The optimal EUS sampling-strategy: a meta-analysis of FNA and new generation FNB devices

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ABSTRACT

BACKGROUND

EUS guided tissue acquisition is extensively used, but the optimal sampling device is still a matter of debate. Since the last meta-analysis on this subject, a substantial number of studies have been published. Thus, an update was required.

METHODS

EMBASE, MEDLINE/PubMed, Web of Science, the Cochrane Library, and Google Scholar were systematically searched. We included randomized controlled trials that involved at least 50 cases with a suspected solid gastrointestinal lesion and that compared one of the novel FNB needles (ProCore, SharkCore, and Acquire) to FNA. Outcome measures included diagnostic accuracy, adequacy, number of passes, presence of tissue cores, and adverse events. Quality was assessed based on the QUADAS-2 tool.

RESULTS

We identified 18 RCT that compared 1046 FNA to 1004 FNB cases, and 648 cases that were sampled with both needles. All studies involved ProCore as FNB needle. The pooled diagnostic accuracy was higher for FNB (OR1.70 95%CI 1.19 to 2.41, p=0.003), as was the tissue core rate after sensitivity analysis (OR2.17, 95%CI 1.21 to 3.91, p=0.01). In addition, less passes were performed with FNB (MD -0.54, 95%CI -1.03 to -0.04, p=0.03). Complication rate was low and did not differ between FNA and FNB (p=0.80). These findings equally applied to solid gastrointestinal lesions and pancreatic lesions. Studies were sufficiently powered, well designed, and harbored a low risk of bias.

CONCLUSION

The ProCore FNB needles outperform FNA in establishing a diagnosis of any type of solid gastrointestinal lesion. Moreover, they secure a higher tissue core rate, with comparable complications.

INTRODUCTION

Endoscopic ultrasound (EUS) guided tissue sampling is a well-established technique to provide a pathology-based diagnosis of lesions in and around the gastrointestinal tract [1, 2]. Also, it is increasingly used to enable pre-therapeutic tissue analysis for targeted treatment [3]. Traditionally, EUS-guided tissue sampling was performed with a fine-needle aspiration (FNA) needle, which mainly harvests loose cells or cytology. Apart from its limited ability to establish tumor invasion and diagnose certain conditions (i.e. auto-immune pancreatitis, submucosal or stromal lesions, and neuro-endocrine tumors [4-6], it strongly depends on rapid on-site tissue evaluation (ROSE) by a dedicated pathologist, which is not always available [7-10]. Also, it may not provide enough material for ancillary testing.

Fine-needle biopsy (FNB) devices were introduced to overcome these limitations, by harvesting histologically intact tissue fragments. The first devices, the TruCut^{tm} (Travenol Laboratories) and Quick-Core$^{®}$ (Cook Medical) needles, were hampered by a rigid design and difficult deployment. Since then, several novel FNB devices have been introduced, including the ProCore reversed and forward facing bevel needles (Cook Medical, Ireland), the Fork-tip (SharkCore, Medtronic), and Franseen needle (Acquire, Boston Scientific).

Despite growing evidence on the diagnostic benefits of FNB over FNA, so far, just one meta-analysis found a higher diagnostic accuracy for FNB, but only for pancreatic masses [11]. As several large studies have been published since then, we aimed to provide an updated review and meta-analysis of studies comparing FNA to the novel FNB needles, including ProCore, SharkCore and Acquire (Figure 1A-D).

METHODS

Study selection

EMBASE, MEDLINE/PubMed, Web of Science, the Cochrane Library, and Google Scholar were systematically searched to identify studies that had compared FNA to the new generation of FNB needles, including the ProCore reversed and forward facing bevel needles (Cook Medical, Ireland), and the Fork-tip (SharkCore, Medtronic) and Franseen needles (Acquire, Boston Scientific) for sampling of a solid lesion reachable from the gastrointestinal tract. A combination of subject headings and text words were used. The key search words were 'endoscopic ultrasound', 'fine needle aspiration', 'fine needle biopsy', 'core biopsy', 'procore', 'sharkcore', 'franseen', 'acquire', 'fork-tip', 'histology' and 'cytology'. The EMBASE search strategy was adapted for use in the other databases. The search focused on human studies without language restrictions. All searches were performed on April 8, 2019. Two independent authors (PvR and DC) systematically reviewed the title and abstract of every retrieved record. If this information suggested that inclusion criteria were met, available full text articles were read and evaluated.

Any disagreement between the reviewers was resolved by discussion with the third author (MB).

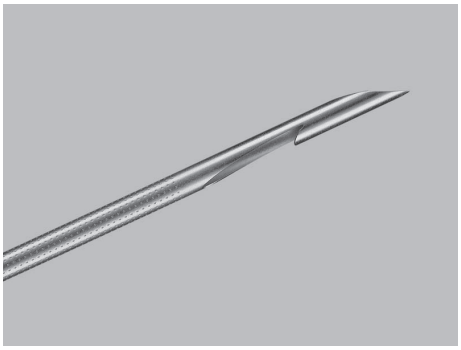


Figure 1A. 22G ProCore FNB reversed bevel needle

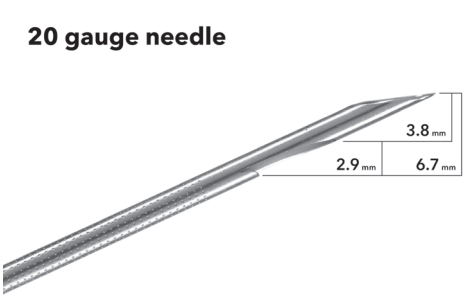


Figure 1B. 20G ProCore FNB forward facing bevel needle

Figure 1C. SharkCore FNB needle

Figure 1D. Acquire FNB needle

In- and exclusion criteria

We included randomized controlled trials (RCTs) that involved at least 50 patients and reported on at least two outcome measures. Studies were excluded if they lacked data to reliably extract the outcome measures. In case of multiple publications on the same population, the most recent publication was included. Conference abstracts were included from the year 2017, as they are still likely to be published as a manuscript.

Outcome measures: definitions and data extraction

Data was extracted on; 1) diagnostic accuracy, based on the final diagnosis (or confirmation of malignancy) obtained from a resection specimen or clinical follow-up period; 2) diagnostic adequacy, defined as the macroscopic sample sufficiency for diagnosis (yes/no) ; 3) presence of tissue cores, defined as a measurable microscopic cylinder, containing target organ cells with preserved histological architecture preserved tissue architecture, adequate for histologic

evaluation (yes/no); 4) the number of needles passes required for final diagnosis or diagnostic adequacy; and 5) procedure-related adverse events. In addition, general study, patient, lesion, sampling and tissue handling characteristics were recorded, as well as the definition of the gold standard diagnosis.

Assessment of methodological quality

Study quality and risk of bias were assessed using a scoring system based on the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool with the Cochrane Collaboration's tool for assessing risk of bias [12]. Risk of bias was assessed based on; random sequence generation (selection bias), allocation concealment (selection bias), comparable study arms (patient and EUS-characteristics), statistical design (power analysis and data interpretation), blinding of participants and personnel (performance bias), blinding of the data analyst to the final outcome (detection bias), coping with incomplete outcome data (attrition bias), selective reporting (reporting bias), the gold standard used (resection specimens, FNA/B or clinical follow-up), and whether the study design was single or multicenter. Any disagreement was resolved by discussion with the third author (MB).

Statistical analysis

Categorical outcome measures were summarized as weighted proportions and 95% Confidence Interval (CI) for both needle types. The number of needle passes was summarized as the standardized mean difference (SMD) and 95% CIs. The meta-analysis was performed by pooling the estimates of effect of the included studies using the random effect Manzel-Haenszel method. P-values of < 0.05 were considered to be statistically significant. The degree of heterogeneity was calculated using the I^2 index, and the presence of publication bias was assessed by examination of funnel plot asymmetry. Statistical analyses were executed by Review manager 5.3 (The Cochrane Collaboration, Oxford, UK) and R (version 3.4.2).

To assess the influence of lower quality studies, those with a 'high risk of bias' in more than four QUADAS-2 categories were in turn removed from the analysis. In addition, to rule out small study effects and correct disparity of the underlying data, studies with a wide CI or a sample size of less than 100 were excluded in a sensitivity analysis. A wide CI was defined as more than five times the Odds ratio. Sensitivity analyses were only performed if at least three studies remained for analysis.

RESULTS

Results of the search

Our search identified 2841 titles, of which 1770 potential eligible studies were reviewed (Figure 2). 1697 studies were excluded based on their title and/or abstract. Reviewing the full text

of the remaining 73 articles resulted in an additional 55 exclusions, as these studies met our exclusion criteria. This resulted in 18 full text articles on FNA versus FNB.

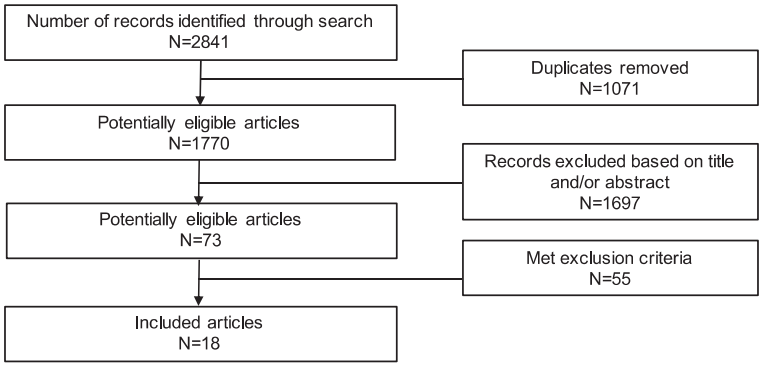


Figure 2. Flowchart of search and included studies.

FNA versus FNB

Study and case characteristics

The 18 studies comparing FNA to an FNB device comprised 2698 patients [13-30]; 1046 allocated to FNA and 1004 to FNB. The remaining 648 patients were alternately sampled with both needles. Study characteristics are presented in table 1-3. FNA was generally performed using the EchoTip Ultra needle (Cook Medical), mostly 22-gauge (G), followed by 25G and 19G. For FNB, all trials used a ProCore needle; 17 reversed and one forward-facing bevel. 12 studies assessed comparable needle sizes [14-16, 19-22, 24-27, 29] and three studies compared needles of different sizes [17, 28, 30]. One study varied needle size according to the target lesion location [23] and two left the decision up to the endosonographer [13, 18].

Eight studies concerned solid pancreatic masses [14, 15, 17, 21, 23, 25, 29, 30] and one subepithelial lesions [18]. The remainder 10 included any solid gastrointestinal lesion (Table 1). The number of needle passes varied considerably, ranging from a single to more than six passes per target lesion (Table 2). ROSE was available in 11 of the 18 studies. Tissue handling differed greatly for FNA samples, ranging from processing as smears or liquid based cytology (LBC, comprising ThinPrep or cell block) to collection in formalin. FNB specimens were generally collected in formalin (Table 2).

Quality and risk of bias

The quality and risk of bias of the trials is summarized in figures 3A and B. Overall, more than 75% of the studies harbored a low risk of selection, performance, detection, attrition, and reporting bias. Also, most studies were sufficiently powered, well designed and had comparable study arms for FNA and FNB. However, FNA or FNB diagnosis was used as the gold standard

Table 1: Characteristics of patients and studies included, FNA versus FNB

Study details	Full text	N	Target lesions	Needle sizes	Dual needle use**	Lesion size, mean ±SD, or median (range) mm		Primary endpoint	Gold standard
						FNA	FNB		
Aadam et al. 2016, USA	Yes	140	Solid lesions in the GI-tract	**FNA**: EchoTip, Expect 22, 25G **FNB:** ProCore 19, 22, 25G	No	30.2 ±18.7	29.2 ±14.1	Diagnostic accuracy	FNA/B diagnosis
Alatawi et al. 2015, France	Yes	100	Solid pancreatic lesions	**FNA**: EchoTip 22G **FNB:** ProCore 22G	No	33 ±2.7	32 ±5.1	No. of passes to obtain a diagnosis	Resection or 1 yr FU
Bang et al. 2012, USA	Yes	56	Solid pancreatic lesions	**FNA**: Expect 22G **FNB:** ProCore 22G	No	33.7 ±7.2	32.5 ±9.0	No. of passes to obtain a diagnosis	Resection or >6 mo. FU
Cheng 2018, China	Yes	377	Solid GI lesions	**FNA**: EchoTip 22G **FNB:** ProCore 22G	No	29.5 (4.5-90)	29.1 (6.0-85)	Diagnostic accuracy after 4 passes	Resection or 48 weeks FU
Hedenström 2017, Sweden	Yes	68	Solid pancreatic lesions	**FNA:** Various brands 25G **FNB:** ProCore 22G	Yes	30 (8-150)	30 (8-150)	Diagnostic accuracy	Resection or 12 mo. FU
Hedenström 2017, Sweden	Yes	70	Subepithelial lesions	**FNA:** Various brands 22, 25G **FNB**: ProCore 22, 19G	Yes	30 (6-220)	30 (6-220)	Diagnostic accuracy	Resection or 12 mo. FU
Hucl et al. 2013, India	Yes	139	Solid pancreatic lesions and lymph nodes	**FNA**: EchoTip 22G **FNB:** ProCore 22G	Yes	38.7 ±15.0	38.7 ±15.0	Diagnostic accuracy	Resection or 6 mo. FU
Iwashita 2017, Japan	Yes	110	Solid lesions around upper intestine	**FNA:** EchoTip 19G **FNB:** ProCore 19G	Yes	36 (27-45)	35 (27-43)	Diagnostic accuracy of a histological diagnosis	Resection or 6 mo. FU
Kamata et al. 2016, Japan	Yes	214	Solid pancreatic lesions	**FNA:** EchoTip 25G **FNB:** ProCore 25G	No	27.9 ±14.4	29.3 ±15.6	Diagnostic accuracy	Resection or >1 yr FU
Lee et al. 2014, Korea	Yes	116	Solid pancreatic lesions	**FNA:** EchoTip 22, 25G **FNB:** ProCore 22G, 25G	No	36.5 (17-74)	36.5 (15-100)	Diagnostic accuracy	Resection or >6 mo. FU
Lee 2017, Korea	Yes	58	Solid GI lesions	**FNA:** EchoTip 22G **FNB**: ProCore 22G	No	44.3 ±32.3	37.5±20.6	Area of overall specimen and core tissue	Resection, EUS-FNA/B or >1 yr FU
Nagula 2018, USA	Yes	274	Solid GI lesions	**FNA:** EchoTip, Expect 22G **FNB**: ProCore 22G	No	33.0 ±16.6* 23.9 ±16* 29.2 ±6.7*	35.1 ±23.8* 21.9 ±8.1* 32.7 ±10.8*	Diagnostic yield	EUS-FNA/B or 3-6 mo. FU

Table 1: Characteristics of patients and studies included, FNA versus FNB (*continued*)

Study details	Full text	N	Target lesions	Needle sizes	Dual needle use**	Lesion size, mean ±SD, or median (range) mm		Primary endpoint	Gold standard
Noh 2018, Korea	Yes	60	Unresectable pancreatic cancer	**FNA:** EZ shot 22G **FNB**: ProCore 22G	Yes	31 ±8.0	31 ±8.0	Diagnostic accuracy for malignancy	Repeated EUS-guided sampling
Othman 2017, USA	Yes	107	Pancreatic, peripancreatic and submucosal lesions	**FNA:** EZ shot, Expect 22G **FNB**: 22G ProCore	No	NR	NR	Specimens adequacy	Resection or 6 mo. FU
Sterlacci 2016, Germany	Yes	56	Solid GI lesions	**FNA:** EchoTip 22G **FNB**: ProCore 22G	Yes	33 ±12	33 ±12	Diagnostic accuracy	Resection, FU until end of study
Van Riet, 2019, The Netherlands	Yes	608	Solid GI lesions	**FNA:** EchoTip 25G **FNB:** ProCore 20G	No	27 (20-40)	29 (20-40)	Diagnostic accuracy	Resection or FU > 9 mo.
Vanbiervliet et al. 2014, France	Yes	80	Solid pancreatic lesions	**FNA**: EchoTip 22G **FNB**: ProCore 22G	Yes	33.9 ±10.8 (11-60)	34 ±11 (11-60)	Diagnostic accuracy	FNA/B diagnosis
Weston, 2017, USA	Yes	60	Solid pancreatic lesions	**FNA**: EchoTip 25G **FNB**: ProCore 22G	Yes	NR	NR	Diagnostic adequacy	NR

*NR: not reported; FNA: fine-needle aspiration; FNB; fine-needle biopsy; SD: standard deviation; FU: follow-up; mo: months; yr: year, no.: number. *Lesion size of solid mass lesions (pancreas, mediastinum, liver, and other), Lymph nodes, and submucosal tumors respectively. **Dual needle use: both needles used for the same target lesion during the same EUS-procedure.*

Table 2: Summary of EUS-procedure details in included studies, FNA versus FNB

Study details	No. of passes according to protocol	No. of to-and fro movements	Fanning	Sampling technique	ROSE	Preparation of cytology	Preparation of histology
Aadam et al. 2016, USA	≤3	10-15	NR	**FNA**: suction or slow pull **FNB**: slow pull	Yes	- air dry, DiffQuick and PAP stain - cell block of remaining specimens	- smash preparation on slides - rest specimens in formalin
Alatawi et al. 2015, France	NA	10-20	Yes	suction	No	- formalin, cell block, HE and PAP stain	- formalin, HE stain
Bang et al. 2012, USA	NA	**FNA**: 12-16 **FNB**: 4	NR	**FNA**: none **FNB**: suction	Yes	- air dry, DiffQuick, alcohol dry, PAP stain	- Hank buffered salt solution, formalin, HE stain
Cheng 2018, China	4	**20**	No	Pass 1 and 2: slow pull Pass 3 and 4: suction	Yes	- smear preparation	- macroscopic cores in formalin
Hedenström 2017, Sweden	2-6	**8-10**	Yes	suction	Yes	-air dry, Giemsa stain -ThinPrep of remaining specimens or when ROSE was not available	- formalin
Hedenström 2017, Sweden	2-6	NR	Yes	suction	Yes	-air dry, Giemsa stain -ThinPrep of remaining specimens or when ROSE was not available	- formalin
Hucl et al. 2013, India	NA	10	NR	suction	No	- formalin	
Iwashita 2017, Japan	1	3-5	NR	suction	No	-alcohol fixation, PAP stain	-whitish parts in formalin
Kamata et al. 2016, Japan	1	20	Yes	slow Pull	No	- formalin, mercurochrome and HE stain	
Lee et al. 2014, Korea	≤3	10-20	NR	suction	Yes	- air and alcohol dry, DiffQuick and PAP stain - rest material in formalin, HE and PAS stain	
Lee 2017, Korea	1-3	NR	NR	slow pull, if unsuccessful suction	No	-formalin	

Table 2: Summary of EUS-procedure details in included studies, FNA versus FNB (*continued*)

Study details	No. of passes according to protocol	No. of to-and fro movements	Fanning	Sampling technique	ROSE	Preparation of cytology	Preparation of histology
Nagula 2018, USA	1-4	NR	NR	**FNA**: suction **FNB**: slow pull	Yes	-air dry, DiffQuick stain on-site -Alcohol fixed off site, PAP stain -remaining aspirate or in absence of ROSE, specimen in standard solution for cell block	
Noh 2018, Korea	2	15-20	NR	**FNA**: suction **FNB**: slow pull	No	-alcohol fixed smears, PAP stain	- formalin
Othman 2017, USA	1-7	10	NR	suction	Yes	-air dry or fixation in Carnoy's solution and staining with DiffQuick or PAP	
Sterlacci 2016, Germany	1-3	10-20	NR	suction	No	-air dry, Giemsa staining	-macroscopic cores in formalin -remaining material alcohol fixed on smear and stained with PAP
Van Riet, 2019, The Netherlands	≥3	NR	Yes	suction, slow pull, a combination, or none	Yes	-smears DiffQuick, HE, PAP stain -remaining material CytoLyt, alcohol, formalin or CytoRich Red -cell suspension processed using ThinPrep or cell block technique	- CytoLyt or formalin
Vanbiervliet et al. 2014, France	**FNA**: 2 **FNB**: 1	10	Yes	suction	Yes	- collected in CytoLyt, ThinPrep[1], fixed in 95% ethanol, PAP stain	- collected in CytoLyt, fixed in formalin, cell block and HE stain
Weston, 2017, USA	2 with each needle	5-10	NR	**FNA**: suction **FNB**: suction or capillary suction	Yes	-air dry or alcohol fixed and DiffQuick or PAP stain -cell block specimens in formalin	-formalin

FNA: fine-needle aspiration; HE: Hematoxylin and eosin; LBM: liquid based medium; NA: not applicable; NR: not reported; PAP: Papanicolaou; PAS: periodic acid-Schiff; ROSE: rapid on-site pathological examination, No.: number. [1]ThinPrep: Hologic Inc., Marlborough, Massachusetts, USA.

Table 3: Outcome measures for individual studies (all lesion types) of meta-analysis comparing FNA to FNB

Study details	Diagnostic accuracy n/n (%)		No. of passes performed, mean±SD, or median (range)		Diagnostic adequacy n/n (%)		Tissue cores n/n (%)		Adverse events n/n (%)	
	FNA	FNB	FNA	FNB	FNA	FNB	FNA	FNB	FNA	FNB
Aadam et al. 2016, USA	47/70 (67.1)	63/70 (90)	3.0±1.0	2.8±1.0	42/70 (60)	58/70 (83)	NR	NR	0/70 (0)	0/70 (0)
Alatawi et al. 2015, France	45/50 (90)	50/50 (100)	3.28±1.0	2.59±0.49	NR	NR	16/50 (32)	38/50 (76)	0/50 (0)	0/50 (0)
Bang et al. 2012, USA	28/28 (100)	25/28 (89)	1.61±0.88	1.28±0.54	28/28 (100)	26/28 (93)	19/28 (68)	23/28 (82)	1/28 (4)	1/28 (4)
Cheng 2018, China	152/190 (80)	171/187 (91)	4	4.	NR	NR	152/190 (80)	171/187 (91)	3/190 (2)	1/187 (1)
Hedenström 2017, Sweden	53/68 (78)	47/68 (69)	3 (2-4)	2 (2-3)	NR	NR	NR	NR	1/68 (1)	0/68 (0)
Hedenström 2017, Sweden	34/70 (49)	58/70 (83)	3 (1-4)	2 (1-4)	NR	NR	NR	NR	0/70 (0)	1/70 (1)
Hucl et al. 2013, India	112/139 (80.6)	110/139 (79)	2.5±0.9	1.2±0.5	127/144 (88)	125/144 (87)	84/127 (66)	86/125 (69)	0/144 (0)	0/144 (0)
Iwashita 2017, Japan	87/110 (79)	99/110 (90)	1	1	NR	NR	89/110 (81)	93/110 (85)	4/110 (4)	4/110 (4)
Kamata et al. 2016, Japan	82/108 (76)	90/106 (85)	1	1	NR	NR	75/108 (69)	86/106 (81)	0/108 (0)	0/106 (0)
Lee et al. 2014, Korea	55/58 (95)	57/58 (98)	2.0 (1-5)	1.0 (1-5)	NR	NR	45/58 (78)	48/58 (83)	1/58 (2)	3/58 (5)
Lee 2017, Korea	22/27 (82)	25/31 (81)	2 (1-3)	1 (1-3)	NR	NR	27/29 (93)	29/29 (100)	0/29	0/29
Nagula 2018, USA	123/135 (91)	123/139 (89)	1.83 ±1.17	1.65 ±0.93	NR	NR	NR	NR	1/135 (1)	2/139 (1)
Noh 2018, Korea	57/60 (95)	56/60 (93)	2	2	NR	NR	NR	NR	0/60 (0)	0/60 (0)
Othman 2017, USA	NR	NR	2.74±1.32	2.67±1.37	50/73 (68)	27/36 (75)	NR	NR	3/72 (4)	1/35 (3)
Sterlacci 2016, Germany	48/54 (89)	49/51 (96)	1.5±0.6	1.7±0.6	54/56 (96)	51/56 (91)	35/56 (63)	36/56 (64)	0/56 (0)	0/56 (0)
Van Riet, 2019, The Netherlands	237/306 (78)	263/302 (87)	NR	NR	248/306 (82)	263/302 (87)	136/306 (45)	232/302 (77)	3/306 (1)	2/302 (1)
Vanbiervliet et al. 2014, France	74/80 (93)	72/80 (90)	1	2	75/80 (94)	71/80 (89)	70/80 (88)	56/80 (70)	1/80 (1)	0/80 (0)
Weston, 2017, USA	NR	NR	2	2	49/60 (82)	48/59 (81)	NR	NR	0/60 (0)	0/60 (0)

NR: not reported.

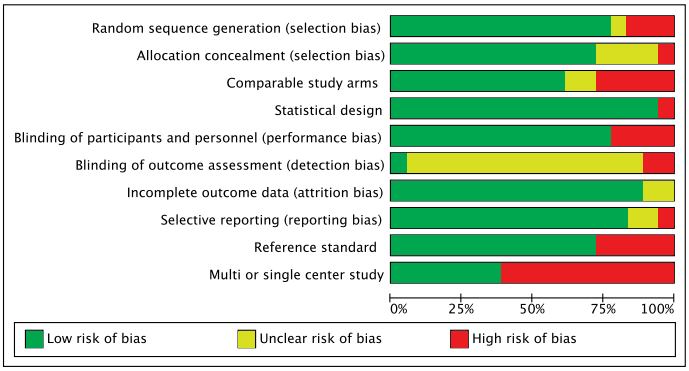


Figure 3A. Quality and risk of bias of studies comparing FNA to FNB based on the QUADAS-II and Cochrane Collaboration's tool.

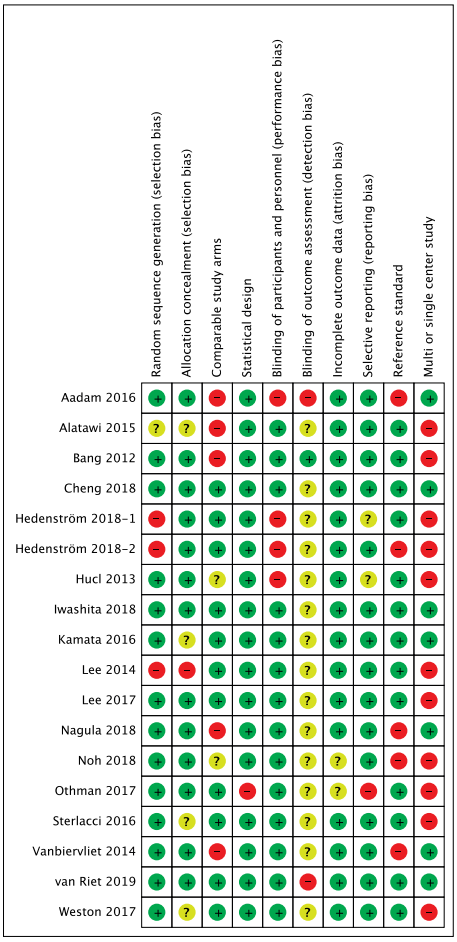


Figure 3B. Summary of quality and risk of bias in all studies comparing FNA to FNB based on the QUADAS-II and Cochrane Collaboration's tool.

diagnosis for malignancy in approximately 30% of the studies [13, 18, 24, 25, 29], which we considered to be suboptimal. Lastly, only seven out of 18 studies were multicenter trials [13, 16, 20, 21, 24, 28, 29].

Outcome parameters of the included studies

The outcome measures of all individual studies from this meta-analysis are presented in table 3 and will be discussed separately below.

Diagnostic accuracy

16 studies, involving 2528 patients, reported on the diagnostic accuracy [13-25, 27-29]. The pooled accuracy for sampling any solid lesion was significantly better for the ProCore FNB of than for the FNA needles (OR1.70, 95%CI 1.19 to 2.41, p=0.003, table 4 and figure 4A). Heterogeneity amongst the studies was moderate (I^2=59%) and the funnel plot did not demonstrate signs of publication bias (Figure 4E). Sensitivity analyses did not change outcomes (Table 4 and figure 4B). Subgroup analyses for solid pancreatic target lesions demonstrated a similar outcome, with a higher pooled diagnostic accuracy for FNB than FNA (Table 4, figure 4C), without change after sensitivity analysis (Table 4, figure 4D).

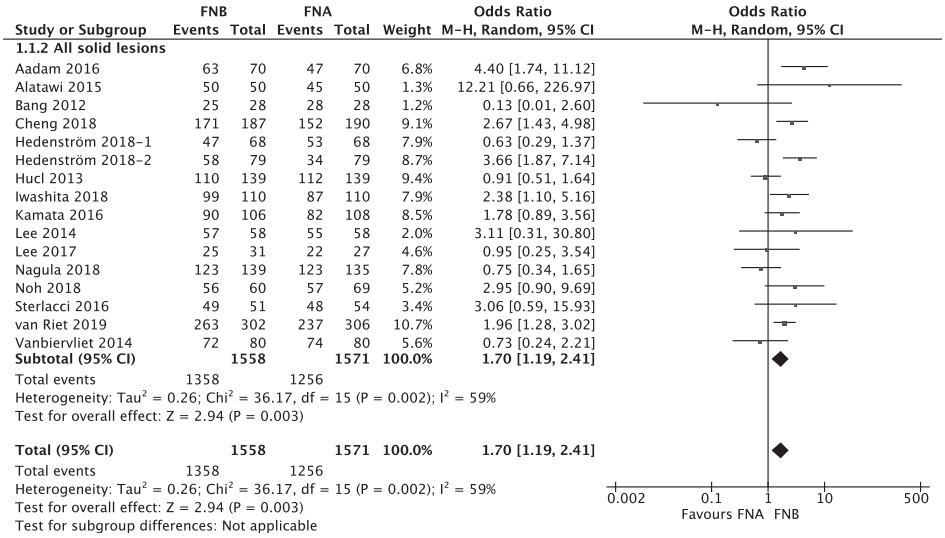
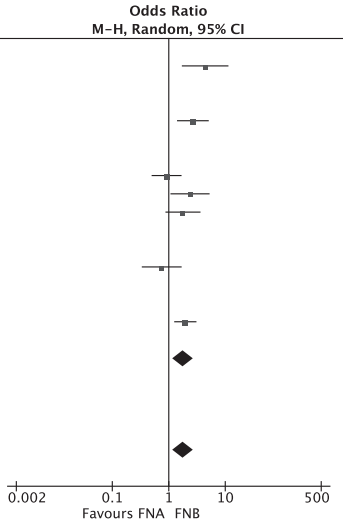


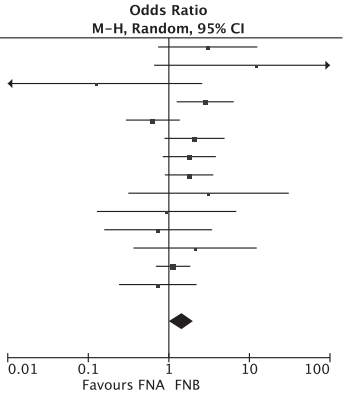
Figure 4A-D. Forest plots comparing diagnostic accuracy between FNA and FNB.
A: All studies

Study or Subgroup	FNB Events	FNB Total	FNA Events	FNA Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.2 All solid lesions						
Aadam 2016	63	70	47	70	10.6%	4.40 [1.74, 11.12]
Alatawi 2015	50	50	45	50	0.0%	12.21 [0.66, 226.97]
Bang 2012	25	28	28	28	0.0%	0.13 [0.01, 2.60]
Cheng 2018	171	187	152	190	15.3%	2.67 [1.43, 4.98]
Hedenström 2018-1	47	68	53	68	0.0%	0.63 [0.29, 1.37]
Hedenström 2018-2	58	79	34	79	0.0%	3.66 [1.87, 7.14]
Hucl 2013	110	139	112	139	15.9%	0.91 [0.51, 1.64]
Iwashita 2018	99	110	87	110	12.7%	2.38 [1.10, 5.16]
Kamata 2016	90	106	82	108	14.1%	1.78 [0.89, 3.56]
Lee 2014	57	58	55	58	0.0%	3.11 [0.31, 30.80]
Lee 2017	25	31	22	27	0.0%	0.95 [0.25, 3.54]
Nagula 2018	123	139	123	135	12.5%	0.75 [0.34, 1.65]
Noh 2018	56	60	57	69	0.0%	2.95 [0.90, 9.69]
Sterlacci 2016	49	51	48	54	0.0%	3.06 [0.59, 15.93]
van Riet 2019	263	302	237	306	18.9%	1.96 [1.28, 3.02]
Vanbiervliet 2014	72	80	74	80	0.0%	0.73 [0.24, 2.21]
Subtotal (95% CI)		**1053**		**1058**	**100.0%**	**1.78 [1.19, 2.66]**
Total events	919		840			
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 15.60$, df = 6 (P = 0.02); $I^2 = 62\%$						
Test for overall effect: Z = 2.80 (P = 0.005)						
Total (95% CI)		**1053**		**1058**	**100.0%**	**1.78 [1.19, 2.66]**
Total events	919		840			
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 15.60$, df = 6 (P = 0.02); $I^2 = 62\%$						
Test for overall effect: Z = 2.80 (P = 0.005)						
Test for subgroup differences: Not applicable						



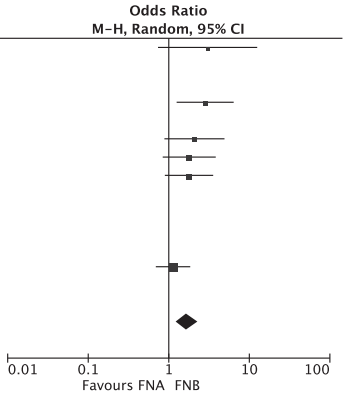
B: Sensitivity analysis

Study or Subgroup	FNB Events	FNB Total	FNA Events	FNA Total	Weight	Odds Ratio M-H, Random, 95% CI
Aadam 2016	33	36	29	37	4.6%	3.03 [0.74, 12.52]
Alatawi 2015	50	50	45	50	1.2%	12.21 [0.66, 226.97]
Bang 2012	25	28	28	28	1.2%	0.13 [0.01, 2.60]
Cheng 2018	114	123	103	126	10.6%	2.83 [1.25, 6.39]
Hedenström 2018-1	47	68	53	68	11.4%	0.63 [0.29, 1.37]
Hucl 2013	59	69	51	69	9.9%	2.08 [0.88, 4.92]
Iwashita 2018	55	70	47	70	11.6%	1.79 [0.84, 3.83]
Kamata 2016	90	106	82	108	13.0%	1.78 [0.89, 3.56]
Lee 2014	57	58	55	58	2.0%	3.11 [0.31, 30.80]
Lee 2017	5	9	4	7	2.5%	0.94 [0.13, 6.87]
Noh 2018	56	60	57	60	4.0%	0.74 [0.16, 3.44]
Sterlacci 2016	36	38	34	38	3.2%	2.12 [0.36, 12.32]
van Riet 2019	112	154	111	158	17.9%	1.13 [0.69, 1.85]
Vanbiervliet 2014	72	80	74	80	6.9%	0.73 [0.24, 2.21]
Total (95% CI)		**949**		**957**	**100.0%**	**1.44 [1.03, 2.01]**
Total events	811		773			
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 17.89$, df = 13 (P = 0.16); $I^2 = 27\%$						
Test for overall effect: Z = 2.15 (P = 0.03)						



C: Pancreatic lesions only

Study or Subgroup	FNB Events	FNB Total	FNA Events	FNA Total	Weight	Odds Ratio M-H, Random, 95% CI
Aadam 2016	33	36	29	37	4.4%	3.03 [0.74, 12.52]
Alatawi 2015	50	50	45	50		Not estimable
Bang 2012	25	28	28	28		Not estimable
Cheng 2018	114	123	103	126	13.4%	2.83 [1.25, 6.39]
Hedenström 2018-1	47	68	53	68		Not estimable
Hucl 2013	59	69	51	69	12.0%	2.08 [0.88, 4.92]
Iwashita 2018	55	70	47	70	15.4%	1.79 [0.84, 3.83]
Kamata 2016	90	106	82	108	18.5%	1.78 [0.89, 3.56]
Lee 2014	57	58	55	58		Not estimable
Lee 2017	5	9	4	7		Not estimable
Noh 2018	56	60	57	60		Not estimable
Sterlacci 2016	36	38	34	38		Not estimable
van Riet 2019	112	154	111	158	36.2%	1.13 [0.69, 1.85]
Vanbiervliet 2014	72	80	74	80		Not estimable
Total (95% CI)		**558**		**568**	**100.0%**	**1.68 [1.24, 2.26]**
Total events	463		423			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.04$, df = 5 (P = 0.41); $I^2 = 1\%$						
Test for overall effect: Z = 3.39 (P = 0.0007)						



D: Sensitivity analysis of pancreatic lesions

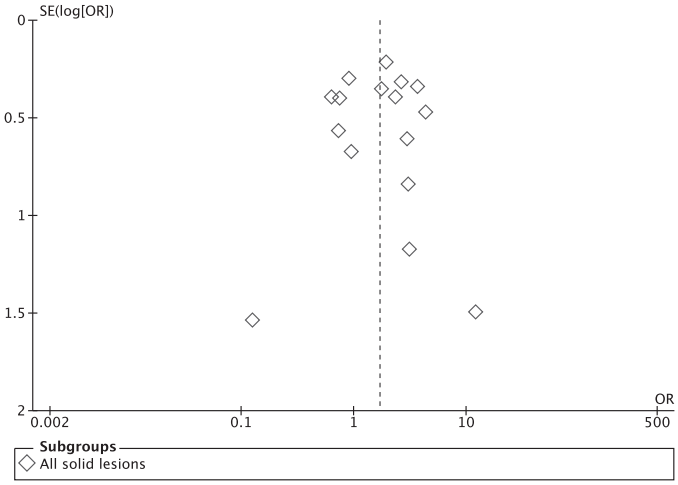


Figure 4E. Funnel plot of the diagnostic accuracy for all included studies.

Diagnostic adequacy

Seven studies concerning 1186 patients reported on diagnostic adequacy [13, 15, 19, 26-29], with moderate heterogeneity (I^2=54%). There was no difference in sample adequacy between FNA and FNB (OR1.17, 95%CI 0.70 to 1.96, p=0.55, table 4, figure 5A), even after sensitivity analysis (Table 4, figure 5B). The same was true for pancreatic lesions (Table 4, figure 5C). Sensitivity analysis on this subgroup was not performed as this would leave less than three studies for analysis.

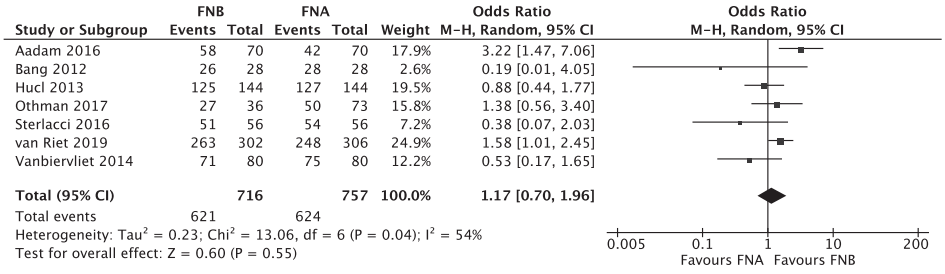
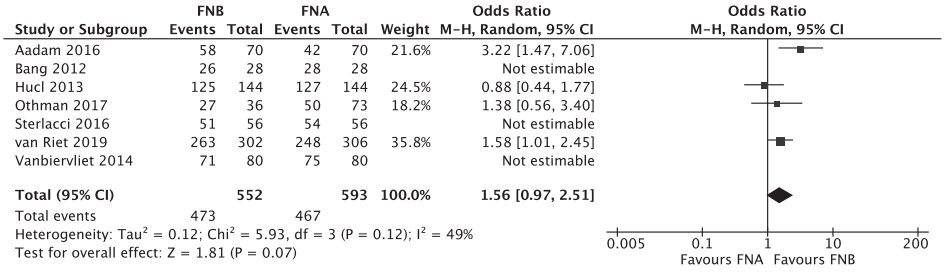
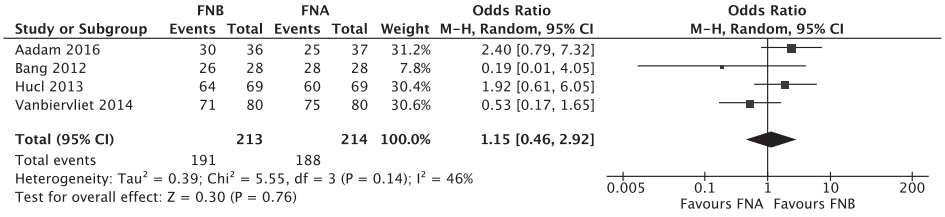


Figure 5A-C. Forest plots comparing sample adequacy between FNA and FNB.
A: All studies



B: Sensitivity analysis



C: Pancreatic lesions only

Number of passes performed

Five studies reported on the mean or average number of passes performed to establish a diagnosis [14, 15, 24] or obtain an adequate sample according to the on-site pathologist [13, 19]. The mean number of passes was lower for FNB than FNA needles (MD -0.54, 95%CI -1.03 to -0.04, p=0.03, table 4, figure 6A). Heterogeneity was high amongst the studies (I^2=94%). Sensitivity analysis could not be performed, as this would involve less than three studies. Subgroup analysis for pancreatic lesions showed similar results, requiring fewer passes with FNB (Table 4, figure 6B).

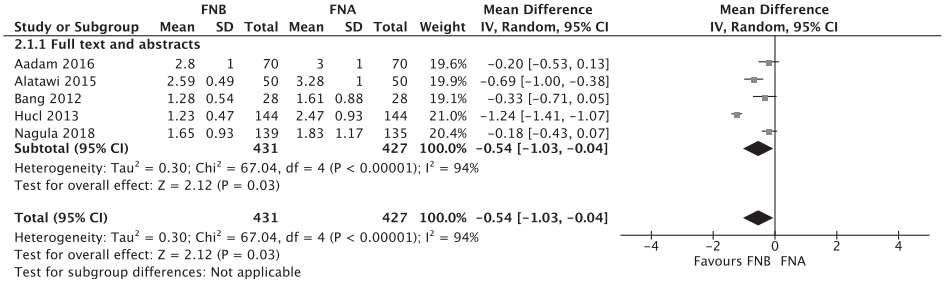
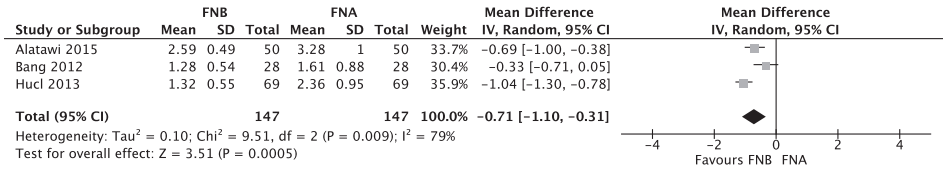


Figure 6A-D. Forest plots comparing the mean number of needle passes to obtain a diagnosis between FNA and FNB.

A: All studies



B: Pancreatic lesions only

Presence of tissue cores

Ten studies reported on presence of tissue cores in 1537 patients [14, 15, 19-23, 27-29]. Heterogeneity amongst the studies was high (I^2=83%). Before sensitivity analysis, a trend towards better tissue core yield for ProCore FNB was observed, with a pooled estimate rate of 77% (95%CI 75 to 80) for ProCore, and 63% (95%CI 61 to 68, table 4, figure 7A) for FNA. After sensitivity analysis, this became a significant benefit (OR2.34, 95%CI 1.21 to 4.51, p=0.01, table 4, figure 7B). Similarly, subgroup analysis for pancreatic lesions demonstrated a trend towards a higher tissue core rate for FNB (Table 4, figure 7C), and a significantly higher yield after studies of suboptimal quality were removed (OR3.64 95%CI 1.85 to 7.13, p<0.001, table 4, figure 7D).

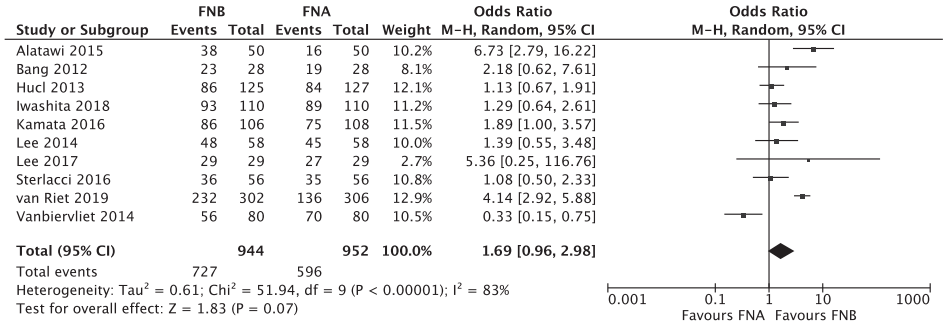
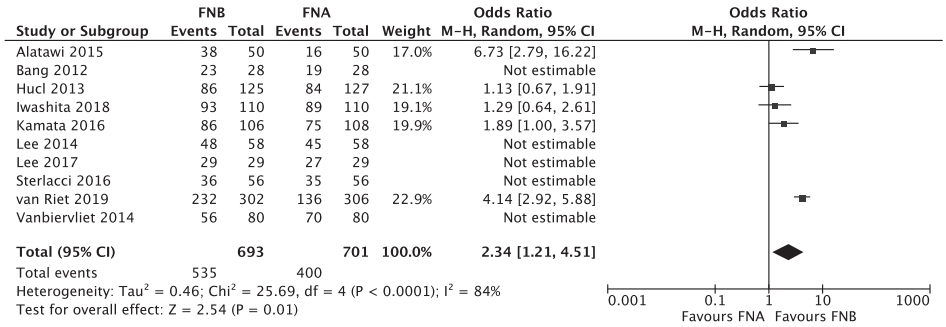
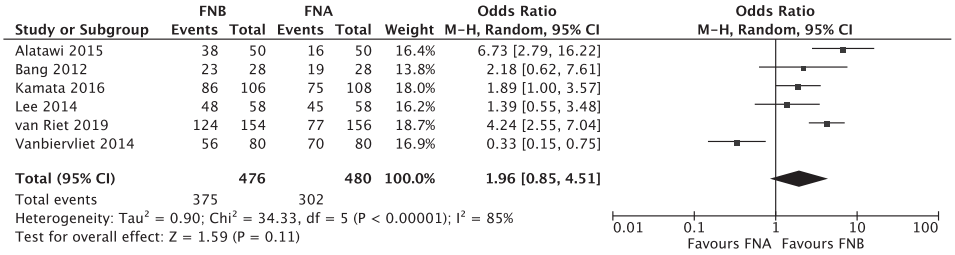


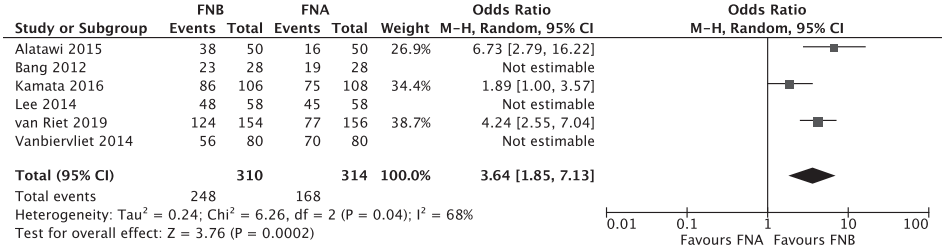
Figure 7A-D. Forest plots comparing the presence of tissue cores between FNA and FNB samples.
A: All studies



B: Sensitivity analysis



C: Pancreatic lesions only



D: Sensitivity analysis of pancreatic lesions

Adverse events

All studies reported on the occurrence of procedure-related adverse events, which did not differ between FNA and FNB (OR 0.91, 95%CI 0.45 to 1.86, p=0.80, table 4, figure 8). The pooled estimate for complications was 0.9% (95%CI 0.5 to 1.4) for the ProCore and 1.1% (95%CI 0.6 to 1.6) for the FNA devices. There was no heterogeneity amongst the studies for this endpoint (I^2=0%).

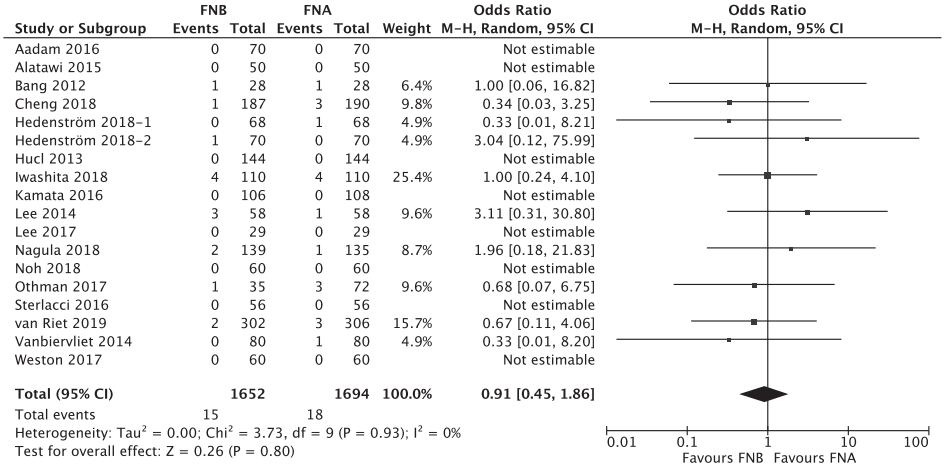


Figure 8. Forest plot comparing the adverse event rate between FNA and FNB.

Table 4: Summary of findings: pooled estimates of all outcome measures comparing FNA to FNB.

Outcome measure	Pooled estimate % (95%CI)		Pooled OR (95%CI)	p-value
	FNA	FNB		
Diagnostic accuracy				
All studies	81 (79 - 82)	87 (86 - 89)	1.70 (1.19 - 2.41)	0.003
Sensitivity analysis	79 (76 – 82)	87 (85 - 89)	1.78 (1.19 - 2.66)	0.005
Pancreas only	81 (78 – 83)	85 (83 – 88)	1.44 (1.03 – 2.21)	0.030
Sensitivity analysis	74 (71 – 78)	83 (80 – 86)	1.68 (1.24 – 2.26)	<0.001
Diagnostic adequacy				
All studies	82 (80 – 85)	87 (84 – 89)	1.17 (0.70 – 1.96)	0.550
Sensitivity analysis	79 (75 – 82)	86 (83 – 88)	1.56 (0.97 – 2.51)	0.070
Pancreas only	88 (83 – 92)	90 (85 – 93)	1.15 (0.46 – 2.92)	0.760
Sensitivity analysis	Not performed	Not performed	Not performed	
Mean no. of passes performed[1]				
All studies			-0.54 (-1.03 to – 0.04)	0.030
Pancreas only			-0.71 (-1.10 to -0.31)	0.009
Presence of tissue cores				
All studies	64 (61 – 67)	78 (75 – 80)	1.69 (0.96 – 2.98)	0.070
Sensitivity analysis	57 (53 – 61)	77 (74 – 80)	2.34 (1.21 – 4.51)	0.010
Pancreas only	63 (59 – 67)	79 (75 – 82)	1.96 (0.85 – 4.51)	0.110
Sensitivity analysis	54 (50 – 59)	80 (75 – 84)	3.64 (1.85 – 7.13)	<0.001
Adverse events				
All studies	1.0 (0.6 – 1.6)	0.8 (0.5 – 1.4)	0.91 (0.45 – 1.86)	0.800

OR: Odds ratio, No. : number, NP: not performed.

[1]*Standardized mean difference.*

DISCUSSION

The current meta-analysis is the first to demonstrate a convincing diagnostic benefit of the new generation FNB needles, specifically of the ProCore design, over FNA. The recent wave of publications enabled us to include a considerable number of new randomized controlled trials and limit our evaluation to high quality studies [11, 31-34]. Compared to FNA, FNB needles achieved a higher diagnostic accuracy and a higher tissue core rate, both in pancreatic and non-pancreatic lesions, with less needle passes. Complication rates were low and comparable for FNA and FNB. Since all of the included studies comprised ProCore needles, these results may not be straightly extrapolated to the other new FNB needles.

FNB outperformed FNA in several ways. First, the current meta-analysis confirmed their superior tissue core rate. Interestingly, sample adequacy did not differ between FNA and FNB. New preparation techniques such as ThinPrep and cell block enable pathologists to perform comparable tests on cytology and histology. However, these preparation techniques were widely applied in the current study population, yet diagnostic accuracy was still better for the ProCore FNB needles. The same applied for ROSE. The fact that most EUS-centers lack such

additional techniques and services is another reason to endorse FNB sampling, especially in low-volume or non-academic centers.

Furthermore, FNB required less passes to obtain a diagnosis. Although the complication rate was comparable for FNA and ProCore, fewer passes will minimize the risk of traumatic tissue traversing. Furthermore, less passes will limit procedure time and costs. The single study that assessed procedure time and costs [13] found FNB cost saving, which is in line with two other reports [35, 36].

Despite the better diagnostic performance and other above-mentioned benefits of FNB over FNA needles, the significant heterogeneity amongst studies should not be overlooked. This has already been described in previous meta-analyses to results from a diversity in EUS-sampling protocols and inconsistent use of outcome definitions. Regarding diverse practice patterns, it is well known that EUS-guided tissue sampling and processing techniques vary substantially [10]. Although present EUS-guidelines offer some recommendations, solid evidence is scarce [7, 37-40]. On top of this, many recommendations are dated, and keep running behind on the latest innovations [7, 40]. The subsequent lack of uniformity in EUS-practice renders EUS-device studies difficult to compare.

In addition, the lack of universal definitions for diagnostic outcome measures plays a role. The inconsistent use of terms for diagnostic accuracy, adequacy, and yield create confusion and hamper comparison of results. For example, diagnostic accuracy can refer to the accuracy in establishing a diagnosis or just accuracy in establishing presence of malignancy. Also, certain studies equate the diagnostic yield and diagnostic accuracy, whereas others use 'diagnostic yield' as a more subjective term, describing the presence of sufficient tissue for ROSE or pathological analyses. In addition, presence of malignancy (as gold standard) is variably established from resection specimens or FNA/B specimens. Another confusing definition is that of 'tissue cores'. It may be described as the presence of intact histologically tissue fragments or 'whitish material', the proportion or ratio of intact tissue fragments compared to the entire sample, or an intact 'tissue core' of a certain length and/or size.

Despite the fact that we selected large randomized controlled trials and removed studies of inferior quality in our sensitivity analyses, heterogeneity remained substantial. To improve the precision of our pooled estimates, we chose to perform a random rather than a fixed effect model for our analyses, as this model includes the variance within and between studies. The fact that this approach resulted in the inclusion of ProCore needles only (mainly with the reversed bevel design) results from the lack of trials that assessed SharkCore, Acquire, or the novel ProCore forward facing bevel design. As these needles are relatively new on the market, data on their performance is limited to small sized, single center, retrospective studies.

According to ClinicalTrials.gov, multiple studies comparing different design FNB needles are currently ongoing including two randomized controlled trials comparing FNA to Acquire (NTC02911974 and NTC0 3109639), two studies comparing FNA to SharkCore (NCT02678442 and NTC0 3532347), one comparing SharkCore to FNA with ROSE (NTC03485924), one compar-

ing a side-fenestrated needle to an Acquire needle (NTC03622229), one comparing SharkCore to Acquire (NTC03672032), and lastly one study that compares an unspecified core needle to FNA (NTC03435588). So far, no randomized controlled trials have compared ProCore to SharkCore. Unfortunately, two studies that aimed to do so were withdrawn, one because ProCore was no longer used in that clinic (NTC02766842), and another one because of a slow inclusion rate (NTC03011229).

In conclusion, this study demonstrates that the FNB ProCore needles outperform conventional FNA needles in diagnosing any solid lesion surrounding the gastrointestinal tract. This observation is of paramount importance in light of the increased need of EUS-guided tissue acquisition for personalized medicine and targeted therapy. However, head to head comparison studies between each of the new generation of FNB devices are needed to further establish the optimal needle design, preferably in an (international) multicenter randomized controlled setting.

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