BMJ Open Gastroenterology

EUS-guided through the needle microbiopsy: a useful adjunct in the investigation of pancreatic cystic lesions

Wafaa Ahmed ,[1] Mikaeil Mirzaali,[1] Caroline Young,[2] Latifu Sanni,[2]
Simon Everett ,[1] Bharat Paranandi,[1] Matthew T Huggett,[1] Wei On [1]

To cite: Ahmed W, Mirzaali M, Young C, *et al*. EUS-guided through the needle microbiopsy: a useful adjunct in the investigation of pancreatic cystic lesions. *BMJ Open Gastroenterol* 2023;**10**:e001184. doi:10.1136/bmjgast-2023-001184

Received 27 April 2023
Accepted 21 June 2023

ABSTRACT

Objective Endoscopic ultrasound-guided through-the-needle microbiopsy (EUS-TTNB) forceps is a recent development that facilitates sampling of the walls of pancreatic cystic lesions (PCL) for histological analysis. We aimed to assess the impact of EUS-TTNB and its influence on patient management in a tertiary pancreas centre.

Design A prospective database of consecutive patients who underwent EUS-TTNB from March 2020 to August 2022 at a tertiary referral centre was retrospectively analysed.

Results Thirty-four patients (22 women) were identified. Technical success was achieved in all cases. Adequate specimens for histological diagnosis were obtained in 25 (74%) cases. Overall, EUS-TTNB led to a change in management in 24 (71%) cases. Sixteen (47%) patients were downstaged, with 5 (15%) discharged from surveillance. Eight (24%) were upstaged, with 5 (15%) referred for surgical resection. In the 10 (29%) cases without change in management, 7 (21%) had confirmation of diagnosis with no change in surveillance, and 3 (9%) had insufficient biopsies on EUS-TTNB. Two (6%) patients developed post-procedural pancreatitis, and 1 (3%) developed peri-procedural intracystic bleeding with no subsequent clinical sequelae.

Conclusion EUS-TTNB permits histological confirmation of the nature of PCL, which can alter management outcomes. Care should be taken in patient selection and appropriately consented due to the adverse event rate.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pancreatic cystic lesions are commonly encountered on cross-sectional imaging.
⇒ They pose a distinct challenge in differentiating benign lesions from those with malignant potential.
⇒ There is a need to optimise patient pathways with appropriate allocation to surveillance programmes.

WHAT THIS STUDY ADDS

⇒ Endoscopic ultrasound-guided through-the-needle microbiopsy (EUS-TTNB) allows histological diagnosis of the nature of pancreatic cystic lesions (PCL).
⇒ EUS-TTNB provides additional diagnostic information which can lead to change in patient management including removal from surveillance programmes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ EUS-TTNB can be considered to enable definitive diagnosis of PCL.
⇒ Histological diagnosis can facilitate more personalised recommendations in patients under surveillance.
⇒ Further research is needed on the risk of pancreatitis after cyst wall sampling with measures implemented to reduce this risk.

[1]Department of Gastroenterology, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[2]Department of Histopathology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Correspondence to
Dr Wafaa Ahmed;
wafaa.ahmed@nhs.net

INTRODUCTION

Pancreatic cystic lesions (PCL) are frequently encountered on cross-sectional imaging.[1 2] The prevalence increases with age, and there is increasing detection with improvements in imaging modalities.[2 3] They pose a distinct clinical challenge due to the need to differentiate between those with benign and malignant potential. PCL warrants discussion in dedicated pancreatic multidisciplinary meetings (MDM) prior to being enrolled in a surveillance programme. The appropriateness of surveillance should take into account the risk of progression to malignancy within the patient's anticipated life expectancy and the appropriateness of surgery in the context of the patient's comorbidities and wishes. Discussion in a dedicated MDM has been shown to alter management in one-third of patients.[4]

Although endoscopic ultrasound fine needle aspiration (EUS-FNA) for cytological analysis of cyst fluid is highly specific for the diagnosis of malignancy, its sensitivity is reduced due to cellular paucity in the samples.[5] PCL fluid aspirate carcinoembryonic antigen (CEA) (cut-off value 192 ng/mL) remains key in differentiating mucinous from non-mucinous cysts; however, it cannot be relied on to differentiate benign from malignant cysts definitively.[5 6] Fluid glucose measurement may lead to better differentiation between mucinous and non-mucinous

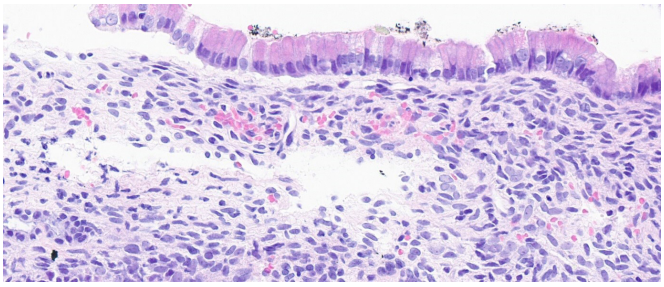

Figure 1 Mucinous cystic neoplasm with low-grade dysplasia.

PCL.[6–8] Therefore, although EUS-FNA is integral in the diagnostic pathway, PCL continues to pose a clinical conundrum in indeterminate cases. There is a need to optimise patient pathways with the appropriate discharge of patients and to determine surveillance intervals based on individual risk stratification.

Through-the-needle microbiopsy (TTNB) via EUS is a recent development that facilitates sampling of the walls of PCL for histological analysis with high clinical and technical success.[9 10] We sought to assess the impact of EUS-TTNB on the patient management pathway in a tertiary pancreas centre.

METHODS

A prospective database of consecutive patients who underwent EUS-TTNB between March 2020 to August 2022 at Leeds Teaching Hospitals NHS Trust (LTHT) was retrospectively analysed.

EUS was performed using Olympus GF-UCT260 linear-array echoendoscopes with ALOKA ARIETTA 850 processor (Olympus America, Center Valley, Pennsylvania, USA). All patients with PCL are discussed in a dedicated regional pancreas MDM with a catchment area of approximately 3.1 million people across the North and West Yorkshire region in the UK.[11] All patients with PCL under surveillance or newly diagnosed are discussed at the regional pancreas MDM. Patients are referred for EUS-FNA if worrisome features are detected on cross-sectional imaging or if there is diagnostic uncertainty. Indication for EUS-TTNB was when fine needle aspiration was indicated and a consensus on the nature of the lesion was not achieved following discussion at the MDM. Patient demographics, procedural characteristics, technical success, histological results, adverse events (AE) and management outcomes were recorded. All patient details were de-identified. This study was registered as a clinical audit and approved by the audit department at LTHT. The reporting of this study conforms to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.[12]

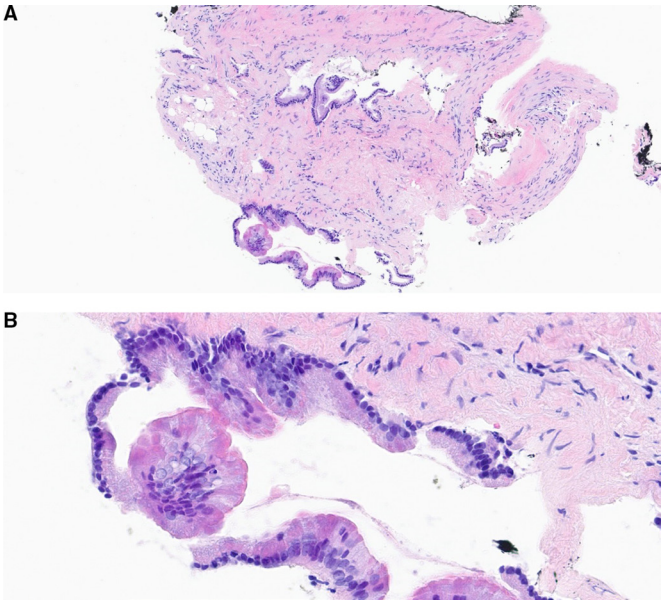

Figure 2 Intraductal papillary mucinous neoplasm with low-grade dysplasia.

Sampling method

Informed consent for EUS-TTNB was obtained. The EUS-TTNB forceps (Moray Micro forceps, Steris, Ireland) have a length of 230 cm, a sheath diameter of 0.8 mm and a jaw opening width of 4.3 mm. The forceps are introduced after puncture of the PCL with a 19G FNA needle (Expect Slimline Flexible, Boston Scientific, Marlborough, Massachusetts, USA) and allow sampling of pancreatic cyst walls, septations or mural nodules. As the standard of care, FNA was performed during the same cyst puncture, and cyst fluid aspirate was sent for biochemical (CEA and amylase) and cytological analysis. TTNB samples were sent for histological analysis with supplemental immunohistochemical staining performed at the histopathologist's discretion (figures 1 and 2). The surveillance strategies were defined by the MDM after review of the TTNB histology results. Patients did not receive pancreatitis prophylaxis.

Definitions

High-risk and worrisome features are defined as per the Fukuoka guidelines.[13] High-risk features are; a proximal lesion with obstructive jaundice, enhancing nodules, dilated main duct ≥10 mm. Worrisome features are; cyst size ≥3 cm, enhancing mural nodule ≥5 mm, thickened and enhancing cyst wall, main pancreatic duct (MPD) dilatation 5–9 mm, abrupt change in MPD calibre with distal pancreatic atrophy, presence of lymphadenopathy, elevated CA 19–9 or a cyst growth rate >5 mm/2 years.[13]

Technical success was defined as cyst puncture with a 19G FNA needle with successful aspiration and acquisition of at least one tissue specimen via TTNB. Specimen adequacy was defined as the acquisition of sufficient tissue for histological assessment. AE were defined according to the American Society of Gastrointestinal Endoscopy lexicon for AEs.[14] Acute pancreatitis was defined as per the revised Atlanta classification of acute pancreatitis.[15]

Downstaging was defined as a lengthening of surveillance intervals or discharge from a surveillance pathway. Upstaging was defined as the shortening of surveillance

intervals or progression to surgery or chemotherapy. Continuous variables were expressed as median and range. Categorical variables were displayed as a number and percentages.

RESULTS

Demographics

In the study period 70 patients underwent assessment of PCL by EUS. Thirty-four patients (22 women) were identified as having had EUS-TTNB. The median age at EUS was 61 years old (range 28–83 years old). The median cyst size was 35 mm (range 10–90 mm). Twenty (59%) cysts were incidental findings, 13 (38%) scans were done for pain and 1 (3%) for raised alkaline phosphatase. Sixteen (47%) had already been enrolled in a surveillance programme but demonstrated worrisome features prompting EUS examination. The location of the PCL were in the head (n=13, 38%), body (n=12, 35%), tail (n=8, 24%) and uncinate process (n=1, 3%). Twenty-five (74%) had worrisome features on imaging with no high risk stigmata, and there was diagnostic uncertainty in the remaining 9 (27%). Six (18%) had previously undergone a previous FNA of the PCL, 5 (15%) had new worrisome features, and there was diagnostic uncertainty in 1 (3%). Patient demographics and procedural characteristics are displayed in table 1.

Procedural data

Technical success was achieved in all cases. All patients received co-amoxiclav 1.2 g or ciprofloxacin 400 mg intravenously as antibiotic prophylaxis. EUS-FNA biochemistry and cytology in isolation were non-diagnostic in 18 (53%) cases.

The number of forceps bites was available for 17 patients (50%), and the median number was 4 (range 1–10 passes). Adequate specimens for histological diagnosis were obtained in 25 (74%) cases. Final diagnoses were intraductal papillary mucinous neoplasm (IPMN) (n=12, 35%), mucinous cystic neoplasm (MCN) (n=6, 18%), inflammatory cyst (n=4, 12%), lymphoepithelial cyst (n=3, 9%), serous cystic neoplasm (n=3, 9%) and neuroendocrine tumour (n=2, 6%). Four (12%) cases were indeterminate despite TTNB. Eleven (32%) cases had additional immunohistochemistry performed, but despite this, the diagnoses in four patients (12%) remained inconclusive. Immunohistochemistry was guided by the morphology, and was performed for the following reasons: to confirm cystic neuroendocrine tumour (neuroendocrine markers), to confirm/exclude mucinous cystic neoplasm (Carcinoembryonic antigen staining of epithelium, progesterone receptor, estrogen receptor and inhibin staining of ovarian-like stroma) and to confirm/exclude serous cystic neoplasm (Periodic acid–Schiff/Periodic acid–Schiff–diastase, inhibin).

Table 1 Patient demographics and procedural details

Characteristics	N (%)
Number of patients	34
Female gender	22 (65)
Cyst characteristics	
Size (mm), median (range)	35 (10–90)
Method of diagnosis	
Incidental finding	20 (59)
Investigation for pain	13 (38)
Investigation for raised ALP	1 (3)
Already under surveillance	16 (47)
Location of cyst	
Head	13 (38)
Body	12 (35)
Tail	8 (24)
Uncinate	1 (3)
Previous FNA	6 (18)
Worrisome features on EUS*	25 (74)
Procedural characteristics	
Prophylactic antibiotics	34 (100)
Median number of forceps passes median (range)	4 (1–10)
Technical success	34 (100)
Specimen adequacy	25 (74)
Final diagnosis	
IPMN	12 (35)
MCN	6 (18)
Inflammatory	4 (12)
Indeterminate	4 (12)
Lymphoepithelial cyst	3 (9)
SCN	3 (9)
NET	2 (6)

*Worrisome features were defined cyst size ≥3 cm, enhancing mural nodule ≥5 mm, thickened and enhancing cyst wall, main pancreatic duct (MPD) dilatation 5–9 mm, abrupt change in MPD calibre with distal pancreatic atrophy, presence of lymphadenopathy, elevated CA 19–9 or a cyst growth rate >5 mm/2 years.
ALP, alkaline phosphatase; EUS, endoscopic ultrasound; FNA, fine needle aspiration; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; NET, neuroendocrine tumour; SCN, serous cystic neoplasm.

Change in management

EUS-TTNB added additional diagnostic information in 26 (77%) cases. EUS-TTNB led to a change in management in 24 (71%) cases. Sixteen (47%) patients were downstaged, with five (15%) being discharged. Of the remaining 11 (32%) cases who were downstaged, 7 (64%) were already in a surveillance programme and underwent EUS-TTNB due to worrisome features being found on imaging (figure 3).

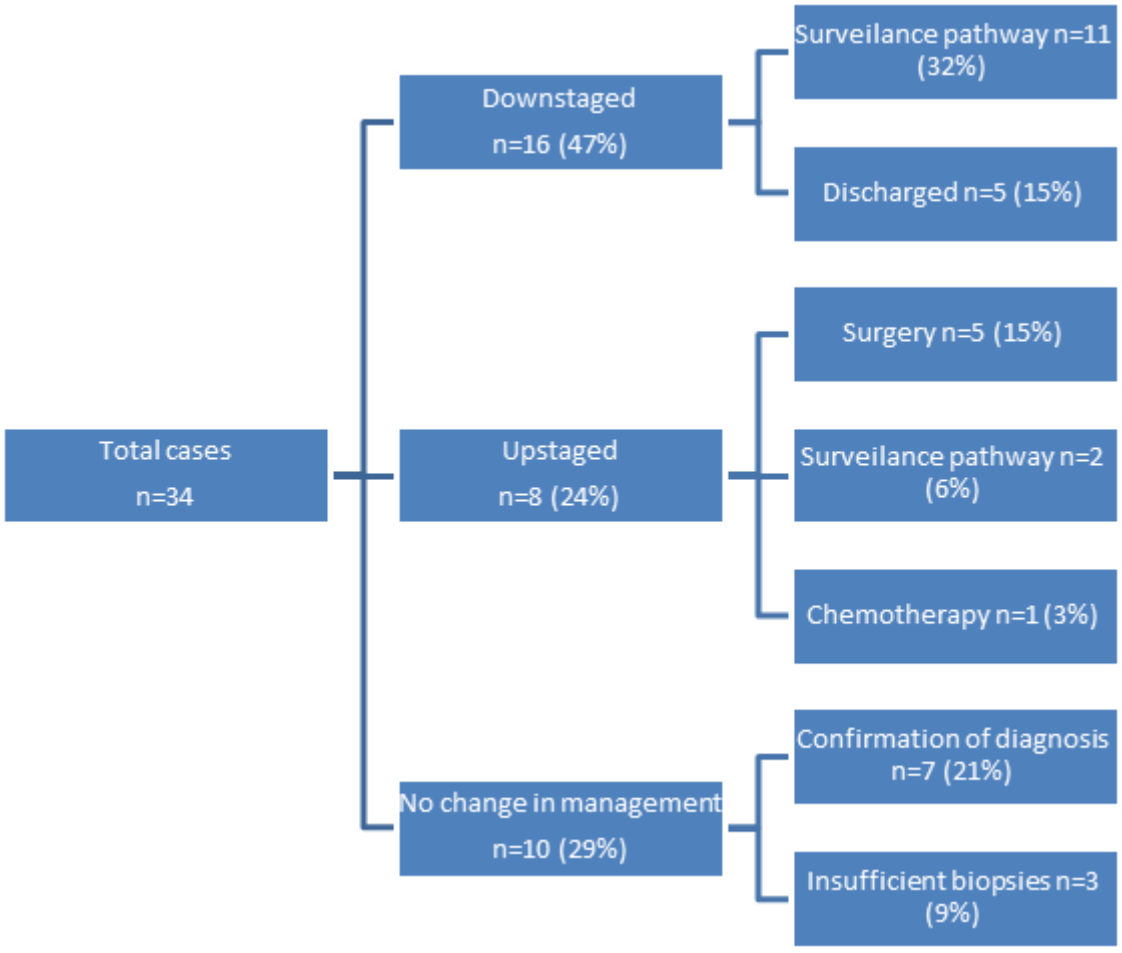

Figure 3 Changes to the patient pathway with endoscopic ultrasound-guided through-the-needle microbiopsy.

Eight (24%) were upstaged; five (15%) underwent surgical assessment for resection, two (6%) had increased surveillance and one (3%) underwent chemotherapy for malignant transformation of an IPMN. Of the patients referred for surgery, four (80%) underwent surgery. The available histology from the resection specimen confirmed MCN in three patients. One patient had an indeterminate 90 mm cyst, and the resected specimen showed a benign cystic lymphangioma. One patient died in the postoperative period secondary to a hepatic artery haemorrhage. Table 2 demonstrates the histological findings leading to upstaging and downstaging.

In the 10 (29%) cases without change in management, 7 (70%) had confirmation of the presumed diagnosis with no change in surveillance, and 3 (30%) did not receive a conclusive diagnosis despite EUS-TTNB and remained on surveillance.

In the six patients who had previous EUS-FNA, a definitive diagnosis was obtained in five (83%).

AEs

There were two (6%) cases of mild acute pancreatitis as per the revised Atlanta classification.[15] They required an inpatient hospital stay and recovered with conservative management. One case of intracystic bleeding occurred at the time of the cyst puncture. The patient was asymptomatic and did not require hospital admission.

DISCUSSION

PCL are incidental findings in 2% of asymptomatic patients undergoing imaging.[16 17] Due to the advances in medical imaging, this number is likely to increase further.[1 2 18] The incidence increases with age and can be associated with other disorders, including polycystic kidney disease.[19 20] PCL are classified into mucinous and non-mucinous lesions. The mucinous lesions, IPMN and MCNs, are known precursors to pancreatic adenocarcinoma (PDAC), which remains one of the leading causes of cancer deaths.[21 22] Early diagnosis of PDAC remains integral to better treatment outcomes.[23] In this study, we demonstrated a real-world experience of the utility of EUS-TTNB as an additional tool in the management of patients with PCL, which led to a change in management in 71% (24/34) of patients.

Identification and surveillance of patients with PCL represent a strategy to prevent the progression to cancer. However, differentiating between those that may harbour malignant potential and those that are benign remains challenging. Although the risk of incidental cysts having

Table 2 Histological diagnosis leading to upstaging or downstaging

	Location of lesion	Cyst size (mm)	Final diagnosis	Nature of management
Patients who were downstaged				
1	HOP	35	IPMN	Decreased surveillance
2	HOP	32	Post-inflammatory pseudocyst	Decreased surveillance
3	HOP	30	IPMN	Decreased surveillance
4	HOP	22	Indeterminate	Decreased surveillance
5	HOP	25	IPMN	Decreased surveillance
6	HOP	50	Lymphoepithelial cyst*	Decreased surveillance
7	BOP	90	Inflammatory	Decreased surveillance
8	BOP	45	IPMN	Decreased surveillance
9	TOP	33	Inflammatory	Decreased surveillance
10	TOP	12	NET	Decreased surveillance
11	Uncinate	35	IPMN	Decreased surveillance
12	HOP	40	SCN	Discharged
13	BOP	50	SCN	Discharged
14	BOP	35	Lymphoepithelial cyst	Discharged
15	BOP	30	Lymphoepithelial cyst	Discharged
16	BOP	20	SCN	Discharged
Patients who were upstaged				
1	HOP	66	MCN	Surgery
2	BOP	50	MCN	Surgery
3	BOP	40	MCN	Surgery
4	TOP	90	Indeterminate†	Surgery
5	TOP	36	MCN	Surgery
6	BOP	55	Malignant transformation of IPMN	Chemotherapy
7	TOP	20	NET	Increased surveillance
8	TOP	32	MCN	Increased surveillance

*A suspicion of a dermoid cyst remained and in view of the cyst size the patient joined the cyst surveillance pathway.
†The patient was a young woman and after counselling elected to undergo surgery.
BOP, body of pancreas; HOP, head of pancreas; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; NET, neuroendocrine tumour; SCN, serous cystic neoplasm; TOP, tail of pancreas.

invasive cancer or intraductal malignancy is low, identifying those at increased risk is of clinical importance.[24] Although surgery is indicated in patients with high-risk stigmata (proximal lesion with obstructive jaundice, enhancing nodules, dilated main duct (≥10 mm), it is sometimes performed for those with worrisome features.[13] However, it is associated with high morbidity, with final histology showing benign lesions in a not insignificant proportion of resected specimens.[25 26]

Worrisome features include cyst size ≥3 cm, non-enhancing mural nodule ≥5 mm, thickened and enhancing cyst wall, MPD dilatation 5–9 mm, abrupt change in MPD calibre with distal pancreatic atrophy, presence of lymphadenopathy, elevated CA 19–9 or a cyst growth rate >5 mm/2 years. These features are associated with an increased risk of high-grade dysplasia or cancer.[20 27] Patients should be counselled on the benefits of surgery versus surveillance. Patients can remain on surveillance programmes for many years, submitting them to repeated investigations, follow-up and potentially repeated endoscopic ultrasound. Our study shows that TTNB from the PCL could influence management outcomes in terms of upstaging or downstaging. Facilitation of discharge from surveillance in patients who would otherwise be enrolled in a surveillance programme is likely to reduce patients' anxiety regarding follow-up and lessens the burden on healthcare resources. In other patients, the confirmation of a histological diagnosis leads to the justification of the subsequent outcome, be it ongoing surveillance or surgery.

In this study, adequate samples from TTNB were obtained in 74% of cases. This is in comparison to EUS-FNA, where obtaining sufficient fluid for a cytological and biochemical analysis is usually possible in less than half of patients.[8] Sufficient samples allow

for immunohistochemistry and further molecular processing on the cyst walls that could be incorporated into future management pathways.[22 28] The use of TTNB has been shown to have a higher sensitivity and specificity than cytology in the diagnosis of PCL, with the addition of immunohistochemical stains conferring additional diagnostic advantage in establishing the cyst subtype.[29] Confocal laser endomicroscopy is another tool that can aid in diagnosing PCL with comparable technical and clinical success to TTNB; however, it is expensive, requires significant training in its use and is not routinely available.[30 31]

Although the most frequently detected mucinous PCL are IPMN, they can be difficult to distinguish from MCN, more so when the size is ≤30 mm.[27 32] They may harbour different characteristics, and differentiation may help decision-making around surgical intervention.[25 32] In this study, histological samples were sufficient to perform immunohistochemical studies and detect pathognomonic features of MCN, including the presence of ovarian-like stroma. Such features may provide more information to clinicians when making decisions in conjunction with patients on follow-up strategies.

In this cohort, EUS-FNA in isolation was diagnostic in less than 50% of patients, which is consistent with previous studies.[8] Mucinous lesions' viscosity can mean that aspiration is sometimes difficult.[9] EUS-TTNB needles allow an aspirate to be taken and microbiopsy forceps to be advanced through the FNA needle, which remains in the intracystic space. When a mural nodule is present, TTNB may allow more targeted sampling of the nodule in comparison to FNA. The number of TTNB needed to reach a histological diagnosis is not defined, in this study the median number of passes was four, limiting the samples to two macroscopically visible specimens may be sufficient to reach a histological diagnosis and potentially reduce the AE rate associated with this method.

AE rates for FNA have been reported in the region of 2%.[23 33 34] Although the 9% AE rate in this cohort is comparable to the 5%–16.7% previously reported, EUS-TTNB confers an added risk in comparison to FNA alone.[9 31 35] Although the patients in this cohort had moderate pancreatitis with no long-term sequelae, a 3% risk of severe pancreatitis has been reported with one fatal case.[36] The pathogenesis of this increased risk may be due to cyst wall disruption with activation of inflammatory pathways. It remains to be determined if patients undergoing EUS-TTNB should have rectal non-steroidal anti-inflammatory drugs similar to those undergoing endoscopic retrograde cholangiopancreatography with similar pancreatitis risk. In view of the additional risk in comparison to EUS-FNA alone, it is imperative to have appropriate patient selection and informed consent.

Limitations

This was a retrospective study with the inherent bias associated with a retrospective study. Management decisions were made in an MDT environment at a single tertiary centre which may introduce bias. The data were collected over a 2-year period and there may be an associated learning curve associated with sampling and histological analysis which was not addressed by this paper. In terms of histological analysis, we do not report on histological subtypes of IPM as subtype is only assessed on resected specimens in our centre and immunohistochemistry was only performed in selected cases. In addition, due to the nature of data acquisition at a tertiary referral centre, some patients may have presented to other hospitals with AEs, so some may not have been captured. There is also no standardised number of TTNB passes which may impact specimen adequacy with the number of visible tissue specimens not consistently recorded.

CONCLUSION

EUS-TTNB is a valuable adjunct in the diagnosis of PCL and can alter management significantly. Care should be taken in patient selection and consent due to the AE rate.

Contributors WA wrote and prepared the manuscript. WA, MM and CY collected data. CY, LS, SE, BP and MTH reviewed and corrected the manuscript. WO supervised, reviewed and edited the manuscript. All authors have read and agreed to the final version of the manuscript. WO is the guarantor and accepts full responsibility for the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs
Wafaa Ahmed http://orcid.org/0000-0003-4034-7570
Simon Everett http://orcid.org/0000-0002-4251-5323
Wei On http://orcid.org/0000-0002-9672-282X

REFERENCES

1 Laffan TA, Horton KM, Klein AP, *et al*. Prevalence of unsuspected pancreatic cysts on MDCT. *AJR Am J Roentgenol* 2008;191:802–7.
2 Moris M, Bridges MD, Pooley RA, *et al*. Association between advances in high-resolution cross-section imaging technologies and increase in prevalence of pancreatic cysts from 2005 to 2014. *Clin Gastroenterol Hepatol* 2016;14:585–93.
3 Kimura W, Nagai H, Kuroda A, *et al*. Analysis of small cystic lesions of the pancreas. *Int J Pancreatol* 1995;18:197–206.
4 Lennon AM, Manos LL, Hruban RH, *et al*. Role of a multidisciplinary clinic in the management of patients with pancreatic cysts: a single-center cohort study. *Ann Surg Oncol* 2014;21:3668–74.
5 Suzuki R, Thosani N, Annangi S, *et al*. Diagnostic yield of EUS-FNA-based cytology distinguishing malignant and benign IPMNs: a systematic review and meta-analysis. *Pancreatology* 2014;14:380–4.
6 McCarty TR, Garg R, Rustagi T. Pancreatic cyst fluid glucose in differentiating mucinous from nonmucinous pancreatic cysts:

a systematic review and meta-analysis. *Gastrointest Endosc* 2021;94:698–712.
7 Brugge WR, Lewandrowski K, Lee-Lewandrowski E, *et al*. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology* 2004;126:1330–6.
8 de Jong K, Poley J-W, van Hooft JE, *et al*. Endoscopic ultrasound-guided fine-needle aspiration of pancreatic cystic lesions provides inadequate material for cytology and laboratory analysis: initial results from a prospective study. *Endoscopy* 2011;43:585–90.
9 Shakhatreh MH, Naini SR, Brijbassie AA, *et al*. Use of a novel through-the-needle biopsy forceps in endoscopic ultrasound. *Endosc Int Open* 2016;4:E439–42.
10 Barresi L, Crinò SF, Fabbri C, *et al*. Endoscopic ultrasound-through-the-needle biopsy in pancreatic cystic lesions: a multicenter study. *Dig Endosc* 2018;30:760–70.
11 England N. Available: https://www.england.nhs.uk/digitaltechnology/connecteddigitalsystems/digital-roadmaps/footprints/north-england/yorkshire-and-humber/
12 von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;147:573–7.
13 Tanaka M, Fernández-del Castillo C, Adsay V, *et al*. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology* 2012;12:183–97.
14 Cotton PB, Eisen GM, Aabakken L, *et al*. A lexicon for endoscopic adverse events: report of an ASGE workshop. *Gastrointest Endosc* 2010;71:446–54.
15 Banks PA, Bollen TL, Dervenis C, *et al*. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013;62:102–11.
16 Chang YR, Park JK, Jang J-Y, *et al*. Incidental pancreatic cystic Neoplasms in an asymptomatic healthy population of 21,745 individuals. *Medicine (Baltimore)* 2016;95:e5535.
17 de Jong K, Nio CY, Hermans JJ, *et al*. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. *Clin Gastroenterol Hepatol* 2010;8:806–11.
18 Lee KS, Sekhar A, Rofsky NM, *et al*. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. *Am J Gastroenterol* 2010;105:2079–84.
19 de Jong K, Bruno MJ, Fockens P. Epidemiology, diagnosis, and management of cystic lesions of the pancreas. *Gastroenterol Res Pract* 2012;2012:147465.
20 Stutchfield BM, Nayar M, Penman ID. Pancreatic cystic lesions: risk stratification and management based on recent guidelines. *Frontline Gastroenterol* 2019;10:182–7.
21 Rahib L, Smith BD, Aizenberg R, *et al*. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014;74:2913–21.
22 Pereira SP, Oldfield L, Ney A, *et al*. Early detection of pancreatic cancer. *Lancet Gastroenterol Hepatol* 2020;5:698–710.
23 Strobel O, Neoptolemos J, Jäger D, *et al*. Optimizing the outcomes of pancreatic cancer surgery. *Nat Rev Clin Oncol* 2019;16:11–26.
24 Vege SS, Ziring B, Jain R, *et al*. American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology* 2015;148:819–22.
25 Valsangkar NP, Morales-Oyarvide V, Thayer SP, *et al*. 851 resected cystic tumors of the pancreas: a 33-year experience at the massachusetts general hospital. *Surgery* 2012;152:S4–12.
26 Sahora K, Mino-Kenudson M, Brugge W, *et al*. Branch duct intraductal papillary mucinous neoplasms: does cyst size change the tip of the scale? a critical analysis of the revised International consensus guidelines in a large single-institutional series. *Ann Surg* 2013;258:466–75.
27 European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. *Gut* 2018;67:789–804.
28 Springer S, Masica DL, Dal Molin M, *et al*. A multimodality test to guide the management of patients with a pancreatic cyst. *Sci Transl Med* 2019;11:eaav4772.
29 Rift CV, Scheie D, Toxværd A, *et al*. Diagnostic accuracy of EUS-guided through-the-needle-biopsies and simultaneously obtained fine needle aspiration for cytology from pancreatic cysts: a systematic review and meta-analysis. *Pathol Res Pract* 2021;220:153368.
30 Fugazza A, Gaiani F, Carra MC, *et al*. Confocal laser endomicroscopy in gastrointestinal and pancreatobiliary diseases: a systematic review and meta-analysis. *Biomed Res Int* 2016;2016:4638683.
31 Kovacevic B, Antonelli G, Klausen P, *et al*. EUS-guided biopsy *Versus* confocal laser endomicroscopy in patients with pancreatic cystic lesions: a systematic review and meta-analysis. *Endosc Ultrasound* 2021;10:270–9.
32 Crippa S, Fernández-Del Castillo C, Salvia R, *et al*. Mucin-producing neoplasms of the pancreas: an analysis of distinguishing clinical and epidemiologic characteristics. *Clin Gastroenterol Hepatol* 2010;8:213–9.
33 Razik R, James PD, Khan R, *et al*. Risk of adverse events associated with upper and lower endoscopic ultrasound: a population-based cohort study. *Endosc Int Open* 2021;9:E1427–34.
34 Kanno A, Yasuda I, Irisawa A, *et al*. Adverse events of endoscopic ultrasound-guided fine-needle aspiration for histologic diagnosis in Japanese tertiary centers: multicenter retrospective study. *Dig Endosc* 2021;33:1146–57.
35 Stigliano S, Covotta F, Di Matteo FM. A new micro-forceps for endoscopic ultrasound-guided through-the-needle biopsy in the diagnosis of pancreatic cystic lesions: single center experience. *JGH Open* 2021;5:1004–8.
36 Kovacevic B, Klausen P, Rift CV, *et al*. Clinical impact of endoscopic ultrasound-guided through-the-needle microbiopsy in patients with pancreatic cysts. *Endoscopy* 2021;53:44–52.