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Original Article

Factors Influencing the Diagnostic Performance of Repeat Endoscopic Ultrasound-Guided Fine-Needle Aspiration/Biopsy after the First Inconclusive Diagnosis of Pancreatic Solid Lesions

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Background/Aims: Endoscopic ultrasound-guided fine-needle aspiration/biopsy (EUS-FNA/B) is essential in diagnosing solid pancreatic lesions (SPLs), but without rapid on-site evaluation (ROSE), a repeat EUS-FNA/B is crucial for clarifying an inconclusive diagnosis. We aimed to evaluate factors associated with improved diagnostic performance of repeat EUS-FNA/B for initially inconclusive SPL diagnoses without ROSE.

Methods: Of 5,894 patients subjected to EUS-FNA/B, 237 (4.0%) with an initially inconclusive diagnosis of SPLs were retrospectively enrolled from five tertiary medical centers between January 2016 and June 2021. Diagnostic performance and procedural factors of EUS-FNA/B were analyzed.

Results: The diagnostic accuracies of first and repeat EUS-FNA/B were 96.2% and 67.6%, respectively. Of 237 patients with an inconclusive diagnosis from initial EUS-FNA/B, 150 were pathologically diagnosed after repeat EUS-FNA/B. In multivariate analysis of repeat EUS-FNA/B, tumor location (body/tail vs head: odds ratio [OR], 3.74; 95% confidence interval [CI], 1.48 to 9.46), number of needle passes (≥4 vs ≤3: OR, 4.80; 95% CI, 1.44 to 15.99), needle type (FNB vs FNA: OR, 3.26; 95% CI, 1.44 to 7.36), needle size (22 gauge vs 19/20 gauge: OR, 2.35; 95% CI, 1.19 to 4.62), and suction method (suction vs others: OR, 5.19; 95% CI, 1.30 to 20.75) were associated with a significantly improved diagnostic performance.
Conclusions: Repeat EUS-FNA/B is essential for patients with an inconclusive EUS-FNA/B without ROSE. To improve the diagnostic performance of repeated EUS-FNA/B, it is recommended that 22-gauge FNB needles, ≥4 needle passes, and suction methods are used. **(Gut Liver 2024;18:184-191)**

Key Words: Endoscopic ultrasound-guided fine needle aspiration; Biopsy; Pancreatic neoplasms

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States. Unfortunately, only 15% to 20% of patients can be treated surgically because pancreatic cancer is often diagnosed in an advanced stage, even though surgical resection is the exclusive curative method.[1,2] The incidence of pancreatic cancer has increased steadily over the past 30 years, and the 5-year survival rate is only approximately 10%. Furthermore, diagnosis of pancreatic cancer is extremely difficult as the organ is deeply situated in the retroperitoneum, and aggressive behavior elicits poor prognosis even after complete resection.

Endoscopic ultrasound-guided fine-needle aspiration/biopsy (EUS-FNA/B) is not only an essential diagnostic imaging modality[3] but can also be used to obtain targeted tissues of solid pancreatic lesions (SPLs) for neoadjuvant and palliative anticancer treatment.[4,5] The diagnosis accuracy of EUS-FNA/B has significantly increased, compared to the past, due to newly developed FNA/B needles. According to a recently published meta-analysis and guidelines, the diagnosis rate of initial EUS-FNA/B is 90% to 95% for pancreatic solid lesions, and repeat EUS-FNA/B is essential in 5% to 10% of patients with inconclusive diagnosis of SPLs.[6-9]

Although repeat EUS-FNA/B exhibits a relatively lower diagnostic accuracy than initial EUS-FNA/B, the usefulness of repeat EUS-FNA/B has been demonstrated in several studies.[6,7,10-13] However, the utility of repeat EUS-FNA/B without rapid on-site evaluation (ROSE) remains unclear, and studies on means with which to maximize its diagnostic performance are lacking. Therefore, we aimed to analyze the outcomes of repeat EUS-FNA/B in inconclusive EUS-FNA/B diagnoses without ROSE and to identify procedural and patient factors that increase the diagnostic performance of repeat EUS-FNA/B.

MATERIALS AND METHODS

1. Patients and study design

Of 5,894 patients subjected to EUS-FNA/B between January 2016 and June 2021, 237 (4.0%) with an inconclusive SPL diagnosis after their initial EUS-FNA/B were retrospectively enrolled from five tertiary medical centers in the Republic of Korea (Yonsei University College of Medicine, Gangnam Severance Hospital, Seoul National University Bundang Hospital, Asan Medical Center, and Gil Medical Center). This study was approved by each center's institutional review board (Yonsei University College of Medicine, IRB number: 2020-0378-002). The informed consent was waived.

The inclusion criteria were age >20 years and having undergone more than two EUS-FNA/B procedures because of initial inconclusive diagnoses of EUS-FNA/B. An inconclusive diagnosis was defined as cytopathological diagnostic uncertainty, which included cases in which material obtained from EUS-FNA/B was inappropriate and led to false negative results for pancreatic malignancies. The exclusion criteria included pancreatic cystic lesions, gastric and hepatobiliary surgical history, severe blood coagulation disorders, and pregnancy.

Clinicopathological data were collected by reviewing medical records, and the final diagnosis of SPL was made based on the cytopathology results of EUS-FNA/B samples or surgical specimens. Among patients for whom a pathological diagnosis was not possible, malignancy was confirmed when lesion progression or metastasis was observed on 6-month follow-up imaging, whereas benign disease was confirmed in cases with a stable lesion without increasing size or metastasis. Additionally, factors influencing the diagnostic performance of EUS-FNA/B were evaluated.

2. EUS-guided FNA/B

EUS-FNA/B procedures were performed with a linear array echoendoscope (GF-UCT2000; Olympus Medical Systems, Tokyo, Japan) using commercially available FNA needles (EchoTip Ultra needle; Cook Medical, Bloomington, IN, USA) or FNB needles (ProCore needle, Cook Medical; Acquire needle, Boston Scientific, Marlborough, MA, USA; EZ Shot3 needle, Olympus, Tokyo, Japan).

In this study, the diagnostic yield and procedure-related factors of EUS-FNA/B were analyzed: needle type (FNA or FNB), puncture route (transgastric or transduodenal), number of needle passes, and needle size (19/20-, 22-, and 25-gauge) were analyzed. Moreover, the application of suction, slow pull back (capillary), or combined methods for EUS-FNA/B was also reviewed (Tables 1 and 2).

3. Statistical analysis

The baseline characteristics of EUS-FNA/B are expressed as means (with standard deviations) or medians (with interquartile range and full range) for continuous data and as frequency and proportion for categorical data. The analysis of factors influencing EUS-FNA/B results was undertaken using univariate and multivariate logistic

Table 1. Baseline Characteristics (n=237)

Variable	No. (%)
Patients related variable	
Male sex	128 (54.0)
Age at diagnosis, mean±SD, yr	63.87±9.79
Tumor-related variable	
Site	
Head	162 (68.4)
Body or tail	75 (31.6)
Size, mm	
Mean±SD	27.27±10.92
≤20 mm (T1 stage)	51 (21.5)
>20 mm	186 (78.5)
Final diagnosis	
Pancreatic ductal adenocarcinoma	212 (89.5)
Pancreatic neuroendocrine neoplasms	6 (2.5)
Benign disease	10 (4.2)
Tuberculous lymphadenopathy	1 (0.4)
Autoimmune pancreatitis	9 (3.8)
Other malignancy	9 (3.8)

Table 2. Baseline Characteristics of First and Second (Repeat) EUS-Guided FNA/B

Variable	1st FNA/B-related variable, No. (%)	Repeat FNA/B-related variable, No. (%)
Route of FNA/B		
Transgastric approach	94 (39.7)	92 (38.8)
Transduodenal approach	143 (60.3)	145 (61.2)
No. of FNA/B passes		
≤3 Passes	216 (91.1)	208 (87.8)
≥4 Passes	21 (8.9)	29 (12.2)
Needle type		
FNA needle	49 (20.7)	42 (17.7)
FNB needle	188 (79.3)	195 (82.3)
Needle size		
19G	0	3 (1.3)
20G	80 (33.8)	86 (36.3)
22G	147 (62.0)	141 (59.5)
25G	10 (4.2)	7 (2.9)
EUS		
Conventional EUS	216 (91.1)	230 (97.0)
CEH-EUS	21 (8.9)	7 (3.0)
Method		
Suction	223 (94.1)	223 (94.1)
Others	14 (5.9)	14 (5.9)

EUS, endoscopic ultrasound; FNA/B, fine-needle aspiration/biopsy; G, gauge; CEH, contrast-enhanced harmonic.

regression analysis. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Diagnostic performance of EUS-FNA/B

Of 5,894 patients who underwent EUS-FNA/B, 237 (4.0%) patients underwent repeat EUS-FNA/B. One hundred and fifty (63.3%) had a definite pathological diagnosis: 140 (93.3%) with pancreatic ductal adenocarcinoma and five (3.3%) with pancreatic neuroendocrine neoplasms and other malignancies. Compared with the 96.2% accuracy of the first EUS-FNA/B (sensitivity 96%, specificity 100%, positive predictive value 100%, and negative predictive value 46.84%), that of the second EUS-FNA/B was 67.5% (sensitivity 66%, specificity 100%, positive predictive value 100%, and negative predictive value 11.5%). Among 87 patients whose diagnoses remained inconclusive in repeat EUS-FNA/B, pancreatic ductal adenocarcinoma, pancreatic neuroendocrine neoplasm, other malignancies, tuberculosis, and autoimmune pancreatitis were finally

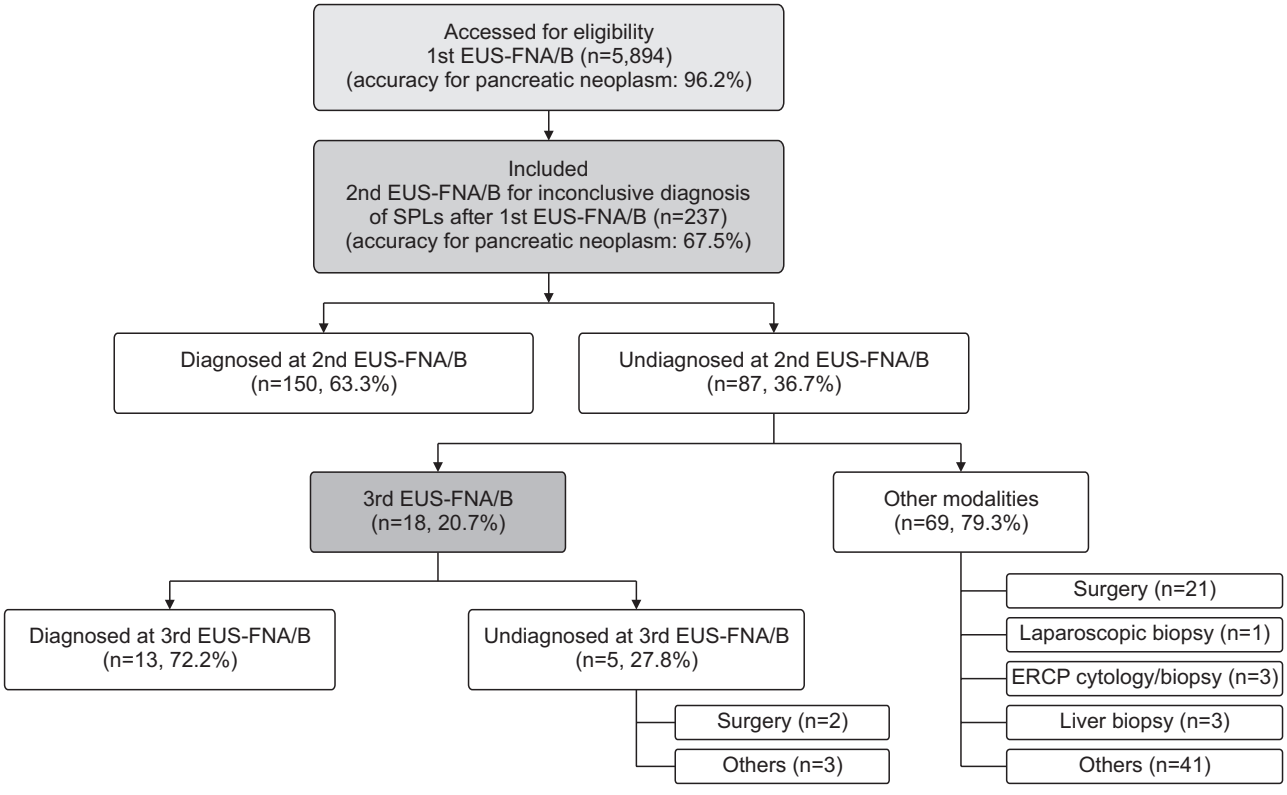

Fig. 1. Flowchart of the study population and design. EUS, endoscopic ultrasound; FNA/B, fine-needle aspiration/biopsy; SPLs, solid pancreatic lesions; ERCP, endoscopic retrograde cholangiopancreatography.

confirmed in 72, one, four, one, and nine patients, respectively, via various diagnostic modalities, including a third EUS-FNA/B, endoscopic retrograde cholangiopancreatography biopsy, liver biopsy, and surgery. In particular, in the third EUS-FNA/B for 18 patients, 13 (72.2%) were finally diagnosed with pancreatic cancer. The accuracy of the third EUS-FNA/B was 83.3% (Fig. 1).

2. Baseline characteristics of repeat EUS-FNA/B

Of 237 patients, 128 (54.0%) were men, with an average age of 63.9±9.6 years. The lesions were located in the pancreatic head and body/tail in 162 (68.4%) and 75 (31.6%) patients, respectively. The size of SPLs was 27.3±10.9 mm. Fifty-one patients (21.5%) had lesions ≤20 mm and 186 (78.5%) had lesions >20 mm. In the first and second EUS-

Table 3. Characteristics of Repeat EUS-Guided FNA/B Depending on Whether or Not a Final Diagnosis Was Made

Variable	Definitive diagnosis at 2nd FNA/B (n=150)	Inconclusive diagnosis at 2nd FNA/B (n=87)	p-value
Patient-related variable			
Male sex	77 (51.3)	51 (58.6)	0.278
Age at diagnosis, mean±SD, yr	63.93±9.57	63.76±10.19	0.895
Tumor-related variable			
Site			0.01
Head	93 (62.0)	69 (79.3)	
Body or tail	57 (38.0)	18 (20.7)	
Size, mm			0.162
Mean±SD	28.08±11.34	25.86±10.06	0.131
≤20 mm (T1 stage)	28 (18.7)	23 (26.4)	
>20 mm	122 (81.3)	64 (73.6)	
Final diagnosis			
Pancreatic ductal adenocarcinoma	140 (93.3)	72 (82.8)	
Pancreatic neuroendocrine neoplasms	5 (3.3)	1 (1.1)	
Benign disease	0	10 (11.5)	
Pancreatic tuberculosis	0	1 (1.1)	
Autoimmune pancreatitis	0	9 (10.3)	
Other malignancy	5 (3.3)	4 (4.6)	
Metastatic renal cell carcinoma	4 (2.7)	1 (1.1)	
Gastrointestinal stromal tumor	1 (0.7)	0	
Lymphoma	0	1 (1.1)	
Schwannoma	0	1 (1.1)	
Multiple myeloma	0	1 (1.1)	
2nd FNA/B-related variable			
Route of FNA/B			0.11
Transgastric approach	64 (42.7)	28 (32.2)	
Transduodenal approach	86 (57.3)	59 (67.8)	
No. of FNA/B passes			0.006
≤3 Passes	125 (83.3)	83 (95.4)	
≥4 Passes	25 (16.7)	4 (4.6)	
Needle type			0.02
FNA needle	20 (13.3)	22 (25.3)	
FNB needle	130 (86.7)	65 (74.7)	
Needle cross over			0.185
Same needle as the first one	115 (76.7)	73 (83.9)	
Different needle from the first one	35 (23.3)	14 (16.1)	
Needle size			0.138
19G/20G	51 (34.0)	38 (43.7)	
22G	96 (64.0)	45 (51.7)	
25G	3 (2.0)	4 (4.6)	
EUS			
Conventional EUS	144 (96.0)	86 (98.9)	0.212
CEH-EUS	6 (4.0)	1 (1.1)	
Method			0.027
Suction	145 (96.7)	78 (89.7)	
Others	5 (3.3)	9 (10.3)	

Data are presented as number (%) unless otherwise indicated.
EUS, endoscopic ultrasound; FNA/B, fine-needle aspiration/biopsy; G, gauge; CEH, contrast-enhanced harmonic.

FNA/B, 94 (39.7%) and 92 (38.8%) patients underwent a transgastric approach, respectively. Of these patients, 21 (8.9%) and 29 (12.2%) patients underwent more than four needle passes in the first and second EUS-FNA/B, respectively. Based on the fine needle type of initial EUS-FNA/B, 20-, 22-, and 25-gauge needles were selected for 80 (33.8%), 147 (62.0%), and 10 (4.2%) patients, respectively; however, in repeat EUS-FNA/B, 19-, 20-, 22-, and 25-gauge needles were used in three (1.3%), 86 (36.3%), 141 (59.5%), and seven (2.9%) patients, respectively. In both the first and second EUS-FNA/B, samples were obtained from 223 (94.1%) patients by the suction method (Tables 1 and 2).

3. Factors related to the diagnostic performance of repeat EUS-FNA/B

The baseline characteristics of the enrolled patients who underwent repeat EUS-FNA/B were compared according to confirmative tissue diagnosis. In the univariate analysis of factors affecting repeat-EUS-FNA/B, tumor location in the body/tail, more than four FNA/B passes, FNB needles, and application of suction during the procedure were related to successful pathological diagnosis. However, needle type crossover between the initial and repeat EUS-FNA/B was not significantly associated with diagnosis rate (odds ratio [OR], 1.587; p=0.187) (Table 3).

Factors with a significance of p<0.2 (tumor site, tumor size, route of FNA/B, number of FNA/B passes, needle type, needle cross over, needle size, and suction method) in the univariate analysis were included in the multivariate logistic regression model to identify independent factors. In the multivariate analysis of factors associated with confirmative diagnosis upon repeat EUS-FNA/B, tumor location

Table 4. Logistic Regression Analysis of Factors Related to Confirmative Diagnosis with Repeat EUS-Guided FNA/B

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Patient-related variable				
Male sex	1.000			
Female sex	1.343 (0.788–2.290)	0.278		
Tumor-related variable				
Site				
Head	1.000		1.000	
Body or tail	2.349 (1.271–4.344)	0.006	3.742 (1.480–9.462)	0.005
Size				
≤20 mm (T1 stage)	1.000		1.000	
>20 mm	1.566 (0.835–2.937)	0.162	1.807 (0.890–3.669)	0.101
Procedure-related variable				
Route of FNA/B				
Transgastric approach	1.000		1.000	
Transduodenal approach	0.638 (0.366–1.110)	0.112	1.437 (0.616–3.350)	0.401
No. of FNA/B passes				
≤3 Passes	1.000		1.000	
≥4 Passes	4.150 (1.393–12.360)	0.011	4.795 (1.439–15.985)	0.011
Needle type				
FNA needle	1.000		1.000	
FNB needle	2.200 (1.120–4.320)	0.022	3.260 (1.443–7.363)	0.004
Needle cross over				
Same needle as the first one	1.000		1.000	
Different needle from the first one	1.587 (0.799–3.150)	0.187	1.808 (0.816–4.009)	0.145
Needle size				
19G or 20G	1.000		1.000	
22G	1.590 (0.918–2.753)	0.098	2.345 (1.189–4.623)	0.014
25G	0.559 (0.118–2.645)	0.463	1.475 (0.168–12.919)	0.726
EUS				
Conventional EUS	1.000			
CEH-EUS	3.583 (0.424–30.268)	0.241		
Method				
Others	1.000		1.000	
Suction	3.346 (1.084–10.331)	0.036	5.188 (1.297–20.746)	0.020

EUS, endoscopic ultrasound; FNA/B, fine-needle aspiration/biopsy; OR, odds ratio; CI, confidence interval; G, gauge; CEH, contrast-enhanced harmonic.

in the pancreatic body/tail had a relatively higher diagnosis rate (OR, 3.742; p=0.005). However, the route of FNA/B was not found to be significant. In terms of procedure-related factors, the number of fine needle passes (≥4 vs ≤3: OR, 4.795; 95% confidence interval [CI], 1.439 to 15.985), needle type (FNB vs FNA: OR, 3.260; 95% CI, 1.443 to 7.363), needle size (22 gauge vs 19/20 gauge: OR, 2.345; 95% CI, 1.189 to 4.623), and suction method (suction vs others: OR, 5.188; 95% CI, 1.297 to 20.746) significantly improved the diagnostic performance of repeat EUS-FNA/B (Table 4).

DISCUSSION

Currently, several studies have shown repeat EUS-FNA/B to be beneficial and necessary because it increases diagnostic yield after obtaining inconclusive and nondiagnostic results. However, there is a lack of recommendations on the technical aspects of repeat EUS-FNA/B. Accordingly, we aimed to identify factors that improve the diagnostic performance of repeat EUS-FNA/B in this study. In repeat EUS-FNA/B without ROSE, the diagnostic yield increased when SPLs were located in the pancreatic body/tail and when using 22-gauge FNB needles, as well as application of more than four needle passes and the suction method.

In this study, clinical and technical factors of EUS-FNA/B were analyzed, the accuracy of which was affected by the location of the target lesion. In EUS-FNA/B, SPLs of the pancreas head, which is more difficult to access, had low diagnostic yield. In contrast, SPLs of the pancreatic body/tail had relatively high diagnostic accuracy as they are readily accessible via a transgastric route.

In terms of technical factors influencing repeat EUS-FNA/B sampling, several important factors were identified. In initial EUS-FNA/B, at least three needle passes are recommended.[14] However, in this study, the diagnostic yield was improved when the number of needle passes was four times or more.[12,13] Increasing the number of FNA/B passes to obtain more tissue for analysis is considered a reasonable option.

Regarding needle size, it is assumed that larger diameter needles are advantageous for tissue diagnosis. However, in this study, 19/20-gauge and 25-gauge needles showed lower diagnostic accuracy than 22-gauge needles. This is probably because a 22-gauge needle targets the pancreatic tissue in EUS-FNA/B more accurately and easily, and facilitates procurement of a histologic core. Similarly, a recent study on the use of FNB needles also reported a higher diagnostic rate with 22-gauge needles.[15-17]

Among needle types, the FNB needle obtains a larger histology core and is also useful in difficult diagnosis cases, such as neuroendocrine tumors and autoimmune pancreatitis.[18,19] Similarly, although the suction method is subject to blood contamination, it can retain more tissue than the slow pullback method, contributing to a higher diagnostic yield in repeat EUS-FNA/B.[20,21]

In this study, only 87 of 5,894 patients (1.4%) were not diagnosed after repeat EUS-FNA/B. However, additional histological diagnosis was attempted for these patients using a third EUS-FNA/B, surgery, percutaneous biopsy, and endoscopic retrograde cholangiopancreatic biopsy. Interestingly, a third EUS-FNA/B was performed in 18 undiagnosed patients after repeated EUS-FNA/B, and the accuracy was 83%, which was higher than 67.5% for a second EUS-FNA/B. However, with a small number of samples, statistical comparison is difficult and additional research is needed. Furthermore, in five patients with nondiagnostic and inconclusive results, a final diagnosis could only be made by surgery (two patients) and percutaneous liver biopsy (one patient). As such, in actual clinical practice, if possible, histological diagnosis through a route other than EUS-FNA/B should be considered.

This study has several strengths and limitations. The major strength of this study was that numerous, meaningful variables of EUS-FNA/B were analyzed to authenticate the influence of needles and technical aspects on EUS-FNA/B outcomes based on a multicenter, large-scale study. The first limitation was selection bias from retrospective study design. Second, the heterogeneity of the EUS-FNA/B procedure is another limitation. Although the participating institutions are tertiary medical centers that perform many EUS-FNBs, there may be differences in the proficiency of the EUS endoscopists and the types of FNB needles could not be unified due to various products from different manufacturers. Third, the absence of ROSE was the shortcoming of this study. The usefulness of ROSE in repeat EUS-FNA/B is controversial. While previous studies have reported that ROSE is helpful in repeat EUS-FNA for the diagnosis of nondiagnostic results,[11] a recent large-scale multicenter study demonstrated that comparable diagnostic accuracies were obtained between FNB with ROSE and FNB without ROSE (96.4% vs 97.4%, p=0.396).[22] As such, although there are debates about the value of ROSE, our findings are clinically meaningful. Lastly, there is an imbalance in that needle sizes of 19- and 25-gauge were scarcely used in this study. This is because of operator concerns regarding the technical difficulty related to manipulation of 19-gauge needles and the insufficient tissue yield from 25-gauge needles.

In conclusion, repeat EUS-FNA/B for SPLs is helpful to obtaining confirmative histologic diagnosis in patients

with initially inconclusive and nondiagnostic results of EUS-FNA/B, especially without ROSE. In order to improve the diagnostic yield of repeat EUS-FNA/B, using FNB needles, 22-gauge size, four or more needle passes, and the suction method could be recommended. Nevertheless, further prospective multicenter studies will be required to expand our technical understanding of EUS-FNA/B.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: J.H.C., S.B. Data acquisition: S.J.R., S.I.J., J.K., E.J.K., H.K., S.S.L., T.J.S. Data analysis and interpretation: J.H.C., H.S.L., S.J.R. Drafting of the manuscript: J.H.C., S.J.R. Critical revision of the manuscript for important intellectual content: S.B., J.K., T.J.S. Statistical analysis: J.H.C. Obtained funding: J.H.C. Administrative, technical, or material support; study supervision: S.B., T.J.S. Approval of final manuscript: all authors.

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