Confocal endomicroscopy for evaluation of pancreatic cystic lesions: a systematic review and international Delphi consensus report

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ABSTRACT

Background and study aims The aim of thi systematic review and consensus report is to standardize the practice of endoscopic ultrasound (EUS-guided needle-based confocal laser endomicroscopy (nCLE) for pancreatic cystic lesion (PCL) evaluation.

Methods We performed an international, systematic, evidence-based review of the applications, outcomes, procedural processes, indications, training, and credentialing of EUS-nCLE in management of PCLs. Based on available clinical evidence, preliminary nCLE consensus statements (nCLE-CS) were developed by an international panel of 15 experts in pancreatic diseases. These statements were then voted and edited by using a modified Delphi approach. An a priori threshold of 80 % agreement was used to establish consensus for each statement.

Results Sixteen nCLE-CS were discussed. Thirteen (81 %) nCLE-CS reached consensus addressing indications (non-communication PCL meeting criteria for EUS-FNA or with prior non-diagnostic EUS-FNA), diagnostic outcomes (improved accuracy for mucinous PCLs and serous cystadeno-

mas with substantial interobserver agreement of image patterns), low incidence of adverse events (fluorescein-associated and pancreatitis), procedural processes (nCLE duration, manipulation of needle with probe), and training (physician knowledge and competence).

Conclusion Based on a high level of agreement pertaining to expert consensus statements, this report standardizes the practice of EUS-nCLE. EUS-nCLE should be systematically considered when EUS-FNA is indicated for PCL evaluation.

Introduction

Over the last decade, Confocal Laser Endomicroscopy (CLE) has emerged as a promising technology to overcome the inherent limitations of endoscopic sampling techniques by providing both the endoscopist and the pathologist, real-time imaging of tissue and vascular microstructures. Needle-based confocal laser endomicroscopy (nCLE) enables real-time in vivo microscopic imaging during endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) with the potential to improve the differentiation of various types of pancreatic lesions [1, 2].

The first study used prototype probes and demonstrated the technical feasibility, established an imaging protocol, and assessed the safety of EUS-nCLE [3]. A subsequent preliminary study targeted the development of descriptive criteria for image interpretation and classification of the nCLE findings for pancreatic masses, pancreatic cystic lesions (PCLs), and lymph nodes [4]. Following these initial feasibility studies, several multicenter trials were conducted [5–15].

Overall, more than 600 patients have been enrolled since 2011 in these studies involving EUS-nCLE evaluation of PCLs (▶ **Fig. 1**).

In 2015, an initiative was announced to establish the first consensus report on probe-based confocal laser endomicroscopy (pCLE) pertaining to four different gastrointestinal pathologies (Barrett's esophagus, biliary strictures, colorectal lesions, and inflammatory bowel diseases) [16]. The present consensus document reports on proposed indications and use of EUS-guided nCLE for evaluation of PCLs. It aims to provide guidance to nCLE users and to other interested healthcare professionals on standardization of practice, recommendations on training, and credentialing for the procedure.

Methods

The principal steps in the methodology included: (1) selection of the consensus group; (2) development of draft statements; (3) systematic review of the literature to identify evidence to support consensus statements; (4) voting on draft statements to reach consensus; and (5) grading of the strength and quality of the evidence, and strength of the recommendations using accepted a priori criteria.

All invited panelists on the consensus group had to comply with the following criteria:

1. Be either an advanced nCLE user or an expert in endoscopy of pancreatic pathology for at least two years prior to participation in the consensus process;
2. Have published or lectured in international meetings on nCLE applications or pancreatic pathology;
3. Agree to review literature and participate in the voting process.

The clinical evidence considered to establish the statements in this consensus was collected through literature search and review of published articles available on PubMed/MEDLINE, Embase, Cochrane Database, and Google Scholar, from January 1, 2000 to May 31, 2017. The following search terms were used: CLE, confocal, confocal endomicroscopy, endomicroscopy, needle-based confocal laser endomicroscopy for a pancreatic indication, and PCLs. No language restriction was applied.

Four consensus meetings attended by the members of the panel were conducted between April 2015 and May 2017 (▶ **Fig. 2**). Additional approval from members was obtained electronically to accommodate individual study (CONTACT II and INDEX) updates till June 30, 2019 (▶ **Fig. 2**).

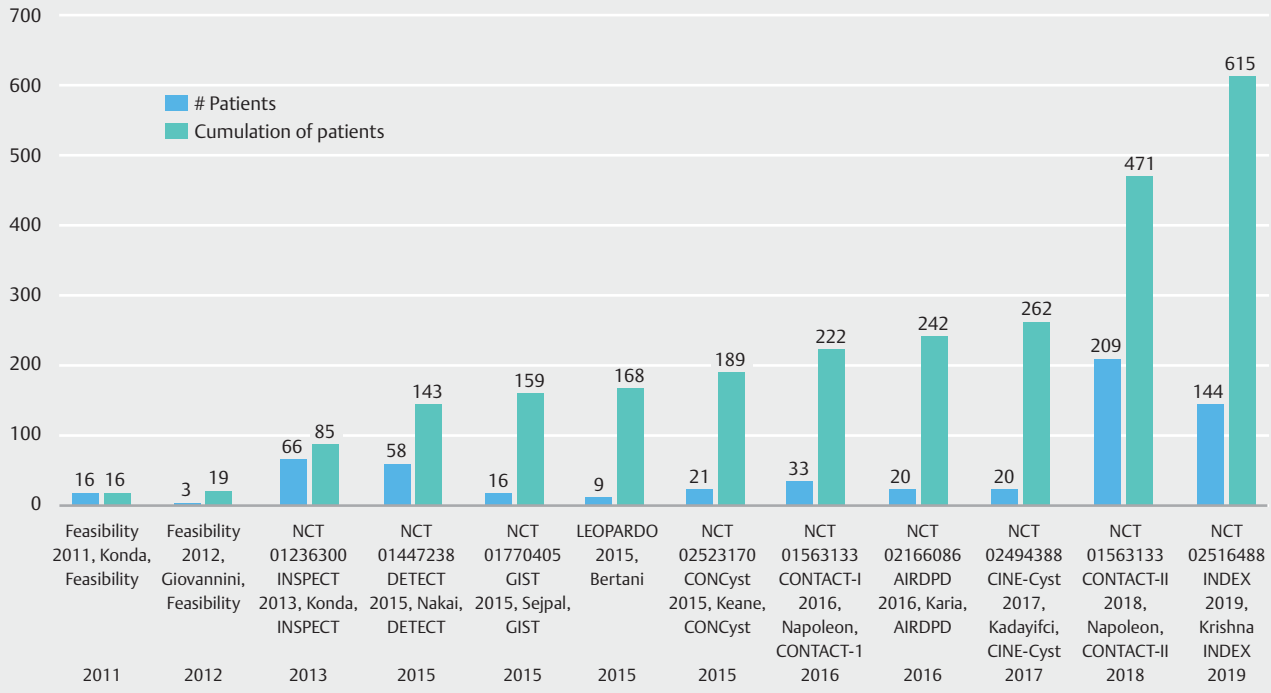
A compiled revision of the statements was prepared by the chairmen and shared with the members, who independently voted on each statement via an electronic web-based survey (SurveyMonkey.com) regarding the grade of clinical evidence and their level of agreement or disagreement. Participants could refuse to vote for a statement if they believed that they were not familiar with the topic to avoid any bias. The classification used for agreement level and grade of evidence (▶ **Table 1**) was available to all the participants. For grading the agreements, a five-point Likert scale was used (▶ **Table 1**) [17]. Consensus was achieved when 80 % or more of voting members indicated "agree completely" or "agree with some reservation." In all other cases, the statements were rejected.

Statistical analysis

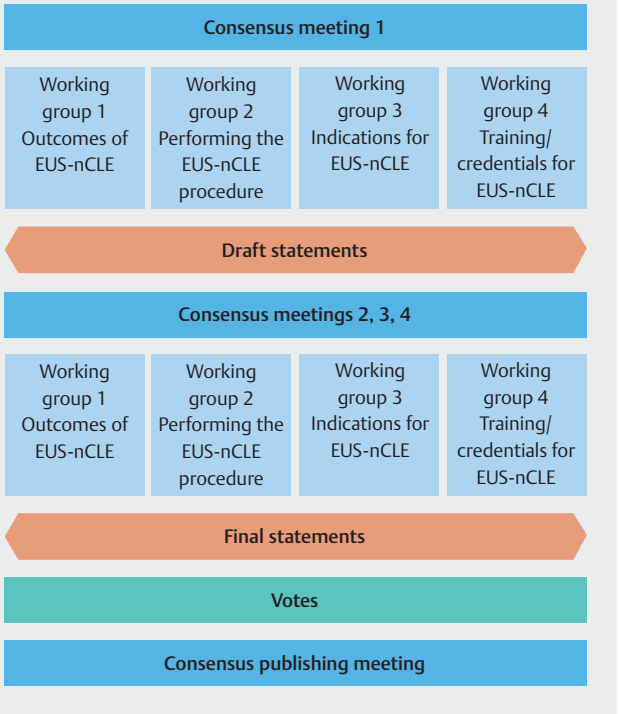
Diagnostic outcomes were pooled through a random-effects model based on DerSimonian and Laird test, and summary estimates were expressed in terms of rate and 95 % confidence interval (CI). Comparison between EUS-nCLE and EUS-FNA was based on a random-effects model. Chi-square and I2 tests were used across studies for comparison of the percentage of variability attributable to heterogeneity beyond chance. The analyses were performed by using the "metaphor" and "meta" packages in R software (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 16 statements were proposed. Among these, 13 (81 %) nCLE-CS reached consensus, while three (19 %) were rejected. The level of agreement and the grade of evidence for each statement are reported in ▶ **Table 2**.



▶ **Fig. 1** Cumulative number of patients enrolled in clinical trials evaluating EUS-guided needle based confocal laser endomicroscopy of pancreatic cystic lesions.



▶ **Fig. 2** Methodology workflow.

▶ **Table 1** Classification of evidence levels and voting on recommendation/agreement level with descriptions.

Evidence level/agreement level descriptions
Evidence level
I-A Evidence from meta-analysis of RCTs
I-BE vidence from at least 1 RCT
II-AE vidence from at least 1 controlled study without randomization
II-BE vidence from at least 1 other type of quasi-experimental study
III Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both
Voting on recommendation / Agreement level
AA Agree strongly
A Agree with minor reservation
N Agree with major reservation
D Disagree with reservation
DD Disagree completely

▶ **Table 2** nCLE statement agreement and evidence level poll result summary.

Statement #	Statement	AA + A Agreement	Results
1.1	nCLE can improve the diagnosis of non-communicating pancreatic cystic lesions compared to current standard of care		
Agreement	AA: 53 %, A: 47 %, N: 0 %, D: 0 %, DD: 0 %	AA + A: 100 %	Adopted
Evidence	I-A: 6.7 %, I-B: 0.0 %, II-A: 66.7 %, II-B: 13.3 %, III: 13.3 %, or IV: 0.0 %		II-A
1.2	nCLE is reliable to differentiate between mucinous and non-mucinous pancreatic cystic lesions		
Agreement	AA: 47 %, A: 47 %, N: 7 %, D: 0 %, DD: 0 %	AA + A: 94 %	Adopted
Evidence	I-A: 0.0 %, I-B: 6.7 %, II-A: 66.7 %, II-B: 13.3 %, III: 13.3 %, or IV: 0.0 %		II-A
1.3	nCLE is reliable to diagnose SCA accurately		
Agreement	AA: 67 %, A: 33 %, N: 0 %, D: 0 %, DD: 0 %	AA + A: 100 %	Adopted
Evidence	I-A: 6.7 %, I-B: 6.7 % II-A: 60.0 %, II-B: 20.0 %, III: 6.7 %, or IV: 0.0 %		II-A
1.4	nCLE is highly accurate to diagnose cystic NEN		
Agreement	AA: 20 %, A: 20 %, N: 53 %, D: 7 %, DD: 0 %	AA + A: 46 %	Rejected
Evidence	I-A: 0.0 %, I-B: 6.7 %, II-A: 6.7 %, II-B: 46.7 %, III: 33.3 %, or IV: 6.7 %		II-B
1.5	Inter-observer agreement of nCLE for the diagnosis of cystic lesion is substantial		
Agreement	AA: 40 %, A: 53 %, N: 7 %, D: 0 %, DD: 0 %	AA + A: 93 %	Adopted
Evidence	I-A: 6.7 %, I-B: 13.3 % II-A: 60.0 %, II-B: 0.0 %, III: 20.0 %, or IV: 0.0 %		II-A
2.1	The incidence of adverse events associated with intravenous fluorescein injection is extremely low		
Agreement	AA: 93 %, A: 7 %, N: 0 %, D: 0 %, DD: 0 %	AA + A: 100 %	Adopted
Evidence	I-A: 20.0 %, I-B: 0.0 % II-A: 60.0 %, II-B: 0.0 %, III: 20.0 %, or IV: 0.0 %		II-A
2.2	The largest surface area of the cyst epithelium must be examined, however the procedure must be stopped once diagnostic nCLE features of a PCL are observed		
Agreement	AA: 93 %, A: 0 %, N: 7 %, D: 8 %, DD: 0 %	AA + A: 93 %	Adopted
Evidence	I-A: 6.7 %, I-B: 6.7 % II-A: 60.0 %, II-B: 13.3 %, III: 20.0, or IV: 20.0 %		IV
2.3	Duration of nCLE procedure should not exceed 6 minutes		
Agreement	AA: 40 %, A: 47 %, N: 13 %, D: 0 %, DD: 0 %	AA + A: 87 %	Adopted
Evidence	I-A: 0.0 %, I-B: 6.7 %, II-A: 13.3 %, II-B: 46.7 %, III: 20.0 %, or IV: 13.3 %		IV
2.4	Needle and probe should be manipulated with caution to minimize disruption of the cyst epithelium		
Agreement	AA: 67 %, A: 26 %, N: 7 %, D: 0 %, DD: 0 %	AA + A: 93 %	Adopted
Evidence	I-A: 0.0 %, I-B: 13.3 %, II-A:33.3 %, II-B: 20.0 %, III: 6.7 %, or IV: 26.7 %		IV
2.5	The onsite presence of cytopathologist can facilitate nCLE image interpretation		
Agreement	AA: 7 %, A: 33 %, N: 33 %, D: 20 %, DD: 7 %	AA + A: 40 %	Rejected
Evidence	I-A: 0.0 %, I-B: 6.7 %, II-A: 0.0 %, II-B: 0.0 %, III: 53.3 %, or IV: 40.0 %		IV
3.1	nCLE is indicated in patients with indeterminate non-communicating cysts when EUS- FNA is indicated		
Agreement	AA: 60 %, A: 33 %, N: 7 %, D: 0 %, DD: 0 %	AA + A: 93 %	Adopted
Evidence	I-A: 6.7 %, I-B: 6.7 % II-A: 53.3 %, II-B: 6.7 %, III: 6.7 %, or IV: 20.0 %		II-A
3.2	nCLE is indicated when a pancreatic cyst remains indeterminate despite previous EUS-FNA		
Agreement	AA: 60 %, A: 27 %, N: 13 %, D: 0 %, DD: 0 %	AA + A: 87 %	Adopted

▶ **Table 2** (Continuation)

Statement #	Statement	AA + A Agreement	Results
Evidence	I-A: 0.0 %, I-B: 13.3 %, II-A: 6.7 %, II-B: 6.7 %, III: 46.7 %, or IV: 26.7 %		II-A
3.3	Repeat nCLE on subsequent follow-up procedures should be routinely performed		
Agreement	AA: 00 %, A: 0 %, N: 0 %, D: 7 %, DD: 93 %	DD + D: 93 %	Rejected
Evidence	I-A: 6.7 %%, I-B: 0.0 %, II-A: 6.7 %%, II-B: 0.0 %, III: 20.0 %, or IV: 66.7 %		IV
4.1	Physicians are expected to have a good understanding of pancreatic cystic lesions, and procedural indications and contraindications for EUS-nCLE		
Agreement	AA: 100 %, A: 0 %, N: 0 %, D: 0 %, DD: 0 %	AA + A: 100 %	Adopted
4.2	Trainees in EUS-nCLE of PCLs need to be fully competent in pancreatic EUS and EUS-FNA		
Agreement	AA: 100 %, A: 0 %, N: 0 %, D: 0 %, DD: 0 %	AA + A: 100 %	Adopted
4.3	Trainees should learn how to obtain optimal nCLE images of the intracystic epithelium to achieve satisfactory images		
Agreement	AA: 100 %, A: 0 %, N: 0 %, D: 0 %, DD: 0 %	AA + A: 100 %	Adopted

nCLE, needle-based confocal laser endomicroscopy; PCL, pancreatic cystic lesion; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration

Consensus statements

Outcomes of EUS-nCLE

nCLE can improve the diagnosis of non-communicating pancreatic cystic lesions compared to current standard of care (Statement 1).

In the absence of histology, cyst fluid CEA (Carcinoembryonic Antigen) and cytology are considered standard of care in the differential diagnosis of PCLs [18]. CEA values of ≥ 192 ng/mL signify a mucinous PCL, however sensitivity and specificity are sub-optimal [19] (0.73 and 0.84 respectively). Moreover, the optimal cut-off value of CEA varies and ranges from 30 ng/mL to 480 ng/mL [20–23]. Spurious fluctuations of intra-individual CEA levels occur in approximately 20 % of patients [24]. Cytology is accurate in only 50 % to 60 % of cases due to scant cellularity of cyst fluid [19, 25]. EUS-FNA cytology yield for serous cystadenomas (SCA) is very low and hence a cytopathological diagnosis is difficult to establish [26]. Preliminary studies in EUS-nCLE have demonstrated improved diagnostic accuracy in the detection of mucinous PCLs compared to current standard of practice (CEA and cytology) [6, 9,27,28]. In four clinical trials evaluating EUS-nCLE (▶ **Table 3,** ▶ **Fig. 3,** ▶ **Fig. 4**), the pooled diagnostic yield and accuracy of nCLE were significantly higher than those of CEA; 88 % (82–93, 95 % CI) and 77 % (64–86, 95 % CI) for yield (odds ratio 2.84 (1.15–7.01, 95 % CI) with P = .02) and 96 % (92–98, 95 % CI) and 64 % (57–71, 95 % CI) accuracy (odds ratio 13.89 (5.72–33.69, 95 % CI) with P < .0001), respectively. A recent meta-analysis also demonstrated an EUS-nCLE pooled diagnostic accuracy of 89 % (84–93, 95 % CI) which was significantly higher than that of EUS-FNA (odds ratio 3.94 (1.58–9.82, 95 % CI)) [29].

nCLE is reliable to differentiate between mucinous and non-mucinous pancreatic cystic lesions (Statement 2).

While papillary projections and/or dark rings (cross-sectional view of papillae) during nCLE imaging represent the villous pattern of intraductal papillary mucinous neoplasms (IPMNs), the horizon type epithelial bands represent the lining of mucinous cystic neoplasms (MCNs). A summary of the different studies evaluating the diagnostic performance of nCLE for differentiation of mucinous versus non-mucinous PCLs is shown in ▶ **Table 4** and ▶ **Fig. 5**. While the pooled specificity was 97 % (92–99 % 95 %CI), sensitivity was 95 % in two of the largest trials [14, 15] with the highest number of subjects with surgical histopathology as diagnostic gold standard. In their meta-analysis, Facciorusso et al. [29] indicated that the diagnostic accuracy for mucinous lesions reached 91 % (86 %-97 %, 95 % CI).

nCLE is reliable to diagnose serous cystadenoma (SCA) accurately (Statement 3).

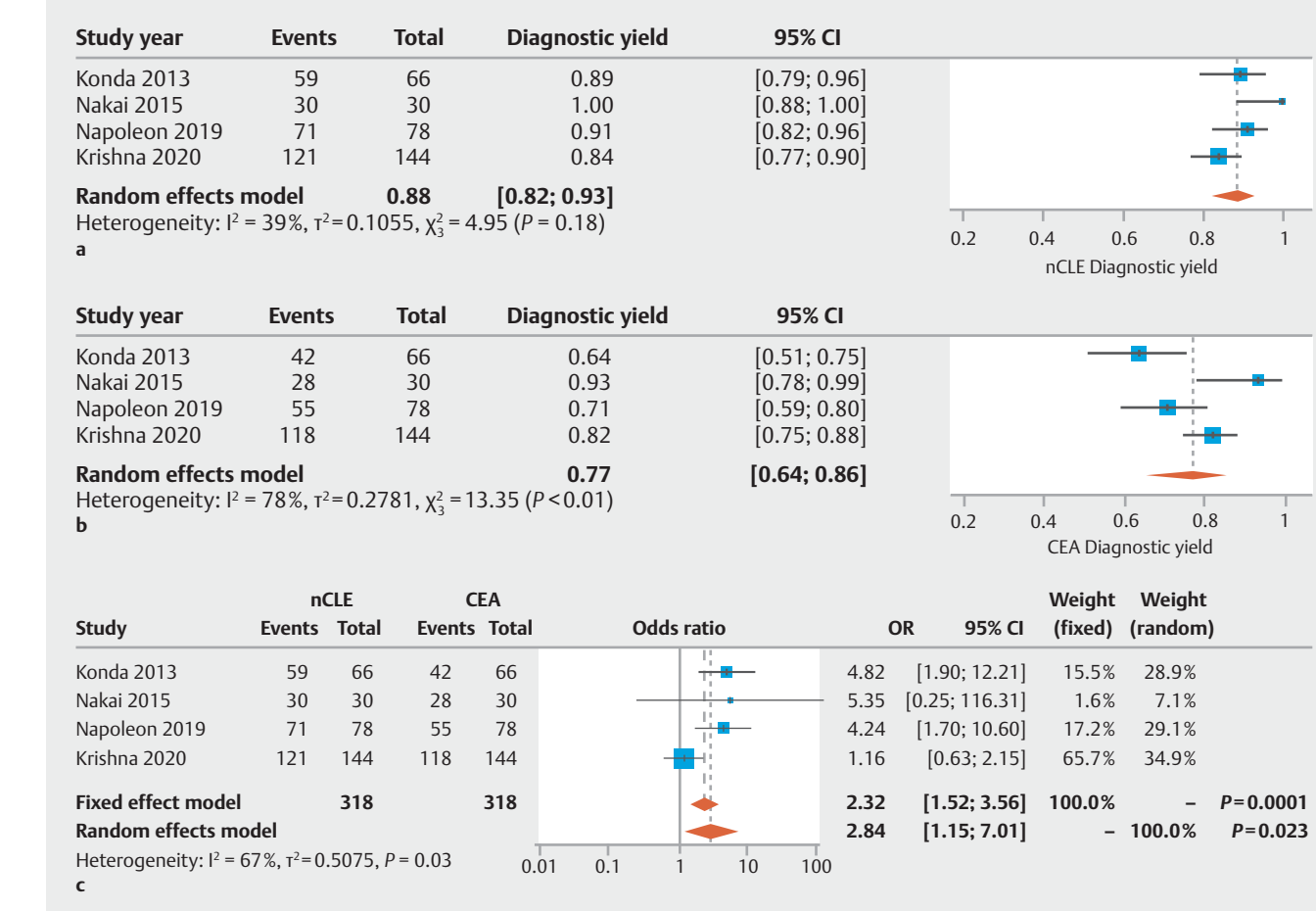
For diagnosing SCAs, a pooled analysis has demonstrated that cyst fluid CEA < 5 ng/mL has a specificity of 95 % albeit a low sensitivity of 50 % [30]. Importantly however, cystic neuroendocrine neoplasms (NEN) and IPMNs were not included in this analysis.

Histologically, SCAs are unique and are characterized by dense subepithelial capillary vascularization [6, 9,28]. In several studies [6, 9,10] this histological [31] . The diagnostic performance of this particular nCLE feature was then assessed in three clinical studies [6, 9,10] (▶ **Table 4,** ▶ **Fig. 6**) with an almost perfect pooled specificity (97 %, 92–99 % 95 %CI) and sensitivity over 95 % in two of the studies [6, 14]. One study also showed a diagnostic performance for nCLE significantly higher than that of CEA (< 5 ng/mL) for predicting benign lesions with areas under the receiver operating characteristic (AUROC) of 96 % and 84 % for nCLE and CEA ($P < 0.05$), respectively [14].

▶ **Table 3** Diagnostic yield and accuracy for diagnosis of mucinous pancreatic cystic lesions using carcinoembryonic antigen (CEA) (≥ 192 ng/mL), nCLE, and EUS.

Publication year	First author	Study name	N[1]	nDD [1] (surgery)	CEA yield[1]	EUS yield[1]	nCLE yield[1]	CEA ACC1[1]	EUS ACC[1]	nCLE ACC[1]
2013	Konda, VJ. [27]	INSPECT	66	57 (14)	62 %	NA	89 %	NA	NA	71 %[2]
2015	Nakai, Y. [28]	DETECT	30	18 (2)	93 %	100 %	100 %	61 %	73 %	87 %
2019	Napoleon, B. [14]	CONTACT II	206	78 (39)	71 %[3]	47 %[3]	91 %[3]	78 %[3]	81 %[3]	97 %[3]
2020	Krishna, S. G. [15]	INDEX	144	113 (65)	82 %	NA	84 %	70 %[3]	NA	97 %[4]

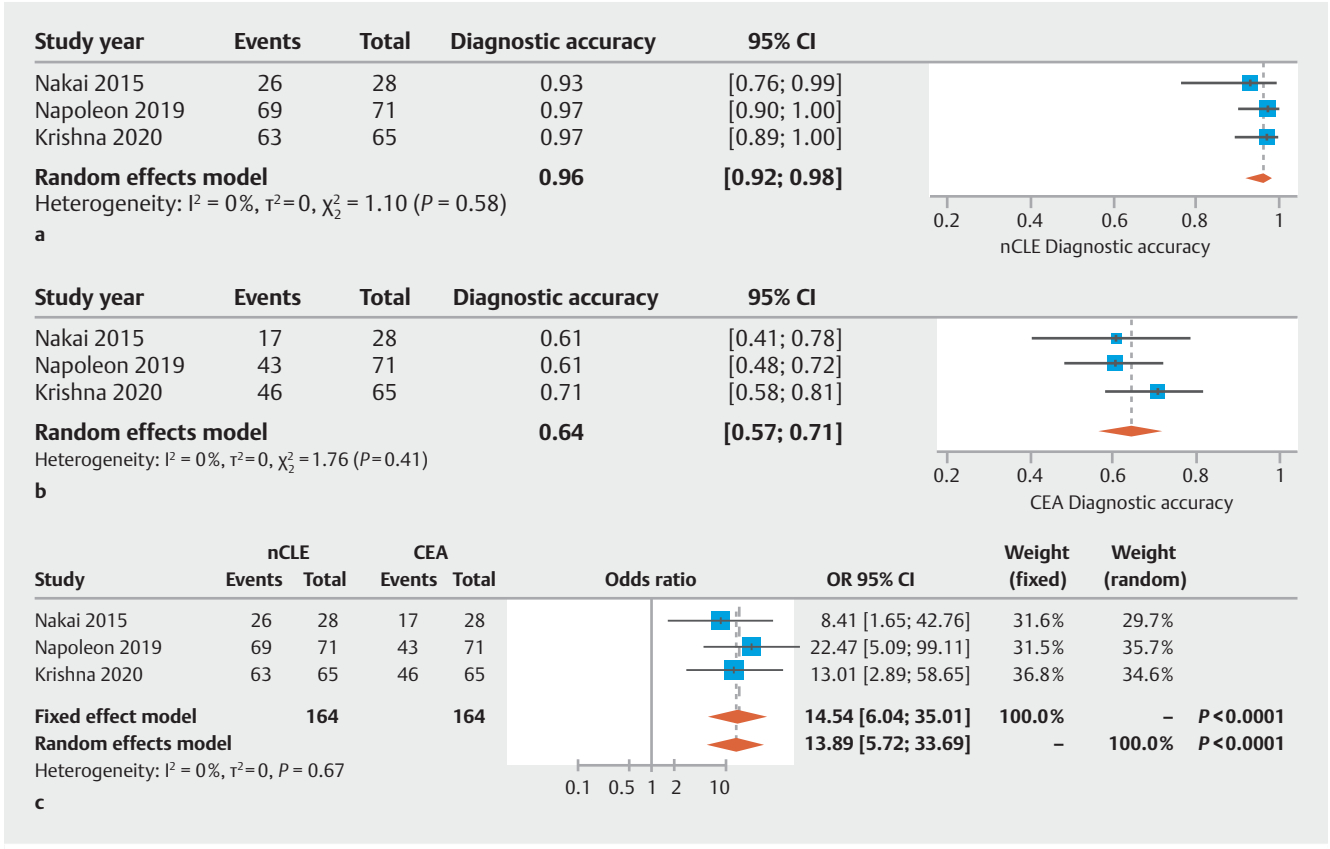
[1] N represents the total number of patients. Surgery is the number of patients with pancreatic surgery. CEA, carcinoembryonic antigen; nCLE, needle-based confocal laser endomicroscopy; EUS, endoscopic ultrasound; nDD: Patients with definitive diagnosis (histology from surgery and/or cytopathology); ACC, diagnostic accuracy; yield, diagnostic yield; NA, not available.
[2] Calculated on a subpopulation of 31 patients (26 patients served for criteria identification).
[3] Calculated on a subpopulation of 78 patients for which definitive diagnostic was reached either based on surgery or on cytohistology
[4] Calculated on a subpopulation of 65 patients for which definitive diagnostic was reached either based on surgery.



▶ **Fig. 3** Pooled diagnostic yields of **a** needle-based confocal laser endomicroscopy (nCLE) and **b** CEA (carcinoembryonic antigen) for pancreatic cyst lesions diagnosis. Meta-analysis comparing diagnostic yields of nCLE and CEA (**c**). OR, odds ratio.

nCLE is highly accurate to diagnose cystic NEN (Statement 4).

Napoleon et al. [9] also reported a new diagnostic nCLE criterion of "dark spots surrounded by grey areas" in cystic NEN [9]. Both Karia et al. [32] and a case report published by Kamboj et al. [33] confirmed this observation and reported visualization of well-demarcated clusters of cells with surrounding areas of fibrosis and vascularity. In a recent multicenter, prospective, controlled study [14] (CONTACT-II), seven NENs were included in the cohort of PCLs and the sensitivity, specificity, and accuracy for their diagnosis with the above criterion was 100 %, 95 %, and 98 % respectively. In addition, Krishna et al. (INDEX study)



▶ **Fig. 4** Pooled diagnostic accuracies of a needle-based confocal laser endomicroscopy (nCLE) and b CEA (carcinoembryonic antigen) for pancreatic cyst lesions diagnosis. c Meta-analysis comparing diagnostic accuracies of nCLE and CEA. OR, odds ratio.

correlated in vivo and ex vivo endomicroscopic images of resected cystic-NENS in which dark clusters or trabeculae of cells separated by cystic stroma were observed that corresponded with histological biopsies showing well-differentiated NENs [31]. In the INDEX study in which there were six patients with NEN, a trabecular nCLE pattern revealed a sensitivity, specificity, and accuracy of 100% each, respectively [13].

Inter-observer agreement of nCLE for the diagnosis of cystic lesion is substantial (Statement 5).

Four studies [9, 10,32,34] have assessed inter-observer Aareement (IOA) for nCLE criteria (▶ **Table 5**) in 77 patients (including two IOAs, internal and external observers) on the INDEX study population by Krishna et al. [10]. All studies were conducted with blinded reviewers. Except for the study of Karia et al. [32], specific and global IOAs were substantial or almost perfect (> 0.60), for mucinous lesions, SCA and PC. A notable limitation for this latter study [32] was the low number of patients with a definitive diagnosis (8 patients) and the low confidence level for the final diagnosis (53%). This study also had a lower IOA (kappa 0.04 to 0.22) when compared to the three other studies [9, 10, 34]. The image criteria assessed were villi, dark clumps, reticular pattern, acinar cells pattern, and debris, which are very different and lacked refinement compared to the validated nCLE characteristics that includes papillary fronds for IPMNs, epithelial bands for MCNs, bright particles on a dark background for pseudocysts, and superficial vascular network or fern pattern for SCAs.

Moreover, the image criteria used by Karia et al. [32] are not specific to differentiate PCLs. Intra-observer reliability (IORs) was addressed by the two IOR studies (internal and external observers) using the INDEX-study population [10, 34] IORs were reported for all nCLE criteria as substantial ranging from 0.68 to 0.78 for nCLE naïve blinded reviewers (n = 6) and as almost perfect (κ ranging from 0.85 to 0.91) among six blinded nCLE experts (experience > 30 nCLE cases) [10].

EUS-nCLE procedure and technique

The incidence of adverse events associated with intravenous fluorescein injection is extremely low (Statement 6).

The risks associated with intravenous (IV) fluorescein injection are extremely low (< 0.01%) [35]. The most common adverse event (AE) is hypotension (70%) followed by nausea and vomiting (60%) [35]. Although risk of anaphylaxis is rare, it is imperative to discuss it with the patient prior to the procedure [35]. None of the nCLE studies reported AEs related to intravenous (IV) fluorescein administration.

▶ **Table 4** Diagnostic performance of EUS-nCLE for differentiating mucinous versus non-mucinous pancreatic cystic lesions (PCL) and serous cyst adenoma (SCA) versus non-SCA PCL.

Publication year	First author	Study name	N	nDD (surgery)	nCLE yield	Mucinous versus non-mucinous PCL				
						SE	SP	PPV	NPV	ACC
2013	Konda, VJ. [27]	INSPECT	66	57 (14)	89 %	59 %[1]	100 %[1]	100 %[1]	50 %[1]	71 %[1]
2015	Nakai, Y. [28]	DETECT	30	18 (2)	100 %	80 %	100 %	100 %	80 %	89 %
2016	Napoleon, B. [9]	CONTACT-I	33	20 (9)	90 %	91 %	95 %	91 %	95 %	94 %
2016	Karia, K. [32]	AIRDPD	20	8 (3)	75 %	NA	NA	NA	NA	46 %
2017	Kadayifci, A. [12]	CINE-Cyst	20	11 (5)	75 %	66 %	100 %	NA	NA	83 %
2018	Napoleon, B. [14]	CONTACT-II	206	78 (39)	91 %	95 %[2]	100 %[2]	100 %[2]	94 %[2]	97 %[2]
2019	Krishna, S. G. [15]	INDEX	144	113 (65)	100 %	98 %[3] 96 %[4]	94 %[3] 95 %[4]	97 %[3] 96 %[4]	94 %[3] 93 %[4]	97 %[3] 97 %[4]
						SCA				
						SE	SP	PPV	NPV	ACC
2016	Napoleon, B. [9]	CONTACT-I	33	20 (9)	90 %	69 %	100 %	100 %	82 %	87 %
2018	Napoleon, B. [14]	CONTACT-II	206	78 (39)	91 %	95 %[2]	100 %[2]	100 %[2]	98 %[2]	99 %[2]
2019	Krishna, S. G. [15]	INDEX	144	113 (65)	100 %	100 %[3]	97 %[3]	50 %[3]	100 %[3]	97 %[3]

EUS, endoscopic ultrasound; nCLE, needle-based confocal laser endomicroscopy; SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy; NA, not available.
N represents the total number of patients
nDD represents patients with definitive diagnosis (histology from surgery and/or cytopathology)
Surgery is the number of patients with pancreatic surgery.
[1] Calculated on a subpopulation of 31 patients (26 patients served for criteria identification)
[2] Calculated on a subpopulation of 71 patients for which definitive diagnostic was reached either based on surgery or on cytohistology.
[3] Calculated on a subpopulation of 113 patients for which definitive diagnostic was reached either based on surgery or on cytohistology
[4] Calculated on a subpopulation of 65 patients for which definitive diagnostic was reached based on surgery

The largest surface area of the cyst epithelium must be examined, however, the procedure must be stopped once diagnostic nCLE features of a PCL are observed (Statement 7).

To reduce risk of post-procedural acute pancreatitis, it is recommended that the nCLE exam should be as short as possible with a minimum of catheter manipulation. Based on expert opinion, as soon as a diagnostic nCLE criterion is observed, the exam should be stopped and the probe removed [36].

Duration of nCLE procedure should not exceed 6 minutes (Statement 8).

Details of the AE risks (overall risk 4.50 % (95 % confidence interval [CI] 2.44 %-6.40 %) that occurred in the major trials using EUS-nCLE for evaluation of PCLs are shown in ▶ **Table 6** and ▶ **Fig. 7**. The main risk was post-procedural acute pancreatitis. The highest rate was reported in the DETECT study (6.6 %) combining Spyglass cystoscopy and nCLE imaging in the same procedure. Among a total of 514 patients who have undergone EUS-nCLE [9, 11, 14, 15, 27, 28, 32], a total of 15 subjects developed post-procedure acute pancreatitis with an estimated pooled risk of 2.92 % (95 % CI 1.6 %–5.0 %) with only one severe case [37] and a global AE pooled rate of 4.50 % (95 % CI 3.0 %–6.6 %). This is similar to the pooled pancreatitis rate of 1.63 % (95 % CI 0.55 %–3.81 %) and global AE pooled rate of 5.48 % (95 % CI 0.88 %–13.64 %) from a recently published meta-analysis including five studies (n = 242 patients) evaluating morbidity associated with EUS-guided FNA for PCLs performed using a 19G needle [38].

A correlation between mean nCLE procedure duration and pancreatitis rate (Pearson correlation = 0.86, $P = 0.03$) was noticed when including the six published studies [9, 11, 14, 15, 27, 28, 32] reported in ▶ **Table 6**.

Nevertheless in the latest update of the INDEX study [15], there was no difference in mean duration of nCLE comparing subjects with and without post-procedural acute pancreatitis (mean 6.0 vs. 7.3 minutes, $P = 0.33$). In summary, reducing EUS-nCLE image acquisition time to 6 minutes or less should decrease risk of post-procedural acute pancreatitis, but these data remain to be confirmed. In the meta-analysis from Facciorusso et al. [29] mentioned that the mean time of nCLE procedure was 6.094 minutes (4.91, 7.26, 95 % CI).

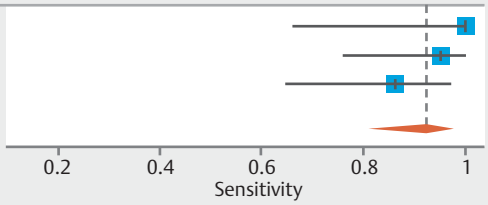
Needle and probe should be manipulated with caution to minimize disruption of the cyst epithelium (Statement 9).

Examining different foci within a cyst may be helpful for its characterization. The FNA needle (preloaded with the nCLE probe) should be carefully positioned within the cyst. The nCLE probe should maintain a soft contact with the epithelium of the cyst to obtain relevant images. After examining a specific area of the cyst, the needle needs to be repositioned to exam-

Sensitivity

Study year	Events	Total	Sensitivity	95% CI
Napoleon 2016	9	9	1.00	[0.66; 1.00]
Napoleon 2019	20	21	0.95	[0.76; 1.00]
Krishna 2020	19	22	0.86	[0.65; 0.97]
Random effects model			**0.92**	**[0.81; 0.97]**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi^2_2 = 0.92$ ($P = 0.63$)

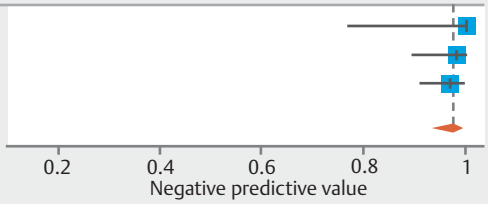


a

Negative predictive value

Study year	Events	Total	Negative predictive value	95% CI
Napoleon 2016	14	14	1.00	[0.77; 1.00]
Napoleon 2019	50	51	0.98	[0.90; 1.00]
Krishna 2020	91	94	0.97	[0.91; 0.99]
Random effects model			**0.97**	**[0.93; 0.99]**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi^2_2 = 0.18$ ($P = 0.91$)

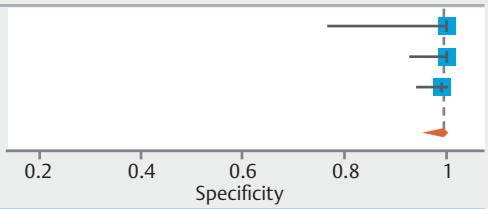


b

Specificity

Study year	Events	Total	Specificity	95% CI
Napoleon 2016	14	14	1.00	[0.77; 1.00]
Napoleon 2019	50	50	1.00	[0.93; 1.00]
Krishna 2020	91	92	0.99	[0.94; 1.00]
Random effects model			**0.99**	**[0.96; 1.00]**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi^2_2 = 0.00$ ($P = 1.00$)

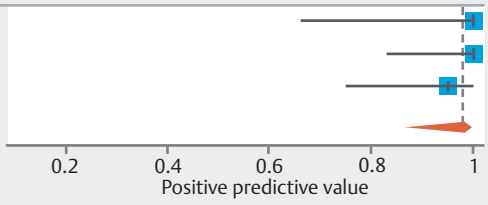


c

Positive predictive value

Study year	Events	Total	Positive predictive value	95% CI
Napoleon 2016	9	9	1.00	[0.66; 1.00]
Napoleon 2019	20	20	1.00	[0.83; 1.00]
Krishna 2020	19	20	0.95	[0.75; 1.00]
Random effects model			**0.98**	**[0.87; 1.00]**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi^2_2 = 0.00$ ($P = 1.00$)

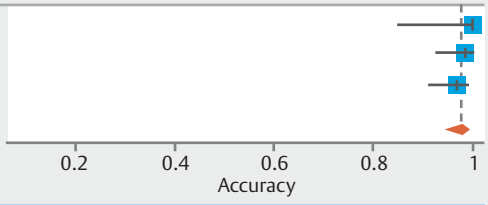


d

Accuracy

Study year	Events	Total	Accuracy	95% CI
Napoleon 2016	23	23	1.00	[0.85; 1.00]
Napoleon 2019	70	71	0.99	[0.92; 1.00]
Krishna 2020	110	114	0.96	[0.91; 0.99]
Random effects model			**0.98**	**[0.94; 0.99]**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi^2_2 = 0.69$ ($P = 0.71$)

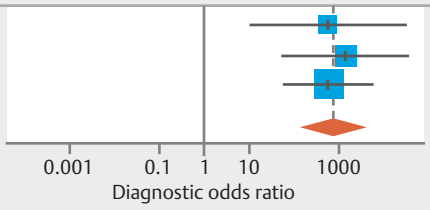


e

Diagnostic odds ratio

Study	Experimental Events	Experimental Total	Control Events	Control Total	Odds ratio	OR	95% CI
Napoleon 2016	9	9	0	14		551.000	[10.048; 30215.894]
Napoleon 2019	20	20	1	51		1380.333	[53.978; 35298.089]
Krishna 2020	19	20	3	94		576.333	[56.835; 5844.303]
Random effects model		**49**		**159**		**727.964**	**[132.287; 4005.934]**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = 0.90$



f

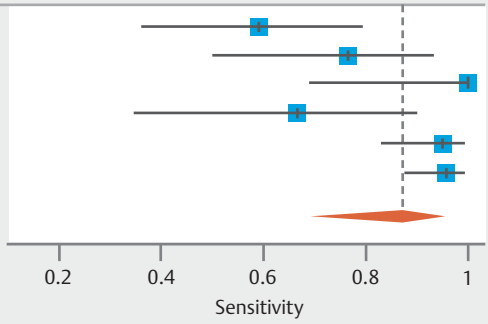
▶ **Fig. 5** Needle-based confocal laser endomicroscopy **a** pooled sensitivity, **b** specificity, **c** negative predictive value, **d** positive predictive value, **e** accuracy, and **f** diagnostic odds ratio for mucinous lesion diagnosis. OR, odds ratio.

Sensitivity

Study year	Events	Total	Sensitivity	95 % CI
Konda 2013	13	22	0.59	[0.36; 0.79]
Nakai 2015	13	17	0.76	[0.50; 0.93]
Napoleon 2016	10	10	1.00	[0.69; 1.00]
Kadayifci 2017	8	12	0.67	[0.35; 0.90]
Napoleon 2019	38	40	0.95	[0.83; 0.99]
Krishna 2020	68	71	0.96	[0.88; 0.99]
Random effects model			**0.87**	**[0.70; 0.95]**

Heterogeneity: $I^2 = 76\%$, $\tau^2 = 1.2635$, $\chi^2_5 = 20.19$ ($P<0.01$)

a

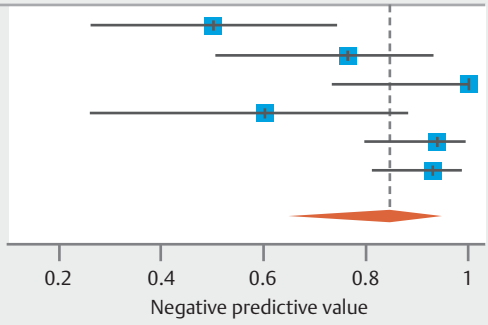


Negative predictive value

Study year	Events	Total	Negative predictive value	95 % CI
Konda 2013	9	18	0.50	[0.26; 0.74]
Nakai 2015	13	17	0.76	[0.50; 0.93]
Napoleon 2016	12	12	1.00	[0.74; 1.00]
Kadayifci 2017	6	10	0.60	[0.26; 0.88]
Napoleon 2019	31	33	0.94	[0.80; 0.99]
Krishna 2020	40	43	0.93	[0.81; 0.99]
Random effects model			**0.85**	**[0.65; 0.94]**

Heterogeneity: $I^2 = 76\%$, $\tau^2 = 1.3136$, $\chi^2_5 = 17.83$ ($P<0.01$)

b

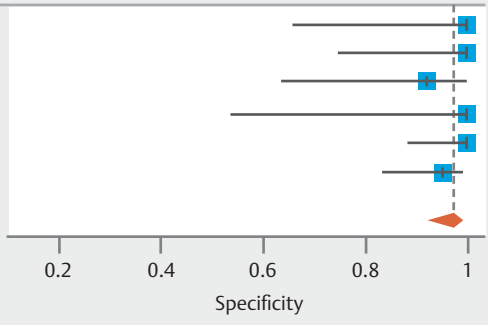


Specificity

Study year	Events	Total	Specificity	95 % CI
Konda 2013	9	9	1.00	[0.66; 1.00]
Nakai 2015	13	13	1.00	[0.75; 1.00]
Napoleon 2016	12	13	0.92	[0.64; 1.00]
Kadayifci 2017	6	6	1.00	[0.54; 1.00]
Napoleon 2019	31	31	1.00	[0.89; 1.00]
Krishna 2020	40	42	0.95	[0.84; 0.99]
Random effects model			**0.97**	**[0.92; 0.99]**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi^2_5 = 0.16$ ($P = 1.00$)

c

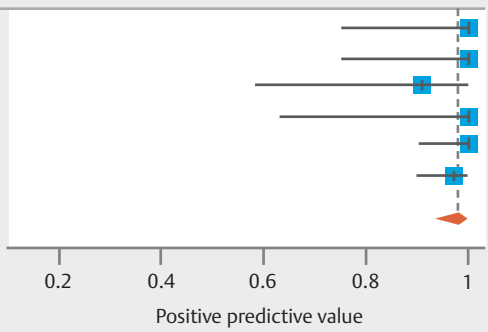


Positive predictive value

Study year	Events	Total	Positive predictive value	95 % CI
Konda 2013	13	13	1.00	[0.75; 1.00]
Nakai 2015	13	13	1.00	[0.75; 1.00]
Napoleon 2016	10	11	0.91	[0.59; 1.00]
Kadayifci 2017	8	8	1.00	[0.63; 1.00]
Napoleon 2019	38	38	1.00	[0.91; 1.00]
Krishna 2020	68	70	0.97	[0.90; 1.00]
Random effects model			**0.98**	**[0.94; 0.99]**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi^2_5 = 0.93$ ($P = 0.97$)

d



▶ **Fig. 6** Needle-based confocal laser endomicroscopy **a** pooled sensitivity, **b** specificity, **c** negative predictive value, **d** positive predictive value, **e** accuracy, and **f** diagnostic odds ratio for serous cystadenoma diagnosis. OR, odds ratio. *Continuation see next page*

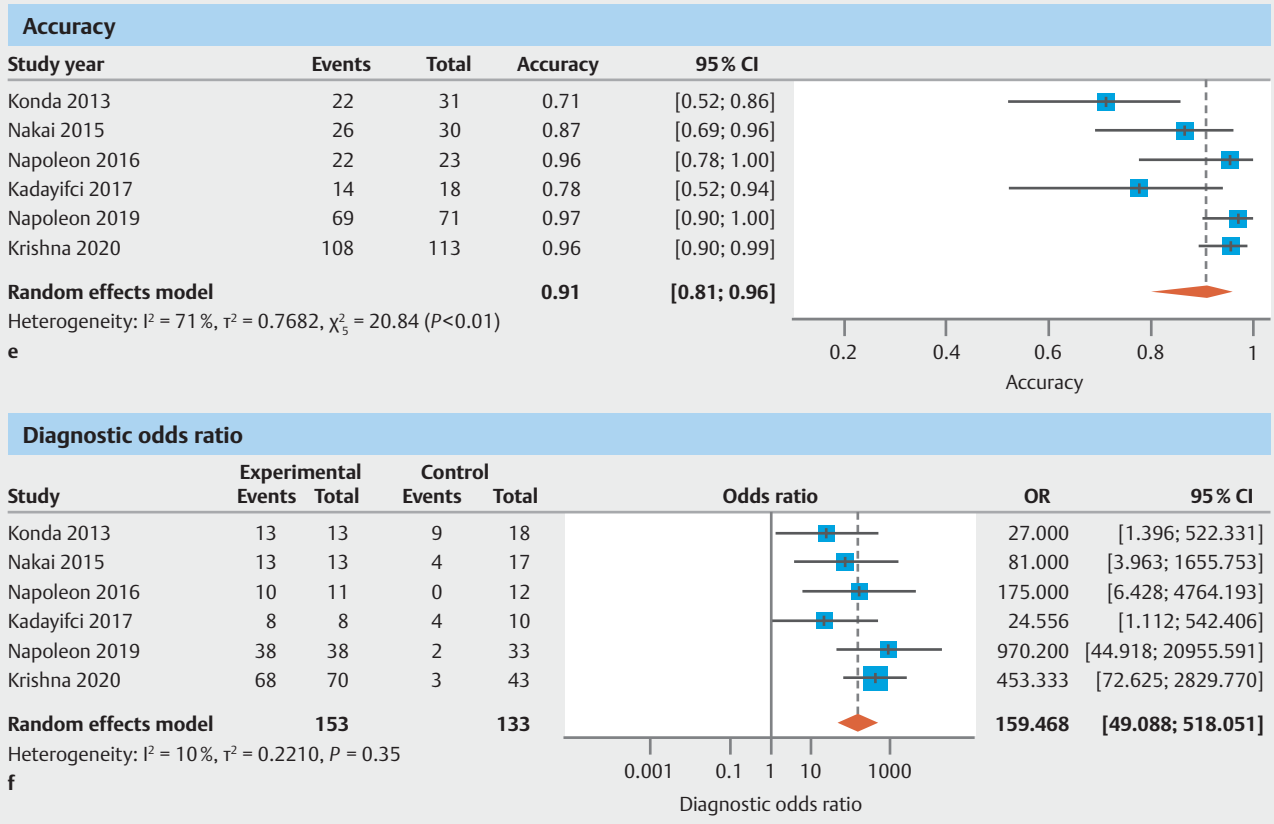


Fig. 6 *Continuation.*

▶ **Table 5** Interobserver agreement (IOA) of endoscopic ultrasound-guided, needle-based confocal endomicroscopy for evaluation of pancreatic cystic lesions (PCL).

Publication year	First author	Study name	N	nDD (surgery)	Reviewers #	Global IOA	Mucinous (IPMN or MCN)	Bright particles on a dark background (pseudocyst)	Superficial vascular network (SCA)
2016	Napoleon, B. [9]	CONTACT-I	33	20 (9)	4 blinded	0.72 (0.52–0.87)	0.56 (0.23–0.82)	1.00 (1.00–1.00)	0.88 (0.68–1.00)
2016	Krishna, S. G. [34]	INDEX	26	26 (23)	6 blinded	NA	0.66 (0.56–0.76)	0.79 (0.69–0.89)	0.70 (0.60–0.80)
2017	Krishna, S. G.[10]	INDEX	29	29 (23)	6 blinded experts	NA	NA	0.79 (0.70–0.88)	0.83 (0.73–0.92)
2016	Karia, K. [32]	AIRDPD	15 (3)	8 (3)	6 blinded	0.13	NA	NA	NA

N represents the total number of patients.
nDD is the number of patients with definitive diagnosis (histology from surgery and/or cytopathology)
Surgery is the number of patients with pancreatic surgery.
IOA, intrer-observer agreement; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; NA, not available; SCA: serous cystadenoma

ine another area of the cyst wall. While repositioning, "brushing" the cyst wall with the needle tip/probe can potentially damage the membrane wall or vessels and cause bleeding. Krishna et al. [10] underlined the difficulty to assess the whole inside wall of a cyst with a 19G needle. However, the authors felt confident that approximately 30% of the intra-cystic epithelium in a two-dimensional plane could be comfortably visualized [10].

▶ **Table 6** nCLE procedure adverse events.

	First author	Study name	N	nCLE mean duration (minutes)	Pancreatitis rate (%) with 95% CI	Intracystic bleeding (%) with 95% CI	Global adverse events (%) With 95% CI
2013	Konda, VJ. [27]	INSPECT	66	6	3.0%	0.0%	3.0%
2015	Nakai, Y. [28]	DETECT	30	10[1]	6.6%	0.0%	6.6%
2016	Napoleon, B. [9]	CONTACT-I	33	7	3.0%	0.0%	3.0%
2016	Karia, K. [32]	AIRDPD	15	2	0.0%	0.0%	0.0%
2020	Krishna, S. G. [15]	INDEX	144	7.3	4.9%	0.0%	4.9%
2017	Kadayifci, A. [12]	CINE-Cyst	20	6	0.0%	0.0%	0.0%
2019	Napoleon, B. [14]	CONTACT-II	206	5	1.5%	3.88%	5.23%
Total (95% CI)			514	6.2 (4.3–8.1)	2.92% (1.6%–5.0%)	0.7% (0%–3.6%)	4.50% (3.0%–6.6%)

N represents the total number of patients.
nCLE, needle-based confocal laser endomicroscopy.
[1] for Nakai et al [28] nCLE procedure time had a mean of 6 minutes followed by cystoscopy with mean duration of 4 minutes

Onsite presence of cytopathologist can facilitate nCLE image interpretation (Statement 10)

In the preliminary observational and pilot studies [3, 6, 9, 27, 34], gastrointestinal pathologists have been instrumental in identifying and validating nCLE criteria for different types of PCLs. Since the nCLE image patterns of specific PCLs have been described and validated, an endoscopist with proper training and credentialing should be able to accurately identify and interpret the validated criteria with high IOA as reported in the literature [9, 10, 32, 34] (▶ **Table 5**). However, it might be helpful to partner with a pathologist during the initial learning curve based on the individual interest of the pathologist and institutional provisions.

Indications for EUS-nCLE

nCLE is indicated in patients with indeterminate non-communicating cysts when EUS-FNA is performed (Statement 11)

Currently, EUS-FNA with cyst fluid analysis is the standard of care for evaluating PCLs but the accuracy (< 50%) is very low for differential diagnosis of PCLs [19]. For this reason, the major society guidelines for managing PCLs are controversial when it comes to the value of cyst fluid analyses [39, 40]. Lack of clear and undisputed guidelines is eventually reflected in incongruent and suboptimal patient management across the globe with superfluous imaging, endoscopy procedures or pancreatic surgeries [41, 42].

In a recent study, the addition of nCLE to EUS-FNA with cyst fluid analysis changed diagnosis and management strategy of PCLs in nearly one-third of cases, while improving inter-observer agreement [43]. In the INDEX study [13], nCLE and cyst fluid molecular markers were complementary with a diagnostic accuracy for mucinous-PCLs of 100% when applied in tandem. Thus, performing nCLE for a PCL at the time of the index procedure when EUS-FNA is performed could be advantageous by reducing the number of follow-up procedures including repeat EUS-FNA. This might lead to savings in healthcare resource utilization [44].

nCLE is indicated when a pancreatic cyst remains indeterminate at previous EUS-FNA (Statement 12).

In the CONTACT II [14] cohort, 67 of 206 patients had undergone a previous inconclusive EUS-FNA (inconclusive CEA, no cytology). In these patients, nCLE was able to establish a diagnosis in 61 cases (91%), while a repeat attempt at cytology performed during the procedure was contributive in 25 cases (37%) and CEA concentrations greater than 192 ng/mL noticed in 19 cases (28%).

Repeat nCLE on subsequent follow-up procedures should not be routinely performed (Statement 13).

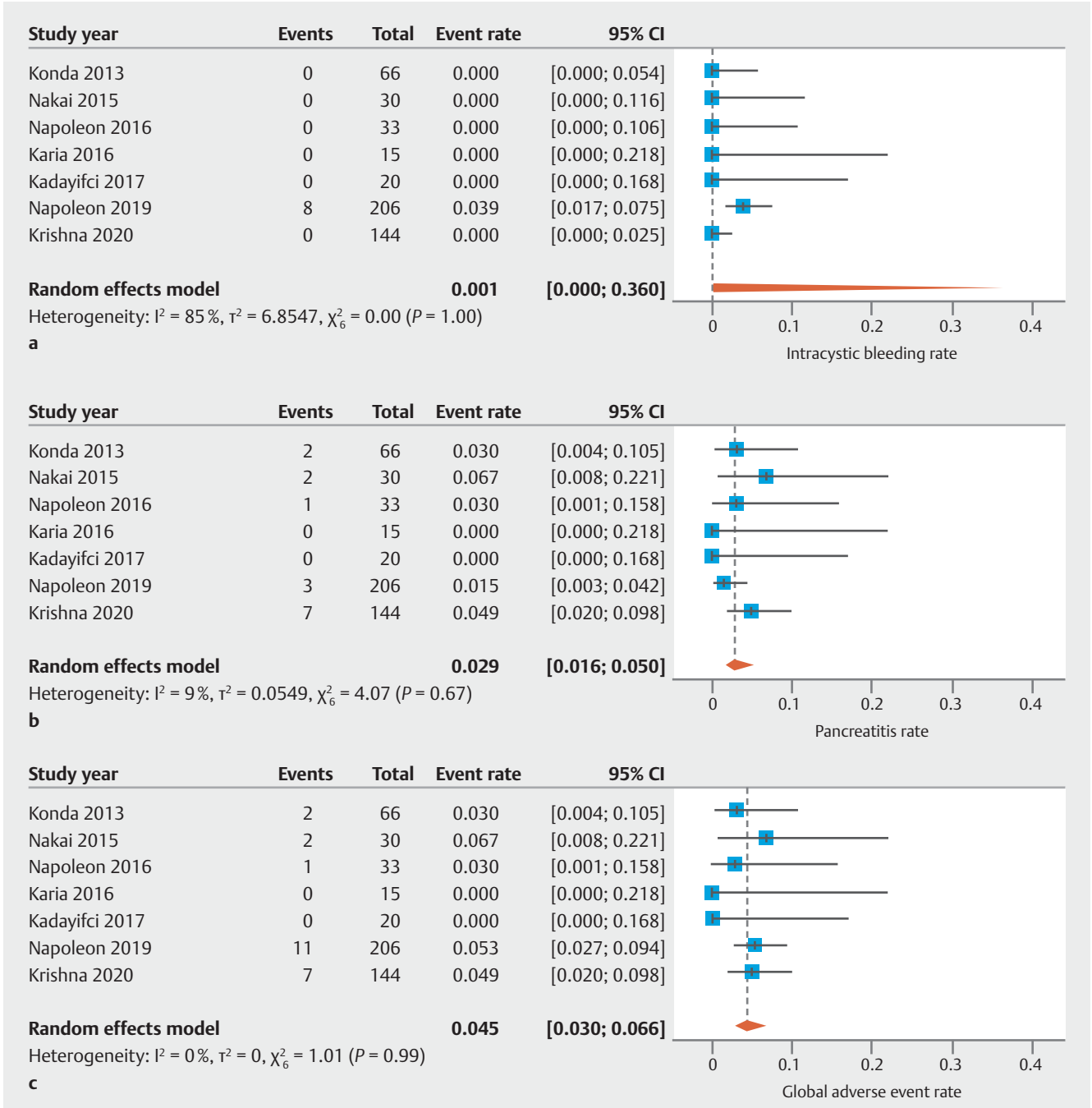
To date, there is no evidence in the literature supporting repeat nCLE during follow-up EUS. In the absence of clear-cut indications (such as non-diagnostic nCLE and development of new worrisome features) repeat EUS-nCLE should not be performed on subsequent follow-up procedures.

Training and credentialing in EUS-nCLE

A consensus report based on clinical evidence for probe-based confocal laser endomicroscopy (pCLE) use has been published for gastrointestinal [16]. Some statements have already been described and are applicable to nCLE. We propose complementary statements specific to EUS-nCLE (4–1 to 4–3).

Physicians are expected to have a good understanding of pancreatic cystic lesions, and procedural indications and contraindications for EUS-nCLE (Statement 14).

In order to maximize the outcomes of the procedure and execute it safely, the physician must weigh the benefits versus



▶ **Fig. 7** Needle-based confocal laser endomicroscopy pooled adverse event rates: **a** intracystic bleeding rate, **b** pancreatitis rate, and **c** global event rate.

risks and proceed with nCLE only when indicated for an eligible patient, under optimal conditions.

Trainees in EUS-nCLE of PCLs need to be fully competent in pancreatic EUS and EUS-FNA (Statement 15).

nCLE is considered to be an advanced endoscopic imaging technique. Before starting with nCLE, physicians are expected to have completed training in EUS and EUS-FNA (advanced endoscopy training) with appropriate credentialing in addition to a standard gastroenterology fellowship or specialty program.

Trainees should learn how to obtain optimal nCLE images of the intracystic epithelium to achieve satisfactory images (Statement 16).

During EUS-nCLE, the probe must be positioned in tight contact with the intracystic epithelium at a perpendicular or slight-

ly tangential angle. Because scope maneuvering and duration of the examination can influence risk of post-procedural pancreatitis, trainees must master scope and needle control to minimize risks.

Discussion

A major hurdle in management of PCLs is accurate and reliable differentiation of pre-malignant or neoplastic lesions (mucinous PCLs, cystic-NENs) from benign PCLs (SCA, pseudocysts). Only patients with mucinous PCLs need to be followed according to the Fukuoka Consensus Guidelines (2012 and 2017 revision) [45]. With these aspects in mind, our international nCLE group has developed a consensus to help practicing clinicians use a novel diagnostic modality with high diagnostic accuracy (EUS-nCLE) when managing patients with PCLs.

The methodology of this consensus report involved a thorough literature search performed by experts in pancreatology and/or endomicroscopy involving all the published literature evaluating EUS-nCLE in the management of PCLs. A structured methodology was used to develop the consensus statements. Adoption of a statement was based on the agreement level voted by the panelists. The grade of evidence was also assessed for each statement. The four group leaders provided up-to-date literature to the participants, who undertook responsibility for voting based on their individual expertise and appraisal of the literature.

The consensus process resulted in a high level of agreement for the majority of the statements. This suggests that in defined circumstances, there is ample clinical evidence for an added benefit of application of nCLE in management of PCLs. First, EUS-nCLE provides better differentiation of mucinous and non-mucinous PCLs compared to the current standard of care. Second, EUS-nCLE can improve the accuracy of diagnosis of SCAs, thus reducing the rate of unnecessary follow-up investigations or inappropriate resections. Third, the interobserver agreement for EUS-nCLE to differentiate mucinous from non-mucinous PCLs is high.

Finally, EUS-nCLE is as safe as a currently used diagnostic standard of care procedure, that is, EUS-guided FNA with a 19G needle. Further research is required to assess the cost-effectiveness of this approach.

The consensus panel recognizes the challenge of measuring the benefit of specific interventions in assessment of learning. Hands-on nCLE experience and cognitive training are mandatory during the initial training phase. Continued self-training is recommended for better understanding and interpretation of nCLE findings. This includes review of the literature, published videos, online resources, and attending focused conferences. The panel recommends a minimum number of 10 EUS-nCLE procedures under supervision of an experienced operator to achieve competency and the same number of EUS-nCLE procedures performed per year to maintain competency. Because these statements involving training are not based on scientific evidence but on consensus agreement, formal prospective research is necessary to validate these propositions.

There are a number of potential limitations to this study. The first is the low number of studies addressing training in nCLE, including the technical procedure and nuances of nCLE image interpretation. Second, because data are lacking, we were unable to compare nCLE to more recent techniques for characterizing PCLs, such as intracystic biopsies and molecular DNA analysis.

Despite these limitations, this report represents the most inclusive consensus paper available to date on EUS-nCLE for management of PCLs. The outcomes are clinically relevant and the high degree of consensus disclosed for the majority of statements makes a strong case for application of EUS-nCLE in clinical practice. In addition, areas in which consensus was not achieved were identified to direct future work and research efforts.

Conclusions

This consensus established that EUS-guided nCLE is a minimally invasive procedure that improves evaluation of PCLs. The routine addition of nCLE to standard EUS-FNA could positively impact patient management and improve healthcare resource utilization by reducing the number of misdiagnoses and preventing redundant follow-up investigations and unnecessary surgery. Structured training of endosonographers in this novel technology for competent application is needed. Complementary research on cost-effectiveness and in areas where consensus was not achieved is required.

Competing interests

Dr. Napoleon has received honoraria and grants from Mauna Kea Technologies and Boston Scientific. Dr. Krishna is currently receiving a travel grant from Mauna Kea Technologies. Dr. Marco has received honoraria and grants from Boston Scientific, Cook Medical, Pentax Medical, 3M, and Mylan. Dr. Carr-Lock has received honoraria and grants from Mauna Kea Technologies, Boston Scientific, and US Endoscopy. Dr. Chang has received honoraria and grants from Boston Scientific, Cook Medical, Pentax Medical, NinePoint, and Erbe. Dr. Sejpal has received grants from Boston Scientific, Cook Medical, and Olympus. Dr. Palazzo has received grants from Mauna Kea Technologies. Dr. Brugge has received honoraria and grants from US Endoscopy and NinePoint.

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