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Diagnostic performance of EUS-guided tissue acquisition for solid pancreatic lesions ≤10 mm

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ABSTRACT

Background and Objectives: EUS tissue acquisition (EUS-TA) is the standard diagnostic method for solid pancreatic lesions (SPLs); however, there are few reports on EUS-TA results for SPLs ≤10 mm. Furthermore, given the recent advent of fine-needle biopsy, the current diagnostic accuracy of EUS-TA for SPLs ≤10 mm is unknown. This study aimed to evaluate the diagnostic accuracy and efficacy of EUS-TA for SPLs ≤10 mm.

Methods: We retrospectively analyzed the data of 109 patients with SPLs ≤10 mm who underwent EUS-TA. All patients underwent rapid on-site specimen evaluation.

Results: The median tumor diameter was 8 mm (range, 2.5–10 mm), and the technical success rate was 99.1% (108/109). Adverse events were observed in 3 patients (2.8%). The diagnostic performance was as follows: sensitivity, 90.1% (64/71); specificity, 97.3% (36/37); accuracy, 92.6% (100/108); positive predictive value, 98.5% (64/65); and negative predictive value, 83.7% (36/43). Multivariate analysis revealed that the number of punctures (odds ratio, 7.03; 95% confidence interval, 1.32–37.5; $P = 0.023$) and tumor type (odds ratio, 11.90; 95% confidence interval, 1.38–102.0; $P = 0.024$) were independent risk factors for inaccurate EUS-TA results. The diagnostic accuracy of EUS-TA for pancreatic ductal adenocarcinoma was 87.5% (14/16). No EUS-TA–related needle-tract seeding was observed in patients with pancreatic ductal adenocarcinoma during the observation period.

Conclusions: EUS-TA for SPLs ≤10 mm showed adequate diagnostic accuracy and was safe for use with rapid on-site specimen evaluation in all cases.

Keywords: Adverse events; Diagnostic accuracy; EUS-guided tissue acquisition; Fine-needle biopsy; Solid pancreatic lesion

INTRODUCTION

EUS tissue acquisition (EUS-TA) has become the standard diagnostic method for solid pancreatic lesions (SPLs), with an overall diagnostic accuracy of 89.7% to 96.2%.[1,2] In recent years, with advances in various imaging modalities such as computed tomography (CT), magnetic resonance imaging, and EUS, as well as the widespread use of EUS-TA, the number of cases diagnosed as pancreatic cancer and nonfunctional small pancreatic neuroendocrine tumors (NETs) has been increasing.[3–5] For pancreatic NETs, which are common among SPLs ≤10 mm, an accurate histopathological diagnosis with immunostaining is essential for grading and determining a treatment plan.

Currently, only 6 studies have reported on the diagnostic performance of EUS-TA for SPLs ≤10 mm, indicating a diagnostic accuracy of 73.3% to 96.0% when combined with cytology and histology, which is lower than the overall EUS-TA accuracy.[6–11] However, the number of lesions in each of the aforementioned studies was small, ranging from 11 to 40. Furthermore, only one of the aforementioned studies reported the histological diagnostic accuracy of EUS-TA for SPLs ≤10 mm, which at 64.3% was even lower than that for combined cytological diagnosis and for lesions >10 mm.[7] In addition, a meta-analysis of the diagnostic accuracy of EUS-TA according to lesion size revealed significantly lower diagnostic accuracy for lesions ≤10 mm than for lesions >10 mm (odds ratio [OR], 3.27; 95% confidence interval [CI], 1.55–6.89; $P < 0.01$).[12] However, with the advent of fine-needle biopsy (FNB) and improvements in puncture needles in recent years, the diagnostic accuracy of EUS-TA for small lesions is considered to have improved. However, there are few reports on EUS-TA results for SPLs ≤10 mm, and the current diagnostic accuracy for SPLs ≤10 mm is unclear.

Therefore, we aimed to evaluate the recent diagnostic accuracy and efficacy of EUS-TA for SPLs ≤10 mm.

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PATIENTS AND METHODS

Patients

We retrospectively analyzed patients with SPLs ≤10 mm who underwent EUS-TA from November 2017 to September 2022. The selection flowchart is shown in Figure 1. During the study period, EUS-TA was attempted in 1790 lesions; among them, 456 (25.5%) were excluded because of extrapancreatic lesions. Among the remaining 1334 lesions, 1225 (91.8%) were >10 mm and thus were excluded. Finally, 109 (8.2%) SPLs ≤10 mm for which EUS-TA was attempted were included in this study. None of the included SPLs were symptomless, and they were observed on CT, magnetic resonance imaging, or abdominal ultrasound performed during medical check-ups or screening for other diseases. All patients underwent contrast-enhanced CT before EUS-TA; magnetic resonance imaging was performed if cystic lesions were suspected based on CT results.

EUS tissue acquisition

All patients underwent elastography before EUS-TA, and contrast-enhanced EUS was performed when necessary. If cystic lesions were suspected, EUS-TA was not indicated. Contrast-enhanced EUS was also used to identify small NETs and cystic contents, which are difficult to identify, as an auxiliary diagnosis. All EUS-TA procedures were performed using rapid on-site specimen evaluation (ROSE) to determine the puncture site and to decide on the completion of specimen collection. Identical EUS devices were used in all cases, including the EUS scope (UCT-260; Olympus Medical Systems, Tokyo, Japan) and ultrasonic observation equipment (EU-ME2; Olympus Medical Systems). The first choice of needle type and aspiration method was fine-needle aspiration (FNA) with a 22-gauge needle without a side trap (EZshot3plus; Olympus Medical Systems) and 20-mL negative pressure from September 2017 to December 2020 and FNB (Franseen needle [Acquire, Boston Scientific Corporation, Marlborough, Mass; TopGain, Medi-Globe, Achenmuhle, Germany], fork-tip needle [SharkCore; Medtronic Corporation, Newton, Mass]) with the slow pull method starting in January 2021. For resectable lesions, 22-gauge FNA/FNB was the first choice of needle size, giving priority to a benign or malignant diagnosis. For unresectable lesions, 22-gauge FNB was the first choice, although 19-gauge FNB was selected when comprehensive cancer genome profiling was considered. The final choice of puncture needle type (FNA/FNB) and gauge was made at the discretion of the endoscopist, prioritizing safety in each case. The endoscopist who performed the EUS-TA, the cytologist who performed the ROSE, and the pathologist who made the final diagnosis were specialists with sufficient experience in the pancreatic field. Even when a trainee performed the EUS-TA, it was supervised by an endoscopist with ≥5 years of EUS experience and who had performed ≥100 cases of EUS-TA; the supervising endoscopist also performed the final puncture. The pathologist made the diagnosis based not only on EUS-TA specimen pathology but also on the endoscopist's suspected diagnosis and other modalities. All patients underwent EUS-TA on admission, and a blood examination was performed 2 hours after the procedure, followed by a physical examination for the incidence of adverse events.

Outcome measures

The primary endpoint was the diagnostic performance (technical success rate, diagnostic accuracy, adverse events, and pathologic results) of EUS-TA for SPLs ≤10 mm. The secondary endpoint included factors contributing to the diagnostic inaccuracy of EUS-TA.

Definitions

In the present study, pathological diagnoses of EUS-TA specimens were based on both histological and cytological findings. When multiple types of puncture needles were used, the puncture needle type (FNA/FNB) and gauge (19/22/25) that finally yielded atypical cells or sufficient tissue for ROSE were used for analysis. Tumor diameter was the largest diameter of the lesion measured on EUS at the time of the EUS-TA attempt. The technical success rate was defined as the percentage of lesions for which EUS-TA was attempted and that could be punctured. The diagnostic accuracy of EUS-TA was defined as the percentage of lesions for which EUS-TA was performed and a pathologically confirmed diagnosis was obtained. Malignancy on EUS-TA was defined as malignancy or suspected malignancy on histological diagnosis and suspected or definitive

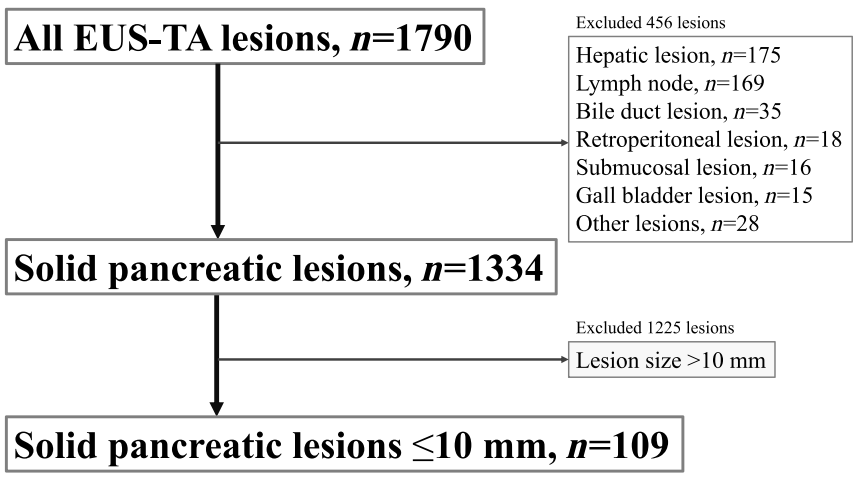

Figure 1. Study flowchart. EUS-TA: EUS-guided tissue acquisition.

malignant cells on cytological diagnosis. The final diagnosis was defined as a definitive diagnosis of malignancy obtained from a surgically resected specimen or clinical/imaging findings of malignancy obtained during follow-up. Malignancies were defined as diseases with a potentially malignant course, including NETs, solid pseudopapillary neoplasms (SPNs), perivascular epithelioid cell tumors (PEComas), and pancreatic cancer. In EUS diagnosis, "benign" was characterized by the inclusion of individuals diagnosed with benign diseases, such as inflammation, as well as those with only normal pancreatic tissue (no malignancy). "Benign at final diagnosis" was defined as a confirmed diagnosis of a benign disease on surgical specimens or a confirmed diagnosis of a benign disease based on clinical and imaging findings during a follow-up period of at least 6 months after EUS-TA. The staging of pancreatic cancer was based on the TNM classification of malignant tumors, eighth edition, by the Union for International Cancer Control.[13]

Adverse events were defined according to the classification of endoscopic adverse events described by the American Society for Gastrointestinal Endoscopy.[14] The follow-up period was defined as the period between EUS-TA and the last imaging examination.

Statistical analyses

Continuous variables are presented as medians and ranges and categorical variables as proportions. Univariate analyses were performed using the χ^2 or Fisher exact test for categorical variables and the Mann-Whitney U test for continuous variables. Values of $P < 0.05$ were considered to indicate statistical significance. Multivariate analysis was performed using a logistic regression model; factors with $P < 0.05$ in the univariate analysis were entered into the multivariate model. All data analyses were performed using IBM SPSS Statistics for Macintosh (version 22.0; IBM Corp, Armonk, NY).

Table 1

Clinical characteristics and EUS-TA results of the study population.

Variables	*n* = 109
Median age (range),[a] y	63 (29–86)
Male sex, *n* (%)	59 (53.6)
Median tumor size (range), mm	8 (2.5–10)
Tumor location, *n* (%)	
Pancreatic head	34 (31.2)
Pancreatic body	25 (22.9)
Pancreatic tail	50 (45.9)
Needle type, *n* (%)	
EUS-FNA	64 (58.7)
EUS-FNB	45 (41.3)
Needle size, *n* (%)	
19-Gauge	1 (0.9)
22-Gauge	102 (93.6)
25-Gauge	6 (5.5)
Mean no. of passes for EUS-TA (IQR)	3 (2–4)
Technical success rate, % (*n*)	99.1 (108/109)
Adverse events, *n* (%)	3 (2.8)
Moderate bleeding	2
Mild pancreatitis	1
Median follow-up period after EUS-TA (range), d	745 (112–2117)

[a] Age at which EUS-TA was performed.

EUS-FNA/FNB: EUS fine-needle aspiration/biopsy; EUS-TA: EUS tissue acquisition; IQR: Interquartile range.

Ethics approval

This study was approved by the National Cancer Center Institutional Review Board (no. 2108-149) and conformed to the provisions of the Declaration of Helsinki (revised in Fortaleza, Brazil, in October 2013). With approval from the National Cancer Center Institutional Review Board (no. 2108-149), informed consent was obtained through an opt-out method. In this method, instead of obtaining written consent from each individual, the research content was disclosed on a web homepage, and the opportunity to refuse participation in the research was provided; no patient refused participation in the present study.

RESULTS

Patient background characteristics and EUS-TA outcomes

The clinical characteristics of the 109 patients are shown in Table 1. The median tumor diameter was 8 mm (range, 2.5–10 mm). Tumor localization was as follows: pancreatic head, 34 (31.2%) lesions; pancreatic body, 25 (22.9%); and pancreatic tail, 50 (45.9%). All cases comprised single lesions, with no overlapping lesions. No distant metastases were observed when performing EUS-TA. EUS-TA was performed using FNA in 64 lesions (58.7%) and FNB in 45 lesions (41.3%) and with a 19-gauge needle in 1 lesion (0.9%), 22-gauge needle in 102 lesions (93.6%), and 25-gauge in 6 lesions (5.5%). The median number of punctures was 3 (interquartile range 2–4). A 22-gauge needle was not sufficient to obtain a specimen in the one lesion that required a 19-gauge needle; hence, the latter was used. The technical success rate was 99.1% (108/109). One lesion could not be punctured because of an unavoidable splenic artery. Adverse events were observed in 3 patients (2.8%): moderate bleeding in 2 patients (22-gauge FNA and FNB), and mild pancreatitis in 1 patient (22-gauge FNB). The lesions with bleeding showed active bleeding on contrast-enhanced CT and required interventional radiology hemostasis. The median follow-up period after EUS-TA was 747.5 days (range, 112–2117 days).

Pathological diagnosis by EUS-TA

The pathological diagnosis by EUS-TA for 108 lesions that were technically puncturable was as follows: NET, 42 (38.9%) lesions; pancreatic ductal adenocarcinoma (PDAC), 15 (13.9%); metastatic tumor, 4 (3.7%) (1 lesion each of lung cancer, colon cancer, breast cancer, and sarcoma); intrapancreatic accessory spleen, 4 (3.7%); SPN, 3 (2.8%); serous cystic neoplasm (SCN), 2 (1.9%); chronic pancreatitis, 2 (1.9%); PEComa, 1 (0.9%); and no malignancy, 35 (32.4%) (Table 2). In all cases, there were no discrepancies between the cytological and histological diagnoses of benign and malignant diseases. All patients with PDAC were at clinical stage IA with no lymph node and distant metastasis. A comparison between the 28 lesions diagnosed as nonmalignant and the 80 lesions diagnosed as malignant showed no significant differences in age, sex, median tumor diameter, needle type, needle diameter, or mean number of punctures. However, there was a trend suggesting a higher prevalence of nonmalignant cases in lesions located in the pancreatic head compared with those in the pancreatic tail (Table 3).

Table 2

Pathological results of EUS-TA of SPLs ≤10 mm, *n* (%).

Pathological results	*n* (%) (Total *n* = 108)
Neuroendocrine tumor	42 (38.9)
Pancreatic ductal adenocarcinoma	15 (13.9)
clinical stage IA	15 (100)
Metastatic tumor	4 (3.7)
Lung carcinoma	1 (25)
Colorectal carcinoma	1 (25)
Breast carcinoma	1 (25)
Sarcoma	1 (25)
Intrapancreatic accessory spleen	4 (3.7)
SPN	3 (2.8)
SCN	2 (1.9)
Chronic pancreatitis	2 (1.9)
PEComa	1 (0.9)
No malignancy	35 (32.4)

EUS-TA: EUS tissue acquisition; PEComa: Perivascular epithelioid cell tumor; SCN: Serous cystic neoplasm; SPL: Solid pancreatic lesion; SPN: Solid pseudopapillary neoplasm.

Final diagnosis of SPLs ≤10 mm

A flowchart of EUS-TA and the final diagnoses is shown in Figure 2. EUS-TA yielded a malignant diagnosis for 65 lesions (60.2%). Of these, a final diagnosis of malignancy was obtained from surgically resected specimens for 17 lesions (PDAC, 12; NET, 5). Malignancy in the remaining 47 lesions (NET, 37; PDAC, 2; metastatic tumor, 4; SPN, 3; and PEComa, 1) was confirmed by clinical/imaging follow-up. One lesion that was diagnosed as adenocarcinoma by EUS-TA was surgically confirmed as a hamartoma and thus was considered to be a false-positive.

EUS-TA yielded a diagnosis of benign disease or no malignancy for 43 lesions (39.8%). Of 7 lesions with no malignancy, 5 were suspected to be NETs based on various imaging findings; these lesions were small and were followed up, although no changes were observed. The remaining 2 lesions with no malignancy, as analyzed by EUS-TA, were suspected to be PDACs based on imaging and clinical findings. One lesion was treated surgically, and PDAC (stage IA) was diagnosed. The other lesion could not be treated surgically as the patient was elderly and could not tolerate surgery; the clinical and imaging course led to the diagnosis of PDAC. A total of 7 lesions (6.5%), 2 PDACs and 5 NETs, were considered to be false-negatives.

During 6 months of follow-up, 4 cases of intrapancreatic accessory spleen and 2 SCNs, which were diagnosed as benign diseases, as well as 2 cases of chronic pancreatitis and 28 lesions with a diagnosis of no malignancy, remained unchanged; accordingly, 36 lesions were considered to be true-negatives. Figure 3 shows a cross table of the EUS-TA and final diagnoses for 109 SPLs ≤10 mm for which EUS-TA could be performed. The diagnostic performance of EUS-TA for SPLs ≤10 mm was as follows: sensitivity, 90.1% (64/71); specificity, 97.3% (36/37); accuracy, 92.6% (100/108); positive predictive value, 98.5% (64/65); and negative predictive value 83.7% (36/43) (Table 4).

Risk factors for inaccuracy in EUS-TA of SPLs ≤10 mm

Results of the univariate and multivariate analyses of the effect of age (≥70 years, <70 years), sex, tumor diameter (>5 mm, ≤5 mm), localization of punctured lesion (head of pancreas, body/tail of pancreas), needle type (FNA, FNB), needle size (19-/22-gauge, 25 gauge), number of punctures (≤3, >3), and tumor type (NET, non-NET) on histological diagnostic inaccuracy are shown in Table 5. Univariate analysis revealed that the number of punctures (>3) (OR, 13.2; 95% CI, 1.56–111.63; $P = 0.02$) and tumor type (NET) (OR, 9.44; 95% CI, 1.12–79.62; $P = 0.04$) were significantly associated with the risk of inaccuracy in EUS-TA. In addition, the number of punctures (>3) (OR, 7.03; 95% CI, 1.32–37.5; $P = 0.02$) and tumor type (NET) (OR, 11.90; 95% CI, 1.38–102.0; $P = 0.02$) were independent risk factors for inaccuracy in EUS-TA in the multivariate analysis.

Patients with a final diagnosis of PDAC ≤10 mm

The characteristics of the 16 patients with a final diagnosis of PDAC are shown in Table 6. All tumors were resectable when EUS-TA was attempted. The diagnostic accuracy of EUS-TA was 87.5% (14/16). There were 8 tumors in the pancreatic head and 8 in the pancreatic body or tail. Surgical treatment was performed

Table 3

Clinical characteristics and EUS-TA results of nonmalignant lesions.

Variables	Total *n* = 108	No malignancy *n* = 28	Other than no malignancy *n* = 80	*P*
Median age (range),[a] y	63 (29–86)	63 (30–79)	61 (29–86)	0.93
Male sex, *n* (%)	59 (54.6)	13 (46.4)	46 (57.5)	0.29
Median tumor size (range), mm	8 (2.5–10)	7.45 (2.5–9.8)	8 (2.5–10)	0.49
Tumor location, *n* (%)				0.069
Pancreatic head	34 (31.5)	13 (46.4)	21 (25.9)	
Pancreatic body or tail	74 (68.5)	15 (53.6)	59 (74.1)	
Needle type, *n* (%)				0.77
EUS-FNA	63 (58.3)	17 (60.7)	46 (57.5)	
EUS-FNB	45 (41.7)	11 (39.3)	34 (42.5)	
Needle size, *n* (%)				0.35
19-Gauge or 22-gauge	102 (94.4)	26 (92.9)	76 (95)	
25-Gauge	6 (5.6)	2 (7.1)	4 (5)	
Mean no. of passes for EUS-TA (IQR)	3 (2–4)	3.9 (2–4)	3.1 (2–4)	0.86

[a] Age at which EUS-TA was performed.

EUS-FNA/FNB: EUS fine-needle aspiration/biopsy; EUS-TA: EUS tissue acquisition; IQR: Interquartile range.

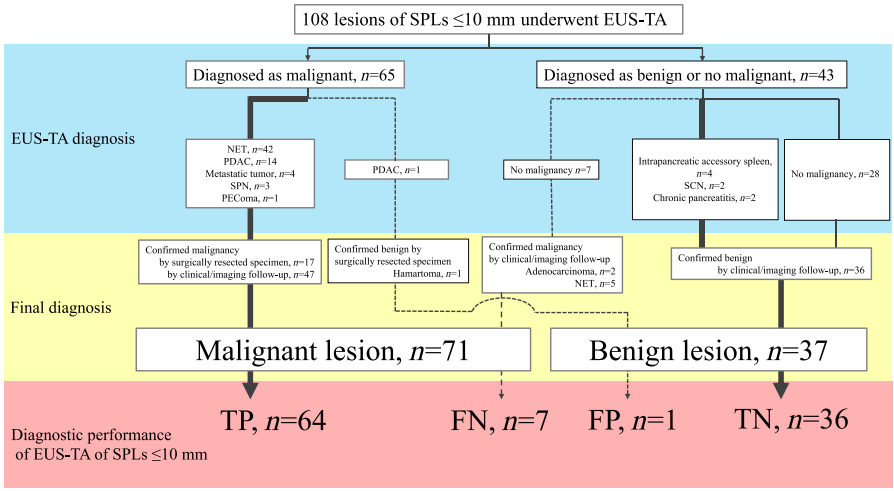

Figure 2. Flowchart of the EUS-TA and final diagnoses. EUS-TA: EUS-guided tissue acquisition; FN: False negative; FP: False positive; NET: Neuroendocrine tumor; PDAC: Pancreatic ductal adenocarcinoma; PEComa: Perivascular epithelioid cell tumor; SCN: Serous cystic neoplasm; SPL: Solid pancreatic lesion; SPN: Solid pseudopapillary neoplasm; TN: True negative; TP: True positive.

in 12 patients (75%). Nonsurgical treatment was performed in the remaining 4 patients because of nontolerance for surgery; radiation was used in 2 patients (12.5%), and 2 were only followed up (12.5%). Neoadjuvant chemotherapy (NAC) with gemcitabine and S-1 was administered to 11 patients (91.7%). The median time from EUS-TA to surgery was 58 days (range, 33–104 days). Pancreatoduodenectomy was performed in 5 patients (41.7%), and distal pancreatectomy in 7 (58.3%). Among surgically treated patients, the final pathological staging was 0 in 2 patients (16.7%), IA in 6 (50%), and IB in 4 (33.3%), with 2 (12.5%) having intraepithelial carcinoma (Tis). Postoperatively, patients received 6 months of adjuvant chemotherapy with S-1 and underwent regular monitoring of tumor marker levels, as well as imaging follow-up with contrast-enhanced CT every 6 months. The median observation period after EUS-TA was 799 days (range, 386–1764 days), and no EUS-TA–related needle-tract seeding was observed in any patient during this period.

DISCUSSION

The present study found that the diagnostic accuracy and rate of adverse events of EUS-TA in combination with ROSE for SPLs ≤10 mm were comparable to those of EUS-TA for all sizes of SPLs in previous reports.[1,2,15–19] The histological diagnostic accuracy in the present study for SPLs ≤10 mm was 92.6%. In comparison, the overall diagnostic accuracy of EUS-TA for all SPLs was reported to be 96.2% (95% CI, 95.5%–96.9%) in combination with ROSE[15] and 91.3% (95% CI, 88.6%–93.3%) in combination with microscopic on-site evaluation in previous meta-analyses.[16] Moreover, the previously reported histological diagnostic accuracy

		Final diagnosis	
		Malignant *n*=71	Benign *n*=37
EUS-TA diagnosis	Malignant *n*=65	64 (TP)	1 (FP)
	Benign *n*=43	7 (FN)	36 (TN)

Figure 3. Cross table of EUS-TA and final diagnoses for 108 SPLs ≤10 mm for which EUS-TA could be performed. EUS-TA: EUS-guided tissue acquisition; FN: False negative; FP: False positive; TN: True negative; TP: True positive.

Table 4

Diagnostic performance of EUS-TA of SPLs ≤10 mm.

Sensitivity	90.1% (64/71)
Specificity	97.3% (36/37)
Accuracy	92.6% (100/108)
PPV	98.5% (64/65)
NPV	83.7% (36/43)

EUS-TA: EUS tissue acquisition; NPV: Negative predictive value; PPV: Positive predictive value; SPL: Solid pancreatic lesion.

of EUS-TA for SPLs ≤10 mm was lower, at 64.3%.[7] Because there was no significant difference in diagnostic accuracy between FNA and FNB in the present study, the observed high diagnostic accuracy may be due to the high level of experience of the endoscopists, cytologists, and pathologists and the fact that ROSE was performed in all cases, which allowed sufficient specimens to be collected for diagnosis. Sundaram et al[20] reported no difference in diagnostic performance in a recent report comparing ROSE and macroscopic on-site evaluation (MOSE) using the FNB needle. With advances in FNB needles, it is possible that MOSE could produce comparable results. However, this study did not include small lesions <10 mm, and the diagnostic performance of MOSE alone for these lesions remains unclear.

Only 1 lesion showed false positivity (EUS-TA diagnosis, PDAC; final diagnosis, hamartoma), with a specificity of 97.3%. A meta-analysis of studies published from 1997 to 2009 reported a specificity of 98% (95% CI, 97%–99%), and a meta-analysis of studies published from 2012 to 2018 reported a specificity of 100% for both EUS-FNA and FNB.[17] Thus, the possibility of improvement in specificity has been highlighted in recent years. In the present case with a false-positive result, the specimens were highly degenerated because of severe inflammation, and 1 of the 5 specimens that underwent EUS-TA had a high Ki-67 index positivity in some cells on immunostaining, leading to a diagnosis of suspected adenocarcinoma. This high degree of inflammation was associated with chronic pancreatitis and not with the EUS-TA procedure or the formation of hamartoma. This was the only suspected case; the remaining cases were definitively diagnosed as malignant in our series.

The incidence of adverse events in EUS-TA has been reported to be 0.5% to 2%,[1,17–19] which is a little lower than the 2.8% reported in the present study. With the increased inclusion of NETs, which are hypervascular tumors, and combined ROSE procedures, an increased risk of bleeding is expected, related to the increased number of punctures in cases that are difficult to diagnose. However, the rate of adverse events in the present study was considered acceptable. Another late adverse event of EUS-TA is needle-tract seeding. In Japan, the incidence rate of EUS-TA–associated needle-tract seeding has been reported to be 0.33% to 3.4%.[19,21] Kitano et al[21] reported that the median time from EUS-TA to the observation of needle-tract seeding was 19.3 months, which is comparable to that in this study (747.5 days). However, Nakatsubo et al[22] reported in their study of FNB needles using resected specimens that 2.7% of patients had needle-tract seeding. As previously stated, there was no difference in diagnostic performance between FNA and FNB needles in this study, but the most common lesions were NETs. Although follow-up is an option in various guidelines for NETs smaller than 20 mm, the Ki-67 index is necessary to diagnose the grade of NETs. Immunostaining is essential to accurately differentiate

Table 5

Factors affecting the histopathological diagnostic accuracy of EUS-TA of SPLs ≤10 mm.

			Univariate analysis			Multivariate analysis		
Variable	***n***	**Diagnostic accuracy, %**	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age, y								
≥70	31	96.8 (30/31)						
<70	77	90.9 (70/77)	3.1	0.37–26.3	0.3	—	—	—
Sex								
Female	50	92.0 (46/50)						
Male	58	93.1 (54/58)	1.20	0.28–5.05	0.81	—	—	—
Lesion size								
>5 mm	97	91.8 (89/97)						
≤5 mm	11	100 (11/11)	-	0	1	—	—	—
Location								
Head	35	91.4(32/35)						
Body/tail	73	93.2 (68/73)	2.17	0.51–9.17	0.3	—	—	—
Needle type								
FNA	63	93.8 (60/64)						
FNB	45	91.1 (41/45)	1.41	0.33–5.94	0.64	—	—	—
Needle size								
25-Gauge	6	100 (6/6)						
19-/22-Gauge	102	92.2 (94/102)	-	0	1	—	—	—
No. of needle passes								
≤3	66	98.5 (65/66)						
>3	42	83.3 (35/42)	13.2	1.56–111.63	0.02	7.03	1.32–37.5	0.02
Tumor type								
Non-NET	58	96.6 (56/58)						
NET	50	88.0 (44/50)	9.44	1.12–79.62	0.04	11.90	1.38–102.0	0.02

CI: Confidence interval; EUS-TA: EUS tissue acquisition; FNA: Fine-needle aspiration; FNB: Fine-needle biopsy; NET: Neuroendocrine tumor; OR: Odds ratio; SPL: Solid pancreatic lesion.

Table 6

Characteristics of primary pancreatic invasive ductal adenocarcinoma.

Variables	*n* = 16
Diagnostic accuracy of EUS-TA, %	87.5 (14/16)
Tumor location, *n* (%)	
Pancreatic head	8 (50)
Pancreatic body or tail	8 (50)
Resectable, *n* (%)	16 (100)
Treatment, *n* (%)	
Surgery	12 (75)
Neoadjuvant chemotherapy	11 (91.7)
Upfront surgery	1 (8.3)
Radiation	2 (12.5)
Follow-up (nontolerance for surgery)	2 (12.5)
Surgical method, *n* (%)	
Pancreatoduodenectomy	5 (41.7)
Distal pancreatectomy	7 (58.3)
Final pathological staging after surgery, *n* (%)	
0	2 (16.7)
IA	6 (50)
IB	4 (33.3)
Median follow-up period (range), d	799 (386–1764)

EUS-TA: EUS tissue acquisition.

NETs from SPN and SCN and for determining whether the NET is a metastasis of another cancer or a primary tumor. We have previously reported the results of EUS-TA for small NET-suspect lesions[23] and maintain that EUS-FNB, provided there is sufficient specimen volume, is necessary. However, in light of the report by Nakatsubo et al,[22] we believe that EUS-TA should still be considered when primary PDAC is strongly suspected and there are no plans of resection via the puncture route. Although the number of cases was relatively small and the postprocedural observation period was not long enough in the present study of SPLs ≤10 mm, fortunately needle-tract seeding was not observed.

The number of punctures and NETs were identified as risk factors for diagnostic difficulty. The lower diagnostic accuracy with a higher number of punctures may be related to the use of ROSE in all cases. As a result, punctures were performed until suspicious tissues could be obtained. The reason for the latter finding is unclear as there are no reports comparing NETs with other SPLs in terms of EUS-TA results. However, the present results suggest that pancreatic NETs as small as ≤10 mm contribute to the poor diagnostic accuracy of EUS-TA.

It is well-documented that using a 19-gauge needle in the pancreatic head can be challenging,[24] and consequently, a 22-gauge needle is preferred. However, normal pancreatic tissue could not be obtained using a 22-gauge needle in 1 lesion from this study, and atypical cells were obtained using a 19-gauge needle, leading to the diagnosis of SCN. When the 22-gauge needle did not provide a stable puncture route, a 25-gauge needle was used to puncture the center of the lesion accurately. Therefore, in cases where the 22-gauge needle does not yield a reliable ROSE diagnosis, the use of a 19- or 25-gauge needle may be a viable option to enhance diagnostic accuracy. Furthermore, lesions in the pancreatic head tended to show a diagnosis of nonmalignancy in the present study. Togliani et al[25] reported that pancreatic head lesions are more prone to fibrosis and decreased specimen adequacy and diagnostic performance. In pancreatic head lesions, intentionally increasing the number of punctures to ensure adequate specimen volume may provide a more accurate diagnosis.

Although pancreatic head lesions are generally reported to account for 60% to 70% of PDACs,[26] the localization of pancreatic head and body-tail lesions was the same in this study. Kanno et al[27] reported a similar finding for stage 0 and stage 1 early pancreatic cancer, where localization to the body/tail was equal to or slightly more common (57% [114/200]) than localization in the pancreatic head. In many PDACs, jaundice, abdominal pain, elevated tumor markers, and worsening of diabetes mellitus were identified as triggers. However, early-stage PDAC (<10 mm on EUS), the subject of this study, is often symptomless and detected incidentally when pancreatic duct dilatation is observed during medical check-ups or intraductal papillary mucinous neoplasm follow-up. This discrepancy in localization may be attributed to the absence of symptoms in microscopic lesions, in contrast to PDACs as a whole.

Postoperative pathological examinations revealed Tis (stage 0) in 2 patients. In 1 patient, NAC was effective, and the lesion was no longer visible on preoperative CT. This patient, with the final pathological stage being Tis, may have been affected by NAC. The other patient did not receive NAC but directly underwent surgery. Although it was an intraepithelial carcinoma, EUS showed a hypoechoic area, and EUS-TA of the same area led to the diagnosis of adenocarcinoma. This hypoechoic area might have resulted from microscopic inflammatory effusion and fibrosis of the pancreatic parenchyma.[28] There have been 2 reports of high-grade pancreatic intraepithelial neoplasia diagnosed using EUS-TA, including the present case.[28,29] The reason for the ability to diagnose intraepithelial carcinoma by EUS-TA is assumed to be related to the widespread presence of high-grade pancreatic intraepithelial neoplasia in the branch pancreatic duct and weak cell adhesion of the carcinoma, resulting in malignant cells that can be identified by TA.

This study had some limitations, including its single-center, retrospective study design. In addition, the sample size, although larger than that in previous reports, is still insufficient. All cases mandated ROSE, and the endoscopist, cytologist, and pathologist involved were all experts. However, it is essential to acknowledge that the applicability of these findings in real-world clinical scenarios may be limited, as clinicians with less experience might not be able to replicate the same level of expertise and may not be able to perform ROSE as consistently. Therefore, an accumulation of cases of EUS-TA for SPLs ≤10 mm from multiple centers, including those that do not perform ROSE, is needed. In addition, the possibility that the final diagnosis may be incorrect in some cases cannot be ruled out because it was not based on pathological examinations of surgically resected specimens.

In conclusion, EUS-TA for SPLs ≤10 mm showed adequate diagnostic accuracy and was safe for use with ROSE in all cases.

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Conflicts of Interest

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author Contributions

Yuki Kawasaki designed the research, conducted the research, analyzed the data, and wrote the paper. Susumu Hijioka had primary responsibility for the final content. All authors have read and approved the final manuscript.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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