Agreement on eus-guided tissue specimens: comparing a 20-gauge fnb to a 25-gauge fna needle amongst academic and non-academic pathologists

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ABSTRACT

OBJECTIVE

A recently performed randomized controlled trial demonstrated the benefit of a novel 20G fine needle biopsy (FNB) over a 25G fine needle aspiration (FNA) needle. The current study evaluated the reproducibility of these findings among expert academic and non-academic pathologists.

DESIGN

This study was a side-study of the ASPRO (Aspiration vs PROcore) study. Five centers retrieved 74 (59%) consecutive FNB and 51 (41%) FNA samples from the ASPRO study according to randomization; 64 (51%) pancreatic and 61 (49%) lymph node specimens. Samples were re-reviewed by five expert academic and five non-academic pathologists and rated in terms of sample quality and diagnosis. Ratings were compared between needles, expert academic and non-academic pathologists, target lesions, and cytology versus histological specimens.

RESULTS

Besides a higher diagnostic accuracy, FNB also provided for a better agreement on diagnosing malignancy (κ=0.59 vs κ=0.76, $p<0.001$) and classification according to Bethesda (κ=0.45 vs κ=0.61, $p<0.001$). This equally applied for expert academic and non-academic pathologists and for pancreatic and lymph node specimens. Sample quality was also higher rated for FNB, but agreement ranged from poor (κ=0.04) to fair (κ=0.55). Histology provided better agreement than cytology, but only when a core specimen was obtained with FNB ($p=0.004$ vs $p=0.432$).

CONCLUSION

This study demonstrates that the 20G FNB outperforms the 25G FNA needle in terms of diagnostic agreement, independent of the background and experience of the pathologist. This endorses the use of the 20G FNB needle in both expert and lower volume EUS centers.

KEYWORDS

FNA, FNB, interobserver agreement, pathology

INTRODUCTION

Traditionally, endoscopic ultrasound (EUS)-guided tissue sampling has been carried out using a thin and flexible fine-needle aspiration (FNA) needle, which mainly yields individual cells (cytology) rather than histologically intact tissue fragments. Although diagnostic accuracy rates of FNA are fair, intact tissue fragments are preferred to enable identification of tumor invasion and allow for ancillary immunological and molecular testing, for example in submucosal and neuro-endocrine tumors [1-9]. Furthermore, histology enables genetic profiling and a patient tailored approach, which is becoming increasingly relevant in this era of personalized medicine [10-14]. The growing need for histology resulted in the introduction of the fine needle biopsy (FNB) needles.

So far, most studies reported an equal performance of FNA and FNB needles [6-9, 15], but recently, two large randomized trials showed a significant diagnostic benefit of FNB [16, 17]. One of these studies, the randomized controlled ASPRO (ASpiration *vs* PROcore) trial, was carried out in 13 EUS-clinics, worldwide [17]. This study showed a diagnostic benefit of a novel 20G FNB needle (ProCore, Cook Medical, Bloomington, IN, USA) over a widely used 25G FNA needle (EchoTip Ultra, Cook Medical), irrespective of lesion type, size, and the number of passes performed. However, general applicability of these findings cannot be warranted, as study participation was confined to expert centers only.

Ideally, the superiority of a diagnostic device is reproducible in expert and non-expert hands. Therefore, the present study compares the diagnostic agreement on samples obtained with the novel 20G FNB to the 25G FNA needle amongst expert academic pathologists and non-academic pathologists.

METHODS

Study design

In the course of the ASPRO trial (ClinicalTrials.gov: NCT02167074), 13 EUS centers randomized 608 consecutive patients with a solid pancreatic lesion, lymph node, or submucosal or other solid lesion to sampling with a 20G FNB (ProCore, Cook Medical) or 25G FNA needle (EchoTip Ultra, Cook Medical), between February 2015 and September 2016. Parameters regarding specimen characteristics and diagnostic accuracy were compared. Gold standard diagnosis was based on the prior ASPRO study [17] either on pathological evaluation of the surgical resection specimens or clinical follow up for at least 9 months when surgical resection was not indicated. Gold standard diagnosis was recorded by the principal investigator of each of the participating centers.

For the present side-study, the first 125 pancreatic and lymph node cases that were enrolled in the ASPRO study were included. The samples of these cases were reassessed by five expert

academic and five non-academic pathologists. Diagnosis of malignancy and quality scores were assessed, and agreement on these outcome measures was compared between the two needles and between academic and non-academic pathologists.

As our study was a clinical trial, all authors could access the study data and have reviewed and approved the final manuscript.

Center, pathologist and case selection

Aspiration versus PROcore study centers were invited to contribute to this study if they had collected at least 20 solid pancreatic and lymph node samples by April 2016, and their pathologist was trained to read both cytology and histology. Five ASPRO study centers fulfilled these criteria (Milan, Osaka-Sayama, Rome, Rotterdam, and Santiago de Compostela). Each center was represented by the specialized 'academic' pathologist, who was also involved in the original ASPRO study. This academic pathologist invited a 'non-academic' colleague from a local community practice hospital with a general clinical profile to participate. Expert academic pathologists had reviewed between 3000 and 40 000 EUS samples, including both, FNA and FNB, during their career, whereas the non-academics had a sample review track record between 50 and 1000. Per case, the academic pathologists selected the minimum number of slides required to obtain a tissue diagnosis, including immunohistochemically stained slides, if available.

EUS-guided tissue sampling

Endoscopic ultrasonography procedures were carried out with a convex array echoendoscope (either Pentax EG-3870 UTK or EG-3270UK; Pentax, Tokyo, Japan, or Olympus UTC 140/180/26; Olympus, Tokyo, Japan) as is described in the ASPRO study [17]. Three study sites had on-site pathological evaluation at their disposal (Milan, Rotterdam, and Santiago de Compostela).

Specimen processing

Tissue samples were preserved according to local practice. Cytological tissue samples were smeared on to glass slides and stained with Diff Quick (RAL diagnostics) (Rotterdam and Santiago de Compostela) or Hematoxylin and eosin staining (HE) (Milan, Osaka-Sayama, Rome). Remainder of the cytological specimens were collected in CytoLyt (CytoLyt Solution, Marlborough, MA, USA) (Rome, Rotterdam, Santiago de Compostela), saline (Osaka-Sayama), or formalin (Milan). Cell suspensions were processed into cell blocks, using the Cellient™ automated cell block system (Hologic, Toronto, Canada) (Rotterdam) or Agar technique (Milan, Rome, Santiago de Compostela). Osaka-Sayama did not further process cytology. Histology was collected in CytoLyt (Santiago de Compostela and Rotterdam) or formalin (Milan, Rome, Rotterdam, Osaka-Sayama). Samples collected in formalin were processed as paraffin blocks, sectioned at 3-4 microns, and stained with HE for morphological evaluation.

Review session

Cases were reviewed during a 2-day session at the Erasmus MC University Medical Center Rotterdam, the Netherlands in April 2016. Each expert academic pathologist presented the selected cases providing information on the patient's gender, age and relevant medical history, type of target lesion (lymph node or solid pancreatic lesion) and a summary of the EUS report. Pathologists were blinded for the final clinical and pathological outcome. Slides were viewed simultaneously, using a multi-headed light microscope, but assessed individually. Slides, representative of a case, were presented, including immunohistochemically stained slides, if available. Each pathologist reviewed all cases, including their own.

Outcome measures and definitions

The primary outcome measure was to compare the diagnostic agreement on samples obtained with the two needles. First, samples were assessed for malignancy (yes/no) and classified according to Bethesda (non-diagnostic, benign, atypical/suspect of malignancy, and malignant) [18]. Solid-pseudopapillary neoplasms were classified as malignant. Neuroendocrine and spindle cell tumors were classified malignant only if they harbored high-grade dysplasia or an invasive component. Secondly, we evaluated if diagnostic agreement for the two needles differed between expert academic and non-academic pathologists, between pancreatic and lymphatic lesions, and between specimens containing cytology and histology.

Furthermore, agreement on specimen quality parameters was assessed and compared between the two needles, and between expert academic and non-academic pathologists. The following quality parameters were scored: presence of artifacts, sample sufficiency, presence of target cells and tissue cores and suitability for additional analysis. Artifacts were subdivided in five categories; poor fixation or drying artifacts, thick smears, blood clots, contamination with other cells (mesothelial, liver, gastric or intestinal epithelium), and other. Sample sufficiency was defined as the presence of sufficient target cells to obtain or exclude a certain diagnosis. Target cells were classified as less or more than 50%. Presence of tissue core was defined as the presence of a measurable microscopic cylinder containing target organ cells with preserved histologic structure.

Last, we assessed if and to what extent, pathologist's experience or specimen characteristics influenced diagnostic accuracy.

Statistics

The sample size for this study was derived from Walter et al [19]. Given the availability of 10 observers (5 academic and 5 non-academic pathologists), 50 samples are needed to be analyzed per needle type (50 x 2 = 100 in total), given a one-sided alpha of 0.05, a power of 80%, a minimally acceptable interrater reliability of 0.6 for agreement on the presence of malignancy, and a minimal deviation from the interrater reliability of 0.2 between the two needles, n=10. Inter-observer agreement was calculated by the use of kappa statistics Fleiss'κ-

statistic and 95% confidence intervals (CIs). Kappa- statistics were interpreted according to the convention of Landis and Koch; <0, no agreement; 0-0.20, slight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; and 0.81-1.0; almost perfect agreement. The chi-squared test was used to compare the diagnostic agreement between the two study needles, academic and non-academic pathologists, target lesion types, and cytological and histological samples. Although all 10 observers assessed the samples for each of the outcome parameters, we only report the average outcome per parameter. Last, univariate logistic regression analysis was applied to assess if a pathologist's expertise and sample quality influenced diagnostic accuracy. Outcomes of this analysis were expressed as odds ratio (OR) with 95% CI. Statistical significance was defined as $p<0.05$ (two-tailed). Analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA), and SPSS version 22, Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA).

RESULTS

Target lesion and procedure characteristics

A total of 125 samples were reviewed, of which 74 were collected by FNB (59%) and 51 by FNA (41%), with a mean of 2.8 needle passes. Sixty-four were solid pancreatic lesions (51%) and 61 lymph nodes (49%), with a mean size of 30.4 ± 1.3 mm. Table 1 shows the case and sampling specifics. Techniques intended to increase the sample yield were applied in 94% of cases; suction with a syringe in 74 (63%), the slow-pull technique in 50 (37%), and a combination of the two in five (4%). The gold standard diagnosis comprised 26 (21%) non-malignant cases, and 99 (79%) malignant cases (Table 1). The gold-standard diagnosis was based on surgical resection specimens in 31 cases (25%).

Diagnostic accuracy and agreement

In line with the ASPRO study results, FNB samples provided higher accuracy than FNA for malignancy (88% vs 77%, p=0.002) and classification according to Bethesda (76% vs 61%, p=0.002). Regarding the primary question of diagnostic agreement, FNB samples provided better agreement on the presence of malignancy (κ=0.76 vs 0.59, p<0.001) and classification according to Bethesda (k=0.61 vs 0.45, p<0.001, table 2). This was true for both, expert academic and non-academic pathologists (Table 2).

Assessment per target lesion showed that for lymph nodes, FNB provided higher agreement on the presence of malignancy and classification according to Bethesda. However, in pancreatic lesions FNB only outperformed FNA for agreement on the Bethesda classification, not for the presence of malignancy (Table 3). When comparing histology to cytology, agreement on the presence of malignancy was better for histological samples, but agreement on the Bethesda classification was better for histological samples if they had been obtained with the FNB needle (Table 4).

Table 1. Case and sampling specifics.

Variables, n (%)	All (n=125)	FNB (n=74)	FNA (n=51)
Center of origin			
Rotterdam	33 (26)	23 (31)	10 (20)
Rome	30 (24)	20 (26)	10 (20)
Milan	22 (18)	11 (15)	11 (20)
Santiago De Compostela	20 (16)	10 (14)	10 (20)
Osaka-Sayama	20 (16)	10 (14)	10 (20)
Target lesion,			
Solid pancreatic lesion	64 (51)	39 (53)	25 (49)
Lymph node	61 (49)	35 (47)	26 (51)
Size (mm), mean ± SD	30.4 ± 1.3	31.5 ± 1.8	28.8 ± 1.8
Location pancreatic lesions			
Head	40 (62)	28 (72)	12 (48)
Neck	5 (8)	2 (5)	3 (12)
Corpus	12 (19)	7 (18)	5 (20)
Tail	7 (11)	2 (5)	5 (20)
Location lymph nodes			
Mediastinal	21 (34)	14 (40)	7 (27)
Abdominal	40 (66)	21 (60)	19 (73)
Gold Standard diagnosis			
Benign, normal tissue	18 (14)	14 (19)	4 (8)
Sarcoidosis	1 (1)	0 (0)	1 (2)
Pancreatitis	2 (2)	1 (1)	1 (2)
Leiomyoma	1 (1)	0 (0)	1 (2)
GIST, low grade	2 (2)	0 (0)	2 (4)
NET low grade	2 (2)	1 (1)	1 (2)
NET high grade	4 (3)	3 (5)	1 (2)
Leiomyosarcoma	1 (1)	1 (1)	0 (0)
Solid pseudopapillary neoplasm	3 (2)	2 (3)	1 (2)
Metastatic disease	13 (10)	6 (8)	7 (13)
Malignant lymphoma	11 (9)	5 (7)	6 (11)
Adenocarcinoma	67 (53)	41 (55)	26 (50)

FNB; fine needle biopsy, FNA; fine needle aspiration, mm; millimeter, SD; standard deviation, GIST; gastrointestinal stromal lesion, NET; neuroendocrine tumor.

Specimen quality and agreement

Compared to FNA, FNB samples contained fewer artifacts (52% vs 45%, p=0.007, table 2), but agreement was low for both FNB (κ=0.10; 95% CI 0.07-0.14) and FNA samples (κ=0.17; 95% CI 0.13-0.21). Agreement did not differ between expert academic and non-academic pathologists for FNA (p=0.132) or FNB (p=0.212). Sample sufficiency for diagnosis, percentage of target cells, presence of tissue cores, and suitability for additional analysis were all better for FNB than FNA, but again, agreement on these parameters was poor (κ=0.04) to fair (κ=0.55, table 2). As for the collection of histology, FNB obtained histological samples more often than FNA (70% vs 36%, p<0.001, table 2). Agreement on all of the above-mentioned quality parameters was highest for the expert academic pathologists. Furthermore, agreement amongst the expert academic

pathologists was higher for FNB than FNA specimens. In non-academic pathologist however, FNB only provided for better agreement than FNA for the identification of tissue cores (κ=0.26 vs 0.04, p<0.001).

Table 2. Agreement on sample diagnosis and quality amongst the pathologist groups per needle type

Cases scored as	FNB (n=74)	FNA (n=51)	p-value
Malignant– no. (%)	47 (63)	27 (52)	<0.001
Agreement - κ (95% CI)			
All	0.76 (0.73-0.79)	0.59 (0.55-0.63)	<0.001
Expert academic	0.74 (0.66-0.81)	0.54 (0.45-0.62)	<0.001
Non-academic	0.78 (0.71-0.85)	0.64 (0.55-0.72)	<0.001
Bethesda classification – no. (%)			
Non-diagnostic	6 (9)	8 (16)	<0.001
Benign	9 (12)	3 (6)	
Neoplastic	12 (16)	13 (26)	
Malignant	47 (63)	27 (52)	
Agreement - κ (95% CI)			
All	0.61 (0.60-0.64)	0.45 (0.43-0.48)	<0.001
Expert academic	0.62 (0.57-0.67)	0.43 (0.37-0.49)	<0.001
Non-academic	0.59 (0.55-0.64)	0.46 (0.40-0.52)	<0.001
Sufficient quality – no. (%)	67 (91)	40 (79)	<0.001
Agreement - κ (95% CI)			
All	0.49 (0.46-0.53)	0.48 (0.44-0.52)	0.366
Expert academic	0.50 (0.43-0.58)	0.33 (0.28-0.37)	<0.001
Non-academic	0.42 (0.35-0.49)	0.46 (0.37-0.54)	0.358
Target cells ≥50% – no. (%)	50 (68)	29 (56)	<0.001
Agreement - κ (95% CI)			
All	0.31 (0.28-0.34)	0.38 (0.33-0.41)	<0.001
Expert academic	0.33 (0.26-0.40)	0.55 (0.47-0.64)	<0.001
Non-academic	0.27 (0.20-0.34)	0.33 (0.24-0.42)	0.127
Tissue core present – no. (%)	52 (70)	18 (36)	<0.001
Agreement - κ (95% CI)			
All	0.37 (0.34-0.41)	0.14 (0.10-0.18)	<0.001
Expert academic	0.41 (0.34-0.48)	0.08 (0.00-0.16)	<0.001
Non-academic	0.26 (0.19-0.33)	0.04 (-0.04-0.13)	<0.001
Additional analysis possible – no. (%)	56 (76)	28 (54)	<0.001
Agreement - κ (95% CI)			
All	0.47 (0.43-0.50)	0.42 (0.38-0.46)	0.016
Expert academic	0.51 (0.44-0.58)	0.43 (0.34-0.51)	0.042
Non-academic	0.38 (0.30-0.45)	0.38 (0.29-0.47)	0.593

FNB; fine needle biopsy, FNA; fine needle aspiration, no.; number, κ; kappa statistic, CI; confidence interval.

Table 3. Diagnostic agreement of FNA and FNB per target lesion.

Scored variables Agreement κ (95% CI)	FNB (n=74)	FNA (n=51)	p-value
Bethesda classification			
Pancreas	0.54 (0.51-0.58)	0.47 (0.43-0.52)	<0.001
Lymph node	0.64 (0.61-0.67)	0.43 (0.39-0.47)	<0.001
Presence of Malignancy			
Pancreas	0.64 (0.59-0.69)	0.60 (0.54-0.66)	0.114
Lymph node	0.84 (0.79-0.89)	0.58 (0.52-0.63)	<0.001

FNB; fine needle biopsy, FNA; fine needle aspiration, CI; confidence interval.

Table 4: Diagnostic agreement on cytological and histological specimens per needle type.

Agreement κ (95% CI)	Cytology	Histology	p-value
Bethesda classification			
All samples (n=121)	0.51 (0.49-0.52)	0.60 (0.59-0.61)	<0.001
FNA (n=47)	0.49 (0.46-0.50)	0.52 (0.49-0.55)	0.432
FNB (n=74)	0.52 (0.49-0.54)	0.62 (0.61-0.63)	<0.001
Presence of Malignancy			
All samples (n=121)	0.76 (0.74 – 0.78)	0.97 (0.95-0.99)	<0.001
FNA (n=47)	0.73 (0.71-0.76)	0.89 (0.86-0.92)	0.002
FNB (n=74)	0.78 (0.75-0.81)	0.99 (0.79-1.00)	<0.001

FNB; fine needle biopsy, FNA; fine needle aspiration, CI; confidence interval.

Factors affecting diagnostic accuracy

Besides the type of needle, other factors affecting EUS-sample diagnosis are shown in table 5. A pathologist's background (expert academic or non-academic) did not influence the diagnostic accuracy of either needle (p=0.250). The presence of artifacts did have an effect, as this resulted in a lower diagnostic accuracy (p=0.030). Last, the presence of tissue cores significantly improved diagnostic accuracy (p=0.003).

Table 5. Factors affecting diagnostic accuracy, univariable analysis**.**

Diagnostic accuracy Bethesda classification	Univariate OR (95%CI)	p-value	Diagnostic accuracy for malignancy	Univariate OR (95%CI)	p-value
Pathologist experience			**Pathologist experience**		
Expert academic	0.96 (0.82-1.12)	0.587	Academic	0.88 (0.70-1.10)	0.250
Non-academic			Non-academic		
Presence of artifacts			**Presence of artifacts**		
No	1.45 (1.22-1.74)	<0.001	No	1.34 (1.03-1.75)	0.030
Yes			Yes		
Type of tissue			**Type of tissue**		
Histology	0.55 (0.32-0.94)	0.030	Histology	0.39 (0.21-0.72)	0.003
Cytology			Cytology		

OR; Odds ratio, CI; confidence interval.

DISCUSSION

In addition to the previously reported diagnostic benefit of a novel 20G FNB over a commonly used 25G FNA needle, the present study shows that diagnostic agreement is also higher for the FNB than FNA samples. More importantly, agreement on FNB samples was higher amongst pathologists from different backgrounds (academic vs community practice) and with different levels of experience (high vs lower volume). The benefit of FNB equally applies to pancreatic and lymphatic target lesions. The finding that FNB samples were of better quality and harbored histology more often, likely contributed to their superior diagnostic performance.

Most studies on EUS-needle devices have been carried out in expert high-volume centers. However, EUS-guided tissue sampling is increasingly applied in lower-volume centers. So far, few studies have evaluated the reproducibility of EUS-FNA/FNB results. Moreover, most of these studies had a limited number of observers, concerned one type of target lesion, or were carried out in an academic practice only [20-24]. Previous studies reported diagnostic agreement rates ranging from moderate to excellent for FNA (κ=0.45-0.89) and FNB (κ=0.61-0.94). Recently, a promising study aimed to validate a novel scoring system to further optimize diagnostic agreement amongst cytopathologists [24]. Unfortunately, despite the fact that observers were selected from tertiary centers, diagnostic agreement for pancreatic FNA specimens was still suboptimal (κ=0.56). Compared to these agreement rates, the 20G FNB needle performed well, especially when taken into account pathologists from all over the world were included, academics and non-academics alike. The 20G FNB needle may thus contribute to improve reproducibility of EUS-FNA/B diagnosis.

The first explanation for a better agreement on FNB samples is its high tissue core rate, as the collection of histology rather than cytology was positively associated with a higher agreement. This is supported by the finding that the cytological yield of FNB was also higher than for FNA, but only availability of tissue cores for histology, and not cytology, contributed to a better diagnostic accuracy. The importance of tissue core samples over cytological ones to reach a correct diagnosis when using an FNB needle has been previously described by others [20]. Compared to other FNB needles, the cytological yield of the current 20G FNB needle was high as well [9, 20, 22, 25-31]. Whereas previous studies reported sufficient cellularity in 19% to 52%, in the current study this was 68%. The only device that provides higher histology and cytology rates is the 19G needle [22, 25], which obtains cores in 88% of samples and an adequate amount of loose target cells in 91%. However, the reported clinical applicability of being able to obtain tissue with the 19G FNB needle (81%) is much lower than the 20G FNB needle (99%). Although the increased flexibility of the 20G FNB needle is likely a major contributor to its better performance, other needle design adjustments may have improved the tissue acquisition rate too[32, 33].

Another quality parameter that may have contributed to the high diagnostic agreement on samples obtained with FNB is a low artifact rate. Although artifacts not necessarily decrease ac-

curacy when abundant tissue is collected, previous studies have shown that they may hamper for example advanced genetic testing [34]. Interestingly, agreement on the presence of artifacts was low for both needles (although slightly better for FNB than FNA). This is in line with the fact that agreement on all sample quality parameters was rather low, similar to reports from others [21, 24]. This may result from a lack of EUS-sample quality definitions. In the current study, we tried to minimize this limitation by using the predefined scoring system, as proposed by the Papanicolaou Society of Cytopathology in 2014 [18].

There are several limitations to our study. First, each academic pathologist brought and presented his or her own slides. Although they too were blinded for the final outcome, we cannot exclude recall bias. However, this only applied to a few cases per pathologist. Secondly, pathologists assessed samples individually, while in daily practice, difficult cases are often discussed amongst colleagues. Therefore, interobserver agreements reported in the current study may underestimate real-life reproducibility. Thirdly, our study involved pathologists from 10 centers from around the world, while previous studies were confined to no more than five centers from the same geographical region. In the absence of uniform guidelines for EUS-guided tissue sampling and processing, it is inevitable that there are geographical and institutional differences in the work-up of specimens. These differences may have resulted in slight differences in the appearance of specimens, which may have hampered interpretation by pathologists not familiar with certain preparation techniques. Lastly, it must be considered that all samples were collected by expert endosonographers. For an ideal assessment of the reproducibility of the outcome of the ASPRO study, the study should be repeated in low volume centers, with less experienced endosonographers.

In conclusion, this study demonstrates that the novel 20G FNB needle outperforms the 25G FNA needle in terms of diagnostic agreement, as its diagnostic superiority is not limited by the expertise and experience of the reviewing pathologist. Better sample quality and presence of histology seem to be the responsible determinants for the better diagnostic performance of the 20G FNB needle. Together with the favorable accuracy rates from the previous ASPRO study, current findings advocate the use of the novel 20G FNB needle in high as well as lower volume EUS centers.

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