REVIEW

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CLINICAL ENDOSCOPY

Endoscopic ultrasound-guided needle-based confocal laser endomicroscopy for pancreatic cystic lesions: current status and future prospects

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Pancreatic cystic lesions (PCLs) have increased in prevalence due to the increased usage and advancements in cross-sectional abdominal imaging. Current diagnostic techniques cannot distinguish between PCLs requiring surgery, close surveillance, or expectant management. This has increased the morbidity and healthcare costs from inappropriately aggressive and conservative management strategies. Endoscopic ultrasound (EUS) needle-based confocal laser endomicroscopy (nCLE) allows for microscopic examination and delineation of the surface epithelium of PCLs. Landmark studies have identified characteristics distinguishing various types of PCLs, confirmed the high diagnostic yield of EUS-nCLE (especially for PCLs with an equivocal diagnosis), and shown that EUS-nCLE helps to change management and reduce healthcare costs. Refining procedure technique and reducing procedure length have improved the safety of EUS-nCLE. The utilization of artificial intelligence and its combination with other EUS-based advanced diagnostic techniques would further improve the results of EUS-based PCL diagnosis. A structured training program and device improvements to allow more complete mapping of the pancreas cyst epithelium will be crucial for the widespread adoption of this promising technology.

Keywords: Confocal laser scanning microscopy; Endoscopic ultrasound-guided fine needle aspiration; Pancreatic cyst

INTRODUCTION

Prevalence and clinical significance of pancreatic cystic lesions

Pancreatic cystic lesions (PCLs) are increasing in prevalence due to improved detection by more frequent use of cross-sectional imaging[1] and advances in magnetic resonance imaging (MRI).[2] The reported overall prevalence of PCLs is 15% in MRI-based studies.[3] Incidental detection of PCLs in transabdominal ultrasound and computed tomography studies may further increase the prevalence of PCLs.[4,5]

Early detection of malignancy or premalignant lesions in PCLs remains important as it significantly improves patient survival.[6,7] Most patients with pancreatic cancer are diagnosed with metastatic disease at presentation, conferring a poor prognosis and a median survival of three months.[8] The growing importance of early detection comes as pancreatic cancer is projected to be the second leading cause of cancer-related deaths in the United States before 2030.[9]

Distinguishing between different cyst types

Pancreatic resection remains the only definitive management for PCLs. However, with significant mortality and morbidity rates of 2.1% and 30%, respectively,[10] there is a crucial need to

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distinguish the cysts that require surgical resection from those that do not.

PCLs that are considered neoplastic include solid-pseudopapillary tumors and cystic pancreatic neuroendocrine tumors (NETs). Among PCLs considered benign, mucinous types such as intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) carry malignant potential, while non-mucinous types such as pancreatic pseudocysts and serous cystadenomas (SCAs) do not. Diagnosis may be made on imaging alone, depending on the presence of characteristic MRI findings, and for pancreatic pseudocysts, further supported by a prior history of acute pancreatitis. Where the diagnosis remains unclear or high-risk features are present, endoscopic ultrasound (EUS) followed by fine needle aspiration (FNA) of the cyst can be done. Fluid analysis using cytology can detect cancer and high-grade dysplasia in PCLs, while the use of carcinoembryonic antigen (CEA) levels helps to differentiate between mucinous and non-mucinous PCLs, and raised amylase levels suggest communication with pancreatic ducts.[11]

Pancreatic cyst fluid biochemistry is highly sensitive for diagnosing mucinous PCLs, with a sensitivity of 91%.[12] However, the presence of malignancy or high-grade dysplasia is not well detected with cytology, reaching a sensitivity of only 50%.[13] PCLs with high-risk features should undergo further evaluation to confirm if there is any malignancy or high-grade dysplasia that would necessitate surgical resection instead of continued close surveillance.

Role of needle-based confocal laser endomicroscopy

Needle-based confocal laser endomicroscopy (nCLE) is a valuable adjunct in EUS-guided assessment of PCLs to improve diagnostic yield for lesions ≥2 cm.[11] nCLE facilitates *in vivo* microscopy of PCL epithelium for real-time histopathological assessment using high-resolution images. *In-vivo* microscopy allows the preservation of greater histological detail compared to biopsy samples. Real-time histological assessment provides the endoscopist with on-site diagnostic capability, reducing sampling error and the number of passes needed for diagnosis. This may potentially avoid the need for conventional histological slide preparation in the future. A contraindication specific to using nCLE during EUS is a patient allergy to fluorescein and/or pregnancy.

METHODS

Selection of papers

Two authors conducted separate searches using PubMed and Google Scholar to review the literature from inception to December 2022. Keywords and Medical Subject Heading terms used included "needle-based confocal laser endomicroscopy" and "pancreatic cyst". All relevant original studies, systematic reviews, and meta-analyses that discussed nCLE for PCLs were included. The reference lists of selected studies were manually screened to identify further studies of relevance. Non-English articles, abstracts, and duplicate articles were excluded. Each study was carefully reviewed, including the procedures conducted, technical success rates, clinical outcomes, adverse events, and follow-up.

nCLE

The Cellvizio AQ-Flex 19 miniprobe (Mauna Kea Technologies) measures 3 m in length and is compatible with an operating channel equal to or more than 0.91 mm, which correlates with the size of a 19-G FNA needle (Fig. 1). The miniprobe provides a 325 μm field of view at a resolution of 3.5 μm. The reported depth of observation is between 40 and 70 μm. FNA needles compatible with the miniprobe are listed in Table 1.[14] The miniprobe contains three safety features (Fig. 2). First, a 4 mm metallic ferrule protects the distal end of the miniprobe

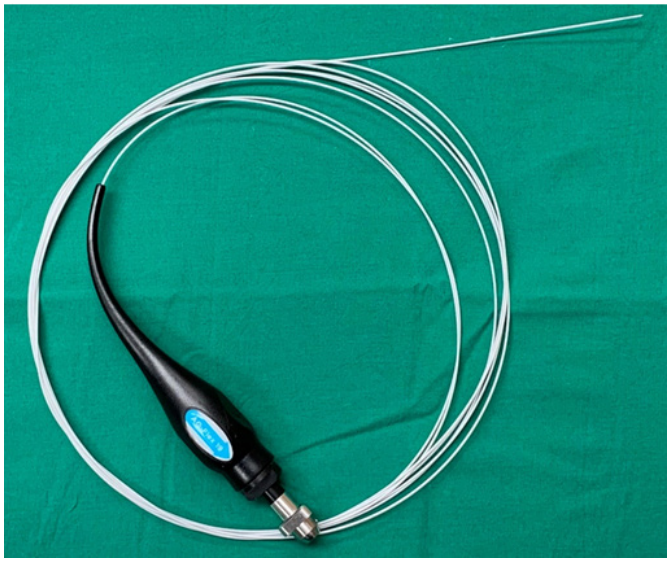

Fig. 1. The AQ-Flex 19-needle confocal laser endomicroscopy miniprobe (Cellvizio AQ-Flex 19 miniprobe; Mauna Kea Technologies).

Table 1. Compatibility of endoscopic ultrasound-fine needle aspiration needle with needle-based confocal laser endomicroscopy probe

Type of needle	Manufacturer	Compatible
EchoTip Ultra Endoscopic Ultrasound Needle	Cook Medical	Yes
EZShot 2 Aspiration Needle	Olympus	Yes
Expect Needle 19 Flex	Boston Scientific	Yes
SonoTip Pro Control	Medi-Globe Gmbh	Yes
SonoTip II	Medi-Globe Gmbh	Yes
BNX Fine Needle Aspiration System	Medtronic	Yes
EchoTip Ultra Endoscopic Ultrasound Access Needle	Cook Medical	No
EchoTip ProCore	Cook Medical	No
Quick-Core Endoscopic Ultrasound Needle	Cook Medical	No
19-G FlexNeedle Clearview	CONMED	No

All needles are in 19-G size. Adapted from Mauna Kea Technologies, France.[14]

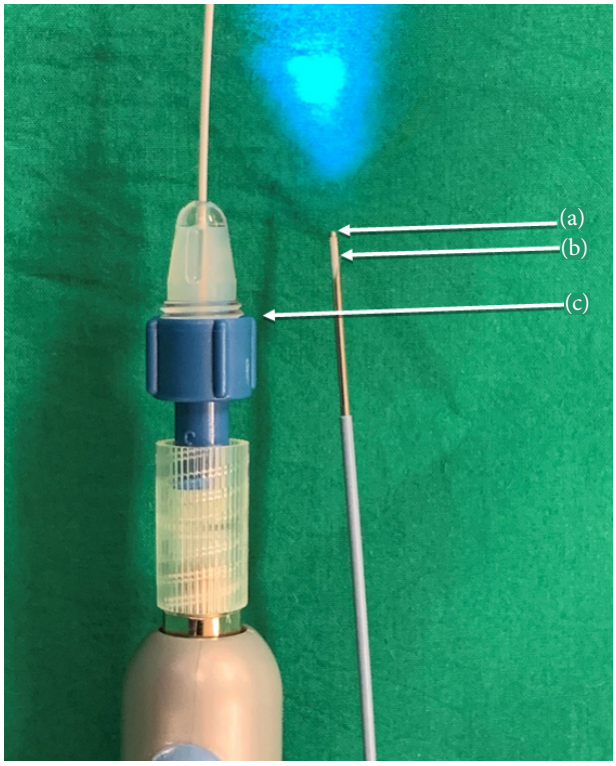

Fig. 2. (a) The ferrule is a metallic tap at the distal end of the probe that protects the device from the beveled needle tip. (b) The sheath of the probe comprises a robust, protective, biocompatible coating. (c) A locking device is attached by a Luer lock on the fine needle aspiration needle's proximal hub and is secured onto the probe to maintain needle position and prevent migration.

from beveled FNA needles and ensures device integrity during the insertion and extraction process. Second, the miniprobe is encased by a protective sheath that is coated with a biocompatible material. Third, the position of the miniprobe at the distal end of the FNA needle is held steady using a locking device at the other end of the needle.

A 19-G FNA needle is first prepared by removing the stylet and attaching the locking device. The miniprobe can then be inserted through the locking device and advanced until the distal end can be seen. The miniprobe must be retracted into the needle before they are both inserted into the endoscope working channel. After cyst puncture, the miniprobe is advanced again up to the opposite cyst wall (Fig. 3). Then, 2.5 mL of intravenous 10% fluorescein is given to allow fluorescent imaging. Real-time sequences of microscopic images of the cyst wall and its structures are taken for a maximum of 10 minutes. After nCLE is done, pancreatic cyst fluid is aspirated for biochemical analysis, tumor markers, and cytology. Antibiotic prophylaxis is routinely given for EUS-nCLE just before the start of the procedure.

REVIEWING THE EVIDENCE

Feasibility studies and refining of procedural technique

Konda et al.[15] first described the clinical application of nCLE for the assessment of PCLs. The multicenter feasibility study included 18 patients who underwent EUS-FNA for pancreatic cysts or masses. Although technical success was eventually achieved in 17 patients (94.4%), technical difficulty was encountered in six of 18 patients (33.3%). This was postulated to result from loading the miniprobe with the FNA needle within the endoscope and the longer length of the ferrule.

Konda et al.[16] then proceeded with the INSPECT (*in vivo* nCLE study in the pancreas with endosonography of cystic tumors) to establish nCLE image characterization of PCLs among expert endosonographers. The first part of the study involved an expert consensus panel reviewing nCLE images of PCLs

from 26 patients and describing imaging features that may help to distinguish various PCLs, which were then diagnosed based on histology. The next part of the study assessed the diagnostic performance of these imaging features in another 31 patients with PCLs, including mucinous cystadenoma, IPMN, or adenocarcinoma. Epithelial villous structures seen on nCLE were associated with pancreatic cystic neoplasms (p=0.004) with 59% sensitivity and 50% negative predictive value but 100% specificity and positive predictive value. This suggested that nCLE has a high specificity for diagnosing pancreatic cystic neoplasms but was limited by low sensitivity.

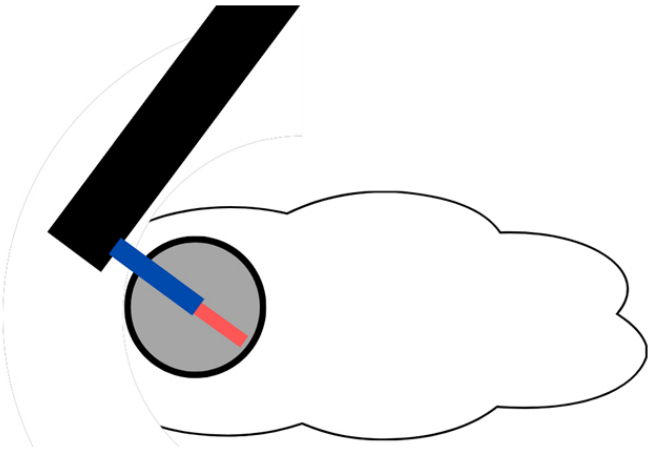

Fig. 3. A schema of endoscopic ultrasound-guided needle-based confocal laser endomicroscopy (nCLE) being performed for a pancreatic cystic lesion. Black: duodenoscope; blue: 19G FNA needle; red: nCLE miniprobe; gray circle: pancreatic cyst.

Nakai et al.[17] sought to better visualize the interior of a cyst by combining both cystoscopy and nCLE in the DETECT study (diagnosis of pancreatic cysts: endoscopic ultrasound, through-the-needle confocal laser endomicroscopy and cystoscopy trial). The sensitivity of nCLE for diagnosis of mucinous cysts was 80%, while that of cystoscopy was 90%, and combining both cystoscopy and nCLE further improved the sensitivity to 100% with a diagnostic accuracy of 89%. Cystoscopy was performed using a through-the-needle fiber optic probe before nCLE, and both were done via a 19G FNA needle.

Establishing nCLE diagnostic criteria

Table 2 summarizes the landmark studies on the role of nCLE in the diagnosis of PCLs,[15-27] while Table 3 provides an overview of the diagnostic features of various PCLs as well as their respective validity scores on sensitivity, specificity, and accuracy.[16-18,20-22,24,25,28-30]

The CONTACT study was a prospective study of EUS-FNA combined with nCLE conducted by Napoléon et al.[28] on 31 patients with a solitary PCL of unknown diagnosis. The authors found that a superficial vascular network (Fig. 4) seen on nCLE had a sensitivity of 69%, specificity of 100%, accuracy of 87%, positive predictive value of 100%, and negative predictive value of 82% for the diagnosis of SCA when confirmed against histological assessment of surgical specimens. There was also good interobserver agreement (IOA) on this finding (k=0.77; 95%

Table 2. Key clinical studies on using nCLE to diagnose pancreatic cystic lesions

Study	Year	Study design	Country	Accuracy rate of EUS-nCLE	Basis of final diagnosis	*n*	Sex (male/female)	Age (mean in years)	Size (mm)
Konda et al.[15]	2011	Prospective study	United States	Safety and feasibility study	Histology Cytology Imaging on EUS	18	7/11	57.9	43
Konda et al.[16] (INSPECT)	2013	Retrospective study	United States	71%	Clinical consensus PCF analysis Imaging on EUS Cross-sectional imaging Follow-up imaging	31	15/16	59.7	32
Nakai et al.[17] (DETECT)	2015	Prospective study	United States	89%	Histology Cytology PCF analysis Imaging on EUS Cross-sectional imaging	30	9/21	72	30

(Continued to the next page)

Table 2. Continued

Study	Year	Study design	Country	Accuracy rate of EUS-nCLE	Basis of final diagnosis	*n*	Sex (male/female)	Age (mean in years)	Size (mm)
Napoleon et al.[18] (CONTACT 1)	2016	Prospective study	France	87%	Clinical consensus Histology Cytology	31	6/25	57	39
Karia et al.[23]	2016	Retrospective study	United States	46%	Histology Cytology PCF analysis Imaging on EUS Cross-sectional imaging	15	10/5	66.6	25
Krishna et al.[24]	2016	Retrospective study	United States	95%	Clinical consensus Histology Cytology	26	10/16	54.8	32
Kadayifci et al.[22]	2017	Retrospective study	United States	83%	Histology PCF analysis Imaging on EUS	18	8/10	65.4	34
Krishna et al.[25]	2017	Retrospective study	United States	95%	Clinical consensus Histology	29	13/16	53	32
Napoleon et al.[20] (CONTACT 2)	2019	Prospective study	France	91%	Histology Cytology PCF analysis Imaging on EUS Cross-sectional imaging	78	26/52	57	40
Chin et al.[19]	2018	Prospective study	Singapore	80%	Histology Cytology PCF analysis Imaging on EUS Cross-sectional imaging	12	6/6	66.5	34
Keane et al.[21] (CONCYST-01)	2019	Prospective study	United Kingdom	77%	Clinical consensus Cytology Imaging on EUS Cross-sectional imaging	56	35/21	68	25
Palazzo et al.[26]	2020	Retrospective study	France	85%	Clinical consensus PCF analysis Imaging on EUS Cross-sectional imaging	206	69/137	57	38
Cheesman et al.[27]	2020	Retrospective study	United States	84%	Histology Cytology PCF analysis Imaging on EUS Cross-sectional imaging	44	16/28	66	34

nCLE, needle-based confocal laser endomicroscopy; EUS, endoscopic ultrasound; PCF, pancreatic cystic fluid; INSPECT, *in vivo* nCLE study in the pancreas with endosonography of cystic tumors; DETECT, Diagnosis of pancreatic cysts: endoscopic ultrasound, through-the-needle confocal laser endomicroscopy and cystoscopy trial; CONCYST-01, Confocal endomicroscopy in cystic lesions of the pancreas.

confidence interval [CI], 0.55–0.99).

A subsequent retrospective study (CONTACT 1) by Napoleon et al.[18] developed nCLE criteria for other PCLs that was able to make a conclusive diagnosis for 23 out of 31 patients (74%). On nCLE, IPMNs had papillary projections seen as a white center with a relatively darker epithelial border (Fig. 5). MCNs had an epithelial border seen as a thin dark line that outlined a gray band (Fig. 6), and pseudocysts displayed a mix

Table 3. nCLE diagnostic features for specific pathology and their sensitivity, specificity, and accuracy in key clinical studies

Pattern	Study	Year	*n*	Sensitivity (%)	Specificity (%)	Accuracy (%)
Serous cystadenoma						
Fern pattern	Krishna et al.[25]	2017	13	98	97	92
Fern pattern	Krishna et al.[29]	2020	113	87	100	97
Superficial vascular network	Napoléon et al.[28]	2015	31	69	100	87
Superficial vascular network	Napoleon et al.[20]	2019	71	95	100	99
Superficial vascular network	Keane et al.[21]	2019	56	56	-	38
Pseudocyst						
Bright particles on a dark background	Napoleon et al.[18]	2016	31	43	100	87
Bright particles on a dark background	Krishna et al.[29]	2020	65	67	97	95
A field of bright, grey, and black particles	Keane et al.[21]	2019	56	67	-	67
IPMN						
Papillae with finger-like projections	Nakai et al.[17]	2015	30	77	100	87
Papillae with finger-like projections	Napoleon et al.[18]	2016	31	80	92	90
Papillae with finger-like projections	Krishna et al.[29]	2020	65	98	94	97
Papillae with finger-like projections	Keane et al.[21]	2019	56	90	-	77
MCN						
Epithelial bands	Napoleon et al.[18]	2016	31	67	96	90
Epithelial bands	Krishna et al.[29]	2020	65	98	94	97
Mucinous cyst (both IPMN and MCN)						
Papillae with finger-like projections or epithelial bands	Krishna et al.[30]	2015	33	91	95	94
	Krishna et al.[24]	2016	26	94	82	89
	Napoleon et al.[20]	2019	71	95	100	97
Papillae with finger-like projections, or dark rings, or gland-like structures, or epithelial bands	Kadayifci et al.[22]	2017	18	66	100	83
Rope ladder, or branch vascular pattern, or papillae with finger-like projections, or epithelial bands	Krishna et al.[25]	2017	16	93	89	91
Neuroendocrine neoplasm						
Trabeculae of compact cells surrounded by grey tissue	Krishna et al.[25]	2017	13	98	97	92
	Krishna et al.[29]	2020	65	100	96	96
	Napoleon et al.[20]	2019	71	100	95	96

nCLE, needle-based confocal laser endomicroscopy; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; -, The authors did not comment on the specificity of nCLE diagnostic features for specific pathology, and the number of false positive and true negative cases was not available.

of scattered particles that were bright, gray, and black (Fig. 7). These newly established criteria, along with previously described features for IPMNs and SCAs, were externally validated by four observers. Diagnostic accuracy ranged from 87% to 94% depending on the type of PCL, allowing these findings to reliably form an atlas of nCLE interpretation criteria for PCLs. Chin et al.[19] conducted a prospective study using this interpretation criteria and achieved similar sensitivity (83%) and specificity (75%) rates and an overall accuracy of 80% when compared to histology.

Using the previously validated nCLE interpretation criteria, Napoleon et al.[20] performed a larger, multicenter prospective study (CONTACT 2), overcoming limitations experienced by prior studies, such as a small sample size and an inadequate number of diagnoses based on histology. Seventy-eight patients with a diagnosis based on histology were included in the analysis out of an initial 209 enrolled patients with a single noncommunicating PCL. The overall diagnostic accuracy of nCLE was 91%, with more than 95% sensitivity and 95% specificity for the main types of PCLs. In addition, there was a 100% specificity of nCLE for SCA and premalignant mucinous cysts. nCLE had a better diagnostic performance (based on area under the curve) than CEA (for mucinous vs. non-mucinous cysts ($p<0.01$] and EUS morphology (for premalignant vs. benign PCLs [$p<0.05$]). However, nCLE was not specific for diagnosing pseudocysts and neuroendocrine neoplasms. For 91% of patients with an

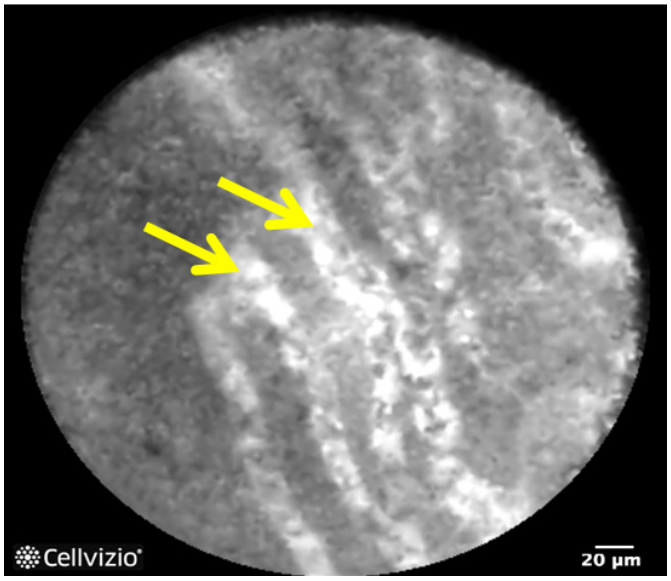

Fig. 4. The superficial vascular network is seen on needle-based confocal laser endomicroscopy of a serous cystadenoma. Arrows indicate blood vessels forming a superficial vascular network.

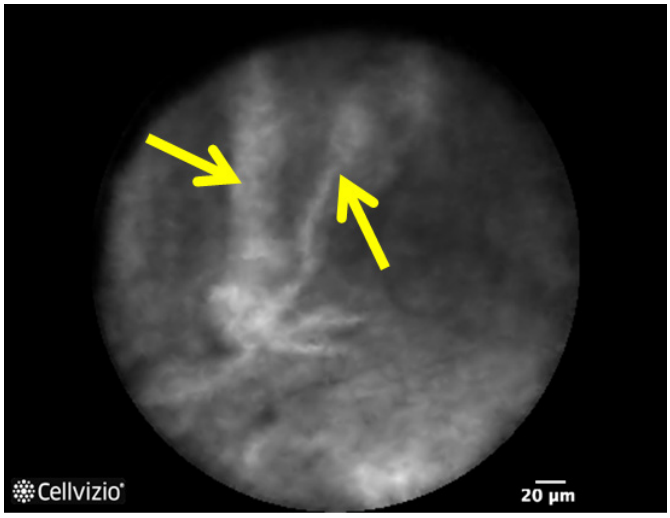

Fig. 5. Papillary projections characterized by a vascular core (in white, indicated by arrows) surrounded by an epithelial border (in gray) are seen on needle-based confocal laser endomicroscopy of an intraductal papillary mucinous neoplasm.

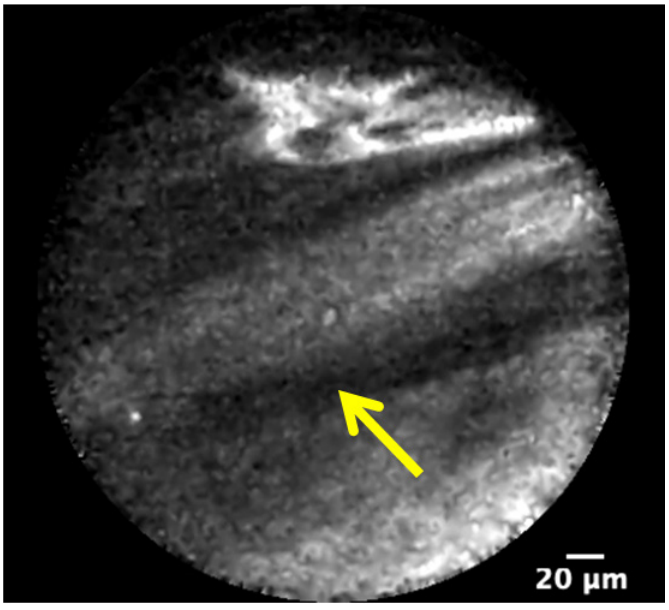

Fig. 6. A thick epithelial band (indicated by an arrow) is seen on needle-based confocal laser endomicroscopy of a mucinous cystadenoma.

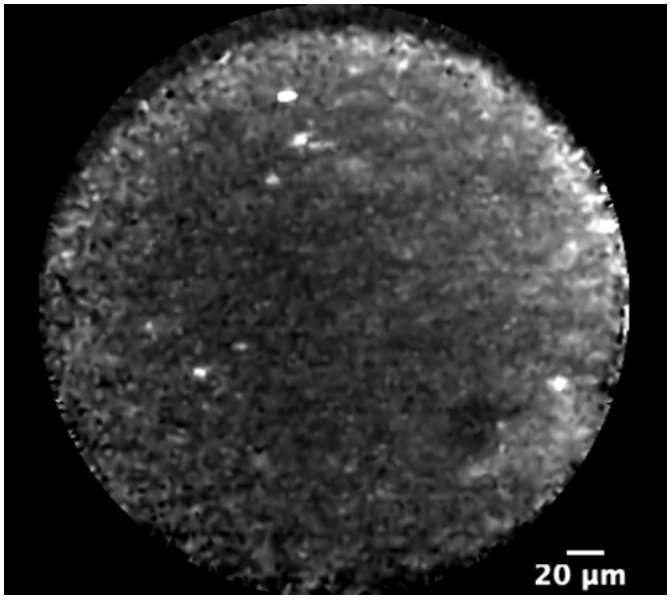

Fig. 7. Bright uniform particles are seen against a dark background on needle-based confocal laser endomicroscopy of a pseudocyst.

inconclusive diagnosis on EUS-FNA, nCLE achieved a conclusive diagnosis, which was also 100% accurate compared to the eventual histological diagnosis.

The CONCYST-01 study (confocal endomicroscopy in cystic lesions of the pancreas) was a phase II prospective study conducted by Keane et al.[21] on nCLE imaging in 67 patients with indeterminate PCLs. In this study, EUS-nCLE achieved an overall diagnostic accuracy of 77% compared to EUS and cytology at 66%. The difference in diagnostic accuracy was even more pronounced for IPMN or pancreatic adenocarcinoma (87% and

100%, respectively).

Kadayifci et al.[22] conducted a prospective study of 20 patients who underwent EUS for the evaluation of a PCL that was ≥2 cm in size. For mucinous cysts, nCLE achieved a sensitivity, specificity, and diagnostic accuracy of 66%, 100%, and 80%, respectively.

Analysis of IOA on nCLE findings showed varying results across different studies. In the CONTACT 1 study, which evaluated the IOA of four external reviewers,[28] the diagnostic accuracy for mucinous cysts was 94% with a substantial global IOA (k=0.72; 95% CI, 0.52–0.87). In a retrospective study by Karia et al.,[23] six interventional endoscopists at five institutions reviewed the de-identified nCLE videos of 15 patients with PCLs. The mean accuracy of the observers was 46%, ranging between 20% and 67%. Postulated reasons for the low accuracy rates were poor image quality and the steep learning curve for nCLE imaging, which the interventional endoscopists had yet to overcome.

A study was done by Krishna et al.[24] to evaluate IOA and intraobserver reliability (IOR) among six observers, split equally between expert endosonographers and non-endosonographers. Forty-nine participants underwent nCLE, and 26 (53%) had a definitive diagnosis. Mucinous PCLs were diagnosed with a sensitivity, specificity, and accuracy of 94%, 82%, and 89%, respectively. The study was conducted in two phases with a two-week wash-out period. Prior to each phase, the observers were given teaching slides, nCLE images, and nCLE videos. IOA and IOR were deemed substantial among the group for detecting all characteristic nCLE image patterns and differentiating mucinous vs. non-mucinous cysts (k=0.67; 95% CI, 0.57–0.77 and k=0.78±0.13, respectively). In another study performed by Krishna et al.,[25] six expert endosonographers with experience in using nCLE (performed more than 30 nCLE cases) did a blinded review of nCLE images of PCLs from 29 participants diagnosed based on histology (n=23) or clinical consensus (n=6). Using known nCLE image patterns, the IOA and IOR were found to be almost perfect for the diagnosis of both mucinous PCLs (k=0.81 and k=0.86, respectively) and SCAs (k=0.83 and k=0.85, respectively). nCLE was also found to have 95% accuracy in diagnosing mucinous PCLs and 98% accuracy in diagnosing SCA. The same group studied the characteristic nCLE features of IPMN on a post hoc analysis.[29] For the detection of high-grade dysplasia or adenocarcinoma in IPMNs, an increased "width" and "darkness" of the papillary epithelial border was the most sensitive (90% and 91%, respectively) and accurate (85% and 84%, respectively) feature, which also achieved substantial (k=0.61; 95% CI, 0.51–0.71) and moderate (k=0.55; 95% CI, 0.45–0.65) IOA, respectively. Papillary width of ≥50 μm and papillary darkness of ≤90 pixel-intensity had receiver operating characteristic curves of 0.95 and 0.90, respectively. These quantifications were shown to identify high-grade dysplasia or adenocarcinoma in IPMNs with good accuracy.

A retrospective and comparative study conducted by Palazzo et al.[26] showed that adding nCLE findings to conventional EUS-FNA and fluid analysis can improve IOA on the diagnosis of PCLs in 206 patients among five pancreatic disease experts. nCLE increased the IOA from 0.36 (95% CI, 0.33-0.49) to 0.64 (95% CI, 0.61–0.67) and the proportion of complete agreement from 30% to 54%.

In a recent study by Machicado et al.,[31] 13 endosonographers with experience in nCLE evaluated 76 EUS-nCLE videos of PCLs. Both the IOA (k=0.82; 95% CI, 0.77–0.87) and IOR (k=0.82; 95% CI, 0.78–0.85) were "almost perfect" in differentiating mucinous and non-mucinous PCLs. nCLE also had high diagnostic accuracy, which was slightly better in non-mucinous cysts (SCA 98%, cystic-NET/solid pseudopapillary neoplasm 96%, and pseudocyst 96%) compared to mucinous cysts (IPMN 86%, MCN 84%).

Impact on clinical management and cost-effectiveness

Using nCLE as an adjunct to EUS-FNA significantly changes clinical management. Palazzo et al.[26] reported a significant change in the proposed management for PCLs in 28% of patients after nCLE findings were made known, resulting in a decrease in the number of recommendations for continued surveillance and a corresponding increase in recommendations for either surgery or no surveillance. The largest change was for benign SCAs in which those recommended for continued surveillance decreased from 40% to 5%. Likewise, in a 44-patient prospective study conducted by Cheesman et al.,[27] combining nCLE with EUS-FNA showed a significant increase in diagnostic yield (84.1% vs. 34.1%, p<0.05). Compared to EUS-FNA alone, the combination of nCLE and EUS-FNA resulted in a change of management in 43.2% of patients (p<0.05) and resulted in an overall decrease in discontinuation of surveillance by 31.8% (p<0.05).

A cost-effectiveness modeling study by Le Pen et al.[32] showed that while the cost of performing EUS-FNA with nCLE was higher than EUS-FNA alone, the diagnostic accuracy was improved and resulted in a 23% reduction in surgical resection.

Overall cost savings between 13% in the public sector and 14% in the private sector were achieved as unnecessary surgery and inpatient stays were averted. Further cost savings if unnecessary surveillance could be averted were not considered in this study. In addition, from a patient safety perspective, four in 1,000 patients would have avoided mortality associated with unnecessary surgery.

Complications

Multiple studies have reported nCLE-related complications (Table 4).[15-17,19-21,24,26-28] Post-procedure pancreatitis was consistently found to be the most common complication of EUS-nCLE, with an incidence ranging from 0% to 12%. A few factors have been postulated for the increased rate of post-procedure pancreatitis: performing cystoscopy using a large-caliber Spyglass cholangioscope (Boston Scientific), greater extent of needle movement for intracystic visualization, long duration of needle placement within the PCL, and loading the nCLE miniprobe into the needle after the latter is inserted through the endoscope. Intracystic bleeding was reported in one study, but it was self-limiting in all three patients. Risk factors for intracystic bleeding included prolonged procedure duration and using the needle tip to brush the cyst lining.[16] Different maneuvers were found to improve the safety of the EUS-nCLE examination, such as the change in practice to preload rather than backload the miniprobe, avoiding interposition of the pancreatic duct and blood vessels during FNA, avoiding rubbing of the miniprobe tip against the cyst wall and limiting intracystic needle time to 10 minutes. There have been no reported cases of nCLE-related fatalities to date.

Use of artificial intelligence

A prospective single-center study conducted by Machicado et al.[33] evaluated the use of the nCLE-based convoluted neural network (CNN) algorithms for risk stratification of IPMNs. Over 15,000 nCLE video frames were used from 35 consecutive patients who had EUS-nCLE done and subsequently a histopathological diagnosis of IPMN; half of these patients had high-grade dysplasia or adenocarcinoma. Two CNN algorithms were used: firstly, a segmentation-based model, which was trained to detect and measure only papillary epithelial thickness and darkness, and secondly, a holistic-based model, which allowed automatic extraction of nCLE features. When compared with the American Gastroenterological Association (AGA) and revised Fukuoka guidelines for high-risk PCLs, both the segmentation-based and holistic-based models displayed better sensitivity (both at 83.3%) than the AGA or Fukuoka criteria (both at 55.6%) and comparable specificity (83.3% and 88.2% vs. 82.4% and 94.1%, respectively) in predicting high-grade dysplasia or adenocarcinoma. The overall diagnostic accuracy was also higher in the CNN models (82.9% and 85.7% vs. 68.6% and 74.3%, respectively) compared to the AGA or Fukuoka criteria.

DISCUSSION

Clinical guidelines and strength of evidence

nCLE plays an important role in diagnosing and managing PCLs but has yet to be widely adopted into clinical practice guidelines. The American College of Gastroenterology guidelines published in 2018 highlighted the utility of nCLE in differentiating SCAs, IPMNs, and MCNs from other pancreatic cysts

Table 4. Needle-based confocal laser endomicroscopy-related complications in the diagnosis of pancreatic cystic lesions

Study	Year	*n*	Complications					
			Pancreatitis	Bleeding	Infection	Fluorescein-related	Death	Overall
Konda et al.[15]	2011	18	2 (11.1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (11.1)
Konda et al.[16]	2013	66	2 (3.0)	3 (4.5)	0 (0)	0 (0)	0 (0)	6 (9.1)
Nakai et al.[17]	2015	30	2 (6.7)	0 (0)	0 (0)	0 (0)	0 (0)	2 (6.7)
Napoleon et al.[28]	2015	31	1 (3.2)	4 (12.9)	0 (0)	0 (0)	0 (0)	5 (16.1)
Krishna et al.[24]	2016	49	3 (6.1)	0 (0)	0 (0)	0 (0)	0 (0)	3 (6.1)
Chin et al.[19]	2018	12	0 (0)	1 (8.3)	0 (0)	0 (0)	0 (0)	1 (8.3)
Napoleon et al.[20]	2019	78	1 (1.3)	1 (1.3)	0 (0)	0 (0)	0 (0)	2 (2.6)
Keane et al.[21]	2019	56	0 (0)	0 (0)	1 (1.8)	1 (1.8)	0 (0)	2 (3.6)
Palazzo et al.[26]	2020	209	3 (1.4)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1.4)
Cheesman et al.[27]	2020	44	0 (0)	0 (0)	1 (2.3)	0 (0)	0 (0)	1 (2.3)
Overall		593	14 (2.4)	9 (1.5)	2 (0.3)	1 (0.2)	0 (0.0)	28 (4.7)

Values are presented as number (%).

but do not make any recommendations for its use, citing the need for additional data.[11] The guidelines from the European Study Group on Cystic Tumours of the Pancreas, also published in 2018, suggest that nCLE should not be used for the diagnosis of PCLs due to the high rate of adverse events compared to conventional modalities such as EUS-FNA.[34] The latest revision of the Fukuoka consensus guidelines does not feature nCLE in the management algorithm of IPMNs.[35] There is a need for randomized controlled trials and more large prospective studies to examine the role of nCLE in changing the management of PCLs.

Barriers to adoption and opportunities for development: an analysis of strengths, weaknesses, opportunities, and threats

The strengths-weaknesses-opportunities-threats (SWOT) analysis was first described in 1969 and is a tool that can add clarity to the challenges faced by organizations and new technologies alike.[36] nCLE is a useful diagnostic tool for PCLs. Notably, SWOT analysis changes the management of a substantial proportion of patients. Unnecessary surgery and surveillance can be avoided, leading to improved healthcare outcomes. The availability of real-time nCLE diagnosis when EUS is performed reduces the risk of sampling error and false negative results and may even avoid the need for histopathology.

Potential barriers to the adoption of nCLE include the high upfront cost and a steep learning curve for both technical expertise and interpretation of nCLE findings. The minimum number of cases to attain expertise in EUS-nCLE is approximately 30.[25] Consequently, EUS-nCLE is still being done only in specialized high-volume centers with experienced endoscopists. The EUS-nCLE modeling study by Le Pen et al.[32] has provided reassuring data that the high initial cost of nCLE has resulted in greater overall cost savings after patients were appropriately discharged from surveillance or need for surgery. Given the wide variation in healthcare financing in different healthcare systems across various geographic regions, more cost-effectiveness studies are needed.

The need for high levels of training and expertise has restricted EUS-nCLE to the remit of experienced endosonographers in certain high-volume tertiary referral centers. This limits the number of patients who can receive EUS-nCLE. This may be mitigated in the future when the role of EUS-nCLE is established in clinical practice guidelines. Slightly higher rates of procedural complications, such as post-procedure pancreatitis and intracystic bleeding, can be surmounted with appropriate training (limiting scope movement and needle dwelling time) and technological advances (production of smaller miniprobes compatible with 22-G FNA needles).[37]

The excellent performance of convolutional neural networks in diagnosing PCLs is a promising development and its widespread availability may further improve EUS-nCLE performance overall. The use of artificial intelligence may also help to minimize the needle dwelling time in EUS-nCLE with quick recognition of nCLE image patterns to achieve a diagnosis, addressing concerns on the risk of post-procedure pancreatitis related to needle dwelling time.

The use of novel diagnostic tools such as next-generation sequencing of EUS-acquired cyst contents offers insight into the genetic composition of the cells shed from neoplastic cyst epithelium. Both EUS-nCLE and cyst-fluid next-generation sequencing have complementary roles in PCL diagnosis and would enhance the diagnostic accuracy of cyst type and advanced neoplasia.[38] The use of pancreatic cyst fluid glucose has been shown to be a viable alternative biomarker to fluid CEA in differentiating mucinous from non-mucinous cysts. It is more accessible, incurs a lower cost, and can provide greater diagnostic accuracy.[39]

CONCLUSIONS

The accurate diagnosis of PCLs remains challenging. nCLE plays an important role in ascertaining the exact nature of PCLs as they assist in selection of high-risk lesions for surgery and preventing unnecessary surgery and surveillance for low-risk lesions. The evidence supporting the role of nCLE in PCL diagnosis is strong; however, various challenges need to be surmounted. The development of artificial intelligence and complementary diagnostic enhancements may aid the widespread adoption of EUS-nCLE.

Conflicts of Interest

Damien Meng Yew Tan is a consultant for Boston Scientific and Pentax Medical. The other authors declare no potential conflicts of interest.

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Author Contributions

Conceptualization: all authors; Data curation: all authors; Formal analysis: all authors; Project administration: all authors; Supervision: DMYT; Writing–original draft: all authors; Writing–review & editing: all authors.

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