Comparative accuracy of needle sizes and designs for EUS tissue sampling of solid pancreatic masses: a network meta-analysis

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Background and Aims: Variable diagnostic performance of sampling techniques during EUS-guided tissue acquisition of solid pancreatic masses based on needle type (FNA versus fine-needle biopsy [FNB]) and gauge (19-gauge vs 22-gauge vs 25-gauge) has been reported. We performed a systematic review with network meta-analysis to compare the diagnostic accuracy of EUS-guided techniques for sampling solid pancreatic masses.

Methods: Through a systematic literature review to November 2018, we identified 27 randomized controlled trials (2711 patients) involving adults undergoing EUS-guided sampling of solid pancreatic masses that evaluated the diagnostic performance of FNA and FNB needles based on needle gauge. The primary outcome was diagnostic accuracy. Secondary outcomes were sample adequacy, histologic core procurement rate, and number of needle passes. We performed pairwise and network meta-analyses and appraised the quality of evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology.

Results: In the network meta-analysis, no specific EUS-guided tissue sampling technique was superior, based on needle type (FNA vs FNB) or gauge (19-gauge vs 22-gauge vs 25-gauge) (low-quality evidence). Specifically, there was no difference between 25-gauge FNA versus 22-gauge FNA (relative risk [RR], 1.03; 95% confidence interval [CI], 0.91-1.17) and 22-gauge FNB versus 22-gauge FNA (RR, 1.03; 95% CI, 0.89-1.18) needles for diagnostic accuracy, sample adequacy, and histologic core procurement. Findings were confirmed in sensitivity analysis restricted to studies with no rapid on-site cytologic evaluation and no use of the fanning technique.

Conclusion: In a network meta-analysis, no specific EUS-guided tissue sampling technique was superior with regard to diagnostic accuracy, sample adequacy, or histologic procurement rate for solid pancreatic masses, with low confidence in estimates.

INTRODUCTION

EUS-guided tissue acquisition (EUS-TA) for cytology through FNA or fine-needle biopsy (FNB) using specialized core needles has become a central technique in the assessment of pancreatic masses.[1] However, EUS-TA is a multistep process involving several factors that determine procedural outcomes, with a wide variation in reported outcomes for diagnostic sensitivity in pancreatic masses, ranging from 78% to 100%.[2] Thus, the most important pitfall associated with this procedure is a false-negative diagnosis, which has the potential to delay patient care and have a negative impact on patient outcomes.

Several variables that may potentially affect the diagnostic characteristics of EUS-TA (use of suction, stylet, fanning technique, use of rapid on-site cytopathology evaluation [ROSE], and endosonographer training and volume) have been investigated in previous studies.[3-6] However, the 2 variables that have garnered the most attention are the type of needle (FNA and FNB) and needle gauge (19-gauge vs 22-gauge vs 25-gauge). Although there is no standard definition of FNB, and different FNB needle designs have been described reporting variable success rates,[7] obtaining histologic specimens or core biopsies using EUS-FNB has generated a great deal of interest in the field of EUS-TA. This aspect is of interest given the potential advantages of improving diagnostic performance, assessing tissue architecture, and allowing for immunohistochemistry (required for diagnoses such as autoimmune pancreatitis, lymphoma, metastasis, etc).

Two recent pairwise meta-analyses reached the conclusion that EUS-FNB needles show comparable diagnostic accuracy and sample adequacy in comparison with EUS-FNA but with the need for a lower number of passes.[8,9] Furthermore, 2 newer FNB needles were introduced recently in clinical endoscopic practice: one with fork-tip design (SharkCore, Medtronic, Minneapolis, Minn, USA), and another with Franseen tip design (Acquire, Boston Scientific, Natick, Mass, USA). Based on the theoretical advantages of these newer needles, designed to improve tissue capture due to the higher number of cutting edges, widespread use of these expensive devices was noted despite the lack of robust comparative data and the low-quality evidence derived mainly from single-cohort or retrospective studies.

Therefore, there are currently limited data on the comparative diagnostic performance of different EUS-TA techniques, based on needle design and gauge, for pancreatic masses. In addition, there is no systematic assessment of the quality of evidence, which can inform clinical guidelines. In contrast to pairwise meta-analyses, network meta-analysis can inform the comparative effectiveness of multiple interventions and synthesize evidence across a network of randomized controlled trials (RCTs).[10] This method involves the simultaneous analysis of direct evidence (from RCTs directly comparing diagnostic modalities of interest) and indirect evidence (from RCTs comparing diagnostic modalities of interest with a common comparator) to calculate a mixed effect estimate as the weighted average of the two. In comparative effectiveness research, this approach can produce strong evidence against the null hypothesis more often and earlier than conventional, pairwise meta-analyses.[11] Such a systematic and comparative synthesis of the entire body of evidence, with critical appraisal of the quality of evidence, can directly and optimally inform clinical practice guidelines.[12-15]

We performed pairwise and network meta-analysis comparing the diagnostic accuracy of EUS-FNA (22-gauge, 25-gauge, 19-gauge) and EUS-FNB (22-gauge, 25-gauge) needles for pancreatic masses. Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for network meta-analysis were used to appraise the quality of evidence.[16]

METHODS

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and was conducted following an a priori established protocol.[17]

Inclusion and exclusion criteria

Our focused question on the comparative diagnostic accuracy of different EUS-TA techniques for solid pancreatic masses was transformed into Patient, Intervention, Comparator, Outcomes (PICO) format. Studies included in this meta-analysis were parallel or cross-over RCTs, published either as full text or in conference proceedings, that met the following inclusion criteria: (1) patients: adults with solid pancreatic masses who underwent EUS-TA, using (2) intervention: EUS-FNA needles (22-gauge, 25-gauge, 19-gauge), or FNB needles (22-gauge core biopsy needle [ProCore, Cook Medical, Bloomington, Ind, USA], 22-gauge Franseen biopsy needle [Acquire], 22-gauge Fork-Tip biopsy needle [SharkCore], 25-gauge), (3) comparator: compared with each other, and reported (4) outcomes: diagnostic accuracy.

We excluded (1) observational studies, (2) trials reporting the performance of different needles for extrapancreatic masses, (3) trials conducted with needles not currently in use in clinical practice, (4) trials not reporting diagnostic accuracy or sample adequacy of techniques, (5) trials not reporting data stratified by needle size, and (6) studies comparing different sampling techniques with the same needle (eg, based on different aspiration volumes or use of ROSE).

Search strategy

Supplementary Table 1 (available online at www.giejournal.org) reports the search strategy followed in the meta-analysis. A computerized bibliographic search was performed on PubMed/Medline, Scopus, and Web of Science on November 1, 2018, without language restriction. The search was supplemented by checking the references of key review articles on this topic. Two investigators (A.F., S.S.) independently selected articles of interest based on the inclusion and exclusion criteria. In cases of multiple publications from the same study, only the most recent and complete article was included.

Data abstraction and risk of bias assessment

Data on study-, participant-, and intervention-related characteristics were abstracted onto a standardized form by 2 sets of investigators (A.F., G.T., K.T., N.M., R.C.) independently; discrepancies were resolved by consensus, referring back to the original article, in consultation with a third reviewer (S.S.). The quality of the included studies was assessed by 2 authors independently (A.F., S.S.) according to the Cochrane Collaboration's tool for assessing the risk of bias.[18]

Outcomes

The primary outcome of interest was diagnostic accuracy, defined as (true positive + true negative) divided by the total number of patients. Secondary outcomes included sample adequacy (defined as the proportion of patients deemed to have adequate samples), histologic core procurement, number of needle passes, pooled sensitivity (defined as true positive/[true positive + false negative]) and specificity (defined as true negative/[true negative + false positive]), and safety of techniques (rate of serious adverse events).

Statistical analysis

For categorical outcomes (diagnostic accuracy, sample adequacy, histologic core procurement), we reported pooled estimates as the relative risk (RR) and 95% confidence interval (CI), and for continuous outcomes (number of needle passes), we reported pooled estimates as the weighted mean difference along with their respective 95% CI, using DerSimonian and Laird's random effects approach.[19] Sensitivity and specificity were also pooled using the random effects model by DerSimonian and Laird. Safety data were inconsistently reported and were synthesized qualitatively. We assessed statistical heterogeneity using the I^2 statistic, with values over 50% indicating substantial heterogeneity. Small-study effects were assessed by examining funnel plot asymmetry. All pairwise meta-analyses were performed using RevMan v5.3 (Cochrane Collaboration, Copenhagen, Denmark).

We then conducted network meta-analysis for diagnostic accuracy and sample adequacy using a multivariate random effects meta-regression and through a frequentist approach based on a random effects consistency model and provided a point estimate (RR) from the network along with 95% CI from the frequency distribution of the estimate.[20] Network consistency was evaluated by comparing the direct estimates with the indirect estimates for each comparison, using a node-splitting technique. Network meta-analysis was conducted with the R package *netmeta* (Foundation for Statistical Computing, Vienna, Austria).

Multiple sensitivity analyses were performed to assess the robustness of our findings for the primary outcome. These were based on (1) restricting the analysis to studies conducted in the absence of ROSE, (2) exclusion of studies using the fanning technique, (3) exclusion of cross-over trials, (4) analysis considering different designs of 22-gauge FNB needle, (5) lesion location (head/uncinate vs body/tail), and (6) target lesion (pancreatic adenocarcinoma vs other disease).

Quality of evidence

Quality of evidence for the primary outcome (diagnostic accuracy) derived from pairwise and network meta-analysis was judged using the GRADE framework (see Supplementary Table 2, available online at www.giejournal.org).[16] Briefly, evidence from RCTs started at high quality and was rated down for the presence of any of the following factors: risk of bias in the body of literature, inconsistency, indirectness, imprecision, and publication bias. Quality of indirect estimates was initially derived from the lowest quality of first-order loops for direct estimates contributing to the indirect estimates. The quality of the estimate from network meta-analysis was derived from the quality of the combination of direct and indirect estimates and transitivity of trials. When moderate- to high-quality evidence was available from direct pairwise estimates, it was used preferentially; when pairwise estimates provided only low or very low quality evidence or if there were no pairwise comparisons, then estimates from network meta-analysis were used to rate the quality of evidence.

RESULTS

Characteristics of the studies

From 3298 unique studies identified using our search strategy, 27 RCTs (2711 patients) were included for quantitative synthesis (Fig. 1). Eight RCTs compared 25-gauge FNA versus 22-gauge FNA,[21-28] 11 trials compared 22-gauge FNB versus 22-gauge FNA,[29-39] 2 trials compared 22-gauge FNA versus 19-gauge FNA,[40,41] 1 trial compared 25-gauge FNB versus 22-gauge FNA,[42] 1 trial compared 25-gauge FNB versus 25-gauge FNA,[43] 2 trials compared 25-gauge FNB versus 22-gauge FNB,[44,45] 1 trial compared 2 different 22-gauge FNB needles (Franseen vs Fork-Tip),[46] and 1 trial compared 22-gauge FNB (Fork-Tip) versus 25-gauge FNA.[47] Figure 2 shows the direct comparisons and network of the trials.

The main characteristics of the RCTs are reported in Table 1. The recruitment period ranged from 2007 to 2018. Fifteen RCTs[21-23,26-30,32,35,37,40,41,43,45] were parallel trials and 12[24,25,31,33,34,36,38,39,42,44,46,47] were cross-over studies (ie, the same lesion was sampled using both interventions in a randomized order). Nine RCTs were conducted in Asia.[26,31,34-36,41,43-45] ROSE was available in 11 studies, mainly conducted in the United States.[21-25,27,30,31,37,46,47] The FNB needle was a ProCore needle in all studies except 3 RCTs[31,46,47] where Acquire and SharkCore needles were used.

Risk of bias assessment was performed in the context of the primary outcome, and overall, the studies were thought to be at moderate risk of bias, mainly due to performance bias related to the unblinded design of the included RCTs. Two abstracts[33,47] and 13 full-text papers[22-28,32,36-38,41,42] were considered to have a high risk of bias due to incomplete outcome reporting. Overall and study-level quality assessments are summarized in

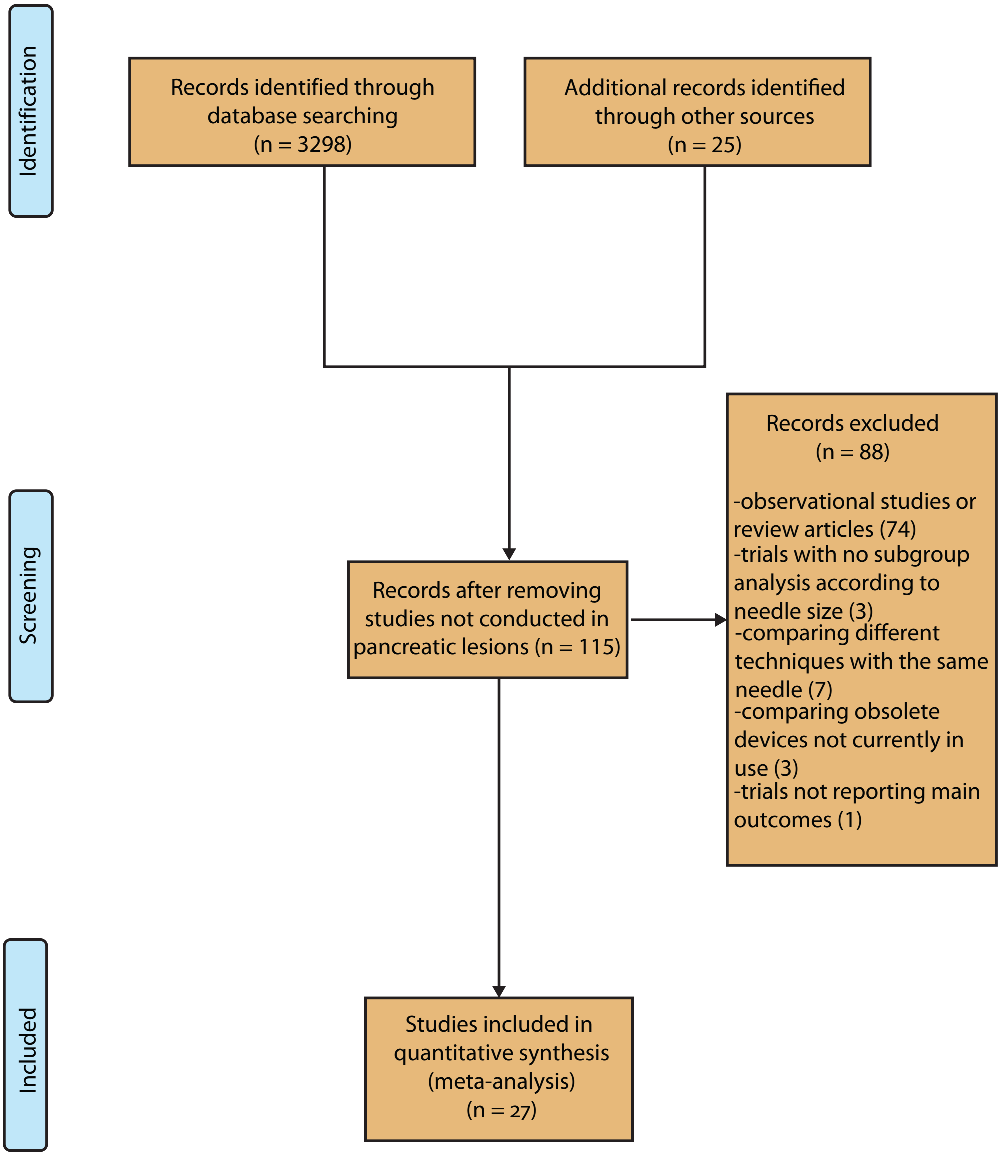

Figure 1. Flowchart of the studies.

Supplementary Figures 1A and B (available online at www.giejournal.org), respectively.

Primary outcome

Diagnostic accuracy. As depicted in Figure 3, where available, pairwise meta-analyses failed to demonstrate superiority in diagnostic accuracy of any approach over another in head-to-head randomized trials. Specifically, there was no difference in the diagnostic accuracy between the 25-gauge versus 22-gauge FNA approach (RR, 1.03; 95% CI, 0.98-1.07) or between the 22-gauge FNB versus 22-gauge FNA approach (RR, 1.02; 95% CI, 0.97-1.08). Similar results were noted in a pairwise comparison between the 22-gauge FNA versus 19-gauge FNA approach (RR, 1.07; 95% CI, 0.78-1.46). No significant difference was observed between the two 22-gauge FNB needles (Fork-Tip vs Franseen: RR, 0.96; 95% CI, 0.87-1.06). A low to moderate level of heterogeneity was noted in this analysis (I^2 = 16%-32%).

When combining direct and indirect evidence through network meta-analysis and evaluating the entire body of evidence, no specific EUS-TA approach had higher diagnostic accuracy than others. Table 2 and Supplementary Table 3 (available online at www.giejournal.org) provide the results of all comparisons. Specifically, there was no difference between 25-gauge FNA versus 22-gauge FNA needles (RR, 1.03; 95% CI, 0.91-1.17) and 25-gauge FNB versus 22-gauge FNA needles (RR, 1.09; 95% CI, 0.85-1.39). Similarly, there was no difference between 22-gauge FNB versus 22-gauge FNA needles (RR, 1.03; 95% CI, 0.89-1.18) and 25-gauge FNB versus 25-gauge FNA needles (RR, 1.05; 95% CI, 0.82-1.33).

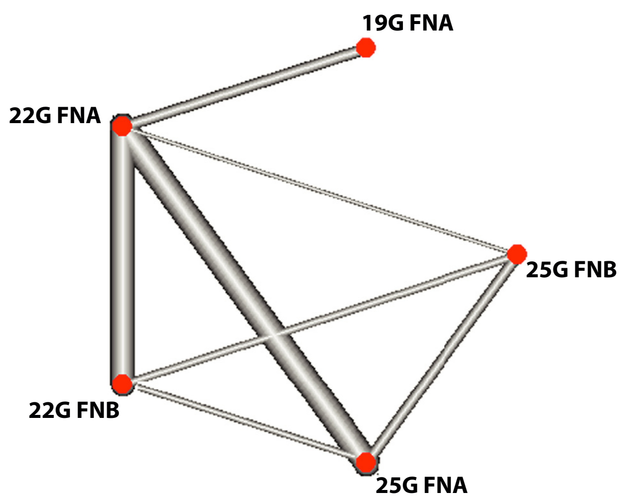

Figure 2. Network geometry of the trials. Network of the studies with the available direct comparisons between needles for EUS-guided sampling of pancreatic lesions. The size of the nodes and the thickness of the edges are weighted according to the number of studies evaluating each treatment and direct comparison, respectively.

Secondary outcomes

Sample adequacy. Forest plots for comparison of sample adequacy are reported in Supplementary Figure 2 (available online at www.giejournal.org). On pairwise meta-analysis, a significant difference between 25-gauge FNA and 22-gauge FNB needles was registered (RR, 0.79; 95% CI, 0.68-0.92), whereas a 22-gauge FNA needle was more likely to provide an adequate sample compared with a 19-gauge FNA needle (RR, 1.13; 95% CI, 1.00-1.28); no significant difference was found in any of the other direct comparisons. Low to moderate evidence of heterogeneity was observed (I^2 = 19%-47%). On network meta-analysis, none of the needles tested was superior in obtaining an adequate sample (Table 2 and Supplementary Table 3).

Optimal histologic core procurement. On pairwise meta-analyses, the histologic core procurement rate was comparable for different needles where head-to-head comparisons were available (Supplementary Fig. 3, available online at www.giejournal.org), except in 2 RCTs in which 25-gauge FNB was superior to 25-gauge FNA (RR, 1.17; 95% CI, 1.00-1.36)[43] and 22-gauge FNB outperformed 25-gauge FNA (RR, 4.56; 95% CI, 2.49-8.35).[47] There was no difference between the 22-gauge FNB and 22-gauge FNA needles (RR, 1.01; 95% CI, 0.89-1.15).

Number of passes. On pairwise meta-analysis, there was no significant difference in the number of needle passes required to obtain an adequate sample with 22-gauge FNB versus 22-gauge FNA (mean difference, −0.32; 95% CI, −0.66 to 0.02; P = .07), although considerable heterogeneity was observed (I^2 = 89%) (Supplementary Fig. 4, available online at www.giejournal.org). No difference was found when comparing 25-gauge FNA and 22-gauge FNA (mean difference, −0.01; 95% CI, −0.11 to 0.10; P = .88; I^2 = 0%).

Sensitivity and specificity. Thirteen RCTs[21,22,24,25,27-29,33,38,39,42,43,44] reported sensitivity and specificity. The pooled sensitivity of 22-gauge FNA, 25-gauge FNA, 22-gauge FNB, and 25-gauge FNB needles was 90.8% (95% CI, 87.5%-94.1%), 89.9% (95% CI, 84.1%-95.6%), 94.7% (95% CI, 91.5%-97.9%), and 87.9% (95% CI, 71.8%-100%), respectively. Specificity was 100% with all needles.

Adverse events. Details on the safety profile of different devices are reported in Supplementary Table 4 (available online at www.giejournal.org). Adverse events were rare and usually mild, without significant impact on patient outcomes.

Small-study effects, network coherence, and sensitivity analyses

We did not find any evidence of small-study effects based on funnel plot asymmetry for the primary outcomes (data not shown). There was no significant difference between direct and indirect estimates in closed loops that allowed assessment of network coherence. Sensitivity analysis reporting the comparative efficacy of different needles for diagnostic accuracy and sample adequacy restricted to studies in absence of ROSE (Table 3), considering different designs of 22-gauge FNB (Franseen vs Fork-Tip; Supplementary Table 5, available online at www.giejournal.org), with no use of the fanning technique and restricted to parallel trials (Supplementary Table 6, available online at www.giejournal.org), and based on different lesion locations (head/uncinate vs body/tail) and target lesions (pancreatic adenocarcinoma vs other disease; Supplementary Table 7, available online at www.giejournal.org) confirmed the findings of the primary analyses.

Quality of evidence

The overall body of evidence was rated down for serious risk of bias because the RCTs were unblinded and at high risk of performance bias. For several comparisons, evidence was rated down because of imprecision due to wide confidence intervals crossing unity. There was no inconsistency, indirectness, or publication bias for any of the direct comparisons. Where available, there was no intransitivity between the results of direct and indirect meta-analysis. The overall body of evidence supporting comparable accuracy of FNA versus FNB needles, and 25-gauge versus 22-gauge needles, was rated as low quality (Supplementary Table 3).

DISCUSSION

EUS-TA plays a pivotal role in the diagnostic evaluation of pancreatic masses. The overarching goal is to arrive at an accurate diagnosis, avoiding the most common pitfall

TABLE 1. Characteristics of the randomized controlled trials

Study	Arm	Sample size	Study period/design	Country	Age (years)	Gender male, n (%)
25G FNA vs 22G FNA						
Bang et al, 2018[21,*]	25G FNA	176	2014-2016/parallel	USA	66.2 ± 14	102 (58)
	22G FNA	176			68.4 ± 9.6	98 (55.7)
Camellini et al, 2011[23,†]	25G FNA	41	2008-2010/parallel	Italy	66 (35-84)	Overall 54 (64.1)
	22G FNA	43				
Carrara et al, 2016[22,†]	25G FNA	55	2013-2014/parallel	Italy	67 ± 12	34 (61.1)
	22G FNA	47			66 ± 12	27 (56.9)
Fabbri et al, 2011[24]	25G FNA	50	2007-2008/cross-over	Italy	68.2 ± 7.4	30 (60)
	22G FNA	50				
Gimeno-Garcia et al, 2014[25,†]	25G FNA	78	2012/cross-over	Canada	65.6 ± 11.3	38 (49.2)
	22G FNA	78				
Lee et al, 2013[26]	25G FNA	94	2014-2010/parallel	Korea	61.3 ± 11.1	52 (55.3)
	22G FNA	94			58.5 ± 11.8	54 (57.4)
Siddiqui et al, 2009[27]	25G FNA	67	2007-2008/parallel	USA	71.5	47 (70.2)
	22G FNA	64			69.3	35 (54.7)
Vilmann et al, 2013[28,†]	25G FNA	31	2009-2010/parallel	Denmark, Romania, Germany	64 ± 11.4	16 (52.1)
	22G FNA	28			62 ± 13.6	17 (63)
22G FNB vs 22G FNA						
Alatawi et al, 2015[29]	22G FNB	50	2012-2013/parallel	France	67.8 ± 13.1	28 (56)
	22G FNA	50			68 ± 11.2	35 (70)
Bang et al, 2012[30]	22G FNB	28	2011/parallel	USA	65 ± 15.4	15 (53.6)
	22G FNA	28			65.4 ± 11.1	16 (57.1)
Bang et al, 2018[31]	22G FNB	46	Cross-over	USA	67.9 ± 14.7	28 (60.9)
	22G FNA	46				
Cheng et al, 2018[32,†]	22G FNB	123	2014-2016/parallel	China	58.3 ± 11.1	59.30
	22G FNA	126			58.3 ± 12.2	63.60
Ganc et al, 2014[33,‡]	22G FNB	30	Cross-over	Brazil	NR	NR
	22G FNA	30				
Hucl et al, 2013[34,†]	22G FNB	69	2011-2012/cross-over	India	51.7 ± 13.6	37 (53.6)
	22G FNA	69				
Lee et al, 2017[35,†]	22G FNB	9	2013-2014/parallel	Korea	69 (26-85)	62
	22G FNA	7			66 (36-81)	75.80
Noh et al, 2018[36]	22G FNB	60	2013-2015/cross-over	Korea	61.6 ± 10	35 (58.3)
	22G FNA	60				
Othman et al, 2017[37,§]	22G FNB	29	2013-2014/parallel	USA	67.9 ± 10.3	16 (55.1)
	22G FNA	60			63.4 ± 10	27 (45)
Sterlacci et al, 2016[38,†]	22G FNB	38	2011-2013/cross-over	Germany	68 ± 12	51.80
	22G FNA	38				
Vanbierlviet et al, 2014[39]	22G FNB	80	2012/cross-over	France	67.1 ± 11.1	49 (61.2)
	22G FNA	80				
22G FNA vs 19G FNA						
Laquière et al, 2019[40]	22G FNA	63	2013-2016/parallel	France	73 (69-76)	37 (59)
	19G FNA	59			70 (61-80)	37 (63)
Song et al, 2010[41]	22G FNA	57	2007-2008/parallel	Korea	56.7 ± 12.1	28 (15.9)
	19G FNA	60			58.6 ± 11.7	34 (20.4)
25G FNB vs 22G FNA						
Mavrogenis et al, 2015[42,†]	25G FNB	19	2012-2013/cross-over	Belgium	69 (38-88)	9 (47.3)
	22G FNA	19				
25G FNB vs 25G FNA						
Kamata et al, 2016[43]	25G FNB	106	2013/parallel	Japan	68 (43-90)	53 (50)
	25G FNA	108			67 (34-89)	59 (50)
25G FNB vs 22G FNB						
Park et al, 2016[44]	25G FNB	56	2014/cross-over	Korea	65.8 ± 9.5	35 (62.5)
	22G FNB	56				
Woo et al, 2017[45]	25G FNB	103	2013-2014/parallel	Korea	61.3 ± 11.6	66 (64)
	22G FNB	103			61.2 ± 12.8	62 (60.1)
22G FNB ForkTip vs 22G FNB Franseen						
Bang et al, 2018[46,§]	22G FNB ForkTip	50	2016-2017/cross-over	USA	71.3 ± 11	28 (56)
	22G FNB Franseen	50				
22G FNB vs 25G FNA						
Kandel et al, 2018[47,‡]	22G FNB	50	2016-2018/cross-over	USA	68 ± 13	25 (50)
	25G FNA	50				

ROSE, Rapid on-site evaluation; *NR*, not reported; *FNB*, fine-needle biopsy; *G*, gauge.

[*] Four-arm trial comparing 22-gauge FNA with/without suction and 25-gauge FNA with/without suction.

[†] Trials including pancreatic and extra-pancreatic masses. Only pancreatic lesions are reported in the table and included in the analysis.

[‡] Conference abstract.

[§] Three-arm trial comparing 2 different FNA needles and FNB. Data from the 2 FNA arms were merged.

TABLE 1. Continued

Lesion size (cm)	Location head/uncinate, n (%)	Stylet use	Pancreatic tumor	ROSE	Needle
3.1 ± 1.1	120 (68.2)	No	128 (72.7)	Yes	Expect
3.1 ± 1.2	108 (61.4)		138 (78.4)		Expect
2.8 ± 1.1	33 (80)	Yes	37 (90.2)	Yes	EchoTip
2.7 ± 1.2	31 (72)		35 (81.4)		EchoTip
3.1 ± 1.9	41 (74.5)	NR		Yes	Beacon system
3.8 ± 1.9	28 (59.5)		87 (85.4)		Beacon system
2.9 ± 0.7	42 (84)	No	NR	Yes	EchoTip
					EchoTip
NR	48 (61.5)	NR	NR	Yes	EchoTip
					EchoTip
3.77 ± 1.9	53 (56.3)	No	66 (70.2)	No	EchoTip
3.32 ± 1.5	31 (32.9)		66 (70.2)		EndoCoil
3	39 (58.2)	NR	67 (100)	Yes	EchoTip
2.9	44 (68.8)		64 (100)		EndoCoil
2.8 ± 1.2	NR	NR	16 (51.6)	No	SonoTip II
3.9 ± 1.4			15 (53.4)		SonoTip II
3.2 ± 0.5	34 (68)	No	45 (905)	No	ProCore
3.3 ± 0.2	38 (76)		43 (86)		Echo Ultra
3.2 ± 0.9	20 (71.4)	No	25 (89.3)	Yes	ProCore
3.3 ± 0.7	20 (71.4)		25 (89.3)		Expect
2.9 ± 0.8	28 (60.9)	NR	41 (89.1)	Yes	Acquire
					Expect
2.91	NR	Only at first two passes	117 (95)	No	ProCore
2.95			115 (91.3)		EchoTip
NR	NR	NR	NR	No	ProCore
					EchoTip
4.19 ± 1.7	54	No	49 (71)	No	ProCore
					EchoTip
4.4 ± 3.2	NR	Yes	5 (55.5)	No	ProCore
3.7 ± 2			4 (57.1)		EchoTip
3.1 ± 0.8	23 (38.4)	No	60 (100)	No	ProCore
					EZShot 2
NR	16 (55.1)	No	NR	Yes	ProCore
	30 (50)				EZShot 2/
					Expect
3.3 ± 1.2	NR	No	35 (92.1)	No	ProCore
					EchoTip
3.3 ± 1	50 (62.5)	No	70 (87.5)	No	ProCore
					EchoTip
3 (2.5-4)	100	Yes	54 (85.7)	No	EchoTip
3 (2.5-3.8)	100		35 (59.3)		GFlex
3.2 ± 1.3	29 (16.5)	No	52 (91.2)	No	EchoTip
3.6 ± 1.7	26 (15.6)		56 (93.3)		EchoTip
3.9 (1-7)	NR	Yes	19 (100)	No	ProCore
					EchoTip
2.93 ± 1.5	NR	Yes	90 (85)	No	ProCore
2.79 ± 1.4			84 (78)		EchoTip
3.53 ± 1.71	28 (50)	No	52 (92.8)	No	ProCore
					ProCore
2.6 ± 1.1	48 (56.4)	NR	93 (90.3)	No	ProCore
2.7 ± 1	41 (48.2)		97 (94.2)		ProCore
2.4 ± 0.6	29 (58)	No	47 (94)	Yes	SharkCore
					Acquire
3.8 ± 1.7	27 (54)	No	37 (74)	Yes	SharkCore

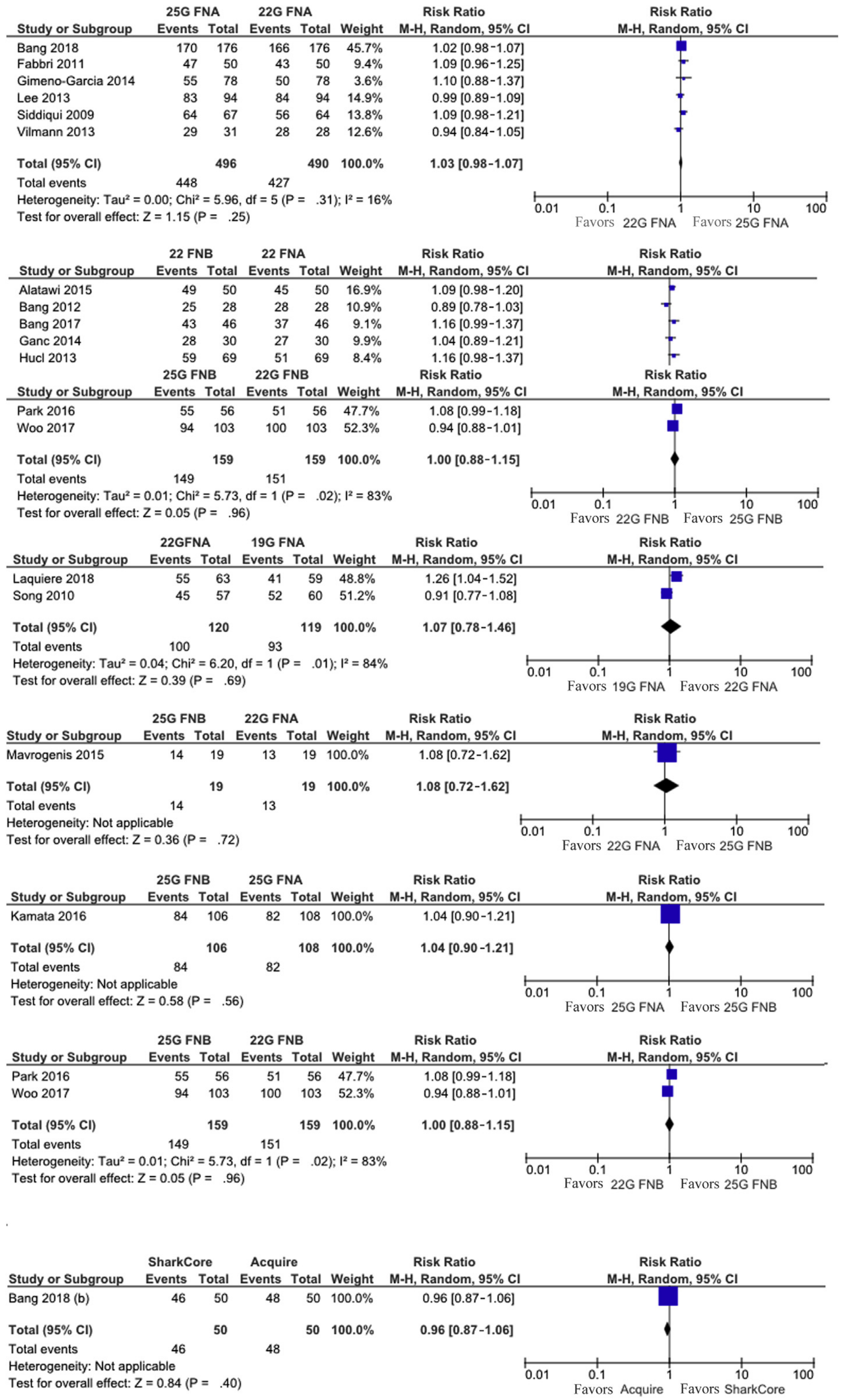

Figure 3. Pairwise meta-analyses directly comparing several needles for EUS-guided sampling of pancreatic lesions. None of the devices tested was significantly superior. Heterogeneity was mainly low or moderate ($I^2 = 16\%$-32%). *FNB,* fine-needle biopsy; *G,* gauge.

associated with EUS-TA (false-negative diagnosis) and ultimately improve patient outcomes. Multiple efforts have been made to establish an ideal EUS-TA technique; one that is efficient, effective, and associated with high diagnostic accuracy with a low adverse event rate.[9] These outcomes may be affected by several variables of which needle type (FNA vs FNB) and needle gauge (19-gauge vs 22-gauge vs 25-gauge) are the 2 most widely studied.

TABLE 2. Summary of findings reporting the comparative efficacy of different needles for improving the diagnostic accuracy and sample adequacy of EUS-guided sampling of pancreatic masses

	Diagnostic accuracy				
	19-gauge FNA	**22-gauge FNA**	**22-gauge FNB**	**25-gauge FNA**	**25-gauge FNB**
Sample adequacy	19-gauge FNA	1.06 (0.80-1.41)	1.10 (0.80-1.50)	1.10 (0.81-1.51)	1.16 (0.58-1.69)
	0.87 (0.66-1.14)	22-gauge FNA	1.03 (0.89-1.18)	1.03 (0.91-1.17)	1.09 (0.85-1.39)
	0.85 (0.63-1.15)	0.98 (0.86-1.11)	22-gauge FNB	1.00 (0.83-1.20)	1.05 (0.82-1.36)
	0.84 (0.62-1.13)	0.96 (0.86-1.08)	1.06 (0.89-1.25)	25-gauge FNA	1.05 (0.82-1.33)
	0.83 (0.58-1.18)	0.95 (0.76-1.19)	1.00 (0.79-1.26)	0.99 (0.79-1.23)	25-gauge FNB

In each cell, the numerator of the ratio is the column-defining treatment and the denominator is the row-defining treatment. Risk ratios (95% confidence intervals) for diagnostic accuracy are reported in the upper part of the table, risk ratios (95% confidence intervals) for sample adequacy are reported in the lower part. None of the comparisons were statistically significant.
FNB, Fine-needle biopsy.

TABLE 3. Summary of the findings reporting the comparative efficacy of different needles for improving diagnostic accuracy and sample adequacy of EUS-guided sampling of pancreatic masses in the absence of rapid on-site cytologic evaluation

	Diagnostic accuracy				
	19-gauge FNA	**22-gauge FNA**	**22-gauge FNB**	**25-gauge FNA**	**25-gauge FNB**
Sample adequacy	19-gauge FNA	1.06 (0.80-1.41)	1.09 (0.79-1.50)	1.06 (0.73-1.52)	1.13 (0.76-1.67)
	0.87 (0.66-1.14)	22-gauge FNA	1.02 (0.87-1.19)	0.99 (0.78-1.24)	1.06 (0.81-1.39)
	0.85 (0.63-1.16)	0.98 (0.85-1.13)	22-gauge FNB	0.97 (0.74-1.25)	1.03 (0.79-1.36)
	0.85 (0.60-1.20)	0.97 (0.78-1.21)	0.99 (0.77-1.27)	25-gauge FNA	1.07 (0.83-1.37)
	0.84 (0.58-1.21)	0.96 (0.74-1.24)	0.98 (0.75-1.27)	0.98 (0.78-1.23)	25-gauge FNB

In each cell, the numerator of the ratio is the column-defining treatment and the denominator is the row-defining treatment. Risk ratios (95% confidence intervals) for diagnostic accuracy are reported in the upper part of the table, risk ratios (95% confidence intervals) for sample adequacy are reported in the lower part. None of the comparisons resulted statistically significant.
FNB, Fine-needle biopsy.

There is currently limited and conflicting evidence to inform whether any specific technique is superior for sampling pancreatic masses.

Using network meta-analysis to optimally inform evidence and the GRADE methodology to critically appraise the evidence, we observed that there was no significant difference in diagnostic accuracy between different EUS-TA approaches for sampling pancreatic masses, based on low quality evidence. In particular, there was no difference in the diagnostic accuracy between FNA versus FNB needles, and between 22-gauge versus 25-gauge needles. Similarly, we found no significant difference between needle types and gauges for adequacy of samples, histologic core procurement rate, and number of needle passes. In this regard, direct comparisons based on single head-to-head trials showed a significant benefit with some FNB needles (25-gauge and Fork-Tip FNB) with respect to standard 25-gauge FNA needles in terms of sample adequacy and histologic core procurement; however, given the paucity of such comparative studies, these findings did not have a significant impact on network meta-analysis, thus requiring a particular caution in interpreting these results.

Sensitivity analyses confirmed these findings with no difference between FNA versus FNB needles in the absence of ROSE. Lesion location also did not affect the testedcomparisons, thus confirming the comparable performances of FNA with respect to FNB even in less accessible lesions (eg, in the pancreatic tail).

The use of EUS-FNB needles has generated a great deal of interest in the field of EUS-TA, primarily based on proposed advantages over EUS-FNA needles in improving diagnostic accuracy, improving procurement of samples with preserved tissue architecture, and allowing for immunohistochemistry or special stains required for certain diagnoses, obviating ROSE, and obtaining results in fewer passes and thus potentially improving the efficiency and costs associated with EUS-TA.[1] Although different EUS-FNB needle designs have been evaluated with variable success rates, the results of this study demonstrate no difference in the diagnostic accuracy between EUS-FNB and EUS-FNA techniques in pancreatic masses accounting for different needle gauges. These results suggest that EUS-FNA would suffice for most cases in routine clinical practice (patients with pancreatic adenocarcinoma) and add credence to the recently published European guidelines that equally recommend FNA and FNB for routine sampling of solid masses.[6] We were unable to examine the role of EUS-FNB versus EUS-FNA for conditions that require assessment of tissue architecture, such as suspected autoimmune pancreatitis.[48]

Although histologic core procurement was comparable overall in this review, the finding of superior performance for FNB needles seen in individual studies may warrant further evaluation using larger well-designed trials.

The strengths of this study were as follows: first, through a network meta-analysis, we were able to assess the comparative diagnostic performance of all available needle designs and gauges synthesizing evidence across a network of RCTs. Second, our rigorous analysis using an a priori designed protocol was accompanied by a critical appraisal of the quality of evidence based on the GRADE criteria and can directly and optimally inform clinical practice guidelines related to EUS-TA for solid pancreatic masses. However, our results should be interpreted with caution, due to limitations related to both the network meta-analysis as well as individual studies. First, there was a paucity of head-to-head trials supporting some of the comparisons, in particular, newer 22-gauge and 25-gauge FNB needles. The promising results in tissue procurement and diagnostic performance observed with newer FNB needles, such as the Franseen and Fork-tip needle in trials and cohort studies,[31,46,47,49,50] need to be confirmed in further comparative RCTs, and the limited number of studies suitable to be included in our network meta-analysis does not currently allow definitive conclusions to be drawn in this regard. Second, all the studies were unblinded RCTs, prone to performance biases. This aspect, in addition to the heterogeneity and imprecision observed in some comparisons, downrated the quality of evidence, which was low overall. Third, there are several technical aspects, such as use of a stylet, ROSE availability, or sampling techniques, that may influence the diagnostic accuracy of the procedure; these differences could not be adequately adjusted for in our study-level synthesis, although sensitivity analyses confirmed our primary findings. The eventual impact of these technical aspects is inconsistent.[4,51] Fourth, network meta-analyses may be subject to misinterpretation due to conceptual heterogeneity in trial design and the definition of specific outcomes, in particular concerning histologic core procurement. Not all trials were conducted in a parallel design, although our results were confirmed through sensitivity analysis excluding crossover studies. Finally, we were not able to explore the impact of different needle sizes and designs in particular conditions, such as autoimmune pancreatitis, due to the lack of available data, and we did not perform a comparative cost-effectiveness analysis, which was beyond the scope of our work.

In conclusion, based on a systematic review with network meta-analysis of different EUS-TA techniques for sampling pancreatic tissue masses, there was no difference in diagnostic accuracy, sample adequacy, and histologic core procurement between EUS-TA using EUS-FNA and FNB needles, accounting for different needle gauges. Larger pragmatic trials comparing different devices and estimating the real impact of novel devices on improving accuracy and histologic core procurement are warranted.

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SUPPLEMENTARY TABLE 1. Details of the search strategy

("endosonography"[MeSH Terms] OR "endosonography"[All Fields] OR ("endoscopic"[All Fields] AND "ultrasound"[All Fields]) OR "endoscopic ultrasound"[All Fields]) AND ("pancreatic neoplasms"[MeSH Terms] OR ("pancreatic"[All Fields] AND "neoplasms"[All Fields]) OR "pancreatic neoplasms"[All Fields] OR ("pancreatic"[All Fields] AND "tumor"[All Fields]) OR "pancreatic tumor"[All Fields])

SUPPLEMENTARY TABLE 2. GRADE categories of quality of evidence

GRADE quality of evidence	Meaning	Interpretation
High	We are very 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 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 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 estimate of 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 effect is very uncertain

Quality of the evidence is rated based on the GRADE methodology. Trials of direct comparison are rated down for the presence of any of the following factors: risk of bias in the literature, inconsistency, indirectness, imprecision, and publication bias.
GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

SUPPLEMENTARY TABLE 3. GRADE summary of the findings reporting the comparative efficacy of different needle sizes and designs for improving diagnostic accuracy and sample adequacy of EUS-guided tissue acquisition of solid pancreatic lesions

	Diagnostic accuracy		Sample adequacy	
	Risk ratio (95% CI)	Quality of evidence	Risk ratio (95% CI)	Quality of evidence
All needles vs 19 G FNA				
22 G FNA	1.07 (0.78-1.46)	Low (D)	1.13 (1.00-1.28)	Low (D)
22 G FNB	1.10 (0.80-1.50)	Low (NMA)	1.17 (0.86-1.58)	Low (NMA)
25 G FNA	1.10 (0.81-1.51)	Low (NMA)	1.16 (0.84-1.53)	Low (NMA)
25 G FNB	1.16 (0.58-1.69)	Low (NMA)	1.18 (0.89-1.61)	Low (NMA)
vs 22 G FNA				
22 G FNB	1.02 (0.97-1.08)	Low (D)	1.01 (0.96-1.06)	Low (D)
25 G FNA	1.03 (0.98-1.07)	Low (D)	1.04 (0.92-1.16)	Low (NMA)
25 G FNB	1.09 (0.85-1.39)	Low (NMA)	1.07 (0.79-1.44)	Low (NMA)
vs 22 G FNB				
25 G FNA	1.00 (0.83-1.20)	Low (NMA)	0.79 (0.68-0.92)	Low (D)
25 G FNB	1.00 (0.88-1.15)	Low (D)	1.04 (0.98-1.10)	Low (NMA)
vs 25 G FNA				
25 G FNB	1.05 (0.82-1.33)	Low (NMA)	1.00 (0.98-1.02)	Low (NMA)

Quality of the evidence was rated based on the GRADE methodology (see Supplementary Table 2). The quality of indirect estimates was initially derived from the lowest quality of first-order loops for direct estimates contributing to the indirect estimates. The quality of the network meta-analysis was derived from the quality of the combination of direct and indirect estimates and transitivity of trials. When moderate-high quality evidence was available from direct/pairwise estimates, they were used preferentially (marked as D); when pairwise estimates provided only low or very quality of evidence or if there were no pairwise comparisons, then estimates from network meta-analysis were used to rate quality of evidence (marked as NMA).
GRADE, Grading of Recommendations, Assessment, Development and Evaluation; *CI*, confidence interval; *FNB*, fine-needle biopsy; *G,* gauge.

SUPPLEMENTARY TABLE 4. Safety data reported in the trials

Study	Adverse events, n (%)	
	25G FNA	22G FNA
25G FNA vs 22G FNA		
Bang et al, 2018[21]	17 (10)	7 (3.9)
Carrara et al, 2016[22]	1 (1.8)	1 (2.1)
Lee et al, 2013[26]	3 (3.2)	10 (10.6)
	22G FNB	22G FNA
22G FNB vs 22G FNA		
Bang et al, 2012[30]	1 (3.6)	1 (3.6)
Cheng et al, 2018[32]	None	2, mild bleeding
Othman et al, 2017[37]	None	1, bleeding
Vanbiervliet et al, 2014[39]	None	1, mild bleeding
	22G FNA	19G FNA
22G FNA vs 19G FNA		
Laquiere et al, 2019[40]	4 (6.3), minor events	9 (15.2), minor events
Song et al, 2010[41]	None	3 (5), mild pancreatitis
	25G FNB	22G FNB
25G FNB vs 22G FNB		
Woo et al, 2017[45]	1 (0.97), mild pancreatitis	4 (3.8), mild pancreatitis

FNB, Fine-needle biopsy; *G,* gauge.

SUPPLEMENTARY TABLE 5. Summary of findings reporting the diagnostic accuracy and sample adequacy analysis distinguished by 22G fine-needle biopsy design

	Diagnostic accuracy					
	19 G FNA	**22 G FNA**	**22 G FNB Franseen**	**22 G FNB Fork-Tip**	**25 G FNA**	**25 G FNB**
Sample adequacy	19 G FNA	0.91 (0.61-1.35)	1.05 (0.58-1.91)	1.01 (0.49-2.08)	0.94 (0.62-1.43)	0.98 (0.61-1.58)
	0.91 (0.63-1.32)	22 G FNA	1.16 (0.74-1.80)	1.11 (0.61-2.02)	1.03 (0.91-1.17)	1.08 (0.85-1.38)
	0.87 (0.50-1.52)	0.95 (0.63-1.44)	22 G FNB Franseen	0.95 (0.63-1.43)	0.89 (0.56-1.40)	0.93 (0.56-1.54)
	0.84 (0.42-1.66)	0.91 (0.51-1.63)	0.95 (0.64-1.43)	22 G FNB Fork-Tip	0.93 (0.50-1.71)	0.97 (0.51-1.86)
	0.88 (0.60-1.30)	0.96 (0.86-1.08)	1.01 (0.65-1.55)	1.15 (0.98-2.09)	25 G FNA	1.04 (0.82-1.33)
	0.88 (0.57-1.35)	0.96 (0.76-1.20)	1.00 (0.62-1.60)	1.04 (0.56-1.94)	0.99 (0.79-1.23)	25 G FNB

In each cell, the numerator of the ratio is the column-defining treatment and the denominator is the row-defining treatment. Risk ratios (95% confidence intervals) for diagnostic accuracy are reported in the upper part of the table, risk ratios (95% confidence intervals) for sample adequacy are reported in the lower part. None of the comparisons were statistically significant.
FNB, Fine-needle biopsy; *G,* gauge.

SUPPLEMENTARY TABLE 6. Summary of the findings reporting the diagnostic accuracy analysis restricted to studies not using the fanning technique and parallel trials

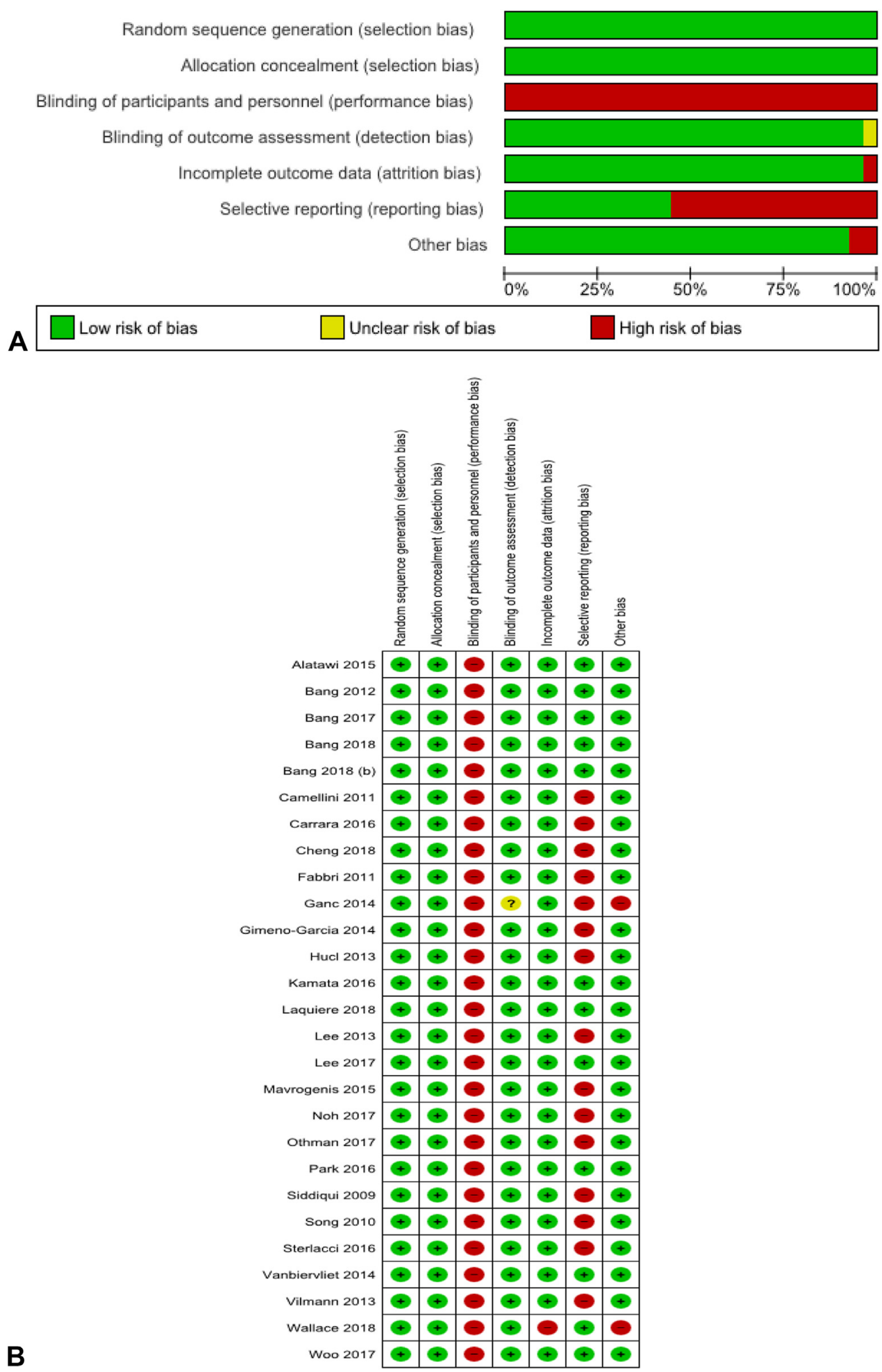
	Studies not using fanning technique: risk ratio (95% CI)	Parallel trials: risk ratio (95% CI)
All needles vs 19G FNA		
22G FNA	0.91 (0.61-1.35)	1.06 (0.80-1.41)
22G FNB	0.91 (0.59-1.41)	1.07 (0.70-1.64)
25G FNA	0.95 (0.61-1.46)	1.09 (0.78-1.53)
25G FNB	0.98 (0.57-1.69)	1.14 (0.73-1.79)
Versus 22G FNA		
22G FNB	1.00 (0.85-1.18)	1.01 (0.73-1.38)
25G FNA	1.04 (0.88-1.23)	1.02 (0.86-1.22)
25G FNB	1.08 (0.75-1.56)	1.07 (0.75-1.52)
Versus 22G FNB		
25G FNA	1.03 (0.81-1.31)	1.01 (0.71-1.45)
25G FNB	1.07 (0.76-1.51)	1.06 (0.66-1.70)
Versus 25G FNA		
25G FNB	1.03 (0.69-1.55)	1.04 (0.76-1.41)

None of the comparisons were statistically significant.
FNB, Fine-needle biopsy; *G,* gauge.

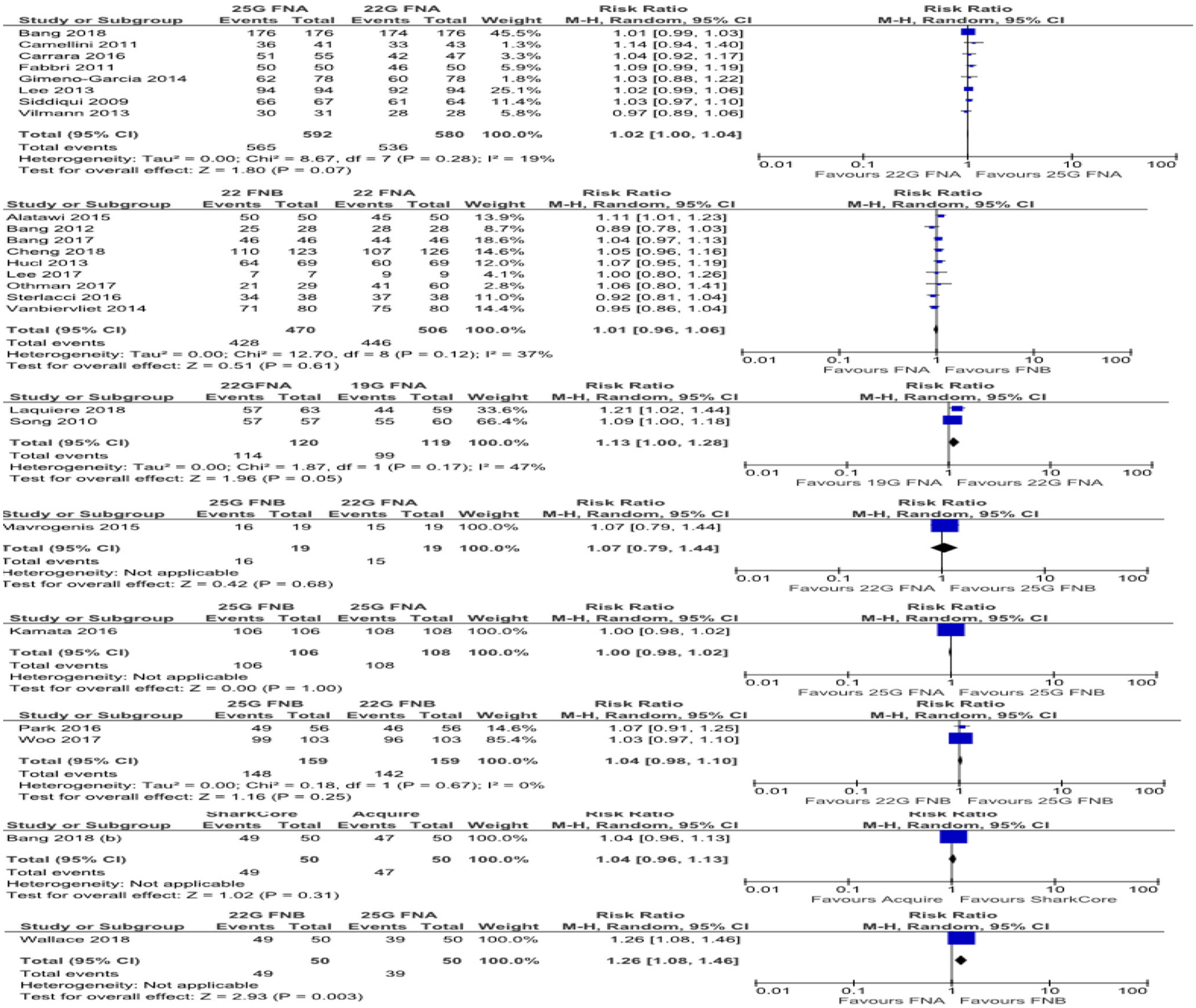
SUPPLEMENTARY TABLE 7. Sensitivity analysis of the diagnostic accuracy performed based on lesion location (head/uncinate vs body/tail) and target lesion (pancreatic adenocarcinoma vs other disease)

	Head/uncinate: risk ratio (95% CI)	Body/tail: risk ratio (95% CI)
All needles vs 19G FNA		
22G FNA	1.04 (0.73-1.41)	0.83 (0.59-1.28)
22G FNB	1.03 (0.82,1.53)	0.93 (0.67-1.45)
25G FNA	1.02 (0.84,1.51)	0.82 (0.78-1.53)
25G FNB	1.04 (0.68,1.62)	1.02 (0.79-1.81)
Versus 22G FNA		
22G FNB	1.07 (0.88-1.12)	1.04 (0.72-1.39)
25G FNA	1.04 (0.91-1.23)	1.03 (0.86-1.22)
25G FNB	1.08 (0.72-1.59)	1.05 (0.73-1.57)
Versus 22G FNB		
25G FNA	1.08 (0.84-1.27)	1.04 (0.72-1.45)
25G FNB	1.07 (0.71-1.52)	1.03 (0.68-1.70)
Versus 25G FNA		
25G FNB	1.07 (0.71-1.58)	1.11 (0.74-1.41)
	Pancreatic adenocarcinoma: risk ratio (95% CI)	Other disease: risk ratio (95% CI)
All needles vs 19G FNA		
22G FNA	–	–
22G FNB	–	–
25G FNA	–	–
25G FNB	–	–
Versus 22G FNA		
22G FNB	1.03 (0.85-1.22)	1.01 (0.75-1.41)
25G FNA	1.03 (0.89-1.32)	1.05 (0.89-1.22)
25G FNB	1.11 (0.73-1.64)	–
Versus 22G FNB		
25G FNA	1.03 (0.81-1.31)	0.89 (0.71-1.35)
25G FNB	1.07 (0.76-1.51)	–
Versus 25G FNA		
25G FNB	1.06 (0.71-1.58)	–

FNB, Fine-needle biopsy; *G,* gauge.



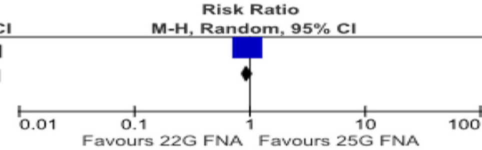
Supplementary Figure 1. Risk of bias across the studies. **A**, Risk of bias summary. **B**, Risk of bias graph.



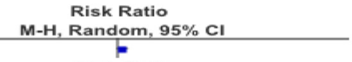
Supplementary Figure 2. Pairwise meta-analyses for sample adequacy. *FNB,* Fine-needle biopsy; *G,* gauge.

Study or Subgroup	25G FNA Events	25G FNA Total	22G FNA Events	22G FNA Total	Weight	Risk Ratio M-H, Random, 95% CI
Bang 2018	127	176	134	176	100.0%	0.95 [0.84, 1.07]
Total (95% CI)		**176**		**176**	**100.0%**	**0.95 [0.84, 1.07]**
Total events	127		134			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.85 (P = 0.39)

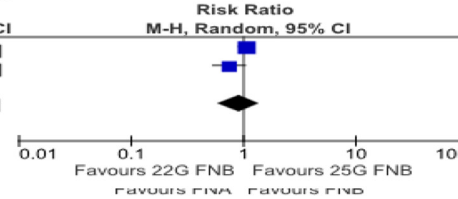


Study or Subgroup	22 FNB Events	22 FNB Total	22 FNA Events	22 FNA Total	Weight	Risk Ratio M-H, Random, 95% CI
Alatawi 2015	50	50	45	50	19.8%	1.11 [1.01, 1.23]



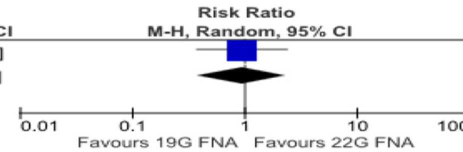
Study or Subgroup	25G FNB Events	25G FNB Total	22G FNB Events	22G FNB Total	Weight	Risk Ratio M-H, Random, 95% CI
Park 2016	49	56	46	56	55.2%	1.07 [0.91, 1.25]
Woo 2017	38	103	51	103	44.8%	0.75 [0.54, 1.03]
Total (95% CI)		**159**		**159**	**100.0%**	**0.91 [0.59, 1.39]**
Total events	87		97			

Heterogeneity: Tau² = 0.08; Chi² = 5.90, df = 1 (P = 0.02); I² = 83%
Test for overall effect: Z = 0.44 (P = 0.66)



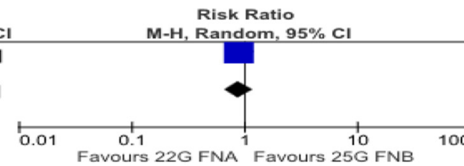
Study or Subgroup	22GFNA Events	22GFNA Total	19G FNA Events	19G FNA Total	Weight	Risk Ratio M-H, Random, 95% CI
Laquiere 2018	8	63	8	59	100.0%	0.94 [0.38, 2.33]
Total (95% CI)		**63**		**59**	**100.0%**	**0.94 [0.38, 2.33]**
Total events	8		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.14 (P = 0.89)



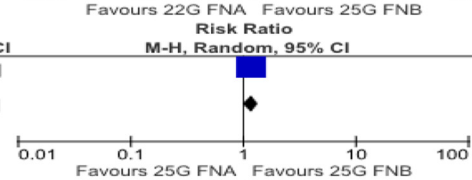
Study or Subgroup	25G FNB Events	25G FNB Total	22G FNA Events	22G FNA Total	Weight	Risk Ratio M-H, Random, 95% CI
Mavrogenis 2015	15	19	17	19	100.0%	0.88 [0.67, 1.17]
Total (95% CI)		**19**		**19**	**100.0%**	**0.88 [0.67, 1.17]**
Total events	15		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)



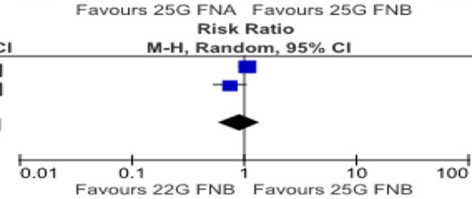
Study or Subgroup	25G FNB Events	25G FNB Total	25G FNA Events	25G FNA Total	Weight	Risk Ratio M-H, Random, 95% CI
Kamata 2016	86	106	75	108	100.0%	1.17 [1.00, 1.36]
Total (95% CI)		**106**		**108**	**100.0%**	**1.17 [1.00, 1.36]**
Total events	86		75			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.96 (P = 0.05)



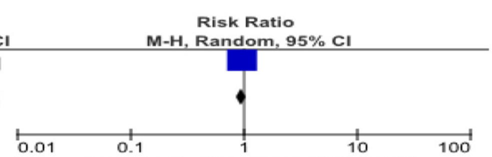
Study or Subgroup	25G FNB Events	25G FNB Total	22G FNB Events	22G FNB Total	Weight	Risk Ratio M-H, Random, 95% CI
Park 2016	49	56	46	56	55.2%	1.07 [0.91, 1.25]
Woo 2017	38	103	51	103	44.8%	0.75 [0.54, 1.03]
Total (95% CI)		**159**		**159**	**100.0%**	**0.91 [0.59, 1.39]**
Total events	87		97			

Heterogeneity: Tau² = 0.08; Chi² = 5.90, df = 1 (P = 0.02); I² = 83%
Test for overall effect: Z = 0.44 (P = 0.66)



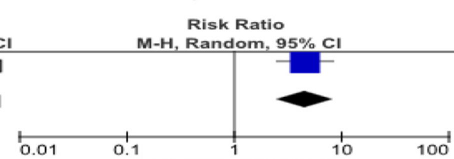
Study or Subgroup	SharkCore Events	SharkCore Total	Acquire Events	Acquire Total	Weight	Risk Ratio M-H, Random, 95% CI
Bang 2018 (b)	46	50	48	50	100.0%	0.96 [0.87, 1.06]
Total (95% CI)		**50**		**50**	**100.0%**	**0.96 [0.87, 1.06]**
Total events	46		48			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)



Study or Subgroup	FNB Events	FNB Total	FNA Events	FNA Total	Weight	Risk Ratio M-H, Random, 95% CI
Wallace 2018	41	50	9	50	100.0%	4.56 [2.49, 8.35]
Total (95% CI)		**50**		**50**	**100.0%**	**4.56 [2.49, 8.35]**
Total events	41		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.91 (P < 0.00001)



Supplementary Figure 3. Pairwise meta-analyses for optimal histologic core procurement. *FNB,* Fine-needle biopsy; *G,* gauge.

Study or Subgroup	25G FNA Mean	25G FNA SD	25G FNA Total	22G FNA Mean	22G FNA SD	22G FNA Total	Weight	Mean Difference IV, Random, 95% CI
Bang 2018	1.6	1.4	176	1.8	1.9	176	9.0%	-0.20 [-0.55, 0.15]
Camellini 2011	3	1.3	41	3	1.1	43	4.1%	0.00 [-0.52, 0.52]
Carrara 2016	2.2	1.2	55	2.2	1.1	47	5.5%	0.00 [-0.45, 0.45]
Fabbri 2011	2	0	50	2	0	50		Not estimable
Gimeno-Garcia 2014	1.3	0.5	78	1.3	0.5	78	44.3%	0.00 [-0.16, 0.16]
Lee 2013	3.1	1.1	94	2.8	1.2	94	10.1%	0.30 [-0.03, 0.63]
Siddiqui 2009	2.6	1.2	67	2.6	1.2	64	6.5%	0.00 [-0.41, 0.41]
Vilmann 2013	2.7	0.5	31	2.8	0.4	28	20.6%	-0.10 [-0.33, 0.13]
Total (95% CI)			**592**			**580**	**100.0%**	**-0.01 [-0.11, 0.10]**

Heterogeneity: Tau² = 0.00; Chi² = 5.16, df = 6 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.88)

Study or Subgroup	22 FNB Mean	22 FNB SD	22 FNB Total	22 FNA Mean	22 FNA SD	22 FNA Total	Weight	Mean Difference IV, Random, 95% CI
Alatawi 2015	2	2	50	3	2	50	7.5%	-1.00 [-1.78, -0.22]
Bang 2012	1.28	0.54	28	1.61	0.88	28	10.8%	-0.33 [-0.71, 0.05]
Bang 2017	1.15	0.47	46	1.18	0.58	46	11.9%	-0.03 [-0.25, 0.19]
Cheng 2018	4	1	123	4	1	126	11.8%	0.00 [-0.25, 0.25]
Hucl 2013	1.32	0.55	69	2.36	0.95	69	11.7%	-1.04 [-1.30, -0.78]
Lee 2017	1.26	1.09	9	1.73	1.84	7	3.5%	-0.47 [-2.01, 1.07]
Noh 2017	2	1	60	2	1	60	11.0%	0.00 [-0.36, 0.36]
Othman 2017	2.8	1.5	29	2.5	1.3	60	8.7%	0.30 [-0.34, 0.94]
Sterlacci 2016	1.7	0.6	38	1.5	0.6	38	11.6%	0.20 [-0.07, 0.47]
Vanbiervliet 2014	1	1	80	2	1	80	11.4%	-1.00 [-1.31, -0.69]
Total (95% CI)			**532**			**564**	**100.0%**	**-0.32 [-0.66, 0.02]**

Heterogeneity: Tau² = 0.24; Chi² = 84.90, df = 9 (P < 0.00001); I² = 89%
Test for overall effect: Z = 1.82 (P = 0.07)

Study or Subgroup	22G FNA Mean	22G FNA SD	22G FNA Total	19G FNA Mean	19G FNA SD	19G FNA Total	Weight	Mean Difference IV, Random, 95% CI
Laquiere 2018	2	0.1	63	2	0.1	59	57.1%	0.00 [-0.04, 0.04]
Song 2010	2.78	0.88	57	2.35	0.88	60	42.9%	0.43 [0.11, 0.75]
Total (95% CI)			**120**			**119**	**100.0%**	**0.18 [-0.23, 0.60]**

Heterogeneity: Tau² = 0.08; Chi² = 6.89, df = 1 (P = 0.009); I² = 85%
Test for overall effect: Z = 0.87 (P = 0.39)

Study or Subgroup	25G FNB Mean	25G FNB SD	25G FNB Total	25G FNA Mean	25G FNA SD	25G FNA Total	Weight	Mean Difference IV, Random, 95% CI
Kamata 2016	1	0.1	106	1	0.1	108	100.0%	0.00 [-0.03, 0.03]
Total (95% CI)			**106**			**108**	**100.0%**	**0.00 [-0.03, 0.03]**

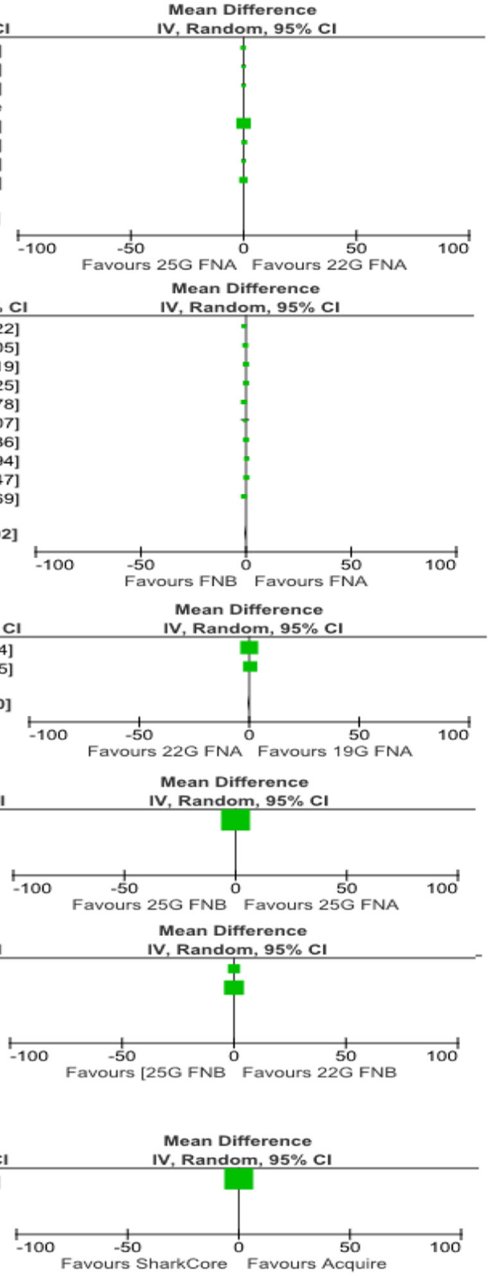
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

Study or Subgroup	25G FNB Mean	25G FNB SD	25G FNB Total	22G FNB Mean	22G FNB SD	22G FNB Total	Weight	Mean Difference IV, Random, 95% CI
Park 2016	2	0.1	56	2	0.1	56	35.2%	0.00 [-0.04, 0.04]
Woo 2017	3	0.1	103	3	0.1	103	64.8%	0.00 [-0.03, 0.03]
Total (95% CI)			**159**			**159**	**100.0%**	**0.00 [-0.02, 0.02]**

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

Study or Subgroup	SharkCore Mean	SharkCore SD	SharkCore Total	Acquire Mean	Acquire SD	Acquire Total	Weight	Mean Difference IV, Random, 95% CI
Bang 2018 (b)	1.04	0.2	50	1.04	0.2	50	100.0%	0.00 [-0.08, 0.08]
Total (95% CI)			**50**			**50**	**100.0%**	**0.00 [-0.08, 0.08]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Supplementary Figure 4. Pairwise meta-analyses for the number of needle passes through the lesion needed to achieve a diagnostic sample. *FNB,* Fine-needle biopsy; *G,* gauge.