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Establishing the optimal number of passes during EUS-FNB for diagnosis of pancreatic solid lesions: Prospective multicenter study

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ABSTRACT

Background and study aims The optimal number of needle passes during endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB) is not yet established. We aimed to perform a per-pass analysis of the diagnostic accuracy of EUS-FNB of solid pancreatic lesions using a 22G Franseen needle.

Patients and methods Consecutive patients with solid pancreatic lesions referred to 11 Italian centers were prospectively enrolled. Three needle passes were performed; specimens were collected after each pass and processed individually as standard histology following macroscopic on-site evaluation (MOSE) by the endoscopist. The primary endpoint was diagnostic accuracy of each sequential pass. Final diagnosis was established based on surgical pathology or a clinical course of at least 6 months. Secondary endpoints were specimen adequacy, MOSE reliability, factors impacting diagnostic accuracy, and procedure-related adverse events.

Results A total of 504 samples from 168 patients were evaluated. Diagnostic accuracy was 90.5% (85.0%–94.1%) after one pass and 97.6% (94.1%–99.3%) after two passes ($P=0.01$). Similarly, diagnostic sensitivity and sample adequacy were significantly higher adding the second needle pass (90.2%, 84.6%–94.3% vs 97.5%, 93.8%–99.3%, $P=0.009$ and 91.1%, 85.7%-94.9% vs 98.2%, 95.8%–99.3%, $P=0.009$, one pass vs two passes, respectively). Accuracy, sensitivity, and adequacy remained the same after the third pass. The concordance between MOSE and histological evaluation was 89.9%. The number of passes was the only factor associated with accuracy. One case of mild acute pancreatitis (0.6%) was managed conservatively.

Conclusions At least two passes should be performed for the diagnosis of solid pancreatic lesions. MOSE is a reliable tool to predict the histological adequacy of specimens.

Introduction

Endoscopic ultrasound-guided tissue acquisition (EUS-TA) is the recommended technique for the sampling of solid pancreatic lesions. In recent decades, EUS-TA has evolved owing to improvements in diagnostic sensitivity, such as needle size [1], sampling technique [2], use of different types of suction [3], and the employment of rapid on-site evaluation (ROSE) [4]. However, one of the major breakthroughs has been reached with the availability of third-generation needles, which carry the design of end-cutting tips (e.g., Franseen or fork-tip needles). The excellent diagnostic and histological yields over standard fine-needle aspiration (FNA) [5, 6] have shifted clinical practice from FNA to fine-needle biopsy (FNB).

Furthermore, the role of ROSE has been weighed [4] in favor of macroscopic on-site evaluation (MOSE). The MOSE of acquired tissue by the endoscopist was first proposed by Iwashita et al, using an 19G FNA needle [7]. More recently, MOSE using end-cutting needles has been associated with high sample adequacy, suggesting the possibility of replacing ROSE [8, 9]. Finally, in the absence of ROSE, guidelines have recommended three to four needle passes using an FNA needle and two to three passes using a reverse-bevel FNB needle.

However, the optimal number of needle passes performed using end-cutting needles for the sampling of pancreatic solid lesions has not yet been established. In addition, specifically designed studies aimed at determining the optimal number of needle passes are lacking. A recent randomized study demonstrated that the adequacy (based on MOSE) of samples collected with a Franseen needle was associated with a lower number of needle passes compared with the conventional three passes [8]. Moreover, in a recent randomized study in which fork-tip needles were used, a minimal incremental value of accuracy was observed with the second pass [6]. However, the study reported no further gain after adding a third pass. In contrast, no data about the number of passes to be performed using a Franseen needle have been published.

To fill this gap, we performed a prospective, multicenter study with the primary aim of evaluating the diagnostic accuracy of FNB performed using a 22G Franseen needle with one, two, and three needle passes. Secondary aims were specimen adequacy with one, two, and three needle passes, reliability of MOSE to establish sample adequacy at histology, factors impacting diagnostic accuracy, and the procedure-related adverse events (AE) rate.

Patients and methods

Study design and patient population

This was a multicenter, prospective study conducted at 11 Italian centers. After local ethics committee approval (protocol number HMD 487/22, June 14, 2022), the protocol was registered on ClinicalTrials.gov (NCT05436704). Consecutive adult patients referred for EUS-FNB for the diagnosis of solid pancreatic lesions were assessed for eligibility. Exclusion criteria were: 1) previous biopsy of the lesion with a diagnosis of malignancy; 2) cystic component larger than 25% of volume; 3) uncorrectable coagulopathy or use of anticoagulant that cannot be discontinued; 4) pregnancy or breast-feeding; and 5) lack of informed consent.

Procedures and specimens processing

All the procedures were performed after obtaining informed consent under deep sedation or conscious sedation according to institutional policy. Only experienced endosonographers with >400 EUS performed and not trained in cytopathology were involved. The needle used for the study was the 22G Franseen needle (Acquire Boston Scientific; Natick, Massachusetts, United States). The slow-pull technique was used in all cases: After the needle tip was inserted into the target lesion, the stylet was slowly withdrawn while several to-and-fro movements of the needle were performed [3]. The fanning technique was also used whenever possible [2]. As suggested by European Society of Gastrointestinal Endoscopy (ESGE) guidelines [1], up to three needle passes were performed for each lesion.

The specimen collected after each needle pass was handled and inspected by the endosonographer for MOSE evaluation. The worm-like whitish or yellowish material was aligned on a slide using a syringe needle and the length was assessed using a ruler [8]. After MOSE, the whole sample (including bloody material and clots) was placed in a labeled formalin-filled vial and processed independently as standard histology. A dedicated pathologist with at least 5 years of experience in gastrointestinal pathology at each participating site provided a diagnosis for each container and was not blinded from the results of the previous sample.

Technical failure was defined when biopsy was not performed at all. Incomplete procedure was defined when less than three passes were performed.

Definition and study endpoints

The primary endpoint was diagnostic accuracy of each sequential pass. Diagnostic accuracy was defined as the percentage of lesion corresponding to the final diagnosis [10] that was assessed on surgical specimen. In non-resected patients, final diagnosis was based on the evolution of the disease assessed for at least 6 months by a combination of clinical course, imaging studies, and/or additional tissue sampling demonstrating progression in cancer-related lesions or disease stability in the benign lesions [10]. Histologic evaluations followed the Papanicolaou classification [11]. EUS samples reported as suspicious for malignancy were considered as malignant whereas those that contained inadequate material were included in the analysis and considered as negative for malignancy. In addition, other performance measures (i.e., sensitivity and specificity) were evaluated for each needle pass.

Specimen adequacy was defined as the percentage of lesions sampled in which the obtained material is representative of the target site and sufficient for diagnosis [10].

MOSE reliability was defined as the concordance rate between MOSE adequacy and presence of histologic core (i.e., presence of a tissue sample that allows for histologic and tissue architectural assessment) [10]. MOSE was defined as adequate if a macroscopic visible core (MVC) was obtained. MVC was defined as worm-like whitish or yellowish material, not including fluid-like specimens, measuring at least 10 mm in the major axis [8].

Potential factors impacting diagnostic accuracy, such as age, sex, lesion location and size, biopsy route and number of needle passes, were evaluated.

AEs were evaluated according to the American Society for Gastrointestinal Endoscopy workshop report [12].

Follow-up

After EUS-FNB, patients were observed in the recovery room for at least 2 hours and were contacted at 24 hours and 14 and 30 days after the procedure to record any AEs.

Follow-up was performed by the study investigator at each participating center by electronic chart review, outpatient visits, and telephone contacts. Follow-up was terminated in case of surgical resection or death.

Statistical analysis

Sample size was calculated based on evaluation of the primary outcome of diagnostic accuracy for evaluation of solid pancreatic lesions. The study hypothesis was that the first needle pass was equivalent to the conventional three passes. A sample size of 140 patients was required, based on the expected diagnostic accuracy of 96.7% after three passes and 93.4% after one needle pass with a 22G FNB needle [6], an equivalence margin of ± 5%, power of 90%, and an alpha level of 5% (1-sided). Considering an expected drop-out rate of 20%, we decided to enroll 170 patients.

Equivalence was met for the primary endpoint if the limits of a two-sided 90% confidence interval (CI) excluded a difference between the two groups of more than 10%.

Continuous data were presented as mean and standard deviation whereas categorical data were presented as numbers (percentages).

Normal distribution of variables was checked through Kolmogorov-Smirnov test.

Comparisons between paired groups were performed through McNemar's test and *P* values were corrected through Bonferroni's correction for multiple comparisons. Correlation between adequacy rates of samples evaluated on MOSE and adequacy evaluated by means of histology was performed by means of Cramer's Φ test, where a Φ test between 0 and 0.3 represents weak correlation, between 0.3 and 0.6 moderate correlation, and between 0.6 and 1 strong correlation [13].

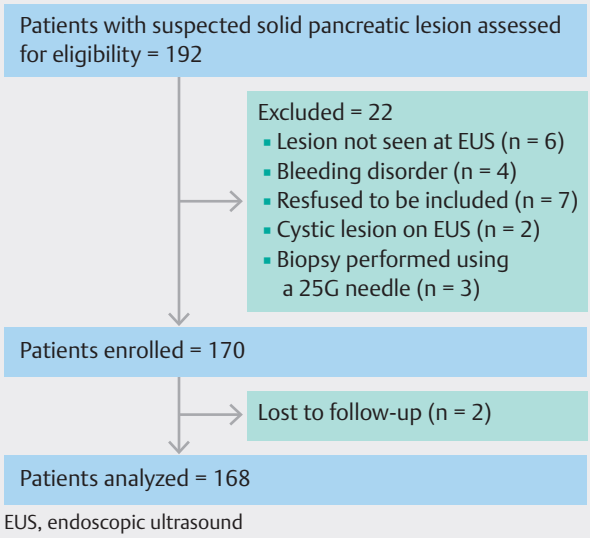
Correlation between baseline parameters and diagnostic accuracy was tested through univariate logistic regression analysis and the results were expressed in terms of odds ratio (OR) and 95% CIs.

All analyses were performed with *rms* package in R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

From July 2022 to October 2022, 170 consecutive patients (75 males, mean age 67.1 years) were enrolled and two were lost to follow-up. All patients underwent EUS-FNB with three passes. Therefore, 168 patients were analyzed, and the per-protocol population completely reflected an intention-to-treat analysis.



▶ **Fig. 1** Study flow chart. EUS, endoscopic ultrasound.

The flow chart of the patients recruited in this study is shown in ▶ **Fig. 1**. ▶ **Table 1** summarizes baseline features of the patient population.

Diagnostic accuracy

Diagnostic accuracy was 90.5% (95% CI 85.0%-94.1%) after one needle pass, 97.6% (95% CI 94.1%-99.3%) after two passes, and 97.6% (95% CI 94.1%-99.3%) after three needle passes, with 90.2% (95% CI 84.6%-94.3%), 97.5% (95% CI 93.8%-99.3%), and 97.5% (95% CI 93.8%-99.3%) diagnostic sensitivity after one, two, and three needle passes, respectively. Specificity was 100% in all study groups. No statistically significant difference in terms of diagnostic accuracy was found between two and three passes ($P=1.0$), whereas both two and three passes significantly outperformed a single pass ($P=0.01$). Per-pass analysis of diagnostic measures is reported in ▶ **Table 2**.

The difference in the accuracy between two or three passes and one pass was 7.1% (5% to 9.2%). The lower limit of the CI for the difference in diagnostic accuracy exceeded the equivalence margin of ±5%, therefore, equivalence was not shown for the primary outcome.

Univariate regression analysis showed that only the number of passes was a significant predictor of diagnostic accuracy (OR 4.3, 95% CI 1.4–13.2; $P=0.01$) (▶ **Table 3**).

▶ **Table 1** Baseline features of 168 patients analyzed.

Age, yr Mean (SD)	**67.1 (11.5)**
Sex, N (%)	
Male	75 (44.7%)
Female	93 (55.3%)
Tumor site, N (%)	
Uncinate process	16 (9.5%)
Head	75 (44.6%)
Neck	10 (6%)
Body	40 (23.8%)
Tail	27 (16.1%)
Tumor size, mm	
Mean (SD)	31.9 (12.2)
Biopsy route, N (%)	
Transgastric	84 (50.0%)
Transduodenal	84 (50.0%)
Final diagnosis, N (%)	
PDAC	127 (75.5%)
NET	18 (10.7%)
Metastasis	12 (7.1%)
Inflammatory	5 (3.2%)
Other*	6 (3.5%)
Follow-up	
Median time, days (95% CI)	212 (168–254)
Surgical resection, N (%)	39 (23.2%)

*Other includes: Neuroendocrine carcinoma (2), autoimmune pancreatitis (1), intrapancreatic spleen (1), lymphoid tissue (1), schwannoma (1)
SD, standard deviation; PDAC, pancreatic ductal adenocarcinoma; NET, neuroendocrine tumor; CI, confidence interval.

▶ **Table 2** Diagnostic measures after one, two, and three needle passes observed in 168 patients who underwent endoscopic ultrasound-guided fine-needle biopsy of solid pancreatic lesions.

	One pass	**Two passes**	**Three passes**	**Two passes vs one pass**	**Three passes vs one pass**	**Three passes vs two passes**
Sensitivity, % (95% CI)	90.2 (84.6–94.3)	97.5 (93.8–99.3)	97.5 (93.8–99.3)	***P*=0.009**	***P*=0.009**	p=1
Specificity, % (95% CI)	100 (94.3–100)	100 (93.4–100)	100 (93.4–100)	/	/	/
Accuracy, % (95% CI)	90.5 (85.0–94.1)	97.6 (94.1–99.3)	97.6 (94.1–99.3)	***P*=0.01**	***P*=0.01**	*P*=1
Adequacy, % (95% CI)	91.1 (85.7–94.9)	98.2 (95.8–99.3)	98.2 (95.8–99.3)	***P*=0.009**	***P*=0.009**	*P*=1

CI, confidence interval.

▶ **Table 3** Univariate analysis investigating factors associated with diagnostic accuracy.

Variable	Odds ratio	95% CI	*P* value
Age (ref. ≤67 years)	2.7	0.3–26.7	0.39
Sex (ref. female)	1.8	0.7–5.4	0.76
Location (ref. head/uncinate)	0.4	0.03–3.8	0.41
Size (ref. ≤30 mm)	2.5	0.3–24.8	0.45
Biopsy route (ref. transgastric)	3.1	0.3–30.2	0.33
Number of passes (ref. one pass)	4.3	1.4–13.2	**0.01**

CI, confidence interval.

Secondary outcomes

Specimen adequacy rates were 91.1% (95% CI 85.7%-94.9%) after one needle pass, 98.2% (95% CI 95.8%-99.3%) after two passes, and 98.2% (95% CI 95.8%-99.3%) after three needle passes. Again, a significant difference was observed in the comparison between three passes and one pass ($P=0.009$) and between two passes and one pass ($P=0.009$), whereas no difference was observed when comparing two vs three passes ($P=1.0$).

For MOSE reliability, 504 samples were evaluated and compared with histological assessment. MOSE was deemed adequate in 473 of 504 cases (93.8%) with a concordance rate with histology of 89.9% (453/504). Discordancy was observed in 25 of 31 cases deemed inadequate and 26 of 473 cases recorded as adequate at MOSE and eventually resulted adequate and inadequate at histology, respectively (▶ **Table 4**). There was strong correlation between MOSE adequacy and adequacy assessed on histology (Cramer's $\Phi=0.63$, $P=0.007$). The concordance between MOSE and histologic adequacy was 85.7%, 90.5%, and 93.5% after the first, second, and third passes, respectively.

One case of mild acute pancreatitis (0.6%) was registered and managed conservatively with 2 days of hospitalization. Moreover, 16 intraprocedural bleeding cases (9.5%) were registered and considered as "incidents" for not requiring any medical intervention nor prolongation of hospitalization. No cases of procedure-related death were observed.

Discussion

In recent years, EUS-FNB with end-cutting needles has revolutionized the practice of EUS-TA of solid lesions. Major changes included the possibility of abandoning ROSE, the retrieval of histological specimens for the diagnosis of rare conditions [14, 15, 16, 17], and the reduction in needle passes. To this end, most endoscopists hold that, in most cases, a sufficient sample for diagnosis is retrieved after the first pass using an end-cutting needle. Indeed, a recent study by Bang et al reported that a single pass of FNB with the Franseen needle could achieve a sensitivity of more than 90% for diagnosis of pancreatic cancer [18]. However, ESGE guidelines suggest two to three passes with a reverse-bevel needle [1] and a recent prospective study comparing two different end-cutting needles demonstrated that at least two passes of FNB are required to achieve a diagnostic sensitivity of 90% in pancreatobiliary cancers [19]. Therefore, the number of passes is not yet standardized when an end-cutting needle is used for sampling solid pancreatic lesions.

For this reason, we performed a multicenter prospective study assessing the diagnostic accuracy of EUS-FNB after the first, second, and third needle pass using a Franseen 22G needle. We observed 90% accuracy after the first pass. This result can undoubtedly be considered (by itself) an amazing achievement compared with the reported performance of FNA. However, we found that the addition of a second pass significantly increased the diagnostic accuracy to 97%. In contrast, the accuracy remained the same after the third pass. The overall rate of accuracy reported in the present study agrees with recent literature [4, 5, 6, 20, 21, 22].

Our results reflect those of two randomized trials. In the first study, fork-tip needles were compared with reverse-bevel needles; the fork-tip needle was reported having 93%, 97%, and 97% accuracy after one, two, and three needle passes, respectively [6]. In the second RCT, the Franseen needle was compared with a different end-cutting needle with a three-prong asymmetric tip [19]. The authors found that the second pass improved the diagnostic sensitivity from 85.1% to 91.5% and from 82.4% to 90.2%, for the Franseen needle and the end-cutting needle with a three-prong asymmetric tip, respectively [19]. Moreover, we tested the equivalence of one pass versus three passes (that in this study reflect the comparison between one and two passes). Our hypothesis was not confirmed. In-

▶ **Table 4** Concordance between macroscopic on-site evaluation adequacy and presence of histologic core on 504 specimens collected during endoscopic ultrasound-guided fine-needle biopsy of solid pancreatic lesions.

		Histological evaluation					
		Adequate	Inadequate	Total	Concordance	Cramer's Φ	*P* value
MOSE evaluation	Adequate	447	26	473	89.9%	0.63	0.007
	Inadequate	25	6	31			
	Total	472	32				

MOSE, macroscopic on-site evaluation

deed, the difference in accuracy proportion between two or three passes and one pass was 7.1%, thus exceeding the equivalence margin of 5%.

The robustness of our findings was confirmed using univariate analysis investigating factors associated with accuracy. We found that the number of passes was the only variable significantly associated with accuracy with an OR of 4.3. Similar results were observed when specimen adequacy was evaluated, with a significant improvement from 91% to 98% by adding a second needle pass. Based on our findings, at least two needle passes should be performed during EUS-FNB with end-cutting needles.

We also assessed the reliability of MOSE for establishing histologic adequacy. Overall, 504 passes were independently evaluated and MOSE results were compared with histological evaluation. The rate of concordance was close to 90% with a Cramer Φ of 0.63, representing a strong correlation. Overall, 51 of 504 specimens (10%) not concordant with histopathology were observed. Interestingly, among 31 cases deemed inadequate with MOSE, 25 (80.6%) were eventually adequate on histology. On the other hand, only 26 of 473 cases (5.5%) evaluated as adequate with MOSE were deemed indequate on histology. This finding possibly suggests that the adequacy cut-off of 10-mm white-yellowish core previously suggested [23] and used in the study should be reassessed in specifically designed clinical trials. Similar results were observed in a recent randomized trial comparing EUS-FNB driven by MOSE and EUS-FNB with three passes [8] where 7% of discordant specimens were observed. Moreover, in the same study, the addition of a second sample that was collected after MOSE adequacy to reach three passes, as suggested by guidelines, improved the diagnostic adequacy and accuracy from 90% to 95% and from 93% to 98%, respectively. However, in the aforementioned study, both pancreatic and nonpancreatic lesions were included, and the number of passes was established on MOSE. In contrast, the present study assessed the crude association between MOSE and histology for each individual pass. Importantly, in the present study, diagnostic accuracy was evaluated regardless of the MOSE results. MOSE was compared with histologic adequacy that does not always reflect diagnostic accuracy. Therefore, even if the concordance of MOSE and histologic adequacy was close to 90% after the first pass, the present study demonstrated that a second pass should be performed to increase diagnostic accuracy regardless of the result of MOSE after the first pass.

Besides accuracy, EUS-FNB represents a tool to provide tissue for molecular tests in the preoperative setting [24]. In a recent study, after the diagnosis was confirmed at ROSE, patients were randomized to undergo EUS-FNB with two or three dedicated passes for DNA and RNA extraction from paraffin blocks. Two passes performed similarly to three, with no significant difference in the median concentration of DNA and RNA. Future studies should address whether two passes only are sufficient for both diagnostic and molecular testing purposes.

Finally, our study confirms the excellent accuracy of EUS-FNB for the sampling of pancreatic solid lesions performed with an end-cutting needle even in the absence of ROSE. Our results support the data reported in a recent meta-analysis that highlighted the non-superiority of EUS-FNB + ROSE over EUS-FNB with newer end-cutting needles [19]. However, ROSE may still have a role when FNA needles are used.

Overall, the current data suggest sampling solid pancreatic lesions by performing two needle passes. After the collection of samples with two passes, MOSE can be performed where additional passes can be added in cases of MOSE inadequacy. This could shorten the procedure time with significant advantages, especially for patients in poor general condition.

Our study has several limitations. First, the designated pathologist at each center evaluated all three specimens from each patient. Therefore, the evaluation of the second sample could potentially be biased by the evaluation of the first specimen. To overcome this, future studies should be specifically designed to compare samples containing one pass with those containing two passes together. Second, only the 22G Franseen needle with the slow-pull technique was used; thus, our result could be different by using other devices or aspiration techniques. On the other hand, the performance of Franseen needles was comparable to fork-tip ones, and both ranked the highest-performing FNB needles in a recent large meta-analysis including 16 randomized controlled trials [22]. Therefore, it is likely that these needles will become the most used in clinical practice. Similarly, the slow-pull technique showed equal histologic and accuracy rates compared with wet-suction for the evaluation of solid pancreatic lesions [3, 21]. Third, MOSE reliability in terms of agreement with histological adequacy was evaluated for each single pass; thus, it could be higher when two passes are performed together and assessed macroscopically. Finally, we limited our study to solid pancreatic lesions and no information was provided about extra-pancreatic masses.

Conclusions

In conclusion, the rates of accuracy and specimen adequacy with only one pass using the 22G Franseen needle is remarkably high. Our study showed that the addition of a second pass significantly increases the performance of EUS-FNB whereas a third pass could be avoided. MOSE is a reliable tool to assess specimen adequacy and can be used to evaluate the need for additional passes.

Conflict of Interest

The authors declare that they have no conflict of interest.

Clinical trial

Trial registry: ClinicalTrials.gov (http://www.clinicaltrials.gov/)
Registration number (trial ID): NCT05436704
Type of Study: Prospective, longitudinal

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