Title page

Title: Diagnostic performance of endoscopic ultrasound-guided tissue acquisition by EUS-FNA versus EUS-FNB for solid pancreatic mass without ROSE: A retrospective study.

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Short title: Diagnostic performance of EUS-TA by FNA vs FNB for solid pancreatic mass without ROSE.

Diagnostic performance of endoscopic ultrasound-guided tissue acquisition by EUS-FNA versus EUS-FNB for solid pancreatic mass without ROSE: A retrospective study.

Abstract.

Background: Endoscopic ultrasound-guided tissue acquisition (EUS-TA) is an established diagnostic procedure for solid pancreatic mass. However, the diagnostic yield between fine-needle aspiration (FNA) and fine-needle biopsy (FNB) remains unclear. Thus, we aimed to evaluate and compare the diagnostic yields between FNA and FNB using conventional FNA and Franseen needles of the same size (22 gauge), respectively, in patients with solid pancreatic mass who underwent EUS-TA without rapid onsite cytopathology evaluation (ROSE).

Methods: All cases of EUS-TA by FNA or FNB for solid pancreatic mass between January 2017 and October 2020 in a single center university hospital were retrospectively reviewed. The procedure was performed without an onsite cytologist. After macroscopic onsite evaluation (MOSE), the endoscopist finished the procedure. The diagnostic yield and the average number of needle passes between FNB and FNA were then compared.

Results: A total of 151 patients (FNA, n = 77; FNB, n = 74) with solid pancreatic mass detected by cross-sectional imaging underwent EUS-TA. The mean age was 62.3 ± 12.8 years, with 88 (58.3%) males. Age, gender, mass location, tumour size and disease stage from imaging were not significantly different. The diagnostic performance was dramatically higher in EUS-FNB (100%) than in EUS-FNA (89.6%). The mean number of needle passes was clearly fewer in FNB than FNA (2.8 vs. 3.8, $p < 0.001$). The total procedure time was less in FNB (34.7 minutes) than in FNA (41 minutes). The adverse event rate between FNB and FNA was not significantly different.

Conclusions: The diagnostic performance for solid pancreatic mass without ROSE was significantly higher in FNB than in FNA. The number of needle passes and the total procedure time was also lesser in FNB.

Keyword: endoscopic ultrasound-guided tissue acquisition, Fine-needle aspiration, Fine-needle biopsy, Solid pancreatic mass, Franseen needle, Diagnostic performance

Introduction

Pancreatic cancer has an unfavorable prognosis, partly because of delayed diagnosis due to its asymptomatic state in the early stage. Unfortunately, the curative treatment in the advanced stage cancer is already ineffective, with a 5-year survival rate of below 5%. Hence, early diagnosis and treatment of pancreatic cancer are necessary for longer survival.^[1,2]

Endoscopic ultrasound-guided tissue acquisition (EUS-TA) has been the main diagnostic tool for solid pancreatic mass.^[3,4] Currently, EUS-guided fine-needle aspiration (FNA) is the standard procedure for the tissue sampling of solid pancreatic mass, with sensitivity and specificity of 64%-95% and 75%-100% respectively.^[5,6,7,8] However, EUS-FNA often provides small tissue samples and inadequate specimen for definite diagnosis. Optimal EUS-TA depends on many factors, including an experienced endosonographer, needle type and size, tissue sampling technique (stylet slow-pull or standard suction), tumour location, tumour size and rapid onsite cytopathology evaluation (ROSE) availability; in many centers, ROSE is unavailable.^[8] In pancreatic adenocarcinoma, cytology is sufficient for diagnosis; meanwhile, other diseases (such as neuroendocrine tumour, lymphoma, autoimmune pancreatitis, tuberculosis and mass-forming chronic pancreatitis), require core tissue sample and immunohistochemistry staining.^[9] The diagnostic yield reportedly has no significant difference between EUS-FNB using first and second generation biopsy needles and the conventional FNA needles.^[10,11,12] In recent years, the trend of tissue acquisition using third-generation biopsy needles, including forward-facing bevel needles (Procore; COOK Medical, Bloomington, Indiana, USA), fork-tip needles (SharkCore; Medtronic, Dublin, Ireland) and Franseen needles (Acquire; Boston Scientific, Marlborough, Massachusetts, USA), for solid pancreatic mass has changed. This third generation biopsy needle showed a higher histological core tissue specimen for definite diagnosis.^[13,14] Panic N, et al. concluded that EUS-FNB demonstrated better diagnostic yield than EUS-FNA, with fewer needle passes, decreased procedure time and adverse events and increased histopathology yield.^[15] Moreover Rodrigues-Pinto E. et al. concluded that EUS-FNB without ROSE had a higher (90%) diagnostic yield for malignancy than EUS-FNA with ROSE (77.5%), the difference was not statistically significant.^[16] And, Stefano Francesco Crino. Et al. reported that EUS-FNB using new generation FNB needles without ROSE demonstrated comparable diagnostic accuracy EUS-FNB with ROSE in solid pancreatic lesion.^[17]

Currently, the European Society of Gastrointestinal Endoscopy (ESGE) guideline recommends both 25- and 22-gauge needles for the tissue sampling in solid pancreatic mass regardless of the needle type.[8] In Thailand, needle biopsy is more expensive than needle aspiration and unavailable of ROSE. In this retrospective study, we aimed to compare the diagnostic yield between EUS-FNA and EUS-FNB using the same needle size (22-gauge) in patients with solid pancreatic mass without ROSE. The average number of needle passes, the total procedure time and the adverse events were also compared between these of two groups.

Methods

This retrospective single center study enrolled patients with solid pancreatic mass admitted at Songklanagarind Hospital and underwent EUS-TA between January 2017 and October 2020. Specifically, all procedures were performed in Nantana-Kriangkrai Choti Wattanaphan(NKC) Institute of Gastroenterology and Hepatology, a tertiary university hospital in Southern Thailand. Using the hospital's electronic database, we collected patient data including the baseline characteristics, computed tomography (CT) scan, magnetic resonance imaging (MRI) results, endoscopic ultrasound and histopathology report.

The diagnosis of solid pancreatic mass was revealed by a radiologist. A pathologist confirmed the histopathology with adequate tissue sample and specific diagnosis after performing the FNA or FNB.

With patients under conscious sedation, the EUS examination was performed by four experienced endosonographers (TP, NN, JS and BO) using a linear array echoendoscope (GF-UCT/P-180 series; Olympus Medical System CORP, Tokyo, Japan). The EUS procedures were reviewed in the electronic hospital database. All patients with first time experience of FNA or FNB for tissue acquisition in solid pancreatic mass were included.

The inclusion criteria were as follows: 1) Evidence of solid pancreatic mass confirmed by CT scan or MRI; 2) Age >18 years; 3) Technical success of EUS-FNA or EUS-FNB without ROSE; 4) First-time experience of EUS-TA.

The local institutional review board approved this study, and informed consent was obtained from all patients before the procedures.

EUS-FNA or EUS-FNB

EUS was performed using a large-channel linear array echoendoscope (GF-UCT/P-180 series; Olympus Medical System, CORP., Tokyo, Japan) and ultrasound machine (Aloka; model SSD alpha 10, Tokyo, Japan). After the previous abdominal cross-sectional imaging was reviewed, the solid pancreatic mass was identified by endoscopic ultrasound. The decision to perform tissue acquisition was at the discretion of the attending physicians; either the standard suction technique (20 mL, negative pressure) or the stylet slow pull technique, with or without fanning method, was applied in the FNA and FNB procedures. The FNA needle was 22-gauge EZ-Shot (model number NA-200H-8022; Olympus Medical system, CORP., Japan), whereas the FNB needle was a 22-gauge Franseen needle (Acquire; Boston Scientific, USA). The needle was moved backward and forward within the lesion for at least 15 throws. In the NKC institute, ROSE was unavailable for this procedure. Moreover, procedure-related data (total procedure time, needle type, location of tissue acquisition, number of needle passes, number of aspirations per pass and immediate complication) were recorded in the Endo Smart programme. Lastly, glass slides and cell block were sent to Songklanagarind hospital's Anatomical Pathology Center, where they were reviewed by experienced cytopathologists.

FNB and FNA were performed using an aspiration needle (Olympus) and a Franseen biopsy needle (Boston), respectively, both at 22- gauge. The tissue samples were expelled from the needle in a standardized manner. The stylet was firstly introduced at the tip of the needle to expel the tissue sample on the glass slide, followed by flushing the needle with air or normal saline to expel the retained tissue, which called "touch imprint cytology technique".^[18]

The gross tissue specimen was initially evaluated by an endoscopist for adequate tissue sample (white or yellowish tissue). This procedure is known as macroscopic onsite

evaluation (MOSE). The core tissues were collected in 10% neutral buffered formalin, and the draw glass slide was fixed in 95% alcohol solution for cytology.

The adequacy of the tissue sample and the provisional diagnosis were reviewed by a pathologist. The pathological results of 'positive for adenocarcinoma or adenocarcinoma and carcinoma' were considered adenocarcinoma. The pathological results of 'suspicious for malignancy' were reviewed by two pathologists for decision making to diagnosis of malignancy. The results of a specific diagnosis, such as lymphoma, tuberculosis or neuroendocrine tumour, were also reviewed. However, the definite diagnosis of mass-forming chronic pancreatitis was difficult to attain; it required not only a pathological result indicating fibrosis or chronic inflammation without malignant cell suspicion, but also a cross-sectional imaging compatible with chronic pancreatitis and a stable clinical condition without evidence of malignancy on interval cross-sectional imaging after 6 months of follow-up. Meanwhile, the pathological results of unremarkable pancreatic tissue, nonpancreatic elements, atypical pancreatitis or acute pancreatitis were identified as nondiagnostic.

Data collection

We collected the following demographic and clinical characteristics; age, gender, tumour location, initial laboratory data, ECOG status, disease stage (based on cross-sectional imaging), specific diagnosis, diagnostic yield, needle type, EUS procedure time, technical details, complications and the needle and procedure costs.

Statistical analysis

Patient baseline characteristics (demographic, clinical and laboratory data) were compared between the two groups through Wilcoxon for non-normally distributed data and student's *t*-test for normally distributed data. The categorical data were compared by chi-square test or Fisher's exact test. The significant differences between curves, as classified by variable category, were evaluated using the log-rank test for univariate analysis. A $p < 0.05$ was considered statistically significant. Statistical data were analysed using the R programme (Apical package R foundation for statistical computing, 2008).

Results

We included 151 consecutive patients (88 males; mean age, 62.3 ± 12.8 years), with 77 in the EUS-FNA group and 74 in EUS-FNB group. Age, gender, ECOG status and baseline basic laboratory tests were not significantly different between the two groups. Table 1 summarizes the patient's baseline characteristics in each group. The FNB group had slightly higher in advanced stage and unresectable stage compared with the FNA group.

Table1: Demographic characteristics of patients in FNA and FNB group

Variables	EUS-FNA (n = 77)	EUS-FNB (n = 74)	P value
Gender (male), n (%)	46 (60)	42 (57)	0.836
Age (year)*	62.7 ± 12.8	62.3 ± 12.8	0.676
Malignancy, n (%)			
Stage of disease, n (%)			0.049
I	8 (14.5)	4 (9.8)	
II	10 (18.2)	5 (12.2)	
III	23 (41.8)	30 (43.1)	
IV	14 (25.5)	29 (35)	
Unresectable stage, n (%)	40 (72.7)	62 (91.2)	0.014
ECOG status, n (%)			0.569
0	1 (1.3)	2 (2.7)	
1	65 (84.4)	58 (78.4)	
2	10 (13)	13 (17.6)	
3	1 (1.3)	1 (1.3)	
Initial total bilirubin (mg/dL)*	4.7 ± 8.4	6.7 ± 10.6	0.204
Initial platelet count (10^3)*	272 ± 102	318 ± 100	0.006
Initial haematocrit (%)*	36 ± 5.2	35.1 ± 5.3	0.309
Initial PT (seconds)*	13.1 ± 2.5	13.7 ± 4	0.096
Initial INR *	1.2 ± 0.2	1.2 ± 0.3	0.724

*Data are expressed as mean $\pm$ SD, ECOG; Eastern Cooperative Oncology Group, PT; prothrombin time, INR; international normalized ratio

The solid pancreatic masses were mostly located in the pancreatic head in both groups (FNA, 65%; FNB, 47%), and the mean tumour size in each group was 40 mm in the FNA group and 42 mm in the FNB group, with no significant difference (shown in Table.2). Given that most tumours were in the pancreatic head, the transduodenal approach was used in approximately 65%. In addition, the procedure time was significantly lesser in the FNB group (34.7 minutes) than in the FNA group (41 minutes). The mean number of needle passes was also dramatically different between these groups (FNA, 3.7 passes; FNB, 2.8 passes).

Table 2: Baseline tumour characteristics

Variables	EUS-FNA (n = 77)	EUS-FNB (n = 74)	p-value
Tumour size, (mm)*	40 $\pm$ 20	42 $\pm$ 17	0.558
Tumour location (pancreas), n(%)			0.166
- Head	50 (64.9)	35 (47.3)	
- Uncinate process	6 (7.8)	9 (12.2)	
- Body	16 (20.8)	23 (31.1)	
- Tail	4 (5.2)	4 (5.4)	
- > 1 location	1 (1.3)	3 (4)	
Procedure technique, n (%)			0.728
Transgastric approach	25 (32.5)	27 (36.5)	
Transduodenal approach	52 (67.5)	47 (63.5)	
EUS-TA technique, n(%)			1
- Suction	5 (6.5)	4 (5.4)	< 0.01
- Stylet slow-pull	15 (19.5)	64 (86.5)	< 0.01
- Both suction and stylet slow-pull	57 (74)	6 (8.1)	< 0.01
Procedure time, minutes *	41.3 $\pm$ 9.2	34.7 $\pm$ 9.6	< 0.001
Number of needle passes, n*	3.7 $\pm$ 0.6	2.8 $\pm$ 0.6	< 0.001
Number of needle throw /pass, n*	18.9 $\pm$ 1.9	19.5 $\pm$ 2.5	0.079

*Data are expressed as mean $\pm$ SD.

In the NKC Institute, the EUS-TA tissue sample was initially evaluated by an endoscopist for tissue adequacy (white or yellow tissue) before being sent to the pathologist. The appropriate tissue sampling was reported by a pathologist, the FNB group had a higher rate of tissue adequacy (100%) than the FNA group (74%). The pathologist also confirmed the definite diagnosis. In table 3 illustrates cause of solid pancreatic mass was adenocarcinoma followed by pancreatic neuroendocrine tumour, mass-forming chronic pancreatitis, tuberculosis and lymphoma respectively. The diagnostic yield after first time tissue sampling was 100% in the FNB group while 89.6% in the FNA group, indicating a statistically significant difference. Only one patient in the FNB group experienced an adverse event, that is, post-procedure bleeding, which was successfully treated by endoscopic haemostasis. In addition, the FNB needle were significantly more expensive than the FNA needles; thus, the FNB group would subsequently have a higher total procedure cost.

Table 3: Diagnostic performance and complications

Variables	EUS-FNA (n = 74)	EUS-FNB (n = 77)	P value
Diagnostic yield, n (%)	69 (89.6)	74 (100)	0.007
Definite diagnosis, n (%)			0.01
- Pancreatic adenocarcinoma	40 (51.9)	54 (65.7)	
- Pancreatic neuroendocrine tumour	8 (10.4)	5 (9.1)	
- Mass forming chronic pancreatitis	10 (13)	4 (9.8)	
- Pancreatic tuberculosis	2 (2.6)	3 (2.1)	
- Pancreatic lymphoma	4 (5.2)	7 (4.9)	
- Other diseases	5 (6.5)	12 (8.4)	
- Nondiagnostic	8 (10.4)	0 (0)	
Severe adverse event, n(%)	0 (0)	1 (0.7)	0.49
Systemic chemotherapy, n (%)	17 (22)	30 (31)	0.023
Surgical treatment, n (%)	12 (15.6)	7 (9.5)	0.374
Cost, (USD) *			
EUS procedure cost	322 $\pm$ 4.6	325 $\pm$ 0.9	< 0.001
Needle cost	245 $\pm$ 45	400 $\pm$ 37.1	< 0.001
Total procedure cost	567 $\pm$ 45	725 $\pm$ 37.7	< 0.001

*Data are expressed as mean $\pm$ SD.

Furthermore, several factors could potentially confound the diagnostic yield. The tumour size ≥ 40 mm showed a diagnostic performance of 100% in both FNA and FNB needles. However, the tumour size < 40 mm showed a significantly lesser diagnostic yield in FNA than in FNB (shown in Table.4). Meanwhile, the tumour location was not associated with diagnostic performance between such groups. However, the location of tumour at the pancreatic head might have a slightly lesser diagnostic yield in the FNA group than in the FNB group.

Table 4: Factors associated with the diagnostic yield

Variables	EUS FNA (n = 77)	EUS FNB (n = 74)	P value
Tumour size, n (%)			0.006*
- ≤ 4 cm	39/47 (83%)	43/43 (100%)	
- > 4 cm	30/30 (100%)	31/31 (100%)	
Tumour location			
Head	45/50 (90%)	35/35 (100%)	0.074
Uncinate process	5/6 (83.3%)	9/9 (100%)	0.4
Body	15/16 (93.75%)	23/23 (100%)	0.41
Tail	3/4 (75%)	4/4 (100%)	1
> 1 location	1/1 (100%)	3/3 (100%)	1

*Fisher's-exact test.

Discussion

The pathological diagnosis of solid pancreatic mass has a crucial role in achieving definite diagnosis and early proper management, which correlates with prognosis in patients with cancer. Adequate tissue sampling might improve the diagnosis and avoid unnecessary surgery in some conditions, including autoimmune pancreatitis, lymphoma and tuberculosis.^[9,19,20] The EUS guided core needle biopsy has been designed for larger tissue samples, leading to good architecture and histological assessment. In addition, the pathologist can conduct immunohistochemistry staining or genetic testing in solid or haematologic malignancy, however, these procedures can be challenging in FNA.^[13]

In this study, we evaluated the diagnostic yield of EUS-TA by either FNA or FNB (FNA and FNB use different needle types) without ROSE in patients with solid pancreatic mass lesion detect by cross-sectional imaging. The Franseen (Acquire) FNB needle, which is a third-generation biopsy needle, had significantly higher diagnostic yield than the FNA needle (100% vs. 89.6%). In previous reports, the diagnostic yields of EUS-TA without ROSE by FNA were 70%, 81% and 82%, whereas those by FNB were 70%, 89.9% and 89%, respectively.^[10,14,21,22] However, in several studies, EUS-TA with ROSE increased the diagnostic performance to 77.5% and 80% in FNA and 87% and 90% in FNB, respectively.^[16,23] In our study, tissue acquisition was evaluated in a tertiary hospital, with the aspiration and biopsy needles having the same size (22-gauge); the endoscopists' level of experience and tissue sampling techniques were also not different according to the institute's guidelines. Recent studies and recommendations showed that ROSE availability helps achieve the highest specific diagnosis in both needles. Unfortunately, most centres in Thailand have no onsite cytopathologists.

Additionally, the number of needle passes for tissue sampling on solid pancreatic mass by FNB was significantly reduced; the mean number of passes in the FNB and FNA groups was 2.8 and 3.7, respectively. Moreover, the total procedure time was significantly higher when using the FNA needle (41 minutes) than when using the FNB needle (34.7 minutes). The tissue acquisition technique was performed according to the discretion of the endoscopist, aiming to achieve the white core tissue, which can increase confidence in tissue adequacy and procedure completion. These findings are consistent with the recent studies, which reported that the FNB with different core needles had a significantly fewer number of passes than the FNA.^[22,24] Additionally, minor bleeding after tissue acquisition occurred in only one patient in the FNB groups and was successfully treated by endoscopic haemostasis. The complication rate of EUS-FNA is approximately 1%-2%.^[25] Moreover, the adverse event rate was comparable between the EUS-FNB and the EUS-FNA.^[26]

The ESGE guideline recommends both 25 and 22-gauge needle sizes for the tissue sampling of solid pancreatic mass regardless of the needle type.^[8] In a previous meta-analysis, the diagnostic sensitivity and specificity in both 25 and 22-gauge FNA needles were comparable.^[27] The needle type (fork-tip shape or Franseen needle) used in FNB was not significantly different in diagnostic accuracy,^[28] while the needle type used in FNA was also not significantly different in diagnosis accuracy or sampling adequacy.^[29] In addition, ROSE is reportedly a significant predictor of accuracy (OR, 2.6; 95% CI, 1.41-4.79).^[23] In a multicentre retrospective study of comparing 22-gauge Sharkcore needle and 22-gauge FNA needle in patients with solid pancreatic mass with ROSE availability, the diagnostic performance was not significantly different between the two needles, but the number of needle passes was fewer in the FNB group.^[12,30] Hence, for endoscopic centres without available of ROSE, the benefits of EUS-FNB for tissue acquisition in solid pancreatic mass might outweigh those of EUS-FNA in term of tissue sample adequacy, specific diagnosis, reduction in the number of passes and the total procedure time, which was support by a recent report.^[17] This study illustrated that the FNB needles achieved a higher diagnostic yield than the FNA needles in limited resource of onsite cytologist centre. The factors associated with unfavorable outcomes in the FNA group were tumour size < 40 mm and tumour location at the pancreatic head. Hence, if the tumour size is larger than 40 mm and

not located in the pancreatic head, the diagnostic yields might be comparable between the FNA and FNB needle without available of ROSE country.

The total cost of the EUS-TA was higher in the FNB group than in the FNA group by approximately 150 USD. The reason is that the price of all biopsy needles in Thailand is higher than that of FNA needles by approximately 150-200 USD; thus, the total procedure cost in EUS-TA with FNB is higher.

This study showed that the diagnostic yield of solid pancreatic lesion was higher when using the Franseen FNB needle for tissue acquisition than when using the conventional FNA needle. In addition, the number of passes and the total procedure time was significantly reduced in the FNB group. Although the total cost of EUS-FNB was considerably higher than that of EUS-FNA, patients achieved early specific diagnosis and early treatment, especially those with malignancy, when EUS-FNB was applied. In nondiagnosis, patients needed repeat EUS-TA procedure, causing delayed diagnosis and may higher total procedure cost.

Our study was performed in a tertiary university hospital and included patients with solid pancreatic mass initially assessed by cross-sectional imaging. All of the patients underwent EUS-TA through FNA or FNB using the same needle size (22-gauge); the FNB and FNA groups had similar baseline characteristics. However, in Thailand, ROSE was unavailable and some patients such as tuberculosis and lymphoma of the pancreas require core tissue and culture for definite diagnosis. Meanwhile, our study encourage to use of biopsy needle for tissue acquisition in solid pancreatic mass for early and definite diagnosis in country limited of ROSE, especially in tumor size less than 40 mm and disease location at head of pancreas. The limitation of this study is the retrospective design and the uncontrollable factors such as the tissue acquisition technique and MOSE definition.

Conclusion

The diagnostic yield of solid pancreatic mass was significantly higher in FNB using the Franseen needle than FNA using the conventional FNA needle, without ROSE. In addition, FNB had fewer needle passes and lesser the total procedure time.

Abbreviations

1. EUS: endoscopic ultrasonography
2. TA: Tissue acquisition
3. FNA: Fine needle aspiration
4. FNB: Fine needle biopsy
5. ROSE: rapid onsite evaluation
6. MOSE: macroscopic onsite evaluation
7. ECOG: Eastern Cooperative Oncology Group
8. MRI: Magnetic resonance imaging
9. CT scan: computerized tomography scan

Declarations

Ethical approval and consent to participate

This study was approved by the Ethic Committees of The Faculty of Medicine, Prince of Songkla University with approval number REC. 63-203-21-1 and written informed consent was obtained from the patient. This committee adheres to the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization in Good Clinical Practice.

Consent for publication

Written informed consent was obtained from the patient for publication. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

Availability of data and materials: Due to ethical restrictions, the dataset related to current study are available upon request to the corresponding author.

Completing interests: The authors declare that we have no completing interests.

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Author contributions: TW have made substantial contribution to the conception and design of the study, data collection as well as manuscript writing. TP have made contributions to the design of the study, data analysis and also manuscript writing. NN, BO and JS performed and completely reported endoscopic EUS-TA data. NC, PS, SJ, AK have made a contributions to analysis and interpretation of data. Teerha Piravisuth has made contributions to manuscript writing and English language approving. Thanawin Wong is the first author. Tanawat Pattapuntakul is corresponding author, and responsible for ensuring that all listed authors have approved the manuscript before submission. All authors read and approved the final manuscript.

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Table Legends.

Table1. Demographic characteristics of patients in FNA and FNB group

Table 2. Baseline tumour characteristics

Table 3. Diagnostic performance and complications

Table 4. Factors associated with the diagnostic yield