

Evaluation of Fine Needle Biopsy (FNB) for Endoscopic Ultrasound (EUS)-guided Tissue Acquisition of Pancreatic Masses to Negate the Need for Rapid On-site Evaluation: A Randomized Control Trial

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ABSTRACT

Background and Objectives. The benefits of rapid on-site evaluation (ROSE) of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of solid masses have not been convincingly shown in large, randomized trials. New equipment using EUS-guided fine needle biopsy (FNB) allows for more material to be acquired that may obviate the need for ROSE. This study aimed to evaluate if EUS-FNB without ROSE was non-inferior to EUS-FNA with ROSE in solid pancreatic masses (SPMs).

Methods. Patients with SPMs requiring tissue sampling were randomly assigned to undergo either EUS-FNA with ROSE or EUS-FNB without ROSE. The touch-imprint cytology technique was used to perform ROSE. The primary endpoint was diagnostic accuracy and secondary endpoints were specimen quality, complication rates, and procedure time.

Results. Seventy-eight patients were randomized and analyzed (39 EUS-FNA with ROSE and 39 EUS-FNB without ROSE). Non-significantly different diagnostic accuracies were noted in both groups (97% with ROSE and 100% without ROSE, $P < 0.371$). The bloodiness of histologic samples and complication rates were not significantly different between groups. A significantly shorter mean sampling procedural time was noted for EUS-FNB over EUS-FNA with ROSE (30.4 ± 10.4 vs 35.8 ± 9.8 minutes, $P < .02$).

Conclusions. EUS-FNB demonstrated equal diagnostic accuracy with shorter procedure times in evaluating SPMs compared to EUS-FNA with ROSE. These new-generation FNB needles may obviate the need for ROSE.

Keywords: pancreatic masses, pancreatic cancer, endoscopic ultrasound tissue acquisition, diagnostic accuracy



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INTRODUCTION

Historically, endoscopic ultrasound (EUS)-guided fine-needle aspiration (EUS-FNA) with cytologic rapid on-site evaluation (ROSE) is the standard of care in the diagnostic evaluation of solid pancreatic masses (SPMs).¹⁻³ ROSE can also provide direct feedback to the endosonographer on sample adequacy and can minimize the number of needle passes needed. However, several meta-analyses have not convincingly proven its efficiency and accuracy.⁴⁻⁶

EUS-FNA is becoming vital for the evaluation of SPMs.¹ It has been found safe with rare complications^{2,3} and its diagnostic accuracy for pancreatic lesions has been found in several studies to be more than 85%.⁴⁻⁶ Studies to further

increase diagnostic accuracy of EUS-FNA have looked at needle gauge size, frequency of sampling passes, and presence or absence of suction.⁷⁻⁹ Early studies showed that the use of ROSE increased diagnostic accuracy and decreased frequency of needle samplings.¹⁰⁻¹² Later studies however, show contradicting results with ROSE having no significant impact on outcomes if employed with EUS-FNA.^{13,14}

A recent meta-analysis concluded that even with ROSE, diagnostic yield and adequacy of specimens may not be significantly higher compared to without.¹⁵ High volume referral centers with experienced endosonographers reported sensitivity, specificity, and diagnostic accuracy over 94% even without ROSE^{16,17} suggesting that it should only be used for low volume centers or inexperienced endosonographers.

ROSE, unfortunately, is not ubiquitous, even in large tertiary centers. In Asian countries, particularly in the Philippines where EUS technology is not common, availability of ROSE is less than 10%. Additional equipment is required and staff availability, particularly for highly experienced cytopathologists, is needed.¹⁸ Thus, alternatives to the use of ROSE are currently sought.

The fine needle biopsy (FNB) needle was recently developed to increase tissue acquisition by improving the shape of the needle tip. Tissue specimens are more easily evaluated by majority of pathologists, more appropriate for molecular diagnostics, and immunohistochemical stains using tissue specimens are more feasible than using cytologic samples.¹⁹ Several small studies have already shown the benefits of the FNB needle over the FNA needle for acquiring larger core specimens and higher cellularity with a high diagnostic accuracy.²⁰⁻²³ However, larger studies with convincing data comparing the performance of FNB without ROSE versus FNA with ROSE are still currently lacking. This study therefore aimed to compare the diagnostic yield of solid pancreatic masses using EUS-FNA with ROSE versus EUS-FNB without ROSE. The hypothesis was that the diagnostic accuracy of EUS-FNB alone was non-inferior to EUS-FNA with ROSE.

OBJECTIVES

The general objective of this study was to compare the diagnostic yield of EUS-FNA with ROSE versus EUS-FNB without ROSE for solid pancreatic masses.

The specific objectives were (1) to compare the lengths of procedure time between the two groups, (2) to compare acquired tissue characteristics between the two groups, and (3) to determine complication rates.

METHODS

Study Design

This study is a single center, randomized, noninferiority study conducted at the Philippine General Hospital (PGH).

Inclusion and Exclusion Criteria

Eligible participants included all patients aged 18 years old and above, requiring endoscopic ultrasound and tissue sampling of solid lesions in the pancreas greater than 1 cm in diameter that are visualized and within the reach of EUS-FNA or FNB needles.

Patients with an uncorrectable coagulation disorder (INR > 1.5) or those actively taking medications that may increase the risk of bleeding from the EUS-guided tissue acquisition (including but not limited to NOACs, warfarin, clopidogrel) were excluded from the study. Likewise, those with medical co-morbidities that preclude them from sedation (as determined by anesthetic team) were also excluded.

Sample Size Estimation

The number of subjects was 78 patients at 39 per arm, based on a diagnostic accuracy of 90%, and a power of 0.80 with significance of 0.05 to establish equivalence of 5 percentage points.

Study Procedure

Included patients were randomly assigned to undergo EUS-FNA with ROSE (Group A) or EUS-FNB (Group B). Patients included were well-aware that ROSE is not meant to diagnose but to get adequacies of samples for a higher chance of final diagnostic output, with no delay in diagnosing potentially malignant lesions.

Randomization (1:1) was automatically generated by a computer software with allocation concealment between groups. An uninvolved third party (i.e., endoscopy unit staff) did the allocation sequence. Patients and their caregivers were blinded to treatment assignment. Data were collected using digital case record forms. In both groups, the procedure was performed at the Central Endoscopy Unit of PGH. The procedure was done under sedation, administered by qualified anesthesiologists. Time started was recorded upon endoscopic insertion.

After the lesion was evaluated by EUS, the endoscopist performed the tissue sampling using the most appropriate pathway deemed at the time. Sampling technique (e.g., full suction, half suction, or slow-pull,) were left at the discretion of the endosonographer, who utilized the fanning technique whenever feasible.²⁴ The endoscopist was only made aware of the randomization immediately prior to the procedure to minimize bias.

Group A underwent EUS-FNA with the 22G needle. Each pass underwent ROSE by a trained cytopathologist or cytotechnician. The degree of suction was determined by the endoscopist and the degree of "bloodiness" of the specimen. The endoscopist performed passes until the cytopathologist or cytotechnician satisfied the quality of specimen that allowed determination of the diagnosis or adequacy, to a maximum of 7 passes.

Group B underwent EUS-FNB with the 22G needle without the presence of ROSE. Between 2 to 5 passes were

done per lesion with or without suction via a 10ml syringe (with the fanning technique performed when possible) to ensure sufficient tissue was obtained. All aspirated material was placed in formalin to undergo direct histological processing.

All patients from both groups were observed in recovery for a minimum of 2 hours following the procedure for any complications.

Trained cytologists and pathologists assessed the final processed samples from each group in order to determine the diagnosis. The cytologists/ pathologists were blinded to the assigned groups. The diagnostic reports were stratified into the following categories: (a) positive for malignancy, (b) suspicious for malignancy, (c) atypia, (d) negative for malignancy, (e) other diagnosis.

The primary endpoint was diagnostic accuracy defined as the percentage of sampled lesions that corresponded to the final diagnosis.²⁵ Definitive diagnosis was defined by histopathologic evaluation of the surgical specimen or in non-resected patients by the evolution of the disease assessed for at least six months by a combination of clinical course, imaging studies, and/or additional tissue sampling.²⁵ Follow-up was performed by outpatient visits, electronic chart review, and telephone contacts, and was terminated in case of surgical resection or death. Specimens defined as malignant and suspicious for malignancy were categorized as positive. Those specimens reporting a specific tumor (low-grade or benign, e.g., neuroendocrine tumor, solid pseudopapillary tumor, gastrointestinal stromal tumor, paraganglioma, solid serous cystadenoma) or disease/condition (e.g., tuberculosis, autoimmune pancreatitis, intrapancreatic spleen) were counted as positive and deemed accurate if the specific tissue diagnosis matched the final diagnosis. Nonspecific benign conditions (e.g., chronic pancreatitis) and atypical samples were considered negative.

Safety was defined by the rate of adverse events (AEs) classified according to the international American Society for

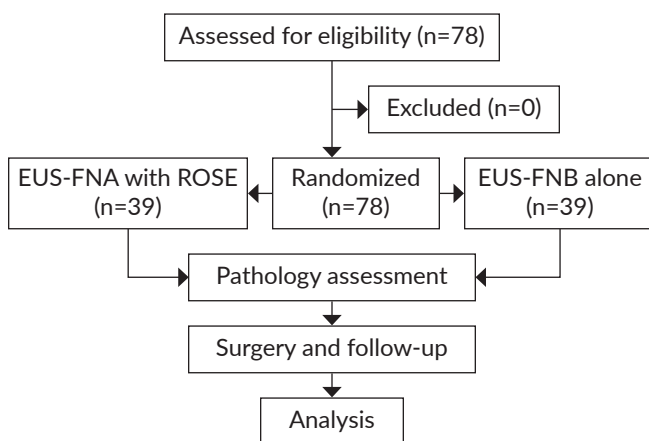


Figure 1. Diagrammatic workflow of enrolment and randomization.

Gastrointestinal Endoscopy lexicon.²⁶ AEs were assessed by phone contact or by outpatient visit 3 to 15 days after the procedure.²⁷ Time of the sampling procedure was calculated from needle insertion in the echoendoscope working channel for the first pass until its removal after the last pass. Number of passes were recorded as frequencies. Sample quality was evaluated by blood contamination.^{27,28}

Ethical Considerations

The protocol was reviewed and approved by the University of the Philippines Manila Research Ethics Board (UPMREB), where the full trial protocol can be accessed. Written informed consent from the patient was obtained. All personal patient information was kept anonymous and confidential.

RESULTS

Among 78 patients evaluated, all patients were considered eligible for the study and randomized between August 2019 and January 2020 (Figure 1). Thirty-nine (39) were allocated to the EUS-FNA with ROSE arm and 39 to the EUS-FNB arm. No differences in patient demographics and clinical characteristics were observed (Table 1). Comparison between the two groups regarding primary outcomes, procedure details, and cytopathology characteristics are summarized in Table 2.

Table 1. Baseline Characteristics

Variable	EUS-FNA with ROSE (n=39)	EUS-FNB (n= 39)
Gender (n, %)		
Male	212 (53.8%)	19 (50%)
Female	18 (46.1%)	19 (50%)
Mean age (SD)	62.2 (12.9)	62.6 (12.5)
Mean size, cm (SD)	30.8 (13.8)	31.2 (13.6)
Location (n, %)		
Head	21 (53.8%)	22 (56.4%)
Uncinate	2 (5.1%)	1 (2.6%)
Neck	2 (5.1%)	3 (7.7%)
Body	9 (23.2%)	10 (25.6%)
Tail	5 (12.8%)	3 (7.7%)
Biopsy route (n, %)		
Stomach	22 (56.4%)	24 (61.5%)
Duodenal bulb	10 (25.6%)	9 (23.1%)
2 nd duodenum	7 (18%)	6 (15.4%)
Sampling style (n, %)		
Full suction	3 (7.7%)	0
Half suction	32 (82%)	0
Stylet pull	4 (10.3%)	39 (100%)

Table 2. Diagnostic Performance of Two Groups

	EUS-FNA with ROSE	EUS-FNB
Accuracy (%)	97.4%	100.0%
Sensitivity (%)	97.4%	94.8%
Specificity (%)	100.0%	100.0%

Table 3. Comparison of Two Groups with regard to Final Diagnosis

Variable	Overall	EUS-FNA with ROSE (n=39)	95% CI	EUS-FNB (n= 39)	95% CI	P value
Primary outcome						
Final diagnosis						0.22
Adenocarcinoma	75	38		37		
Atypical cells	1	1		0		
Tuberculosis	2	0		2		

Table 4. Comparison of Two Groups with regard to Outcomes

Variable	Overall	EUS-FNA with ROSE (n=39)	95% CI	EUS-FNB (n= 39)	95% CI	P value
Mean number of passes (SD)		3.64 (0.67)	3.4-3.9	3.12 (0.66)	2.9-3.3	< 0.0001
Mean procedure time, minutes (SD)		35.8 (9.8)	32.6-39.0	30.4 (10.4)	27.0-33.9	< 0.02
Adverse events (n)	0	0	-	0	-	-
Blood contamination						< 0.021
No blood	46	7		39		
Minimal	28	28		0		
Bloody	4	4		0		

Primary Outcome

The diagnostic performance of EUS-FNA and EUS-FNB is highlighted in Table 2. In the EUS-FNA with ROSE arm, the overall diagnostic accuracy of 97% (38/39) is not significantly different from the EUS-FNB arm with an overall diagnostic accuracy of 100% (39/39), based on the outcomes on the final diagnosis, as shown in Table 3. Chi-square was used for statistical significance analysis.

Secondary Outcomes

Secondary outcomes, including number of passes, AE rates, procedure time, and sample blood contamination between the two groups, are shown in Table 4. For continuous variables, Welch t-test and Wilcoxon signed-rank test was used for statistical significance analysis. No postprocedural AEs (0%) were observed in both groups. A significantly less bloody tissue core was obtained in the EUS-FNB arm compared with EUS-FNA with ROSE (0% vs 82%, $P < .021$), with a significant shortened procedural time (30.4 ± 10.4 vs 35.8 ± 9.8 minutes, $P < .02$) and significantly more number of passes (3.64 ± 0.67 vs 3.12 ± 0.66 , $P < 0.0001$).

DISCUSSION

In this randomized controlled trial using a new-generation biopsy needle for evaluation of SPMs, we found that EUS-FNB was not inferior to EUS-FNA with ROSE.

Currently, EUS-FNA with ROSE has been the most important factor in increasing diagnostic yield for EUS-guided tissue acquisition.²⁹ Recently however, newly introduced needles with redesigned needle tips labeled as EUS-FNB needles have been shown to have a significantly better diagnostic accuracy over standard FNA needles.^{16-18,21,30} Recently, more authors have advocated the use of EUS-FNB over EUS-FNA needles for SPM sampling. Our results

coupled with the above-mentioned findings strongly support that EUS-FNB could definitively replace EUS-FNA with ROSE. The diagnostic accuracy exceeded 95% in both arms suggesting the possibility to forego ROSE and re-evaluate the need for it, and institutions without ROSE can now achieve high diagnostic accuracy using EUS-FNB alone. In resource limited countries such as the Philippines, lack of ROSE may push the use of EUS-FNB, and its eventual availability will increase the use of EUS-guided sampling. Tissue quality and blood contamination was better in the EUS-FNB arm giving credence to the conclusion.

Acquiring adequate and quality tissue core biopsy specimens for histologic examination represent the only available histologic material on which molecular characterization and therapeutic stratification markers can be performed.¹⁵ Post-chemotherapy EUS-FNB may become standard to detect post treatment molecular changes, in the pancreas and may guide further treatment.^{31,32} Finally, the results may further amplify the benefits of personalized management of pancreatic cancers.

No adverse events were reported for both arms in our study. This suggests the safety of both EUS-FNA and EUS-FNB procedures. EUS-FNB was significantly shorter in duration compared with EUS-FNA with ROSE. The EUS-FNB procedure was faster with a mean difference of about 6 minutes in favor of EUS-FNA with ROSE. This may suggest that removing the time the samples are being evaluated by a pathologist shortens the duration of the entire endoscopic procedure. This may further suggest, especially in high-volume centers, that EUS-FNB may be more cost effective. Although ROSE can provide immediate sampling adequacy in most cases, thereby reducing the overall turnaround time, EUS-FNB seems to shorten procedure time by eliminating the need to read the slides for adequacy by as much as 5.8 minutes. This seems practical as the endoscopist can now

predict the length of time the procedure really will last because he now has a finite number of passes, in this case a maximum of 4, that seems to be comparable with EUS-FNA with ROSE.

This study has the following limitations. First, the sample size, if larger, would have increased the impact of the results. Second, study was done in a large tertiary university hospital with expertise that may not equal that seen in smaller hospitals. Third, the sample size was calculated for the primary outcome but not for secondary outcomes, which should be considered as exploratory with the need for specifically designed trials to confirm our findings.

CONCLUSION

Among patients with SPMs, this study showed that the diagnostic accuracy of EUS-FNB alone with 2-4 needle passes reached 97% and was noninferior compared with EUS-FNA with ROSE. This may suggest that use of ROSE during tissue acquisition may not be necessarily superior. The use of EUS-FNB also resulted in a shorter procedural time compared with EUS-FNA with ROSE, with no difference in tissue characteristics (blood contamination) and no adverse events noted. Larger studies are needed to firmly conclude that EUS-FNB without ROSE may become the standard for tissue sampling of SPMs.

Statement of Authorship

MAADL contributed in the conceptualization of work, acquisition and analysis of data, and drafting and revising of manuscript. ANNIP contributed in the analysis of data, and drafting and revising of manuscript.

Author Disclosure

Both authors declared no conflicts of interest.

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