fine-needle biopsy.

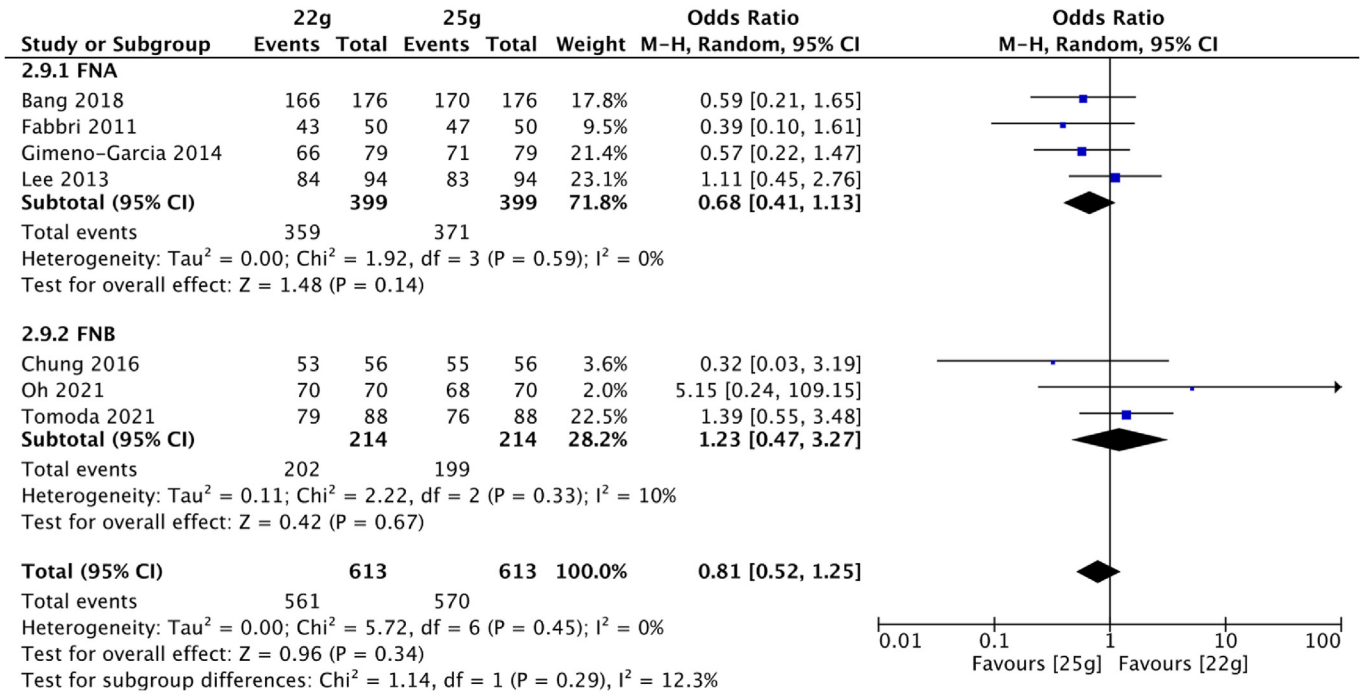


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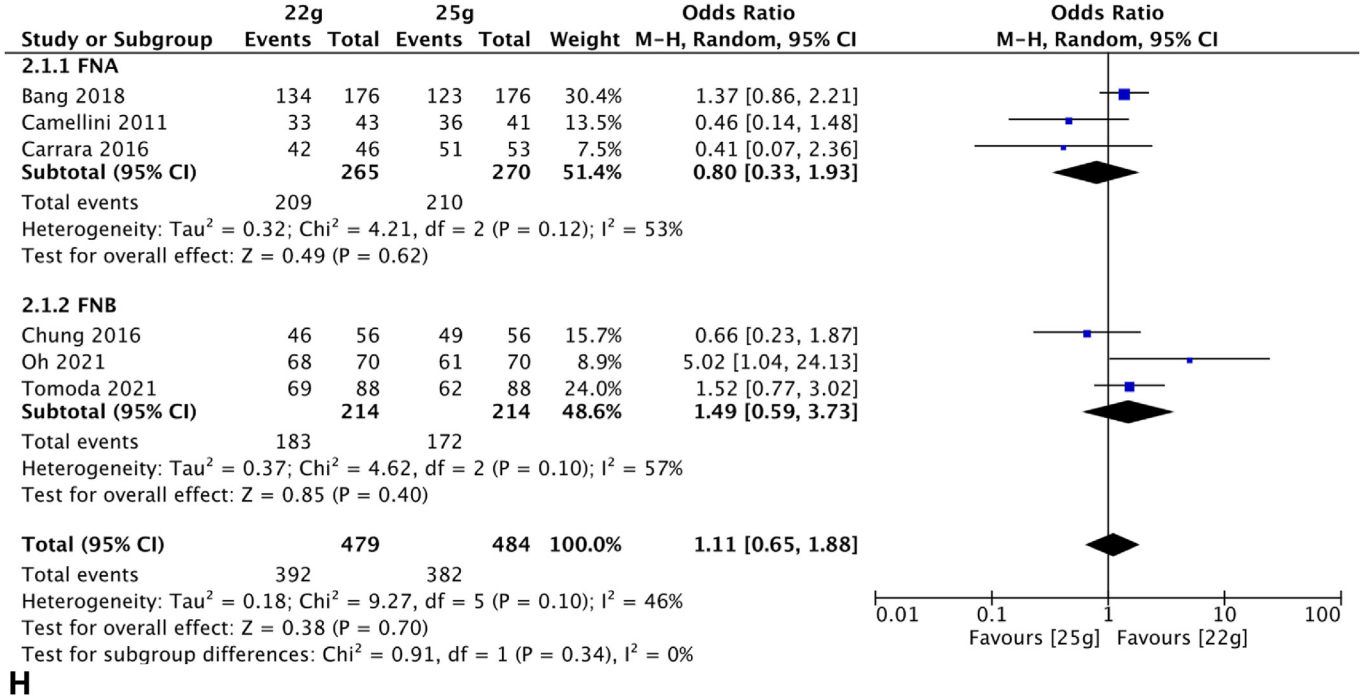


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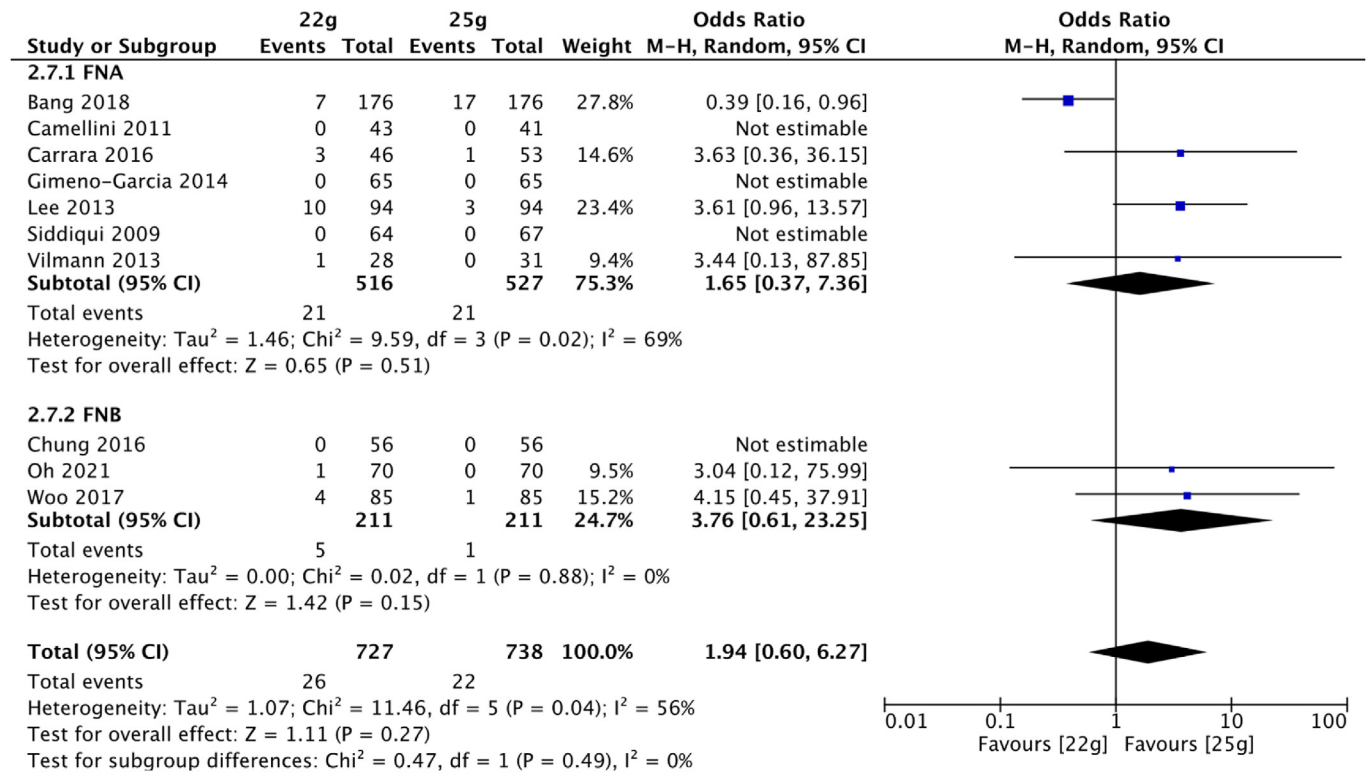


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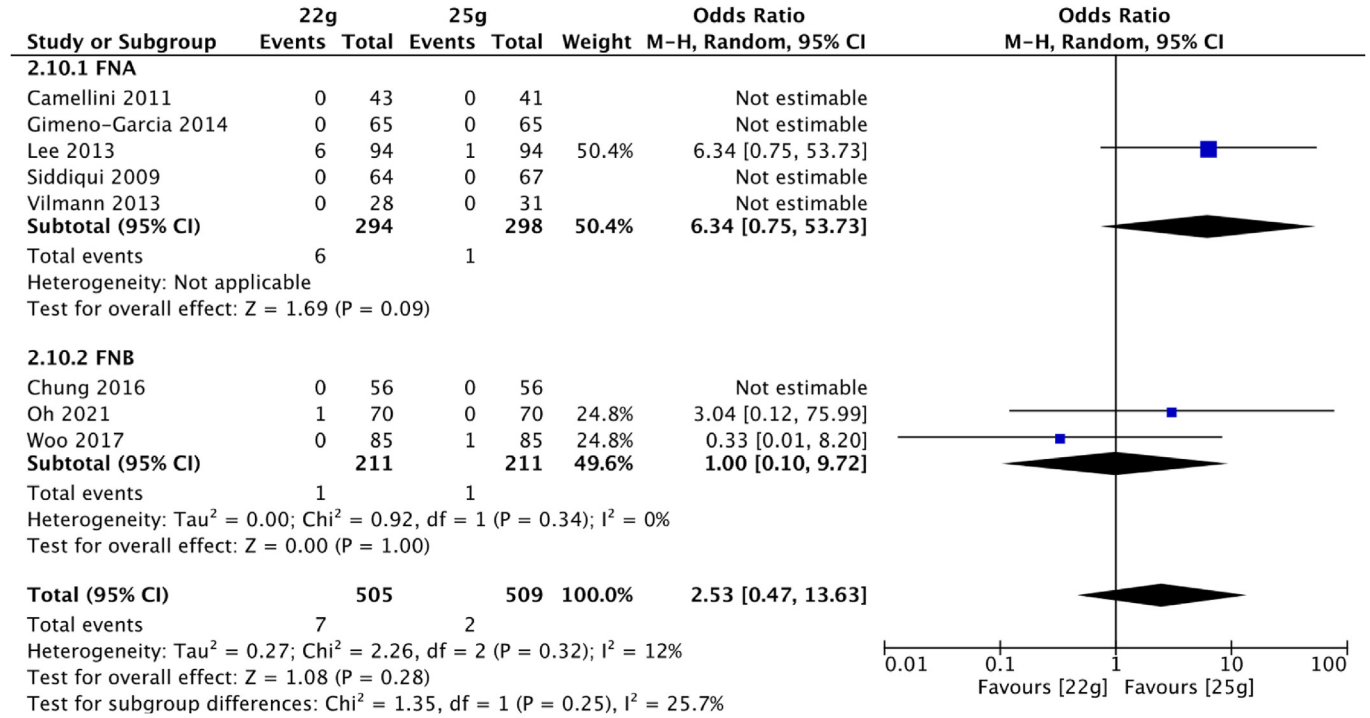


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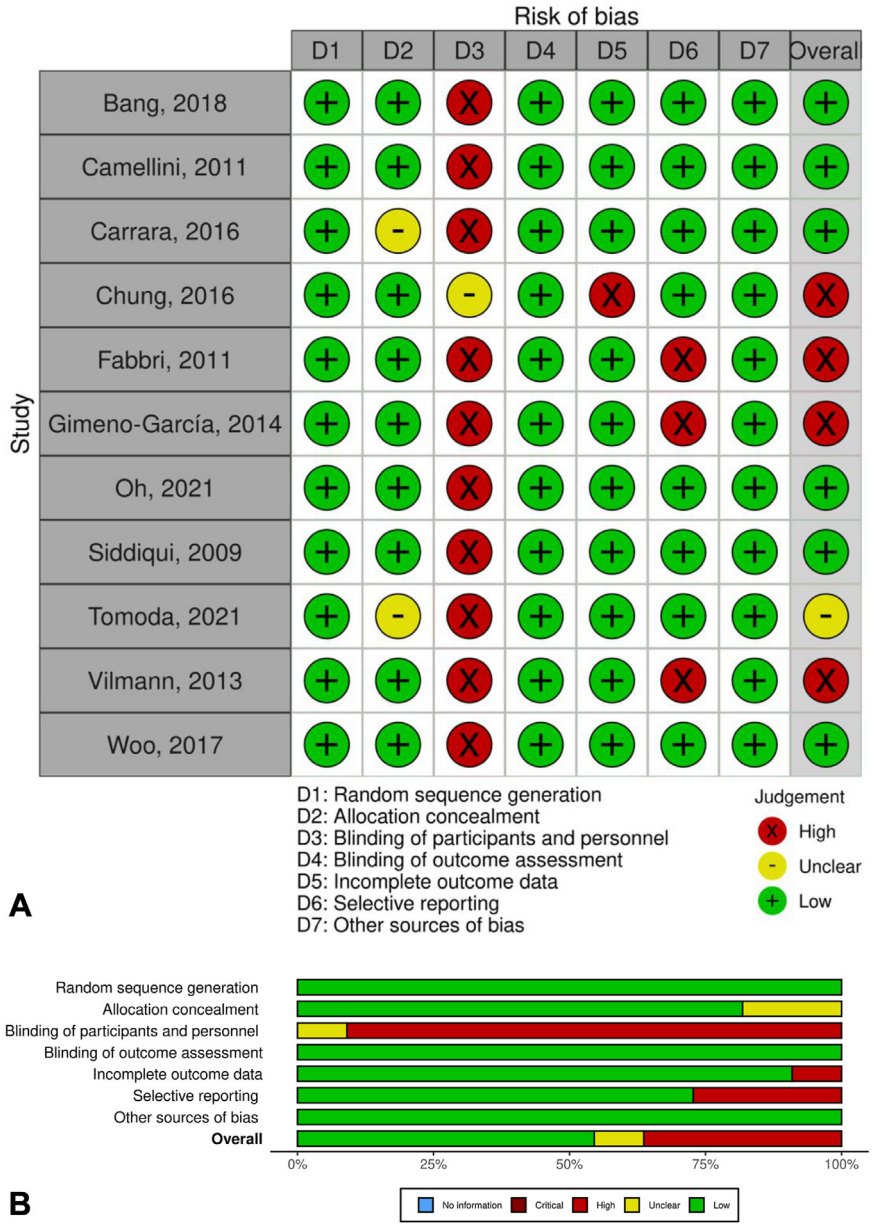


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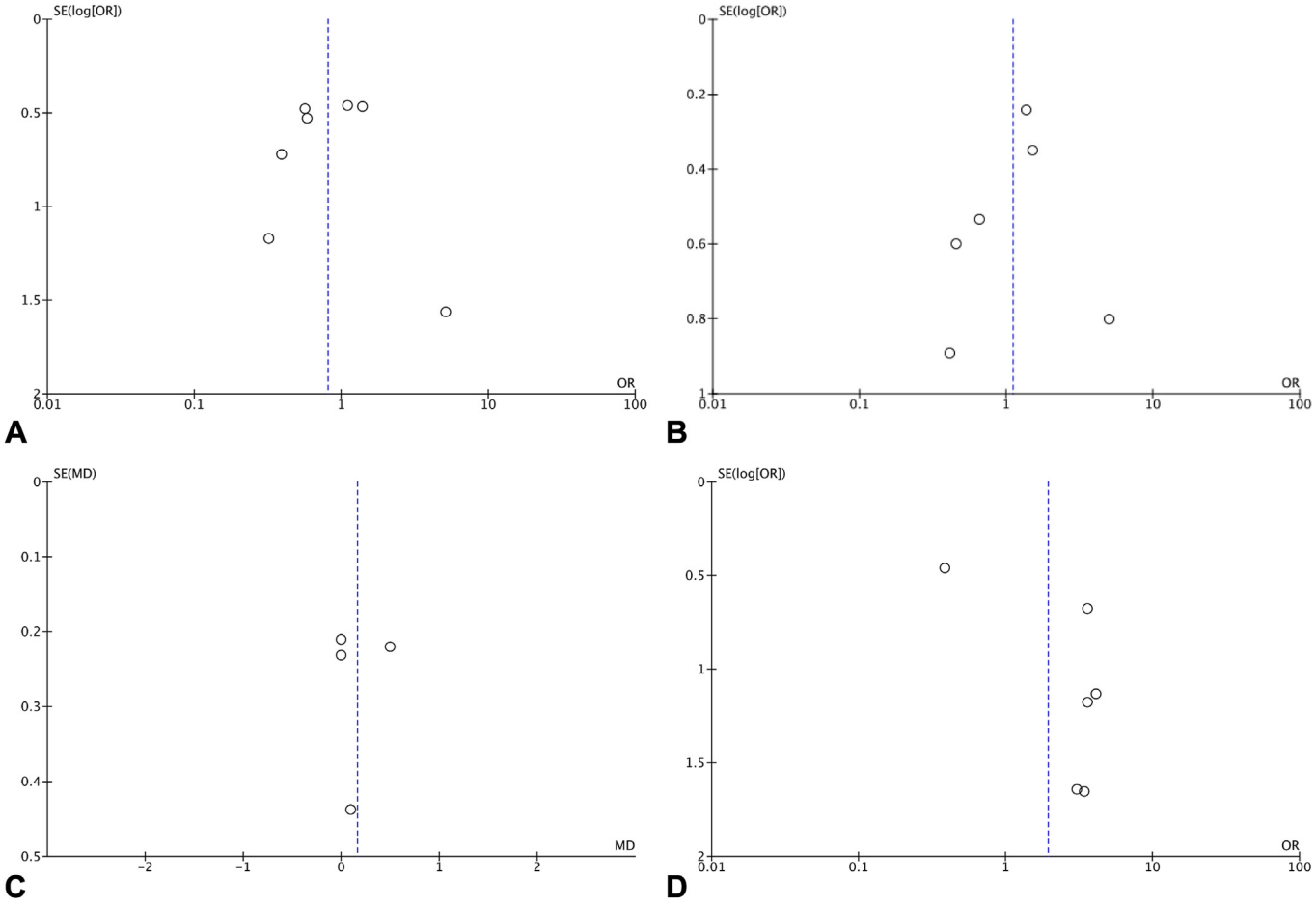


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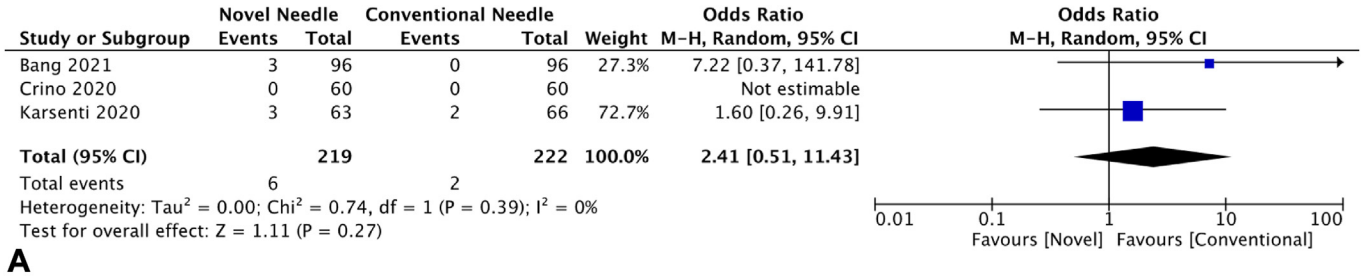
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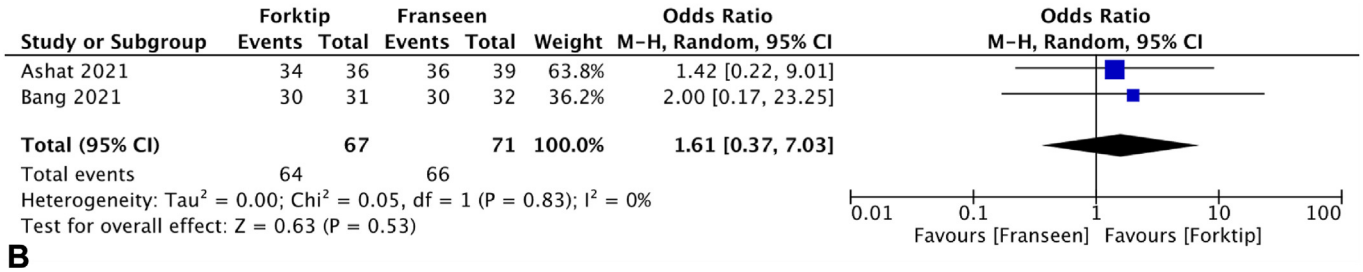
Supplementary Figure 5. (**A**) Risk of bias summary and (**B**) overall quality assessment of randomized controlled trials comparing 22-gauge versus 25-gauge needle for EUS-guided tissue acquisition of solid pancreatic masses.



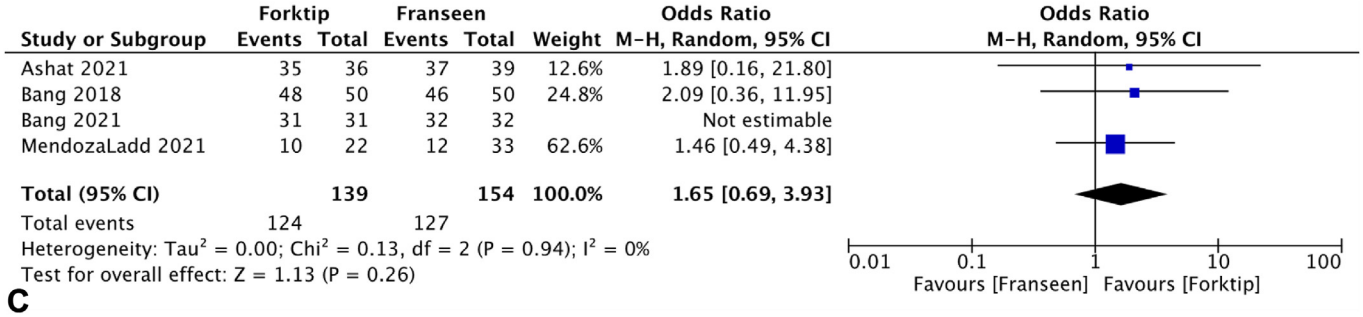
Supplementary Figure 6. Funnel plot comparing (**A**) diagnostic accuracy of, (**B**) sample adequacy of, (**C**) number of needle passes of, and (**D**) adverse events between 22-gauge versus 25-gauge needles for EUS-guided tissue acquisition of solid pancreatic masses. *SE*, Standard error; *OR*, odds ratio; *MD*, mean difference.



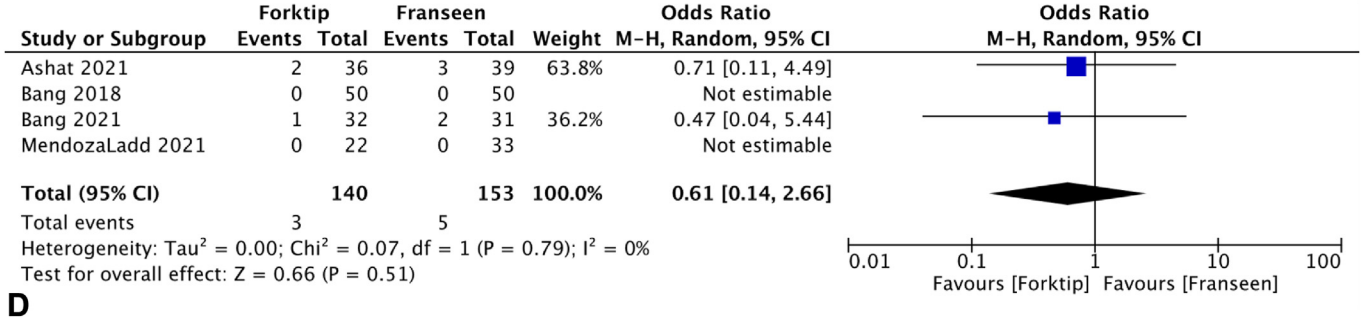
A



B

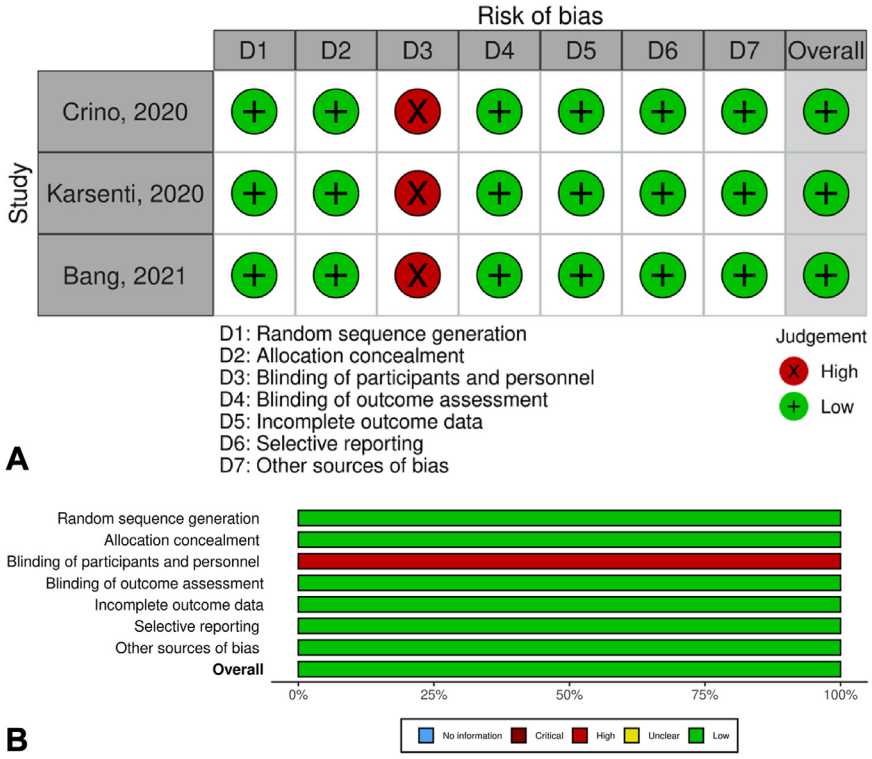


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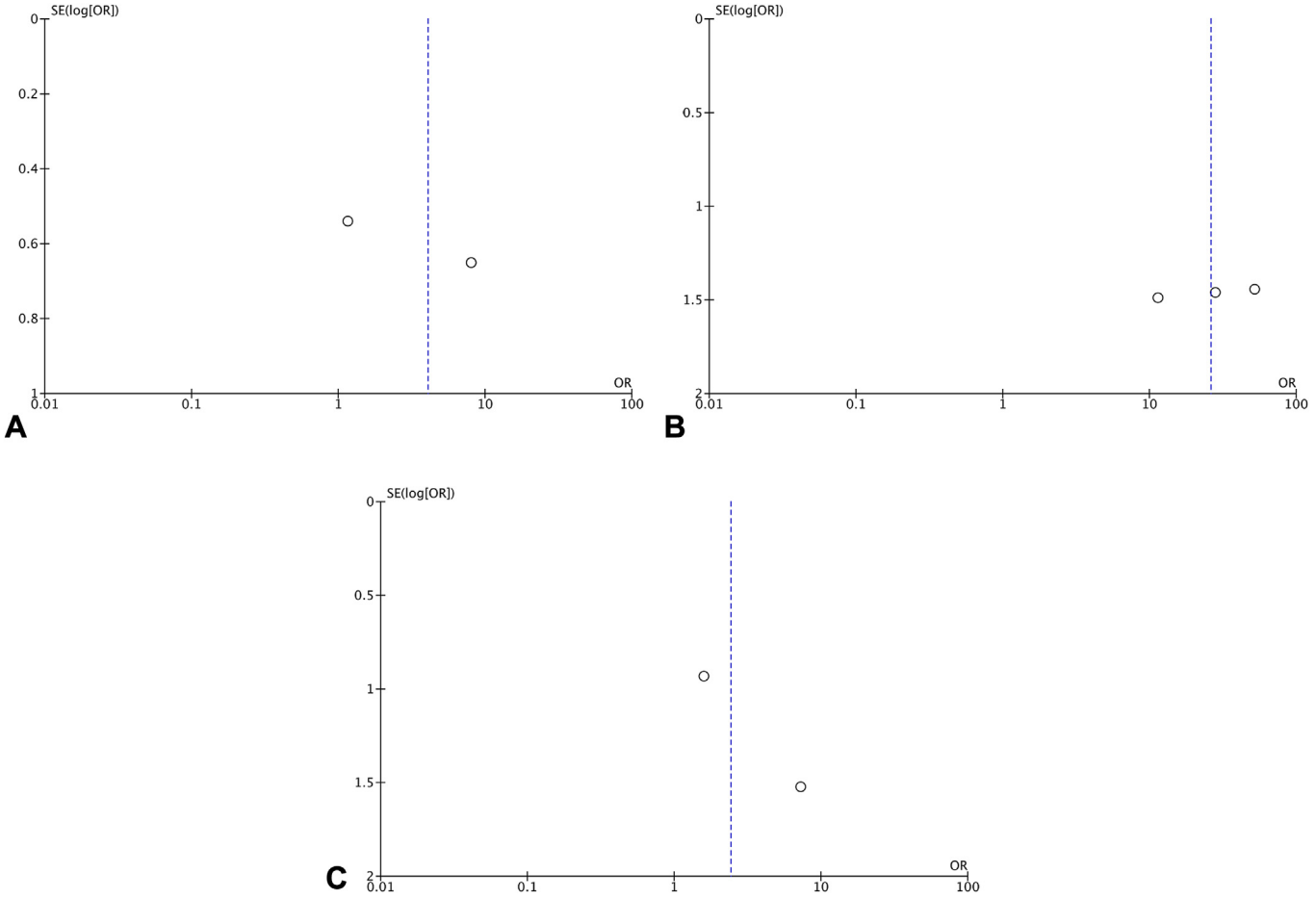


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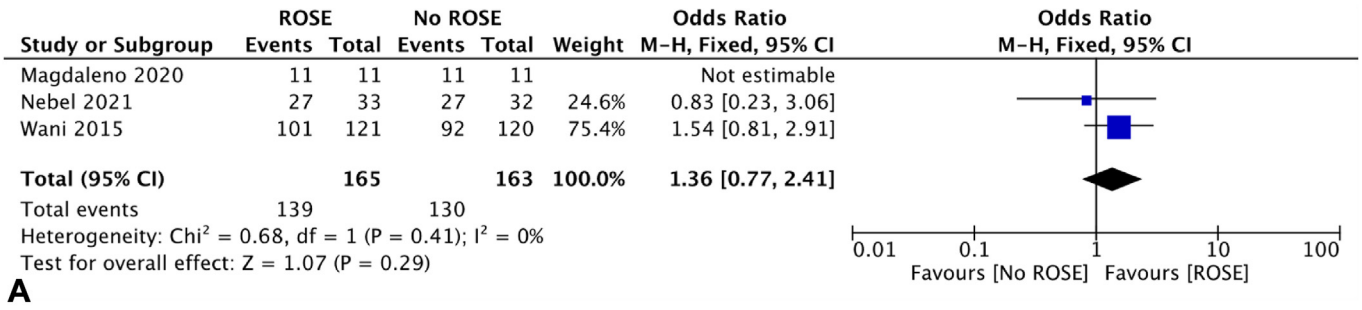
Supplementary Figure 7. Forest plot comparing (**A**) adverse events between novel/contemporary versus alternative fine-needle biopsy (FNB) needles and (**B**) diagnostic accuracy of, (**C**) sample adequacy of, and (**D**) adverse events between Fork-tip versus Franseen FNB needle for EUS-guided tissue acquisition of solid pancreatic masses. *CI*, Confidence interval.



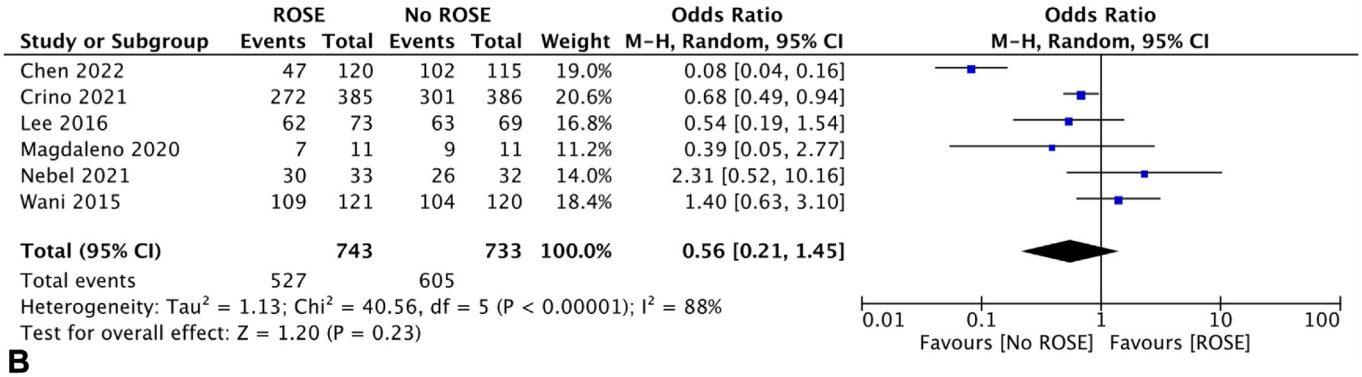
Supplementary Figure 8. (**A**) Risk of bias summary and (**B**) overall quality assessment of randomized controlled trials comparing novel/contemporary versus alternative fine-needle biopsy needles for EUS-guided tissue acquisition of solid pancreatic masses.



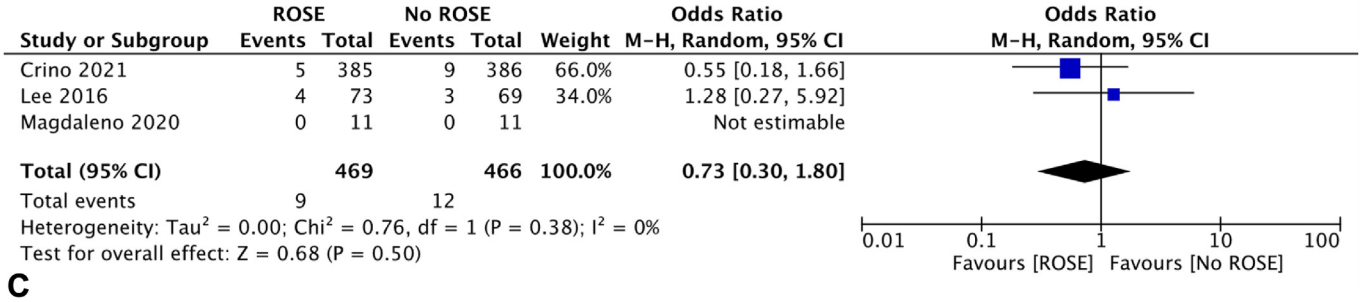
Supplementary Figure 9. Funnel plot comparing (**A**) diagnostic accuracy, (**B**) sample adequacy, and (**C**) adverse events of novel/contemporary versus alternative FNB needles for EUS-guided tissue acquisition of solid pancreatic masses. *SE*, Standard error; *OR*, odds ratio.



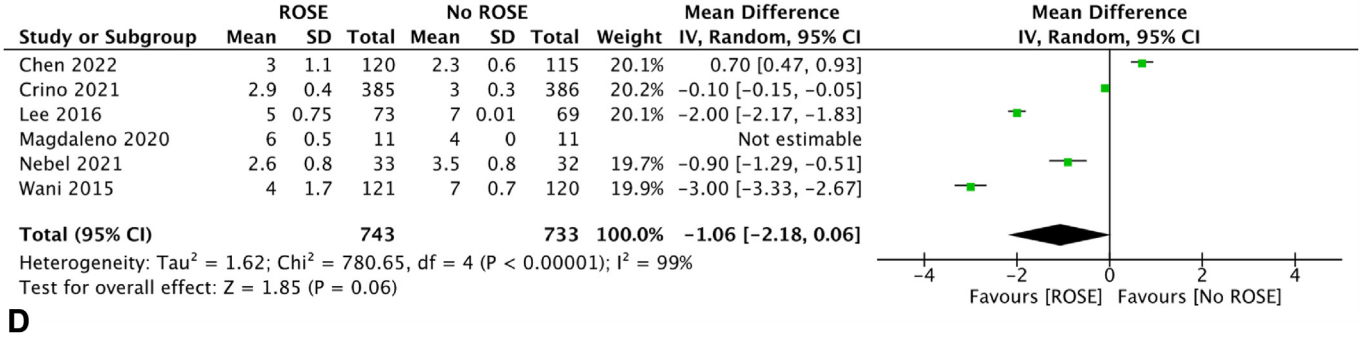
A



B

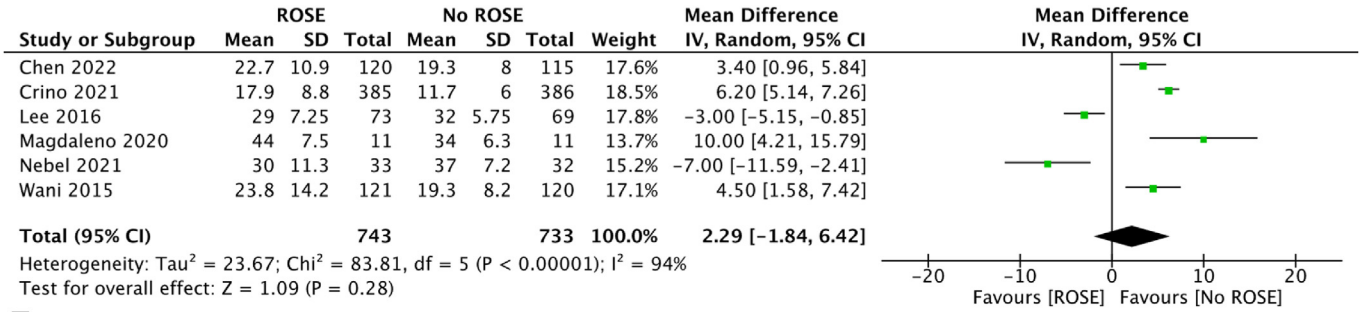


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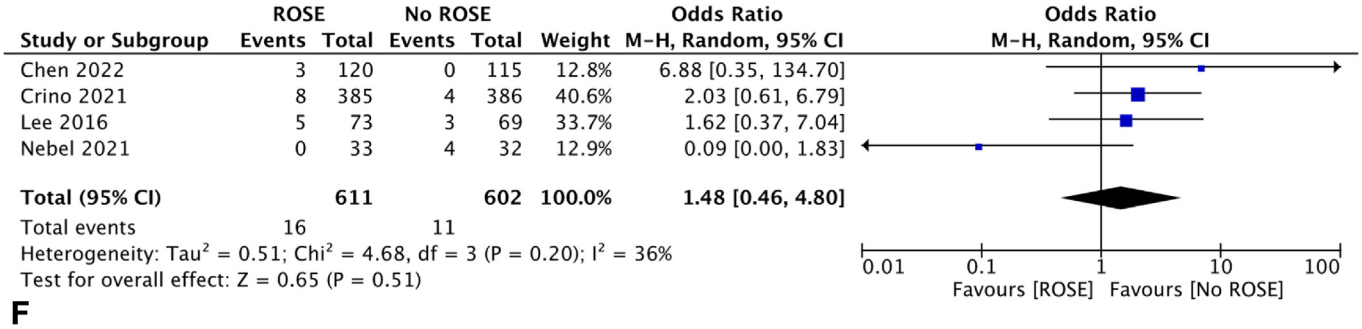


D

Supplementary Figure 10. Forest plot comparing (**A**) diagnostic yield, (**B**) sample adequacy, (**C**) need for repeated biopsy sampling, (**D**) number of needle passes, (**E**) procedure duration, and (**F**) adverse events of EUS-guided tissue acquisition of solid pancreatic masses with or without ROSE. *ROSE*, Rapid on-site evaluation; *CI*, confidence interval; *SD*, standard deviation.

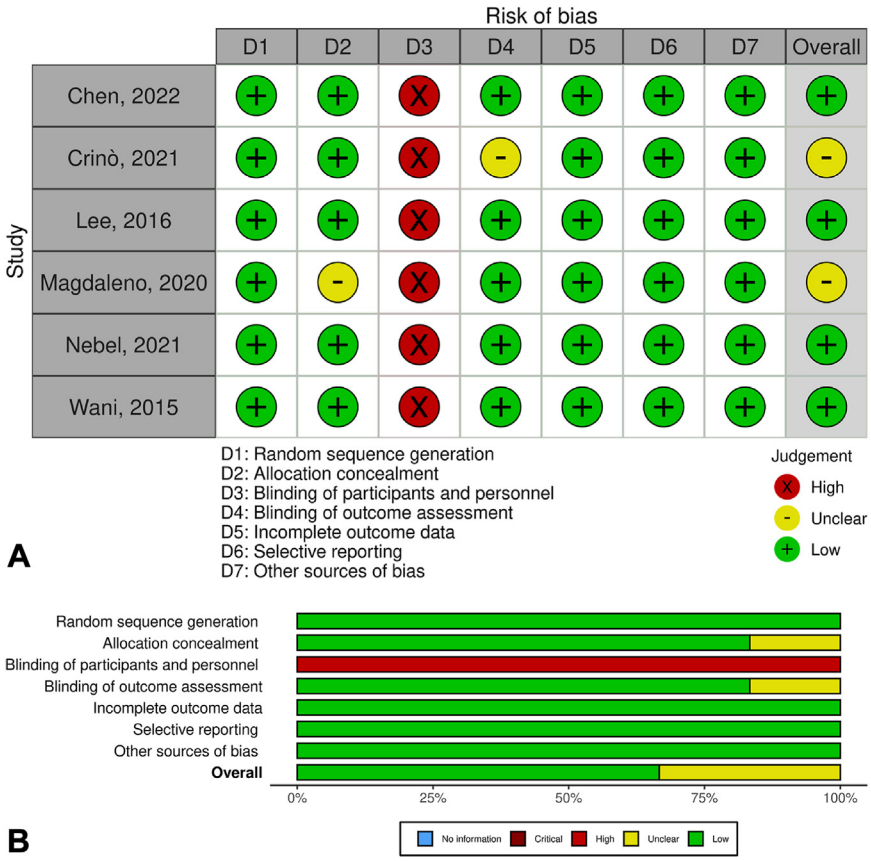


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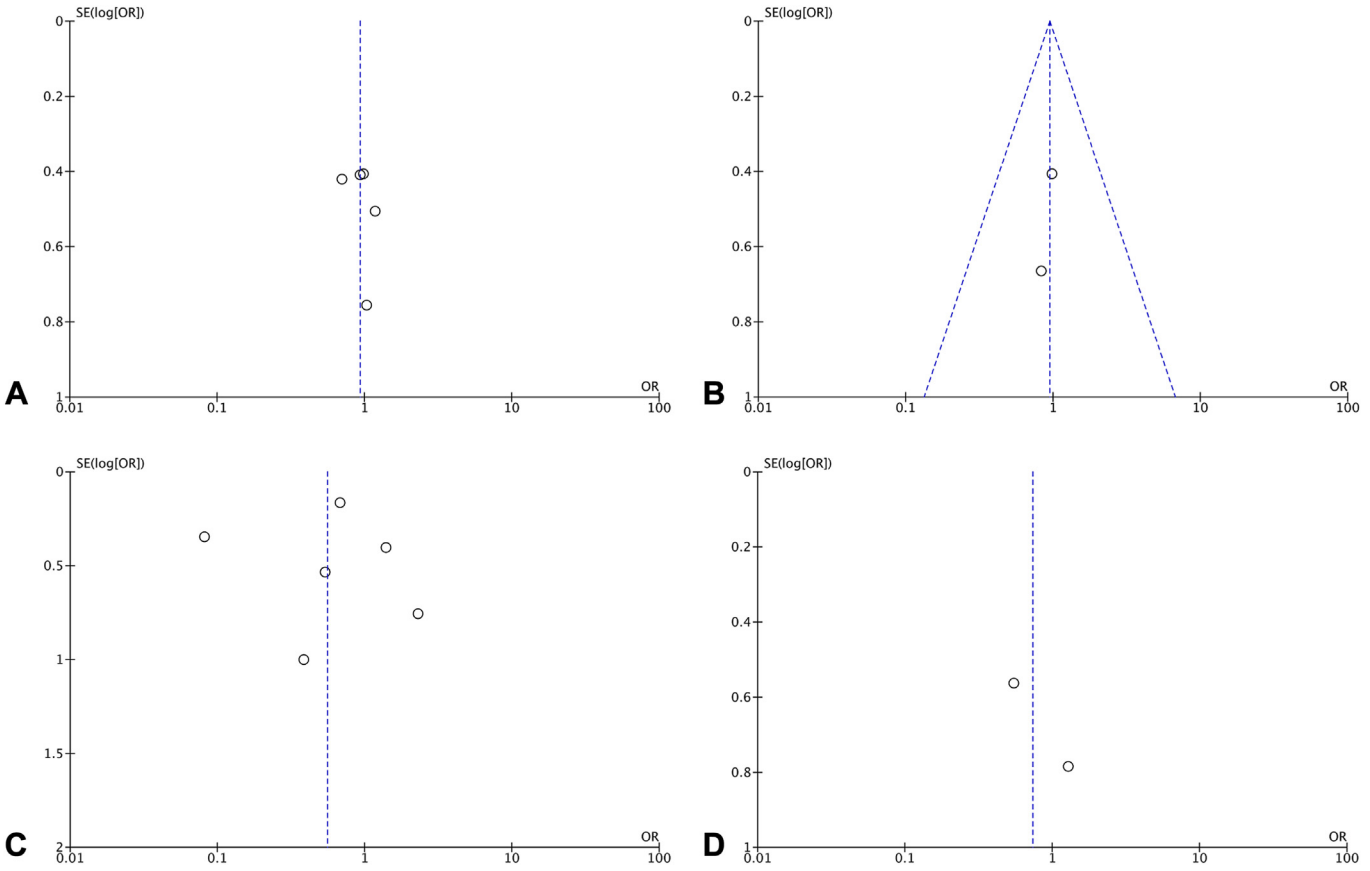


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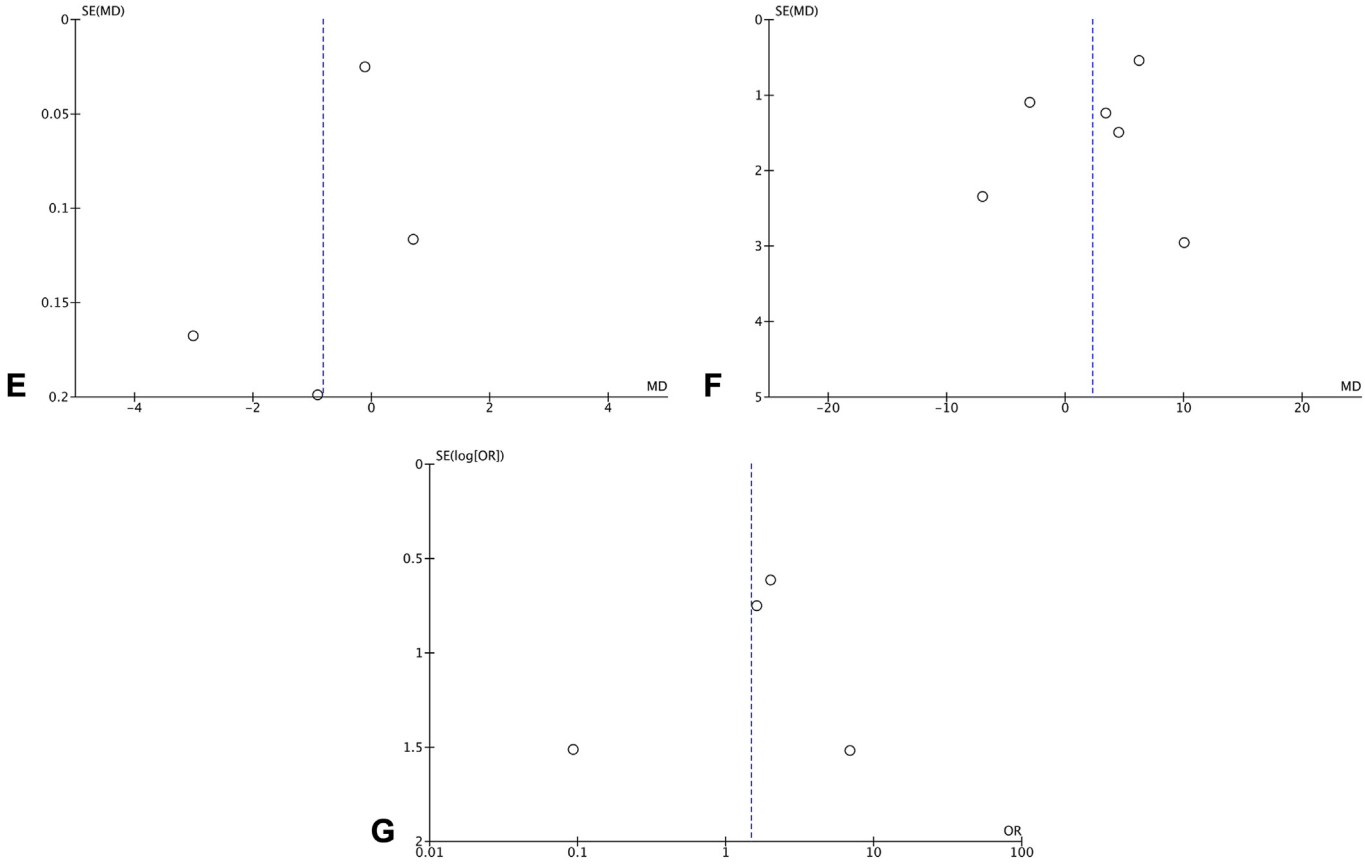
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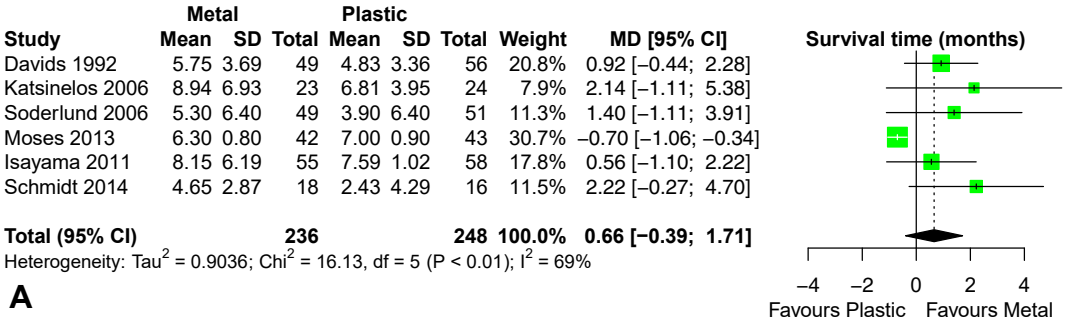
Supplementary Figure 11. (**A**) Risk of bias summary and (**B**) overall quality assessment of randomized controlled trials comparing EUS-guided tissue acquisition of solid pancreatic masses with and without rapid on-site evaluation.

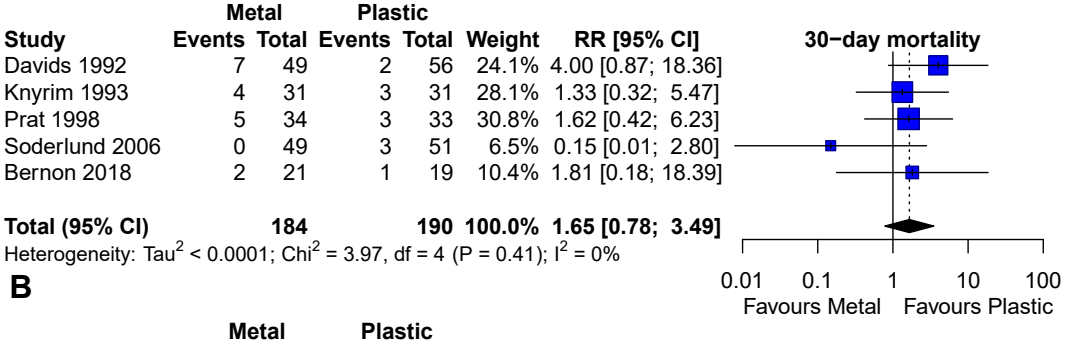


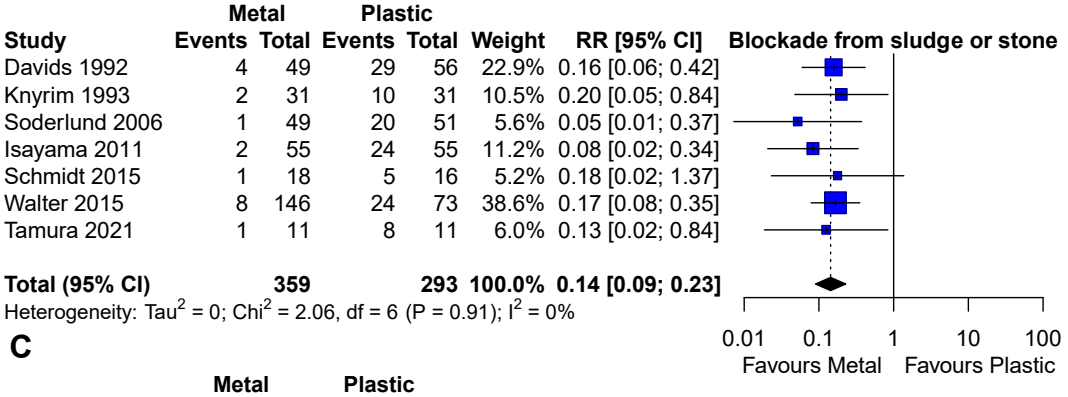
Supplementary Figure 12. Funnel plot comparing (**A**) diagnostic accuracy, (**B**) diagnostic yield, (**C**) sample adequacy, (**D**) need for repeated biopsy sampling, (**E**) number of needle passes, (**F**) procedure duration, and (**G**) adverse events of EUS-guided tissue acquisition of solid pancreatic masses with and without rapid on-site evaluation. *SE*, Standard error; *OR*, odds ratio; *MD*, mean difference.

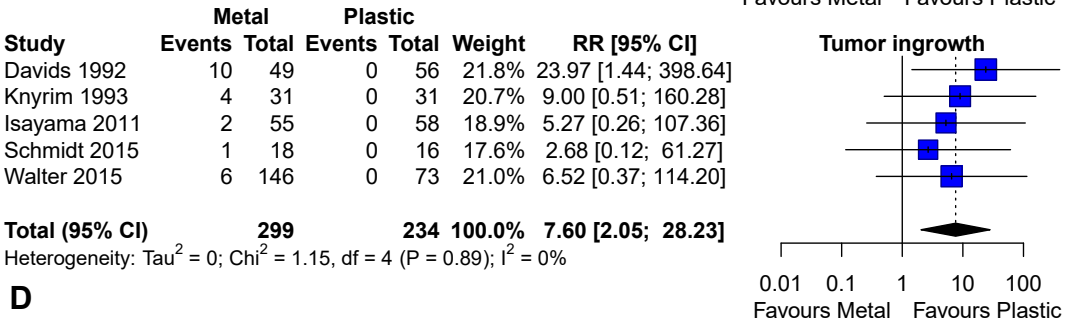


Supplementary Figure 12. Continued

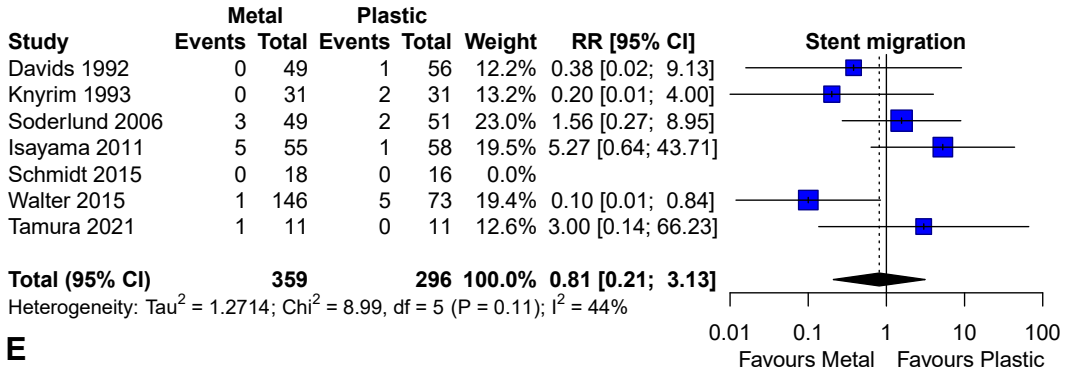




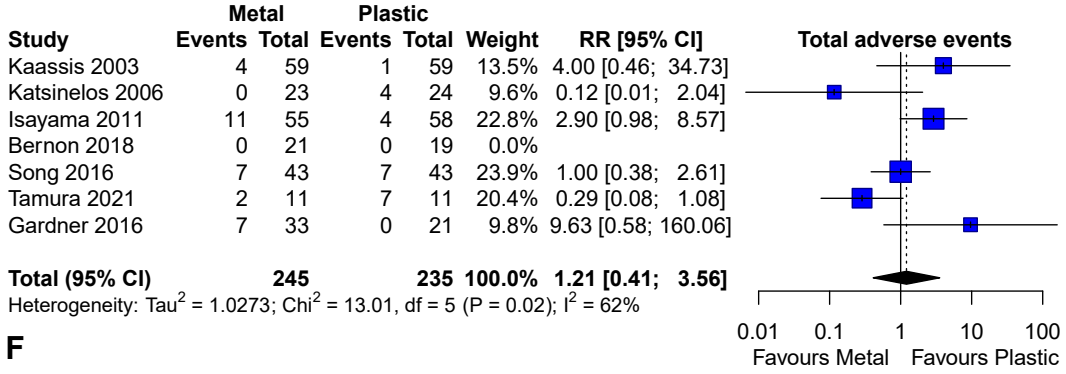




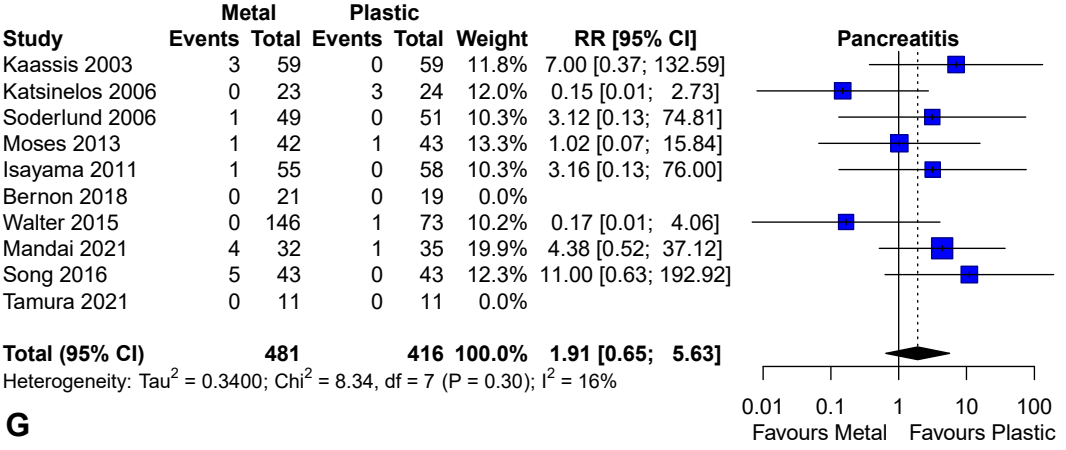
Supplementary Figure 13. Forest plot comparing (**A**) survival time, (**B**) 30-day mortality, (**C**) risk of stent blockade by stone and/or sludge, (**D**) risk of stent tissue ingrowth, (**E**) risk of stent migration, (**F**) risk of postprocedure adverse events, (**G**) risk of post-ERCP pancreatitis, (**H**) risk of post-ERCP cholecystitis, (**I**) risk of surgical resectability, and (**J**) risk of postoperative adverse events after surgical resection between metal and plastic biliary stents in patients with distal malignant biliary obstruction. *CI*, Confidence interval; *SD*, standard deviation; *MD*, mean difference; *RR*, risk ratio.



E

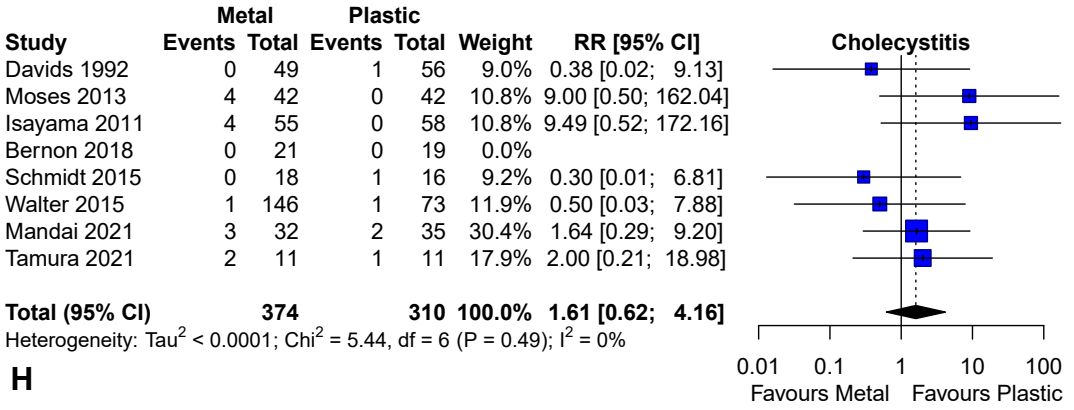


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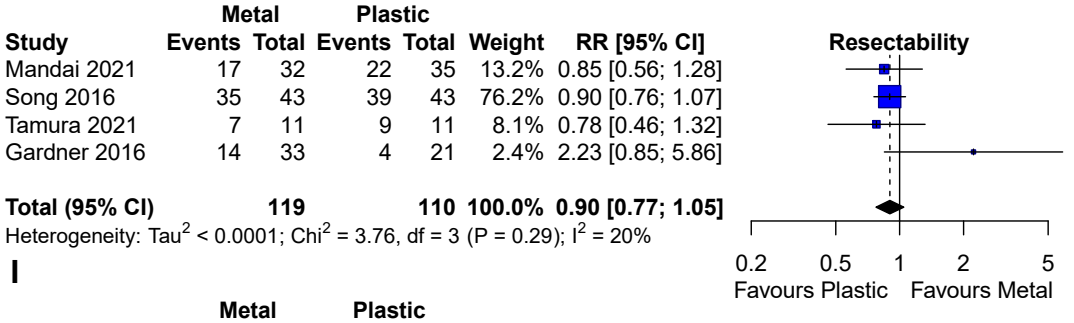


G

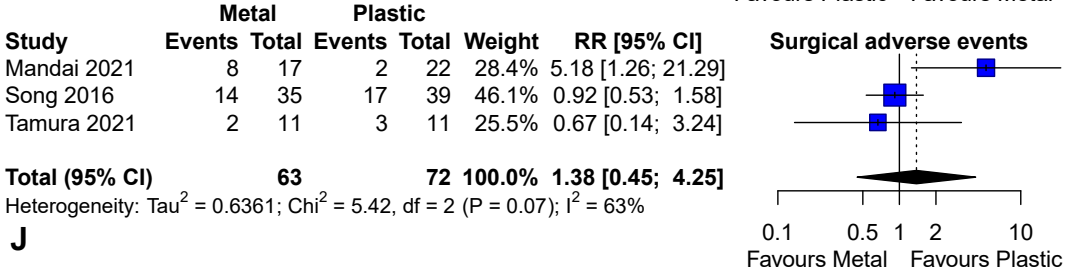
Supplementary Figure 13. Continued



H

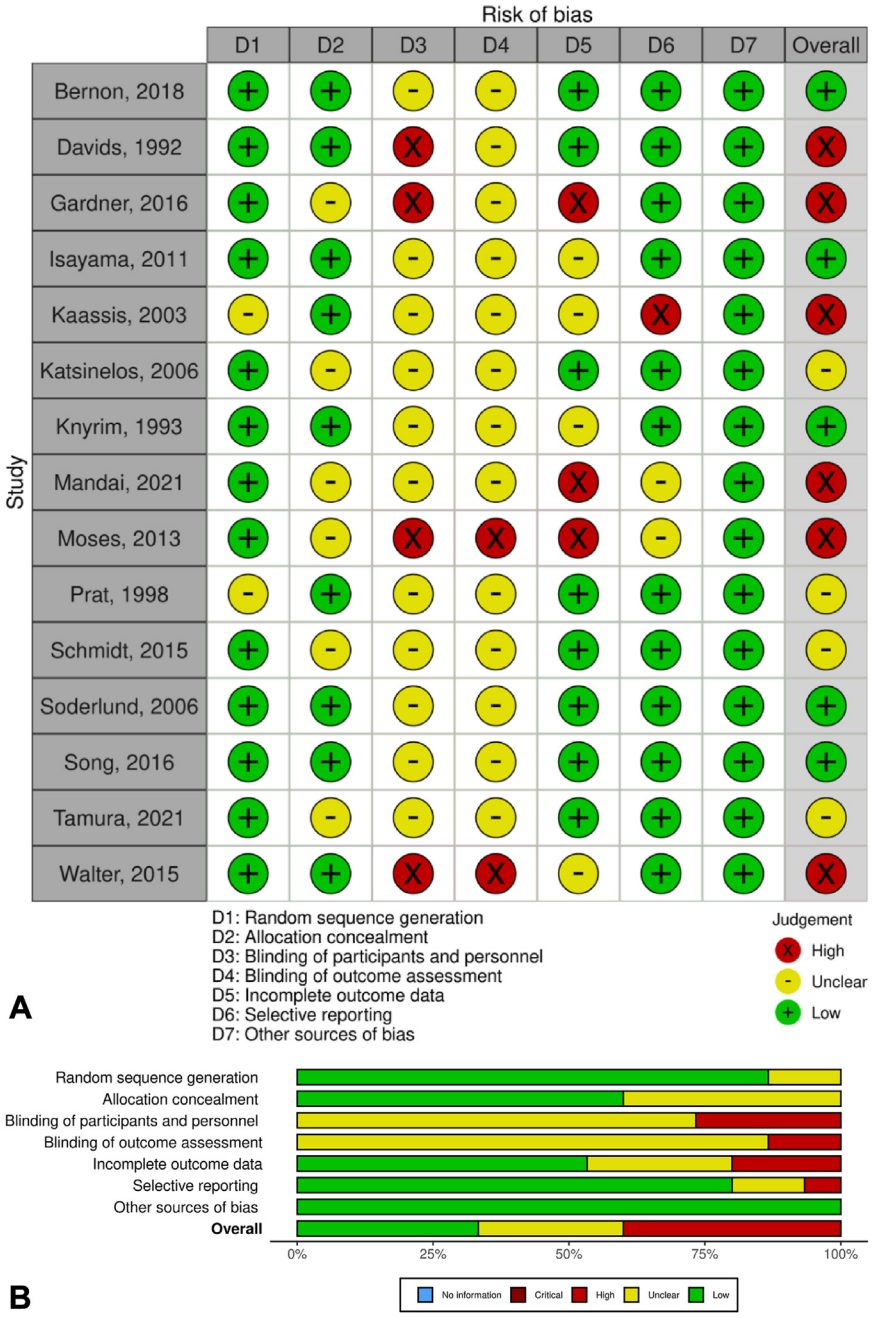


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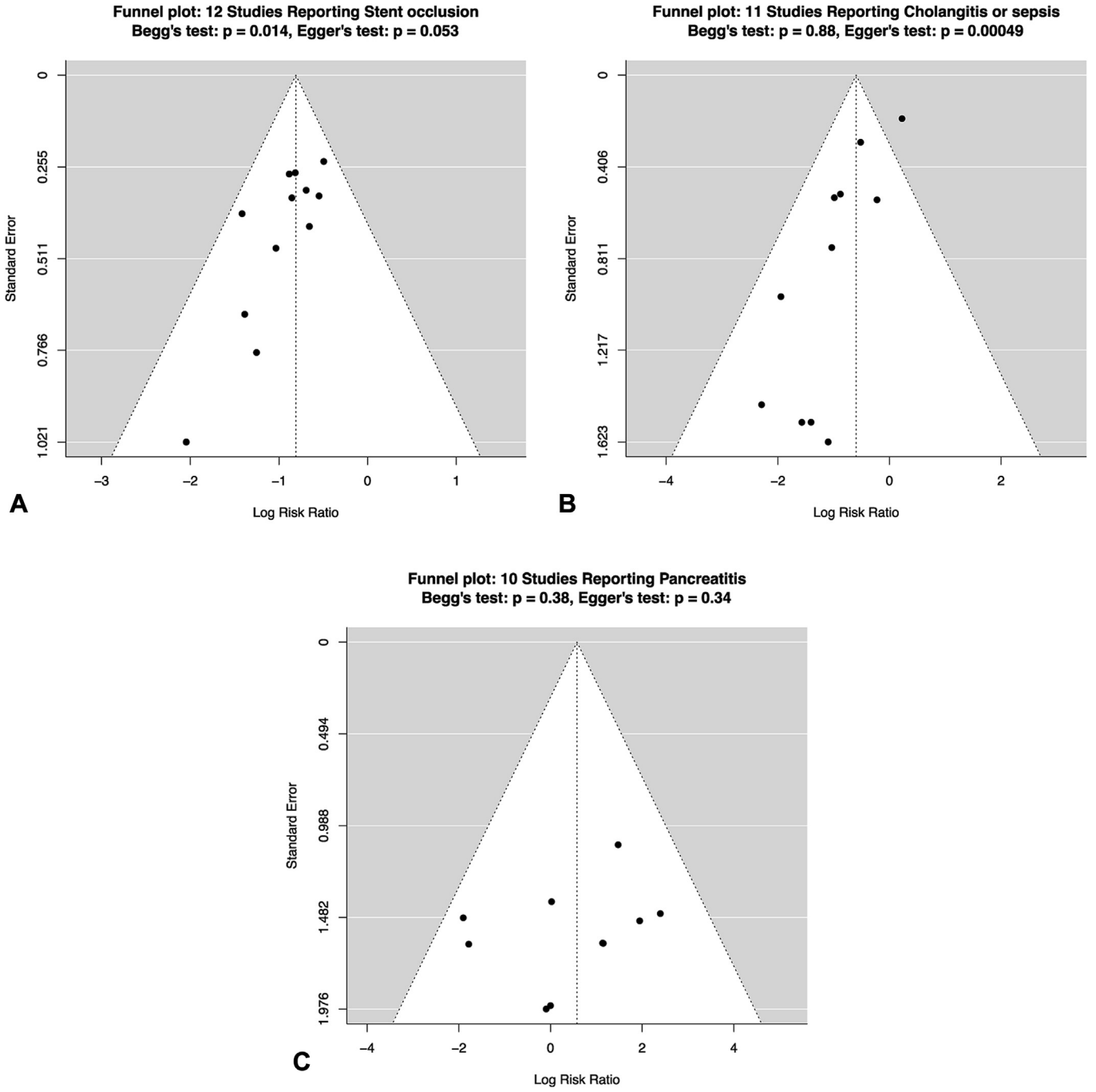


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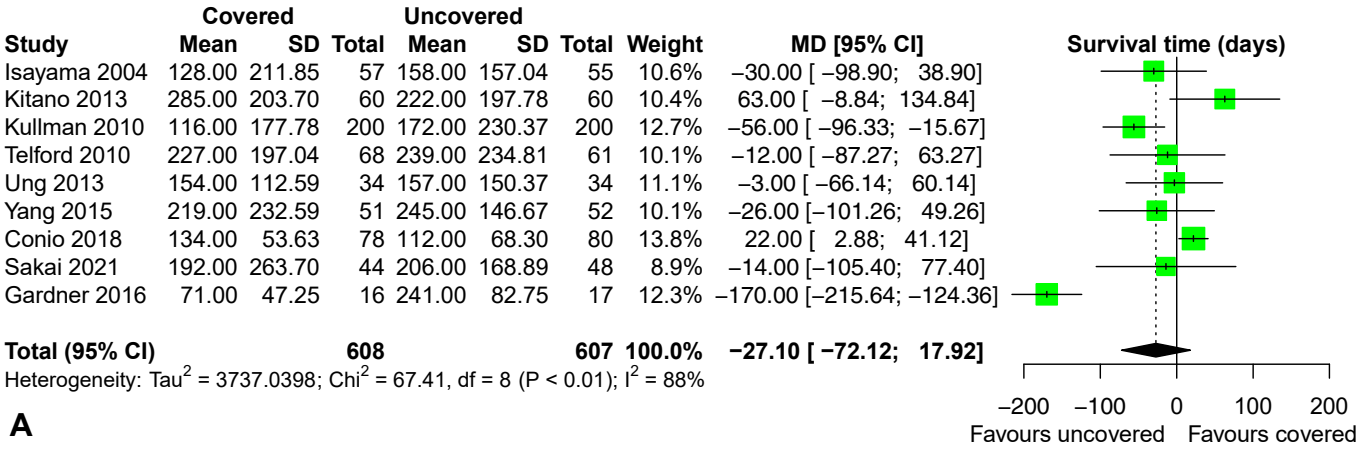
Supplementary Figure 13. Continued



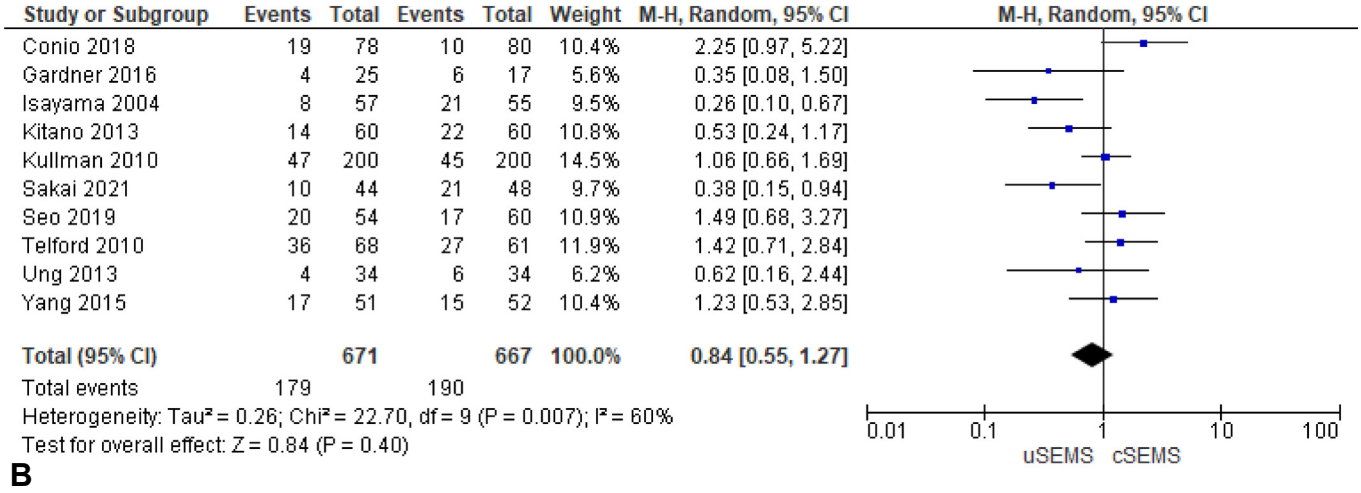
Supplementary Figure 14. (**A**) Risk of bias summary and (**B**) overall quality assessment of randomized controlled trials comparing EUS-guided tissue acquisition of solid pancreatic masses with and without rapid on-site evaluation.



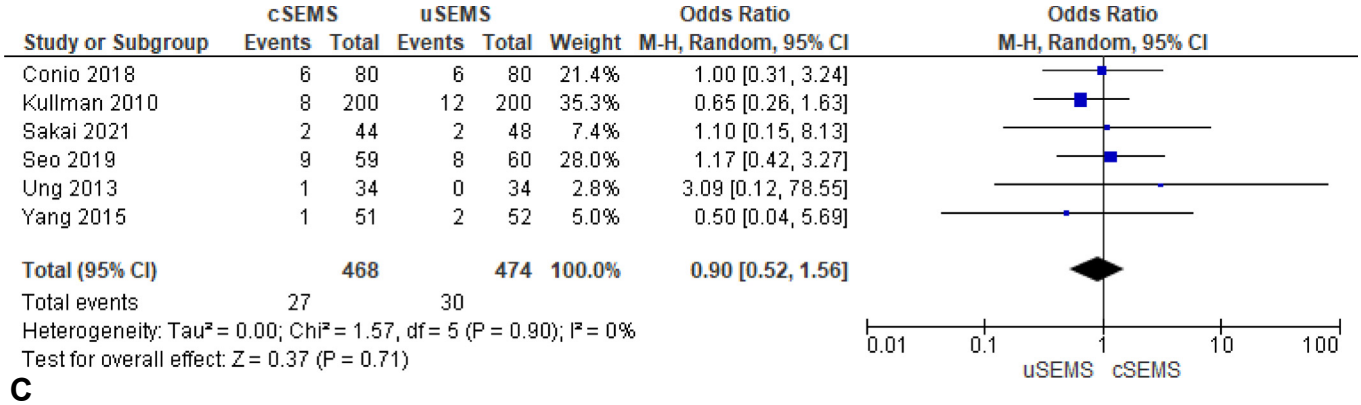
Supplementary Figure 15. Funnel plot of studies comparing (**A**) stent failure, (**B**) cholangitis or sepsis, and (**C**) post-ERCP pancreatitis between metal and plastic biliary stents in patients with distal malignant biliary obstruction.



A

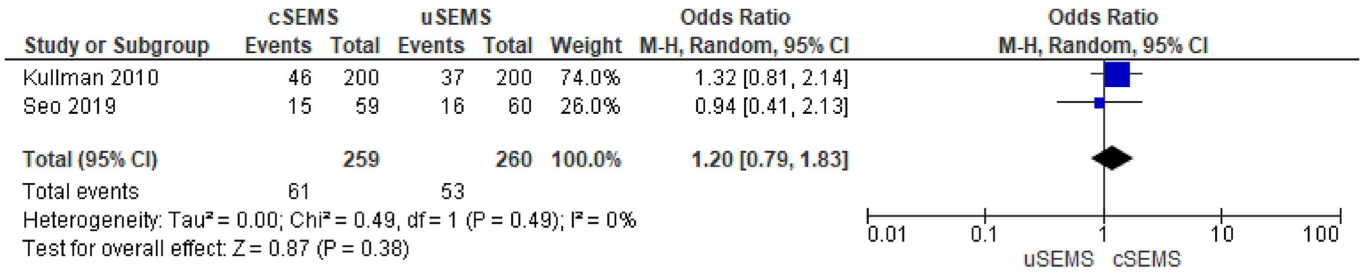


B

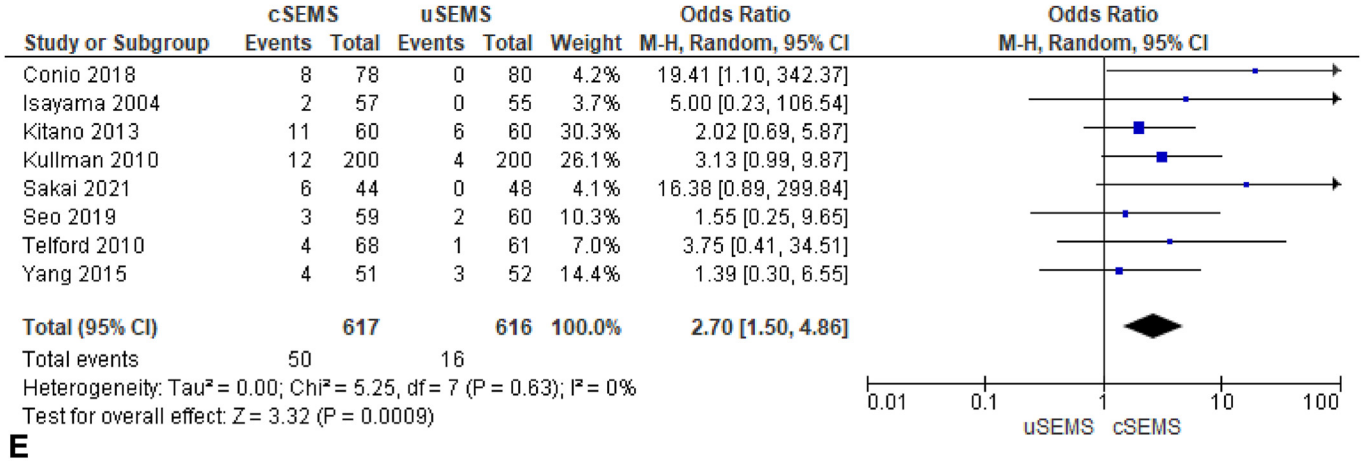


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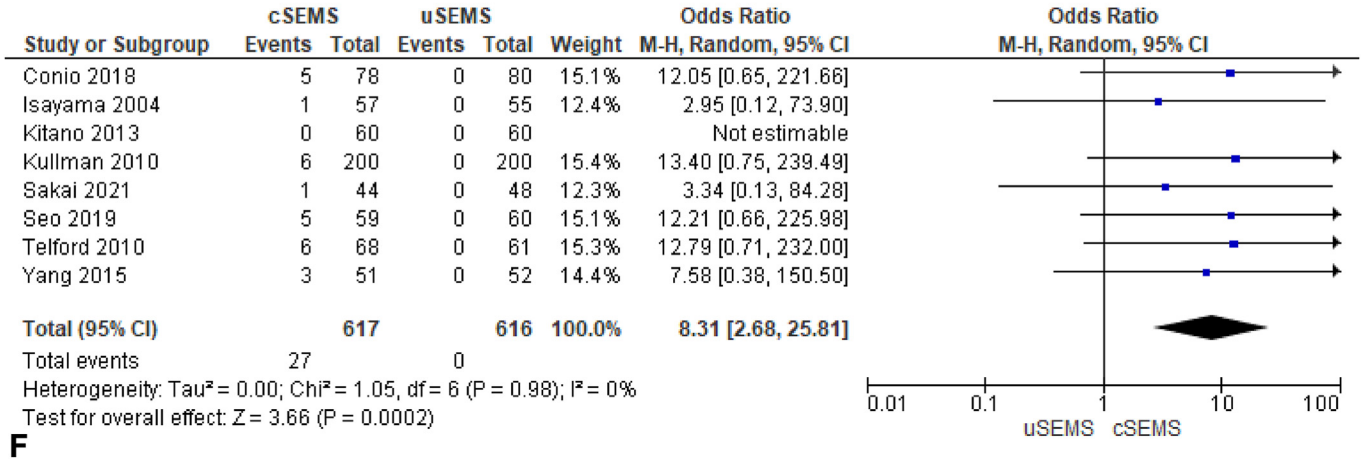
Supplementary Figure 16. Forest plot comparing (**A**) survival time, (**B**) stent failure rate, (**C**) rate of cholangitis, (**D**) rate of reinterventions, (**E**) stent blockade from sludge or stone, (**F**) stent migration, (**G**) stent tumor ingrowth, (**H**) stent tumor outgrowth, (**I**) rate of postprocedure adverse events, (**J**) post-ERCP pancreatitis, and (**K**) acute cholecystitis between covered metal and uncovered metal biliary stents in patients with distal malignant biliary obstruction. *CI*, Confidence interval; *SD*, standard deviation; *MD*, mean difference; *uSEMS*, uncovered self-expandable metal stents; *cSEMS*, covered self-expandable metal stents.



D

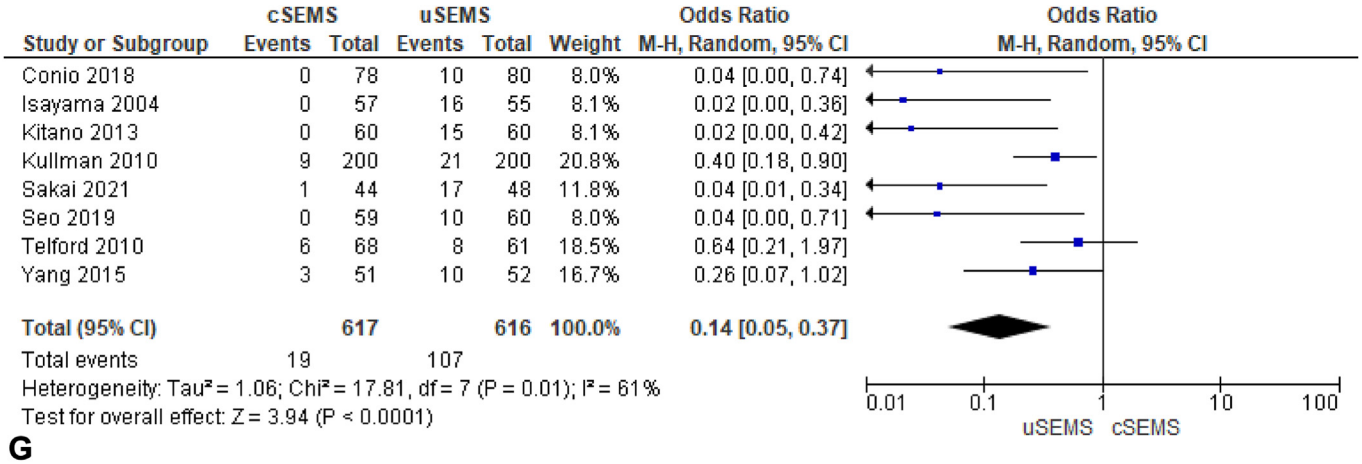


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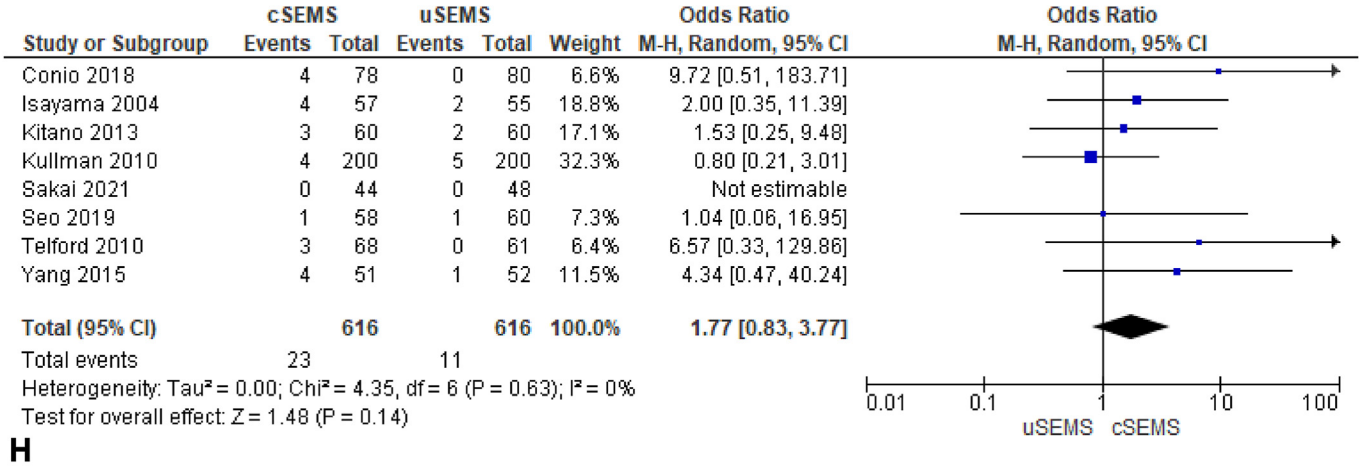


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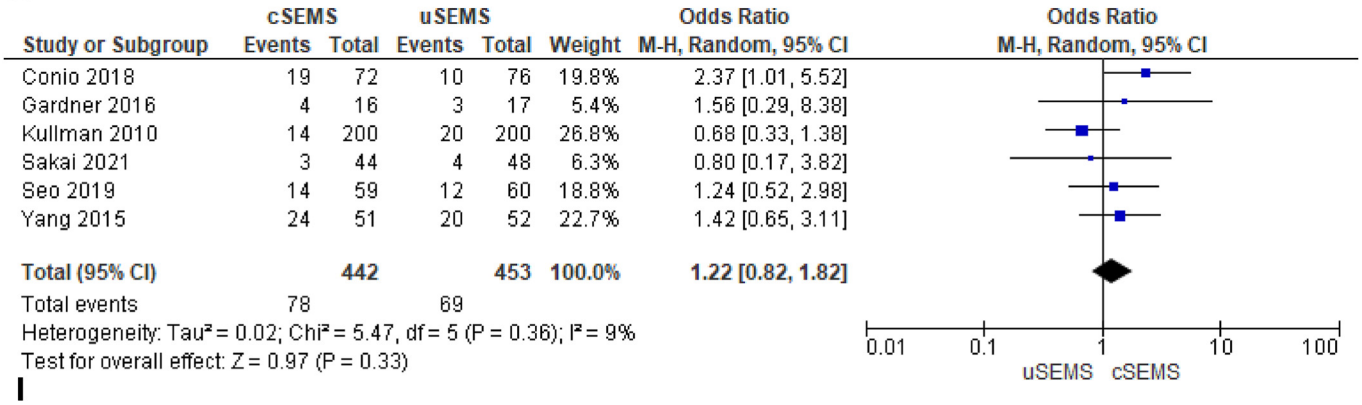
Supplementary Figure 16. Continued



G

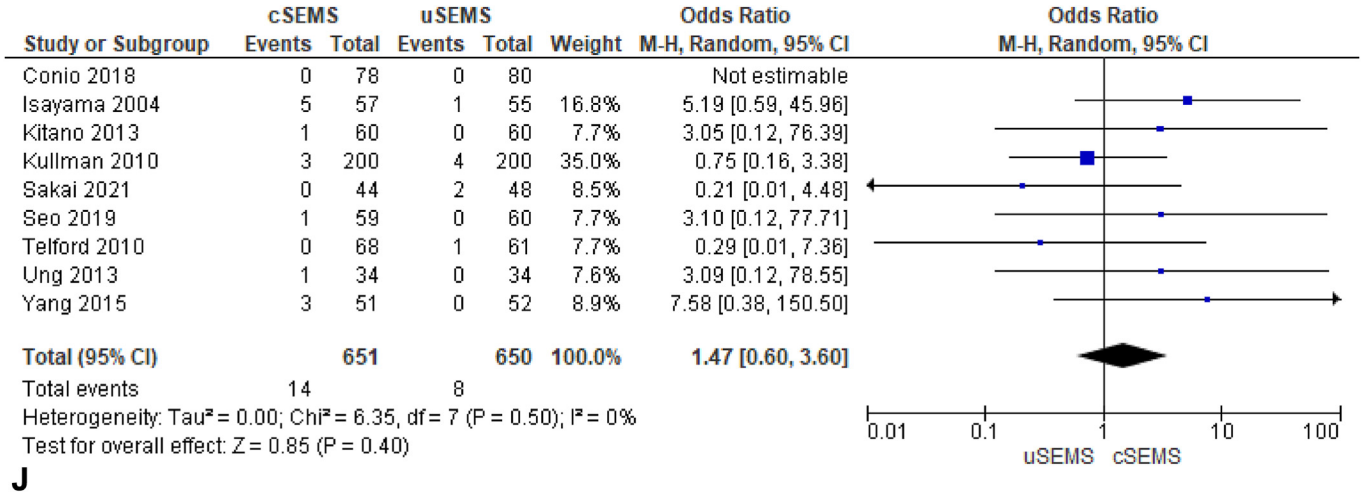


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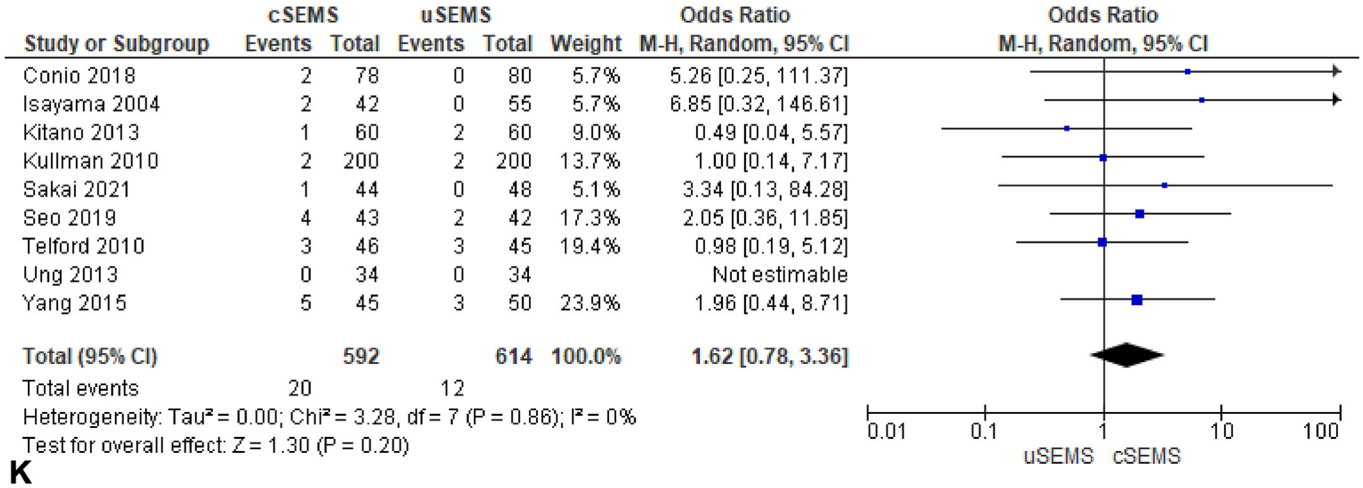


I

Supplementary Figure 16. Continued

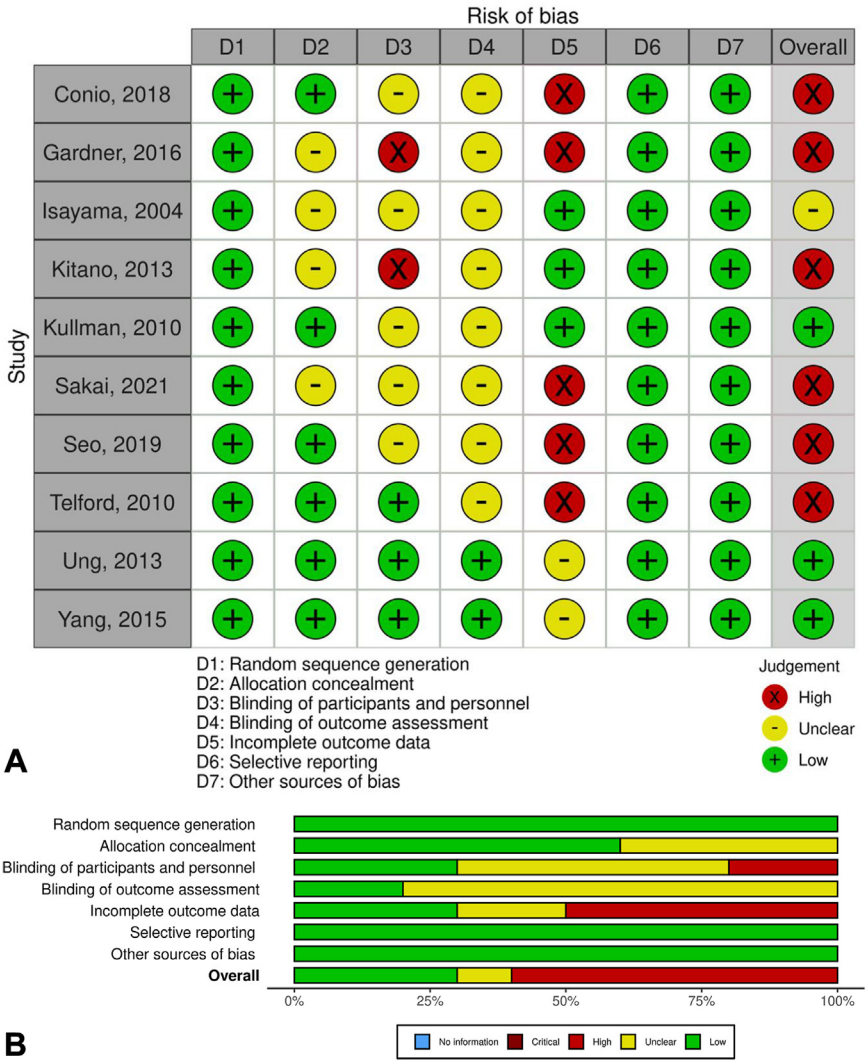


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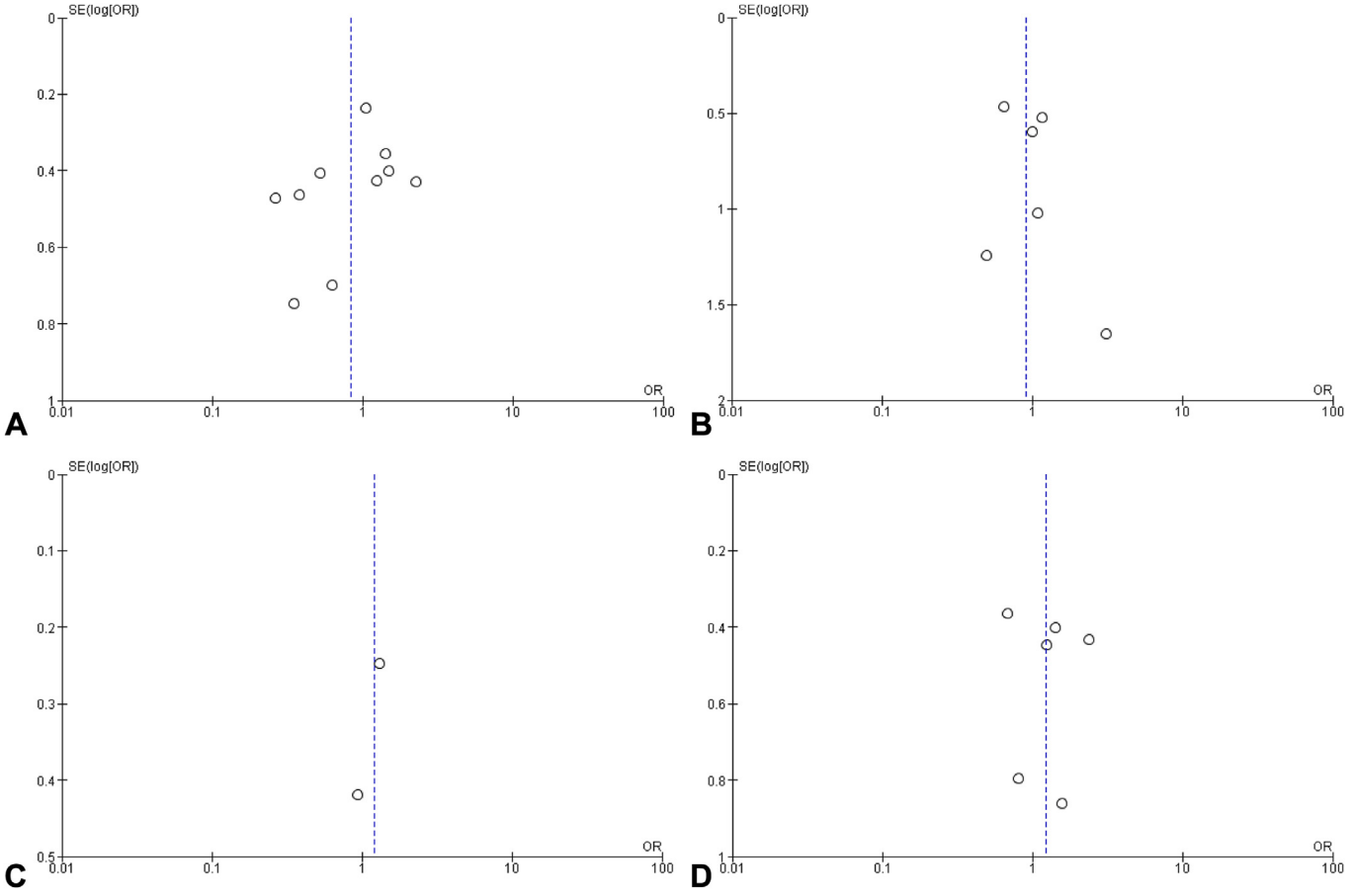


K

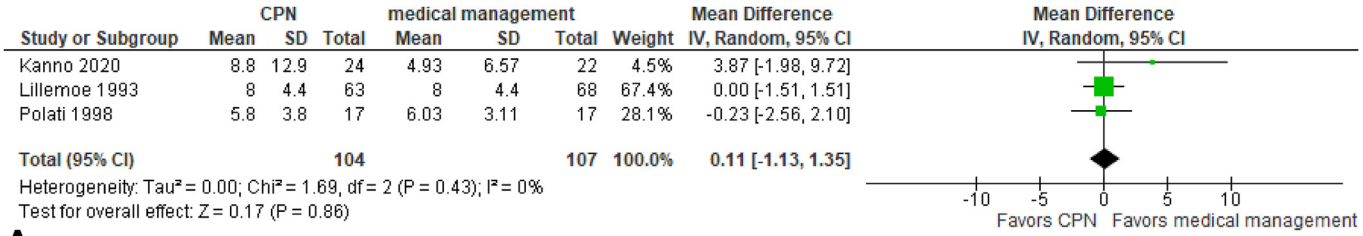
Supplementary Figure 16. Continued



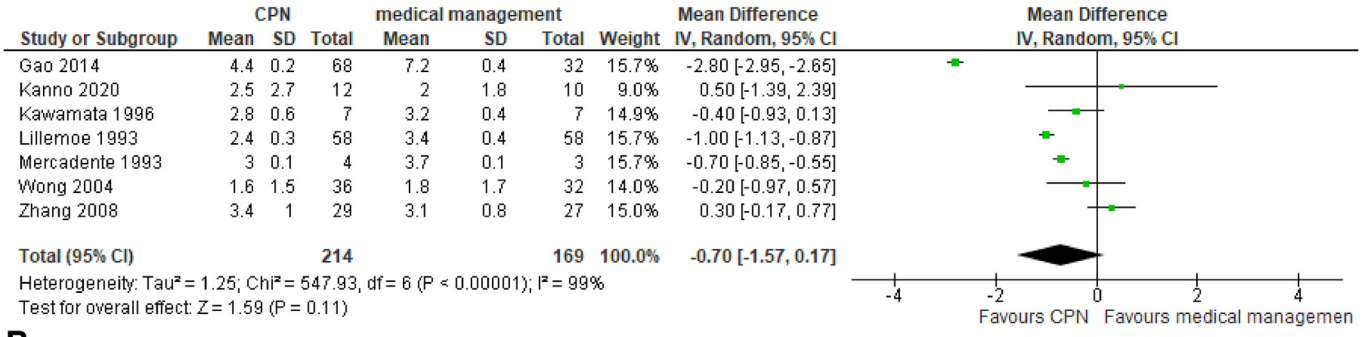
Supplementary Figure 17. (**A**) Risk of bias summary and (**B**) overall quality assessment of randomized controlled trials A comparing covered metal and uncovered metal biliary stents in patients with distal malignant biliary obstruction.



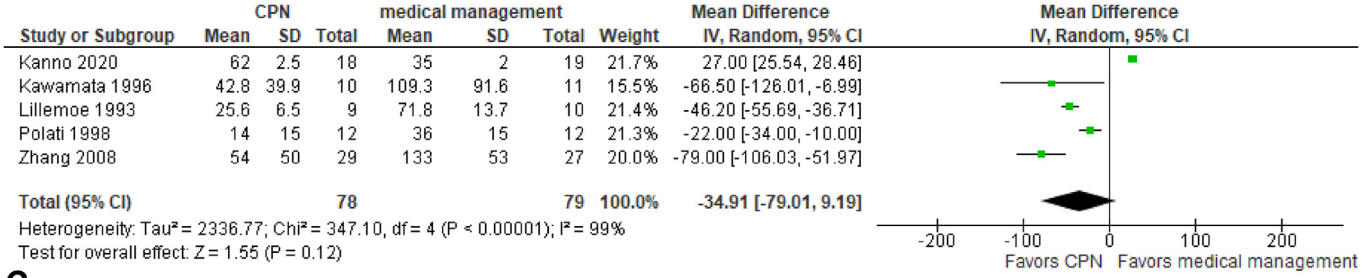
Supplementary Figure 18. Funnel plot of studies comparing (**A**) stent failure, (**B**) acute cholangitis, (**C**) reintervention rate, and (**D**) adverse events between covered metal and uncovered metal biliary stent in patients with distal malignant biliary obstruction. *SE*, Standard error; *OR*, odds ratio.



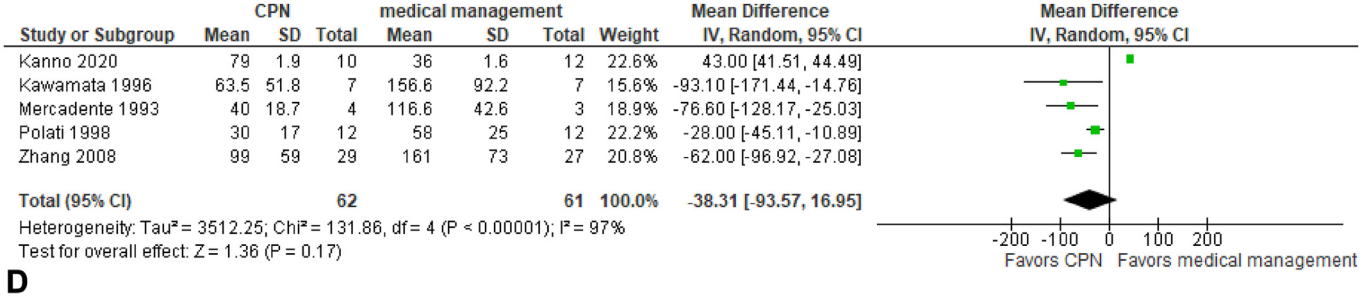
A



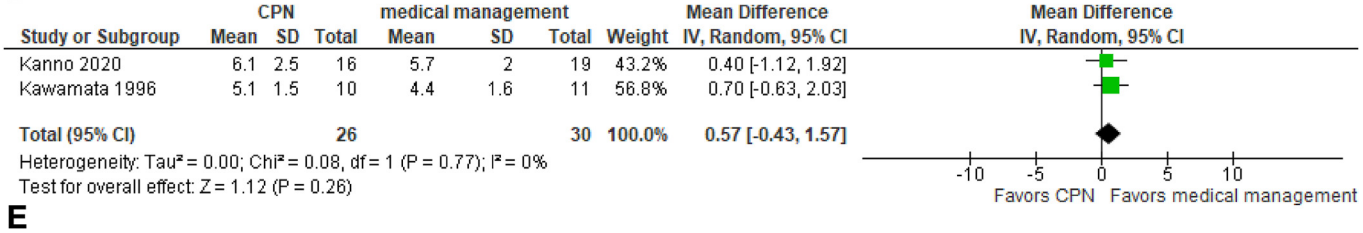
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C



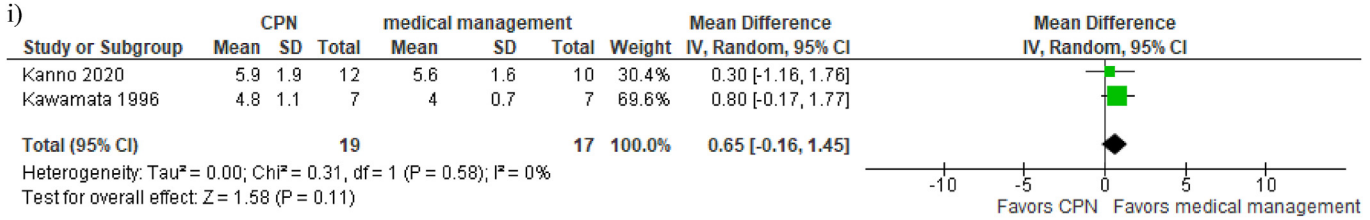
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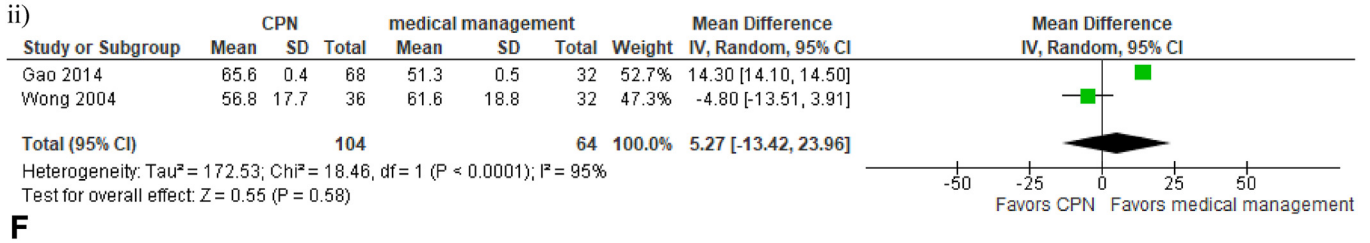
E

Supplementary Figure 19. Forest plot comparing (**A**) mean survival, (**B**) mean pain severity by the visual analog scale at 8 weeks, (**C**) opioid use at 4 weeks, (**D**) opioid use at 8 weeks, (**E**) quality of life (score 0-10) at 4 weeks, (**G**) diarrhea, and (**H**) drowsiness between medical analgesic therapy with and without celiac plexus neurolysis (CPN) in patients with pancreatic cancer. **F,** Forest plot comparing quality of life at 8 weeks between medical analgesic therapy with and without CPN in patients with pancreatic cancerusing the *i)* uniscale (scale, 0-10) and the *ii)* European Organization for Research and Treatment of Cancer QLQ-C30 or Functional assessment of cancer therapy, pancreatic cancer (scale, 0-100). *CI*, Confidence interval; *SD*, standard deviation.

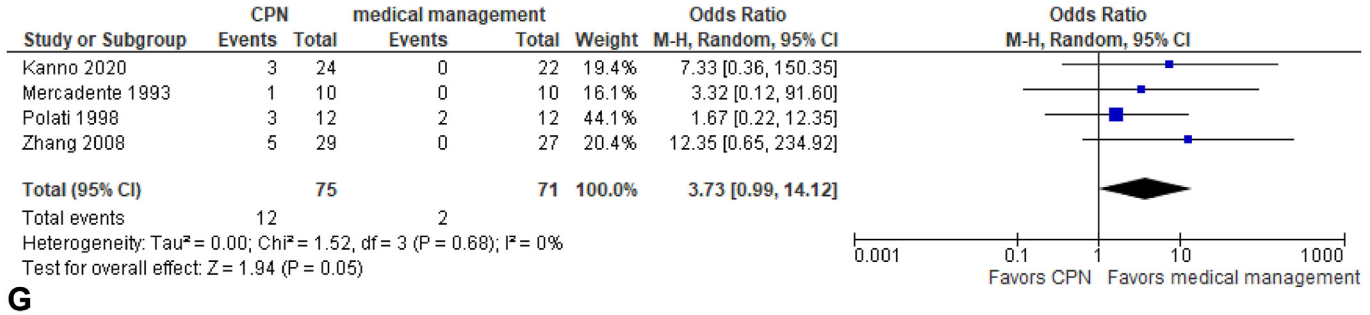
i)



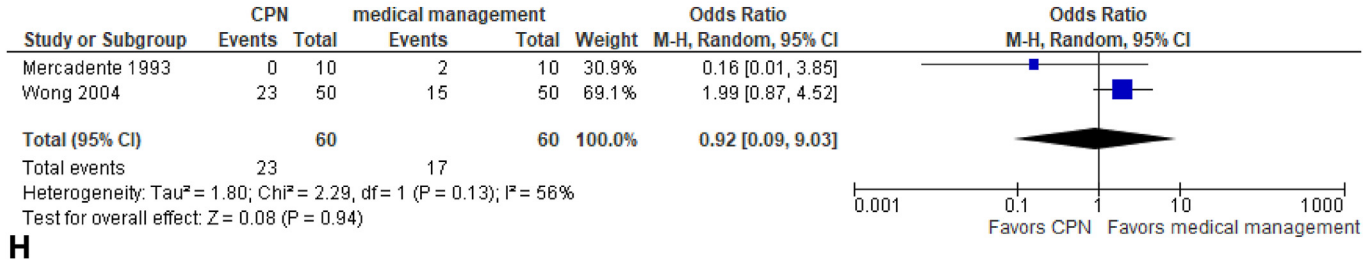
ii)



F

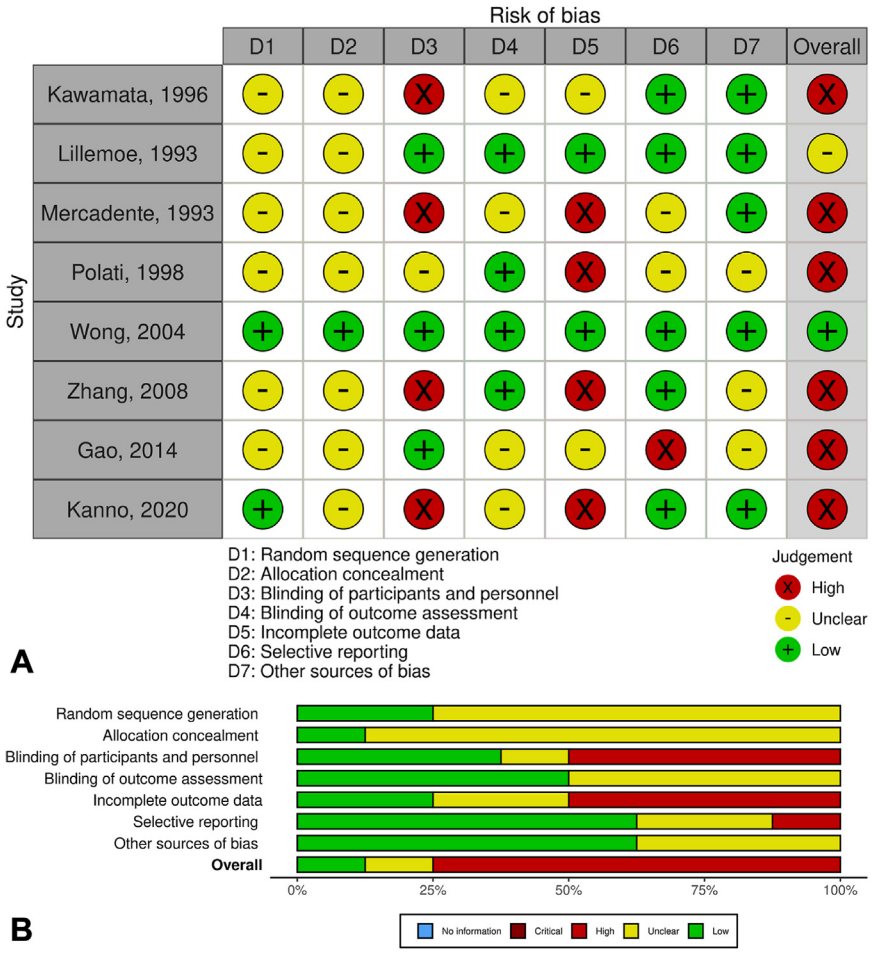


G

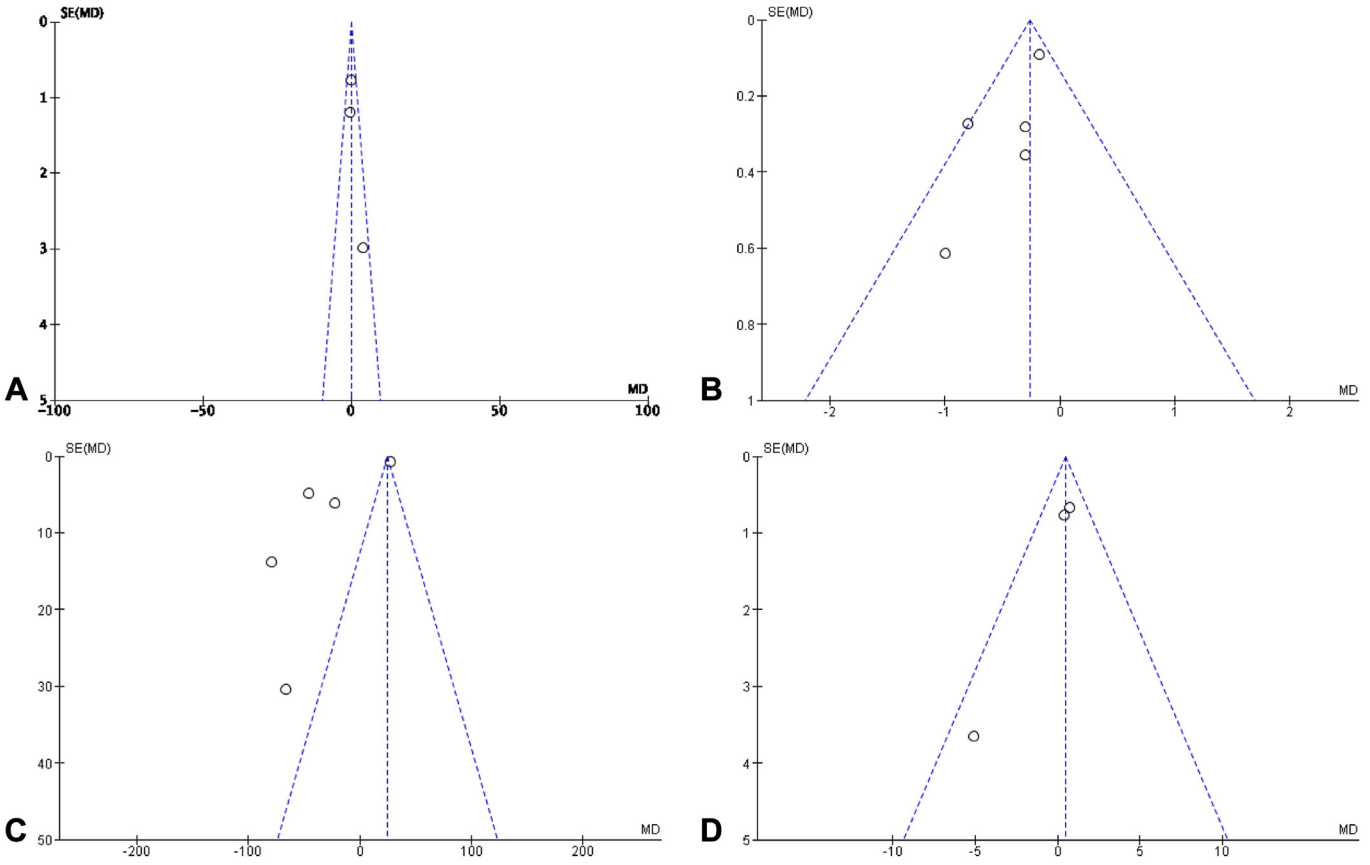


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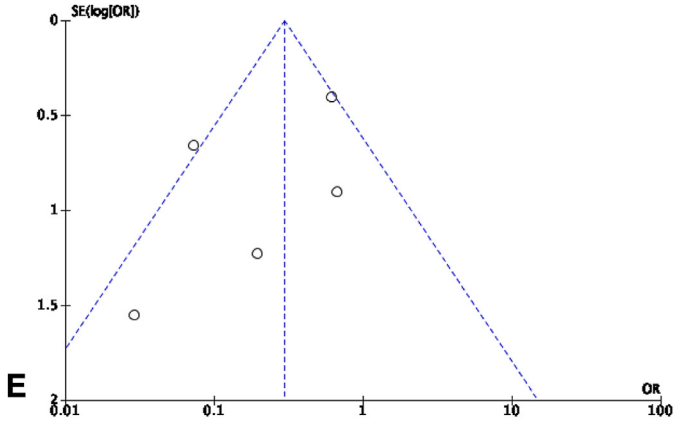
Supplementary Figure 19. Continued



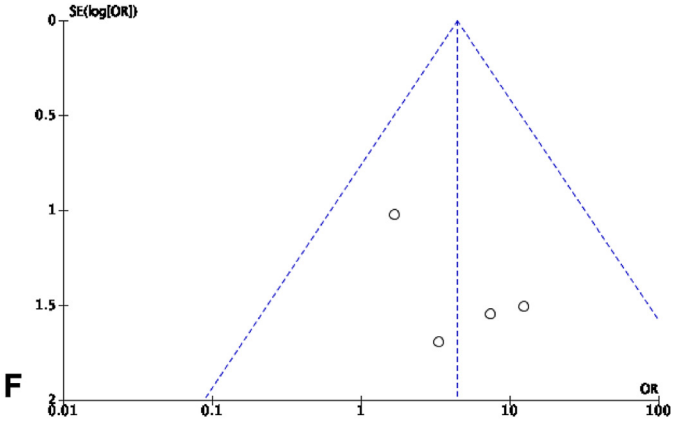
Supplementary Figure 20. (**A**) Risk of bias summary and (**B**) overall quality assessment of randomized controlled trials comparing medical analgesic therapy with and without celiac plexus neurolysis in patients with pancreatic cancer.



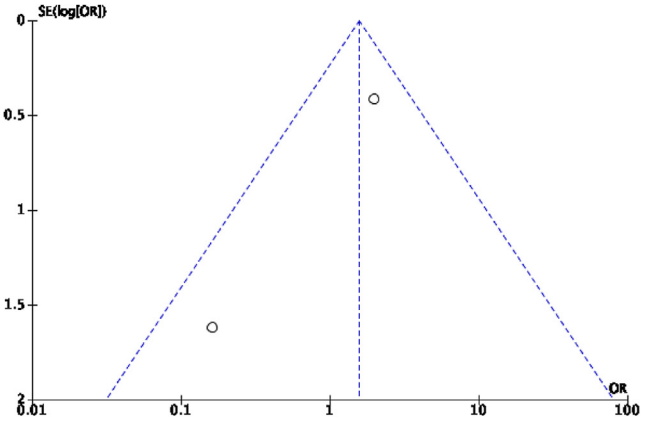
Supplementary Figure 21. Funnel plot of studies comparing (**A**) survival, (**B**) pain at 4 weeks, (**C**) opioid use at 4 weeks, (**D**) quality of life at 4 weeks, (**E**) constipation, (**F**) diarrhea, and (**G**) drowsiness between medical analgesic therapy with and without celiac plexus neurolysis in patients with pancreatic cancer. *SE*, Standard error; *OR*, odds ratio; *MD*, mean difference.



E



F



G

Supplementary Figure 21. Continued

APPENDIX 1
Filters

Study designs: randomized controlled trials (RCTs), cohort/observational studies (prospective and retrospective), systematics reviews, and meta-analyses. Optional: diagnostic studies and comparative studies.

Search strategies for population, intervention, comparator, and outcome (PICO) questions 1 to 4: EUS-guided tissue acquisition of solid pancreatic masses

Database: Ovid MEDLINE ALL.

Search date: February 17, 2022

Limits: RCTs, cohort/observational studies (prospective and retrospective), systematic reviews, meta-analyses, diagnostic studies

Search results: 1508

1	exp "Pancreatic Neoplasms"/di, dg or exp "Pancreatitis, Chronic"/di, dg or "Digestive System Neoplasms"/di, dg or ((pancreas or pancreatic) adj2 (cancer* or malignan* or lesion* or mass or masses or tumor* or tumour* or nodule* or neoplas* or carcinoma* or carcinogen* or growth* or adenocarcin*)).tw,kf.	92947
2	Endosonography/ or (endoscop* adj2 (ultrasound or ultrasonograph* or ultrasonic)).tw,kf. or EUS.ti,ab.	25233
3	1 and 2	5958
4	"Endoscopic Ultrasound-Guided Fine Needle Aspiration"/ or (("Biopsy, Fine-Needle"/ or "Biopsy, Needle"/) and ("Ultrasonography"/ or exp "Endosonography"/ or echography.xs.) and "Endoscopy"/) or (((endoscopic-ultrasound or eus) adj5 (sampl* or biop* or aspirat* or collect* or acquisit* or procur*)) or (eus adj2 (fna or fnb)) or eusfna or eusfnb or eus-fna or eus-fnb).tw,kf.	7103
5	((Needles/ or exp Biopsy, Needle/) and (size* or sizing or ?gauge or ?gauges or 22G or 25G or 22-G or 25-G).ti,ab.) or (needle* adj3 (size* or sizing or ?gauge or ?gauges or 22G or 25G or 22-G or 25-G)).ti,ab.	12653
6	((Rapid adj (on-site or onsite or "on site")) or (rapid adj3 evaluation) or ((on-site or onsite or "on site") adj2 evaluation) or ROSE).tw,kf.	70570
7	Needles/ or (((standard* or core-biop* or type or histology* or cytology* or fnb or convention* or second-generation or new-generation*) adj2 needle*) or (needle* adj3 (random* or blind*)) or (fnb or biop*) or NCB or procore or pro-core or SharkCore or EchoTip or Forktip or Fork-Tip or fork-shaped or Franseen or Acquire or ((forward* or reverse*) adj3 bevel*adj needle*)).tw,kf.	630469
8	or/4-7	707897
9	3 and 8	3038
10	exp "sensitivity and specificity"/	630720
11	false negative reactions/ or false positive reactions/	39874
12	(sensitivity or specificity).ti,ab.	1144108
13	(predictive adj value$1).ti,ab.	14
14	(likelihood adj ratio$1).ti,ab.	17668
15	(false adj (negative$1 or positive$1)).ti,ab.	83840
16	(randomized controlled trial or controlled clinical trial).pt.	648637
17	double blind method/ or single blind method/	200664
18	practice guideline.pt.	29629
19	consensus development conference.pt.	12264
20	random$.ti,ab.	1291960
21	random allocation/	106611
22	(single blind$3 or double blind$3 or triple blind$3).ti,ab.	182181
23	(review or review academic).pt.	2939376
24	meta analysis.pt.	152986
25	(systematic adj review$).ti,ab. or (systematic* adj3 search*).ab.	254118
26	or/10-23	5824737
27	26 and (24 or 25)	229445
28	Randomized controlled trials as Topic/	152764
29	Randomized controlled trial/	558809
30	Random allocation/	106611
31	Double blind method/	170064
32	Single blind method/	31602
33	Clinical trial/	533843
34	exp Clinical Trials as Topic/	370454
35	or/28-34	1265757
36	(clinic$ adj trial$1).tw.	425628
37	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	186289
38	Placebos/	35885
39	Placebo$.tw.	232965
40	Randomly allocated.tw.	32901
41	(allocated adj2 random).tw.	808
42	or/36-41	712400
43	35 or 42	1582352
44	Case report.tw.	355205
45	Letter/	1170414
46	Historical article/	367659
47	Review of reported cases.pt.	0
48	Review, multicase.pt.	0
49	or/44-48	1875729
50	43 not 49	1544833
51	Epidemiologic studies/	9002
52	exp case control studies/	1285331
53	exp cohort studies/	2297303
54	Case control.tw.	140833
55	(cohort adj (study or studies)).tw.	262645
56	Cohort analy$.tw.	9984
57	(Follow up adj (study or studies)).tw.	52962
58	(observational adj (study or studies)).tw.	135176
59	Longitudinal.tw.	285367
60	Retrospective.tw.	642876
61	Cross sectional.tw.	435362
62	Cross-sectional studies/	411516
63	or/51-62	3453308
64	exp "Sensitivity and Specificity"/	630720
65	sensitivity.tw.	889761
66	specificity.tw.	509954
67	((pre-test or pretest) adj probability).tw.	2577
68	post-test probability.tw.	671
69	predictive value$.tw.	122718
70	likelihood ratio$.tw.	17717
71	or/64-70	1614186
72	27 or 50 or 63 or 71	5988642
73	9 and 72	1597
74	(addresses or biography or case reports or comment or directory or editorial or festschrift or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or popular works or congresses or consensus development conference or consensus development conference, nih).pt. or (exp animals/ not humans.sh.)	9332515
75	73 not 74	1508

Database: EMBASE.com (Elsevier).

Search date: February 17, 2022

Limits: RCTs, cohort/observational studies (prospective and retrospective), systematic reviews, meta-analyses, diagnostic studies

Search results: 1056

1	'pancreas tumor'/exp/dm_di OR 'chronic pancreatitis'/exp/dm_di OR ((pancreas OR pancreatic) NEAR/2 (cancer* OR malignan* OR lesion* OR mass OR masses OR tumor* OR tumour* OR nodule* OR neoplas* OR carcinoma* OR carcinogen* OR growth* OR adenocarcin*)):ti,ab,kw
2	'endoscopic ultrasonography'/de OR (endoscop* NEAR/2 (ultrasound OR ultrasonograph* OR ultrasonic)):ti,ab,kw OR EUS:ti,ab
3	#1 AND #2
4	'endoscopic ultrasound guided fine needle biopsy'/de OR (('needle biopsy'/de OR 'ultrasound guided fine needle aspiration'/de OR 'fine needle aspiration biopsy'/de) AND ('echography'/exp OR 'endoscopic ultrasonography'/exp OR echography:lnk) AND 'endoscopy'/de) OR (((endoscopic-ultrasound OR eus) NEAR/5 (sampl* OR biop* OR aspirat* OR collect* OR acquisit* OR procur*)) OR (eus NEAR/2 (fna OR fnb)) OR eusfna OR eusfnb OR eus-fna OR eus-fnb):ti,ab,kw
5	(('needle'/de OR 'biopsy needle'/exp) AND (size* OR sizing OR ?gauge OR ?gauges OR 22G OR 25G OR 22-G OR 25-G):ti,ab) OR (needle* NEAR/3 (size* OR sizing OR ?gauge OR ?gauges OR 22G OR 25G OR 22-G OR 25-G)):ti,ab
6	'rapid on site evaluation'/exp OR ('rapid on site evaluation' OR 'rapid on site cytologic evaluation' OR 'rapid onsite evaluation' OR 'rapid on-site evaluation' OR 'rapid onsite cytologic evaluation' OR 'rapid on-site cytologic evaluation'):ti,ab,kw OR (rose AND (biop* OR specimen OR sampl*)):ti,ab,kw
7	'needle'/de OR (((standard* OR core-biop* OR type OR histology* OR cytology* OR fnb OR convention* OR second-generation OR new-generation*) NEAR/2 needle*) OR (needle* NEAR/3 (random* OR blind*)) OR (fnb OR biop*) OR NCB OR procore OR pro-core OR SharkCore OR EchoTip OR Forktip OR Fork-Tip OR fork-shaped OR Franseen OR (Acquire AND needle) OR ((forward* OR reverse*) NEAR/3 bevel* NEAR needle*)):ti,ab,kw
8	#4 OR #5 OR #6 OR #7
9	#3 AND #8
10	('Clinical trial'/de OR 'Randomized controlled trial'/de OR 'Randomization'/de OR 'Single blind procedure'/de OR 'Double blind procedure'/de OR 'Crossover procedure'/de OR 'Placebo'/de OR Randomi?ed controlled trial*:ti,ab,kw OR Rct:ti,ab,kw OR Random allocation:ti,ab,kw OR Randomly allocated:ti,ab,kw OR Allocated randomly:ti,ab,kw OR (allocated NEAR/2 random):ti,ab,kw OR Single blind*:ti,ab,kw OR Double blind*:ti,ab,kw OR ((treble OR triple) NEAR (blind*)):ti,ab,kw OR Placebo*:ti,ab,kw OR 'Prospective study'/de) NOT ('Case study'/de OR Case report:ti,ab,kw OR 'Abstract report'/de or 'letter'/de) OR 'Clinical study'/de OR 'Case control study'/de OR 'Family study'/de OR 'Longitudinal study'/de OR 'Retrospective study'/de OR ('Prospective study'/de NOT 'Randomized controlled trials'/de) OR 'Cohort analysis'/de OR (Cohort NEAR (study OR studies)):ti,ab,kw OR ("Case control" NEAR (study OR studies)):ti,ab,kw OR ("follow up" NEAR (study OR studies)):ti,ab,kw OR (observational NEAR (study OR studies)):ti,ab,kw OR (epidemiologic* NEAR (study OR studies)):ti,ab,kw OR ("cross sectional" NEAR (study OR studies)):ti,ab,kw OR ('Meta Analysis'/exp OR ((meta NEAR analy*) OR metaanalys*):ti,ab,kw OR (systematic NEAR (review*1 OR overview*1)):ti,ab,kw OR cancerlit:ab OR Cochrane:ab OR Embase:ab OR (psychlit OR psyclit):ab OR (psychinfo OR psycinfo):ab OR (cinahl OR cinhal):ab OR science citation index:ab OR bids:ab OR reference lists:ab OR bibliograph*:ab OR hand-search*:ab OR manual search*:ab OR relevant journals:ab OR ((data extraction:ab OR selection criteria:ab) AND review:it) OR 'sensitivity and specificity'/exp OR (sensitivity OR specificity OR ((pre-test OR pretest) NEAR probability) OR post-test probability OR predictive value* OR likelihood ratio*):ti,ab,kw OR 'Diagnostic Accuracy'/de/mj) NOT (letter:it OR editorial:it OR ('animal'/de NOT ('animal'/de AND 'human'/de)))
11	#9 AND #10
12	([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim OR 'case report'/de OR 'review'/de) OR ((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de) OR ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))
13	#11 NOT #12
14	#13 AND [Embase]/lim

Database: Cochrane Library.

Search date: February 17, 2022

Limits: N/A

Search results: 535

1	[mh "Pancreatic Neoplasms"] OR [mh "Pancreatitis, Chronic"] OR ((pancreas OR pancreatic) NEAR/2 (cancer* OR malignan* OR lesion* OR mass OR masses OR tumor* OR tumour* OR nodule* OR neoplas* OR carcinoma* OR carcinogen* OR growth* OR adenocarcin*)):ti,ab,kw

2	[mh ˝"Endosonography"] OR (endoscop* NEAR/2 (ultrasound OR ultrasonograph* OR ultrasonic)):ti,ab,kw OR EUS:ti,ab	
3	#1 AND #2	
4	[mh ˝"Endoscopic Ultrasound-Guided Fine Needle Aspiration"] OR (([mh ˝"Biopsy, Fine-Needle"] OR [mh ˝"Biopsy, Needle"]) AND ([mh ˝"Ultrasonography"] OR [mh "Endosonography"]) and [mh ˝"Endoscopy"]) OR (((endoscopic-ultrasound OR eus) NEAR/5 (sampl* OR biop* OR aspirat* OR collect* OR acquisit* OR procur*)) OR (eus NEAR/2 (fna OR fnb)) OR eusfna OR eusfnb OR eus-fna OR eus-fnb).:ti,ab,kw	
5	(([mh ˝"Needles"] OR [mh "Biopsy, Needle"]) AND (size* OR sizing OR *gauge OR *gauges):ti,ab) OR (needle* NEAR/3 (size* OR sizing OR *gauge OR *gauges)):ti,ab	
6	((Rapid NEAR (on-site OR onsite OR "on site")) OR (rapid NEAR/3 evaluation) OR ((on-site OR onsite OR "on site") NEAR/2 evaluation) OR ROSE):ti,ab,kw	
7	[mh ˝"Needles"] OR (((standard* OR core-biop* OR type OR histology* OR cytology* OR fnb OR convention* OR second-generation OR new-generation*) NEAR/2 needle*) OR (needle* NEAR/3 (random* OR blind*)) OR (fnb OR biop*) OR NCB OR procore OR pro-core OR SharkCore OR EchoTip OR Forktip OR Fork-Tip OR fork-shaped OR Franseen OR Acquire OR ((forward* OR reverse*) NEAR/3 bevel* NEAR needle*)):ti,ab,kw	
8	#4 OR #5 OR #6 OR #7	
9	#3 AND #8	

Search strategies for PICO questions 5 and 6: ERCP stent placment for distal malignant biliary obstruction

Database: Ovid MEDLINE ALL.

Search date: February 18, 2022

Limits: RCTs, cohort/observational studies (prospective and retrospective), systematic reviews, meta-analyses

Search results: 643

1	exp Pancreatic Neoplasms/ or exp "Digestive System Neoplasms"/ or ((pancreas or pancreatic) adj3 (cancer* or malignan* or lesion* or mass or masses or tumor* or tumour* or nodule* or neoplas* or carcinoma* or carcinogen* or growth* or adenocarcin*)).tw,kf.	705965
2	exp bile ducts/ or exp biliary tract diseases/ or (bile duct* or biliary).tw,kf.	202386
3	exp constriction, pathologic/ or (constriction or stricture* or stenos?s or obstruction or occlusion or blockage).tw,kf.	542020
4	2 and 3	23145
5	exp cholestasis/ or cholestasis.tw,kf. or ((bile duct* or biliary or anastomotic or non-anastomic or nonanastomic) adj2 (stricture* or obstruction or occlusion or stenos?s or blockage)).tw,kf. or exp jaundice, obstructive/ or (jaundice adj3 obstruct*).tw,kf.	57429
6	4 or 5	65261
7	1 and 6	11994
8	exp Cholangiopancreatography, Endoscopic Retrograde/ or "Endoscopy, Gastrointestinal"/ or exp Drainage/ or exp Suction/ or (ERCP or ERCPs).tw,kf. or (endoscop* adj2 retrograd* adj2 (cholangiopancreatograph* or cholangio-pancreatograph*)).tw,kf. or endoscop*.tw,kf,jn,so. or (drain* or suction* or aspirate* or aspiration*).tw,kf.	523353
9	exp Stents/ or exp Catheters/ or exp Catheterization/	280344
10	(stent* or (catheter* or cannula* or tube* or pipe* or "SEMS") or (pancreatic duct* adj5 holder*) or (SEM or SEMTs or SEM or SEMs or FCSEMS)).tw,kf.	1060078
11	9 or 10	1171299
12	(metals or plastics).nm. or exp metals/ or exp plastics/ or metal*.ti,ab. or plastic*.ti,ab. or exp Coated Materials, Biocompatible/ or (covered or uncovered or un-covered or coated or un-coated or uncoated).ti,ab.	2119235
13	9 and 11 and 12	28272
14	7 and 13	1191
15	exp "sensitivity and specificity"/	630832
16	false negative reactions/ or false positive reactions/	39874
17	(sensitivity or specificity).ti,ab.	1144285
18	(predictive adj value$1).ti,ab.	122636
19	(likelihood adj ratio$1).ti,ab.	17677
20	(false adj (negative$1 or positive$1)).ti,ab.	83851
21	(randomized controlled trial or controlled clinical trial).pt.	648768
22	double blind method/ or single blind method/	200699
23	practice guideline.pt.	29631
24	consensus development conference.pt.	12266
25	random$.ti,ab.	1292267
26	random allocation/	106612
27	(single blind$3 or double blind$3 or triple blind$3).ti,ab.	182204
28	(review or review academic).pt.	2939869
29	meta analysis.pt.	153067
30	(systematic adj review$).ti,ab. or (systematic* adj3 search*).ab.	254233
31	or/15-28	5856028
32	31 and (29 or 30)	229886
33	Randomized controlled trials as Topic/	152808
34	Randomized controlled trial/	558939
35	Random allocation/	106612
36	Double blind method/	170096
37	Single blind method/	31605
38	Clinical trial/	533881
39	exp Clinical Trials as Topic/	370519
40	or/33-39	1265993
41	(clinic$ adj trial$1).tw.	425735
42	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	186312
43	Placebos/	35886
44	Placebo$.tw.	232990
45	Randomly allocated.tw.	32914
46	(allocated adj2 random).tw.	808
47	or/41-46	712545
48	40 or 47	1582631
49	Case report.tw.	355292
50	Letter/	1170519
51	Historical article/	367682
52	Review of reported cases.pt.	0
53	Review, multicase.pt.	0
54	or/49-53	1875942
55	48 not 54	1545109
56	Epidemiologic studies/	9002
57	exp case control studies/	1285757
58	exp cohort studies/	2297885
59	Case control.tw.	140857
60	(cohort adj (study or studies)).tw.	262762
61	Cohort analy$.tw.	9987
62	(Follow up adj (study or studies)).tw.	52968
63	(observational adj (study or studies)).tw.	135236
64	Longitudinal.tw.	285439
65	Retrospective.tw.	643102

66	Cross sectional.tw.	435513
67	Cross-sectional studies/	411707
68	or/56-67	3454203
69	32 or 55 or 68	4783973
70	14 and 69	643

Database: EMBASE.com (Elsevier).
Search date: February 18, 2022

Limits: RCTs, cohort/observational studies (prospective and retrospective), systematic reviews, meta-analyses

Search results: 240

1	'pancreas tumor'/exp OR ((pancreas OR pancreatic) NEAR/3 (cancer* OR malignan* OR lesion* OR mass OR masses OR tumor* OR tumour* OR nodule* OR neoplas* OR carcinoma* OR carcinogen* OR growth* OR adenocarcin*)):ti,ab,kw
2	'bile duct'/exp OR 'biliary tract disease'/exp OR (bile duct* OR biliary):ti,ab,kw
3	'stenosis, occlusion and obstruction'/exp OR (constriction OR stricture* OR stenos?s OR obstruction OR occlusion OR blockage):ti,ab,kw
4	#2 AND #3
5	'cholestasis'/exp OR cholestasis:ti,ab,kw OR ((“bile duct*” OR biliary OR anastomotic OR non-anastomic OR nonanastomic) NEAR/2 (stricture* OR obstruction OR occlusion OR stenos?s OR blockage)):ti,ab,kw OR 'obstructive jaundice'/exp OR (jaundice NEAR/3 obstruct*):ti,ab,kw
6	#4 OR #5
7	#1 AND #6
8	'endoscopic retrograde cholangiopancreatography'/exp OR 'gastrointestinal endoscopy'/de OR 'drainage'/exp OR 'suction'/exp OR (ERCP OR ERCPs):ti,ab,kw OR (endoscop* NEAR/2 retrograd* NEAR/2 (cholangiopancreatograph* OR cholangio-pancreatograph*)):ti,ab,kw OR endoscop*:ti,ab,kw,jt OR (drain* OR suction* OR aspirate* OR aspiration*):ti,ab,kw
9	'stent'/exp OR 'catheter'/exp OR 'catheterization'/exp
10	(stent* OR (catheter* OR cannula* OR tube* OR pipe* OR "SEMS") OR (pancreatic duct* NEAR/5 holder*) OR (SEM OR SEMTs OR SEM OR SEMs OR FCSEMS)):ti,ab,kw
11	#9 OR #10
12	(metals OR plastics):tn OR 'metal'/exp OR metal*:ti,ab,kw OR plastic*:ti,ab,kw OR 'biocompatible coated material'/exp OR (covered OR uncovered OR un-covered OR coated OR un-coated OR uncoated):ti,ab,kw
13	#9 AND #11 AND #12
14	#7 AND #13
15	('Clinical trial'/de OR 'Randomized controlled trial'/de OR 'Randomization'/de OR 'Single blind procedure'/de OR 'Double blind procedure'/de OR 'Crossover procedure'/de OR 'Placebo'/de OR Randomi?ed controlled trial*:ti,ab,kw OR Rct:ti,ab,kw OR Random allocation:ti,ab,kw OR Randomly allocated:ti,ab,kw OR Allocated randomly:ti,ab,kw OR (allocated NEAR/2 random):ti,ab,kw OR Single blind*:ti,ab,kw OR Double blind*:ti,ab,kw OR ((treble OR triple) NEAR (blind*)):ti,ab,kw OR Placebo*:ti,ab,kw OR 'Prospective study'/de) NOT ('Case study'/de OR Case report:ti,ab,kw OR 'Abstract report'/de or 'letter'/de) OR 'Clinical study'/de OR 'Case control study'/de OR 'Family study'/de OR 'Longitudinal study'/de OR 'Retrospective study'/de OR ('Prospective study'/de NOT 'Randomized controlled trials'/de) OR 'Cohort analysis'/de OR (Cohort NEAR (study OR studies)):ti,ab,kw OR ("Case control" NEAR (study OR studies)):ti,ab,kw OR ("follow up" NEAR (study OR studies)):ti,ab,kw OR (observational NEAR (study OR studies)):ti,ab,kw OR (epidemiologic* NEAR (study OR studies)):ti,ab,kw OR ("cross sectional" NEAR (study OR studies)):ti,ab,kw OR ('Meta Analysis'/exp OR ((meta NEAR analy*) OR metaanalys*):ti,ab,kw OR (systematic NEAR (review*1 OR overview*1)):ti,ab,kw OR cancerlit:ab OR Cochrane:ab OR Embase:ab OR (psychlit OR psyclit):ab OR (psychinfo OR psycinfo):ab OR (cinahl OR cinhal):ab OR science citation index:ab OR bids:ab OR reference lists:ab OR bibliograph*:ab OR hand-search*:ab OR manual search*:ab OR relevant journals:ab OR ((data extraction:ab OR selection criteria:ab) AND review:it) OR 'sensitivity and specificity'/exp OR (sensitivity OR specificity OR ((pre-test OR pretest) NEAR probability) OR post-test probability OR predictive value* OR likelihood ratio*):ti,ab,kw OR 'Diagnostic Accuracy'/de/mj) NOT (letter:it OR editorial:it OR ('animal'/de NOT ('animal'/de AND 'human'/de)))
16	#14 AND #15
17	([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim OR 'case report'/de OR 'review'/de) OR ((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout: ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de) OR ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))
18	#16 NOT #17
19	#18 AND [Embase]/lim

Database: Cochrane Library (Wiley). Search date: February 18, 2022

Limits: N/A

Search results: 101

1	[mh “Pancreatic Neoplasms”] OR [mh "Digestive System Neoplasms"] OR ((pancreas OR pancreatic) NEAR/3 (cancer* OR malignan* OR lesion* OR mass OR masses OR tumor* OR tumour* OR nodule* OR neoplas* OR carcinoma* OR carcinogen* OR growth* OR adenocarcin*)):ti,ab,kw

2	[mh "bile ducts"] OR [mh "biliary tract diseases"] OR (bile duct* OR biliary):ti,ab,kw	
3	[mh "constriction, pathologic"] OR (constriction OR stricture* OR stenos?s OR obstruction OR occlusion OR blockage):ti,ab,kw	
4	#2 AND #3	
5	[mh cholestasis] OR cholestasis:ti,ab,kw OR ((bile duct* OR biliary OR anastomotic OR non-anastomic OR nonanastomic) NEAR/2 (stricture* OR obstruction OR occlusion OR stenos?s OR blockage)):ti,ab,kw OR [mh "jaundice, obstructive"] OR (jaundice NEAR/3 obstruct*):ti,ab,kw	
6	#4 OR #5	
7	#1 AND #6	
8	[mh "Cholangiopancreatography, Endoscopic Retrograde"] OR [mh "Endoscopy, Gastrointestinal"] OR [mh Drainage] OR [mh Suction] OR (ERCP OR ERCPs):ti,ab,kw OR (endoscop* NEAR/2 retrograd* NEAR/2 (cholangiopancreatograph* OR cholangio-pancreatograph*)):ti,ab,kw OR endoscop*:ti,ab,kw OR (drain* OR suction* OR aspirate* OR aspiration*):ti,ab,kw	
9	[mh Stents] OR [mh Catheters] OR [mh Catheterization]	
10	(stent* OR (catheter* OR cannula* OR tube* OR pipe* OR "SEMS") OR (pancreatic duct* NEAR/5 holder*) OR (SEM OR SEMTs OR SEM OR SEMs OR FCSEMS)):ti,ab,kw	
11	#9 OR #10	
12	[mh metals] OR [mh plastics] OR metal*:ti,ab,kw OR plastic*:ti,ab,kw OR [mh "Coated Materials, Biocompatible"] OR (covered OR uncovered OR un-covered OR coated OR un-coated OR uncoated):ti,ab,kw	
13	#9 AND #11 AND #12	
14	#7 AND #13	

Search strategies for PICO question 7: celiac plexus neurolysis for pancreatic cancer–related abdominal pain

Database: Ovid MEDLINE.

Search date: February 17, 2022

Limits: RCTs, cohort/observational studies (prospective and retrospective), systematic reviews, meta-analyses, comparative studies

Search results: 157

1	exp Pancreatic Neoplasms/ or "Digestive System Neoplasms"/ or ((pancreas or pancreatic) adj3 (cancer* or malignan* or lesion* or mass or masses or tumor* or tumour* or nodule* or neoplas* or carcinoma* or carcinogen* or growth* or abscess* or adenocarcin*)).tw,kf. or pdac.tw,kf.	119559
2	exp Ganglia/ or celiac plexus/ or ("celiac plexus" or "coeliac plexus" or ganglia or ganglion).tw,kf.	139253
3	exp nerve block/ or (neurolysis or "nerve block$" or block?).tw,kf.	366652
4	2 and 3	6319
5	((("celiac plexus" or ganglia or ganglion) adj5 block$) or (("coeliac plexus" or ganglia or ganglion) adj5 block$)).tw,kf.	4084
6	NCPB.ti,ab.	58
7	("neurolytic sympathetic plexus" adj5 block$).tw,kf.	2
8	or/4-7	8003
9	1 and 8	392
10	exp "sensitivity and specificity"/	630720
11	false negative reactions/ or false positive reactions/	39874
12	(sensitivity or specificity).ti,ab.	1144108
13	(predictive adj value$1).ti,ab.	14
14	(likelihood adj ratio$1).ti,ab.	17668
15	(false adj (negative$1 or positive$1)).ti,ab.	83840
16	(randomized controlled trial or controlled clinical trial).pt.	648637
17	double blind method/ or single blind method/	200664
18	practice guideline.pt.	29629
19	consensus development conference.pt.	12264
20	random$.ti,ab.	1291960
21	random allocation/	106611
22	(single blind$3 or double blind$3 or triple blind$3).ti,ab.	182181
23	(review or review academic).pt.	2939376
24	meta analysis.pt.	152986
25	(systematic adj review$).ti,ab. or (systematic* adj3 search*).ab.	254118
26	or/10-23	5824737
27	26 and (24 or 25)	229445
28	Randomized controlled trials as Topic/	152764
29	Randomized controlled trial/	558809
30	Random allocation/	106611
31	Double blind method/	170064
32	Single blind method/	31602
33	Clinical trial/	533843
34	exp Clinical Trials as Topic/	370454
35	or/28-34	1265757
36	(clinic$ adj trial$1).tw.	425628
37	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	186289
38	Placebos/	35885
39	Placebo$.tw.	232965
40	Randomly allocated.tw.	32901
41	(allocated adj2 random).tw.	808
42	or/36-41	712400
43	35 or 42	1582352
44	Case report.tw.	355205
45	Letter/	1170414
46	Historical article/	367659
47	Review of reported cases.pt.	0
48	Review, multicase.pt.	0
49	or/44-48	1875729
50	43 not 49	1544833
51	Epidemiologic studies/	9002
52	exp case control studies/	1285331
53	exp cohort studies/	2297303
54	Case control.tw.	140833
55	(cohort adj (study or studies)).tw.	262645
56	Cohort analy$.tw.	9984
57	(Follow up adj (study or studies)).tw.	52962
58	(observational adj (study or studies)).tw.	135176
59	Longitudinal.tw.	285367
60	Retrospective.tw.	642876
61	Cross sectional.tw.	435362
62	Cross-sectional studies/	411516
63	or/51-62	3453308
64	"Comparative Study"/ or "Comparative Effectiveness Research"/ or "random allocation"/ or (compar* or vs or versus or random* or ((double or single) adj3 blind*) or ((choice or chose or choose) adj3 therap*)).ab,ti.	8125256
65	27 or 50 or 63 or 64	10333035
66	(addresses or biography or case reports or comment or directory or editorial or festschrift or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or popular works or congresses or consensus development conference or consensus development conference, nih).pt. or (exp animals/ not humans.sh.)	9332515
67	65 not 66	8464421
68	9 and 67	157

Database: EMBASE.com (Elsevier).

Search date: February 17, 2022

Limits: RCTs, cohort/observational studies (prospective and retrospective), systematic reviews, meta-analyses, comparative studies

Search results: 106

1	'pancreas tumor'/exp OR ((pancreas OR pancreatic) NEAR/3 (cancer* OR malignan* OR lesion* OR mass OR masses OR tumor* OR tumour* OR nodule* OR neoplas* OR carcinoma* OR carcinogen* OR growth* OR adenocarcin*)):ti,ab,kw OR pdac:ti,ab,kw
2	'ganglion'/exp OR 'celiac plexus'/exp OR ("celiac plexus" OR "coeliac plexus" OR ganglia OR ganglion):ti,ab,kw
3	'nerve block'/exp OR (neurolysis OR "nerve block$" OR block?):ti,ab,kw
4	#2 AND #3
5	((("celiac plexus" OR ganglia OR ganglion) NEAR/5 block$) OR (("coeliac plexus" OR ganglia OR ganglion) NEAR/5 block$)):ti,ab,kw
6	NCPB:ti,ab
7	("neurolytic sympathetic plexus" NEAR/5 block$):ti,ab,kw
8	#4 OR #5 OR #6 OR #7
9	#1 AND #8
10	('Clinical trial'/de OR 'Randomized controlled trial'/de OR 'Randomization'/de OR 'Single blind procedure'/de OR 'Double blind procedure'/de OR 'Crossover procedure'/de OR 'Placebo'/de OR Randomi?ed controlled trial*:ti,ab,kw OR Rct:ti,ab,kw OR Random allocation:ti,ab,kw OR Randomly allocated:ti,ab,kw OR Allocated randomly:ti,ab,kw OR (allocated NEAR/2 random):ti,ab,kw OR Single blind*:ti,ab,kw OR Double blind*:ti,ab,kw OR ((treble OR triple) NEAR (blind*)):ti,ab,kw OR Placebo*:ti,ab,kw OR 'Prospective study'/de) NOT ('Case study'/de OR Case report:ti,ab,kw OR 'Abstract report'/de or 'letter'/de) OR 'Clinical study'/de OR 'Case control study'/de OR 'Family study'/de OR 'Longitudinal study'/de OR 'Retrospective study'/de OR ('Prospective study'/de NOT 'Randomized controlled trials'/de) OR 'Cohort analysis'/de OR (Cohort NEAR (study OR studies)):ti,ab,kw OR ("Case control" NEAR (study OR studies)):ti,ab,kw OR ("follow up" NEAR (study OR studies)):ti,ab,kw OR (observational NEAR (study OR studies)):ti,ab,kw OR (epidemiologic* NEAR (study OR studies)):ti,ab,kw OR ("cross sectional" NEAR (study OR studies)):ti,ab,kw OR ('Meta Analysis'/exp OR ((meta NEAR analy*) OR metaanalys*):ti,ab,kw OR (systematic NEAR (review*1 OR overview*1)):ti,ab,kw OR cancerlit:ab OR Cochrane:ab OR Embase:ab OR (psychlit OR psyclit):ab OR (psychinfo OR psycinfo):ab OR (cinahl OR cinhal):ab OR science citation index:ab OR bids:ab OR reference lists:ab OR bibliograph*:ab OR hand-search*:ab OR manual search*:ab OR relevant journals:ab OR ((data extraction:ab OR selection criteria:ab) AND review:it) OR 'comparative study'/de OR 'comparative effectiveness'/de OR 'randomization'/de OR (compar* OR vs OR versus OR random* OR ((double OR single) NEAR/3 blind*) OR ((choice OR chose OR choose) NEAR/3 therap*)):ti,ab) NOT (letter:it OR editorial:it OR ('animal'/de NOT ('animal'/de AND 'human'/de)))
11	#9 AND #10
12	([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim OR 'case report'/de OR 'review'/de) OR ((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de) OR ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))
13	#11 NOT #12
14	#13 AND [Embase]/lim

Database: Cochrane Library (Wiley).

Search date: February 17, 2022

Limits: N/A

Search results: 77

1	[mh "Pancreatic Neoplasms"] OR [mh "Digestive System Neoplasms"] OR ((pancreas OR pancreatic) NEAR/3 (cancer* OR malignan* OR lesion* OR mass OR masses OR tumor* OR tumour* OR nodule* OR neoplas* OR carcinoma* OR carcinogen* OR growth* OR adenocarcin*)):ti,ab,kw OR pdac:ti,ab,kw
2	[mh Ganglia] OR [mh "celiac plexus"] OR ("celiac plexus" OR "coeliac plexus" OR ganglia OR ganglion):ti,ab,kw
3	[mh "nerve block"] OR (neurolysis OR "nerve block$" OR block?):ti,ab,kw
4	#2 AND #3
5	((("celiac plexus" OR ganglia OR ganglion) NEAR/5 block$) OR (("coeliac plexus" OR ganglia OR ganglion) NEAR/5 block$)):ti,ab,kw
6	NCPB:ti,ab
7	("neurolytic sympathetic plexus" NEAR/5 block$):ti,ab,kw
8	#4 OR #5 OR #6 OR #7
9	#1 AND #8