

Macroscopic on-site evaluation of biopsy specimens for accurate pathological diagnosis during EUS-guided fine needle biopsy using 22-G Franseen needle

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ABSTRACT

Background and Objectives: Measuring a visible core length during macroscopic on-site evaluation (MOSE) can be useful for accurate diagnoses during an EUS-guided fine needle biopsy (EUS-FNB). We aimed to estimate visible core cutoff lengths predictive of a correct diagnosis when using 22-gauge Franseen needles for biopsies from pancreatic masses. **Materials and Methods:** We assessed 77 consecutive patients who underwent EUS-FNB using 22-gauge Franseen needles for pancreatic masses between March 2018 and October 2018. At least two needle passes were performed in all patients, irrespective of the findings on MOSE. The endoscopists measured the visible cores using a ruler during MOSE. The first two passes were analyzed on a per pass basis, and the correlation between visible core lengths and diagnostic accuracy was evaluated. **Results:** We evaluated 150 needle passes of 75 patients. The accuracy per pass was 92% (138/150). The median length of the visible cores was 15 (range: 0–60) mm and they were significantly longer in the correct diagnosis group than in the incorrect diagnosis group. The accuracy correlated positively with the visible core length. Receiver-operating characteristic curve analysis of the visible core length for accuracy demonstrated an optimal cutoff value of 10 mm. On multivariate logistic regression, visible core lengths >10 mm independently affected the correct diagnosis (odds ratio: 5.1, $P = 0.02$). **Conclusions:** Visible cores exceeding 10 mm may be useful for correct diagnosis while using a 22-gauge Franseen needle for EUS-FNB from pancreatic masses.

Key words: EUS, EUS-FNA, fine-needle biopsy, Franseen needle, macroscopic on-site evaluation

INTRODUCTION

Owing to its high diagnostic accuracy, EUS-FNA is the standard method for the pathological assessment of

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pancreatic tissue samples.^[1,2] However, since one needle passes using a standard needle provide inadequate sample tissues, three to four passes are required for correct diagnoses.^[3-7] These may cause complications such as tumor seeding, pancreatitis, and bleeding, which necessitates the reduction of the number of needle passes.^[8-15]

Rapid-on site cytopathological evaluation (ROSE) may reduce the number of FNA needle passes; however, in Asia and Europe, it is not commonly performed due to shortages of pathological staff and additional costs.^[16,17] Direct observation of specimens obtained by FNA, known as macroscopic on-site evaluation (MOSE) or gross visual inspection, can be an alternative to ROSE because of its feasibility and readily available resources.^[18,19] A visible core of the EUS-FNA sample using standard needles indicates sample adequacy and is predictive of correct pathological diagnoses.^[18,19] Nonetheless, the clinical significance of MOSE has not been fully elucidated.

Tissues volumes procured with the Franseen needle for EUS-guided fine needle biopsy (EUS-FNB) are larger than those procured with the standard needles; furthermore, fewer passes are required to obtain adequate diagnostic samples with the Franseen needle.^[20-23] Hence, the Franseen needle is preferred over the standard needles. However, since one needle pass is inadequate for a correct FNB diagnosis,^[2,24-26] evaluation of FNB specimens, which predict a correct diagnosis, by MOSE would avoid unnecessary needle passes.

Nonetheless, false negatives due to macroscopic rather than pathological evaluation may be a drawback of MOSE. Measuring the length of the visible core of FNB specimens may aid in correct diagnoses and reduce false negatives. Studies reporting the use of MOSE for FNB specimens are scarce. Here, we assess the efficacy of MOSE to confirm the adequate core sizes for correct FNB diagnoses of pancreatic masses using a 22-gauge (G) Franseen needle.

MATERIALS AND METHODS

Patients and ethical considerations

This retrospective study was conducted at a tertiary referral cancer center for pancreatobiliary diseases, where more than 700 pancreatobiliary EUS procedures are performed annually. Consecutive patients who underwent EUS-FNB of pancreatic masses using a 22-G Franseen needle between April 2018 and October 2018 were included. Patients with inadequate MOSE

data in the endoscopic reports were excluded. Written informed consent for EUS-FNB was obtained from all the patients. The present study was approved by the Ethics Committee of our institution, and the study protocols conformed to the ethical guidelines outlined in the Declaration of Helsinki.

EUS-guided fine needle biopsy procedure

The EUS-FNB was performed using a curved linear-array echoendoscope (GF-UCT260; Olympus Medical Systems Corp., Tokyo, Japan) with patients under conscious sedation. All procedures were performed or supervised by an expert endoscopist who had performed more than 1000 EUS-FNA/B procedures. The procedures were also performed by three nonexpert endoscopists with experience of 50-200 EUS-FNA/B procedures. The pancreatic masses were punctured using a 22-G Franseen needle (Acquire™, Boston Scientific Corporation, Natick, MA, USA). The stylet was removed after advancing the needle in the target; suction was then applied using a 10 mL syringe, and the needle was moved to-and-fro in the lesion ten times. After EUS-FNB, the patients were monitored for 2 h in the recovery room and discharged if they were asymptomatic. After leaving the hospital, if the patients experienced symptoms, such as abdominal pain or fever, they made a telephone call to the hospital and received medical advice on the best way to manage their symptoms.

Macroscopic on-site evaluation

We introduced a standard MOSE protocol at our institution in March 2018. As per the protocol, after removing the FNB needle from the echoendoscope, the specimen was expelled onto a petri dish using the stylet. MOSE was performed by two endoscopists and the presence and length of a visible core was evaluated by inspecting the specimen. In cases where their interpretations differed, a decision was made after discussion. A visible core defined as white pieces of tissue was extracted from the specimen and measured using a ruler [Figure 1]. In cases where the visible cores were fragmented, the fragments were gathered and aligned using a 23-G injection needle followed by measuring the entire length. In cases where visible cores were not obtained, the length was recorded as 0 mm. At least two punctures or needle passes were performed for each target. Additional punctures were performed if a visible core was not obtained in the first two consecutive passes. ROSE was not performed at our center because of a shortage of pathological staff.

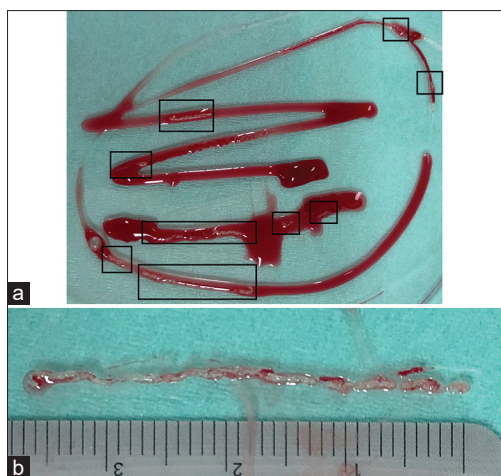


Figure 1. Measurement of the visible core during macroscopic on-site evaluation. (a) A whole specimen with scattered visible cores (in boxes). (b) Total length of multiple aligned visible cores measured using a linear rule

Sample preparation and pathologic assessment

The specimens of the first and second passes were placed in saline and formalin bottles, respectively, in the endoscopy room. These bottles were subsequently sent to the pathology department, where cytotechnologists processed the specimens and prepared the slides. A portion of the first pass specimen was smeared onto two glass slides, which were stained with hematoxylin and eosin (HE) and Papanicolaou for cytological analysis. The remaining portion of the specimen was fixed in formalin and embedded in paraffin; sections from it were then stained with HE for histological evaluation. The entire second pass specimen was embedded in paraffin, and a portion from it was used for histological evaluation after HE staining. Immunohistochemical staining was performed, if necessary. The cell block method^[27] was not used at our center. Specimens that were considered suspicious or positive for malignancy and neuroendocrine neoplasms were categorized as positive for malignancy; conversely, those that were considered negative or atypical were categorized as negative for malignancy. Pathological evaluations were performed for each needle pass. The pathological diagnosis for the first pass specimen was provided after cytological and histological evaluation. The assessment was performed by an experienced pathologist.

Final diagnosis

In cases found to be positive for malignancy on pathological evaluation of specimens obtained by EUS-FNB, the final diagnosis was confirmed based on pathological findings during surgery or the clinical course (true-positive). In cases found to be negative

for malignancy, the benign nature was confirmed through pathological findings during surgery or a clinical follow-up followed by imaging after 6 months or more. The masses were considered benign if stable or resolved (true-negative). The accuracy of EUS-FNB was defined as the sum of the true-positive and true-negative results divided by the total number of analyzed passes.

Data analyses

The first two passes of each EUS-FNB procedure, including MOSE, were analyzed on a per pass basis. Continuous variables pertaining to patient characteristics and MOSE results were presented as medians with ranges and compared using the Mann–Whitney *U*-test. Categorical variables were analyzed using the Fisher's exact test. The correlation between the total length of the visible cores and the accuracy of EUS-FNB was analyzed using the Cochran–Armitage test for trends. Receiver-operating characteristic (ROC) curves of the visible core lengths for ensuring a correct FNB diagnosis were analyzed to assess the accuracy of the area under the curve of the ROC (AUC); they were also analyzed to determine the optimal cutoff length of the visible core for obtaining a correct FNB diagnosis. Univariate and multivariate logistic regression analyses for factors affecting the correct diagnosis were performed based on the following predictor variables: tumor size (<20 *vs.* ≥20 mm), lesion location (head *vs.* body or tail), pass number (first pass *vs.* second pass), operator expertise (expert *vs.* nonexpert), and visible core length (> cutoff value *vs.* ≤ cutoff value). The *P* < 0.05 was considered statistically significant for all tests. All statistical analyses were performed using the EZR (version 3.4.1) software package²⁸ to “EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. Additionally, adverse events (AEs), such as bleeding and pancreatitis, were recorded according to the American Society for Gastrointestinal Endoscopy workshop report.^[28]

RESULTS

Overall, 77 patients with pancreatic masses who underwent EUS-FNB using a 22-G Franseen needle were included; two patients were excluded because of insufficient details in their endoscopic reports. Finally, 150 passes in 75 patients were analyzed. The patients' characteristics and EUS-related data are presented

Table 1. Patient characteristics

Characteristics	Value
Median age, year (range)	71 (45-87)
Sex, male, n (%)	42 (56)
Median tumor size, mm (range)	26 (7-57)
Lesion location, head: body or tail, n	45:30
Operator expertise, expert, n (%)	
1 st pass	17 (23)
2 nd pass	20 (27)
Final diagnosis, n (%)	
Malignant	66 (88)
Adenocarcinoma	60 (80)
Neuroendocrine tumor	4 (5)
Metastatic pancreatic cancer	2 (3)
Benign	9 (12)
Autoimmune-related pancreatitis	3 (4)
Chronic pancreatitis	6 (8)

in Table 1. The final diagnoses were based on the evaluation of the surgical specimen and clinical course in 21 and 54 patients, respectively. The diagnostic accuracy of the first pass was 95% (71/75), and that of the second pass was 89% (67/75). The total accuracy of EUS-FNB per pass was 92% (138/150). The accuracy values of EUS-FNB per pass in malignancy and benign at the final diagnosis were 91% (120/132) and 100% (18/18), respectively. No AEs were reported during and after EUS-FNB.

According to MOSE, a visible core was observed in 95% of all passes (142/150), with a median length of 15 mm (range; 0–60 mm). The visible cores in the correct diagnosis group were longer than in those with an incorrect diagnosis (median: 15 mm *vs.* 7 mm, $P = 0.007$) [Figure 2].

The accuracy of EUS-FNB showed a positive correlation with the visible core length ($P = 0.016$) [Figure 3]. ROC curve analysis of the visible core length for accuracy identified a cutoff value of 10 mm with an AUC of 0.74 (95% confidence interval: 0.60–0.87).

Univariate and multivariate analyses were also performed for factors affecting the correct diagnosis [Table 2]. On univariate analysis, the accuracy of EUS-FNB tended to be higher, with visible core lengths >10 mm (odds ratio: 3.8, 95% confidence interval: 1.1–13.1; $P = 0.038$). Multivariate logistic regression analysis found that only visible core lengths >10 mm independently affected the correct diagnosis (odds ratio: 5.1, 95% confidence interval: 1.3–20.0; $P = 0.020$).

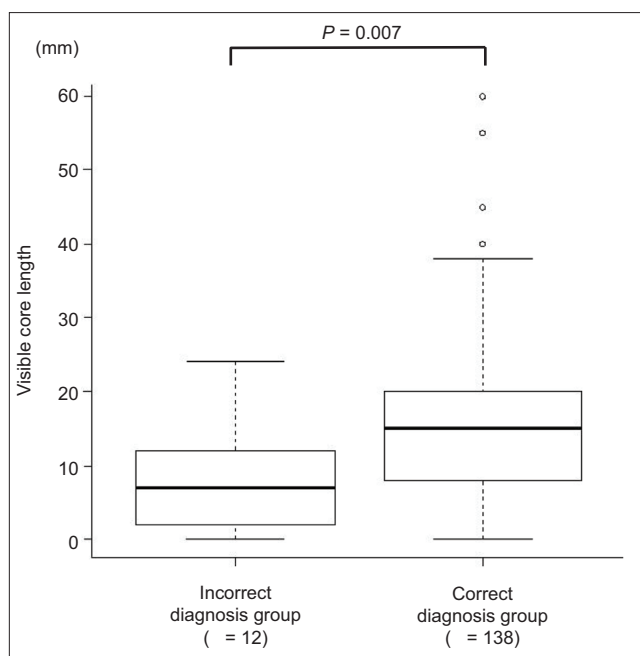


Figure 2. The median visible core length and box plot for incorrect and correct diagnosis groups showing a significantly longer visible core length in the correct diagnosis group than incorrect diagnosis group (median: 15 mm *vs.* 7 mm, $P = 0.007$)

DISCUSSION

Our study demonstrated that the visible core length from MOSE may predict the correct pathological diagnosis in cases of EUS-FNB of pancreatic masses using a 22-G Franseen needle. Visible cores longer than 10 mm can probably provide more accurate diagnoses and can indicate the need for terminating the EUS-FNB procedure.

The utility of MOSE has been reported in studies that employed standard 22-G and 19-G FNA needles.^[18,19] For example, a prospective study using 19-G needles targeting the lymph nodes, submucosal tumors, and local tissues, as well as the pancreas reported that visible cores ≥ 4 mm on MOSE may indicate specimen adequacy for pathological interpretation.^[18] Our findings demonstrated improvements in the accuracy of EUS-FNB with increasing visible core lengths; visible cores of at least 10 mm were strongly associated with the likelihood of obtaining a correct diagnosis. This length is considerably longer than that of the previous study. However, this may not be solely attributed to the difference in needle sizes; rather, it may be related to a significant difference in the indicators. The previous study was intended to assess the amount of tissue while the present study aimed to evaluate the likelihood of a correct diagnosis, which is of greater clinical

Table 2. Univariate and multivariate analyses of factors affecting the accuracy of EUS-FNB

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Tumor size (mm)				
>20	1.0 (0.3-3.5)	1.00	0.6 (0.1-2.4)	0.46
≤20	1		1	
Lesion location				
Body or tail	2.0 (0.5-7.5)	0.32	2.1 (0.5-8.8)	0.30
Head	1		1	
Pass number				
1 st pass	2.1 (0.6-7.4)	0.24	1.9 (0.5-6.7)	0.34
2 nd pass	1		1	
Operator expertise				
Expert	0.63 (0.2-2.2)	0.47	0.5 (0.1-2.0)	0.31
Nonexpert	1		1	
Visible core length (mm)				
>10	3.8 (1.1-13.1)	0.04*	5.1 (1.3-20.0)	0.02*
≤10	1		1	

*P<0.05. OR: Odds ratio; CI: Confidence interval.

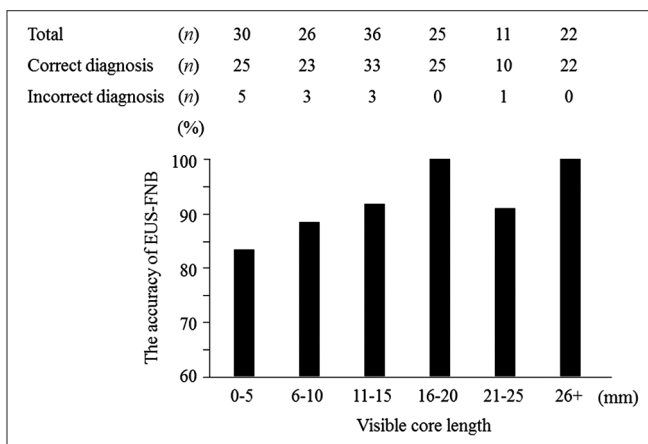


Figure 3. Results of the Cochran-Armitage test for trends showing the positive correlation between the accuracy of EUS-FNB and total length of visible cores ($P = 0.016$). EUS-FNB: EUS-guided fine needle biopsy

significance. Therefore, we selected the indicator as a main outcome measure.

Evaluating the relationship between visible core lengths and correct diagnoses is more challenging than assessing the relationship between lengths and specimen adequacy. Obtaining large specimen quantities does not necessarily result in a correct diagnosis. For instance, in cases where the visible cores contain more tissue from nontarget lesions, the likelihood of an incorrect diagnosis (false negative) is higher. A prospective study on EUS-FNA using 19-G needles reported that pancreatic lesions were more prone to false negative diagnoses and the reliability of the visible cores while obtaining a correct diagnosis was reduced when targeting pancreatic lesions.^[18] This may be because pancreatic lesions are frequently accompanied by fibrous

tissue, such as desmoplastic changes and pancreatitis caused by pancreatic cancer. This would probably be recognized as a visible core on MOSE.^[18,29,30] Since our study evaluated only pancreatic lesions, we presumed that the probability of false negatives, as observed in the previous studies, was higher; therefore, longer visible cores were needed to predict correct diagnoses. However, this may raise concerns regarding whether the method can be applied to small tumors. In the present study, 12 needle passes for six pancreatic masses measuring <10 mm in diameter were included. Consequently, the accuracy of EUS-FNB was 83% (10/12), and the median length of the visible core was 12.5 mm (range: 0–26 mm). Thus, even for a small tumor, a visible core with a size larger than that of its tumor could be obtained, indicating that our result can be applied to small tumors.

It is argued that ROSE and MOSE are not necessary when using the Franseen needle because two needle passes are likely to provide a correct diagnosis in most cases.^[20,22-26] Although a higher number of needle passes may be associated with a higher AE rate, another issue of particular concern is needle tract seeding. The reason is that needle tract seeding originating from EUS-FNA for pancreatic body or tail cancer was observed in 3.4% of the patients who underwent distal pancreatectomy, as reported by a recent multicenter retrospective cohort study.^[12] This AE rate should not be overlooked. Therefore, if an infallible needle is developed, using which a correct diagnosis can be achieved with one needle pass, ROSE and MOSE will not be required. However, until then, an attempt to reduce the number of needle passes by MOSE may

be beneficial in clinical practice, even in the era of the superior FNB needle.

A recent retrospective study reported the use of MOSE during EUS-FNB using 22-G Franseen needles.^[31] In that cohort, a visible core was obtained in 93% (50/54) of patients; histological core fragments were confirmed in 94% (47/50) of those patients. The overall diagnostic accuracy was 94% (48/51), with a median of one pass. Since the accuracy rate per pass was not mentioned, the relationship between the visible core lengths and the accuracy of EUS-FNB was unclear. However, findings from that study indicated the utility of MOSE, and aligned with our findings. Unlike our case, the study also included several lesions, including pancreatic masses. As mentioned previously, the false negative rate of MOSE can increase while targeting pancreatic lesions.^[18] Therefore, when targeting pancreatic lesions, evaluating the length of the visible cores may enhance the diagnostic yield.

The present study had several limitations. First, it was retrospective, which may have caused a selection bias. Second, only 22-G Franseen needles were evaluated in this study, and further studies with 19-G or 25-G needles may provide different outcomes. However, since 22-G needles are most commonly used for EUS-FNA/B, we speculate that our findings may be readily applied to clinical practice. Third, only pancreatic lesions were included in this analysis. Since the probability of a visible core providing a correct diagnosis varies between lesions, the results may not be applicable to other lesions, such as lymph nodes and submucosal masses. Further studies will be needed to evaluate the probability of an accurate diagnosis for these lesion types. Fourth, the proficiency of the endoscopists who performed the EUS-FNB procedures were not uniform. However, trainees who had experience with <50 EUS-FNA/B procedures were not involved in this study. Nevertheless, multiple endoscopists are needed to ensure reproducibility of our findings. Fifth, the specimens of the first and second passes were assessed by different pathological methods in this study. Although the diagnostic accuracy of the first pass was higher than that of the second pass, there was no significant difference between these passes. Therefore, we analyzed the first and second passes together, and multivariate logistic regression analysis showed that the pass number did not independently affect the correct diagnosis. This study also had certain strengths; MOSE, a standardized method, was employed for evaluation.

CONCLUSIONS

Our findings suggest that visible cores exceeding 10 mm may predict the likelihood of a correct diagnosis when using 22-G Franseen needles for EUS-FNB of pancreatic masses. In the absence of ROSE, obtaining a visible core exceeding the cutoff length may be a useful indicator for terminating the procedure. Further prospective studies including larger cohorts are needed to validate our findings.

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Conflicts of interest

There are no conflicts of interest.

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