Comparison between fine-needle biopsy and fine-needle aspiration for EUS-guided sampling of subepithelial lesions: a meta-analysis

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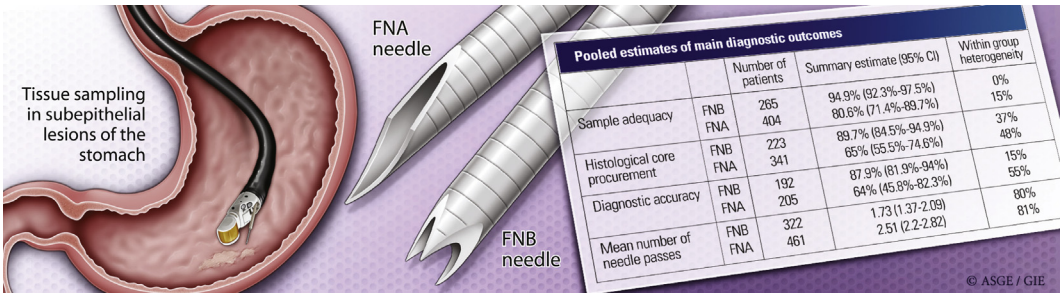
GRAPHICAL ABSTRACT



Background and Aims: There is limited evidence on the diagnostic performance of EUS-guided fine-needle biopsy (FNB) sampling in patients with subepithelial lesions. The aim of this meta-analysis was to compare EUS-guided FNB sampling performance with FNA in patients with GI subepithelial lesions.

Methods: A computerized bibliographic search on the main databases was performed through May 2019. The primary endpoint was sample adequacy. Secondary outcomes were diagnostic accuracy, histologic core procurement rate, and mean number of needle passes. Summary estimates were expressed in terms of odds ratio (OR) and 95% confidence interval (CI).

Results: Ten studies (including 6 randomized trials) with 669 patients were included. Pooled rates of adequate samples for FNB sampling were 94.9% (range, 92.3%-97.5%) and for FNA 80.6% (range, 71.4%-89.7%; OR, 2.54; 95% CI, 1.29-5.01; $P = .007$). When rapid on-site evaluation was available, no significant difference between the 2 techniques was observed. Optimal histologic core procurement rate was 89.7% (range, 84.5%-94.9%) with FNB sampling and 65% (range, 55.5%-74.6%) with FNA (OR, 3.27; 95% CI, 2.03-5.27; $P < .0001$). Diagnostic accuracy was significantly superior in patients undergoing FNB sampling (OR, 4.10; 95% CI, 2.48-6.79; $P < .0001$) with the need of a lower number of passes (mean difference, –.75; 95% CI, –1.20 to –.30; $P = .001$). Sensitivity analysis confirmed these findings in all subgroups tested. Very few adverse events were observed and did not impact on patient outcomes.

Conclusions: Our results speak clearly in favor of FNB sampling, which was found to outperform FNA in all diagnostic outcomes evaluated. (Gastrointest Endosc 2020;91:14-22.)

(footnotes appear on last page of article)

Subepithelial lesions (SELs) are detected incidentally in .8% to 2% of patients undergoing upper GI endoscopy.[1] Because a definitive diagnosis can rarely be established only on the basis of imaging morphology, tissue acquisition plays a pivotal role in the management of SELs. Bite-on-bite forceps biopsy sampling, in particular

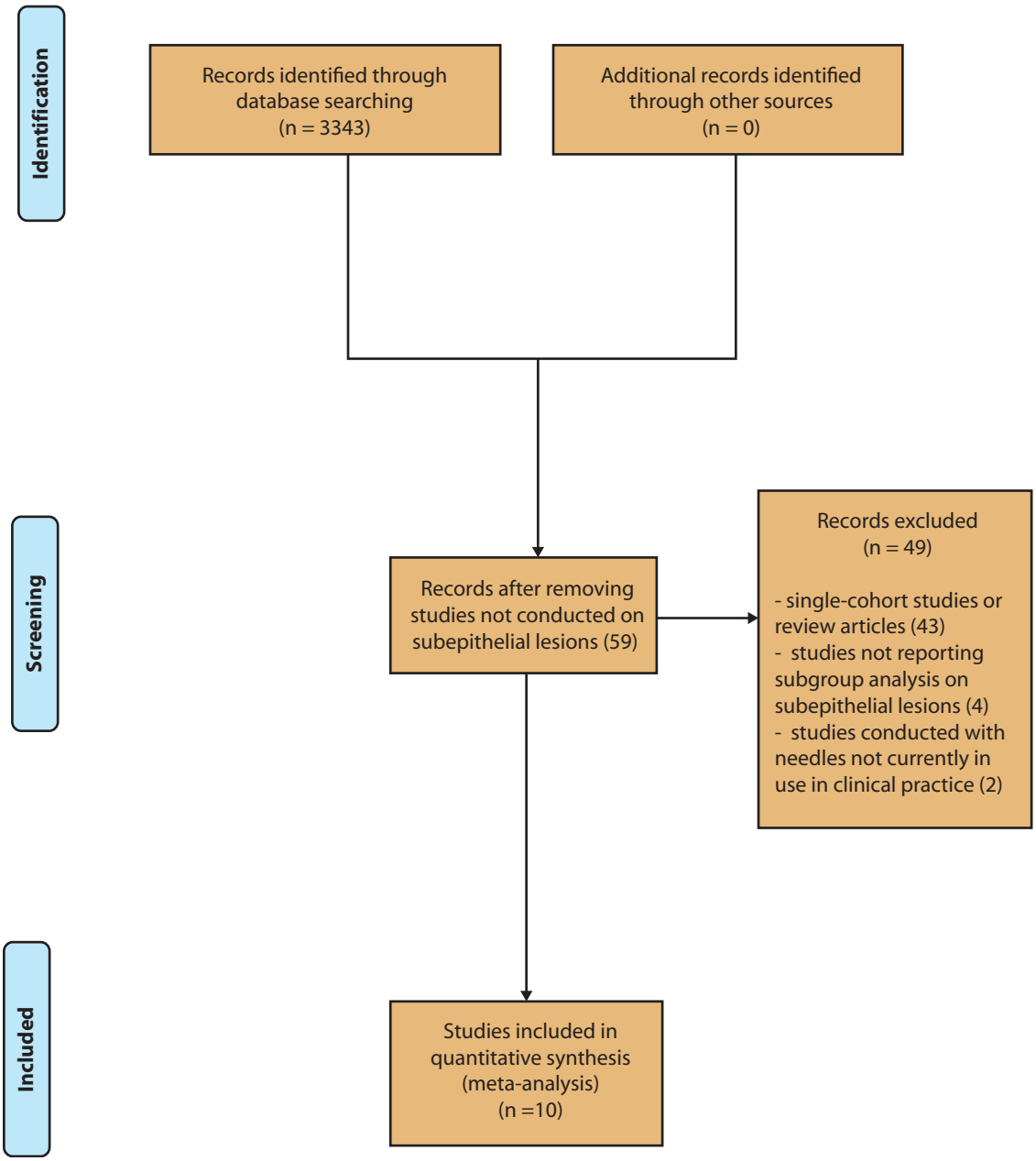


Figure 1. Flowchart of included studies.

the "jumbo unroofing technique," represents often the first-line approach able to determine variable results in terms of diagnostic yield, ranging from 17% to 94%.[2-4]

EUS-guided FNA did not prove to outperform bite-on-bite biopsy sampling in 2 prospective series,[5,6] and a meta-analysis of 17 studies found a pooled diagnostic yield of EUS-guided sampling in patients with SELs as high as 60%.[7] Cellular acquisition through EUS-FNA does not necessarily retain the stroma or associated architecture of surrounding tissue, which may be necessary to provide a definitive diagnosis. EUS-guided fine-needle biopsy (FNB) sampling, which typically uses a core biopsy needle and preserves the cellular architecture, has become an increasingly useful tool in the diagnostic algorithm of other abdominal lesions, such as pancreatic masses.[8] However, preliminary experiences with the Tru-Cut FNB needle (Quick-Core; Wilson-Cook Medical Inc, Winston-Salem, NC, USA) did not increase significantly the diagnostic yield of tissue acquisition in patients with SELs[9]; moreover, the aforementioned meta-analysis showed no difference in subgroup analysis conducted according to tissue-acquisition technique (FNA vs Tru-Cut needle biopsy sampling) or needle caliper (19 gauge vs 22 gauge vs 25 gauge).[7] Based on this evidence, current guidelines recommend EUS-guided sampling only in specific subgroups of patients

TABLE 1. Characteristics of included studies

Study	Arm	Sample size	Study period/design	Country	Age (y)	Gender, male (%)
Bang 2019[16,*]	FNB	86	2014-2017/retrospective	USA	67.1 ± 12.9	54.4
	FNA	132			65.8 ± 13.7	56.7
Fujita 2018[17]	FNB	17	2013-2017/retrospective	Japan	72 (58-74)	58.8
	FNA	44			67 (55-74)	61.3
El Chafic 2017[18]	FNB	16	2011-2016/retrospective	USA	65 ± 12.7	60
	FNA	91			64.8 ± 15.7	48.3
Han 2016[19,*]	FNB	22	2012-2014/crossover RCT	Korea	59.5 (44.2-67.5)	45.
	FNA	22				
Hedenstrom 2018[20]	FNB	70	2012-2015/crossover RCT	Sweden	68 (28-92)	58.5
	FNA	70				
Inoue 2019[21,*]	FNB	57	2010-2017/retrospective	Japan	66 (31-91)	52.6
	FNA	57			66 (25-88)	50
Iwai 2018[22,*]	FNB	23	2015-2016/crossover RCT	Japan	64.3 (35-78)	34.7
	FNA	23				
Kim 2014[23]	FNB	12	2013/RCT	Korea	60 ± 16.2	33
	FNA	10			51 ± 11.5	60
Lee 2017[24,*]	FNB	8	2013-2014/RCT	Korea	66 (36-81)	75.8
	FNA	6			69 (26-85)	62
Nagula 2018[25,*]	FNB	12	2012-2014/RCT	USA	67.8 ± 12.7	52.2
	FNA	6			65.2 ± 13.2	51.1

FNB, Fine-needle biopsy; *NR*, not reported; *ROSE*, rapid on-site evaluation; *RCT*, randomized controlled trial.
*Studies including several kinds of abdominal masses. Only subepithelial lesions were reported here and included in the analysis.

with SELs, particularly in poor surgical candidates with large lesions ≥2 cm or when there is a suspicion of carcinoma or metastasis to the GI wall.[1]

Over the last few years, novel needle designs have been developed. The reverse bevel needle (ProCore; Cook Medical, Limerick, Ireland) seems to address most limitations of previous biopsy sampling devices, thanks to the addition of a reverse bevel just distal to the tip that promotes collection of a core sample. Two newer FNB needles were recently introduced into endoscopic practice: 1 with fork-tip design with 2 leading sharp tips on the opposite side of the lumen (SharkCore; Medtronic, Minneapolis, Minn, USA) and 1 with 3 symmetric cutting edges (Acquire; Boston Scientific Corp, Natick, Mass, USA).[10] Although these novel needle designs are believed to improve tissue capture and were found to obviate the need for pathologic rapid on-site evaluation (ROSE) in pancreatic masses,[8,11] there is limited evidence on their diagnostic performance in patients with SELs. Hence, there is a pressing need to systematically compare currently available FNB needles with FNA to define the optimal EUS-guided sampling technique and to reappraise the role of EUS in patients with SELs.

The aim of this meta-analysis was to compare EUS-guided FNB sampling performance with FNA in patients with GI SELs. The primary endpoint was sample adequacy. Secondary outcomes were diagnostic accuracy, optimal histologic core procurement rate, and mean number of needle passes. Safety data were also analyzed.

METHODS

Inclusion and exclusion criteria

Only studies meeting the following criteria were included: full-text studies directly comparing EUS-FNA and EUS-FNB sampling in patients with GI SELs, studies published in English, and articles reporting at least 1 of the following data: sample adequacy (or data useful for its calculation), diagnostic accuracy (or data useful for its calculation), and histologic core procurement. Single-cohort series or studies not reporting data on SELs were excluded. Studies conducted with needles not currently in use in clinical practice were also excluded (Fig. 1).

Search strategy

Supplementary Table 1 (available online at www.giejournal.org) reports the search strategy followed in the meta-analysis. Bibliographic research was conducted on PubMed, EMBASE, Cochrane Library, and Google Scholar including all studies fulfilling the inclusion criteria published until May 2019. The following search strategy was adopted: ((endoscopic ultrasound[MeSH Terms]) AND biopsy[MeSH Terms]) OR subepithelial[MeSH Terms]. Relevant reviews and meta-analyses on the use of EUS in SELs were examined for potential suitable studies. Authors of the included studies were contacted to obtain full text or further information when needed.

Data extraction was conducted by 2 reviewers (S.P.S. and V.D.P.) using a standardized approach (Preferred Reporting

TABLE 1. Continued

Lesion size (cm)	Location, stomach (%)	Stylet use	Caliper	ROSE	Needle
2.88 ± 1.32 2.69 ± 1.39	NR	No	22 gauge 22/25 gauge	Yes	Acquire/SharkCore Expect
2.67 (1.9-4) 2.39 (1.6-3)	93.8 71.8	No	22 gauge 22 gauge	No	Acquire Expect
2.5 ± .9 2.8 ± 1.65	80 70.3	Yes	19/22/25 gauge 19/22/25 gauge	Yes	SharkCore EchoTip Ultra
2.5 (2.1-4)	100	No	22 gauge 22 gauge	Yes	ProCore EchoTip
3 (.6-22)	79.5	NR	19/22 gauge 22/25 gauge	No	ProCore/Acquire EchoTip
2 (1.5-8) 2 (1.5-9.7)	67 58	No	19/22/25 gauge 19/22/25 gauge	No	ProCore EchoTip/Expect/EZShot
<2 cm: 26% 2-3 cm: 48% >3 cm: 26%	100	No	22 gauge for lesions <3 cm, 19 gauge >3 cm	No	ProCore EchoTip Ultra
3 ± 1 3.2 ± 1.7	66 90	No	22 gauge 22 gauge	No	ProCore EchoTip
3.7 ± 2 4.4 ± 3.2	75 50	Yes	22 gauge 22 gauge	No	ProCore EchoTip
3.2 ± 1 2.9 ± 0-6	50 50	Yes	22/25 gauge 22/25 gauge	81.8%	ProCore EchoTip/Expect

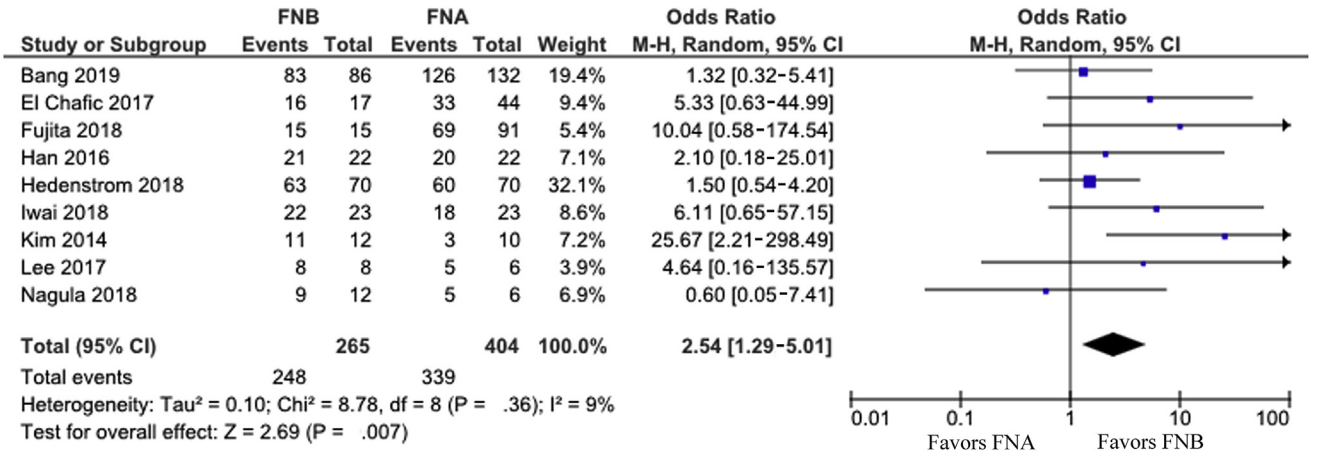


Figure 2. Meta-analysis comparing sample adequacy of fine-needle biopsy (FNB) sampling and FNA. FNB sampling clearly outperformed FNA in terms of sample adequacy (odds ratio, 2.54; 95% CI, 1.29-5.01; $P = .007$) with no evidence of heterogeneity ($I^2 = 9\%$).

Items for Systematic Reviews and Meta-Analyses statement[12]). The quality of the included studies was assessed by 2 authors independently (A.F., M.A.) according to the Cochrane Collaboration's tool for assessing the risk of bias[13] for randomized controlled trials (RCTs) and the Newcastle-Ottawa scale[14] for nonrandomized studies. Disagreements were solved by discussion and after a third opinion (N.M.).

Outcomes

The primary outcome was sample adequacy, defined as the ability to procure cytologic and/or histologic samples adequate for interpretation. Secondary outcomes were diagnostic accuracy (defined as true positive + true negative/total number of patients), histologic core procurement rate (defined as samples with high cellularity and quality enabling appropriate core assessment in terms of tissue architecture), number of needle passes, and safety.

Statistical analysis

The χ^2 and I^2 tests were used for across-study comparison of the percentage of variability attributable to heterogeneity beyond chance. $P < .10$ for the χ^2test and $I^2 < 20\%$ were interpreted as low-level heterogeneity.

As recommended by recent Cochrane guidelines, random-effects model with the DerSimonian and Laird test was chosen a priori for all analyses (regardless of the level of heterogeneity).[15] Summary estimates were expressed in terms of odds ratio (OR) and 95% confidence interval (CI) in the case of dichotomous variables (sample adequacy, diagnostic accuracy, and histologic core procurement rate) and mean difference along with standard deviation in the case of continuous variables (number of needle passes). Furthermore, pooled summary estimates of the above-cited outcomes were separately computed for each needle. Safety data were inconsistently reported; hence, they were analyzed descriptively.

Probability of publication bias was assessed through visual inspection of funnel plots. Sensitivity analysis was conducted according to study design (randomized trial vs retrospective), availability of ROSE, FNB needle design (reverse bevel vs newer needles), and needle caliper (22 gauge).

All statistical analyses were conducted using RevMan version 5 from the Cochrane Collaboration and OpenMeta [Analyst] software (Brown University; Providence, RI, USA). For all calculations, a 2-tailed $P < .05$ was considered statistically significant.

RESULTS

Characteristics of included studies

As shown in Figure 1, of 3343 studies initially identified, after exclusion of articles not fulfilling the inclusion criteria, 10 studies[16-25] with 669 patients (208 sampled with EUS-FNB sampling, 346 with EUS-FNA, and 115 with both needles in crossover trials) were included in the meta-analysis. Of 10 included studies, 6 were RCTs[19,20,22-25] and 4 retrospective studies.[16-18,21] Main characteristics of the included studies are reported in Table 1.

The recruitment period ranged from 2010 to 2017. Six RCTs were conducted in Asia,[17,19,21-24] and all studies presented 2 well-balanced arms in terms of lesion features (location and size) and clinical-demographic characteristics (Table 1). ROSE was available in 4 studies,[16,18,19,25] and needle caliper was mainly 22 gauge. The most frequently used FNB needle was ProCore, whereas newer needles were tested in 4 studies.[16-18,20]

Quality was deemed moderate to high in 6 studies.[17,18,21-24] Details on the quality assessment of the included articles are shown in Supplementary Table 2 (available online at www.giejournal.org).

Sample adequacy

Nine studies reported sample adequacy data.[16-20,22-25] Pooled rates of adequate samples were 94.9% (95% CI, 92.3%-97.5%) and 80.6% (95% CI, 71.4%-89.7%) with FNB sampling and FNA, respectively (Supplementary Table 3, available online at www.giejournal.org).

As reported in Figure 2, FNB sampling clearly outperformed FNA in terms of sample adequacy (OR, 2.54; 95% CI, 1.29-5.01; $P = .007$) with low evidence of heterogeneity ($I^2 = 9\%$). There was no evidence of publication bias (Supplementary Fig. 1A, available online at www.giejournal.org). The findings of the main analysis were confirmed in the sensitivity analysis performed according to study design (OR, 2.69; 95% CI, 1.03-7.06 when only RCTs were considered vs OR, 2.77; 95% CI, 1.01-9.48 with retrospective studies), needle design, and caliper (Table 2). Of note, when ROSE was available no significant difference between FNB sampling and FNA was observed (OR, 1.60; 95% CI, .79-3.25) (Table 2).

Optimal histologic core procurement rate and diagnostic accuracy

Pooled analysis of 7 studies[16,18,19,21-24] showed 89.7% (95% CI, 84.5%-94.9%) optimal histologic core procurement rate with FNB sampling and 65% (95% CI, 55.5%-74.6%) with FNA (Supplementary Table 3). A forest plot comparing optimal histologic core procurement rate is reported in Figure 3. Again, FNB sampling was significantly superior to FNA (OR, 3.27; 95% CI, 2.03-5.27; $P < .0001$) with no evidence of heterogeneity ($I^2 = 0\%$) (Fig. 3). Visual inspection of the relevant funnel plot showed no evidence of publication bias (Supplementary Fig. 1B, available online at www.giejournal.org). Sensitivity analysis restricted to RCTs confirmed the aforementioned results (OR, 4.16; 95% CI, 1.56-11.10; vs OR, 3.03; 95% CI, 1.76-5.25 registered with retrospective studies) (Table 2).

Seven studies reported diagnostic accuracy,[18,20-25] which were as high as 87.9% (95% CI, 81.9%-94%) with FNB and 64% (95% CI, 45.8%-82.3%) with FNA needles (Supplementary Table 3). Diagnostic accuracy was significantly superior in patients undergoing FNB sampling compared with FNA (OR, 4.10; 95% CI, 2.48-6.79; $P < .0001$) with no evidence of heterogeneity ($I^2 = 0\%$) (Fig. 4) or publication bias (Supplementary Fig. 1C, available online at www.giejournal.org). Sensitivity analysis confirmed the aforementioned findings in all subgroups tested (Table 2).

Number of passes and adverse events and safety profile

Analysis of the number of needle passes needed to obtain adequate samples showed a significantly positive trend in favor of FNB sampling (mean difference, –.75; 95% CI, –1.20 to –.30; $P = .001$) with high evidence of heterogeneity ($I^2 = 77\%$) (Supplementary Fig. 2, available online at www.giejournal.org). Mean number of needle passes was 1.73 (95% CI, 1.37-2.09) with FNB sampling and 2.51 (95% CI, 2.2-2.82) with FNA (Supplementary Table 3). The superiority of FNB sampling was confirmed in the sensitivity analysis (Table 2). Again, no evidence of publication bias was registered (Supplementary Fig. 1D, available online at www.giejournal.org).

Details on the safety profile of the 2 devices are reported in Supplementary Table 4 (available online at

TABLE 2. Sensitivity analysis of main outcomes performed according to study design (randomized trial vs retrospective), availability of pathologic (ROSE, needle design (reverse bevel vs newer needles), and needle caliper (22 gauge)

Main outcomes	Subgroup	No. of studies	No. of patients	Odds ratio (95% CI)	Within-comparison heterogeneity (I^2) (%)
Sample adequacy					
Study design	RCT	6	284	2.69 (1.03-7.06)	22
	Retrospective	3	385	2.77 (1.01-9.48)	15
ROSE	Yes	5	481	1.60 (.79-3.25)	0
	No	4	188	9.85 (2.64-36.74)	30
Needle design	Reverse bevel	6	284	2.69 (1.03-7.06)	22
	Newer needles	3	385	2.77 (1.01-9.48)	15
Needle caliper	22 gauge	9	647	2.39 (1.14-5.01)	13
Histologic core procurement					
Study design	RCT	4	126	4.16 (1.56-11.10)	0
	Retrospective	3	435	3.03 (1.76-5.25)	0
ROSE	Yes	3	368	2.79 (1.50-5.19)	0
	No	4	196	4.11 (1.95-8.69)	0
Needle design	Reverse bevel	4	126	4.16 (1.56-11.10)	0
	Newer needles	3	435	3.03 (1.76-5.25)	0
Needle caliper	22 gauge	7	552	3.28 (2.03-5.29)	0
Diagnostic accuracy					
Study design	RCT	5	240	4.63 (2.45-8.74)	0
	Retrospective	4	143	3.90 (1.92-7.89)	0
ROSE	Yes	3	201	3.62 (1.17-11.25)	23
	No	4	196	3.90 (1.92-7.89)	0
Needle design	Reverse bevel	5	240	4.63 (2.45-8.74)	0
	Newer needles	2	114	4.42 (1.09-17.90)	0
Needle caliper	22 gauge	7	354	3.94 (2.30-6.73)	0
Number of needle passes					
Study design	RCT	6	284	–.74 (–1.20 to –.28)	53
	Retrospective	4	143	–.56 (–1.32 to –.19)	41
ROSE	Yes	3	526	–1.03 (–1.59 to –.47)	77
	No	5	257	–.40 (–.95 to .15)	46
Needle design	Reverse bevel	6	284	–.74 (–1.20 to –.28)	53
	Newer needles	4	499	–.72 (–1.62 to –.11)	89

Comparison is between fine-needle biopsy sampling and FNA.
CI, Confidence interval; *ROSE*, rapid on-site evaluation; *RCT*, randomized controlled trial.

www.giejournal.org). Of 6 adverse events reported (mainly mild bleeding), 3 were experienced by patients treated with FNB sampling. Of note, all reported adverse events were mild and did not impact on patient outcomes.

DISCUSSION

The role of EUS-guided tissue acquisition in patients with SELs is still unclear. In fact, based on the less than satisfactory results of EUS-FNA in this field and the inconsistent findings reported in the published series, current guidelines restrict recommendations to EUS-guided sampling only in certain subgroups of patients.[1]

A meta-analysis of 17 studies (mainly including studies with FNA or Tru-Cut biopsy needles) found a pooled diagnostic rate of EUS-guided sampling of 59.9%.[7] However, these results should be interpreted with great caution because of the high heterogeneity observed; furthermore, the wider experience with the reverse-bevel FNB needle gained in the last years, the recent development of newer devices, and the lack of comparative studies at the time of the publication of the above-mentioned meta-analysis[7] call for an updated systematic review of the increasing body of evidence in the field.

With a meta-analysis of 10 studies directly comparing EUS-guided FNB sampling and FNA in patients with SELs,

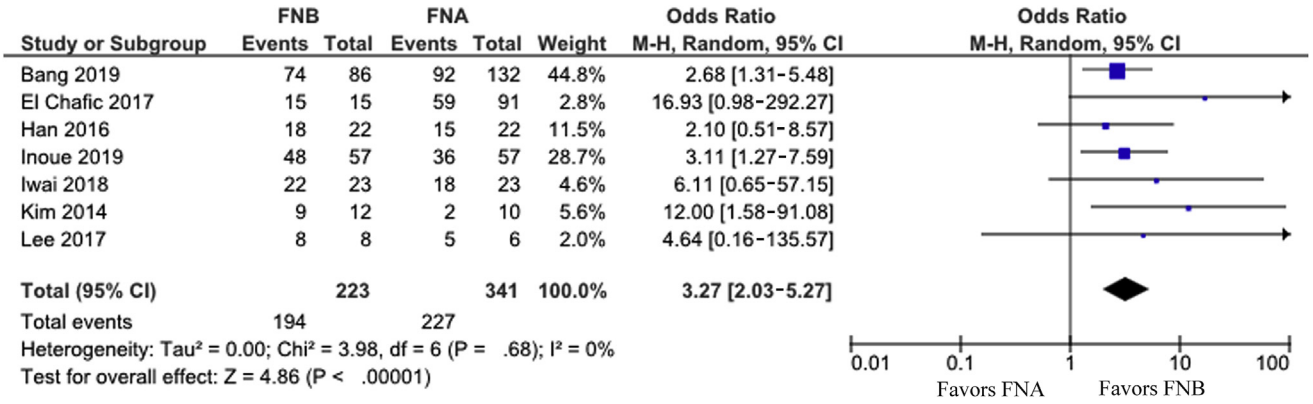


Figure 3. Meta-analysis comparing optimal histologic core procurement of fine-needle biopsy (FNB) sampling and FNA. Odds ratio for optimal histologic core procurement was significantly in favor of FNB sampling as compared with FNA (3.27; 95% CI, 2.03-5.27; $P < .0001$) with no evidence of heterogeneity ($I^2 = 0\%$).

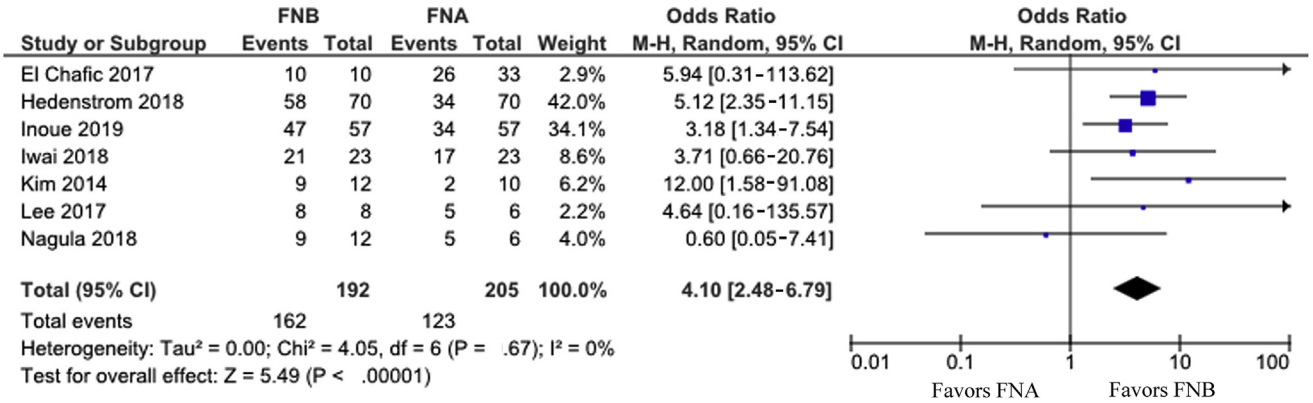


Figure 4. Meta-analysis comparing diagnostic accuracy of fine-needle biopsy (FNB) sampling and FNA. Diagnostic accuracy was significantly superior with FNB sampling as compared with FNA (odds ratio, 4.10; 95% CI, 2.48-6.79; $P < .0001$) with no evidence of heterogeneity ($I^2 = 0\%$).

we made several key observations. First, FNB sampling clearly outperformed FNA in all diagnostic outcomes evaluated. Interestingly enough, this result is in contrast with the concerns regarding the use of FNB sampling in other fields such as in patients with pancreatic masses, where the only clear advantage of EUS-FNB sampling is to obviate the need of ROSE.[8,11] In patients with SELs, FNB sampling showed exciting rates of adequate samples (94.9%), optimal histologic core procurement (89.7%), and diagnostic accuracy (87.9%). On the other hand, our meta-analysis confirmed the poor results achieved with FNA already reported in the literature (80.6% sample adequacy and 65% histologic core procurement rate).[7] Furthermore, the superiority of FNB sampling was supported by multiple sensitivity analyses in several subsets of patients and by the lack of heterogeneity.

Second, in line with the experience with pancreatic masses,[11] the positive results based on FNA with the presence of ROSE may suggest that this strategy is as competitive as FNB sampling in terms of sample adequacy, although a nonsignificant favorable trend with the latter was observed. However, FNB sampling showed clearly superior rates of histologic procurement and diagnostic accuracy even when compared with FNA with the presence of ROSE; therefore, we might conclude that FNB sampling obviates the need of an on-site pathologist, thus enabling a satisfactory diagnostic yield to be achieved even in centers where resource constraints render ROSE not available.

Third, as expected, the number of needle passes through the lesion needed to obtain adequate samples was significantly lower with EUS-FNB sampling (mean difference, –.75), although this finding should be interpreted with caution because of the high heterogeneity observed. In particular, FNB needles achieved optimal diagnostic performances with less than 2 passes (pooled mean, 1.73). This result is likely to impact positively on the procedural length, albeit information on duration of the procedure was lacking in the included studies. Finally, both EUS sampling techniques were safe with a very limited number of adverse events observed (mainly mild bleeding).

These findings, which are considerably more favorable as compared with those reported in previous meta-analyses,[7,11] are likely to be related to the peculiar design of more recent FNB needles. The ProCore needle has 2

distinct cutting surfaces with a distal reverse bevel that promotes collection of a core sample during retrograde movement of the needle within the lesion, thus increasing the tissue acquisition amount while preserving histologic architecture.[10] The higher numbers of cutting points of newer FNB needles (3 in Franseen [Acquire; Boston Scientific Corp, Natick, Mass, USA] and 6 in Fork-tip [SharkCore; Medtronic, Minneapolis, Minn, USA] needles) provide improved control at the puncture site and stability at the tip, allowing for enhanced penetration.[10,26] However, the experience with these newer needles is still limited, and further studies are warranted to draw more general conclusions.

Most included studies used exclusively or prevalently 22-gauge FNB needles, and sensitivity analysis restricted to this specific caliper confirmed the findings of the main analysis. Even if the experience with other needle calipers is scarce, this parameter is unlikely to influence significantly the diagnostic outcomes of EUS-guided sampling as already found in the aforementioned meta-analysis.[7]

There are some limitations to our study. First, the low number of included studies and enrolled patients requires particular caution in interpreting our findings. However, we deliberately decided to restrict inclusion criteria to studies directly comparing FNB sampling and FNA to provide more robust and homogenous outcome estimates. Moreover, all main outcomes (diagnostic accuracy, sample adequacy, histologic procurement, and safety profile) were explored, and this aspect represents a nearly unique analysis in this field. Second, a subgroup analysis based on the location of the sampled lesion was unfeasible because of the lack of individual patient data; therefore, our findings should be considered applicable only to upper GI SELs (particularly gastric lesions). Third, the impact of certain technical aspects such as use of a stylet and fanning or slow-pull techniques could not be explored because of the low number of included studies. Finally, economic considerations and assumptions on the impact of FNB sampling on the duration of the procedure were beyond the scope of the study.

In conclusion, despite these weaknesses, our meta-analysis represents the first attempt to systematically compare EUS-guided FNB sampling and FNA in patients with SELs. Our results speak clearly in favor of FNB sampling, which was found to outperform FNA in all diagnostic outcomes evaluated. Given the high impact of an adequate tissue sampling on the quality of the procedure,[27] we are confident our results will inform forthcoming guidelines concerning the role of EUS in the management of patients with SELs. New-generation devices (Franseen and Fork-tip FNB needles) seem to be very promising but need to be explored in further studies.

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Abbreviations: CI, confidence interval; FNB, fine-needle biopsy; OR, odds ratio; RCT, randomized controlled trial; ROSE, rapid on-site evaluation; SEL, subepithelial lesion.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

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0016-5107/$36.00
https://doi.org/10.1016/j.gie.2019.07.018

Received May 19, 2019. Accepted July 14, 2019.

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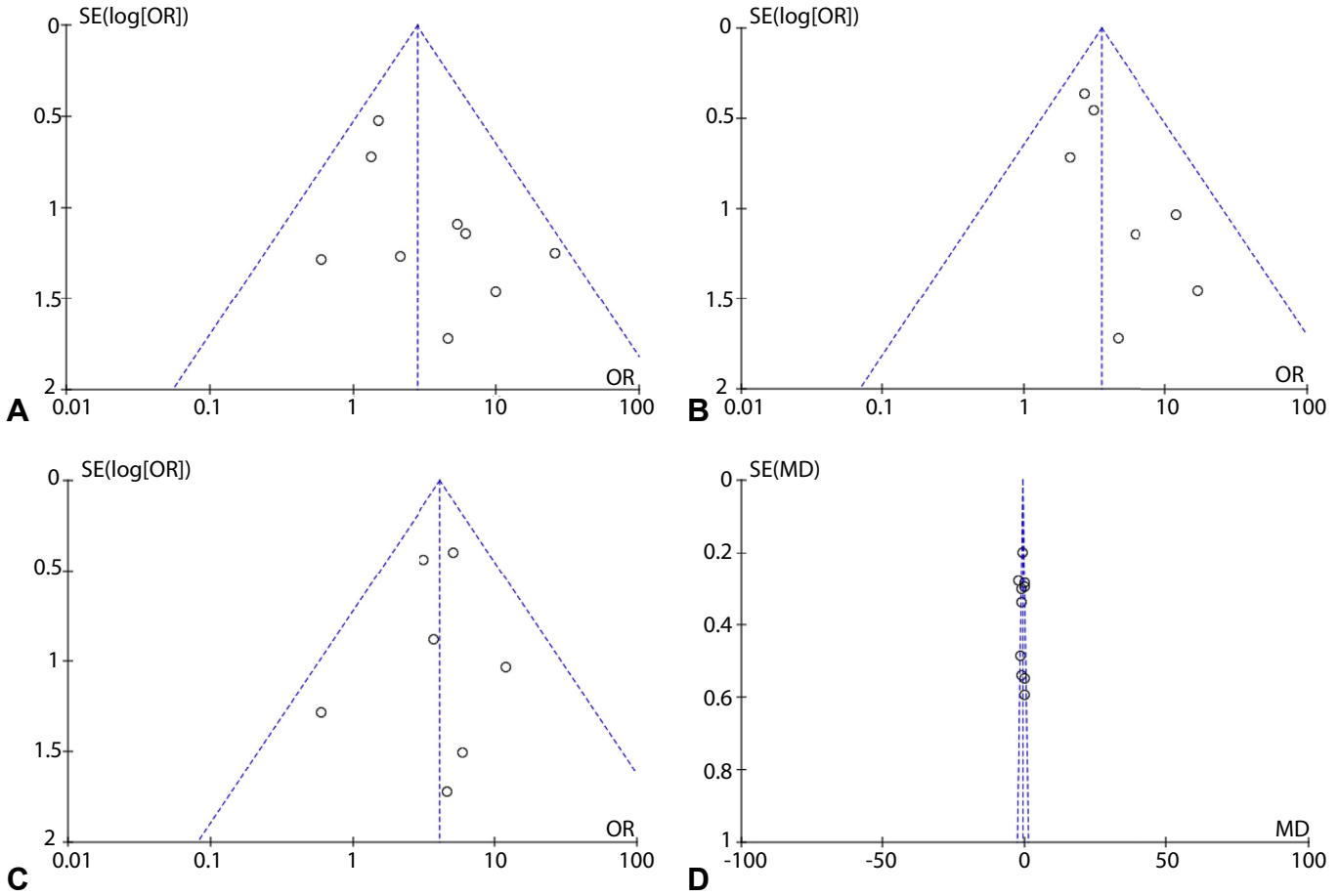
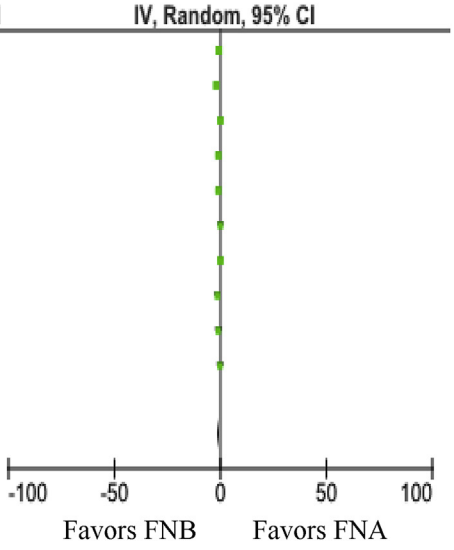


Supplementary Figure 1. Funnel plots for risk of bias assessment. **A,** Sample adequacy. **B,** Histologic core procurement. **C,** Diagnostic accuracy. **D,** Number of needle passes.

	FNB			FNA				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bang 2019	1.8	1.4	86	2.5	1.5	132	12.6%	-0.70 [-1.09, -0.31]	
El Chafic 2017	1	1	15	3	1	91	11.5%	-2.00 [-2.55, -1.45]	
Fujita 2018	3	1	17	3	1	44	11.4%	0.00 [-0.56, 0.56]	
Han 2016	1	1	22	2	1	22	11.2%	-1.00 [-1.59, -0.41]	
Hedenstrom 2018	2	2	70	3	2	70	10.7%	-1.00 [-1.66, -0.34]	
Inoue 2019	2	2	57	2	4	57	7.2%	0.00 [-1.16, 1.16]	
Iwai 2018	2	1	23	2	1	23	11.3%	0.00 [-0.58, 0.58]	
Kim 2014	1.8	0.9	12	3.2	1.3	10	8.5%	-1.40 [-2.35, -0.45]	
Lee 2017	1	1	8	2	1	6	7.8%	-1.00 [-2.06, 0.06]	
Nagula 2018	1.65	0.93	12	1.83	1.17	6	7.7%	-0.18 [-1.25, 0.89]	
Total (95% CI)			322			461	100.0%	-0.75 [-1.20, -0.30]	

Heterogeneity: Tau² = 0.37; Chi² = 39.45, df = 9 (P < .00001); I² = 77%

Test for overall effect: Z = 3.28 (P = .001)



Supplementary Figure 2. Meta-analysis comparing mean number of needle passes of FNB and FNA needles. *FNB*, Fine-needle biopsy.

SUPPLEMENTARY TABLE 1. Details of search strategy

Search ((endoscopic ultrasound[MeSH Terms]) AND biopsy[MeSH Terms]) OR subepithelial[MeSH Terms]

SUPPLEMENTARY TABLE 3. Pooled estimates of main diagnostic outcomes

Main outcomes	Subgroup	No. of patients	Summary estimate (95% CI) (%)	Within-group heterogeneity (%)
Sample adequacy	FNB	265	94.9 (92.3-97.5)	0
	FNA	404	80.6 (71.4-89.7)	15
Histologic core procurement	FNB	223	89.7 (84.5-94.9)	37
	FNA	341	65 (55.5-74.6)	48
Diagnostic accuracy	FNB	192	87.9 (81.9-94)	15
	FNA	205	64 (45.8-82.3)	55
Mean number of needle passes	FNB	322	1.73 (1.37-2.09)	80
	FNA	461	2.51 (2.2-2.82)	81

FNB, Fine-needle biopsy.

SUPPLEMENTARY TABLE 4. Adverse events reported in the included studies

Study, year	Adverse events
Bang, 2019[16]	None
Fujita 2018[17]	None
El Chafic 2017[18]	None
Han 2016[19]	None
Hedenstrom 2018[20]	Mild bleeding (1 patient in FNB group)
Inoue 2019[21]	Bleeding (2 patients in FNB group, 1 patient in FNA group) Aspiration pneumonia (1 patient in FNA group)
Iwai 2018[22]	None
Kim 2014[23]	Mild bleeding (1 patient in FNA group)
Lee 2017[24]	None
Nagula 2018[25]	None

FNB, Fine-needle biopsy.