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Research Article

Enhancing Diagnostic Yield of EUS-Guided FNA Through On-site Cytopathology

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Abstract

Objective: The diagnostic yield of endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) can vary according to many factors. We aimed to determine the predictors that optimize the diagnostic yield of EUS-FNA, particularly the role of on-site cytopathologists.

Methods: A total of 175 patients who underwent EUS-FNA were retrospectively enrolled in this study. Lesion localization, size, characteristics, and the presence of a cytopathologist during the examination were evaluated. A standard endoscope and a Cook Medical Echo Tip 22G needle were used to view, evaluate, and perform FNA on the lesions using the Standard Suction Technique.

Results: The most common lesion location was the pancreas, accounting for 70% of cases. The average lesion size was 3.2 ± 1.7 cm. Rapid on-site pathological evaluations (ROSE) were performed for 64 patients (37%), significantly improving diagnostic rates to 78% compared to 63% without ROSE (OR 2.09, 95% CI 1-4.2, $P = .039$). The diagnostic yield was higher for solid lesions compared to cystic ones (OR 2.2, 95% CI 1-4.7, $P = .03$). A positive correlation was found between lesion size and diagnostic yield (R 0.18, $P = .017$). ROC analysis showed that lesions larger than 2.4 cm had a diagnostic specificity of 73% and sensitivity of 45% (AUC 0.61, $P = .019$).

Conclusion: Our findings clearly revealed that ROSE enhances the diagnostic yield and procedural efficiency of EUS-FNA. This may be related to the high quality of smears prepared by the cytopathologist. Furthermore, larger lesion sizes were associated with higher diagnostic accuracy, particularly in pancreatic lesions.

Keywords: Endoscopic ultrasound-guided fine needle aspiration, rapid on-site evaluation, endoscopic ultrasonography

INTRODUCTION

Endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) and fine-needle biopsy (FNB) are essential techniques for tissue sampling, especially for diagnosing pancreatic, subepithelial, and lymph node lesions.[1] Today, EUS plays a crucial role in both diagnosis and treatment across various domains, including tumor staging in the gastrointestinal tract wall, particularly in the pancreas and hepatobiliary area, evaluation of subepithelial gastrointestinal lesions, assessment of benign and malignant pancreaticobiliary lesions, lung cancer staging, and EUS-guided needle injection treatments.[2,3] EUS-FNA is less invasive and useful for obtaining cellular material, making it sufficient for many conditions. However, it may provide inadequate tissue architecture for certain histopathological analyses and often requires multiple needle passes, increasing the risk of complications such as bleeding or infection.[4] EUS-FNB addresses these limitations by using larger gauge needles to obtain core tissue samples, which offer better histological detail and support comprehensive analyses like immunohistochemistry and molecular testing. EUS-FNB often requires fewer needle passes, reducing procedure time and complication risks.[5] It also shows higher diagnostic accuracy and sample adequacy for certain lesions. However, EUS-FNB can be more challenging to maneuver, particularly in difficult anatomical locations, and may carry a higher risk of adverse events.[6]

Thus, it is clear that factors such as localization, characteristics of the lesion, and the experience of the endoscopist affect the outcome in both techniques. In addition, rapid on-site evaluation (ROSE) by the cytologist accompanying the procedure has been shown to significantly improve the diagnostic accuracy and adequacy of EUS-FNA procedures, particularly for pancreatic lesions, providing quicker and more reliable results compared to procedures without ROSE.[7] Therefore, we aimed to evaluate factors that could potentially affect the diagnostic yield, such as conducting

the EUS-FNA procedure with or without ROSE, while also detailing the characteristics, sampling areas, and diagnoses of patients who underwent EUS-FNA.

METHODS

This retrospective study was performed with the Institutional Review Board protocol approval date 05.08.2016 and number 2016/915 in İstanbul University, Faculty of Medicine, Department of Internal Diseases, Gastroenterohepatology Division, Endoscopy Laboratory between 2012 and 2014. The study sample comprised 175 patients, selected from a total of 315 (152 female and 163 male; 48% female, 52% male), who were suitable for EUS-guided FNA and whose data were accessible. Patients included in the study required a biopsy due to lesions detected by endoscopy or other imaging techniques (CT, MRI, and USG) and subsequently underwent FNA. Additionally, participants were enrolled in the study after obtaining written informed consent.

Sample and Endoscopy Procedure

In addition to evaluating patients' demographic characteristics such as age and gender, we also retrospectively assessed the location, size, and characteristics of lesions, including whether they were subepithelial. Records were also reviewed to determine whether a cytopathologist participated in the procedure. The EUS procedures were performed by two gastroenterologists.

A standard endoscope (Fujinon echoendoscope) and a Cook Medical Echo Tip 22G needle were used to view, evaluate, and perform FNA on the lesions using the Standard Suction Technique with a stylet.

Preparation of Specimens

When a cytopathologist was not present, smears were prepared by air-drying, and cell block material was obtained by washing in a 50% ethanol solution. Direct smear preparations were made from the aspirated material, and some were immediately placed into 95% ethanol for Papanicolaou (PAP) staining. The remaining samples were left to dry at room temperature for May-Grunwald-Giemsa (MGG) staining. If blood clots or tissue particles were present on the smears, forceps were used to remove them and place them into 10% formalin or 50% ethanol solutions for cell block preparation. Excess blood aspirates that were not smeared were allowed to coagulate before being placed in the cell block solution. One of the air-dried smears was stained with Diff-Quick or fast Giemsa for immediate evaluation. If these stains were unavailable, one of the alcohol-fixed preparations was stained with hematoxylin and eosin.

The stained preparations were evaluated under a microscope to determine if they contained a sufficient number of cells from the target lesion for a cytopathological diagnosis. If the sample was adequate, the EUS-FNA procedure was concluded. However, if the sample had a low cell count, extensive necrosis, or complex morphologies such as low-grade carcinoma or reactive atypia, the procedure was repeated. When neoplasia was detected, particularly resembling lesions such as pancreatic endocrine neoplasia or solid pseudopapillary tumors, a separate aspiration procedure for the cell block was recommended. This is crucial as immunohistochemistry is necessary for diagnosis, differential diagnosis, and determining the potential for malignancy. If the aspirate contained only lymphoid cells, including a mix of small mature lymphocytes and germinal center lymphoblasts, a new aspiration procedure was initiated. This step was crucial for diagnosing and differentiating low-grade lymphoproliferative diseases. The aspirate was then preserved in McCoy (RPMI) solution, phosphate-buffered saline (PBS), or physiological saline and sent for flow cytometry analysis.

Statistical Analysis

The data were analyzed using SPSS (Statistical Package for the Social Sciences) software for Windows, version 21.0, provided by IBM in Armonk, NY, USA. The analysis involved summarizing individual and aggregate data using descriptive statistics, which included means, standard deviations, medians (ranging from minimum to maximum), frequency distributions, and percentages. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. For variables with a normal distribution, comparisons were made using the Student's t-test and ANOVA. For non-normally distributed variables, the Mann-Whitney and Kruskal-Wallis tests were employed to compare groups. Categorical variables were evaluated using the Chi-Square test. The recurrence of *H. pylori* and disease-free survival probabilities were examined using the Kaplan-Meier survival analysis method. Correlations were examined using either Spearman's Rho or Pearson tests. ROC (receiver operating characteristic) curve analysis was performed to determine the cut-off value, sensitivity, and specificity. *P*-values of $< .05$ were considered statistically significant.

RESULTS

The 175 patients included in this study comprised 97 females (55%) and 78 males (45%), with a mean age of 56.7 ± 15.2 years (range: 18-84 years). The average age was 57.4 ± 13.7 for male patients and 56.1 ± 16.3 for female patients. A total of 175 EUS-FNA procedures were performed, with details on various lesion locations, ROSE involvement, pathological results, demographic, and clinical characteristics of patients provided in Table 1. Diagnoses were successfully made in 60% of the mediastinal lesion cases (3 out of 5 cases). For the gastrointestinal tract lesions, 61.9% of the cases were diagnosed (13 out of 21 cases). Intra-abdominal mass lesions/lymphadenomegaly had a 50% diagnosis rate (7 out of 14 cases). Finally, 58.3% of the hepatobiliary lesion cases were diagnosed (7 out of 12 cases) (Table 1). In all cases where a diagnosis could not be made, the sample was inadequate (Figure 1).

Out of the 175 procedures, 64 were conducted with a cytopathologist present (with ROSE), while 111 were performed without one (without ROSE). The involvement of a cytopathologist resulted in a sensitivity of 41.6%, a specificity of 74.5%, a positive predictive value (PPV) of 78.1%, and a negative predictive value (NPV) of 36.9%. The diagnostic rate was significantly higher in procedures accompanied by a cytopathologist (OR 2.09, 95% CI 1-4.2, $P = .039$). In the analyses conducted after excluding the patient group with cystic lesions, the sensitivity of the cytopathologist's participation in the procedure was 50.5%, specificity was 68.8%, PPV was 77.7%, and NPV was 39.2% (Table 2). The diagnostic rate was significantly higher in cases with ROSE (OR 2.2, 95% CI 1-4.7, $P = .03$).

The mean lesion size was 3.2 ± 1.7 cm, ranging from 0.5 to 12 cm. A positive correlation ($r = 0.18$, $P = .017$) was observed between lesion size and diagnostic yield, indicating that the probability of obtaining an adequate diagnosis increases with larger lesions. Specifically, the mean size for pancreatic lesions was 3.05 ± 1.43 cm (range: 0.5-12 cm). Additionally, the mean lesion size in non-pancreatic lesions was 3.85 ± 2.3 cm (range: 0.7-10 cm). A statistically significant positive correlation ($r = 0.3$, $P = .018$) was observed between lesion size and diagnostic yield in non-pancreatic lesions (Table 3). Moreover, ROC analysis showed that lesions larger than 2.4 cm had a diagnostic sensitivity of

Table 1. Demographic and Clinical Characteristics of Patients

Lesion Location (n=175)	Mean Age (years)	Lesion Types	ROSE 64 (36.5%)	Pathological Results	n	(%)
Pancreas (n=123)	57.7 ± 14.7	Cystic (26%)	47 (73.4%)	Benign	44	49
		Solid (61%)		Malignant Atypical Cells	8	9
		Mixed (13%)		Adenocarcinoma	29	32
				Neuroendocrine Tumor	4	5
				Lymphoma	1	1
				Mucinous Pancreatic Neoplasm	1	1
				GIST	1	1
				Chronic Inflammation	2	2
Tract (n=21)	55.8 ± 15.8	Solid (95.2%)	6 (9.4%)	Benign	5	38.5
• Esophagus		Mixed (4.8%)		GIST	6	46.2
• Stomach				Malignant Atypical Cells	1	7.7
• Duedonum				Lymphoma	1	7.7
Abdominal (n=14)	47.8 ± 19.6	Solid (85.7%)	2 (3.1%)	Benign	3	42.9
		Mixed (14%)		Malignant Atypical Cells	2	28.6
				GIST	1	14.3
				Inflammation	1	14.3
Hepatobiliary (n=12)	54.6 ± 13	Cystic (8.3%)	6 (9.4%)	Benign	3	42.9
		Solid (91.7%)		Malignant Atypical Cells	1	14.3
				NET	2	28.6
				Adenocarcinoma	1	14.3
Mediastinal (n=5)	64.8 ± 8.9	Solid (100%)	3 (4.7%)	Benign Lymph Node	1	33.3
				Malignant Atypical Cells	2	66.7

73.3% and a specificity of 45.5%, with an AUC of 0.61 (95% CI 0.5-0.7, P=.019).

In the evaluation of 123 pancreatic FNA cases, 26% (n=32) of the lesions were cystic, 61% (n=75) were solid, and 13% (n=16) were mixed. No significant correlation was found between the diagnostic adequacy and the characteristics of the lesions—cystic, solid, and mixed (P=.237), regarding whether material adequacy varied based on these characteristics. Although the diagnostic rates were higher for solid and mixed lesions compared to cystic ones, this difference was not statistically significant (71% vs. 62.75%). In the pancreatic lesions, the involvement of the cytopathologist in the procedure contributed to a diagnostic yield of 43.3%, with a specificity of 75.7%, a PPV of 82.9%, and an NPV of 32.8%. The diagnosis rate was significantly high in cases involving ROSE, though the result was marginally significant (OR 2.3, 95% CI 0.9-5.8, P=.054). After excluding cystic lesions from the analyses, the cytopathologist's participation resulted in a diagnostic yield of 55.8%, specificity of 65.2%, PPV of 82.6%, and NPV of 33.3%.

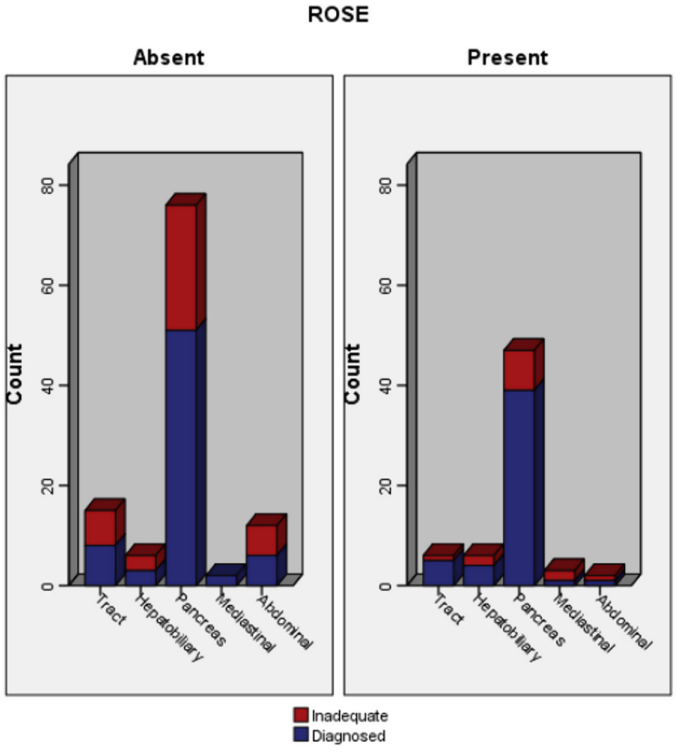

Figure 1. Involvement of rapid on-site evaluation (ROSE) according to lesion locations.

Following the EUS procedures, one patient experienced a ruptured pancreatic cyst and developed pleural effusion during follow-up. Mild pancreatitis was detected in two patients. Aside from fever in two other patients, no adverse reactions were reported. The average number of needle passes during the procedures was three, and no significant correlation was observed between diagnosis rates and the number of needle entries (P > .05).

DISCUSSION

EUS-FNA provides the advantage of simultaneous imaging and sampling from mediastinal, intra-abdominal, pancreatic, and submucosal

Table 2. Contribution of the Cytopathologist's Involment

Lesion Type	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic Yield
All lesions	41.6	74.5	78.1	36.9	OR 2.09, %95 CI 1-4.2 P=.039*
Pancreatic lesions	43.3	75.7	82.9	32.8	OR 2.3 95% CI 0.9-5.8, P=.054
Pancreatic solid lesions	55.8	65.2	82.6	33.3	OR 2.3 95% CI 0.8-6.3, P=.08

NPV, negative predictive value; OR, odds ratio; PPV, positive Predictive value; *P < .05 statistically significant.

Table 3. The Relationship Between Lesion Sizes and Diagnostic Yield

Lesion Type	Lesion Size (Mean ± SD)	Correlation of Diagnostic Accuracy	
		r	*P*-value
All lesions	3.2 ± 1.7	0.18	.017*
Pancreatic lesions	3.05 ± 1.43	0.13	.136
Non-pancreatic lesions	3.85 ± 2.3	0.3	.018*

r, correlation coefficien., *$P < .05$ statistically significant.

lesions. Solid and cystic lesions of the pancreas constitute one of the areas where EUS is most frequently used for tissue sampling. EUS-FNB sampling has emerged as the technique of choice for the pathologic characterization of solid pancreatic tumors, showing optimal PPVs and fair NPVs.[5,6] Supportively in our study, 70% of the EUS-FNA procedures were performed for lesions in the pancreas. Recent studies have consistently highlighted the impact of rapid on-site pathological evaluation (ROSE) on the diagnostic accuracy and efficiency of EUS-FNA procedures, particularly for pancreatic lesions. A randomized controlled trial by Crinó et al. found that the diagnostic accuracy of EUS-FNB with ROSE was slightly higher compared to without ROSE, with diagnostic accuracies of 96.4% and 97.4%, respectively, improving sample adequacy and diagnostic precision.[7] Similarly, Lisotti et al reported that repeat EUS-FNA procedures with ROSE had significantly higher sensitivity (83%) and specificity (98%) compared to those without ROSE (65% sensitivity and 94% specificity), underscoring its value in obtaining adequate diagnostic samples in challenging cases.[8]

In a comprehensive review encompassing 15 studies with a total of 1,860 patients, the overall specificity and sensitivity of EUS-FNA performed for solid lesions of the pancreas (PSL) were found to be 96% and 92%, respectively. A subgroup analysis within this review, focusing on 6 studies, revealed a total sensitivity of 95% when ROSE was employed, compared to 89% without it.[9] Consistent with these findings, our study, which excluded cystic lesions of the pancreas and included a heterogeneous group, demonstrated that the involvement of a cytopathologist in evaluating PSL resulted in a sensitivity of 50.5%, a specificity of 68.8%, a PPV of 77.7%, and an NPV of 39.2%. Notably, the diagnostic yield was significantly higher in cases that utilized ROSE.

Studies on the contribution of ROSE to diagnostic accuracy have generally shown positive results, mainly for solid pancreatic lesions. However, studies on cystic lesions are limited. Estrada P. et al found high non-diagnostic rates for cystic lesions evaluated with ROSE (87.0%) and without ROSE (77.8%), with no significant difference in overall diagnostic yield. The researchers emphasized the need for holistic evaluations, including cyst content analysis (CEA and amylase), endosonographic features, and patient history for accurate diagnosis.[10] The lower diagnostic accuracy of FNA in cystic lesions is due to cell-poor cyst walls, but sampling from solid components can improve accuracy. In our study, a cytopathologist participated in only one cystic lesion procedure, showing no significant impact on diagnosis, likely due to the endoscopist's expertise in integrating clinical and biochemical data with endosonographic findings.

In a study by Klapman et al, which evaluated the diagnostic adequacy of EUS-FNA involving 108 patients with a cytopathologist and 87 without, it was found that the presence of a cytopathologist significantly reduced the number of inadequate material cases and improved the diagnostic rate.[11] In another retrospective study by Shafqat Mehmood et al, which included samples from the mediastinum, abdominal lymph nodes, and pancreas, a cytopathologist accompanied all procedures, leading to sufficient samples for final pathological evaluations in 369 patients. The concordance of the final cytopathological diagnosis with the point-of-care evaluation was 98.2%. The sensitivity, specificity, PPV, and NPV of EUS-FNA were reported as 98.6%, 100%, 100%, and 69.2%, respectively.[12] One potential reason for our lower rates compared to those studies might be the heterogeneity in lesion distributions. Furthermore, the retrospective nature of our study and the inclusion of real-life data may also contribute to the differences in results.

It is well-known that EUS is an ideal non-invasive diagnostic method for mediastinal examinations. In a study evaluating 150 mediastinal EUS-FNA procedures, the diagnostic accuracy was found to be 95%.[13] Additionally, a single-center retrospective study by Ecka RS et al demonstrated that the definitive diagnosis rate (positive or negative for malignancy) increased from 64.8% to 97.7% when a cytopathologist was involved in the evaluation ($P = .001$).[14] Consistently, in our study, the number of cases involving mediastinal and abdominal lymph nodes was limited. Malignant atypical cells were detected in 2 of the 5 patients whose samples were taken from mediastinal lymph nodes. The procedure for one of the 3 diagnosed patients was performed in the presence of a cytopathologist. Additionally, insufficient material was obtained from 8 of the 21 patients who underwent FNA from the GI tract; a cytopathologist was present for 5 of the 13 diagnosed patients. Rapid cytological evaluations were performed for 4 of the 7 patients diagnosed based on biopsies taken from the hepatobiliary region.

Recent studies indicate that 22G needles are the most commonly used in EUS-FNA procedures due to their optimal balance of diagnostic accuracy and tissue adequacy, outperforming both 19G and 25G needles in terms of histological sample quality and safety.[15] Moreover, studies investigating the impact of the number of needle passes on EUS-FNA diagnostic accuracy for pancreatic lesions suggest that an optimal number of passes is critical for maximizing diagnostic yield. Research indicates that performing at least three passes generally achieves high diagnostic accuracy, with diminishing returns observed beyond the third pass. Specifically, using a 22G needle, three passes were sufficient to achieve a diagnostic yield comparable to that of four or more passes, thus optimizing both sample quality and procedure efficiency.[16] Furthermore, the presence of a cytopathologist during an EUS-FNA procedure is expected to reduce the rate of adverse reactions by decreasing the number of needle punctures and increasing diagnostic yield. A study evaluating the effects of a cytopathologist's presence during examinations of solid pancreatic masses observed that both the mean number of needle entries and the adverse reaction rate were lower when a cytopathologist was involved.[3] Consistent with published data, the average number of needle entries in these procedures was 3, and the frequency of adverse reactions was very low. No bleeding was observed in any of the patients, and the cases of pancreatitis (n = 2, 1.62%) encountered were mild. Additionally, we performed FNA using Standard Suction Technique using a 22G needle.

The main strength of this study is its reflection of a single-center experience with the same cytopathologist participating in all procedures. Its retrospective nature also provides real-life data, which mirrors daily routine practice effectively. Furthermore, the inclusion of a cytopathologist typically occurs in more complex cases where previous imaging shows difficult technical accessibility due to factors like anatomical localization or vascularity. These cases often involve patients who may not be suitable for a second procedure due to their general

condition or comorbidities. On the contrary, our study faced several limitations. Firstly, the distribution of lesions among patients was not standardized, and the methods used during procedures involving a cytopathologist varied, which may have affected diagnostic outcomes. Additionally, sedation during endoscopic procedures was not administered by an anesthesiologist, potentially reducing patient compliance. Standardization was challenging because the study was conducted at a tertiary hospital that serves as a referral center for complex cases or patients whose initial procedures elsewhere had failed.

In conclusion, our findings clearly revealed that ROSE enhances the diagnostic yield and procedural efficiency of EUS-FNA. It remains a valuable tool in clinical practice, particularly in settings where its implementation is feasible. This may be related to the high quality of smears prepared by the cytopathologist. Furthermore, larger lesion sizes were associated with higher diagnostic accuracy, particularly in pancreatic lesions.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University (Date: 12.07.2016, Number: 2016/915).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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