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Endoscopic Ultrasound Fine-Needle Aspiration versus Fine-Needle Biopsy for Lymph Node Diagnosis: A Large Multicenter Comparative Analysis

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Background/Aims: Endoscopic ultrasound fine-needle aspiration (EUS-FNA) is preferred for sampling of lymph nodes (LNs) adjacent to the gastrointestinal wall; however, fine-needle biopsy (FNB) may provide improved diagnostic outcomes. This study aimed to evaluate the comparative efficacy and safety of FNA versus FNB for LN sampling.

Methods: This was a multicenter retrospective study of prospectively collected data to evaluate outcomes of EUS-FNA and EUS-FNB for LN sampling. Characteristics analyzed included sensitivity, specificity, accuracy, the number of needle passes, diagnostic adequacy of rapid on-site evaluation (ROSE), cell-block analysis, and adverse events.

Results: A total of 209 patients underwent EUS-guided LN sampling. The mean lesion size was 16.22±8.03 mm, with similar sensitivity and accuracy between FNA and FNB ([67.21% vs. 75.00%, respectively, $p=0.216$] and [78.80% vs. 83.17%, respectively, $p=0.423$]). The specificity of FNB was better than that of FNA (100.00% vs. 93.62%, $p=0.01$). The number of passes required for diagnosis was not different. Abdominal and peri-hepatic LN location demonstrated FNB to have a higher sensitivity (81.08% vs. 64.71%, $p=0.031$ and 80.95% vs. 58.33%, $p=0.023$) and accuracy (88.14% vs. 75.29%, $p=0.053$ and 88.89% vs. 70.49%, $p=0.038$), respectively. ROSE was a significant predictor for accuracy (odds ratio, 5.16; 95% confidence interval, 1.15–23.08; $p=0.032$). No adverse events were reported in either cohort.

Conclusions: Both EUS-FNA and EUS-FNB are safe for the diagnosis of LNs. EUS-FNB is preferred for abdominal LN sampling. EUS-FNA+ROSE was similar to EUS-FNB alone, showing better diagnosis for EUS-FNB than traditional FNA. While ROSE remained a significant predictor for accuracy, due to its poor availability in most centers, its use may be limited to cases with previous inconclusive diagnoses. *Clin Endosc* 2019 Dec 3. [Epub ahead of print]

Key Words: Endoscopic ultrasound-guided tissue acquisition; Lymph nodes; Endoscopic ultrasound; Fine-needle aspiration; Fine-needle biopsy

INTRODUCTION

Differentiation between benign and malignant lymph nodes (LNs) is essential for adequate clinical management, as an incorrect diagnosis may significantly affect patient prognosis. Endoscopic ultrasound (EUS) is well-suited to assess lymphadenopathy in the posterior mediastinum, celiac axis, and peri-intestinal area in patients with benign or malignant gastrointestinal or thoracic diseases, allowing real-time, high-resolution imaging with relatively low cost.¹⁻³ In the past, EUS was used only to provide morphological characteristics

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such as size, echogenicity, architecture, shape, borders, and vascular pattern; however, EUS diagnosis of LN based on morphological characteristics alone has limited accuracy.⁴

While different size cutoffs have been proposed for each anatomical district, diagnosis based on size is associated with reduced accuracy. Previous literature has shown that up to 30% of LNs <5 mm may be malignant, while LNs >20 mm may be benign in the setting of inflammation.¹⁵ Modalities to improve the diagnosis of LN such as contrast enhancement and elastography have been utilized, albeit with widely variable results. Although these innovations have demonstrated higher sensitivity rates than standard EUS imaging, these techniques do not include tissue sampling and yield unsatisfactory specificity rates.² Therefore, these techniques may be helpful in delineating circumscribed malignant infiltration and in directing EUS-guided tissue sampling.⁶

To increase the diagnostic accuracy, EUS-guided sampling has now become the standard of care. In general, this procedure can be safely performed in an outpatient setting without general anesthesia.^{1,4} Compared to alternative techniques available for sampling mediastinal LNs, EUS-guided tissue sampling is safer and less invasive.⁷ Additionally, for abdominal LNs, a prospective study including 142 patients with non-diagnostic or non-feasible percutaneous image-guided sampling demonstrated that EUS-guided sampling was successful in 92% of patients and produced a diagnosis in 91%.⁸ EUS tissue acquisition is typically performed with EUS-fine-needle aspiration (EUS-FNA) providing material for cytological evaluation; however, the reported sensitivity of 88% and specificity of 96.4% remains less than ideal.⁴ These marginal results may, in part, be due to damage of the LN architecture, thereby limiting histological evaluation.^{1,4}

To overcome the limitations of EUS-FNA, novel fine-needle biopsy (FNB) systems have been designed to provide a larger sample and preserve the tissue architecture of the tissue, potentially leading to better results. For the evaluation of LNs of an unknown origin, such as lymphoma, metastasis, mycobacterial infection, and sarcoidosis, core biopsy with preservation of the LN architecture is particularly important.⁸⁻¹⁰ Although FNB appears to be the best modality for LN tissue sampling, both procedures are currently equally recommended by the European Society of Gastrointestinal Endoscopy guidelines, due to lack of studies comparing these techniques.⁷

Because the etiology of lymphadenopathy can radically affect patient management, accurate understanding of and sampling with the best modality are pivotal to obtain precise diagnosis. To determine the best diagnostic method for mediastinal and abdominal LN sampling, we performed a multicenter study, including a large number of patients, to compare the diagnostic outcomes and adverse events associated with

EUS-FNA and EUS-FNB.

MATERIALS AND METHODS

This was a multicenter retrospective study conducted at five 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). The study was approved by the Institutional Review Board from Partners HealthCare. All consecutive patients, aged ≥ 18 years, who had undergone EUS-guided tissue acquisition of LNs from January 2016 to January 2019 were identified from a shared prospective registry. Search terms included endoscopic ultrasound AND lymph node OR lymphadenopathy AND fine-needle aspiration (FNA) OR fine-needle biopsy (FNB). This database contains information on patient demographics (sex, age, and comorbidities), LN characteristics (location, size, shape, heterogeneity, and echogenicity), and procedure details (route of tissue sampling, needle size and type, number of passes, diagnostic adequacy of specimen on rapid on-site evaluation [ROSE] when available, and diagnostic adequacy on cell-block and on slide examination). Additionally, the database contains information regarding patient follow-up, including adverse events, other diagnostic methods if performed, oncological treatment, and surgery.

Procedural technique

All EUS-guided tissue sampling procedures were performed using a linear array echoendoscope (Olympus GF-UCT180; Olympus, Center Valley, PA, USA) under deep sedation with monitored anesthesia care by experienced endosonographers or by gastroenterology fellows under direct expert supervision. Several different needles were used during this study period, including 22 G and 25 G FNA needles (Expect; Boston Scientific Co., Natick, MA, USA or Echotip; Cook Medical, Winston-Salem, NC, USA or Beacon; Medtronic Co., Newton, MA, USA) and 20 G, 22 G, and 25 G FNB needles (Acquire; Boston Scientific, or SharkCore; Medtronic, or ProCore; Cook Medical). No predefined protocol was used in the study. In general, after lesions were identified and punctured under EUS guidance, a fanning technique was performed. Individual operator technique varied between centers, including stylet slow-pull technique and standard suction.

Rapid on-site evaluations

ROSE may be utilized to determine sample adequacy and establish a preliminary diagnosis using a rapid stain. ROSE was not uniformly available for all cases and all institutions

included in our study. Therefore, ROSE was only utilized in more challenging cases, or those that had failed prior sampling. In cases where ROSE was performed, FNA specimens were laid onto slides and smeared for onsite preparation. FNB specimens were prepared using the touch imprint technique. Briefly, the tissue surface was slightly pressed onto the slides prior to staining to reduce the creation of crushing artifacts. All slides were prepared using both wet-fixed (placed in 96% ethyl alcohol for Papanicolaou staining) and air-dried (in some cases stained with Diff-Quik) techniques.

FNA evaluation

Samples obtained through EUS-FNA were transferred onto 3–12 slides. Smears were generated with a slight pressure to avoid crushing artifacts, followed by immediate placement in 96% ethyl alcohol in half of the samples, while the remaining were fixed in the air. When possible, part of the material was placed in formalin for cell-block preparation. Specimens were subsequently transferred to the pathology division for processing and Papanicolaou staining (i.e., slides in alcohol solution), Diff-Quick Staining (i.e., air-dried slides), and hematoxylin and eosin staining (i.e., cell-block). Following these processes, cytology was performed by experienced cytopathologists.

FNB evaluation

FNB samples were fixed in buffered formalin (10% formalin) and dehydrated before embedding in paraffin. Tissues were then sliced into a 4–6- μ m sections and stained with hematoxylin and eosin. Additionally, in some cases, FNB specimens were prepared in slides using the touch imprint technique. All analyses were performed by experienced pathologists.

Immunohistochemical evaluation

Immunohistochemical (IHC) staining was performed for the differential diagnosis of neoplastic and non-neoplastic LNs when needed.

Outcome measures

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-FNA and EUS-FNB from cytological or histological analysis with and without IHC staining. Inconclusive specimen results and atypical cells were considered as non-neoplastic lesions, to not overestimate diagnostic yield. Malignant cells were considered neoplastic LNs, and benign cells were considered non-neoplastic LNs. Secondary outcomes included the proportion of adequate

cellularity for ROSE evaluation, median number of needle passes, diagnostic result from histological (cell-block) and cytological (slides) analysis, and adverse events related to the procedure. Anatomopathological analysis after surgery was the golden standard method. However, because most patients did not undergo surgery due to advanced disease, patient follow-up for at least 6 months was also considered as the reference standard.

Statistical analysis

Baseline patient and procedure characteristics were summarized as mean \pm standard deviation for continuous data and as frequencies and proportions for categorical data. As diagnostic tests were performed in two independent groups of patients, a bivariate model was used to compute pooled sensitivity, specificity, and diagnostic accuracy. Two-sample *t*-tests for binomial proportions were utilized.¹¹ 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.¹² Statistical significance was defined as $p < 0.05$.

Subgroup analyses were then performed to evaluate the diagnostic yield of FNA and FNB for each location (mediastinal and abdominal) of LN. 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 whether ROSE was beneficial. To identify factors associated with diagnostic performance between FNA and FNB needle types, a multivariate logistic regression was performed with adjustment for clinically significant univariate findings as well as age, sex, needle type, needle size, and application of ROSE and cell-block. Results from regression analysis were expressed as beta-coefficient (β) and odds ratio (OR). Statistical analyses were performed using the Stata 15.0 software package (Stata Co. LP, College Station, TX, USA).

RESULTS

Baseline patient, lesion, needle, and sampling characteristics

This was a retrospective chart review of a prospectively collected database that included a total of 209 patients who underwent EUS-guided FNA or FNB LN sampling ($n=108$ FNA and $n=101$ FNB). The mean age of all patients was 63.70 \pm 12.50 years, with no significant difference between FNA and FNB cohorts (64.42 \pm 11.77 years vs. 62.93 \pm 13.26 years, $p=0.333$). Thirty-two percent of all patients were women, and the FNA

Table 1. Characteristics of the Patients, Lesions, and Tissue Acquisition

Results	Total	FNA	FNB	p-value
Patient characteristics				
No. of patients	209	108	101	
Age in years (SD)	63.70 (12.50)	64.42 (11.77)	62.93 (13.26)	0.333
Gender				0.024
No. of males (%)	142 (67.94%)	81 (75.00%)	61 (60.40%)	
No. of females (%)	67 (32.06%)	27 (25.00%)	40 (39.60%)	
Lymph node location (%)				0.244
Peri-esophageal	6 (2.87%)	3 (2.78%)	3 (2.97%)	
Peri-gastric	15 (7.17%)	9 (8.33%)	6 (5.94%)	
Peri-duodenal	2 (0.95%)	1 (0.93%)	1 (0.99%)	
Peri-hepatic	127 (60.76%)	61 (56.48%)	66 (65.35%)	
Peri-pancreatic	21 (10.04%)	9 (8.33%)	12 (11.88%)	
Celiac	13 (6.22%)	6 (5.56%)	7 (6.93%)	
Mediastinal	21 (10.04%)	17 (15.74%)	4 (3.96%)	
Peri-rectal	4 (1.91%)	2 (1.85%)	2 (1.98%)	
Lesion size (mm) (SD)	16.62 (8.03)	16.00 (7.33)	17.26 (8.70)	0.078
Diagnostic sample approach (%)				0.64
Transesophageal	54 (27.55%)	31 (31.31%)	23 (23.71%)	
Transgastric	89 (45.41%)	44 (44.44%)	45 (46.39%)	
Tranduodenal	49 (25.00%)	22 (22.22)	27 (27.84%)	
Transrectal	4 (2.04%)	2 (2.03%)	2 (2.06%)	
Needle size (%)				0.435
20 G	1 (0.48%)	0 (0%)	1 (1.01%)	
22 G	101 (49.03%)	50 (46.73%)	51 (51.52%)	
25 G	104 (50.49%)	57 (53.27%)	47 (47.47%)	
No. of passes (SD)	2.30 (0.97)	2.30 (1.01)	2.30 (0.94)	0.134
No. of samples with ROSE (%)				0.825
Yes	36 (17.22%)	18 (16.67%)	18 (17.82%)	
No	173 (82.78%)	90 (83.33%)	83 (82.18%)	
Adequate sample for ROSE (%)				0.146
Yes	34 (94.44%)	16 (88.89%)	18 (100%)	
No	2 (5.56%)	2 (11.11%)	0 (0%)	
No. of passes for ROSE adequacy (SD)	2.83 (1.00)	2.78 (1.00)	2.89 (1.02)	0.744
No. of samples with cell block (%)				0.053
Yes	164 (78.47%)	79 (73.15%)	85 (84.16%)	
No	45 (21.53%)	29 (26.85%)	16 (15.84%)	
Diagnostic findings with cell block (%)				0.752
Benign	101 (61.58%)	50 (63.29%)	51 (60.00%)	
Malignant	54 (32.93%)	24 (30.38%)	30 (35.29%)	
Inconclusive	9 (5.49%)	5 (6.33%)	4 (4.71%)	
No. of passes for cell block diagnosis (SD)	2.33 (0.98)	2.42 (1.00)	2.26 (1.00)	0.31

FNA, fine-needle aspiration; FNB, fine-needle biopsy; ROSE, rapid on-site evaluation; SD, standard deviation.

group included more men than the FNB group (75.00% vs. 60.40%, $p=0.024$). The most common location of LNs was peri-hepatic (65.13%), which did not differ between the FNA and FNB cohorts ($p=0.224$); mediastinal LN sampling (10.77%) was the next most common location, followed by peri-gastric LNs (7.69%) and celiac LNs (6.67%). The mean LN size was 16.62 ± 8.03 mm, with no difference between the FNA and FNB cohorts (16.00 ± 7.33 mm vs. 17.26 ± 8.70 mm, $p=0.078$).

The most commonly used needle sizes were 22 G (49.03%) and 25 G (50.49%), with no significant difference between the FNA and FNB cohorts ($p=0.435$). The number of passes between lesions sampled with FNA and FNB was also not significantly different (2.30 ± 1.01 vs. 2.30 ± 0.94 , $p=0.134$). Application of ROSE was similar between the FNA and FNB samples (16.67% vs. 17.82%, $p=0.825$). Among patients who underwent ROSE, sample adequacy and the number of passes was comparable between the cohorts (FNA 88.89% vs. FNB 100%, $p=0.146$ and FNA 2.78 ± 1.00 vs. FNB 2.89 ± 1.02 , $p=0.744$, respectively). Cell-blocks were performed more frequently for FNB samples (84.16% vs. 73.15%, $p=0.053$), with no significant difference. Complete baseline characteristics and sampling results for all included patients as well as stratification by FNA or FNB are demonstrated in Table 1.

Comparison of diagnostic characteristics

The overall sensitivity, specificity, and accuracy of EUS-guided tissue sampling for LNs were 71.32% (95% confidence interval [CI], 62.70–78.83), 96.25% (95% CI, 89.43–99.22), and 80.86% (95% CI, 74.86–85.96), respectively. FNA and FNB showed similar sensitivity (67.21% [95%

CI, 54.00–78.69] vs. 75.00% [95% CI, 63.02–84.71], $p=0.216$). However, FNA resulted in a significantly lower specificity than FNB (93.62% [95% CI, 82.46–98.66] vs. 100.00% [95% CI, 89.42–100.00], $p=0.010$). Accuracy was not different between FNA and FNB (78.80% [95% CI, 69.78–86.00] vs. 83.17% [95% CI, 74.42–89.88], $p=0.423$). No adverse events were reported in either FNA or FNB cohorts. Complete diagnostic test characteristics are shown in Table 2.

Subgroup analyses

Subgroup analyses with stratification by LN location (i.e., mediastinal versus abdominal [i.e., peri-gastric, peri-duodenal, peri-hepatic, peri-pancreatic, celiac, and peri-rectal]) were also performed. For mediastinal LNs, no difference between FNA and FNB was found ($p>0.05$). For abdominal LNs, FNB showed significantly higher sensitivity (81.08% [95% CI, 64.84–92.04] vs. 64.71% [95% CI, 50.07–77.57], $p=0.031$) and specificity (100.00% [95% CI, 84.56–100.00] vs. 91.18% [95% CI, 76.32–98.14], $p=0.017$) than FNA. Additionally, the accuracy of FNB was superior than that of FNA (88.14% [95% CI, 77.07–95.09] vs. 75.29% [95% CI, 64.75–84.01], $p=0.053$) (Table 3). For peri-hepatic lesions, FNB was associated with significantly higher sensitivity (58.33% [95% CI, 40.76–74.49] vs. 80.95% [95% CI, 58.09–94.55], $p=0.023$), specificity (88.00% [95% CI, 68.78–97.45] vs. 100.00% [95% CI, 78.20–100.00], $p=0.032$), and accuracy (70.49% [95% CI, 57.43–81.48] vs. 91.67% [95% CI, 61.52–99.79], $p=0.038$) than FNA. There was no difference in the diagnostic yield between LNs in the other locations (Table 4).

Table 2. Comparison of Diagnostic Tests Results

Results	Total	FNA	FNB	<i>p</i> -value
Diagnostic test characteristics				
Sensitivity	71.32% (95% CI, 62.70–78.83)	67.21% (95% CI, 54.00–78.69)	75.00% (95% CI, 63.02–84.71)	0.216
Specificity	96.25% (95% CI, 89.43–99.22)	93.62% (95% CI, 82.46–98.66)	100% (95% CI, 89.42–100.00)	0.01
Positive likelihood ratio	19.02 (95% CI, 6.23–58.03)	10.53 (95% CI, 3.47–31.91)	N/A	N/A
Negative likelihood ratio	0.30 (95% CI, 0.23–0.39)	0.35 (95% CI, 0.24–0.51)	0.25 (95% CI, 0.17–0.38)	0.271
Positive predictive value	96.84% (95% CI, 90.95–98.94)	93.18% (95% CI, 81.85–97.64)	100%	0.01
Negative predictive value	67.54% (95% CI, 61.24–73.27)	68.75% (95% CI, 60.38–76.05)	66.00% (95% CI, 56.26–74.55)	0.672
Accuracy	80.86% (95% CI, 74.86–85.96)	78.80% (95% CI, 69.78–86.00)	83.17% (95% CI, 74.42–89.88)	0.423

CI, confidence interval; FNA, fine-needle aspiration; FNB, fine-needle biopsy; N/A, not applicable.

Table 3. Subgroup Analysis Comparing Endoscopic Ultrasound Fine-Needle Aspiration and Endoscopic Ultrasound Fine-Needle Biopsy in Mediastinal and Abdominal Lymph Nodes

Mediastinal	Total	FNA	FNB	p-value
Sensitivity	81.82% (95% CI, 48.22–97.72)	75.00% (95% CI, 34.91–96.81)	100% (95% CI, 29.24–100.00)	0.961
Specificity	100% (95% CI, 69.15–100.00)	100% (95% CI, 66.37–100.00)	100% (95% CI, 2.50–100.00)	1
Positive likelihood ratio	N/A	N/A	N/A	N/A
Negative likelihood ratio	0.18 (95% CI, 0.05–0.64)	0.25 (95% CI, 0.08–0.83)	N/A	N/A
Positive predictive value	100%	100%	100%	1
Negative predictive value	83.33% (95% CI, 58.80–94.60)	81.82% (95% CI, 57.54–93.73)	100%	0.972
Accuracy	90.48% (95% CI, 69.62–98.83)	88.24% (95% CI, 63.56–98.54)	100% (95% CI, 39.76–100.00)	0.4816
Abdominal	Total	FNA	FNB	p-value
Sensitivity	71.59% (95% CI, 60.98–80.70)	64.71% (95% CI, 50.072–77.57)	81.08% (95% CI, 64.84–92.04)	0.031
Specificity	94.64% (95% CI, 85.13–98.88)	91.18% (95% CI, 76.32–98.14)	100% (95% CI, 84.56–100.00)	0.017
Positive likelihood ratio	13.36 (95% CI, 4.41–40.50)	7.33 (95% CI, 2.44–22.02)	N/A	N/A
Negative likelihood ratio	0.30 (95% CI, 0.21–0.42)	0.39 (95% CI, 0.26–0.57)	0.19 (95% CI, 0.10–0.37)	0.83
Positive predictive value	95.45% (95% CI, 87.39–98.45)	91.67% (95% CI, 78.56–97.06)	100%	0.021
Negative predictive value	67.95% (95% CI, 60.20–74.82)	63.27% (95% CI, 53.93–71.70)	75.58% (95% CI, 61.73–85.96)	0.116
Accuracy	80.56% (95% CI, 73.14–86.67)	75.29% (95% CI, 64.75–84.01)	88.14% (95% CI, 77.07–95.09)	0.053

CI, confidence interval; FNA, fine-needle aspiration; FNB, fine-needle biopsy; N/A, not applicable.

Diagnostic yield with or without ROSE

A comparison between methods with or without ROSE was also performed. The use of ROSE with FNA increased sensitivity compared to FNA alone (97.67% [95% CI, 61.52–99.79] vs. 63.46% [95% CI, 48.96–76.38], $p=0.004$). When the accuracy of FNA+ROSE was compared with that of FNB alone, no statistical difference was found (94.44% [95% CI, 72.71–99.86] vs. 80.72 [95% CI, 70.59–88.56], $p=0.161$) (Tables 5 and 6).

Multivariate logistic regression

Multivariate analysis was then performed to assess predictors for accuracy based on univariate analysis controlling for age, sex, needle type, needle size, the use of ROSE and cell-block analysis. According to this multivariate logistic regression analysis, ROSE was found to be a significant predictor for better accuracy (OR, 5.16; 95% CI, 1.15–23.08; $p=0.032$; $\beta=1.64$).

DISCUSSION

Since EUS-FNA has been considered standard of care, several studies have demonstrated the accuracy of this approach. Despite FNA being the first-line modality, diagnostic data shown in previous studies are variable, with accuracy ranging from 50.0% to 99.4% depending on LN location.^{3,13,14} These results may be related to the limitations of this method, such as damage of the LN architecture limiting histological evaluation.^{1,4} To overcome these limitations, FNB has more recently been used in several centers. Yet, to date, no studies have compared these techniques for LN sampling. To address this highly important question, we performed this first large multicenter study to compare between EUS-FNA and EUS-FNB in this specific population with lymphadenopathy.

The acquisition of histological samples that yield an adequate amount of tissue suitable for IHC staining is pivotal for

Table 4. Subgroup Analyses Comparing Endoscopic Ultrasound Fine-Needle Aspiration and Endoscopic Ultrasound Fine-Needle Biopsy in Different Locations of Abdominal Lymph Nodes

Peri-gastric	Total	FNA	FNB	p-value
Sensitivity	40.00% (95% CI, 21.13–61.33)	100% (95% CI, 54.07–100.00)	100% (95% CI, 39.76–100.00)	N/A
Specificity	100% (95% CI, 47.82–100.00)	100% (95% CI, 29.24–100.00)	100% (95% CI, 15.81–100.00)	N/A
Positive likelihood ratio	N/A	N/A	N/A	N/A
Negative likelihood ratio	0.60 (95% CI, 0.44–0.83)	N/A	N/A	N/A
Positive predictive value	100%	100%	100%	N/A
Negative predictive value	25.00% (95% CI, 19.49–31.46)	100%	100%	N/A
Accuracy	50.00% (95% CI, 31.30–68.70)	100% (95% CI, 66.37–100.00)	100% (95% CI, 54.07–100.00)	N/A
Peri-hepatic	Total	FNA	FNB	p-value
Sensitivity	66.67% (95% CI, 52.94–78.60)	58.33% (95% CI, 40.76–74.49)	80.95% (95% CI, 58.09–94.55)	0.023
Specificity	92.50% (95% CI, 79.61–98.43)	88.00% (95% CI, 68.78–97.45)	100% (95% CI, 78.20–100.00)	0.032
Positive likelihood ratio	8.89 (95% CI, 2.95–26.80)	4.86 (95% CI, 1.62–14.56)	N/A	N/A
Negative likelihood ratio	0.36 (95% CI, 0.25–0.53)	0.47 (95% CI, 0.31–0.72)	0.19 (95% CI, 0.08–0.46)	0.826
Positive predictive value	92.68% (95% CI, 80.77–97.45)	87.50% (95% CI, 70.04–95.45)	100%	0.028
Negative predictive value	66.07% (95% CI, 57.17–73.96)	59.46% (95% CI, 49.26–68.91)	78.95% (95% CI, 60.83–90.06)	0.05
Accuracy	77.32% (95% CI, 67.70–85.21)	70.49% (95% CI, 57.43–81.48)	88.89% (95% CI, 73.94–96.89)	0.038
Peri-pancreatic	Total	FNA	FNB	p-value
Sensitivity	76.92% (95% CI, 46.19–94.96)	60.00% (95% CI, 14.66–94.73)	87.50% (95% CI, 47.35–99.68)	0.156
Specificity	100% (95% CI, 63.06–100.00)	100% (95% CI, 39.76–100.00)	100% (95% CI, 39.76–100.00)	N/A
Positive likelihood ratio	N/A	N/A	N/A	N/A
Negative likelihood ratio	0.23 (95% CI, 0.09–0.62)	0.40 (95% CI, 0.14–1.17)	0.12 (95% CI, 0.02–0.78)	0.899
Positive predictive value	100%	100%	100%	N/A
Negative predictive value	72.73% (95% CI, 49.71–87.80)	66.67% (95% CI, 40.60–85.40)	80.00% (95% CI, 39.00–96.16)	0.5
Accuracy	85.71% (95% CI, 63.66–96.95)	77.78% (95% CI, 39.99–97.19)	91.67% (95% CI, 61.52–99.79)	0.38
Celiac	Total	FNA	FNB	p-value
Sensitivity	81.82% (95% CI, 48.22–97.22)	75.00% (95% CI, 34.91–96.81)	100% (95% CI, 29.24–100.00)	0.275
Specificity	100% (95% CI, 69.15–100.00)	100% (95% CI, 66.37–100.00)	100% (95% CI, 2.50–100.00)	N/A
Positive likelihood ratio	N/A	N/A	N/A	N/A

Table 4. Continued

Celiac	Total	FNA	FNB	p-value
Negative likelihood ratio	0.18 (95% CI, 0.05–0.64)	0.25 (95% CI, 0.08–0.83)	N/A	N/A
Positive predictive value	100%	100%	100%	N/A
Negative predictive value	83.33% (95% CI, 58.80–94.60)	81.83% (95% CI, 57.54–93.73)	100%	0.368
Accuracy	90.48% (95% CI, 69.62–98.83)	88.24% (95% CI, 63.56–98.54)	100% (95% CI, 39.76–100.00)	0.482

CI, confidence interval; FNA, fine-needle aspiration; FNB, fine-needle biopsy; N/A, not applicable.

Table 5. Comparison between Methods with and without Rapid on-Site Evaluation

	FNA alone	FNA with ROSE	FNB alone	FNB with ROSE
Sensitivity	63.46% (95% CI, 48.96–76.38)	97.67% (95% CI, 61.52–99.79)	69.23% (95% CI, 54.90–81.28)	77.22% (95% CI, 66.40–85.90)
Specificity	92.68% (95% CI, 80.08–98.46)	100% (95% CI, 54.07–100.00)	100% (95% CI, 88.78–100.00)	100% (95% CI, 90.97–100.00)
Positive likelihood ratio	8.67 (95% CI, 2.86–26.28)	N/A	N/A	N/A
Negative likelihood ratio	0.39 (95% CI, 0.27–0.57)	0.08 (95% CI, 0.01–0.54)	0.31 (95% CI, 0.20–0.46)	0.23 (95% CI, 0.15–0.34)
Positive predictive value	91.67% (95% CI, 78.40–97.09)	100%	100%	100%
Negative predictive value	66.67% (95% CI, 58.05–74.30)	85.71% (95% CI, 47.88–97.51)	65.96% (95% CI, 56.31–74.44)	68.42% (95% CI, 59.08–76.48)
Accuracy	76.34% (95% CI, 66.40–84.54)	94.44% (95% CI, 72.71–99.86)	80.72% (95% CI, 70.59–88.56)	84.75 (95% CI, 76.97–90.70)

CI, confidence interval; FNA, fine-needle aspiration; FNB, fine-needle biopsy; N/A, not applicable; ROSE, rapid on-site evaluation.

Table 6. Statistical Analysis 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	0.004	0.424	0.030	0.013	0.044	0.205
Specificity	0.238	0.012	0.003	N/A	N/A	N/A
Positive likelihood ratio	N/A	N/A	N/A	N/A	N/A	N/A
Negative likelihood ratio	0.837	0.929	0.835	0.865	0.897	0.913
Positive predictive value	0.206	0.007	0.001	N/A	N/A	N/A
Negative predictive value	0.110	0.922	0.790	0.101	0.135	0.715
Accuracy	0.085	0.485	0.126	0.161	0.271	0.454

FNA, fine-needle aspiration; FNB, fine-needle biopsy; N/A, not applicable; ROSE, rapid on-site evaluation.

the personalized management of LNs, especially in cases of metastasis and lymphoma. Although EUS-FNA is accurate for the identification of neoplastic cells, it has been limiting for providing tissue for IHC staining.^{15,16} An alternative technique

is to collect FNA samples in formalin for cell-block preparation and perform subsequent histological analysis.^{6,9,17,18} However, this technique has demonstrated lower diagnostic rates, independent of the number of FNA passes.¹⁹ In our study, cell-

block analysis was possible in 73.15% of patients after FNA and in 84.16% after FNB. Additionally, the number of passes required to achieve cell-block diagnosis was higher for FNA than for FNB, although this difference was not statistically significant. Despite no statistical difference, the superiority of EUS-FNB and lower number of passes required for diagnostic yield on cell-block in our study are similar to those of previous literature examining solid lesions.^{15,20,21} Accurate diagnosis using EUS-FNA is limited due to the pauci-cellular nature of the aspirate with a significant proportion of the collected tissue being distorted or consumed during automated processing and sectioning.^{15,16}

In our study, EUS-FNA demonstrated an accuracy of 78.80%, which was congruent with several previous reports.^{14,22} Despite the slight superiority of FNB (83.17%), no statistical difference was found between FNA and FNB. Another study also evaluated FNA and FNB in the diagnosis of lymphoma; however, the tru-cut biopsy (TCB) needle, a first generation FNB, was utilized, limiting the extrapolation of these results.¹⁶ Similar to our results, no superiority was found in the TCB group. Additionally, the study illustrated the superiority of EUS-FNA when associated with flow cytometry to EUS-TCB (94.7% vs. 73%). Furthermore, that study concluded that EUS-guided biopsy reported a lower yield to classify Hodgkin's and low-grade lymphomas than to classify high-grade diffuse large B-cell lymphoma.¹⁶

As expected from sampling diagnostic modalities, specificity and PPV were high for both techniques, suggesting that a positive result for a neoplastic lesion is very reliable. Interestingly, our analysis showed that FNB was statistically superior to FNA in specificity (100% vs. 93.62%). However, in both groups, NPV was low, thus a negative result cannot exclude malignant diagnosis. +LR measures how well a test can diagnose a lesion. The higher the +LR, the better the test performs in identifying the precise diagnosis. In our study, because specificity for EUS-FNB was 100%, +LR could not be calculated. -LR of a test measures how well the test performs in excluding the disease. The lower the -LR, the better the test performs in excluding a disease. In our analysis, EUS-FNB had lower -LR than FNA; however, no statistical difference was found.

Different from prior studies evaluating EUS-guided tissue LN sampling, we also performed a subgroup analysis based on LN location.^{3,16,23,24} In the mediastinal LN analysis, the sensitivity and accuracy of EUS-FNB appeared superior to those of EUS-FNA (100% and 100% vs. 75% and 88.24%, respectively). However, no statistical difference was found. This may be related to the small number of patients included in this analysis. Both methods provided 100% specificity. Our results are comparable to those of a previous study that showed no dif-

ference between EUS-FNA and the old generation FNB (TCB) in the diagnosis of thoracic lesions.²⁵ However, in our study, which included the new generation biopsy needle, higher sensitivity and accuracy were found. For abdominal LNs, FNB showed statistically better sensitivity (81.08% vs. 64.71%) and specificity (100% vs. 91.18%) than FNA. Additionally, we also analyzed abdominal LNs according to location. FNB showed significantly higher accuracy than FNA in peri-hepatic lesions (88.89% vs. 70.49%). Regarding peri-gastric, peri-pancreatic, and celiac LNs, no differences between the needle types were found. Similarly, in a prior study that evaluated EUS-FNA in LNs, no association between cytological adequacy and LN location was found when compared pancreatic, subcarinal, aortic pulmonary window, periesophageal and other LNs.²⁴

Literature examining ROSE remains controversial regarding improvement in diagnostic accuracy for solid lesions.^{26,27} Specifically for LNs, a multicenter randomized controlled trial showed that the diagnostic yield and accuracy of EUS-FNA in mediastinal and abdominal LNs with or without ROSE were comparable.²³ However, the time required to review slides was shorter and post-procedural pain was less often reported in the ROSE group. In our study, ROSE was selectively utilized, usually in cases that were more challenging or had failed prior sampling. Therefore, ROSE was performed in only 17.22% of all samples included in our analysis. All FNB samples were adequate for ROSE compared to 88.89% for FNA; however, no statistical difference was observed. In our study, ROSE improved the sensitivity of FNA samples but not of FNB samples. More importantly, and similar to a previous recent meta-analysis, we demonstrated that FNB presented similar accuracy as FNA+ROSE.²⁸

The largest study comparing FNA and FNB in all types of solid lesions has recently shown that a lower number of passes was required for diagnostic adequacy with ROSE for FNB (1 [interquartile range, 1–2] vs. 2 [interquartile range, 1–3], $p < 0.001$).¹⁵ A lower number of passes may reflect a shorter procedure time, lesser risk of adverse events, and better operational efficiency for both endoscopy and cytopathology units. Superior performance of FNB over FNA was observed for both pancreatic and non-pancreatic lesions. In this study, a subgroup analysis of LN sampling was also performed.¹⁵ In contrast to our study, the number of passes required for ROSE analysis was lower for the FNB group. Interestingly, our FNA results are similar to those of that study; however, our FNB results are inferior. These inconsistent results may be explained by various factors: first, our study specifically analyzed the results of FNA and FNB in LNs, including several variables such as patient, LN, and needle characteristics. Additionally, the number of FNA was three-fold higher than that of FNB in the previous study, whereas the number of procedures was similar

between the studies.¹⁵

In our study, we also performed a multivariate logistic regression analysis to identify predictors for better accuracy. Several potential predictors were included, such as age, needle type, needle size, use of ROSE, and cell-block. Based on this analysis, ROSE was found to be the only significant predictor for better accuracy, with an OR of 5.16. This result may be related to the superiority of FNA with ROSE versus FNA alone, as demonstrated in our subgroup analyses, and should be interpreted with caution, especially because only 17.22% of our study population underwent additional testing with ROSE. A study that evaluated EUS-FNA for mediastinal and peri-intestinal LNs also performed a multivariate regression analysis and demonstrated that echo features, the site of LN sampled, and age were associated with malignant involvement. Additionally, mediastinal LNs were 2.77 times less likely to be malignant than other LNs.³ In contrast, a large study of solid masses (not specifically evaluating LNs) showed that FNB and lesion size were associated with the need to perform only one pass to achieve onsite diagnostic adequacy and were associated with acquisition of diagnostically adequate histological specimens for offsite assessment.¹⁵ Additionally, the safety of EUS tissue sampling is well established, and a few or no adverse events have been reported in the literature.²⁹ Severe adverse events are very rare.^{6,23,30} In our study, similar to several studies that compared FNA and FNB, no adverse events were reported.^{30,31}

Currently, this is the largest study to exclusively evaluate EUS-guided LN sampling. However, we recognize some limitations to our study. This was a retrospective study with inherent limitations expected from such a design, including the possibility for selection bias, lack of randomization, and the possibility that patients are lost to follow-up. Despite the retrospective design, we believe that our results are reliable, because baseline patient and lesion characteristics were similar, except for the larger numbers of men in the FNA group, which, in our opinion, did not interfere with our results. We also included different needle sizes, which simulates real-world clinical practice, with no difference between the groups. Furthermore, a meta-analysis of randomized controlled trials did not show a significant difference between different needle sizes.³²

In summary, this is the largest multicenter study to specifically compare the effectiveness and safety of EUS-FNA versus EUS-FNB for LN sampling. Both EUS-FNA and EUS-FNB are safe for the diagnosis of LNs. Our results showed that EUS-FNB and EUS-FNA had similar sensitivity and accuracy in differentiating between benign and malignant LNs, with a higher specificity for FNB. The use of FNB did not reduce the number of passes required for diagnostic yield. For abdominal LNs, EUS-FNB was superior to EUS-FNA. EUS-

FNA with ROSE produced similar results as EUS-FNB alone; thus, the use of EUS-FNB may exclude the need for ROSE as part of routine sampling. Although ROSE in addition to traditional FNA may be deferred in favor of EUS-FNB, ROSE was still found to be a significant predictor for improved accuracy on the multivariate analysis. Despite this finding, we suggest EUS-FNB over EUS-FNA+ROSE, as ROSE is more resource-intensive and is not uniformly available at most centers. However, given its role in improving accuracy, ROSE may still be beneficial for patients with previously inconclusive EUS-FNB sampling.

Conflicts of Interest

Marvin Ryou is a consultant for Medtronic, GI Windows, EnteraSense, FujiFilm, Boston Scientific, Olympus (research grant), and Pentax. Christopher C. Thompson is a consultant for Boston Scientific, Olympus America, and Apollo Endosurgery. The other authors have no financial conflicts of interest.

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