Digestive Endoscopy 2025; **37**: 695–703 doi: 10.1111/den.14983

Original Article

Clinical performance of endoscopic ultrasound-guided tissue acquisition for perivascular soft-tissue cuffing suspected to be extravascular migratory metastases of pancreatic or bile duct cancer (with video)

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Objectives: This study aimed to investigate the diagnostic performance and safety of endoscopic ultrasound-guided tissue acquisition (EUS-TA) for perivascular soft-tissue cuffing (PSTC).

Methods: This single-center, retrospective study evaluated patients in whom EUS-TA was performed for PSTC in pancreatic or bile duct cancer lesions between October 2017 and March 2024. PSTC was defined as a perivascular soft-tissue area contiguous with nearby blood vessels from the suspected primary tumor. EUS-TA procedures and outcomes, including technical success, diagnostic performance, adverse events, and comparison with contrast-enhanced computed tomography (CECT), were analyzed.

Results: Of 1803 patients, 53 underwent EUS-TA for PSTC. The sensitivity, specificity, and accuracy were 92.1%, 100%, and 92.5%, respectively. The technical success rate was 98.1% (52/53). The adverse event rate was 1.9%. EUS-TA for PSTC was significantly superior to CECT for PSTC in terms of diagnostic accuracy. Furthermore, the diagnostic performance and adverse event rates for EUS-TA for PSTC were comparable to those for TA in solid tumors. Shorter puncture lengths were associated with lower accuracy.

Conclusion: EUS-TA for PSTC in pancreatic or bile duct cancer demonstrates high diagnostic accuracy and a low rate of adverse events, showing superior diagnostic performance compared to CECT. These findings suggest that EUS-TA for PSTC can be performed safely and is a clinically beneficial procedure. Despite the technical challenges, EUS-TA for PSTC can influence clinical judgment and should be considered in skilled institutions for future patient treatment decisions. Prospective multicenter studies are warranted to further evaluate its efficacy and safety.

Key words: bile duct cancer, endoscopic ultrasound-guided fine-needle acquisition, endoscopic ultrasound-guided fine-needle aspiration, pancreatic cancer, vascular neoplasm

INTRODUCTION

ENDOSCOPIC ULTRASOUND-GUIDED TISSUE acquisition (EUS-TA) is crucial in the treatment decision-making for pancreatic and bile duct tumors.[1] A recent meta-analysis reported a sensitivity and specificity of 85% and 98%, respectively,[2] for diagnosing pancreatic tumors, with an adverse event rate of 1–2%.[3,4] Overall, EUS-TA is a safe and useful diagnostic method.[2–10] However, diagnosis using EUS-TA is difficult in some cases, particularly for suspected perivascular invasion in close proximity to the primary tumor (i.e., extravascular migratory metastasis [EVMM]) in patients with pancreatic or bile duct cancer. There is a high risk of bleeding from perivascular puncture and a narrow target area, and there are concerns about poor diagnostic performance. Nevertheless, the capability to differentiate between benign and malignant conditions using EUS-TA for perivascular soft-tissue areas (i.e., perivascular soft-tissue cuffing [PSTC]) is highly valuable. Although most PSTCs, suspected to be EVMM on imaging are cancerous, they can also represent benign conditions like inflammatory changes or IgG4-related

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Received 10 July 2024; accepted 1 December 2024.

disease.[11,12] Therefore, EUS-TA for PSTC is valuable in differentiating benign from malignant lesions and in making treatment decisions. Furthermore, in some cases of pancreatic and bile duct cancers, the primary tumor cannot be recognized, and only the PSTC is recognized, thus necessitating EUS-TA for PSTC. Additionally, confirming EVMM using EUS-TA can provide accurate staging, which may prevent unnecessary surgeries. In postoperative patients with pancreatic and bile duct cancer, EUS-TA for PSTC near the resection site is valuable for determining recurrence and providing timely retreatment. A previous study reported that EUS-TA for PSTC had a sensitivity, specificity, and diagnostic accuracy of 81.1%, 100%, and 85.8%, respectively.[13] However, studies on EUS-TA for PSTC are still limited.[13–15] Thus, this study aimed to investigate the diagnostic performance and safety of EUS-TA for PSTC.

METHODS

Study design and population

THIS SINGLE-CENTER, RETROSPECTIVE study was conducted at the National Cancer Center Hospital, Tokyo, Japan. Our institutional database containing information on all patients in whom EUS-TA was attempted for PSTC between October 2017 and March 2024 was reviewed.

Inclusion and exclusion criteria

We reviewed the database for the specified period and extracted cases where EUS-TA was attempted for suspected tumors. We included cases where EUS-TA was performed on lesions suspected to be pancreatic or biliary cancer as part of the inclusion criteria. Conversely, we excluded cases where EUS-TA was attempted for suspected tumors in other organs, as per the exclusion criteria (Fig. 1).

Definitions

PSTC and EVMM

Malignancies potentially migrate along the perimeter or abluminal vessel surface to remote sites.[13,16] Therefore, the present study defined PSTC as a perivascular soft-tissue area that was contiguous with nearby blood vessels from the suspected primary tumor, surrounded the vessels, and was present along the axis of vascular motion, as determined using contrast-enhanced computed tomography (CECT) findings by radiologists and/or endoscopic ultrasound (EUS) findings by two skilled endoscopists specializing in pancreatic and bile duct cancer (Fig. 2). Lesions diagnosed as PSTC on imaging that met the definitions of malignant findings specified below were defined as EVMM.

Endoscopic procedure

For selection of the endoscopist performing EUS-TA for PSTC, the primary operator at the start of the procedure could vary from a trainee with ~100 EUS-TA procedures to an experienced specialist. However, in all cases the procedure was supervised or partially performed by highly skilled endoscopists who have conducted over 500 EUS-TA procedures. All EUS-TA procedures were performed using a linear array echoendoscope (Olympus GF-UCT240 or 260; Olympus Medical Systems, Tokyo, Japan). After color Doppler evaluation of the vessel, the PSTC was punctured through the transgastric, transduodenal, or transreconstructed jejunum. The length of the puncture target was measured as the overlap between the PSTC, as depicted on EUS, and the puncture path on EUS-TA (Fig. S1). All patients underwent a rapid on-site evaluation. The suction method was negative pressure (−20 cc) for EUS-guided fine-needle aspiration (FNA) and the slow-pull method for EUS-guided fine-needle biopsy (FNB). The needle was inserted ~20 times for each puncture. Needle selection and the number of punctures were at the discretion of the endoscopist performing the procedure.

Intended cohort, analysis cohort, technical success, and adverse events

The intended cohort was defined as patients suspected of having PSTC due to pancreatic or bile duct cancer on contrast computed tomography (CT) or EUS and who were indicated for EUS-TA for PSTC. The analysis cohort was defined as the intended cohort of patients in whom EUS-TA for PSTC was technically successful (Fig. 1). Technical success was defined as when there was an actual puncture, with the specimen for cytology and/or histology grossly obtained. Adverse events and their severities were evaluated using the severity grading system of the American Society for Gastrointestinal Endoscopy Lexicon classification.[17]

Malignant or nonmalignant PSTC

The final diagnosis of malignancy or benignity of the punctured PSTC was defined as follows. If a malignant finding was observed in the EUS-TA specimen from PSTC, it was considered a diagnosis. In such patients, histological diagnosis and/or Papanicolaou class 4/5 using cytological diagnosis were considered definite diagnoses of malignancy. For patients who underwent surgical resection within the

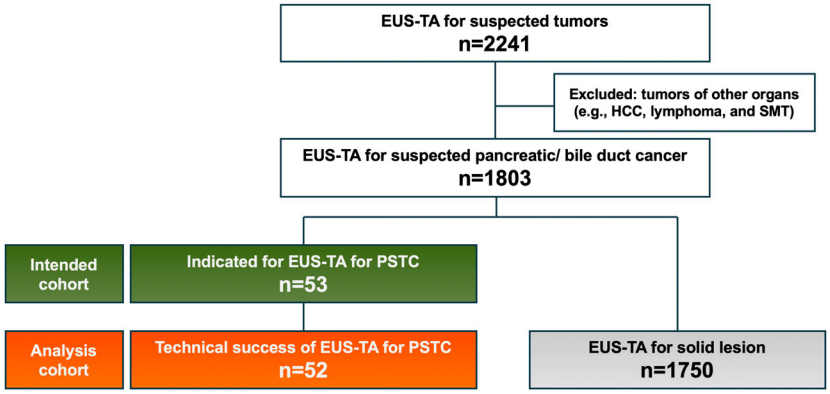

Figure 1 Flow diagram. EUS-TA, endoscopic ultrasound-guided tissue acquisition; HCC, hepatocellular carcinoma; PSTC, perivascular soft-tissue cuffing; SMT, submucosal tumor.

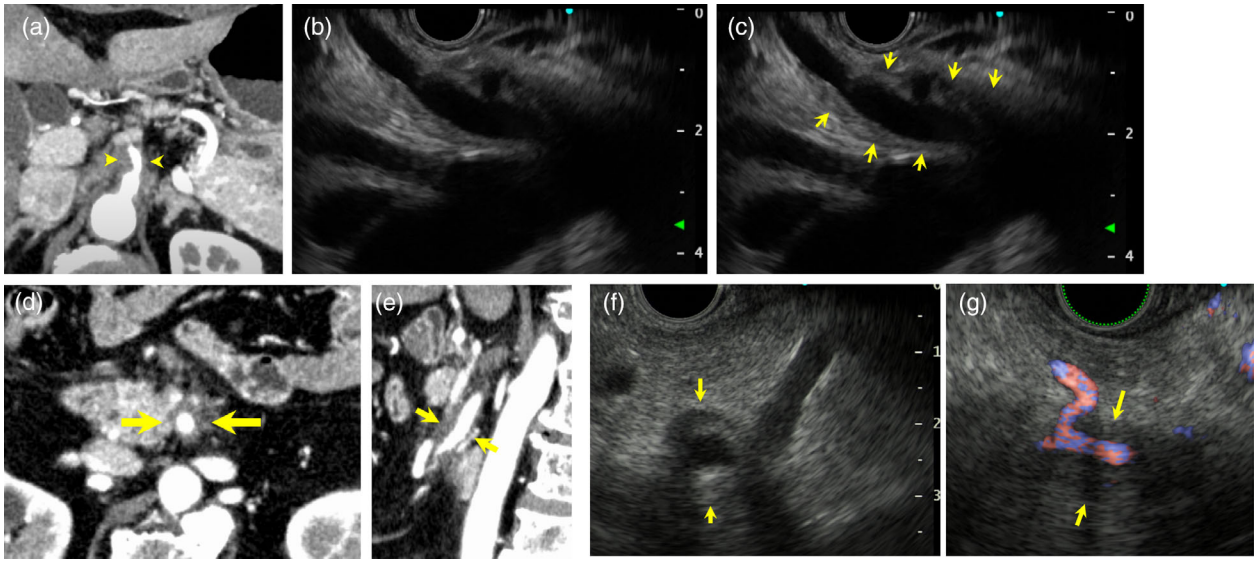

Figure 2 Perivascular soft-tissue cuffing. (a–c) In a patient at celiac artery (arrowhead), (d–g) in a patient at superior mesenteric artery. (a) On computed tomography (b,c) on endoscopic ultrasound, (d,e) on computed tomography, (f,g) on endoscopic ultrasound, perivascular soft-tissue cuffing (arrow).

subsequent 6 months, the histopathology of the resected specimen at PSTC, not the EUS-TA specimen, was used as the final diagnosis of PSTC. For patients with negative histopathology and cytology on EUS-TA and who did not undergo surgery within 6 months, the final diagnosis was made based on the clinical course, including the 6-month imaging course, and was considered benign if there was no tumor clarification on PSTC. If the attending physician judged the PSTC as EVMM based on the clarity of the tumor on PSTC and clinical information, such as blood tests, it was considered malignant. The adequacy or inadequacy of the puncture specimen in EUS-TA for PSTC was evaluated in the same manner as that in EUS-TA for solid pancreatic masses.[18]

Recognition of PSTC and EVMM by CECT prior to EUS-TA

To evaluate diagnostic performance, the CECT used had to be performed within 1 month prior to the EUS-TA for PSTC. The CECT setting was basically an 80- or 160-row multidetector CT (Aquilion PRIME, Aquilion Precision;

Canon, Tokyo, Japan) in dynamic 3-phase, and the main contrast agent used was Iopromide (Iopromide BYL; Bayer Yakuhin, Osaka, Japan). The diagnosis of EVMM using CECT was defined as "CECT findings that meet the definition of a PSTC, plus findings of invasion around the PSTC and/or clear vessel narrowing." PSTC and EVMM recognition on CECT was determined based on the following criteria: three radiologists independently reviewed the scans in a blinded manner, and a scan was classified as positive if at least two of the radiologists identified PSTC or EVMM.

Outcome measure

The primary outcome measure was the diagnostic performance (sensitivity, specificity, and accuracy) of EUS-TA for PSTC in the intended cohort. The secondary outcome measures included the success rate, adverse event rates, target lengths, number of punctures, needle types, and needle sizes in the analysis cohort, as well as a comparison of the diagnostic performance of the intended cohort with that of CECT. EUS-TA for PSTC and that for solid lesion were compared as another outcome measure. Target length, sensitivity, specificity, accuracy, and adverse event rate were compared. Propensity matching score was used for these comparisons.

Statistical analyses

Continuous variables were presented as medians and ranges, whereas categorical variables were presented as numbers. The χ^2-test or Fisher's exact test was used for categorical variables, and the *t*-test was used to compare the means of two normally distributed populations. The Cochran–Armitage test for trend was used to evaluate the differences in accuracy according to puncture length. To minimize bias between groups, a propensity matching score was conducted. The propensity score was estimated using multiple logistic regression analysis, based on baseline data. Using caliper matching, pairs on the propensity score logit were matched 1:1 to within a range of 0.2 standard deviations. All statistical analyses were performed using IBM SPSS Statistics for Windows (version 25; IBM, Armonk, NY, USA). Statistical significance was set at $P < 0.05$.

RESULTS

Patient characteristics

A TOTAL OF 1803 patients were included; among them, 53 and 52 patients belonged to the intended and analysis cohorts, respectively. Solid lesions that were not PSTC were punctured in the remaining 1750 patients (Fig. 1). The characteristics of the 52 patients in the analysis cohort are presented in Table 1. Overall, 45 patients underwent EUS-TA for PSTC-suspected pancreatic cancer invasion, whereas seven underwent EUS-TA for suspected bile duct cancer invasion. There were 10 patients (19.2%) who underwent EUS-TA after primary cancer resection. The primary tumor could be recognized on CT or EUS before EUS-TA in 11 patients (21.2%).

Table 1 Characteristics of patients who underwent endoscopic ultrasound (EUS)-guided tissue acquisition for perivascular soft-tissue cuffing in the analysis cohort (n = 52)

Characteristic	Value
Age, years	66.5 (42–86)
Sex	
Male	30 (57.7)
Female	22 (42.3)
Cancer type	
Pancreatic	45 (86.5)
Bile duct	7 (13.5)
Previous resection of the cancer	
Without previous resection	42 (80.8)
With previous resection	10 (19.2)
Identifiable primary mass on CT or EUS	11 (21.2)

Data are presented as the median (range) or *n* (%).
CT, computed tomography.

Procedure characteristics and outcomes in the analysis cohort

The endoscopic procedures are presented in Table 2, Figure 3, and Video S1. The main vessels targeted for PSTC puncture were the superior mesenteric artery in 15 patients (28.8%), celiac artery in 14 (26.9%), and common hepatic artery in eight (15.4%). The median target length was 8.5 mm (range 2.5–22.0 mm). Both FNA and FNB had a median of three punctures, with no significant difference between the two methods.

Procedural characteristics and outcomes in the intended cohort

The outcomes in the intended cohort are presented in Table 3. The technical success rate was 98.1% (52/53). The final diagnosis of PSTC for the puncture target was EVMM and benign in 96.2% (51/53) and 3.8% (2/53) patients, respectively. Specimen adequacy for histology was met in 84.9% (45/53) of the patients. Malignant findings were confirmed using cytology or histology in 47 patients (88.7%). Of these, 34 were positive in both cytology and

Table 2 Procedure of endoscopic ultrasound-guided tissue acquisition for perivascular soft-tissue cuffing (PSTC) in the analysis cohort (n = 52)

Parameter	Value
Target vessel with PSTC, *n* (%)	
Superior mesenteric artery	15 (28.8)
Celiac artery	14 (26.9)
Common hepatic artery	8 (15.4)
Splenic artery	4 (7.7)
Superior mesenteric vein	3 (5.8)
Aorta	2 (3.8)
Gastroduodenal artery	2 (3.8)
Left gastric artery	1 (1.9)
Proper hepatic artery	1 (1.9)
Right hepatic artery	1 (1.9)
Left hepatic artery	1 (1.9)
Target length (mm)	8.5 (2.5–22.0)
Number of punctures	3 (1–8)
Needle size (25/22/19G)	1 (1.9)/49 (94.2)/2 (3.8)
Needle type (fine-needle aspiration/ fine-needle biopsy)	29 (55.8)/23 (44.2)

Data are presented as the median (range) or *n* (%).

histology, 11 were positive in only cytology, and two were positive in only histology. There were six patients (11.3%) in whom no malignant findings were detected using cytology and histology. Among them, two patients were confirmed as true negatives; one patient confirmed by CECT and EUS at 6 months, while the other on CECT after 1 year of follow-up. Three patients showed no malignant findings on EUS-TA but were subsequently judged to have EVMM based on their CT follow-up and were started on chemotherapy. In the remaining patient, EUS-TA was abandoned because a safe puncture route could not be identified. Regarding the diagnostic performance of EUS-TA for PSTC (intended cohort), the sensitivity, specificity, and accuracy were 92.1% (47/51), 100% (2/2), and 92.5% (49/53), respectively. The adverse event rate was 1.9% (1/53). An adverse event occurred in a patient who underwent EUS-TA for PSTC around the splenic artery due to pancreatic cancer, in which a 12.8 mm puncture target was punctured using an FNB needle, resulting in mild pancreatitis. No patient experienced any bleeding adverse events.

Comparison of diagnostic performance of EUS-TA for PSTC (intended cohort) and CECT for PSTC

Table 4 shows the comparison of diagnostic performance between EUS-TA for PSTC (intended cohort) and CECT for PSTC. EUS-TA for PSTC demonstrated significantly superior diagnostic performance compared to CECT for PSTC (P = 0.0320). Specifically, when evaluating diagnostic performance based on target length, the EUS-TA group exhibited significant superiority over the CECT group for PSTC lesions larger than 10 mm (P = 0.0471).

Accuracy of EUS-TA for PSTC according to the target length

Figure 4 shows the accuracy of EUS-TA for PSTC for each puncture target length. The overall accuracy in the analysis cohort was 94.2% (49/52), with three false negatives. The accuracy for each puncture target was 80% (8/10), 95.4% (21/22), and 100% (20/20) for punctures <5, 5–10, and ≥ 10 mm, respectively. Comparing the diagnostic performance for each puncture length, the shorter the puncture

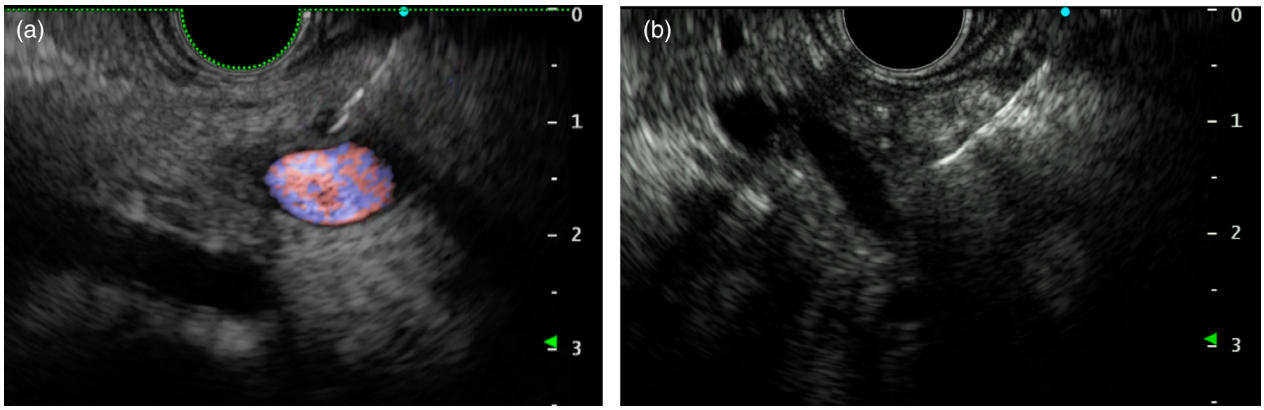

Figure 3 Endoscopic ultrasound-guided tissue acquisition for perivascular soft-tissue cuffing around celiac artery in patients with (a) a puncture length of 3 mm or (b) a puncture length of 6 mm.

Table 3 Results of endoscopic ultrasound-guided tissue acquisition for perivascular soft-tissue cuffing (PSTC) in the intended cohort (n = 53)

Parameter	Value
Technical success	98.1% (52/53)
Final diagnosis of PSTC	
EVMM	96.2% (51/53)
Benign	3.8% (2/53)
Specimens adequate for histology	84.9% (45/53)
Positive in cytology or histology	47 (88.7%)
Positive in both cytology and histology	34 (64.2%)
Positive in only cytology	11 (20.8%)
Positive in only histology	2 (3.8%)
Negative in cytology and histology	6 (11.3%)
True negative (diagnosed by followup)	2 (3.8%)
False negative	4 (7.5%)
Inadequate specimen for cytology and histology	3 (5.7%)
Could not puncture	1 (1.9%)
Sensitivity	92.1% (47/51)
Specificity	100% (2/2)
Accuracy	92.5% (49/53)
Adverse events	1.9% (1[†]/53)

[†]Pancreatitis (mild).
EVMM, extravascular migratory metastasis.

length, the more significantly lower the accuracy (Cochran–Armitage test, P = 0.039).

Comparison of EUS-TA for PSTC (analysis cohort) and for solid lesions

In a comparison of EUS-TA for PSTC and that for solid lesions, the target length was significantly shorter in the PSTC group, and a study using the propensity matching score showed no significant differences in diagnostic performance or adverse event rates in these groups (Table S1).

DISCUSSION

IN THIS STUDY, the diagnostic performance of EUS-TA for PSTC was higher than previously reported. This may be because the cases in the previous report were accumulated up to ≥10 years earlier than those in the present study. Further, the development of EUS imaging equipment has improved the ability to visualize PSTC, with the availability of more appropriate device selection and puncture technique selection with the increased choice of puncture needles.[19–22]

Furthermore, this study revealed that EUS-TA for PSTC exhibited significantly superior diagnostic performance compared to CECT for PSTC, providing novel insights not previously reported. Specifically, when comparing diagnostic performance based on target length, the TA group demonstrated significant superiority over the CECT group for PSTC lesions larger than 10 mm. One possible explanation for this difference could be that CECT may include false positives due to inflammatory changes that are mistakenly identified as EVMM.

Regarding the clinical impact of EUS-TA, the treatment strategy was changed in 16.9% (9/53) of cases (Table S2), an increase from the 11.4% reported earlier,[13] likely due to advancements in diagnostic devices. In 5 of 10 postoperative patients, EUS-TA for PSTC detected malignant findings. Recurrence was detected, and treatment was promptly initiated. In the postoperative setting, when vessels in close proximity to the explanted area are PSTC, it is difficult to determine whether the lesion is a postoperative inflammatory change or recurrence on imaging.[11] EVMM can be detected through elevated tumor markers or by noting the progression of PSTC over time on follow-up CT scans. However, delays in initiating treatment can be detrimental due to the extremely poor prognosis associated with pancreatic or bile duct cancer. Therefore, EUS-TA for postoperative PSTC findings that are difficult to distinguish as malignant or benign is highly valuable because it allows for prompt treatment initiation.

Table 4 Comparison of diagnostic performance between endoscopic ultrasound-guided tissue acquisition (EUS-TA) for perivascular soft-tissue cuffing (PSTC) (intended cohort) and contrast-enhanced computed tomography (CECT) for PSTC

Target length of PSTC (mm)	Malignancy rate	Accuracy		P-value
		CECT	EUS-TA	
<5	100% (11/11)	81.8% (9/11)	72.7% (8/11)	1.0
5–10	95.4% (21/22)	72.7% (16/22)	95.4% (21/22)	0.09
≥10	95.0% (19/20)	75.0% (15/20)	100% (20/20)	0.0471
Total	96.2% (51/53)	75.4% (40/53)	92.4% (49/53)	0.0320

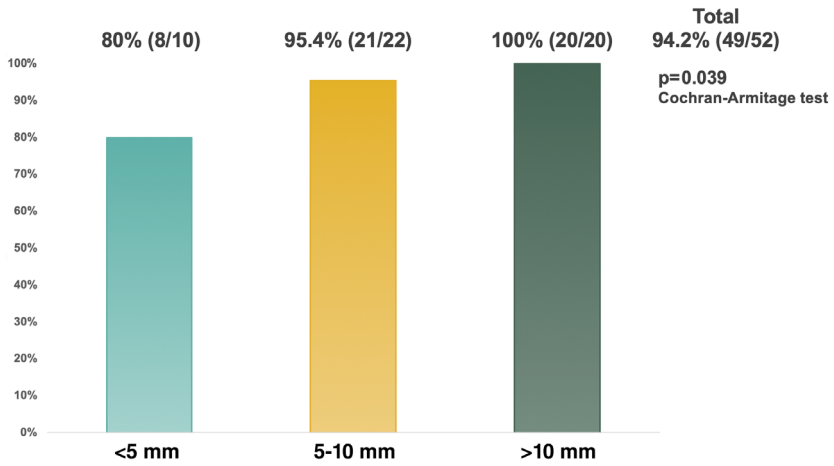

Figure 4 Target length and accuracy of endoscopic ultrasound-guided tissue acquisition for perivascular soft-tissue cuffing.

The diagnostic accuracy of EUS-TA for PSTC, when compared by puncture length, was significantly lower and had a higher rate of false negatives with shorter puncture lengths (P = 0.039). Therefore, EUS-TA for short PSTC targets should weigh diagnostic performance against the risk of vascular puncture.

In the present study the adverse event rate was comparable between the PSTC and solid lesion groups (Table S1). This is a novel finding because no previous comparative study of adverse events exists. The only adverse event in the PSTC group was mild pancreatitis in one patient. Although vascular puncture is considered a risk in PSTC, no bleeding events were observed.

Notably, it should be considered that the PSTC group in the present study was assumed to undergo a highly difficult procedure associated with the risk of accidental vascular puncture and that experienced endoscopists may have been preferentially selected to perform the procedures. Furthermore, a comparison of the target length of the puncture showed that the PSTC group had a significantly shorter puncture target length than the solid lesion group did. This supports that EUS-TA for PSTC is a highly difficult procedure.

For EUS-TA of PSTC, it is crucial to use various technical strategies employed by experienced endoscopists. These include utilizing the right or left angulation control knobs on the endoscope to achieve the optimal angle for the longest possible puncture length, and making slight adjustments to the scope during the puncture to ensure that both the tip of the needle and the maximum length of the PSTC are captured in the same image. Additionally, due to the potential high risk of bleeding during or after EUS-TA for PSTC, it is advisable to conduct this procedure at facilities equipped to manage bleeding adverse events. These facilities should have capabilities such as transarterial embolization or emergency surgery.

Additionally, endoscopists attempted to puncture a patient in the intended cohort, but could not find a safe puncture route and decided to abandon the procedure. In actual clinical practice, it is important to decide not to perform a puncture if the choice of puncture route is difficult or if there is a risk of accidental vascular puncture or a high risk of bleeding due to background diseases.

Unlike in previous reports,[13] in the present study EUS-TA for PSTC exhibited the same diagnostic performance as that for solid lesions, with comparable adverse event rates. EUS-TA for PSTC is a difficult procedure, but it can provide information that can influence clinical judgment, and it may have a significant contribution to patient management. Notably, EUS-TA for PSTC is beneficial for determining postoperative recurrence. Therefore, it should be considered in institutions skilled in the technique, considering the necessity and risk of the procedure for future decisions regarding patient treatment.

This study has some limitations, including its retrospective, single-center design and endoscopist bias. Given that only a few facilities perform EUS-TA for PSTC, there is no fixed view on how to improve the diagnostic performance and safety of this procedure, and each facility is devising its unique method. Therefore, this technique is not yet mature, and further studies should be conducted to increase the quality of the procedure. The efficacy, diagnostic performance, and safety of EUS-TA for PSTC should be evaluated in a multicenter prospective study.

In conclusion, EUS-TA for PSTC in pancreatic or bile duct cancer demonstrates superior diagnostic performance

compared to CECT for PSTC. It also shows comparable diagnostic performance and adverse event rates to EUS-TA for solid lesions. These findings suggest that EUS-TA for PSTC can be performed safely and is a clinically beneficial procedure.

ACKNOWLEDGMENTS

WE THANK THE members of the National Cancer Center Hospital Japan for their support of this work.

CONFLICT OF INTEREST

AUTHOR A.K. IS an Associate Editor of *Digestive Endoscopy*. The other authors declare no conflict of interest for this article.

FUNDING INFORMATION

THIS WORK WAS supported in part by the National Cancer Center Research and Development Fund (grant number 2022-A-16).

ETHICS STATEMENT

APPROVAL OF THE research protocol by an Institutional Reviewer Board: This study was approved by the Institutional Review Board of the National Cancer Center Hospital, Tokyo, Japan (approval number: 2018–149) and was conducted according to the tenets of the Declaration of Helsinki.

Informed consent: N/A.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

Table S1 Cases where endoscopic ultrasound-guided tissue acquisition (EUS-TA) for perivascular soft-tissue cuffing (PSTC) resulted in change in treatment strategy.

Table S2 Comparison of endoscopic ultrasound-guided tissue acquisition (EUS-TA) for perivascular soft-tissue cuffing (PSTC) (analysis cohort) and for solid lesions in the full cohort and propensity score-based matched cohort.

Video S1 Endoscopic ultrasound-guided tissue acquisition for perivascular soft-tissue cuffing.

Figure S1 Measurement of target length. Target length of perivascular soft-tissue cuffing (arrow).