EUS-guided fine-needle biopsy sampling of solid pancreatic tumors with 3 versus 12 to-and-fro movements: a multicenter prospective randomized controlled study

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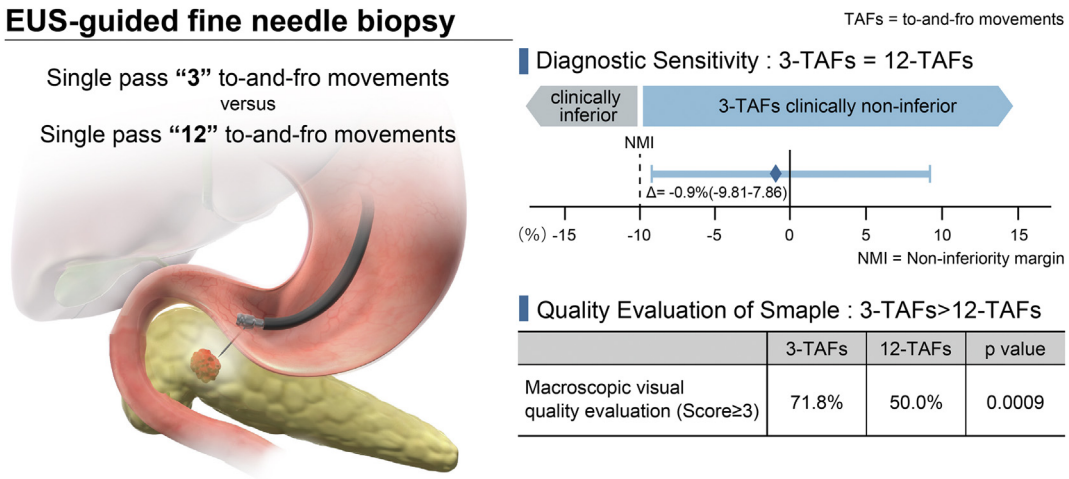
GRAPHICAL ABSTRACT



Background and Aims: A novel EUS-guided fine-needle biopsy sampling (EUS-FNB) needle enabled physicians to obtain sufficient pathologic samples with fewer to-and-fro movements (TAFs) within the lesion. We compared the diagnostic yields of EUS-FNB with 3 and 12 TAFs at each puncture pass.

Methods: The primary endpoint of this multicenter, noninferiority, crossover, randomized controlled trial involving 6 centers was diagnostic sensitivity. Secondary endpoints were diagnostic accuracy and quantity and quality evaluation of EUS-FNB specimens. Length of the macroscopically visible core (MVC) and microscopic histologic quantity were used for quantitative evaluation. Macroscopic visual and microscopic histologic evaluations were performed for qualitative evaluation.

Results: Among 110 patients (220 punctures, 110 for 3 TAFs and 12 TAFs each), 105 (210 punctures) had malignant histology. Diagnostic sensitivity for malignancy of 3 TAFs (88.6%) was not inferior to that of 12 TAFs (89.5%; difference, –.9%; 95% confidence interval, –9.81 to 7.86). Diagnostic accuracy for malignancy was 92.7% for 3 TAFs and 94.6% for 12 TAFs. Overall median MVC length was 13.5 mm in both groups. The 3-TAF group had a significantly higher rate of score ≥3 on macroscopic visual quality evaluation than the 12-TAF group (71.8% vs 52.7%, $P = .009$). No significant intergroup differences existed in microscopic histologic quantity and quality evaluations (quantity evaluation, 88.2% for 3 TAFs vs 83.6% for 12 TAFs; quality evaluation, 90.0% for 3 TAFs vs 89.1% for 12 TAFs).

Conclusions: Diagnostic sensitivity and accuracy of EUS-FNB with 3 TAFs were not inferior to those with 12 TAFs for solid pancreatic lesions. The 3-TAF group showed significantly less blood contamination in sampled tissues than the 12-TAF group. (Clinical trial registration number: UMIN000037309.) (Gastrointest Endosc 2023;97:1092-9.)

(footnotes appear on last page of article)

In general, 10 to 20 postpuncture to-and-fro movements (TAFs) within a lesion during EUS-guided fine-needle aspiration (EUS-FNA) have been recommended.[1-3] However, our previous studies revealed that adequate histopathologic samples could be obtained with fewer TAFs (eg, 5 or 6).[4-6] Recently, a novel EUS-guided biopsy needle with 3 symmetric heels, called the Franseen needle (22-gauge Acquire; Boston Scientific Corporation, Marlborough, Mass, USA), has become popular because it can obtain sufficient histopathologic samples using a normal-size (22-gauge) needle. Although similar to conventional FNA needles, 10 to 20 TAFs are applied with the EUS-guided biopsy needle, and based on our daily clinical practice, we believe that just 3 TAFs would be enough to obtain histopathologic samples. Samples that could be obtained using fewer TAFs would reduce the procedure time and improve the quality of histopathologic specimens by decreasing blood contamination in the biopsy samples. Furthermore, a high number of TAFs would theoretically increase the risk of adverse events because of cellular damage.[7] Therefore, fewer TAFs might reduce the histologic damage associated with puncture and lead to decreased potential adverse events.

We hypothesized that an adequate tissue sample could be obtained by 3 TAFs during EUS-guided fine-needle biopsy sampling (EUS-FNB) using a 22-gauge Franseen needle for solid pancreatic lesions. To validate this hypothesis, we conducted a multicenter, prospective, randomized controlled trial to compare the diagnostic yield of EUS-FNB with 3 TAFs and the diagnostic yield of EUS-FNB with 12 TAFs.

METHODS

Study design

This prospective, multicenter study was conducted at 6 high-volume EUS referral centers (university hospitals and tertiary care centers: Toyama University Hospital [TUH], Gifu University Hospital, Nagasaki University Hospital, Teikyo University Mizonokuchi Hospital, Gifu Municipal Hospital, and Gihoku Kosei Hospital). The study protocol was approved by the institutional review boards (approval number, R2019065; date of registration, November 11, 2019). Written informed consent was obtained from all patients who underwent EUS-FNB and were enrolled in the study. The study was registered at the University Hospital Medical Information Network Trials Registry (UMIN000037309).

Patient eligibility

We included patients aged ≥20 years whose imaging studies such as CT, magnetic resonance imaging, positron emission tomography-CT, or EUS revealed a pancreatic lesion that required EUS-FNB for pathologic diagnosis. Patients who met any of the following criteria were excluded: Eastern Cooperative Oncology Group performance status of 4, hemorrhagic diathesis (prothrombin time-international normalized ratio ≥1.5, platelet count ≤50,000) or use of antiplatelet drugs, confirmed or possible pregnancy, pathologic diagnosis already obtained by other methods, surgically altered anatomy except for Billroth I reconstruction, or refusal to participate in the study.

Randomization

After obtaining informed consent, patients were randomized to EUS-FNB undergoing either 3 or 12 TAFs. Randomization was performed before the procedure. An automated web-based allocation system was used to randomly assign patients in a 1:1 ratio using a minimization method that considered the institution, site of the lesion (head/body and tail), and size of the lesion (<2 cm and >2 cm).

EUS-FNB protocol

Patients underwent EUS-FNB under conscious sedation with midazolam, and their vital signs were monitored. EUS was performed with a curved linear echoendoscope (GF-UCT260; Olympus Corporation, Tokyo, Japan) connected to a US scanning system (EU-ME2; Olympus Corporation). A 22-gauge Franseen needle (22-gauge Acquire; Boston Scientific Corporation) was used for all biopsy sampling.

Under real-time EUS imaging guidance, the lesion was punctured through the stomach or duodenum, and color Doppler imaging was used to confirm that the puncture pathway would not disrupt any major blood vessel or the main pancreatic duct. After removing the stylet, a 20-mL syringe was attached to the needle, and 10 mL of negative pressure was applied. Biopsy sampling was performed with 3 TAFs or 12 TAFs, depending on randomization. Patients were crossed over to the alternate EUS-FNB modality (Fig. 1). For instance, if first assigned to the 3-TAF group,

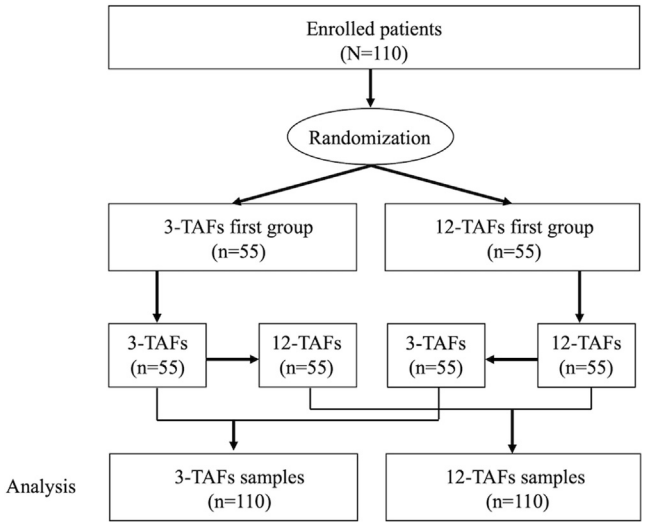


Figure 1. Study flowchart. *TAFs*, To-and-fro movements.

biopsy sampling was performed with 3 TAFs at the first puncture and then by 12 TAFs at the second puncture, and vice versa for the 12-TAF group. If possible, a fanning technique was used.[8] After negative pressure was released, the needle was withdrawn.

Two needle passes were performed on each lesion. If sufficient material was not obtained with 2 passes, additional needle passes were performed at the discretion of the endosonographer. The results of any additional samples were not included in the final analysis. The specimens were macroscopically evaluated, and whitish portions (the macroscopically visible core [MVC]) were collected and placed on a small filter paper. The specimens were then placed in formalin solution for histologic examination, and the remaining material was smeared on glass slides for cytologic examination.[4,6,9]

Macroscopic on-site evaluation of biopsy specimens

Samples extruded from the needle onto a glass slide with a stylet were carefully examined for the presence of MVC, defined as a measurable whitish sample. After collecting the MVCs scattered in the samples, the samples were aligned using a needle, and their length was measured using a ruler. After EUS-FNB was performed, 1 photograph of each sample containing MVCs was taken per pass. Two photographs of 2 passes from each patient were sent to the research secretary at the TUH. Each facility confirmed that the lengths of the reported MVCs matched the lengths received. Endoscopists with extensive experience in macroscopic on-site evaluation (MOSE; I.Y., T.I., T.M., S.A., E.O., and S.D.) performed MOSE of the biopsy specimens at TUH, Gifu University Hospital, Gifu Municipal Hospital, Gihoku Kosei Hospital, Nagasaki University Hospital, and Teikyo University Mizonokuchi Hospital.

In this study, macroscopic visual quantity evaluation of histopathologic samples was defined as the length of the MVC. Additionally, we assessed macroscopic visual quality of histopathologic samples by grading the percentage of red (blood) component ejected from the needle onto a glass slide as follows: grade 1, ≥50% on the glass slide is occupied by blood component; grade 2, 25% to 50% of the glass slide is occupied by blood component; grade 3, 10% to 25% of the glass slide is occupied by blood component; grade 4, <10% of the glass slide shows blood components; and grade 5, white tissue only.

Microscopic histopathologic evaluation

All collected specimens were sent for microscopic histopathologic examination. Specimens were fixed in formalin, embedded in paraffin, sectioned, and subjected to hematoxylin and eosin staining and immunostaining according to the suspected diagnosis. All histologic diagnoses were established by 2 pathologists at TUH specialized in the pancreatobiliary field. Glass slides of tissue specimens obtained from EUS-FNB at institutions other than TUH were also sent to TUH for re-evaluation.

Malignant lesions were defined as adenocarcinomas, carcinomas, neuroendocrine tumors, solid pseudopapillary neoplasms, or pancreatic metastases. Samples considered suspicious or positive for malignancy were assessed as malignant, whereas those considered negative or atypical were assessed as benign.

We assessed the histologic microscopic quantity by grading the percentage of the area of the collected tissue fragments in the entire ×40 field of view (grade 0, none; grade 1, <25%; grade 2, 25%-50%; grade 3, >50%) (Fig. 2). Regarding histologic microscopic quality evaluation, tissue fragments obtained by EUS-FNB were graded according to whether they were of sufficient quality to obtain a definitive diagnosis (grade 0, impossible; grade 1, suspicious [no definitive diagnosis but suspected]; grade 3, possible [conclusive diagnosis possible]).

Endpoints

The primary endpoint was diagnostic sensitivity, defined as (true positive + false positive)/all positive samples. The final diagnosis of malignant disease was based on definite evidence of malignancy from a surgical specimen and diagnosis of malignancy based on the EUS-FNB findings and on clinical and imaging follow-up compatible with malignancy. The final diagnosis of benign disease was defined as FNB samples reported as no malignancy on surgical pathology or exploration and no evidence of malignancy on EUS-FNB findings and on 6-month clinical and imaging follow-up.

Secondary outcomes were diagnostic accuracy and quantitative and qualitative evaluations of the samples. For quantitative evaluation, the length of the MVC and histologic microscopic quantity evaluation were used as macroscopic

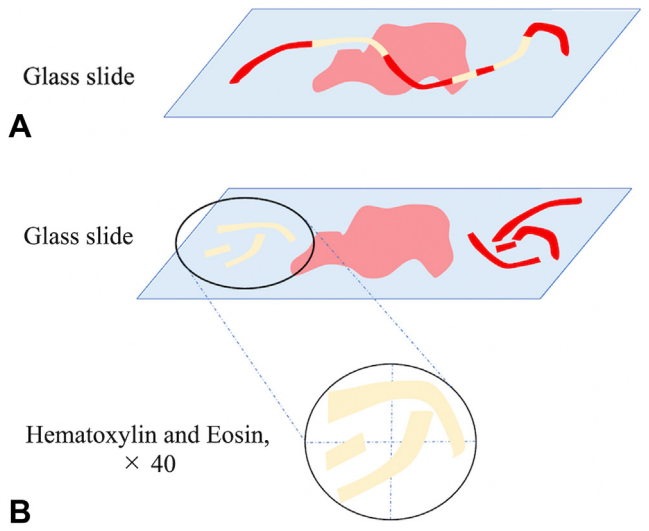


Figure 2. Microscopic histologic quantity evaluation. **A,** The FNA specimen was expelled entirely onto a glass slide. **B,** During sample preparation, each sample obtained by 1 needle pass was divided into a macroscopic visible core and blood clots. The area of the collected tissue fragments was graded according to the percentage of the ×40 field of view: grade 0, none; grade 1, <25%; grade 2, 25% to 50%; grade 3, >50%.

and microscopic findings, respectively. For quality evaluation, macroscopic and microscopic histologic evaluations were used.

Sample size calculations

The sample size was calculated based on prespecified noninferiority margins, considering the crossover design. We assumed the diagnostic sensitivity of EUS-FNB for pancreatic tumors to be 90% to 96% with a noninferiority margin of –10%.[10] A sample size of 96 patients (48 per group) was needed for an α of .05 and a β of .2. Assuming a 10% dropout rate, a final sample size of 110 patients (55 per group) was estimated to be required.

Statistical analysis

Categorical variables are summarized using frequencies and quantitative variables using medians and interquartile ranges. The χ^2 test or Fisher exact test for categorical variables and the *t* test or Wilcoxon rank-sum test for continuous variables were used where appropriate to compare baseline demographics and the EUS-FNB procedure.

To assess the noninferiority of EUS-FNB for pancreatic tumors at 3 rounds over 12 conventional round trips, we estimated the 95% confidence interval (CI) of the difference in accuracy using generalized estimating equations. A noninferiority margin of 10% based on clinical judgment was set, and if the upper limit of the CI was within that range, it was evaluated as noninferior. Statistical analyses were performed using the R (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria) and JMP software (version 15; SAS Institute, Inc, Cary, NC, USA). A $P < .05$ indicated statistical significance.

RESULTS

Two hundred twenty consecutive patients (3-TAF group, 110; 12-TAF group, 110) were enrolled in the study between January and September 2020, with follow-up completed in March 2021 (Fig. 1). The median patient age was 73 years (range, 40-88), and 61 patients (55.5%) were men. The lesions were located in the pancreatic head of 46 patients and in the pancreatic body and tail of 74 patients. Transgastric, duodenal bulb, and the second part of the duodenum puncture routes were performed in 70, 22, and 18 patients, respectively. The median lesion size (largest diameter) was 29.4 mm (range, 9.9-62.7).

There were no significant differences in patient demographics and lesion characteristics between the 2 groups (Table 1). The final lesion diagnoses were 97 ductal adenocarcinomas; 6 neuroendocrine tumors; 5 patients had no evidence of malignancy, such as mass-forming pancreatitis; 1 malignant lymphoma; and 1 metastatic pancreatic tumor derived from lung cancer (Table 2).

Diagnostic yields

The diagnostic sensitivity of the 3-TAF and 12-TAF groups was 88.6% and 89.5%, respectively. The diagnostic sensitivity of the 3-TAF group was not inferior to that of the 12-TAF group because the lower limit of the CI for the absolute difference was greater than the prespecified noninferiority margin of –10% (difference, –.9%; 95% CI, –9.81 to 7.86) (Table 3, Fig. 3). Similar results were also obtained regarding diagnostic accuracy (3-TAF group, 92.7%; 12-TAF group, 94.6%), with an absolute difference greater than –10% (difference, –1.9%; 95% CI, –8.99 to 5.11) (Table 3).

Qualitative and quantitative evaluations of FNB specimens

The results of the qualitative and quantitative evaluations of the FNB specimens are presented in Table 4. For quantitative evaluation, the length of the MVC and histologic microscopic quantity evaluation were used as macroscopic and microscopic findings, respectively. The overall median length of the MVC was 13.5 mm (range, 8-20) in the 3-TAF group and 13.5 mm (range, 9-22) in the 12-TAF group. For histologic microscopic quantity evaluation, grade ≥3 in the 3-TAF and 12-TAF groups was 88.2% and 83.6%, respectively. There were no significant differences in qualitative evaluations between the 2 groups.

For qualitative evaluation, macroscopic and microscopic histologic evaluations were used. The 3-TAF group had a significantly higher rate of score ≥3 on histologic macroscopic quantity evaluation than the 12-TAF group (71.8%

TABLE 1. Characteristics of the enrolled patients

Characteristics	All patients (n = 110)	3 to-and-fro movements first group (n = 55)	12 to-and-fro movements first group (n = 55)	*P* value
Age, y	73 (40-88)	74 (48-88)	72 (40-86)	.386
Sex, male/female	61/49	30/25	31/24	.848
Eastern Cooperative Oncology Group performance status score.				.349
0	76	35	41	
1	26	14	12	
2	6	5	1	
3	2	1	1	
Site of lesion				.439
Pancreatic body and tail	74	30	34	
Pancreatic head	46	25	21	
Puncture route				.428
Transgastric	70	33	37	
Duodenal bulb	22	12	10	
Second part of the duodenum	18	10	8	
Lesion size, mm	29.4 (9.9-62.7)	31 (13.2-62.7)	28 (9.9-59)	.593
Lesion size				.593
0-20 mm	20	8	12	
21-40 mm	71	41	30	
41-60 mm	18	5	13	
61+ mm	1	1	0	

Values are median (interquartile range) or n.

TABLE 2. Final diagnosis of the lesions

Diagnosis	No. of cases
Ductal adenocarcinoma	97
Neuroendocrine tumor	6
Malignant lymphoma	1
Metastatic pancreatic tumor derived from lung cancer	1
No evidence of malignancy	5
Total	110

TABLE 3. Comparison of diagnostic results

	3 strokes (n = 110)	12 strokes (n = 110)	Absolute difference (95% confidence interval)
Diagnostic sensitivity, %	88.6	89.5	–.9 (–9.81 to 7.86)
Diagnostic accuracy, %	92.7	94.6	–1.9 (–8.99 to 5.11)

3-TAF group vs 50.0% 12-TAF group, $P = .009$). However, there were no significant differences in the rate of grade ≥2 in microscopic quantity evaluation between the 2 groups (90.0% 3-TAF group vs 89.1% 12-TAF group).

We also evaluated whether the quantity and quality of the specimens differed according to the order in which the lesions were punctured. In the quantity and quality evaluation, no significant differences between the first

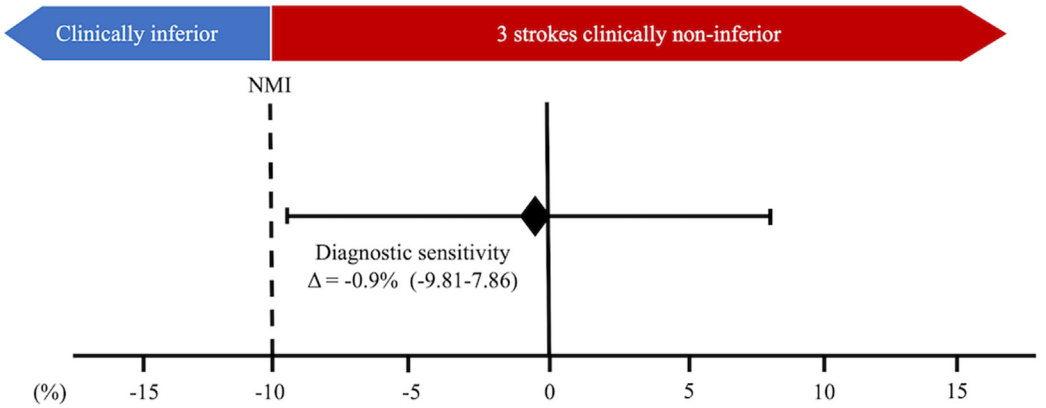


Figure 3. Noninferiority analysis for diagnostic sensitivity of 3 to-and-fro movements (TAFs) compared with 12 TAFs during EUS-FNA of solid pancreatic masses. *NMI*, Noninferiority margin.

and second punctures were found for either 3 TAFs or 12 TAFs.

DISCUSSION

Several studies have previously evaluated the optimal number of needle passes into pancreatic lesions for a correct diagnosis of pancreatic cancer using EUS-FNA.[9,11-14] However, reports have been few regarding the optimal number of TAFs in the lesions at each needle puncture during EUS-FNA.[15,16]

Percutaneous needle biopsy sampling is a popular technique to obtain pathologic samples and to make a diagnosis in several organs such as the liver, kidney, breast, prostate, and thyroid gland. During the procedure, pathologic specimens are generally obtained by a single forward movement without TAFs in most organs.[17-22] In recent years, biopsy guns are favorably used for percutaneous liver biopsy, which take a tissue sample using a single, quick, forward motion.[23] Moreover, sufficient tissue volume has been obtained by puncture using 1 TAF or 3 TAFs in EUS-guided liver biopsy.[16,24] In contrast, 10 to 20 TAFs at each needle puncture have been performed since the initial report of EUS-FNA for pancreatic lesions.[25-27] This might be because of the difficulty encountered when obtaining tissue samples from desmoplastic lesions such as pancreatic cancer.

Originally, we preferred a large-diameter needle (19-gauge) for EUS-FNA to obtain sufficient volume of pathologic samples for histopathologic diagnosis, because most Japanese pathologists prefer histologic diagnosis over cytologic diagnosis. During this procedure, relatively fewer TAFs are made, usually 5 or 6, because an excessive number of TAFs is associated with blood contamination and cellular damage in EUS-FNA. Even by such a method, however, sufficient tissue samples could be collected, and pathologic diagnosis could be confirmed in most cases, including lymphoma cases.[4-6,28,29] Recently, FNB needles have emerged and have been preferably used in clinical practice, because they can easily obtain a larger volume of tissue samples than conventional FNA needles.[30] We also reported that a 22-gauge FNB needle (Franseen needle) yielded comparable tissue collection as a 19-gauge conventional FNA needle.[31] In addition, our study revealed that a 22-gauge FNB needle allowed adequate tissue acquisition even with fewer TAFs.[32] A recent randomized controlled trial also showed high diagnostic sensitivity in EUS-FNA using negative pressure regardless of the number of strokes, leading us to believe that fewer TAFs may reduce blood contamination and cell damage while maintaining diagnostic performance.[15]

To validate the hypothesis that fewer TAFs are sufficient to obtain histopathologic samples during EUS-FNB using a 22-gauge Franseen needle, we conducted a randomized controlled trial to compare the diagnostic yield of EUS-FNB with 3 TAFs and 12 TAFs. As a result, the diagnostic sensitivity and accuracy of EUS-FNB with 3 TAFs were comparable with that of 12 TAFs. The macroscopic quantity, namely the length of the MCV, was also comparable between the 2 groups, and the macroscopic quality was better in the 3-TAF group than in the 12-TAF group. The microscopic quantity and quality of tissue samples of the 3-TAF group were also comparable with those of the 12-TAF group. The higher score of the 3-TAF group in the macroscopic quality evaluation suggested less blood contamination in the sample.

Such reduced blood contamination in the samples may offer several advantages. In the MOSE process, samples obtained by EUS-FNB are carefully examined for the presence of MVCs, which are usually scattered among blood clots. Then, the MVCs are collected separately from blood clots and are placed into a formalin bottle. Therefore, less blood contamination in FNB samples can facilitate MOSE. This may also be helpful for the pathologist because blood contamination can disturb pathologic interpretation.

TABLE 4. Quality and quantity evaluation of EUS-guided fine-needle biopsy sampling pathologic samples

	3 to-and-fro movements			12 to-and-fro movements		
	All (n = 110)	First pass (n = 55)	Second pass (n = 55)	All (n = 110)	First pass (n = 55)	Second pass (n = 55)
Quantity evaluation						
Median length of the macroscopically visible core, mm (interquartile range)	13.5 (8-20)	12.0 (7-20)	14.0 (10-20)	13.5 (9-22)	15.0 (10-22)	13.0 (8-22)
Microscopic quantity evaluation of histopathologic sample (grade ≥3), %	88.2	87.3	89.1	83.6	78.2	89.1
Quality evaluation						
Macroscopic visual quality evaluation of histopathologic sample (score ≥3), %	71.8*	70.1	72.7	50.0*	47.2	52.7
Microscopic quality evaluation of histopathologic sample (grade ≥2), %	90.0	90.9	89.1	89.1	87.3	90.9

*$P = .0009$

Furthermore, fewer TAFs can reduce the procedure time and the risk of blood leakage from the puncture site.

Our study has several limitations that should be acknowledged. First, this study was not designed as a double-blinded protocol. For this study's protocol, it was difficult to blind the operators to whether the number of TAFs was 3 or 12. Therefore, only the pathologists were blinded to the number of TAFs. Second, the final diagnosis was not always determined based on the surgically resected specimens; in some cases, the final diagnosis was based on the EUS-FNB results and on clinical follow-up. Therefore, the diagnostic results might include the potential risk of misclassification. However, most cases (88%) in this study were diagnosed as ductal adenocarcinomas, and 5% of them were diagnosed as neuroendocrine tumors by EUS-FNB. In such malignant cases, false positives are generally rare. Only 5 cases were finally diagnosed as benign by EUS-FNB and follow-up results. Therefore, the potential risk of misdiagnosis only minimally affected the comparative data assessment. Third, the rate of adverse events could not be compared between the 2 groups because this study was conducted by a crossover design, and all cases underwent both 3 and 12 TAFs. Fourth, the number of subjects included was relatively small. In this study, the sample size was calculated based on prespecified noninferiority margins, considering the crossover design; finally, a sample size of 110 patients (55 per group) was estimated to be required. More cases would have been needed if the crossover design had not been used, which is another limitation of this study.

In conclusion, this study demonstrated noninferiority of the diagnostic sensitivity of EUS-FNB with 3 TAFs compared with EUS-FNB with 12 TAFs for solid pancreatic lesions. In addition, the 3-TAF group showed significantly less blood contamination in the pathologic samples than the 12-TAF group. Less blood contamination in the sample may facilitate specimen processing and may reduce the pathologists' burden.

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Abbreviations: CI, confidence interval; EUS-FNA, EUS-guided FNA; EUS-FNB, EUS-guided fine-needle biopsy sampling; MOSE, macroscopic on-site evaluation; MVC, macroscopically visible core; TAF, to-and-fro movement; TUH, Toyama University Hospital.

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