

## Retrospective Study

Endoscopic ultrasound fine needle aspiration vs fine needle biopsy  
in solid lesions: A multi-center analysis

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**Institutional review board statement:** The study was approved by the Research Ethics Committee from Partners Human Research (Protocol No. 2003P001665).

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## Abstract

### BACKGROUND

While endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) is considered a preferred technique for tissue sampling for solid lesions, fine needle biopsy (FNB) has recently been developed.

### AIM

To compare the accuracy of FNB vs FNA in determining the diagnosis of solid lesions.

### METHODS

A retrospective, multi-center study of EUS-guided tissue sampling using FNA vs FNB needles. Measured outcomes included diagnostic test characteristics (*i.e.*, sensitivity, specificity, accuracy), use of rapid on-site evaluation (ROSE), and adverse events. Subgroup analyses were performed by type of lesion and diagnostic yield with or without ROSE. A multivariable logistic regression was also performed.

### RESULTS

A total of 1168 patients with solid lesions ( $n = 468$  FNA;  $n = 700$  FNB) underwent EUS-guided sampling. Mean age was  $65.02 \pm 12.13$  years. Overall, sensitivity, specificity and accuracy were superior for FNB vs FNA (84.70% vs 74.53%; 99.29%

Written informed consent was obtained from all patients.

**Conflict-of-interest statement:**

Diogo Turiani Hourneaux de Moura, Thomas R McCarty, Pichamol Jirapinyo, Igor Braga Ribeiro, Galileu Ferreira Ayala Farias and Antonio Coutinho Madruga-Neto have nothing to disclose. Marvin Ryou reports other from Medtronic, other from GI Windows, other from EnteraSense, other from FujiFilm, other from Boston Scientific, grants from Olympus, other from Pentax, outside the submitted work. Christopher C Thompson reports personal fees from Medtronic, personal fees from Boston Scientific, grants from USGE Medical, grants from Apollo Endosurgery, grants from Olympus, outside the submitted work.

**Data sharing statement:** No additional data are available.

**Country/Territory of origin:** Brazil

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B, B  
Grade C (Good): 0  
Grade D (Fair): 0  
Grade E (Poor): 0

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*vs* 96.62%; and 87.62% *vs* 81.55%, respectively;  $P < 0.001$ ). On subgroup analyses, sensitivity, specificity, and accuracy of FNB alone were similar to FNA + ROSE [(81.66% *vs* 86.45%;  $P = 0.142$ ), (100% *vs* 100%;  $P = 1.00$ ) and (88.40% *vs* 85.43%;  $P = 0.320$ ). There were no difference in diagnostic yield of FNB alone *vs* FNB + ROSE ( $P > 0.05$ ). Multivariate analysis showed no significant predictor for better accuracy. On subgroup analyses, FNB was superior to FNA for non-pancreatic lesions; however, there was no difference between the techniques among pancreatic lesions. One adverse event was reported in each group.

**CONCLUSION**

FNB is superior to FNA with equivalent diagnostic test characteristics compared to FNA + ROSE in the diagnosis of non-pancreatic solid lesions. Our results suggest that EUS-FNB may eliminate the need of ROSE and should be employed as a first-line method in the diagnosis of solid lesions.

**Key Words:** Endoscopic ultrasound-guided tissue acquisition; Fine needle aspiration; Fine needle biopsy; Solid lesions; Endoscopic ultrasound; Cancer

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**Core Tip:** While endoscopic ultrasound-guided fine needle aspiration (FNA) is considered a preferred technique for tissue sampling for solid lesions, fine needle biopsy (FNB) has recently been developed with the capability of tissue extraction for histological evaluation. But what would be the best option? Our study showed that FNB is superior to FNA with equivalent diagnostic test characteristics compared to FNA + rapid on-site evaluation in the diagnosis of solid lesions.

**Citation:** Moura DTH, McCarty TR, Jirapinyo P, Ribeiro IB, Farias GFA, Madruga-Neto AC, Ryou M, Thompson CC. Endoscopic ultrasound fine needle aspiration *vs* fine needle biopsy in solid lesions: A multi-center analysis. *World J Clin Cases* 2021; 9(34): 10507-10517

**URL:** <https://www.wjgnet.com/2307-8960/full/v9/i34/10507.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v9.i34.10507>

**INTRODUCTION**

Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) is a well-established technique for tissue acquisition of a variety of solid gastrointestinal tract lesions including pancreatic masses, subepithelial lesions, and mediastinal or abdominal lymphadenopathy. Despite being a well-described mode of tissue sampling, the diagnostic yield of FNA is highly variable ranging from 49% to 100% depending on the type of lesion[1-4]. Several factors including needle size and type, number of needle passes, lesion location and etiology, use of rapid-on-site evaluation (ROSE), and individual endoscopist experience may influence the diagnostic yield of the procedure. While several studies have shown some impact on diagnostic accuracy, careful focus to improve these characteristics has not consistently demonstrated improvement in diagnostic yield[5,6].

In addition to technical variables, EUS-guided FNA has specific limitations. Due to the small cellular sample provided by the FNA technique, multiple needle passes are often needed to establish a diagnosis. The operating characteristics of EUS-guided FNA are also incumbent upon the availability of a cytopathologist to perform ROSE, a highly technical resource that is not available in most centers[1,7]. Tissue architecture and morphology are often difficult to maintain with FNA samples – as a result, typically only providing specimen for cytological analysis. The reduced ability for histologic examination may reduce the diagnostic yield for lesions that require immunohistochemistry, immunophenotyping, or evaluation of histologic architecture such as lymphoma, metastatic lesions, and some subepithelial lesions[8,9]. Inflammatory processes may also adversely affect the diagnostic yield of FNA through associated cellular atypia resulting in false positive cytology[1,7,8].

[s/by-nc/4.0/](#)**Received:** March 25, 2021**Peer-review started:** March 25, 2021**First decision:** July 15, 2021**Revised:** July 24, 2021**Accepted:** October 20, 2021**Article in press:** October 20, 2021**Published online:** December 6, 2021**P-Reviewer:** Bolivar DJ, Skok P**S-Editor:** Zhang H**L-Editor:** A**P-Editor:** Zhang H

To overcome limitations associated with EUS-guided FNA, core biopsy needles [(fine needle biopsy (FNB))] have been developed, and are being increasingly utilized for tissue acquisition. These newer devices, which include reverse bevel needles, side-open needles, and fork-tip needles, are able to obtain both cytological aspirates and also histologic core samples.

Currently, core tissue samples obtained with these newer FNB needles may improve diagnostic yield and may potentially obviate the need for ROSE[1,5,7,8]. A meta-analysis have demonstrated FNB is a reliable diagnostic tool for solid lesions with similar diagnostic yield to FNA requiring fewer passes when compared to FNA without ROSE[10]. To date, there remains a paucity of high-quality data reporting FNB to be superior to FNA in terms of diagnostic yield and diagnostic accuracy in all types of solid lesions. Consequently, in 2017, the latest European Society of Gastrointestinal Endoscopy guidelines do not indicate that any needle type is superior or preferred for diagnostic sampling of solid lesions[11]. To better understand the comparative effectiveness of FNA *vs* FNB and possible advantages of EUS-guided FNB for solid lesions in daily clinical practice, we performed a large multi-center study to evaluate the diagnostic test characteristics of both sampling techniques with and without ROSE.

## MATERIALS AND METHODS

This was a multi-center, retrospective study conducted at 5 hospitals in Massachusetts, United States (Brigham and Women's Hospital, Massachusetts General Hospital, Brigham and Women's Faulkner Hospital, Newton-Wellesley Hospital, and North Shore Medical Center) following the Standards for the Reporting of Diagnostic accuracy studies recommendations. All hospitals were affiliated with Partners Healthcare though each hospital utilizing different physician groups with varied EUS sampling practice protocols and diverse levels of experience. Ethical approval for the study was also provided the Research Ethics Committee from Partners Human Research (Protocol No. 2003P001665). Written informed consent was obtained from all patients.

Consecutive patients, age  $\geq 18$  years, were included if they had undergone EUS-guided tissue acquisition (FNA or FNB) of solid lesions from January 2016 to January 2019 were identified from a shared prospective registered. Data, including patient and lesion characteristics, were obtained from the electronic health record and registry dataset. Patient demographics, lesion characteristics, and procedure details, and diagnostic methods were recorded. Patient's with incomplete reporting data or cases with more than one needle (*i.e.*, FNA and FNB, or more needle sizes) used were excluded from this analysis.

### Procedural technique

All EUS-guided tissue sampling procedures were performed with a linear array echoendoscope (Olympus GF-UCT180, Olympus, Center Valley, PA) under deep sedation with monitored anesthesia care. Anesthesia provider-administered sedation was performed for all included cases and EUS-guided FNA or FNB performed by experienced endosonographers or by gastroenterology fellows under direct, expert supervision. Several different needles were included, comprising of the 19G, 22G, and 25G FNA needles (Expect, Boston Scientific Corporation, Natick, MA or Echotip, Cook Medical, Winston-Salem, NC, United States or Beacon, Medtronic Corporation, Newton, MA) and 19G, 20G, 21G, 22G, and 25G FNB needles (Acquire, Boston Scientific Corporation, Natick, MA or SharkCore, Medtronic Corporation, Newton, MA or ProCore, Cook Medical, Winston-Salem, NC, United States). Both the decision regarding FNA *vs* FNB and needle size, were at the discretion of the endoscopist performing the procedure. Once the target lesion was properly identified on EUS, the lesion punctured was punctured with the needle under EUS guidance and a general fanning technique was performed. Given the inclusion of multiple hospitals and institutions, individual operator technique varied with respect to stylet use and slow-pull *vs* standard suction technique.

Samples obtained through FNA were transferred to slides. Each smear was made with slight pressure to avoid crushing artifacts, and the slides were placed in the 96% ethyl alcohol or fixed in the air. When possible, part of the specimens were placed in formalin solution for preparation of the cell-block. Samples obtained through FNB were fixed in buffered formalin and in selected cases, FNB specimens were prepared in slides using the touch imprint technique. Immunohistochemistry (IHC) staining was also performed for differential diagnosis of neoplastic and non-neoplastic lesions

when needed, such as differential diagnosis of spindle cell lesions or in cases of lymphoma. In this study, ROSE was utilized to determine sample adequacy and assist in establishing a preliminary diagnosis. To perform ROSE, FNA specimens were expressed onto slides and then smeared for on-site preparation while FNB were prepared using the touch imprint technique. Per pass adequacy was determined based upon minimum number of passes required for the expert cytopathologist to provide a preliminary diagnosis. ROSE was performed in cases of EUS-guided FNA and FNB; however, this technique was not available for all cases. Therefore, separate analyses were performed to determine the impact of ROSE on diagnostic yield for EUS-guided FNA and FNB.

### **Measured outcomes**

The primary outcome was the diagnostic yield [sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-), and accuracy] of EUS-guided FNA and FNB from cytologic or histologic analysis with and without IHC staining. Inconclusive specimen results were considered as non-neoplastic lesions as to not overestimate diagnostic yield. Secondary outcomes included the proportion of adequate cellularity for ROSE evaluation, median number of needle passes, diagnostic result from histologic (cell-block) and cytologic (slides) analysis, as well as adverse events related to the procedure. Surgical pathology of resected specimens was considered the golden standard method for comparison to EUS-guided FNA and FNA diagnostic performance. However, because most patients did not undergo surgery due to benign findings or advanced disease, patient follow-up for at least 6 months was also considered as the reference standard.

### **Statistical analyses**

Baseline patient characteristics and procedure characteristics were summarized as means  $\pm$  SD for continuous data and frequencies and proportions for categorical data. As diagnostic tests were performed on two independent groups of patients, a bivariate model was used to compute the pooled sensitivity and specificity, and diagnostic accuracy. Two-sample *t*-tests for binomial proportions were utilized. Continuous data were compared using the two-sample *t*-test or Wilcoxon rank-sum test and categorical data were compared using the Chi-square or Fisher's exact test as appropriate. Statistical significance was defined as a  $P < 0.05$ .

Subgroup analyses were then performed to evaluate diagnostic yield of FNA and FNB for each location (pancreas subepithelial lesions, lymph nodes, and other lesion sites). Additional analyses were also performed to identify the diagnostic yield of FNA alone, FNA with ROSE, FNB alone, and FNB with ROSE. From this data, sensitivity, specificity, PPV, NPV, LR+, LR-, and accuracy were compared to determine if ROSE was beneficial. In effort to identify factors associated with diagnostic performance between FNA and FNB needle types, a multivariable logistic regression was performed with adjustment for clinically significant univariate findings as well as age, gender, number of passes, needle size, needle type, and application of ROSE, cell-block, and IHC. Results of the regression analysis were expressed as beta-coefficient ( $\beta$ ) and odds ratio. Statistical analyses were performed using the Stata 15.0 software package (Stata Corp LP, College Station, TX).

## **RESULTS**

### **Baseline patient and lesion characteristics**

A total of 1168 consecutive patients (55.82% male) were enrolled in this study. Mean age of patients was  $65.02 \pm 12.13$  years old with no difference between FNA and FNB cohorts ( $P = 0.078$ ). There was no significant difference in gender between groups as well ( $P = 0.098$ ). Of the 1168 patients that underwent EUS sampling, 40.07 ( $n = 468$ ) underwent FNA with 59.93% ( $n = 700$ ) undergoing sampling with FNB. Technical success occurred in all cases. A majority of lesions overall were non-pancreatic (50.14%) with further lesion characteristics highlighted in [Table 1](#). Non-pancreatic lesions included lymph nodes and subepithelial lesions as well as other solid lesions such as hepatic masses and abdominal masses among others. FNB was more commonly performed for pancreatic lesions ( $P < 0.001$ ) with FNA being the more common for non-pancreatic lesions ( $P < 0.001$ ). Mean size of sampled lesions was  $26.14 \pm 13.643$  mm with larger lesions in the FNB group (FNB  $25.52 \pm 13.65$  vs FNA  $22.10 \pm 13.34$ ;  $P < 0.001$ ). Additional baseline characteristics for all included patients as well as

**Table 1** Baseline patient characteristics, lesion details, and sampling characteristics

Results	Total	FNA	FNB	P value
Patient characteristics				
No. of patients	1168	468 (40.07)	700 (59.93)	
Age (yr)	65.02 (12.29)	64.24 (11.59)	65.54 (12.72)	0.078
Gender				0.098
No. of males (%)	652 (55.82)	275 (58.76)	377 (52.86)	
No. of females (%)	516 (44.18)	193 (41.24)	323 (47.14)	
Lesion site				
Pancreatic	574 (49.14)	194 (41.45)	380 (54.29)	< 0.001
Non-pancreatic				
Lymph node	209 (17.89)	108 (23.08)	101 (14.43)	< 0.001
Subepithelial	229 (19.61)	115 (24.57)	114 (16.28)	< 0.001
Other solid lesions	156 (13.36)	51 (10.90)	105 (15.00)	< 0.001
Hepatic mass	48 (4.11)	18 (37.50)	30 (62.50)	
Abdominal mass	29 (2.48)	8 (27.59)	21 (72.41)	
Gastrointestinal wall thickening	20 (1.71)	6 (0.30)	14 (0.70)	
Mediastinal mass	14 (0.43)	4 (28.57)	10 (71.43)	
Peri-rectal mass	11 (0.94)	3 (27.37)	8 (72.73)	
Common bile duct mass	9 (0.77)	5 (55.56)	4 (44.44)	
Duodenal mass	6 (0.51)	1 (16.67)	5 (83.33)	
Ampullary mass	6 (0.51)	1 (16.67)	5 (83.33)	
Retroperitoneal mass	5 (0.43)	1 (20.00)	4 (80.00)	
Esophageal mass	3 (0.26)	0 (0.00)	3 (100.00)	
Gallbladder mass	3 (0.26)	2 (66.67)	1 (33.33)	
Splenic mass	2 (0.17)	2 (100.00)	0 (0.00)	
Lesion size (mm)	24.16 (13.63)	22.10 (13.34)	25.52 (13.65)	< 0.001
Diagnostic sample approach				
Transesophageal	124 (11.02)	63 (50.81)	61 (49.19)	
Transgastric	589 (52.36)	235 (39.90)	354 (60.10)	
Tranduoodenal	388 (34.49)	135 (34.79)	253 (65.21)	
Transrectal	21 (1.87)	11 (52.38)	10 (47.62)	
Other	3 (0.26)	0 (0.00)	3 (100.00)	
Needle size				
19G	8 (0.69)	2 (0.43)	6 (0.86)	
20G	7 (0.61)	0 (0.00)	7 (1.00)	
21G	8 (0.69)	0 (0.00)	8 (1.15)	
22G	644 (55.61)	216 (46.55)	428 (61.49)	
25G	491 (42.40)	246 (53.02)	245 (35.20)	
No. of passes	2.89 (1.51)	2.91 (1.61)	2.88 (1.45)	0.701
No. of samples with ROSE				
Yes	377 (32.28)	182 (38.89)	195 (27.86)	
No	791 (67.72)	286 (61.11)	505 (72.14)	< 0.001

Adequate sample for ROSE				0.474
Yes	291 (77.19)	136 (74.73)	155 (79.49)	
No	86 (22.81)	46 (25.27)	40 (20.51)	
No. of passes for ROSE adequacy	3.37 (1.73)	3.32 (1.74)	3.41 (1.73)	0.664
No. of samples with cell block				< 0.001
Yes	1014 (86.82)	366 (78.21)	648 (92.57)	
No	154 (13.18)	102 (21.79)	52 (7.43)	
No. of passes for cell block diagnosis	2.97 (1.54)	3.09 (1.67)	2.90 (1.46)	0.067

ROSE: Rapid on-site evaluation; FNA: Fine needle aspiration; FNB: Fine needle biopsy.

stratification by FNA or FNB cohort are demonstrated in [Table 1](#).

### **Needle and sampling characteristics**

Multiple needle sizes were utilized in this study, including 19G, 20G, 21G, 22G, and 25G. Of these, 22G and 25G were more commonly used (55.61% and 42.40%, respectively). A majority of FNA cases utilized a 25G needle while the 22G needle was most common for FNB ( $P < 0.001$ ). Despite difference in needle type and size, there was no difference in number of needle passes between groups (FNA  $2.91 \pm 1.16$  vs FNB  $2.88 \pm 1.45$ ;  $P = 0.701$ ). More FNA obtained samples had ROSE performed ( $P < 0.001$ ) with no difference in number of passes needed for ROSE adequacy between both groups ( $P = 0.474$ ). Cell-block was more common among FNB samples (92.57% vs 78.21%;  $P < 0.001$ ) with similar number of passes required to achieve a conclusive diagnosis ( $3.09 \pm 1.67$  vs  $2.90 \pm 1.46$ ;  $P = 0.067$ ). A further breakdown of needle type and sampling characteristics is illustrated in [Table 1](#).

### **Diagnostic characteristics of EUS-guided sampling**

Overall sensitivity, specificity, and accuracy for all lesions, regardless of sampling modality, was 81.02%, 97.92%, and 85.20%, respectively. Sensitivity, specificity, and accuracy of FNB outperformed diagnostic yield characteristics for FNA [(sensitivity: 84.70% vs 74.53%;  $P < 0.001$ ), (specificity: 99.29% vs 96.62%;  $P < 0.001$ ), and (accuracy: 87.62% vs 81.55%;  $P = 0.004$ ). One serious adverse event occurred in each group. Diagnostic characteristics were also stratified by type of lesions (pancreatic vs non-pancreatic lesions). For pancreatic lesions, total sensitivity, specificity, and accuracy of FNA and FNB combined was 87.96%, 97.59%, and 89.35%, respectively. Among pancreatic lesions, there was no difference in diagnostic yield between FNA vs FNB (all  $P > 0.050$ ). However, for non-pancreatic lesions, FNB resulted in a superior sensitivity (78.45% vs 63.29%;  $P < 0.001$ ), specificity (100.00% vs 96.52%;  $P < 0.001$ ) and accuracy (84.57% vs 77.29%;  $P = 0.023$ ). Complete diagnostic test characteristics are shown in [Table 2](#).

### **Diagnostic yield with and without ROSE**

A comparison between methods with and without ROSE was also performed ([Tables 3 and 4](#)). [Table 3](#) shows the diagnostic yield of FNA and FNB with and without ROSE and [Table 4](#) shows the statistical analysis of the comparison between methods. Overall, FNA with ROSE significantly improved the sensitivity, specificity, and accuracy of sampling when compared to FNA alone [(86.45% vs 63.19%;  $P < 0.001$ ), (100.00% vs 96.69%;  $P = 0.014$ ); and (88.40% vs 77.56%;  $P = 0.03$ ), respectively]. When FNB alone was compared to FNA with ROSE, sensitivity, specificity, and accuracy were similar for both sampling modalities [(81.66% vs 86.45%;  $P = 0.142$ ), (100.00% vs 100.00%;  $P = 1.00$ ); and (85.43% vs 88.40%;  $P = 0.320$ ), respectively].

### **Multivariate logistic regression**

Multivariate analysis was then performed controlling for age, gender, number of passes, needle type, needle size, application of ROSE, and application of cell-block, on accuracy. Based upon the results of this multivariate logistic regression, and controlled for the variables above, there was no significant predictor for better accuracy.

Table 2 Summary of diagnostic results

	Total	FNA	FNB	P value
<b>All Lesions</b>				
Sensitivity	81.02% (95%CI 78.27 to 83.56)	74.53% (95%CI 69.37 to 79.23)	84.70% (95%CI 81.45 to 87.57)	< 0.001
Specificity	97.92% (95%CI 95.54 to 99.23)	96.62% (95%CI 92.29 to 98.89)	99.29% (95%CI 96.11 to 99.98)	< 0.001
Positive likelihood ratio	39.03 (95%CI 17.67 to 86.20)	22.06 (95%CI 9.30 to 52.34)	119.42 (95%CI 16.93 to 842.21)	< 0.001
Negative likelihood ratio	0.19 (95%CI 0.17 to 0.22)	0.26 (95%CI 0.22 to 0.32)	0.15 (95%CI 0.13 to 0.19)	0.676
Positive predictive value	99.17% (95%CI 98.18 to 99.62)	97.93% (95%CI 95.23 to 99.12)	99.79% (95%CI 98.54 to 99.97)	< 0.001
Negative predictive value	62.89% (95%CI 59.63 to 66.04)	63.84% (95%CI 59.34 to 68.11)	61.95% (95%CI 57.26 to 66.43)	0.459
Accuracy	85.20% (95%CI 83.03 to 87.19)	81.55% (95%CI 77.72 to 84.96)	87.62% (95%CI 84.96 to 89.97)	0.004
Serious adverse events	2 (0.17)	1 (0.21)	1 (0.14)	0.775
<b>Pancreatic lesions</b>				
Sensitivity	87.96% (95%CI 84.74 to 90.71)	85.62% (95%CI 79.22 to 90.66)	89.09% (95%CI 85.22 to 92.24)	0.229
Specificity	97.59% (95%CI 91.57 to 99.71)	96.88% (95%CI 83.78 to 99.92)	98.04% (95%CI 89.55 to 99.95)	0.387
Positive likelihood ratio	36.50 (95%CI 9.28 to 143.58)	27.40 (95%CI 3.98 to 188.81)	45.44 (95%CI 6.52 to 316.51)	0.714
Negative likelihood ratio	0.12 (95%CI 0.10 to 0.16)	0.15 (95%CI 0.10 to 0.22)	0.11 (95%CI 0.08 to 0.15)	0.253
Positive predictive value	99.54% (95%CI 98.21 to 99.88)	99.28% (95%CI 95.21 to 99.89)	99.66% (95%CI 97.69 to 99.95)	0.529
Negative predictive value	57.86% (95%CI 51.88 to 63.61)	57.41% (95%CI 47.88 to 66.41)	58.14% (95%CI 50.44 to 65.46)	0.867
Accuracy	89.35% (95%CI 86.54 to 91.76)	87.50% (95%CI 81.97 to 91.82)	90.29% (95%CI 86.86 to 93.07)	0.307
Serious adverse events	1 (0.17)	0 (0.00)	1 (0.26)	0.821
<b>Non-pancreatic lesions</b>				
Sensitivity	72.31% (95%CI 67.58 to 76.69)	63.29% (95%CI 55.27 to 70.81)	78.45% (95%CI 72.59 to 83.56)	< 0.001
Specificity	98.07% (95%CI 95.13 to 99.47)	96.52% (95%CI 91.33 to 99.04)	100.00% (95%CI 96.07 to 100.00)	< 0.001
Positive likelihood ratio	37.42 (95%CI 14.15 to 98.95)	18.20 (95%CI 6.90 to 48.01)	NA	NA
Negative likelihood ratio	0.28 (95%CI 0.24 to 0.33)	0.38 (95%CI 0.31 to 0.47)	0.22 (95%CI 0.17 to 0.28)	0.719
Positive predictive value	98.60% (95%CI 96.38 to 99.47)	96.15% (95%CI 90.45 to 98.51)	100.00%	< 0.001
Negative predictive value	65.27% (95%CI 61.53 to 68.84)	65.68% (95%CI 60.86 to 70.20)	64.79% (95%CI 59.01 to 70.17)	0.820
Accuracy	81.24% (95%CI 77.87 to 84.29)	77.29% (95%CI 71.85 to 82.12)	84.57% (95%CI 80.17 to 88.32)	0.023
Serious adverse events	1 (0.16)	1 (0.87)	0 (0.00)	0.321

FNA: Fine needle aspiration; FNB: Fine needle biopsy; ROSE: Rapid on-site evaluation.

## DISCUSSION

This is the first study to compare FNA and FNB with and without ROSE in solid lesions. Additionally, in this large, multi-center study, we compared EUS-FNA and EUS-FNB in many respects. EUS-FNB was superior to EUS-FNA regarding sensitivity, specificity, and accuracy and allowed for more cell-block diagnosis. However, EUS-FNB was comparable to EUS-FNA regarding number of passes required for ROSE and cell-block evaluation. The addition of ROSE to EUS-FNA provided better accuracy as compared to FNA alone and similar accuracy compared to FNB alone. The addition of ROSE to EUS-FNB did not improve the diagnostic accuracy of FNB alone for all solid lesions, suggesting that EUS-FNB may eliminate the need for ROSE in EUS-guided tissue sampling.

EUS-FNA of solid lesions is a safe procedure, associated with high diagnostic accuracy, usually above 85%, and typically better when ROSE is available[6,10]. However, the diagnostic accuracy of EUS-FNA with cytology is insufficient to verify cellular arrangement and tissue architecture. Procurement of histological samples that yield an adequate amount of tissue suitable for IHC staining is pivotal for personalized management of some lesions, such as metastatic lesions, gastrointestinal stromal

**Table 3 Comparison between methods with and without rapid on-site evaluation**

	FNA alone	FNA with ROSE	FNB alone	FNB with ROSE
Sensitivity	63.19% (95%CI 55.29 to 70.60)	86.45% (95%CI 80.04 to 91.41)	81.66% (95%CI 77.50 to 85.34)	82.97% (95%CI 76.70 to 88.12)
Specificity	96.69% (95%CI 91.75 to 99.06)	100.00% (95%CI 86.77 to 100.00)	100.00% (95%CI 95.04 to 100.00)	100.00% (95%CI 75.29 to 100.00)
Positive likelihood ratio	19.12 (95%CI 7.24 to 50.46)	NA	89.82 (95%CI 12.76 to 632.37)	NA
Negative likelihood ratio	0.38 (95%CI 0.31 to 0.47)	0.14 (95%CI 0.09 to 0.20)	0.19 (95%CI 0.15 to 0.23)	0.17 (95%CI 0.12 to 0.23)
Positive predictive value	96.26% (95%CI 90.70 to 98.55)	100.00%	99.69% (95%CI 97.88 to 99.96)	100.00%
Negative predictive value	66.10% (95%CI 61.40 to 70.51)	55.32% (95%CI 45.41 to 64.82)	59.89% (95%CI 54.81 to 64.77)	29.55% (95%CI 23.33 to 36.62)
Accuracy	77.46% (95%CI 72.16 to 82.19)	88.40% (95%CI 82.81 to 92.67)	85.43% (95%CI, 82.06 to 88.39)	84.10% (95%CI 78.20 to 88.94)

FNA: Fine needle aspiration; FNB: Fine needle biopsy; ROSE: Rapid on-site evaluation.

**Table 4 Statistical analyses between methods with and without rapid on-site evaluation**

	FNA vs FNA + ROSE (P value)	FNA vs FNB (P value)	FNA vs FNB + ROSE (P value)	FNA + ROSE vs FNB (P value)	FNA + ROSE vs FNB + ROSE (P value)	FNB vs FNB + ROSE (P value)
Sensitivity	< 0.001	< 0.001	< 0.001	0.142	0.350	0.686
Specificity	0.014	0.014	0.010	1.000	1.000	0.182
Positive likelihood ratio	NA	< 0.001	NA	NA	NA	NA
Negative likelihood ratio	0.637	0.614	0.677	0.891	0.941	0.956
Accuracy	0.003	0.005	0.074	0.320	0.228	0.658

FNA: Fine needle aspiration; FNB: Fine needle biopsy; ROSE: Rapid on-site evaluation.

tumors, lymphomas, and other uncommon lesions[7,9]. The limitation in achieving diagnosis using EUS-FNA is the pauci-cellular nature of the aspirate with a significant proportion of the collected tissue being distorted or consumed during automated processing and sectioning[7]. In our study, cell-block analysis was possible in 78.21% of patients after FNA and in 92.57% after FNB ( $P < 0.001$ ). Our results are similar to a previous systematic review and meta-analysis including eight randomized controlled trials that compared these techniques[12].

In our study, technical success was reported in all patients, similar to several studies evaluating FNB needles[13-15]. These results demonstrate that FNB can be easily performed in any location, unlike the first-generation FNB device (Tru-cut)[16]. Most studies comparing FNA and FNB have demonstrated that FNB typically requires fewer needle passes to achieve adequate sampling for ROSE and cell-block[12,13]. A lower number of passes may be translated into shorter procedure time, less risk of adverse events, and more operational efficiency for both endoscopy and cytopathology units. However, different from previous studies, in our analysis the number of passes required to achieve adequate samples for ROSE (FNA:  $3.32 \pm 1.74$  vs FNB:  $3.41 \pm 1.73$ ;  $P > 0.05$ ) and cell-block (FNA:  $3.09 \pm 1.67$  vs FNB:  $2.90 \pm 1.46$ ;  $P > 0.05$ ) were similar between both techniques. Similar to our study, Bang *et al*[17] also showed no significant difference in mean number of passes required to establish a diagnosis in a randomized controlled trial. Nevertheless, our study illustrated FNB enables a diagnostic yield of more than 90% for cell-block assessment (FNA: 78.21% vs FNB: 92.57%;  $P < 0.001$ ). Additionally, EUS-FNA with ROSE presented similar results to EUS-FNB alone. Similar to our results, a previous meta-analysis also showed that EUS-FNB without ROSE provides a similar diagnostic yield than EUS-FNA with ROSE[10]. Uniquely, in the subgroup analysis we demonstrated that FNB with ROSE is similar to FNB alone, suggesting that this technique may eliminate the need for ROSE.



Different from most studies available in the literature, we analyzed the sensitivity, specificity, LR+, LR-, PPV, NPV, and accuracy of EUS-FNA compared to EUS-FNB in all solid lesions[8,13-15]. EUS-FNB had a better sensitivity (84.70% vs 74.53%), specificity (99.29% vs 96.62%), and accuracy (87.62% vs 81.55%) when compared to EUS-FNA with statistical significance. Our results are similar to a recent large randomized trial comparing EUS-FNA and EUS-FNB in solid lesions including 408 patients (249 pancreatic lesion and 159 non-pancreatic masses)[14].

Interestingly, when we compare pancreatic and non-pancreatic lesions, a statistical difference was found only for the non-pancreatic lesions group. In the pancreatic group, despite superiority of FNB when compared to FNA regarding sensitivity (89.09% vs 85.62%), specificity (98.04% vs 96.88%), and accuracy (90.29% vs 87.50%), no statistical difference was found. The similar diagnostic yield between both techniques in pancreatic lesions reported in our study is compatible with previous studies, including a systematic review and meta-analysis based upon 27 randomized controlled trials[18]. These results may be related to the fact that both procedures have a high accuracy rate, and thus an even larger number of patients (*i.e.*, higher power) may be necessary to determine if FNB is superior.

Studies diverge on consideration of an inconclusive (non-diagnostic) result as benign or the decision to exclude this finding from the analysis. This fact is related to the heterogeneity of the previous results published in the literature[14,19,20]. When excluding inconclusive results, an increase in accuracy is observed, though this may be falsely elevated. In this analysis, we chose to be more rigorous and considered inconclusive results as benign lesions as to not overestimate diagnostic accuracy. As expected from sampling diagnostic modalities, the specificity and PPV were high in both techniques, showing that a positive result for a malignant lesion is very reliable. However, in both groups the sensitivity and NPV were low, and thus a negative result cannot entirely exclude a neoplastic lesion.

In our study, we also performed a multivariate analysis to find an association between several variables, including age, gender, needle type, needle size, use of ROSE, and cell-block assessment on diagnostic accuracy. In our analysis, no predictors were associated with better accuracy. Different from our study, in a multivariable logistic regression of a series including both pancreatic and non-pancreatic solid lesions, FNB and lesion size were associated with the need to perform only one pass to achieve onsite diagnostic adequacy and were associated with procurement of diagnostically adequate histological specimens for offsite assessment[7].

The safety of EUS-tissue sampling is well established, and few adverse events are encountered in the literature. Severe adverse events are especially rare[15,17]. The safety profile of FNB was comparable to that of FNA, with only one adverse event encountered in each cohort. The adverse event occurred after an FNB procedure for suspected neuroendocrine tumor with active acute pancreatitis, which is a contraindication for the procedure. After the procedure, the patient clinically deteriorated, and passed away. We believe that this adverse event was not directly related to FNB as a technique, with any tissue sampling technique possessing the potential to cause this adverse event. Therefore, we do not recommend EUS-tissue sampling in patients with acute pancreatitis. The adverse event in the FNA group was a minor hemorrhage after subepithelial lesions sampling treated with epinephrine injection. In the literature, several studies showed no adverse events related to EUS-FNA or EUS-FNB in the diagnosis of solid lesions[9,13,14].

Despite being the largest study to date to evaluate the role of EUS-FNA and EUS-FNB with and without ROSE in solid lesions, we recognize there are some limitations to our study. This was a retrospective study with the inherent limitations expected with such a design, including potential selection bias, lack of randomization, loss-to-follow-up, and potential for cofounders. This selection bias may be seen in the baseline differences between patients that underwent FNA vs FNB; however, a logistic regression was performed in an attempt to control for these factors. Although none of the patients with benign disease demonstrated disease progression at follow-up, we could not obtain further tissue results for ethical concerns. Furthermore, in effort to simulate clinical practice, multiple available needles sizes were used and thus we cannot discount heterogeneity of our results or fail to acknowledge inter-operator variability using these different needle sizes. Reassuringly, a previous meta-analysis including only high-quality randomized controlled trials, did not show significant difference between varied needles sizes[6]. Procedural costs were not compared between the two cohorts in our study. However, recently a randomized trial showed that the strategy of EUS-FNB was cost saving compared to EUS-FNA over a wide range of cost and outcome probabilities[8].

## CONCLUSION

In summary, EUS-FNB is superior to EUS-FNA in the diagnosis of solid lesions and allows more cell-block evaluation, with similar number of passes required to achieve an adequate sample. EUS-FNA with ROSE and EUS-FNB with ROSE were found to have a similar sensitivity to EUS-FNB alone.

## ARTICLE HIGHLIGHTS

### Research background

While endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) is considered a preferred technique for tissue sampling for solid lesions, fine needle biopsy (FNB) has recently been developed with the capability of tissue extraction for histological evaluation.

### Research motivation

To better understand the comparative effectiveness of FNA vs FNB and possible advantages of EUS-guided FNB for solid lesions in daily clinical practice

### Research objectives

Evaluate the diagnostic test characteristics of EUS-FNA and EUS-FNB sampling techniques with and without rapid on-site evaluation (ROSE).

### Research methods

Multi-center, retrospective study conducted at 5 hospitals in Massachusetts, United States following the Standards for the Reporting of Diagnostic accuracy studies recommendations.

### Research results

A total of 1168 patients with solid lesions underwent EUS-guided sampling. Overall, sensitivity, specificity and accuracy were superior for FNB vs FNA. On subgroup analyses, sensitivity, specificity, and accuracy of FNB alone were similar to FNA + ROSE. There were no difference in diagnostic yield of FNB alone vs FNB + ROSE.

### Research conclusions

FNB is superior to FNA with equivalent diagnostic test characteristics compared to FNA + ROSE in the diagnosis of non-pancreatic solid lesions.

### Research perspectives

Our results suggest that EUS-FNB may eliminate the need of ROSE and should be employed as a first-line method in the diagnosis of solid lesions.

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