

A novel approach to the diagnosis of pancreatic serous cystadenoma: needle-based confocal laser endomicroscopy

Authors

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Bibliography

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Background and study aims: The differential diagnosis of solitary pancreatic cystic lesions is frequently difficult. Needle-based confocal laser endomicroscopy (nCLE) performed during endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is a new technology enabling real-time imaging of the internal structure of such cysts. The aim of this pilot study was to identify and validate new diagnostic criteria on nCLE for pancreatic cystic lesions.

Patients and methods: A total of 31 patients with a solitary pancreatic cystic lesion of unknown diagnosis were prospectively included at three centers. EUS-FNA was combined with nCLE. The final diagnosis was based on either a stringent gold standard (surgical specimen and/or positive cytopathology) or a committee consensus. Six non-blinded investigators reviewed nCLE sequences from patients with the most stringent final diagnosis, and identified a single feature that was only present in serous cystadenoma (SCA). The findings were correlated with the pathology of ar-

chived specimens. After a training session, four blinded independent observers reviewed a separate independent video set, and the yield and interobserver agreement for the criterion were assessed.

Results: A superficial vascular network pattern visualized on nCLE was identified as the criterion. It corresponded on pathological specimen to a dense and subepithelial capillary vascularization only seen in SCA. The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of this sign for the diagnosis of SCA were 87%, 69%, 100%, 100%, and 82%, respectively. Interobserver agreement was substantial ($\kappa = 0.77$).

Conclusion: This new nCLE criterion seems highly specific for the diagnosis of SCA. The visualization of this criterion could have a direct impact on the management of patients by avoiding unnecessary surgery or follow-up.

[Clinicaltrials.gov NCT01563133](http://Clinicaltrials.gov/NCT01563133).

Introduction

The widespread use of cross-sectional imaging techniques has increased the detection of pancreatic cystic lesions in asymptomatic patients [1]. The differential diagnosis of these lesions is crucial given their different evolution. Lesions with a malignant potential are mainly mucin-producing tumors (mucinous cystic neoplasms [MCN] and intraductal papillary mucinous neoplasm [IPMN]), whereas pseudocysts and serous cystadenoma (SCA) are considered to be without malignant risk.

SCA is typically defined as a solitary cyst, without pancreatic duct communication and characterized by microcystic morphology, a central area with calcification, and a nonviscous fluid content. However, most often, SCA presents with a macrocystic or macro- and microcystic appearance that

can cause it to be confused with a mucin-producing tumor. In this situation, the yield of morphological explorations including computed tomography (CT), magnetic resonance imaging (MRI) [2], and endoscopic ultrasound (EUS) remains limited [3]. EUS-guided fine-needle aspiration (EUS-FNA) with cytopathological examination and biochemical analysis of the cyst fluid can be useful [1,4]. Two meta-analyses reported a high specificity (88%–93%) but a moderate sensitivity (54%–63%) for cytology [5,6] especially in SCA as the fluid obtained is frequently acellular [3,7,8]. Levels of carcinoembryonic antigen and amylase can be helpful but no level is definitely discriminating [9,10].

Usually, the final decision between a watchful follow-up and surgery is made after a consensus review of all these criteria. However, the largest multicenter prospective study has shown that a

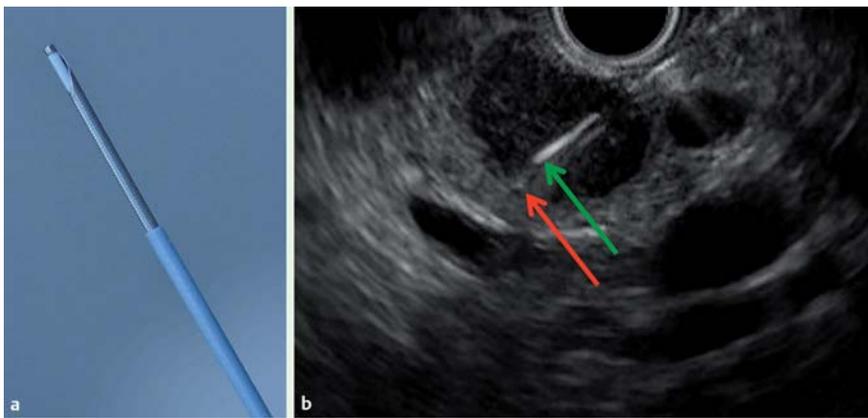


Fig. 1 Needle-based confocal laser endomicroscopy (nCLE). **a** The nCLE probe protruding from a 19-G needle. **b** Endoscopic ultrasound image of a cyst, showing the needle puncturing the cyst. Green arrow: tip of the needle. Red arrow: tip of the nCLE probe.

combination of these standard methods (morphological examinations, cytology, analysis of tumor markers, and pancreatic enzymes in the cyst fluid) enabled the correct diagnosis to be made in no more than 79% of cases [3]. Despite the improvement of imaging examinations and intracystic fluid analysis, the diagnosis of SCA often remains uncertain, and lesions larger than 2 cm are frequently surgically resected in asymptomatic patients [3]. In a large retrospective multinational study on 2622 patients with SCA, 36% of them underwent surgery for an uncertain diagnosis [11]. This approach remains inappropriate given the fact that surgery is associated with substantial morbidity and mortality [12] and that simple surveillance could be sufficient [13]. Probe-based confocal laser endomicroscopy is a novel imaging technology that enables *in vivo* and real-time imaging of the microscopic structures of tissue and surface epithelium during endoscopic procedures [14]. The miniaturization of the probe allows *in vivo* and real-time imaging of the inner wall of pancreatic lesions during the EUS-FNA procedure, by introducing the miniprobe through a 19-G needle (● **Fig. 1**). This innovative technique has been termed needle-based confocal laser endomicroscopy (nCLE) [15, 16]. The first study to report on this technique demonstrated its feasibility and safety for *in vivo* imaging of pancreatic cysts [17]. A second study, INSPECT [18], enabled the characterization of IPMNs and correlated some identified nCLE structures with histological diagnostic features. To date, no study has evaluated the value of nCLE for the characterization of benign pancreatic cystic lesions that could have a direct impact on patient management by avoiding unnecessary surgery. The aim of this pilot study was to describe and validate a diagnostic nCLE criterion for the characterization of SCA.

Patients and methods

Study design

This prospective study took place at three centers in France (Hôpital privé Jean Mermoz in Lyon, Institut Paoli Calmettes in Marseille, and Hôpital Saint-Philibert in Lille). The study was performed with the approval of the local Ethics Committee and the French Health Authority (ANSM), and was registered on clinicaltrials.gov (NCT01563133).

All consecutive patients ($n=43$) who were admitted for EUS diagnosis of a pancreatic cyst of unknown origin were considered for inclusion. Inclusion criteria were a solitary cyst >20 mm in diameter with at least one cavity ≥ 13 mm in size. Exclusion criteria were age < 18 years, known allergy to fluorescein dye, pregnancy,

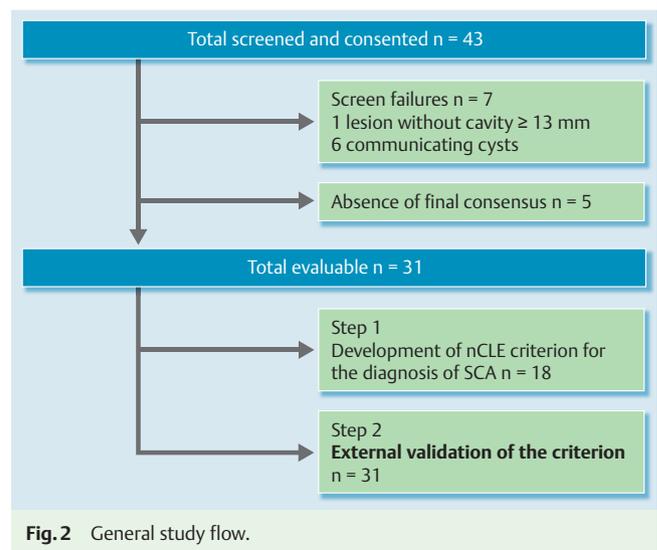


Fig. 2 General study flow.

previous EUS-FNA procedure performed within the past 3 months, chronic calcifying pancreatitis, presence of a communication with the main pancreatic duct on MRI or EUS, presence of criteria for malignancy (tissue mass, metastases, ascites, vascular infiltration), and the usual contraindications to EUS-FNA. Written informed consent was obtained from all patients before the examination.

Preliminary analysis was conducted after 10 months of inclusion and included two steps (● **Fig. 2**). Step 1 aimed at identifying a specific criterion for the characterization of SCA. The identification of specific features relied on side-by-side comparison of nCLE videos and corresponding histopathological pictures from a selected group of patients ($n=18$) whose final diagnosis was based on a surgical specimen and/or positive cytopathology. For each patient, several sequences were initially available; one of them was arbitrarily selected and reviewed in this step. Step 2 consisted of the validation of the identified criterion and assessment of its reproducibility by an independent group of investigators on an independent video set of 66 sequences (including 6 for training purposes) from the 31 patients enrolled in the study.

EUS-FNA and nCLE procedures

All procedures were performed by the investigators (B.N., B.P., M. G., F.C., B.F., and D.L.) as follows. 1) Conventional gray-scale B-mode EUS (Olympus CF-H180 [Olympus Medical Systems Corp.,

Tokyo, Japan] or Pentax EG-3870 UTK [Pentax Corp., Tokyo, Japan]) to assess the EUS characteristics of the pancreatic cyst. 2) EUS-FNA with a 19-G needle (Boston Scientific Expect Flex [Boston Scientific Corp., Natick, Massachusetts, USA] or Cook Medical Echo Tip Ultra [Cook Medical Inc., Bloomington, Indiana, USA]). Prophylactic antibiotic therapy was given before each procedure (cefazoline 2g) and the AQ-Flex 19 confocal miniprobe (Cellvizio; Mauna Kea Technologies Inc., Suwanee, Georgia, USA) was pre-loaded into the needle (Fig. 1). The confocal miniprobe has the following characteristics: 10000 optical fibers, a diameter of 0.85 mm, a field of view of 320 μ m, a lateral resolution of 3.5 μ m, and a length of 4 m.

After EUS imaging, the needle with the preloaded miniprobe was inserted into the cyst under EUS guidance via a transgastric or transduodenal approach. The probe was advanced and securely positioned using the locking device. An intravenous injection of a contrast agent (2.5 mL fluorescein, 10%), was administered simultaneously to optimize nCLE imaging. Video sequences of the inside structure of the cyst were recorded.

After image acquisition, the probe was retrieved from the needle, and the cyst was emptied as completely as possible (depending on the number of cavities). The fluid underwent cytopathological examination, and levels of carcinoembryonic antigen and amylase were assessed. Pathological examination was based on ThinPrep preparation for cytological analysis and cell blocks for histological interpretation. Data regarding clinical history, morphological examinations (MRI, CT, EUS), EUS-FNA samplings, and nCLE procedures, were prospectively recorded on a dedicated case report form.

Final diagnosis

The final diagnosis was described as stringent when based on histological analysis of the surgical specimen and/or when FNA results were undoubtedly positive on ThinPrep preparation, cell block sections, or both. A diagnosis of SCA was considered to be undoubtedly positive when stained slides from ThinPrep preparations and/or stained cell block sections showed sheets and small ribbon of monomorphous cuboidal epithelial cells with a clear cytoplasm and a small, round, and uniform hyperchromatic nuclei, and/or stained cell block sections showed microfragments of cyst wall with lining serous epithelium. A diagnosis of IPMN was made when stained cell block sections showed papillary projection with a vascular core and a mucinous epithelial border (Fig. 3).

For the remaining cases, an adjudication committee made up of the six investigators and two pathologists reviewed all available information (including a systematic follow-up by MRI 3 months after the procedure) in order to make a final diagnosis by consensus. A systematic follow-up at 1 year was scheduled for these cases. Specifically, a final diagnosis of SCA was systematically proposed when all of the following characteristics were met: serous, clear, translucent fluid; absence of nodule, mural nodules or solid tumor on EUS; absence of cytopathological criteria suggesting a mucinous lesion; CEA <5 ng/mL; amylase <250 U/L. Patients without a final consensus diagnosis were excluded from the analysis.

Step 1: Development of nCLE criterion for the diagnosis of SCA

After 10 months of inclusion, four gastroenterologists (B.N., B.P., M.G., and F.C.) and two gastrointestinal pathologists (A.I.L. and B.M.M.) reviewed 18 nCLE videos from 18 patients with stringent

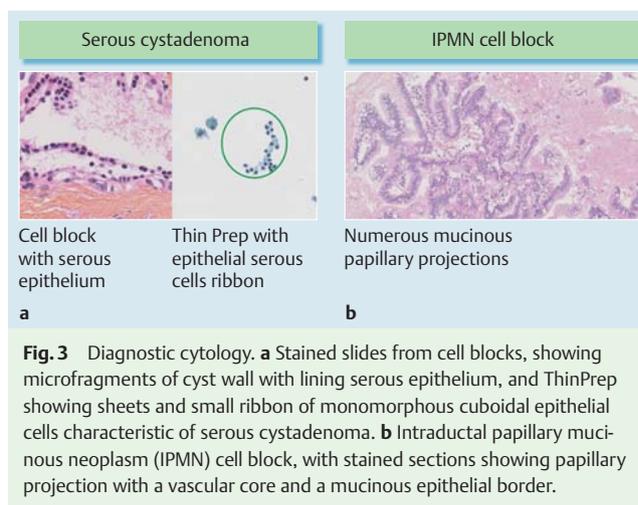


Fig. 3 Diagnostic cytology. **a** Stained slides from cell blocks, showing microfragments of cyst wall with lining serous epithelium, and ThinPrep showing sheets and small ribbon of monomorphous cuboidal epithelial cells characteristic of serous cystadenoma. **b** Intraductal papillary mucinous neoplasm (IPMN) cell block, with stained sections showing papillary projection with a vascular core and a mucinous epithelial border.

final diagnoses in an unblinded manner. In addition, histopathological images of 24 cystic lesions (5 SCAs, 5 IPMNs, 7 MCNs, 4 pseudocysts, and 3 cystic neuroendocrine tumors [NETs]) extracted from an archive database, were reviewed simultaneously in order to identify a specific nCLE criterion for the diagnosis of SCA. Similarities in vascular structures were noted between nCLE videos of SCA and histopathology images. Based on the similarities observed, a common theme, the superficial vascular network, was formulated into an nCLE criterion, by consensus between the six investigators.

Step 2: External validation of the criterion

Four independent reviewers without previous nCLE experience (F.F., C.L., V.L., and L.P.) took part in the validation review. An independent set of 66 nCLE video sequences that were not used in Step 1 were selected, with one or several representative videos for each of the 31 included patients. The videos were obtained in the proprietary .mkt format and converted into .mpeg format without compromising the image ratio or the number of pixels. The investigators underwent basic training before the test, based on the review of six videos, three of which featured the newly defined criterion. The remaining videos (n=60) were used for the test. The cases were presented in a different order for each participant, and viewed on their personal computers. The reviewers were blinded to all clinical data. For each case, reviewers noted the absence or presence of the criterion feature on a standardized scoring sheet. Following these evaluations, the four investigators conducted a consensus review of discrepant cases in order to propose a consensus diagnosis if possible.

Statistical analysis and data management

Data recorded on the case report forms were entered into OpenClinica software (Waltham, Massachusetts, USA) and used in this format for the reviews, definition, and accuracy evaluation. The diagnostic accuracy parameters and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), of the criterion were calculated for each observer. The overall diagnostic accuracy was evaluated using the consensus review. The interobserver variability was calculated using multi-rater Fleiss's kappa statistic. The results were as follows: poor <0.2, fair 0.21–0.4, moderate 0.41–0.6, substantial 0.61–0.8, and excellent 0.81–1. In addition, the permutation test and the Matthews correlation coefficient were used to test for the significance of the test in Step 2.

Table 1 Demographics and clinical presentation of the 31 patients included in the study.

All patients (n=31)	
Patients	
Age, mean (range), years	57 (24–76)
Sex	
Male	6
Female	25
Cyst morphology	
Location	
Head	14
Uncinate	1
Body	12
Tail	4
Lesion size, mean (range), mm	39 (20–120)
Wall thickness > 1 mm	8
Wall nodules / vegetation	3
Calcification	
Yes	2
No	29
Intracystic concentrations	
CEA, mean (range), ng/mL (n=27)	1 070 (0.5–15 000)
Amylase, mean (range), UI/L (n=22)	28 887 (7–255 700)
Final diagnosis definition	
Surgery	7
Positive cytology	11
Adjudication committee consensus	13

CEA, carcinoembryonic antigen.

Results



Population

From June 2012 to March 2013, 43 patients were screened for inclusion in the study and provided consent. A total of 11 patients were excluded due to screening failure (n=7) and absence of final diagnosis consensus (n=5), leaving 31 patients included in the final analysis (Fig. 2). Patient and cyst characteristics are listed in Table 1. The mean cyst size was 39mm, and lesions were distributed throughout all areas of the pancreas.

For patients with a stringent final diagnosis (n=18), the diagnosis was based on the surgical specimen in 7 patients (6 MCNs and 1 pseudocyst) and cytopathological analysis of the cystic fluid in 11 cases (7 SCAs, 4 IPMNs). For the remaining patients (n=13), the adjudication committee consensus diagnoses were 6 SCAs, 1 IPMN, and 6 pseudocysts.

Technical aspect of the procedure and safety

Technical feasibility was demonstrated in all 31 cases, with no technical failures reported. The choice of needle was at the discretion of each participating center. Needle probe manipulation was rated as “moderate” or “difficult” in two cysts (one in the head, one in the uncinate process); probe manipulation was evaluated as “easy” in all of the remaining cases.

The mean duration of the nCLE procedure was 7 minutes (range 3–10 minutes). Fluorescein was well tolerated by all patients, with no complications identified following the procedure. A single event of mild acute pancreatitis was recorded, resulting in an overall complication rate of 3.2%. In four patients with SCA, blood was identified within the imaged cavity, but no external bleeding or further clinical consequences were observed.

Step 1: Development of nCLE criterion for the diagnosis of SCA

The simultaneous review of the nCLE sequences and histopathological images enabled the identification of a particular pattern, which was observed repeatedly and exclusively in the sequences of patients with SCA. The pattern was present independently of the morphological presentation of the SCA (i.e. uni- or multilocular). This striking criterion was described as a densely woven network of tortuous blood vessels with intense and dynamic circulation of blood cells visualized.

To explain the visualization of this dynamic pattern, pathologists referred to reference specimens of SCA. Using an immunohistochemical vascular marker, the presence of a diffuse and homogeneous capillary network was noted all around the cavities. This network lay just under the serous epithelium at a depth of 10–40µm, and was identified as a capillary necklace. On the five specimens analyzed, this feature was seen either on the outlying wall of macrocysts and/or on both sides of all the septa separating the microcystic cavities (Fig. 4). As the depth of imaging permitted by the nCLE probe is 40–70µm, findings from nCLE observation could be matched to this histological vascular organization. When looking at the histology of the other pancreatic cysts (Fig. 4), this striking vascular organization was absent in the seven MCNs, five IPMNs, four pseudocysts, and three cystic NETs. Histologically, MCN are characterized by rare and large vessels located at various depths, IPMNs are characterized by the presence of intrapapillae fibrovascular cores, and in both cystic NET and pseudocysts, the presence of many vessels can be noted, at various depths and without a regular organization. In all these cases, the characteristic necklace observed in SCA is absent.

This characteristic vascular organizational structure of SCA was consensually identified as the superficial vascular network. Its characteristics are: tightly connected tortuous blood vessels of variable width; intense blood circulation with a striking dynamic aspect and varying contrast, depending on the imaging duration; it can appear as white vessels on a dark or grey background, or as dark vessels on a clear background, depending on the density of blood cells within the vessels and fluorescein contrast; it can present a watermelon-shaped or tree-like aspect (Fig. 5, Video 1, Video 2).

Step 2: External validation of the superficial vascular network criterion

In 81% of the cases, the agreement between the four observers was complete. A final consensus was obtained in the remaining 19% of cases. Compared with the final diagnosis, the overall accuracy, sensitivity, specificity, PPV, and NPV of the superficial vascular network criterion were 87% (95% confidence interval [CI] 69%–100%), 69% (95%CI 44%–92%), 100% (95%CI 100%–100%), 100% (95%CI 100%–100%), and 82% (95%CI 66%–98%), respectively.

A subanalysis was conducted on the two categories of patients. For patients with a stringent final diagnosis the accuracy, sensitivity, specificity, PPV, and NPV of the superficial vascular network criterion were 94%, 86%, 100%, 100%, and 92%, respectively. For the remaining patients, these values were 77%, 50%, 100%, 100%, and 70% respectively. The interobserver agreement was substantial ($\kappa=0.77$; 95%CI 0.55–0.99). This concordance was statistically significant, with the 95%CI ($\kappa \pm 1.96$ SE) not crossing the zero value. In addition, the correlation between the consensus diagnosis and the final diagnosis was statistically significant ($P<0.01$). Results are detailed in Table 2.

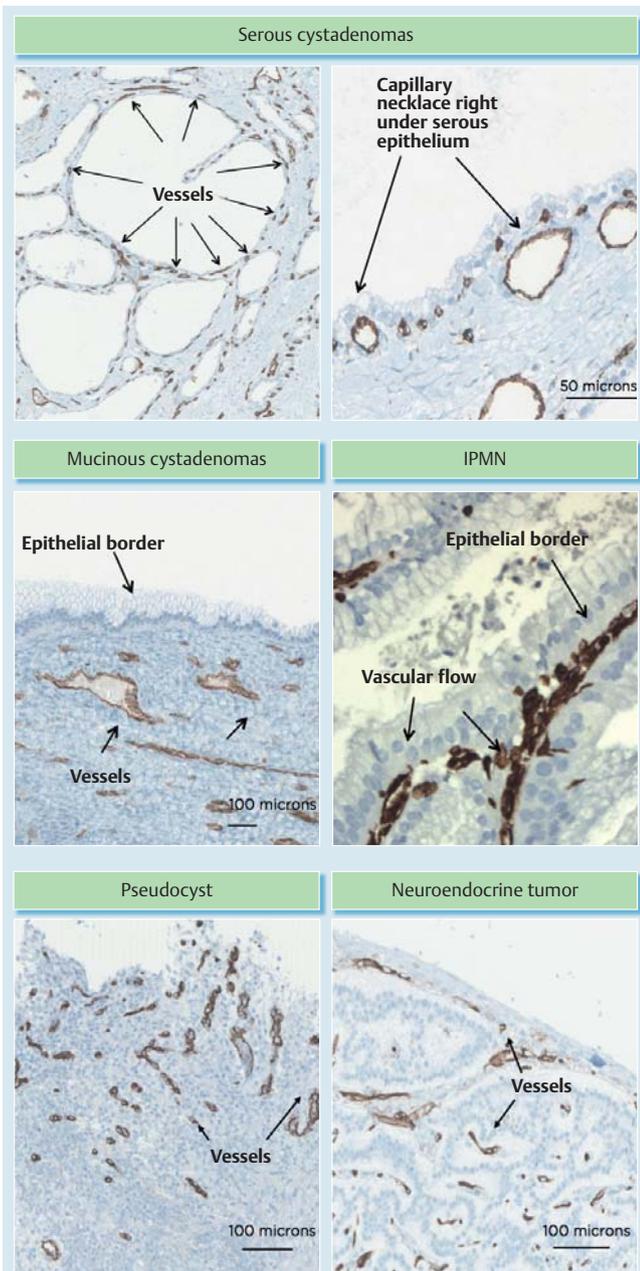


Fig. 4 Reference specimen of different types of cystic lesions with immunohistochemical vascular marker (vessels in brown).

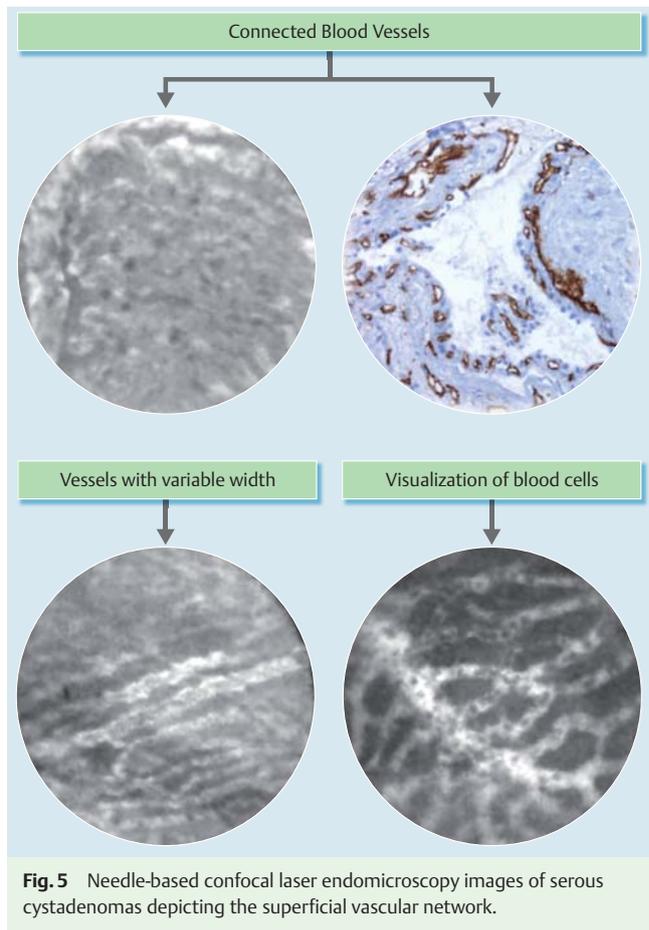


Fig. 5 Needle-based confocal laser endomicroscopy images of serous cystadenomas depicting the superficial vascular network.

Discussion

These are the first data reporting the yield of nCLE for the characterization of pancreatic SCAs. In this study, a new criterion for in vivo diagnosis of SCA was described and validated – the superficial vascular network. The correlation relies on three elements. First, the observation of circulating blood cells inside the opacified channels confirms the vascular nature of the network. Second, this structure is observed at a superficial depth of 50–70 μm , which corresponds to the depth of imaging of the AQ-Flex probe. Third, the pathological examination of pancreatic cyst specimens including SCAs, MCNs, IPMNs, pseudocysts, and NETs showed that the only pancreatic cystic lesion featuring a dense, tortuous, and superficial capillary vascularization was the SCA.

Following the description of the superficial vascular network, postprocedural evaluation of the sign was conducted to assess the validity and reproducibility of this finding. In a validation vid-

Video 1



Needle-based confocal laser endomicroscopy of serous cystadenomas depicting the superficial vascular network.



Online content including video sequences viewable at: www.thieme-connect.de

Video 2



Needle-based confocal laser endomicroscopy of serous cystadenomas depicting the superficial vascular network.



Online content including video sequences viewable at: www.thieme-connect.de

Table 2 Yield of SVN criterion in the two categories of patients.

	All patients n=31	Cases with final stringent diagnosis n=18	Cases with less stringent final diagnosis n=13
Final diagnosis, n			
SCA	13	7	6
MCN	6	6	0
IPMN	5	4	1
Pseudocyst	7	1	6
Specificity	100	100	100
Sensitivity	69	86	50
PPV	100	100	100
NPV	82	92	70
Accuracy	87	94	77

SCA, serous cystadenoma; MCN, mucinous cystic neoplasms; IPMN, intraductal papillary mucinous neoplasm; PPV, positive predictive value; NPV, negative predictive value.

eo set of 60 nCLE sequences reviewed by four independent examiners who were blinded to other results, the superficial vascular network was identified in 69% of patients with SCA. The sensitivity and NPV of the sign were 69% and 82%, respectively, and the corresponding specificity and PPV were both 100%. The superficial vascular network was observed independently of the morphological presentation in 100% of unilocular SCAs, in 75% of SCA with less than 10 cavities, and in 50% of SCA with more than 10 cavities. Interestingly, the subanalysis conducted on both subcategories showed a lower sensitivity when final diagnosis was established based on expert consensus, without a reduction in the specificity (100%). These results confirm the specific aspect of the superficial vascular network pattern. The interobserver agreement of the sign was substantial ($\kappa=0.77$). Considering the limited training required, the learning curve should be short.

The excellent feasibility and safety of nCLE exploration have been demonstrated in this series of 31 cases, with a pancreatitis rate of 3.2%. This is consistent with the value reported in the literature, as well as with the 3% rate reported by Konda et al. on a cohort of 74 patients [18]. Cyst puncture with a 19-G needle was possible in all locations, including the head and uncinete locations. However, the 14 lesions located in the head of the pancreas were mainly accessed via the bulb whereas the only lesion located in the uncinete process was accessed through the second duodenum. Thus, the current pilot study cannot confirm the technical feasibility of puncturing uncinete lesions from the second duodenum, and this could represent a limitation, especially in small lesions. Probe manipulation was rated as “easy” in 93% of the cases, which could be explained by the fact that the AQ-Flex probe is less rigid than the needle stylet, thus facilitating access to the lesion.

Some limitations of the study must be acknowledged, including the choice of gold standard. A surgical diagnosis was available in only seven patients, as only a suspicion of MCN was systematically sent to surgery. Positive cytopathological results of EUS-FNA (11 patients) was also considered as a stringent gold standard. To minimize the risk of false-positive cytology results [19], only strict criteria were taken into account. The unusually high level of positive results for SCA can be explained by the close contact between the probe and the wall, which results in detachment of the epithelium, as has been noted in studies using cytology bru-

shes [20]. For the remaining cases, the final diagnosis relied on a consensus diagnosis based on the evaluation of an expert adjudication committee (13 cases). Cases that did not receive a consensus diagnosis were excluded in order to minimize the risk of misdiagnosis. This can be considered as a less stringent gold standard, and it reflects the difficulties faced in daily practice when trying to obtain an accurate preoperative diagnosis. Interestingly, in the current series, the yield of the superficial vascular network sign was comparable in patients with and those without a stringent final diagnosis.

The second limitation of this pilot study is that data are reported from a limited cohort of patients. Therefore, this analysis is best viewed as exploratory, with the aim of describing and validating a new nCLE diagnostic criterion for the characterization of SCA. Based on the results of this pilot study, future prospective studies with larger populations should be conducted in order to confirm the diagnostic yield and to assess the clinical impact.

Third, examinations were limited to cysts larger than 2 cm with at least one cavity larger than 13 mm. These inclusion criteria were proposed because cysts smaller than 2 cm are very rarely malignant [21], and for technical reasons, as a cavity of at least 13 mm of diameter is necessary to collect a sufficient amount of fluid (1 mL) for further cytological analysis. Moreover, on EUS, cysts with only microcystic components are most likely to be SCAs, and puncture is generally not even considered. Lesions featuring communication with the main pancreatic duct or criteria suggestive of malignancy were excluded, as they do not represent a diagnostic dilemma using conventional diagnostic methods. Finally, the superficial vascular network sign was observed in only 69% of SCA cases. Further series are needed to evaluate whether this sign is absent in 31% of cases or whether this criterion is more frequently observed on specific areas of the lesion (e.g. wall vs. septa).

In conclusion, this study has developed and tested a new diagnostic nCLE criterion that is present in SCA—the superficial vascular network. The examination of pathological specimens confirmed the specificity of this sign. Considering the specificity and PPV of the sign and the substantial interobserver agreement, the visualization of this feature could have a direct impact on the management of patients with pancreatic cystic lesions. The presence of the superficial vascular network during nCLE exploration should allow clinicians to confidently diagnose SCA, rule out unnecessary surgical resection, and limit systematic follow-up. The next phase of investigations should confirm the utility of nCLE by prospectively evaluating the accuracy of the technique for the characterization of mucinous vs. nonmucinous lesions, as well as the impact of the technique on patient management.

Competing interests: None

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