

## Probe based confocal laser endomicroscopy of the pancreatobiliary system

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**Author contributions:** Almadi MA contributed to the concept of the manuscript, study design and acquisition of data, interpretation of data, drafted the manuscript, final revisions and made the final approval; and Neumann H contributed to concept of the manuscript, study design, interpretation of data, made revisions and made the final approval.

**Supported by** Deanship of Scientific Research at King Saud University through the Research Group Project number RGP-VPP-279.

**Conflict-of-interest statement:** Majid A Almadi: "No relevant conflicts of interest exist"; Helmut Neumann: Consultant for Pentax, Mauna Kea Technologies, SpectraScience; Funding from Pentax, SpectraScience, Olympus, Siemens, Smart Medical, Fujifilm.

**Data sharing statement:** No additional data are available.

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Received: March 28, 2015  
Peer-review started: March 29, 2015  
First decision: June 19, 2015  
Revised: July 8, 2015  
Accepted: September 13, 2015  
Article in press: September 14, 2015  
Published online: November 28, 2015

### Abstract

**AIM:** To review applications of confocal laser endomicroscopy (CLE) in pancreatobiliary lesions and studies that assessed training and interpretation of images.

**METHODS:** A computerized literature search was performed using OVID MEDLINE, EMBASE, Cochrane library, and the ISI Web of Knowledge from 1980 to October 2014. We also searched abstracts from major meetings that included the Digestive Disease Week, Canadian Digestive Disease Week and the United European Gastroenterology Week using a combination of controlled vocabulary and text words related to pCLE, confocal, endomicroscopy, probe-based confocal laser endomicroscopy, and bile duct to identify reports of trials. In addition, recursive searches and cross-referencing was performed, and manual searches of articles identified after the initial search was also completed. We included fully published articles and those in abstract form. Given the relatively recent introduction of CLE we included randomized trials and cohort studies.

**RESULTS:** In the evaluation of indeterminate pancreatobiliary strictures CLE with ERCP compared to ERCP alone can increase the detection of cancerous strictures with a sensitivity of (98% vs 45%) and

has a negative predictive value (97% *vs* 69%), but decreased the specificity (67% *vs* 100%) and the positive predictive value (71% *vs* 100%) when compared to index pathology. Modifications in the classification systems in indeterminate biliary strictures have increased the specificity of pCLE from 67% to 73%. In pancreatic cystic lesions there is a need to develop similar systems to interpret and characterize lesions based on CLE images obtained. The presence of superficial vascular network predicts serous cystadenomas accurately. Also training in acquiring and interpretation of images is feasible in those without any prior knowledge in CLE in a relatively simple manner and computer-aided diagnosis software is a promising innovation.

**CONCLUSION:** The role of pCLE in the evaluation of pancreatobiliary disorders might be better suited for those with an intermediate and low probability.

**Key words:** Probe based confocal laser endomicroscopy; Confocal; Endomicroscopy; Probe-based confocal laser endomicroscopy; Bile duct; Pancreatobiliary; Stricture; Endoscopic retrograde cholangiopancreatography; Cholangioscopy; Endoscopic ultrasound; Systematic review

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**Core tip:** Current endoscopic evaluation of biliary and pancreatic duct strictures and pancreatic lesions using standard methods are suboptimal. Confocal laser endomicroscopy (CLE) is starting to establish a role in such cases with multiple studies suggesting that image interpretation is not as difficult as initially perceived. Furthermore the diagnostic discriminatory value of images obtained by CLE could decrease the need for repeated and invasive investigations, as the case in the serous cystadenomas. Although classification systems have been developed and improved with regards to the performance of CLE in biliary strictures they are still evolving for pancreatic lesions and require further validation.

Almadi MA, Neumann H. Probe based confocal laser endomicroscopy of the pancreatobiliary system. *World J Gastroenterol* 2015; 21(44): 12696-12708 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i44/12696.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i44.12696>

## INTRODUCTION

Despite the technological developments in the field of imaging as well as available options for endoscopic evaluation whether through endoscopic retrograde cholangiopancreatography (ERCP), cholangioscopy, or endoscopic ultrasound (EUS) the diagnostic

yield of these tests is still suboptimal with regards to pancreatobiliary disorders, mainly biliary and pancreatic duct strictures as well as pancreatic cystic or solid lesions. The applications of confocal laser endomicroscopy (CLE) have expanded beyond luminal applications to direct tissue imaging including the pancreas<sup>[1]</sup> and the liver<sup>[2]</sup>. Thus, CLE has permitted real time *in-vivo* histological evaluation of areas of suspected neoplasia. With this new technology it has become possible to detect neoplasia and subsequently acquiring targeted biopsies as well as the confirmation of non-diseased tissue and the decreased need of random biopsies<sup>[3]</sup>.

In CLE a low-power laser light is focused on a single point in a microscopic field of view. The light emanating from that point is focused through a pinhole to a detector and thus the point of illumination and the pinhole are focused onto the same point and are said to be "confocal" with each other<sup>[4]</sup>, this process decreases the effect of scattered light thus permitting a higher spatial resolution. The beam focused spot traverses a line rapidly from left to right, and is swept top to bottom that would cover the area of interest and then the detected signal is digitized, resulting in the construction of a two-dimensional grey-scale image (Supplement figure 1).

As the experience with CLE is relatively new we sought to systematically review the literature for the available evidence with regards to the benefits of CLE in patients with pancreatobiliary disorders not overlooking abstracts at major congresses.

## MATERIALS AND METHODS

A computerized literature search was performed using OVID MEDLINE, EMBASE, Cochrane library, and the ISI Web of Knowledge from 1980 to October 2014. We also searched abstracts from major meetings that included the Digestive Disease Week, Canadian Digestive Disease Week and the United European Gastroenterology Week. We used a combination of controlled vocabulary and text words related to pCLE, confocal, endomicroscopy, probe-based confocal laser endomicroscopy, and bile duct to identify reports of trials (Appendix 1). In addition, recursive searches and cross-referencing were performed, and manual searches of articles identified after the initial search was also completed.

### Study selection

We included all clinical studies, both fully published and those to date having appeared only in abstract form that assessed the use of probe based CLE (pCLE) whether it was used through a needle (nCLE), for pancreatic lesions, or through a cholangioscope or catheter for the evaluation of pancreatobiliary disorders. We included all adult human studies published in any language.

**Table 1 Interpretation of findings on confocal endomicroscopy and findings on confocal laser endomicroscopy for specific pancreatic lesions**

Findings on CLE	Interpretation
Normal	
Reticular pattern seen in normal tissue and smaller than blood vessels <sup>[6]</sup>	Lymphatics
Thick white bands <sup>[52]</sup>	Angiogenesis
Reticular arrangement of dark-gray bands on a light-gray background and normal vessels (thin and regular) and no visible glands <sup>[9]</sup>	Normal common bile duct chorion
Black clumps <sup>[69]</sup>	Areas of decreased fluorescein uptake
Large white streaks/bands <sup>[69]</sup>	Dilated, tortuous blood vessels
Loss of mucosal architecture <sup>[6,69]</sup>	Fibrosis
Multiple thin white bands <sup>[15]</sup>	Vascular congestion
Thin dark bands forming a reticular pattern (diameter < 20 μm)	Submucosal collagen network
Thin white bands (diameter < 20 μm)	Small caliber blood vessels
Light grey background	Lymphatic sinuses
Abnormal	
Thick collagen bundles	Desmoplasia (growth of fibrous and connective tissue)
Thick white bands (diameter > 20 μm)	Malignant bile duct stricture
Multiple white bands	Inflammatory bile duct stricture
Dark clumps and epithelium	Malignancy
Type of pancreatic lesion	Characteristics on nCLE
Exocrine adenocarcinomas	Dark cells aggregates with pseudo-glandular aspects
	Straight hyperdense elements more or less thick corresponding to tumoral fibrosis
Tumors with acini cells and neuroendocrine tumors	Very dense network of small vessels on a dark background
Serous cystadenoma	Highly dense and dynamic network of blood capillaries, present in the superficial layer of the cyst wall, superficial vascular network, (pathognomonic)
Intraductal papillary mucinous neoplasm	Papillae characterized by two epithelial borders surrounding a bright vascular flow
Mucinous cystadenoma neoplasm	An epithelial border lined the cyst wall, with or without deep blood vessels, and without papillary organization

CLE: Confocal laser endomicroscopy; nCLE: Needle CLE.

## RESULTS

### Contrast agent used in pancreatobiliary CLE

To enhance the image quality of CLE certain contrast agents are used. Intravenous fluorescein sodium in a concentration of 10% is the most widely used contrast agent in CLE, a portion of it is bound to albumin while the remainder diffuses into the capillaries and causes enhancement of the extracellular matrix of tissue<sup>[5]</sup>. The use of fluorescein has been found safe with only mild adverse events in 1.4% of 2272 procedures performed<sup>[3]</sup>, these included nausea/vomiting, transient hypotension without shock, injection site erythema, diffuse rash and mild epigastric pain. Fluorescein is usually administered about 2 to 3 min prior to acquiring images<sup>[6]</sup>.

### Technical aspects

**Confocal miniprobes used in pancreatobiliary disorders:** The CholangioFlex miniprobe (Mauna Kea Technologies, Paris, France) is usually used for confocal imaging of the pancreatobiliary system. The probe requires a working channel of at least 1.2 mm and has a working length of 4 m. Lateral resolution of the probe is 3.5 μm with a field of view of 325 μm.

For cystic or mass lesions, the nCLE system (Mauna Kea Technologies, Paris, France) is used. The

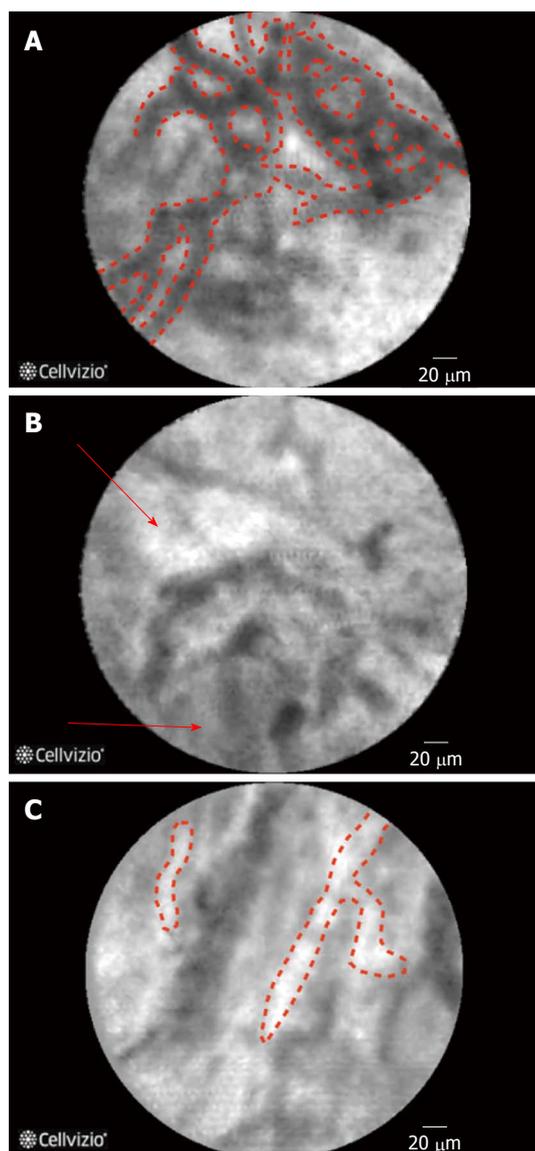
miniprobe is passed through a 19-gauge needle and has a lateral resolution of 3.5 μm and a field of view of 300 μm.

### Interpretation of the findings of CLE

The initial evaluation of pancreatic cells in *ex-vivo* animal studies suggested that microvessel structures and connective tissue structure were better visualized by CLE when compared to conventional histology<sup>[7]</sup> and CLE images have also been correlated very well with histology in animal models<sup>[8]</sup>. The findings on CLE and their interpretation are displayed in (Table 1) (Figure 1), of note during the imaging of the biliary system due to the depth of penetration of the CLE probe the normal mucosa of the CBD, that is very thin, cannot be seen on CLE images that are obtained<sup>[9]</sup>. One of the key features of neoplastic lesions is disorganized angiogenesis<sup>[10]</sup>.

### Classification systems

The Miami classification was an attempt to identify as well as standardize the interpretation of finding on pCLE of the biliary system in cases on indeterminate biliary strictures<sup>[11,12]</sup>. The highest sensitivity was found when there was the combination of thick white bands or dark clumps or epithelial structures, with a sensitivity of 94% and specificity of 46%<sup>[11]</sup>. While



**Figure 1** Confocal laser endomicroscopy images for a normal bile duct. A: Reticular network of thin dark branching bands (< 20 µm); B: Light grey background; C: Normal blood vessels (< 20 µm).

the highest specificity was found when there was a combination of white bands or thick white bands or fluorescein leakage or dark clumps, with a sensitivity of 61% and a specificity of 100%<sup>[11]</sup>.

The interobserver agreement on the findings of pCLE was found to be poor to fair when evaluating videos sent to 6 observers in 5 centers even when the Miami classification was used to standardize image interpretation<sup>[13]</sup>.

A refinement of the Miami classification<sup>[12,14]</sup>, was recently made and was coined the Paris classification<sup>[15]</sup>. The aim of the Paris classification was to decrease the number of false positive results when evaluating indeterminate strictures of the biliary system as in inflammatory strictures. Sixty cases from a prospective registry were reviewed and four criteria for benign inflammatory strictures were described:

vascular congestion, dark granular patterns with scales, increased inter-glandular space, and thickened reticular structure<sup>[15]</sup>. In a validation study for the Paris classification it was found to increase the specificity to 73% compared to 67% when using the Miami criteria<sup>[16]</sup>, a similar finding was obtained in a second study<sup>[17]</sup>.

Giovannini *et al.*<sup>[18]</sup> attempted to identify CLE findings for EUS nCLE in patients in pancreatic lesions whether they were cystic or solid as well as lymph nodes in the celiac area and mediastinum. Although the number of cases in that series was small (11 cases in total), nonetheless the authors found that in benign intraductal papillary mucinous neoplasms (IPMNs) there were finger-like projections corresponding to the villous changes seen in IPMN (Figure 2) while in pancreatic adenocarcinomas, there was vascular leakage with irregular vessels and leakage of fluorescein into the tumor as well as large dark clumps that corresponds to humps of malignant cells<sup>[18]</sup>. The *in vivo* nCLE study in the pancreas with endosonography of cystic tumors (INSPECT) group had also attempted to develop image criteria and a classification of nCLE findings in pancreatic cysts<sup>[19]</sup>. All these proposed criteria will require further validation in future studies.

#### **Learning the technique and interpretation of images**

In one recent study by Meining *et al.*<sup>[20]</sup> the investigators that performed the procedures had no prior experience with the use or interpretation of pCLE, except for one. Each endoscopist had to complete a standard training module of 20 pCLE videos and then had to complete a review of another 20 pCLE video cases and provide a correct diagnosis of benign versus malignant in each video with a minimum score of 90%<sup>[20]</sup>.

Furthermore, when comparing the first 45 cases of the same cohort to the remainder of cases there was an increase in the specificity of the diagnosis reached by the endoscopists from 55% to 71%, but this did not reach statistical significance<sup>[20]</sup>. Ease of obtaining pCLE video sequences and image interpretation slightly improved but the ease of tissue sampling was the same<sup>[20]</sup>. Although these results are encouraging it should be noted that the endoscopists were not blinded to the pre-procedure evaluation and these results might be biased but at the same time they do represent real-life experience.

A study involving gastroenterology fellows with no prior experience with pCLE underwent training with a set of ten video images that were repeated till the trainees were comfortable then they were asked to interpret 20 videos per week over three weeks, at the last session the accuracy by all beginners was 83% with an interobserver agreement of 0.63 which is substantial<sup>[21]</sup>. This study is encouraging with regards to the interpretation of images obtained but does not address the point of the technical skills required for obtaining these images. Another study

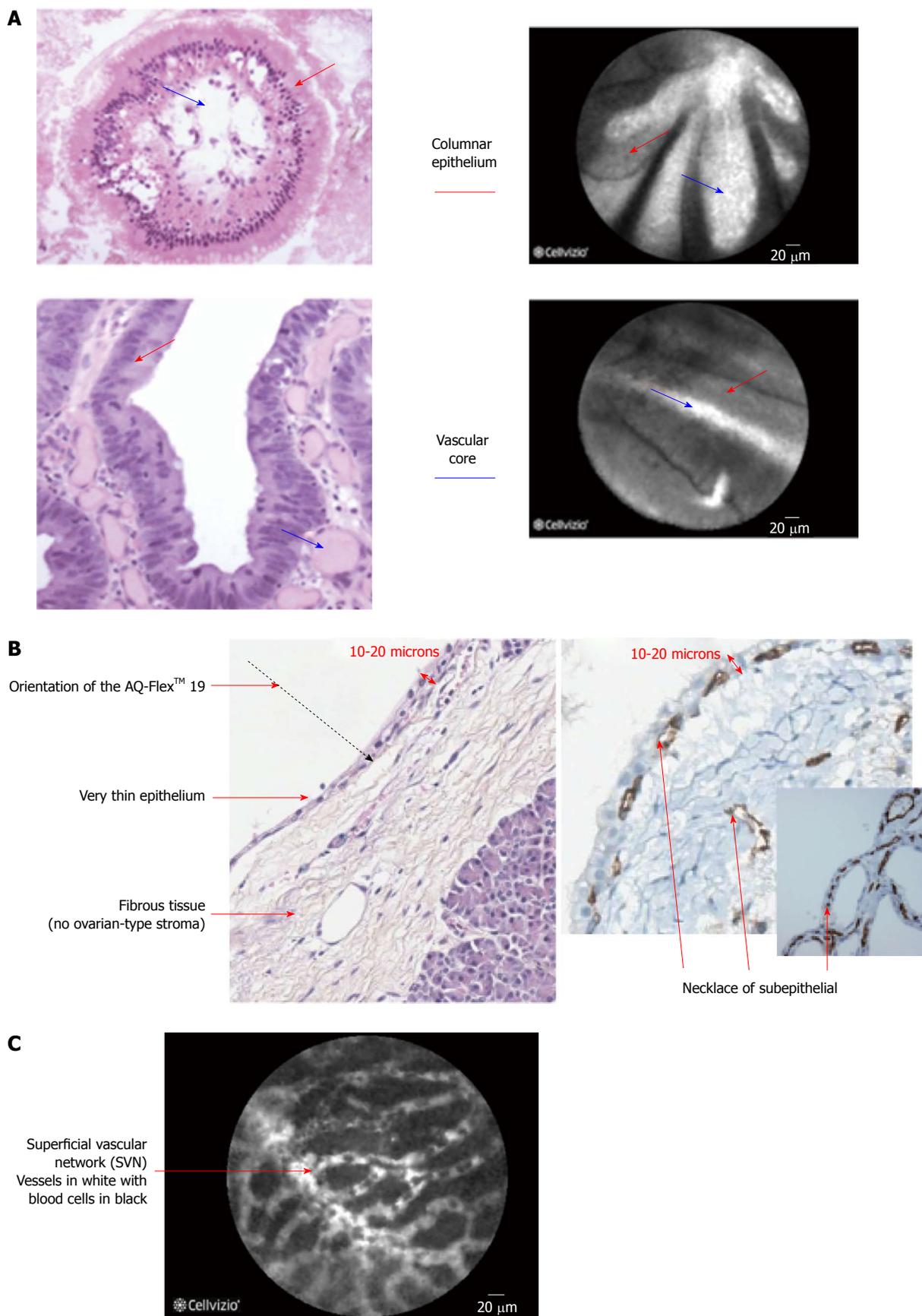


Figure 2 Wall of the intraductal papillary mucinous neoplasms is composed of villous structures consisting of columnar epithelium and a vascular core (A); Histological specimen of a serous cystadenoma that is composed of a thin epithelium lining and underlying fibrous tissue and is characterized by the presence of a necklace of subepithelial vessels all around the cyst (B); Confocal laser endomicroscopy image of a serous cystadenoma (C).

involving five practicing gastroenterologists and the majority with less than 10 cases of experience with pCLE demonstrated that when receiving formal training by an expert (experience with more than 50 procedures) with educational videos pre- and post-training improved the diagnostic accuracy as well as the interobserver agreement<sup>[22]</sup>.

A computer-aided diagnosis software (Smart Atlas; Mauna Kea Technologies, Paris, France) that assist endoscopists interpreting pCLE sequences and automatically discriminates between benign and malignant strictures<sup>[23]</sup> as well as cystic lesions of the pancreas<sup>[24]</sup>. Preliminary results of the performance characteristics of this software are encouraging and the results of prospective trials evaluating the new technique are highly anticipated.

### **Application in different organs and diseases**

**nCLE of solid and cystic pancreatic lesions:** A number of studies reported the use of nCLE *in-vivo* for pancreatic lesions<sup>[25-27]</sup>. A feasibility study on the use of nCLE through a 19-gauge needle inserted into pancreatic lesions, mainly cysts, was technically successful in the majority of the cases (17/18 cases) and the image quality was good to very good in 10/18 cases. Two patients in the study cohort developed pancreatitis<sup>[1]</sup>. To overcome this an investigational prototype pCLE (AQFlex) has been developed that is compatible with a 19-gauge FNA needle. The probe was used through a transgastric as well as a transduodenal approach for a total of 66 patients with cystic lesions in the pancreas<sup>[28]</sup>. In this series the 2 patients had pancreatitis while one developed transient abdominal pain, and three developed intracystic bleeding without need for any intervention<sup>[28]</sup>. Also in the DETECT study the use of nCLE alone had a sensitivity of 75% in differentiating mucinous from non-mucinous cysts while when combined with cystoscopy it had a sensitivity of 100%<sup>[29]</sup>. Although the procedure is safe and feasible, standard criteria for interpretation of obtained images are still to be established<sup>[27]</sup>, some characteristics of pancreatic lesions are displayed in Table 1. Preliminary data from the Clinical evaluation Of nCLE in The lymph nodes Along with masses and Cystic Tumors of the pancreas (CONTACT) demonstrated that the normal pancreatic tissue had an image resembling "coffee beans", histologically corresponding to acini. Exocrine adenocarcinomas had two signs on nCLE; (1) dark cells aggregates with pseudo-glandular aspects; and (2) straight hyperdense elements more or less thick corresponding to tumoral fibrosis. Both these signs were absent in tumors with acinar cells and neuroendocrine tumors, instead these tumors demonstrated a very dense network of small vessels on a dark background<sup>[30]</sup>. The same study described findings in cystic lesions of the pancreas<sup>[31,32]</sup>. One particular finding is that serous cystadenomas have a superficial vascular network, which can be

highlighted by nCLE (Figure 2). The specificity and positive predictive value (PPV) of this sign was found in a preliminary series to be 100%. This is of importance as its presence could avoid unnecessary surgery<sup>[33,34]</sup>.

### **Pancreatic duct strictures**

The first case report of the use of pCLE in the pancreatic duct was by Meining *et al.*<sup>[35]</sup> in 2009. Evaluation of pancreatic duct strictures involves insertion of the pCLE through a cholangioscope<sup>[35]</sup>. A case series of 5 patients who had pancreatic duct strictures underwent pCLE during ERCP and the findings were compared to cytology and when available histology. pCLE was able to identify main duct intraductal papillary mucinous neoplasm with severe dysplasia and adenocarcinoma as well as benign strictures accurately<sup>[36]</sup>. A second series similarly identified IPMN with dysplasia but in this series two pancreatic duct strictures had positive Miami classification criteria although on histology they were proven to be inflammatory<sup>[37]</sup>. Another case series of 18 patients with indeterminate pancreatic duct strictures demonstrate almost perfect agreement between cyto/histopathology and pCLE (kappa coefficient = 0.8,  $P \leq 0.001$ )<sup>[38]</sup>.

### **Molecular imaging of the pancreas**

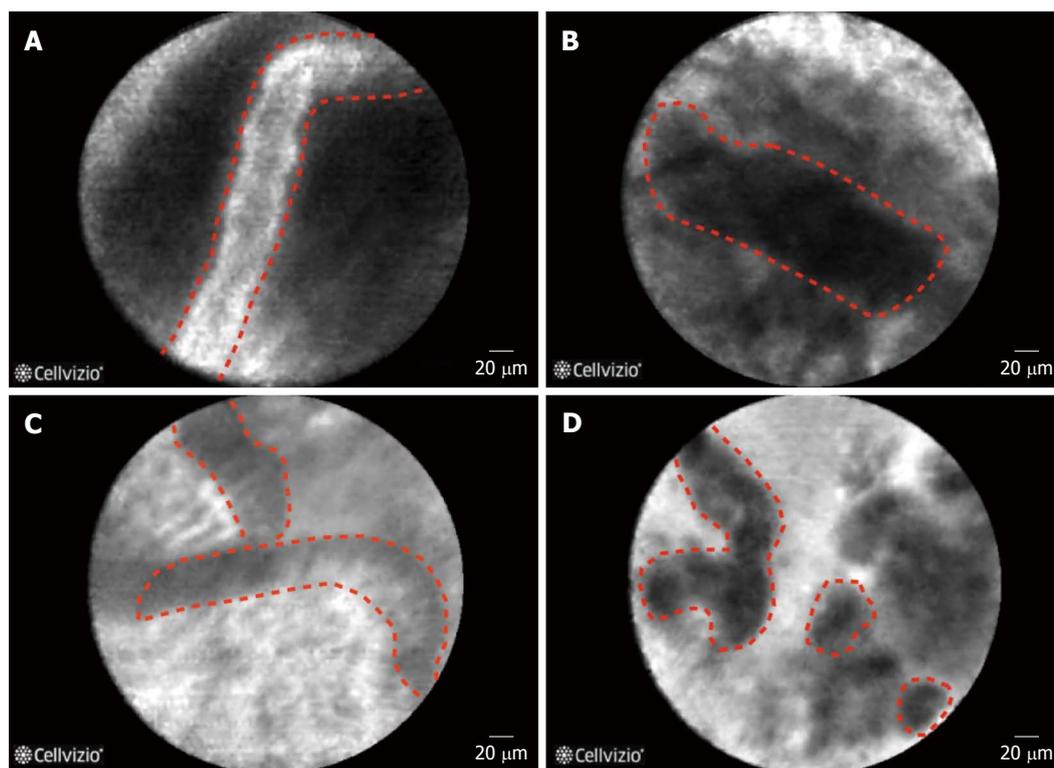
In a pilot study by Nakai *et al.*<sup>[39]</sup> *in vivo* detection of epidermal growth factor receptor (EGF-R) and survivin were possible using a EUS-guided fine needle imaging technique that incorporated nCLE after injection of FITC-labeled specific antibodies against EGF-R and survivin. The EGF-R antibodies were localized to ductal-lining cells and many acinar cells while survivin was confined to acinar cells<sup>[39]</sup>.

### **Ampullary lesions**

Bakhr *et al.*<sup>[40]</sup> assessed the interobserver agreement for five variables for 12 pCLE videos these variables were the presence of an epithelial outer border with irregular thickness, dark epithelium without discernable individual cells, heterogeneously distributed elongated crypts, reduced number of goblet cells, neovascularization, and the final diagnosis. The study included 6 gastroenterologists from five centers and the interobserver agreement was poor to slight for all variables except for the presence of an epithelial outer border with irregular thickness that was fair<sup>[40]</sup>. The results did not differ much when the gastroenterologists were stratified by their level of experience<sup>[40]</sup>.

### **Biliary strictures**

The evaluation of biliary strictures, whether in the context of primary sclerosing cholangitis (PSC) or not, can be a challenge for clinicians, and the current approaches suffer from a low sensitivity. The application of pCLE for the differentiation between



**Figure 3** Features of malignant bile duct strictures on confocal laser endomicroscopy. A: Thick white bands (> 20  $\mu\text{m}$ ); B: Thick dark bands (> 40  $\mu\text{m}$ ); C: Epithelium; D: Dark clumps.

neoplastic and non-neoplastic strictures have yielded very promising results<sup>[41,42]</sup> (Figure 3). The advantage of pCLE is its higher sensitivity in the detection of neoplastic lesions and an earlier detection of disease at a potentially resectable stage<sup>[15]</sup>. Furthermore, the more confident the diagnosis the lesser the need for repeated investigations and thus reducing the costs as well as morbidity associated with repeated manipulation of the biliary system<sup>[15]</sup>. The performance characteristics of CLE in pancreatobiliary strictures are displayed in Table 2 as well as in specific organs in supplement Table 1.

Different probes have been used for pCLE of the biliary system, GastroFlex (UHD; Mauna Kea Technologies, Paris, France) miniprobe<sup>[43]</sup> and CholangioFlex probes. The drawback of the GastroFlex probe is its larger diameter and thus it might be difficult to negotiate through strictures although a case series demonstrated successful insertion of this probe in 10/11 patients with various indications for pCLE with one patient developing pancreatitis after the procedure. Although the GastroFlex probe has a higher lateral resolution when compared to the CholangioFlex probe (1  $\mu\text{m}$  vs 3.5  $\mu\text{m}$ )<sup>[44]</sup> there is no clear advantage of the use of one over the other<sup>[45]</sup>.

The pCLE probe has been delivered successfully through various cholangioscopes as well as catheters<sup>[20,46]</sup>. When using a cholangioscope pCLE had a sensitivity of 96% (95%CI: 84% to 100%) and a specificity of 76% (95%CI: 53% to 91%), while when using a

catheter the sensitivity was 100% (95%CI: 83% to 100%) and the specificity was 62% (95%CI: 45% to 78%)<sup>[46]</sup> but there was no statistical difference in the accuracy between these delivery techniques<sup>[46]</sup> but the operators confidence about the diagnosis was much higher when using cholangioscopy when compared to a catheter based approach for pCLE of biliary strictures (43.2% vs 9.8%, respectively)<sup>[46]</sup>. In a randomized trial for comparison between catheter-guided (Fluoroscopy only) pCLE and cholangioscopy-guided pCLE the accuracy of cholangioscopy-guided pCLE was 82% compared to 78% for catheter-guided pCLE. Of note, the sample size of the study was small<sup>[47]</sup>.

The addition of pCLE with ERCP in the evaluation of indeterminate pancreatobiliary strictures can increase the detection of cancerous strictures<sup>[9,48]</sup> with a sensitivity of (98% vs 45%) and a negative predictive value (NPV) (97% vs 69%), although it decreased the specificity (67% vs 100%) and the PPV (71% vs 100%) when compared to index pathology<sup>[48]</sup>. Similar findings were found in other studies<sup>[6,37,42,49-54]</sup>.

Although conventionally the use of pCLE for the evaluation of biliary strictures is through a side viewing duodenoscope, a case series showed pCLE through direct peroral cholangioscopy in 22 out of 24 patients with biliary strictures<sup>[54]</sup>. An interesting approach for this case series is that they classified patients based on the pre pCLE evaluation for the probability of a malignant etiology for biliary stricture into a range

**Table 2 Performance of characteristics of findings on confocal laser endomicroscopy for pancreatobiliary strictures**

Criterion	Author and the description of the examined area	Sensitivity	Specificity	PPV	NPV
Malignant biliary strictures	Meining <i>et al</i> <sup>[41,53]</sup> Loss of reticular pattern of epithelial bands of less than 20 $\mu\text{m}$ Irregular epithelial lining, villi, or gland-like structures Tortuous, dilated, and saccular vessels with inconsistent branching Presence of "black areas" of more than 60 to 80 $\mu\text{m}$ (focally decreased uptake of fluorescein)	83%	88%	NR	NR
Suggestive of malignancy	Meining <i>et al</i> <sup>[20]</sup> Thick, dark bands (> 40 $\mu\text{m}$ ) Thick, white bands (> 20 $\mu\text{m}$ ) Dark clumps Epithelium visualized (villi, glands) Fluorescein leakage	98%	67%	71%	97%
Suggestive of benign strictures	Thin, dark (branching) bands Thin, white bands Meining <i>et al</i> <sup>[14]</sup>				
Normal bile ducts	Reticular network of thin dark branching bands (< 20 $\mu\text{m}$ ) Light gray background Vessels < 20 $\mu\text{m}$	97%	33%	80%	80%
Malignant biliary strictures	Thick white bands (> 20 $\mu\text{m}$ ) Thick dark bands (> 40 $\mu\text{m}$ ), Dark clumps Epithelial structures Normal vessels (thin and regular) No visible glands Giovannini <i>et al</i> <sup>[18]</sup>				
Benign IPMN	Finger-like projections corresponding to villous changes of intestinal IPMN type	NR	NR	NR	NR
Pancreatic adenocarcinoma	Vascular leakage with irregular vessels with leakage of fluorescein into the tumor Large dark clumps which correspond to humps of malignant cells				
Benign Lymph nodes	Diffuse small cells into a homogeneous stroma with normal vascularization				
Malignant lymph nodes	Glandular structures with dark cells, large dark clumps and neo-vascularization with huge leakage of fluorescein Filoche <i>et al</i> <sup>[56]</sup>				
Benign inflammatory strictures of the common bile duct	Vascular congestion but still regular Roughness aspect Increased inter-glandular space Thickened reticular structure Caillol <i>et al</i> <sup>[15]</sup>	NR	NR	NR	NR
Inflammatory stenosis	Multiple thin white bands (Vascular congestion) Roughness aspect Increased inter-glandular space Thickened reticular structure	96.3%	63.6%	68.4%	95.5%

IPMNs: Intraductal papillary mucinous neoplasms; NR: Not reported; PPV: Positive predictive value; NPV: Negative predictive value.

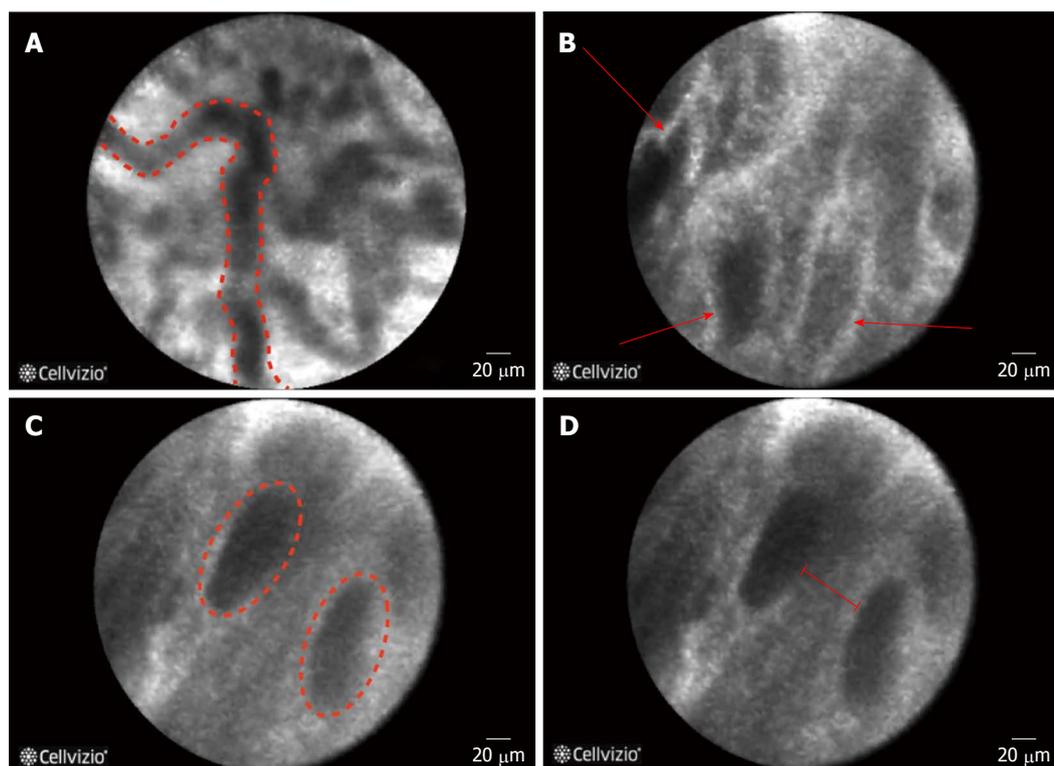
from very unlikely to certainly based on the clinical evaluation as well as imaging<sup>[54]</sup>, pCLE was found to be complementary to peroral cholangioscopy and ERCP in cases where a malignant etiology was suspected and did not effect the management decision but it might be sufficient for confirmation of a malignant etiology when tissue acquisition is not required<sup>[54]</sup>.

The use of pCLE in hilar strictures has also been proven to be of use in a series of 19 patients with the correct identification of all cases with neoplasia but one false positive case was reported<sup>[55]</sup>.

Filoche *et al*<sup>[56]</sup> identified four characteristics on biliary pCLE that were associated with benign inflammatory strictures; vascular congestion, rough-

ness aspect, increased inter-glandular space and thickened reticular structure (Figure 4). In this study the authors sought to explain the false positive cases in 60 cases that were enrolled in a registry and found that pCLE diagnosis was either influenced by the ERCP impression or the presence of less than 3 malignant Miami classification criteria<sup>[56]</sup>.

Giovannini *et al*<sup>[57]</sup> evaluated the effect of biliary stenting in 54 patients with indeterminate biliary stenosis and found that biliary stenting decreased the accuracy of pCLE when using the Miami criteria, similar findings were replicated where a decrease in the sensitivity from 88% to 75% and specificity from 83% to 71% was found in those who had cholangitis



**Figure 4** Features of inflammatory bile duct strictures on confocal laser endomicroscopy. A: Thickened reticular structures; B: Multiple white bands; C: Dark granular pattern in scales; D: Increased spaces between scales.

or a stent inserted prior to pCLE imaging<sup>[58]</sup>. Although this requires validation in other series but it might be prudent to perform pCLE prior to biliary stenting in cases with biliary strictures of unknown etiology. Also, of note, in the study by Caillol *et al.*<sup>[15]</sup> they noted that stricture dilation could induce fluorescein leakage thus giving the impression of a malignant stricture while it was subsequently found to be benign.

A recent consensus report by 16 physicians validated seven statements with regards to the use of pCLE in biliary strictures; (1) CLE can be used to evaluate biliary strictures, and the probe can be delivered via a catheter or a cholangioscope; (2) CLE is more accurate than ERCP with brush cytology and/or forceps biopsy in determining malignant or benign strictures, using established criteria; (3) The accuracy of CLE in indeterminate biliary strictures may be decreased by prior presence of plastic stent; (4) The NPV of CLE is very high; (5) The use of CLE can assist clinical decision-making such as excluding malignancy; (6) CLE should be cited as a valuable tool for an increased diagnostic yield in official guidelines; and (7) The «black bands» that can be seen in pCLE images have been shown to be collagen fibrils that predictably increase in pathologic tissue<sup>[59]</sup>.

A preliminary analysis of the multicenter multinational FOCUS trial demonstrated that the clinical impression of physicians and pCLE during workup of biliary strictures outperform tissue sampling where the combination of brush cytology and biopsy would have

missed 5 malignant strictures out of 36 patients<sup>[60]</sup>. While the addition of histology/cytology to pCLE resulted in a marginal increase in sensitivity (from 89% to 93%) but did not change the specificity (79%) compared to the addition of pCLE alone<sup>[61]</sup>.

### **Primary sclerosing cholangitis**

The work up of patients with PSC who develop strictures can be a challenge. The management will depend on the etiology of these strictures whether they are neoplastic or just inflammatory. In a series of 15 patients with 19 strictures<sup>[62]</sup>, both extra and intrahepatic, were evaluated by ERCP and pCLE. Due to the inflammatory nature of PSC the authors used a scoring system based on the Miami classification when there were 2 of 5 malignant criteria the lesion was classified as “suspicious” and 1 criterion as “reactive” and the finding of a reticular pattern was deemed as “benign”<sup>[62]</sup> the finding on pCLE were compared to ERCP, cholangioscopy, histology/cytology, liver explants, fluorescence in-situ hybridization (FISH), or 12 mo of follow-up. Visualization was successful in 95% of the procedures, pCLE was found to have a sensitivity of 100% (95%CI: 40% to 100%), specificity of 50% (95%CI: 9% to 90%), PPV of 67% (95%CI: 24.5% to 94%) and a NPV of 100% (95%CI: 20% to 100%)<sup>[63]</sup>. The authors suggested the high negative predictive value of pCLE could guide in the interval of surveillance in patients with dominant biliary strictures<sup>[62]</sup>.

## DISCUSSION

The role of pCLE in the evaluation of pancreatobiliary disorders might not be of high value in cases where the pretest probability of a malignant etiology is high but might be better suited for those with an intermediate and low probability. Furthermore it might guide tissue sampling to increase the yield when evaluating pancreatobiliary disorders. It does not seem, at least for now, that pCLE will eliminate the need for tissue acquisition and a histological diagnosis but it does supplement the evaluation of these patients. The field is evolving and as more centers acquire this technology and studies are conducted<sup>[50,63-68]</sup> the definite role of pCLE will be better defined.

The diagnostic criteria might need to be refined to be applicable to clinical practices outside centers of expert endoscopists and might need to be tailored to specific underlying disease like PSC and patients with chronic pancreatitis where discriminating normal from abnormal histology might be more challenging.

## ACKNOWLEDGMENTS

The authors would like to extend their sincere appreciation to the Deanship of Scientific Research at King Saud University for its funding of this research through the Research Group Project number RGP-VPP-279. Also we would like to thank Mauna Kea Technologies for providing images from their e-learning website: [www.cellvizio.net](http://www.cellvizio.net).

## COMMENTS

### Background

Confocal laser endomicroscopy (CLE) is used for real time *in-vivo* histological evaluation of areas of suspected neoplasia allowing targeted biopsies. The applications of CLE in the pancreatobiliary system are relatively new and the added value of this image enhancing technology is evolving.

### Research frontiers

When evaluating indeterminate strictures of the biliary system, a refinement of the Miami classification (the Paris classification) has decreased the number of false positive results. While in the case of pancreatic lesions a classification system is still lacking but some of the imaging features appear to be very specific and might alter the management of how the authors survey patients with pancreatic cystic lesions. Furthermore, computer-aided diagnosis softwares that assist in interpreting CLE sequences are a promising development.

### Innovations and breakthroughs

In this systematic review the authors attempted to review the most recent literature which describes potential applications of CLE in the area of diagnostic evaluation of lesions that are particularly difficult to reach using our current imaging and endoscopic armamentarium. There has been a great deal of advancements in the field but there still remains more to be achieved specifically in the fields of training as well as dissemination of this technology.

### Applications

Probe based CLE is useful in cases of indeterminate biliary strictures where the pretest probability of malignant etiology are intermediate or low while it might not be the case when the pretest probability is high. As for needle based CLE in solid as well as cystic pancreatic lesions the role is still evolving but is very promising.

## Peer-review

Immediate endoscopic optical histology without samples in accessible tissue surfaces is a new tool providing important advances in lesion recognition. CLE is used in assessing histological structure without samples in endoscopy using specially designed scopes but can also be used as thin probes which are able to reach and assess tissue structure in ducts, cysts and accessible tumors. The present paper is an extensive and complete, up-to-date review of the literature available since 2001; nevertheless most the papers were published from 2007 to 2015. This review describes some important aspects of CLE image evaluation, including specificity, sensitivity and positive predictive values, and also the learning curves in image interpretation which all are important for introducing a new device in clinical practice. The paper is long but is a well-designed systematic review and includes one part devoted to technical aspects, another on image interpretation and a third on its application in different localizations.

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**P- Reviewer:** Aktas S, Bordas JM **S- Editor:** Ma YJ **L- Editor:** A  
**E- Editor:** Zhang DN





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ISSN 1007-9327

