Combined versus single use of the 20-gauge FNB and the 25-gauge FNA needle for EUS-guided tissue sampling of solid gastrointestinal lesions

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ABSTRACT

Background

Instead of choosing one endoscopic ultrasound (EUS) needle over the other, some advocate the use of fine-needle aspiration (FNA) and fine-needle biopsy (FNB) consecutively. We explored the yield of combined use of 20-gauge (G) FNB and 25G FNA needles in patients with a suspicious solid gastrointestinal lesion.

Methods

Patients from the ASPRO (Aspiration vs PROcore) study who were sampled with both needles during the same procedure were included. The incremental yield of dual sampling compared with the yield of single needle use on the diagnostic accuracy for malignancy was assessed for both dual sampling approaches – FNA followed by FNB, and vice versa.

Results

73 patients were included. There were 39 (53%) pancreatic lesions, 18 (25%) submucosal masses, and 16 (22%) lymph nodes. FNA was used first in 24 patients (33%) and FNB was used first in 49 (67%). Generally, FNB was performed after FNA to collect tissue for ancillary testing (75%), whereas FNA was used after FNB to allow for on-site pathological assessment (76%). Diagnostic accuracy for malignancy of single needle use increased from 78% to 92% with dual sampling (p = 0.002). FNA followed by FNB improved the diagnostic accuracy for malignancy (p = 0.03), whereas FNB followed by FNA did not (p = 0.13).

Conclusion

Dual sampling only improved diagnostic accuracy when 25G FNA was followed by 20G FNB and not vice versa. As the diagnostic benefit of the 20G FNB over the 25G FNA needle has recently been proven, sampling with the FNB needle seems a logical first choice.

INTRODUCTION

Over the past decades, endoscopic ultrasound (EUS)-guided tissue sampling has become an important tool in the diagnosis and staging of lesions around the gastrointestinal tract. For this purpose, both fine-needle biopsy (FNB) and aspiration (FNA) devices are used. Whereas FNA needles are generally more flexible and easier to use from an angulated scope position, FNB needles are designed to collect histologically intact tissue samples, which enable ancillary testing. As histology is indispensable in this era of personalized medicine, collection of samples for histological analysis has become more important. Recently, two randomized trials demonstrated that FNB needles produce a better diagnostic yield than FNA needles in this context [1,2].

Instead of choosing one needle over the other, some advocate the selective use of both needle types consecutively (dual needle sampling) [3–7]. As the number of passes only seems to improve diagnostic accuracy up to a certain number of passes, the benefit of dual sampling probably lies within the combination of two different needle designs [8]. For example, FNA can be applied to obtain an on-site diagnosis through rapid on-site tissue evaluation (ROSE) and may then be followed by FNB to harvest tissue cores. This sequence prevents costly ancillary testing of unrepresentative tissue. Others start with FNB and switch to FNA in case they are faced with a small or fibrotic lesion that is anatomically difficult to reach. Although endosonographers are confronted with this needle choice dilemma on a daily basis, few studies have addressed the yield of dual needle sampling, and those that have report inconclusive results [8–14].

Owing to scant data, there is no clarity on the indication for dual sampling, the optimal needle order, safety, or costs. The current study aimed to explore the incremental yield of combined needle use in patients requiring EUS-guided tissue sampling of a solid gastrointestinal lesion. This was assessed for two sampling orders: sampling with a conventional 25G FNA needle followed by a 20G FNB needle, and vice versa.

METHODS

Study design and case selection

Patients from the ASpiration vs PROcore needle (ASPRO) study, which was approved by the institutional review boards of the participating centers, were included in the current study. This multicenter trial compared the diagnostic value of a 20G FNB needle (ProCore; Cook Medical, Limerick, Ireland) with a 25G FNA needle (EchoTip Ultra; Cook Medical) in patients undergoing EUS-guided tissue sampling of a solid pancreatic lesion, lymph node, or subepithelial or other solid lesion (ClinicalTrials.gov: NCT02167074). Patients were allocated to one needle, but the protocol allowed additional sampling with the other needle, as long as specimens were ana-

lyzed separately. All patients who were sampled with both needles during the same procedure were included in the present side study (Figure 1).

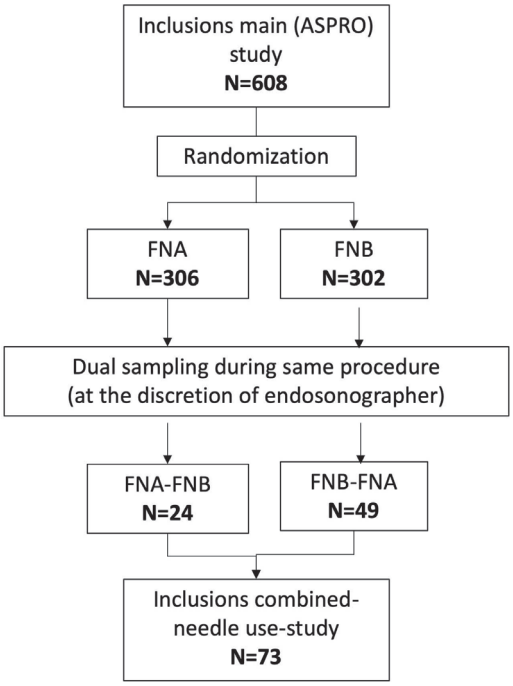

Figure 1. Flow chart of patient selection from the main ASPRO study.

EUS-procedure and tissue acquisition

The participating endosonographers were experts who performed at least 250 EUS-guided sampling procedures per year. They used Pentax (EG-3870UTK; Pentax, Tokyo, Japan) or Olympus echoendoscopes (UTC 140/160/180/190/260 or UC140; Olympus, Tokyo, Japan) with color Doppler. In cases of multiple lesions, the most suspicious lesion was targeted. Lesions were punctured at least three times with the allocated needle, followed by one or more punctures with the alternative needle during the same procedure. For each needle, the number of passes was recorded. ROSE was available at four of the study sites (Irvine, Milan, New Haven, Rotterdam).

Specimen processing protocol

Cytological samples were smeared onto glass slides and stained with Diff-Quik (Adelaide, Irvine, New Haven, Rotterdam), or hematoxylin and eosin staining (HE) (Milan, Osaka-Sayama). The remaining material was collected in CytoLyt (Cytyc Corp., Marlborough, Massachusetts, USA) (Adelaide, Rotterdam), saline (Osaka-Sayama), formalin (Irvine, Milan), or CytoRich Red

(Thermo Fischer Scientific, Kalamazoo, Michigan, USA) (New Haven). Cytological cell suspensions were further processed using the ThinPrep technique (Hologic Inc., Marlborough, Massachusetts, USA) (New Haven) or cell block technique using the Cellient automated cell block system (Hologic Inc.), the agar technique or Histogel (Richard-Allan Scientific Co., Kalamazoo, Michigan, USA) (Irvine, Milan, New Haven, Rotterdam). Histological samples were collected in formalin, processed as paraffin blocks, and stained with HE or Giemsa. In Rotterdam, histological specimens were also collected in CytoLyt and processed according to the cell block technique.

Outcome parameters and definitions

The primary outcome was the incremental yield of dual sampling, compared with single needle use, on the diagnostic accuracy for malignancy for both sampling orders – FNA followed by FNB, and vice versa. A diagnosis of malignancy was confirmed (gold standard) by surgical resection specimens, when available, or, in nonsurgical patients, by a compatible clinical disease course during a 9-month follow-up period. To further specify the type of cases that were selected for the current study, we compared case characteristics of the current cohort with those of patients in the main ASPRO study.

Statistics

Categorical data were recorded as frequencies and percentages. Continuous data were displayed as means with standard error as medians with interquartile range. The student's *t* test was used to compare normally distributed continuous variables, and the Fisher's exact test or chi-squared test was used to compare categorical variables. An exact McNemar test was used to compare the diagnostic accuracy of single vs. combined needle use within the same patient. A chi-squared test was used to compare the accuracy between the two sampling orders, and between cases from the current study and the ASPRO study cohort (patients from the current study were excluded from the ASPRO cohort). Statistical significance was established as $P < 0.05$ (two tailed). Analyses were carried out using SPSS version 22 (IBM Corp., Armonk, New York, USA).

RESULTS

Sampling order and reason for dual sampling

Six of the 13 ASPRO centers used dual sampling (Adelaide, Irvine, Milan, New Haven, Osaka-Sayama, Rotterdam). In total, 73 of the 608 ASPRO patients (12%) were punctured by both needles; FNA was used first in 24 patients (33%) and FNB was used first in 49 patients (67%). According to the endosonographers, the rationale for performing additional sampling differed, depending on the allocated needle ($P < 0.001$, table 1); generally, after FNA, FNB was performed to collect tissue for ancillary testing (75%), whereas after FNB, FNA was used to allow for ROSE (76%).

Table 1. Baseline characteristics.

Variables	All cases (n=73)	FNA – FNB regime (n=24)	FNB-FNA regime (n=49)	p-value
Center of origin, n (%)				
Rotterdam, the Netherlands	2 (3)	0 (0)	2 (4)	0.002
Osaka-Sayama, Japan	6 (8)	5 (21)	1 (2)	
Adelaide, Australia	8 (11)	5 (21)	3 (6)	
Irvine, USA	5 (7)	1 (4)	4 (8)	
New Haven, USA	32 (44)	12 (50)	20 (41)	
Milan, Italy	20 (27)	1 (4)	19 (39)	
Reason sampling alternative needle, n (%)				
To allow for ROSE	38 (52)	1 (4)	37 (76)	<0.001
Obtain tissue for ancillary studies	22 (30)	18 (75)	4 (8)	
Insufficient sample	7 (10)	4 (17)	3 (6)	
Sampling failure	2 (3)	0 (0)	2 (4)	
Other	4 (5)	1 (4)	3 (6)	
Target lesion, n (%)				
Pancreatic	39 (53)	12 (50)	27 (55)	0.563
Lymph node	16 (22)	7 (29)	9 (18)	
Submucosal	18 (25)	5 (21)	13 (27)	
Location, n (%)				
Pancreas				
Head	25 (64)	6 (55)	19 (68)	0.500
Non-head	14 (36)	5 (45)	9 (32)	
Lymph node				
Mediastinal	1 (6)	0 (0)	1 (11)	0.563
Abdominal	15 (94)	7 (100)	8 (89)	
Submucosal				
Esophageal	2 (11)	1 (20)	1 (8)	0.847
Gastric	8 (44)	2 (40)	6 (47)	
Small intestine	3 (17)	1 (20)	2 (15)	
Rectum	3 (17)	1 (20)	2 (15)	
Missing	2 (11)	0 (0)	2 (15)	
Lesion size (mm), median (IQR)	35.0 (20-41)	26 (21-40)	35 (25-43)	0.786
Total number of needle passes, mean ± SE				
Overall	4.93 ± 0.17	5.38 ± 0.26	4.71 ± 0.20	0.059
With randomized needle	2.87 ± 0.08	3.13 ± 0.14	2.87 ± 0.10	0.028
With alternative needle	2.23 ± 0.12	2.46 ± 0.21	2.12 ± 0.14	0.183
Pathologist present, n (%)				
With randomized needle	30 (41)	13 (54)	17 (35)	0.146
With alternative needle	57 (78)	14 (58)	43 (88)	0.004

FNA: fine needle aspiration; FNB: fine needle biopsy; USA: United States of America; ROSE: rapid on-site pathological evaluation; n: number of cases; mm: millimeter; IQR: interquartile range; SE: standard error.

Case characteristics

Target lesions included 39 (53%) solid pancreatic lesions, 18 (25%) submucosal masses, and 16 (22%) lymph nodes. Figure 2 shows endoscopic images of EUS-guided tissue sampling of two cases with solid pancreatic lesions. Most pancreatic lesions were located in the head (64%),

most lymph nodes were located in the abdomen (94%), and submucosal lesions were mostly of gastric origin (44%). There were no significant differences in patient or target lesion characteristics between cases sampled with FNA or FNB first (Table 1 and 2).

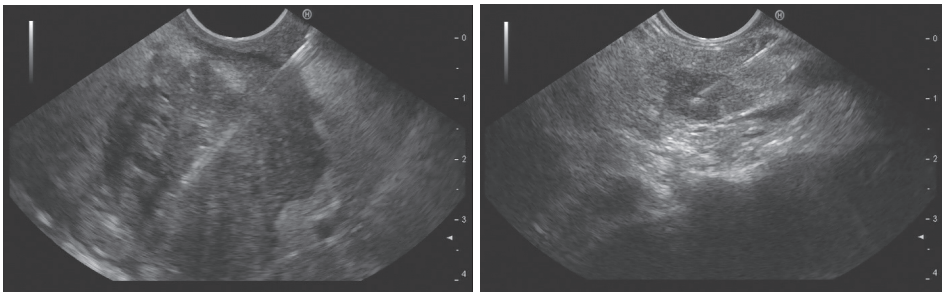

Figure 2. Endoscopic ultrasound images of hypodense lesions of the pancreatic head.
a Lesion, 4 cm in size, irregular borders, and in close proximity to superior mesenteric artery, sampled with the 20G fine-needle biopsy needle.
b Lesion, 2 cm in size, irregular borders, sampled with the 25G fine-needle aspiration needle.

Table 2. final diagnosis

Variables	Overall (n=73)	FNA-FNB (n=24)	FNB-FNA (n=49)	p-value
Malignant lesions, n (%)	59 (81)	18 (75)	43 (88)	0.16
Adenocarcinoma	39	10	29	
GIST	7	2	6	
NET	3	2	2	
Malignant lymphoma	4	1	3	
Squamous cell carcinoma	1	1	0	
Malignant cyst	2	1	1	
Other malignant lesions	3	1	2	
Benign lesions, n (%)	14 (19)	6 (25)	8 (16)	
Lymph adenopathy	4	2	2	
Leiomyoma	1	0	1	
GIST	1	0	1	
NET	2	0	2	
Duplication cyst esophagus	1	1	0	
Benign schwannoma	1	1	0	
Other benign lesions	4	2	2	

FNA: fine needle aspiration; FNB: fine needle biopsy; n: number of cases; GIST: gastrointestinal stromal tumor; NET: neuroendocrine tumor.

Compared with the main ASPRO cohort, patients who were selected for combined needle use had larger target lesions (37.1 ± 2.54 vs. 32.0 ± 0.83 mm; p = 0.04, table 3), were more often sampled from a duodenal scope position (p = 0.04), and more often had a pathologist in the room during the procedure (p < 0.001). As expected, more needle passes were performed per case (p < 0.001). Interestingly, the diagnostic accuracy for single use of either randomized needle (FNA or FNB) was comparable for the cases from the main ASPRO study and the current cohort (Table 3).

Table 3. Patient and target lesion characteristics of combined needle cases compared to other ASPRO study cases.

Variables	Combined cases (n=73)	ASPRO cohort (n=535)	p-value
Male, n (%)	37 (51)	307 (57)	0.279
Age (years), mean ± SE	65.2 ± 1.69	65.8 ± 0.51	0.731
Indication, n (%)			
Pancreatic	39 (53)	273 (51)	0.883
Lymph node	16 (22)	131 (25)	
Submucosal	18 (25)	131 (25)	
Lesion size (mm), mean ± SE	37.1 ± 2.54	32.0 ± 0.83	0.042
Sampling location randomized needle, n (%)			
Duodenum	41 (56)	232 (43)	0.039
Other	32 (44)	303 (57)	
Total number of needle passes randomized needle			
1-3 passes, n (%)	61 (86)	453 (85)	0.892
>3 passes, n (%)	10 (14)	78 (15)	
Total number of needle passes overall			
1-3 passes, n (%)	8 (11)	453 (85)	<0.001
>3 passes, n (%)	65 (89)	78 (15)	
Pathologist present, n (%)			
Randomized needle	30 (43)	70 (13)	<0.001
Overall	57 (78)	70 (13)	<0.001
Final diagnosis			
Benign	14 (19)	131 (24)	0.318
Malignant	59 (81)	404 (76)	
Diagnostic accuracy, n (%)			
Randomized needle overall	57 (78)	430 (81)	0.514
Randomized needle FNA	18 (75)	211 (76)	0.897
Randomized needle FNB	39 (80)	219 (87)	0.181

ASPRO: aspiration versus procore needle; FNA: fine needle aspiration; FNB: fine needle biopsy; n: number of cases; SE: standard error; GIST: gastrointestinal stromal tumor; NET: neuroendocrine tumor

Incremental yield of dual sampling on diagnostic accuracy

Gold standard diagnosis demonstrated 59 malignancies (81%), of which 18 (25%) were diagnosed based on resection specimens (Table 2). Overall diagnostic accuracy for malignancy of single needle use was 78% (57/73), which increased to 92% (67/73) when both needles were

used (p = 0.002, table 4). The incremental yield of dual sampling over single needle use differed depending on which needle was used first: FNA followed by FNB resulted in a significant increase in accuracy (p = 0.03), whereas FNB followed by FNA did not (p = 0.13, table 4).

Table 4. No. of correctly diagnosed cases for single versus combined needle use per sampling regime.

Sampling regime	Single use of randomized needle, n (%)	Combined needle use, n (%)	p-value
Overall, n=73	57 (78)	67 (90)	0.002
FNA-FNB, n=24	18 (75)	24 (100)	0.031
FNB-FNA, n=49	39 (80)	43 (88)	0.125

FNA: fine needle aspiration; FNB: fine needle biopsy; n: number of cases, No: number.

Of all 16 cases (22%) that were incorrectly diagnosed after single needle sampling, 10 (59%) benefited from the alternative needle (Table 5). Cases that benefitted comprised 6 of the 24 cases in which FNB was used after FNA (25%), and 4 of the 49 in which FNA was applied after FNB (8%). FNA cases that benefitted from subsequent FNB sampling comprised a pancreatic adenocarcinoma, a metastatic lymph node, a benign schwannoma of the rectum, and three cases of benign lymphadenopathy. The four FNB cases that benefitted from subsequent FNA sampling included three pancreatic adenocarcinomas and a lymph node metastasis.

Table 5. Specification of all cases that were incorrectly diagnosed after sampling with initial needle/could potentially benefit from combined needle use.

FNB-FNA case no.	Indication	Lesion size (mm)	Puncture location	Use of ROSE	Diagnosis 1st attempt	Diagnosis 2nd attempt	Final Diagnosis
1	Mesenteric mass near stomach and pancreas	35	Gastric corpus	Yes	Atypical	Non-diagnostic	Malignant fibromatosis
2	Lymph node	20	D2, then D1	Yes	Non-diagnostic	Non-diagnostic	Benign lymph adenopathy, resection performed
3	Pancreas	11	Antrum	No	Non-diagnostic	Non-diagnostic	NET, Octreoscan confirmed
4	Pancreas	35	Corpus	Yes	Bile duct tissue only	HG IPMN	HG IPMN
5	Submucosal	140	D2	Yes	Benign	Non-diagnostic	Leiomyosarcoma
6	Lymph node	27	Rectum	Yes	Non-diagnostic	Malignant	Lymph node metastasis
7	Pancreatic head	45	D2	Yes	Non-diagnostic	Malignant	Adenocarcinoma

Table 5. Specification of all cases that were incorrectly diagnosed after sampling with initial needle/could potentially benefit from combined needle use. (*continued*)

FNB-FNA case no.	Indication	Lesion size (mm)	Puncture location	Use of ROSE	Diagnosis 1st attempt	Diagnosis 2nd attempt	Final Diagnosis
8	Pancreatic corpus	10	D1	No	Non-diagnostic	Non-diagnostic	NET on CT
9	Pancreatic head	20	D1	Yes	Benign	Non-diagnostic	Adenocarcinoma
10	Pancreatic head	25	D1	Yes	Benign	Malignant	Adenocarcinoma
11	Lymph node	26	Gastric corpus	No	Insufficient	Adenocarcinoma	Metastasis
12	Pancreatic head	25	D2	No	Few atypical cells	Adenocarcinoma	Adenocarcinoma
13	Lymph node	25	D1	Yes	Suspicious for malignancy	Benign lymph adenopathy	Benign lymph adenopathy
14	Submucosal	29	Rectum	No	Insufficient	Benign	Schwannoma
15	Lymph node	15	Gastric corpus	No	Insufficient	Benign lymph node swelling	Benign lymph node swelling
16	Lymph node	20	D1	Yes	Insufficient	Benign lymph node swelling	Benign lymph node swelling

FNA: fine needle aspiration; FNB: fine needle biopsy; n: number of cases; mm: millimeter; ROSE: rapid on-site pathological evaluation; NET: neuroendocrine tumor; HG: high grade; IPMN: intraductal papillary mucinous neoplasm; D1: superior duodenal part; D2: descending duodenal part; CT: computed tomography

DISCUSSION

Two recent large randomized controlled trials showed that FNB outperforms FNA in terms of histological yield and diagnostic accuracy [1,2]. The current study demonstrated that combined needle sampling only improves diagnostic accuracy when FNA is followed by FNB, but not vice versa. As stated above, the theory behind the benefit of a needle switch, or so called "dual sampling," is that FNA and FNB are complementary. FNA needles collect cytological samples rather than material for histological analysis; their strength lies in their flexibility, which enables them to reach and traverse difficult target lesions, and the fact that they allow for on-site pathological evaluation. FNB devices, however, collect intact histological tissue cores, allowing for a wide range of diagnostic tests. Regarding the use of ROSE, the so-called "sample crush technique" may also allow for on-site specimen assessment of FNB samples [15,16]. However, the optimal method of performing ROSE on FNB samples has yet to be determined.

The explanation as to why FNB following FNA has incremental value and FNA following FNB does not is multifactorial. First, the 20G FNB needle was proven to be diagnostically superior to the 25G FNA needle in our previous study. Thus, this also explains why FNA followed by FNB results in a higher diagnostic accuracy than FNA alone and the limited value of the reversed

approach. Second, puncture with the more traumatic FNB needle poses a higher risk of blood contamination of subsequent specimens. In addition, the larger FNB needle may cause "tracking," impeding the FNA needle from finding its own diagnostic route. Third, secondary FNA was mostly used to allow for ROSE. However, the incremental yield of ROSE is questionable [2,17]. Its impact on diagnostic accuracy has only been demonstrated for endosonographers in training or in centers with low accuracy rates [11]. The current study included only high-volume expert centers, in which the benefit of ROSE is expected to be limited.

The finding that one sampling order benefitted from dual sampling, whereas the other did not, cannot be explained by differences in case or procedure characteristics, as these did not differ between groups. However, we did observe that non-pancreatic lesions mainly benefitted from FNB following FNA. This may be explained by the fact that diagnosing and staging of lymphomas, smooth muscle tumors, and metastases require abundant histological tissue for ancillary testing [8,18–22]. In contrast, three out of four cases that benefitted from additional FNA concerned pancreatic lesions. As these lesions tend to be hard and fibrotic, they may be more easily sampled using a smaller FNA needle.

When comparing the current subgroup with the main ASPRO study cohort, endosonographers selected cases for dual sampling that were bigger in size and more often punctured from the duodenum. Although it was not reported, a larger lesion may have created a desire to harvest more tissue, in order to secure a diagnosis. The high frequency of duodenal punctures seems to indicate that target lesions that were difficult to reach were selected for dual sampling. Interestingly, the diagnostic accuracy of combined needle use did not differ from our previously reported single use [2].

So far, only seven studies have reported on the incremental yield of dual sampling [8–14]. Four studies found a significant increase in diagnostic accuracy when both FNA and FNB were used during the same procedure. However, two studies used the TruCut needle and two used a reversed bevel ProCore device, thus hampering comparison with our results. Furthermore, no study assessed the needle order, and only reported the incremental yield of additional FNB or the combination of the two devices. Our study is the only available study that has looked at the "needle order," and is hypothesis generating, especially with respect to studying the cost-effectiveness of different sampling strategies. Of the previous dual sampling studies, so far only one reported on cost-effectiveness; FNB alone was cost saving compared with FNA alone or FNA followed by FNB [12]. As only one study has reported on this, it would be interesting for future studies to assess the costs of the different sampling strategies, such as FNA with or without ROSE, FNA followed by FNB or FNB alone.

Obviously, this study has limitations. As mentioned earlier, cases were selected based on the endosonographers' choice and not on predefined criteria. This may have introduced selection bias. A second limitation is that dual sampling was not compared with continuous sampling with the allocated needle. As harvesting more tissue alone may be responsible for a diagnostic benefit, this is of interest. Third, the diagnosis of the first needle may have encouraged the

pathologist to find the same diagnosis in the second sample. However, as needle sequence was randomly determined, the effect of this bias is negligible. Finally, we did not assess the impact of dual sampling on procedure time and costs.

In conclusion, for EUS-guided tissue sampling, the 20G FNB needle seems a logical first choice, as it was proven to be superior to the 25G FNA needle, and an incremental value of FNA following FNB was not demonstrated. FNA after FNB may be considered in fibrotic pancreatic lesions, or lesions that are too difficult to reach from an angulated score position. Some may still prefer to start with FNA to assess the accessibility and cellularity of a lesion and to prevent costly ancillary testing of unrepresentative tissue. There seems to be a role for FNB after a non-diagnostic attempt with FNA, especially for lesions of non-pancreatic origin.

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