

# World Journal of *Gastroenterology*

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**EDITORIAL**

- 3195** Liver transplantation for intermediate hepatocellular carcinoma: An adaptive approach

*Biolato M, Marrone G, Miele L, Gasbarrini A, Grieco A*

- 3205** Immune response to vaccines in children with celiac disease

*Anania C, Olivero F, Spagnolo A, Chiesa C, Pacifico L*

**REVIEW**

- 3214** Inflammatory bowel disease in liver transplanted patients

*Filipek Kanizaj T, Mijic M*

- 3228** Platelets in liver disease, cancer and regeneration

*Kurokawa T, Ohkohchi N*

**ORIGINAL ARTICLE****Basic Study**

- 3240** Thiopurine use associated with reduced B and natural killer cells in inflammatory bowel disease

*Lord JD, Shows DM*

- 3252** Hepatitis B virus X protein induces hepatic stem cell-like features in hepatocellular carcinoma by activating KDM5B

*Wang X, Oishi N, Shimakami T, Yamashita T, Honda M, Murakami S, Kaneko S*

- 3262** Artificial liver support in pigs with acetaminophen-induced acute liver failure

*He GL, Feng L, Cai L, Zhou CJ, Cheng Y, Jiang ZS, Pan MX, Gao Y*

- 3269** Effects of sleeve gastrectomy plus trunk vagotomy compared with sleeve gastrectomy on glucose metabolism in diabetic rats

*Liu T, Zhong MW, Liu Y, Huang X, Cheng YG, Wang KX, Liu SZ, Hu SY*

- 3279** Wall shear stress in portal vein of cirrhotic patients with portal hypertension

*Wei W, Pu YS, Wang XK, Jiang A, Zhou R, Li Y, Zhang QJ, Wei YJ, Chen B, Li ZF*

**Case Control Study**

- 3287** Risk of progression of Barrett's esophagus in patients with cirrhosis

*Apfel T, Lopez R, Sanaka MR, Thota PN*

**Retrospective Study**

- 3295 Clinical significance of hypoechoic submandibular gland lesions in type 1 autoimmune pancreatitis  
*Takano S, Fukasawa M, Kadokura M, Shindo H, Takahashi E, Hirose S, Fukasawa Y, Kawakami S, Sato T, Enomoto N*
- 3301 Benefit of neoadjuvant concurrent chemoradiotherapy for locally advanced perihilar cholangiocarcinoma  
*Jung JH, Lee HJ, Lee HS, Jo JH, Cho IR, Chung MJ, Park JY, Park SW, Song SY, Bang S*
- 3309 Ling classification describes endoscopic progressive process of achalasia and successful peroral endoscopy myotomy prevents endoscopic progression of achalasia  
*Zhang WG, Linghu EQ, Chai NL, Li HK*

**Observational Study**

- 3315 Disruptive behavior in the workplace: Challenges for gastroenterology fellows  
*Srisarajivakul N, Lucero C, Wang XJ, Poles M, Gillespie C, Zabbar S, Weinshel E, Malter L*
- 3322 Correlation of endoscopic disease severity with pediatric ulcerative colitis activity index score in children and young adults with ulcerative colitis  
*Kerur B, Litman HJ, Stern JB, Weber S, Lightdale JR, Rufo PA, Bousvaros A*
- 3330 Stress and sleep quality in doctors working on-call shifts are associated with functional gastrointestinal disorders  
*Lim SK, Yoo SJ, Koo DL, Park CA, Ryu HJ, Jung YJ, Jeong JB, Kim BG, Lee KL, Koh SJ*

**Prospective Study**

- 3338 *In vivo* and *ex vivo* confocal endomicroscopy of pancreatic cystic lesions: A prospective study  
*Krishna SG, Modi RM, Kamboj AK, Swanson BJ, Hart PA, Dillhoff ME, Manilchuk A, Schmidt CR, Conwell DL*
- 3349 Chronological age when healthcare transition skills are mastered in adolescents/young adults with inflammatory bowel disease  
*Stollon N, Zhong Y, Ferris M, Bhansali S, Pitts B, Rak E, Kelly M, Kim S, van Tilburg MAL*

**Randomized Controlled Trial**

- 3356 Low-FODMAP diet reduces irritable bowel symptoms in patients with inflammatory bowel disease  
*Pedersen N, Ankersen DV, Felding M, Wachmann H, Végh Z, Molzen L, Burisch J, Andersen JR, Munkholm P*

**EVIDENCE-BASED MEDICINE**

- 3367 Antimicrobial susceptibility testing before first-line treatment for *Helicobacter pylori* infection in patients with dual or triple antibiotic resistance  
*Cosme A, Montes M, Ibarra B, Tamayo E, Alonso H, Mendarte U, Lizasoan J, Herreros-Villanueva M, Bujanda L*

**CASE REPORT**

- 3374** Severe esophageal injury after radiofrequency ablation - a deadly complication

*Katz-Agranov N, Nevah Rubin MI*

## ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Ballarin Roberto, PhD, Assistant Professor, Doctor, Surgeon, Hepatobiliopancreatic Oncologic Surgery and Liver Transplant Center, University of Modena, Modena 41100, Italy

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Fax: +1-925-2238243  
E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
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## Prospective Study

# ***In vivo* and *ex vivo* confocal endomicroscopy of pancreatic cystic lesions: A prospective study**

Somashekar G Krishna, Rohan M Modi, Amrit K Kamboj, Benjamin J Swanson, Phil A Hart, Mary E Dillhoff, Andrei Manilchuk, Carl R Schmidt, Darwin L Conwell

Somashekar G Krishna, Phil A Hart, Darwin L Conwell, Division of Gastroenterology, Hepatology and Nutrition, The Ohio State University Wexner Medical Center, Columbus, OH 43210, United States

Rohan M Modi, Department of Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, OH 43210, United States

Amrit K Kamboj, College of Medicine, The Ohio State University Wexner Medical Center, Columbus, OH 43210, United States

Benjamin J Swanson, Department of Pathology, The Ohio State University Wexner Medical Center, Columbus, OH 43210, United States

Mary E Dillhoff, Carl R Schmidt, Division of Surgical Oncology, The Ohio State University Wexner Medical Center, Columbus, OH 43210, United States

Andrei Manilchuk, Department of General Surgery, The Ohio State University Wexner Medical Center, Columbus, OH 43210, United States

**Author contributions:** Krishna SG designed the protocol, performed all EUS-nCLE and *ex vivo* CLE procedures, *in vivo* and *ex vivo* CLE interpretation, wrote the manuscript, and edited images; Modi RM assisted with background literature, wrote the manuscript, *in vivo* and *ex vivo* CLE interpretation, and edited images; Kamboj AK assisted with background literature search, and edited images; Swanson BJ assisted with *ex vivo* CLE image acquisition, provided pathological interpretation, and edited images; Hart PA performed critical revision of manuscript; Dillhoff ME, Manilchuk A and Schmidt CR performed pancreatic surgeries and provided resected specimens for *ex vivo* CLE; Conwell DL performed critical revision of manuscript.

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**Correspondence to:** Somashekar G Krishna, MD, MPH, Assistant Professor, Division of Gastroenterology, Hepatology and Nutrition, The Ohio State University Wexner Medical Center, 395 W. 12<sup>th</sup> Avenue, Suite 262, Columbus, OH 43210, United States. [somashekar.krishna@osumc.edu](mailto:somashekar.krishna@osumc.edu)  
Telephone: +1-614-2936255  
Fax: +1-614-2938518

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## Abstract

### AIM

To investigate the reproducibility of the *in vivo* endoscopic ultrasound (EUS) - guided needle based confocal endomicroscopy (nCLE) image patterns in an *ex vivo* setting and compare these to surgical histopathology for characterizing pancreatic cystic lesions (PCLs).

### METHODS

In a prospective study evaluating EUS-nCLE for evaluation of PCLs, 10 subjects underwent an *in vivo* nCLE (AQ-Flex nCLE miniprobe; Cellvizio, MaunaKea, Paris, France) during EUS and *ex vivo* probe based CLE (pCLE) of the PCL (Gastroflex ultrahigh definition probe, Cellvizio) after surgical resection. Biopsies were obtained from *ex vivo* CLE-imaged areas for comparative histopathology. All subjects received intravenous fluorescein prior to EUS and pancreatic surgery for *in vivo* and *ex vivo* CLE imaging respectively.

### RESULTS

A total of 10 subjects (mean age  $53 \pm 12$  years; 5 female) with a mean PCL size of  $34.8 \pm 14.3$  mm were enrolled. Surgical histopathology confirmed 2 intraductal papillary mucinous neoplasms (IPMNs), 3 mucinous cystic neoplasms (MCNs), 2 cystic neuroendocrine tumors (cystic-NETs), 1 serous cystadenoma (SCA), and 2 squamous lined PCLs. Characteristic *in vivo* nCLE image patterns included papillary projections for IPMNs, horizon-type epithelial bands for MCNs, nests and trabeculae of cells for cystic-NETs, and a "fern pattern" of vascularity for SCA. Identical image patterns were observed during *ex vivo* pCLE imaging of the surgically resected PCLs. Both *in vivo* and *ex vivo* CLE imaging findings correlated with surgical histopathology.

### CONCLUSION

*In vivo* nCLE patterns are reproducible in *ex vivo* pCLE for all major neoplastic PCLs. These findings add further support the application of EUS-nCLE as an imaging biomarker in the diagnosis of PCLs.

**Key words:** Confocal laser endomicroscopy; Serous cystadenoma; Pancreatic neuroendocrine tumor; Intraductal papillary mucinous neoplasm; Pancreatic cystic neoplasm

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**Core tip:** We performed a prospective study to investigate the reproducibility of *in vivo* endoscopic ultrasound (EUS) - guided needle based confocal

endomicroscopy (nCLE) image patterns in an *ex vivo* setting and compare these to surgical histopathology for pancreatic cystic lesions (PCLs). A total of 10 subjects underwent *in vivo* EUS-nCLE and subsequently *ex vivo* CLE of the PCL following surgical resection. Biopsies were obtained from *ex vivo* CLE-imaged areas for comparative histopathology. We found that characteristic *in vivo* nCLE patterns were observed during *ex vivo* pCLE of resected PCLs. Both *in vivo* and *ex vivo* CLE imaging findings correlated with surgical histopathology. These findings support the application of EUS-nCLE in the diagnosis of PCLs.

Krishna SG, Modi RM, Kamboj AK, Swanson BJ, Hart PA, Dillhoff ME, Manilchuk A, Schmidt CR, Conwell DL. *In vivo* and *ex vivo* confocal endomicroscopy of pancreatic cystic lesions: A prospective study. *World J Gastroenterol* 2017; 23(18): 3338-3348 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i18/3338.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i18.3338>

## INTRODUCTION

Pancreatic cancer is projected to move from the third to second leading cause of cancer mortality before 2020<sup>[1]</sup>. In contrast to the steady survival increase for most other cancers, advances in management for pancreatic cancer have been less than modest with the 5-year relative survival rate is currently 8%<sup>[1]</sup>. The primary reason for the low survival is difficulty in early identification of pancreatic cancer. While pancreatic cystic lesions (PCLs) provide an opportunity for early cancer detection as many have malignant potential. There has been a surge in incidental detection of PCLs due to increasing utilization of cross-sectional imaging, but diagnostic differentiation of these lesions remains challenging<sup>[2,3]</sup>.

Despite judicious utilization of endoscopic ultrasound (EUS), fine needle aspiration (FNA), cyst fluid analysis, and cytology, it is challenging to accurately classify PCLs into non-mucinous [serous cystadenomas (SCA), pseudocysts], pre-malignant mucinous [intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasms (MCN)], and neoplastic [cystic-neuroendocrine tumors (NET), pseudopapillary tumor] PCLs. This is highlighted by a recent study at a large tertiary center involving 851 resected cystic tumors where the associated etiology for one in five cases was benign in nature<sup>[4]</sup>.

Confocal laser endomicroscopy (CLE) offers real-time microscopic imaging of tissue where the system provides tissue-sequences with high resolution (1-3.5  $\mu$ m) facilitating *in vivo* histopathology. Needle-based CLE (nCLE) is a new technology to evaluate PCLs where the device is pre-loaded in a 19-gauge FNA needle for evaluation of the intracystic epithelium. Recent



major trials have established reference standards and have all assessed the safety profile and feasibility of diagnostic capabilities of EUS-guided nCLE in patients with PCLs<sup>[5-8]</sup>. More over *in vivo* nCLE image patterns for PCLs have been internally and externally validated among independent observers<sup>[7-10]</sup>.

While *ex vivo* confirmation of *in vivo* CLE findings has been demonstrated in diagnosis of Barrett's esophagus and gastric adenocarcinoma, there are no human studies corroborating CLE findings of PCLs using *ex-vivo* examination and surgical histopathology<sup>[11-13]</sup>. We have previously published the technique and individual case reports of IPMN, MCN, SCA, and cystic-NET demonstrating potential feasibility for correlation between *in vivo* and *ex vivo* nCLE imaging with surgical histopathology<sup>[14-20]</sup>.

The aim of this study was to validate the *in vivo* EUS-nCLE image patterns of specific types of PCLs by reproducing identical images in *ex vivo* pCLE examination and correlation with surgical histopathology.

## MATERIALS AND METHODS

### Patient population

The Institutional Review Board approved this prospective study, which was conducted at The Ohio State University Wexner Medical Center. From June 2015 to December 2016, all consenting subjects who underwent EUS-nCLE with subsequent surgical resection were enrolled in the INDEX study (Comparison of confocal laser endomicroscopic *in vivo* Diagnosis and *ex vivo* examination against surgical histopathology of cystic pancreatic lesions; ClinicalTrials.gov NCT02516488). An informed consent was obtained for both aspects (*in vivo* and *ex vivo*) aspects of the study. Our criteria for using EUS-nCLE included: (1)  $\geq 18$  years of age; (2) a PCL lesion size of  $\geq 20$  mm (determined by cross-sectional imaging studies); and (3) evaluation for surgical removal based on recommended international consensus guidelines<sup>[21]</sup>. Exclusion criteria were: (1) women with known pregnancy at the time of procedure; (2) coagulopathy (INR  $> 1.5$  and/or platelets  $< 50000/\text{mL}$ ); and (3) known allergy to fluorescein. *Ex vivo* pCLE of PCLs was performed on representative cases of common types of PCLs.

### Data collection

Demographics, history of present illness, laboratory data, and image findings were collected using a standardized data collection form. Imaging data were compiled with those from EUS to describe: location, number and size of the PCLs, lesion characteristics, evidence of dilation of the main pancreatic duct, and presence of communication with the pancreatic duct. One gastrointestinal pathologist reviewed all surgical histopathology specimens and the biopsies obtained during *ex vivo* CLE examination.

### *In vivo* EUS-nCLE image acquisition

All EUS examinations were performed at The Ohio State University Medical Center using a linear echo-endoscope (Olympus America, Center Valley, PA, United States). All EUS examinations were performed under the direction of an anesthesiologist utilizing intravenous (IV) propofol. Fluorescein (5 mL; 10% fluorescein sodium) was intravenously injected 2 to 3 min prior to CLE imaging. The AQ-Flex nCLE miniprobe (Cellvizio, Mauna Kea Technologies, Paris, France) was then advanced through the locking device into the 19-gauge (g) needle (Flex needle, Boston Scientific, Natick, MA, United States). The preloaded 19-g needle was advanced under EUS-guidance into the PCL. The tip of the nCLE probe was negotiated until it opposed the intracystic epithelium. Intracystic endomicroscopic images (video) were captured with permissible angulation of the 19 g needle using the elevator of the echoendoscope. After image acquisition, the nCLE probe was withdrawn and the PCL was aspirated. Antibiotic (quinolone) prophylaxis was administered *via* IV route on the day of procedure followed by 3 d of oral therapy.

### *Ex vivo* pCLE image acquisition

We have recently published a video manual of the *ex vivo* pCLE imaging technique<sup>[19]</sup>. Immediately prior to resection of the part of the pancreas with the cystic lesion and under the direction of the surgeon and anesthesiologist, fluorescein (10%, 5 mL) was intravenously injected before ligation of blood vessels supplying the pancreas. Following resection, the specimen was transported to the pathology-processing laboratory for immediate processing as the pre-ligation IV fluorescein is retained for a maximum of one hour after injection. The pathologist then incised the cyst along the long axis using their standard processing technique. The epithelium of the PCL was then imaged using a Gastroflex ultrahigh definition probe (UHD) probe (Cellvizio, Mauna Kea Technologies, Paris, France) at 3-5 random areas based on the size of the cyst. Site-specific biopsies were then obtained at the pCLE-imaged areas using standard endoscopy biopsy forceps (Radial Jaw 4, Boston Scientific, Natick, MA, United States). The *ex vivo* biopsies were obtained from the PCL sites providing the clearest pCLE image.

### Comparison of the CLE probes

The specific characteristics of the CLE probes used for the study are described in Table 1. The AQ-Flex nCLE probe was used during *in vivo* EUS-guided approach while the Gastroflex-UHD pCLE probe with high-definition image acquisition was used during *ex vivo* post-surgical cyst interrogation. The larger GastroFlex-UHD miniprobe has increased number of fiber optics and provides higher magnification and improved resolution; however, due to its size, the probe cannot be accommodated through the



**Table 1 Comparison of confocal laser endomicroscopy probes and standard microscope**

	Device	Channel size (mm)	Field of view ( $\mu\text{m}$ )	Resolution ( $\mu\text{m}$ )	Confocal depth ( $\mu\text{m}$ )
Gastroflex™ UHD	Probe based	$\geq 2.8$	240	1.00	55-65
AQ-Flex™ 19	Needle based	$\geq 0.91$	325	3.50	40-70
Cholangioflex™	Probe based	$\geq 1.0$	325	3.50	40-70
Standard microscopy $\times 20$	Microscope	NA	NA	0.70	NA
Standard microscopy $\times 40$	Microscope	NA	NA	0.45	NA

UHD: Ultrahigh definition probe.

**Table 2 Classification, description, and associated cyst type confocal laser endomicroscopy image patterns**

Variable	Explanation of patterns	Cyst type where pattern is observed
Papillae	A papilla is a finger-like projection of variable length consisting of an overlying epithelium and underlying vascular core	IPMN
Epithelial bands	Epithelial bands are either single or multiple layers of epithelium without a papillary configuration. These bands demonstrated layering or a horizon-type configuration	MCN
Trabecular pattern	Nests of cells separated by blood vessels of fibrous bands	Cystic-NET
Fern pattern	A concentrated network of parallel vessels emanating from a central vessel similar to a fern-leaf	SCA

PCL: Pancreatic cystic lesion; IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; Cystic-NET: Cystic neuroendocrine tumor; SCA: Serous cystadenoma.

working channel of 19-g EUS needle. This concept of comparing *in vivo* to *ex vivo* imaging is derived from a prior study showing enhanced image acquisition of Gastroflex when compared to CholangioFlex miniprobe (Cellvizio, Mauna Kea Technologies, Paris, France) for assessing indeterminate biliary strictures where individual structures were more easily identified<sup>[22]</sup>. The Gastroflex-UHD probe has a superior lateral resolution of 1  $\mu\text{m}$ , compared to 3.5  $\mu\text{m}$  for the Cholangioflex probe. The lateral resolutions of the AQ-Flex and Cholangioflex probes are identical<sup>[23]</sup>.

### Histopathology

The resected specimen underwent standard histopathologic processing. The biopsies obtained from pCLE imaged specific sites also underwent standard processing under the supervision of a gastroenterologist pathologist.

### Statistical analysis

A dedicated software (Cellvizio Viewer, version 1.6.1; Mauna Kea Technologies, Paris, France) was used to review all *in vivo* and *ex vivo* CLE videos and images. A diligent frame-by-frame review of the videos was performed multiple times to document the most illustrative image patterns. The various image patterns observed during CLE examination of the PCLs are described in Table 2. There was no blinded assessment of the pre-and postoperative CLE images.

### Comparison of standard microscopy and CLE imaging

CLE imaging offers an “en-face” view and has resolutions ranging from 1  $\mu\text{m}$  (Gastroflex probe) to 3.5  $\mu\text{m}$  (AQ-Flex probe). In comparison, standard biopsy

or surgical resection and histopathology reveals a “transverse view”, but offers a much higher resolution than CLE imaging, which increases with magnification (Table 1).

## RESULTS

### Study cohort

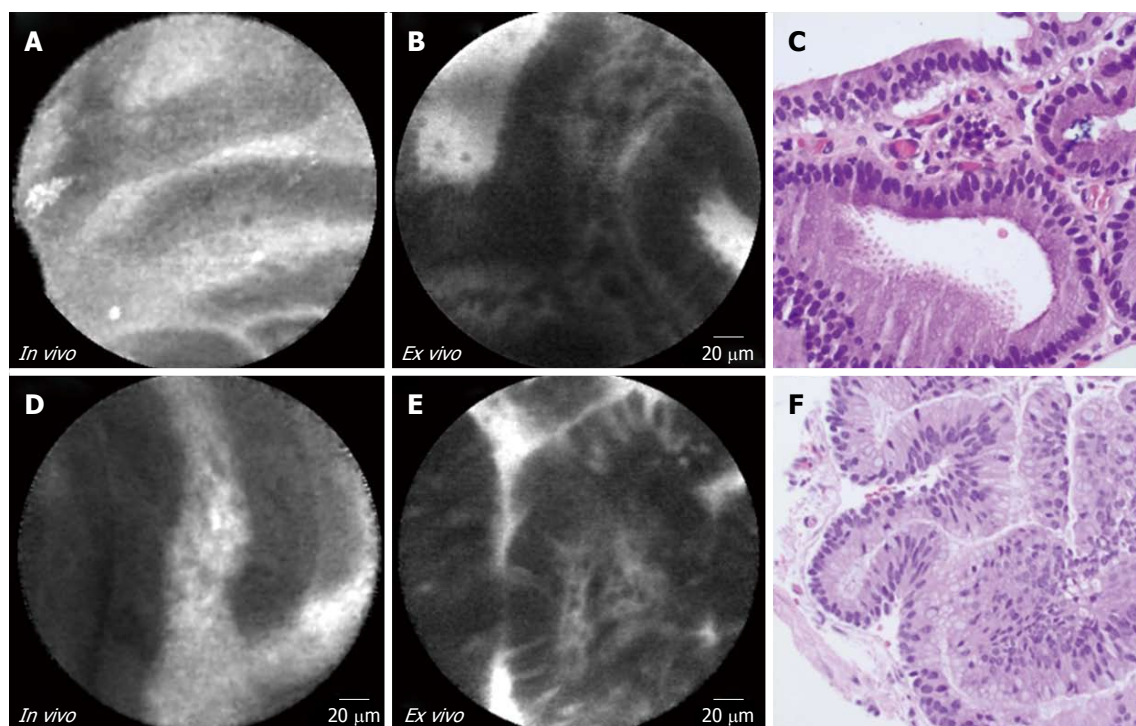
A total of 10 subjects (mean age  $53 \pm 12$  years [SD]; 5 female) underwent EUS-nCLE with surgical resection and subsequent *ex vivo* imaging (Table 3). The mean size of PCLs was  $34.8 \pm 14.3$  mm with the majority of lesions located in the tail ( $n = 5$ ) when compared to head/uncinate ( $n = 2$ ) or neck/body region ( $n = 3$ ). No adverse events occurred during the surgical resection that impacted the quality of the specimen.

### Intraductal papillary mucinous neoplasm

Complete “finger-like” papillary projections were seen on *in vivo* EUS-nCLE and *ex vivo* pCLE imaging for both patients with IPMNs (Figure 1). The vascular cores (lamina propria) of the papillae were better defined in the *ex vivo* imaging. There was no difference in *in vivo* or *ex vivo* imaging between the different subtypes (gastric vs intestinal) of IPMN lesions. The CLE images and histopathology were similar.

### Mucinous cystic neoplasm

EUS-nCLE demonstrated horizon-type epithelial bands of variable thickness without papillary conformation (Figure 2 and Table 3). *Ex vivo* imaging showed thicker epithelial bands with improved definition. MCN with moderate grade dysplasia (Figure 2, panels G to I) revealed a thicker epithelial band. During *in vivo*



**Figure 1** *In vivo* endoscopic ultrasound guided needle based confocal laser endomicroscopy, *ex vivo* confocal laser endomicroscopy, and histopathology of intraductal papillary mucinous neoplasms. Panels A, B and C are from subject 1 (gastric subtype with high grade dysplasia). Panels D, E, and F are from subject 2 (intestinal subtype with high grade dysplasia). Complete “fingerlike” papillae are observed in both *in vivo* and *ex vivo* CLE. The vascular core in *ex vivo* CLE imaging is better defined. Histopathology (panels C, F): 40 × magnification; HE stain.

nCLE, MCNs revealed areas of denuded epithelium as evidenced by lack of visualizing any epithelial bands. Few foci of dark background with bright particles (auto-fluorescent inflammatory cells) were also observed representing areas of chronic inflammation. While the characteristic “ovarian stroma” was detected in histopathology, no corresponding CLE features were observed.

#### **Cystic neuroendocrine tumor**

*In vivo* and *ex vivo* imaging (Figure 3 and Table 3) revealed dark clusters or trabeculae of cells separated by bright vascular spaces. Corroborating this finding, corresponding biopsies from the cystic-NETs revealed characteristic well-differentiated NETs, which were confirmed by immunostaining.

#### **Serous cystadenoma**

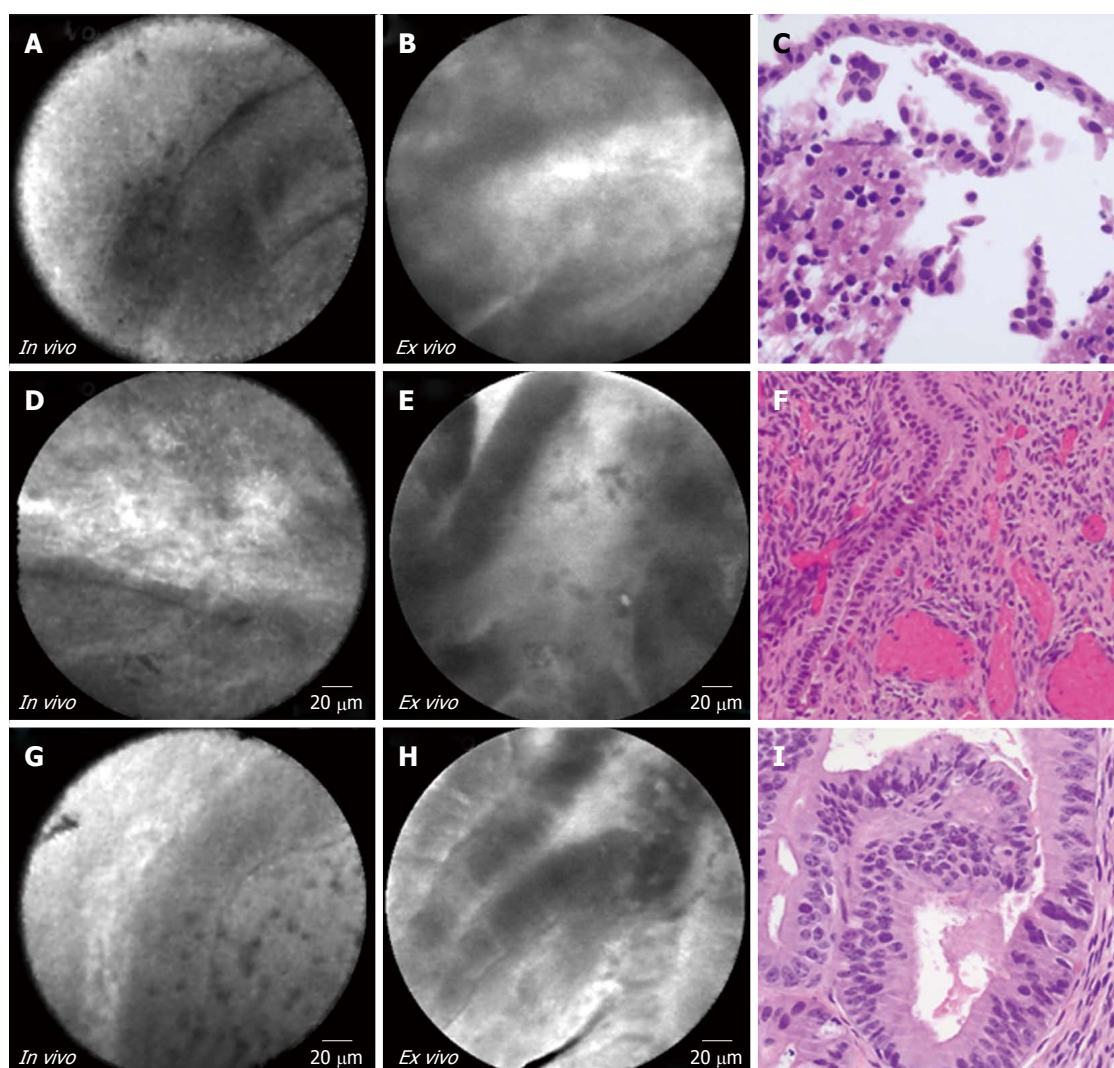
Both EUS-nCLE and *ex vivo* imaging (Figure 4 and Table 3) depict a “fern pattern” of vascularity that is best described as a concentrated parallel or interconnected network of vessels emanating from a larger vessel (similar to a fern leaf). However, the vascular pattern observed in CLE imaging is not represented in histopathology. Characteristic histology of SCAs include multiple cystic spaces lined by cuboidal/flat epithelial cells. The pathology image in Figure 4 (panel C) revealed flattened cystic spaces lined by cuboidal epithelial cells.

#### **Squamous lined cysts (epidermoid and lymphoepithelial cysts)**

Two distinct benign cysts, epidermoid cyst of intra pancreatic accessory spleen (IPAS) and lymphoepithelial cyst, were included in this study. The epidermoid cyst of IPAS demonstrated cords of cells suggestive of ectopic splenic tissue. Pathology confirmed these findings revealing a thin squamous epithelium and underlying splenic red pulp (Figure 5 and Table 3). On the other hand, the lymphoepithelial cyst had clusters of bright particles that correlated to keratinous debris seen on pathologic slides (Figure 6 and Table 3). Microscopy demonstrated keratin flakes and the cyst wall was lined by squamous epithelium bordered by abundant lymphoid tissue.

## **DISCUSSION**

This study confirms the reproducibility of *in vivo* EUS-nCLE image patterns in *ex vivo* pCLE examination of surgically resected PCLs. The histopathology from CLE imaged site-specific biopsies were comparable to CLE patterns. Some variations in histological views can be explained by higher resolution and the plane of image reproduction. While EUS-nCLE produces *en-face* microscopic imaging of the epithelium of PCLs, tissue histology reveals transverse views. To our knowledge, this is the largest study describing *in vivo* and *ex vivo* CLE findings in definitively diagnosed PCLs. We have



**Figure 2** *In vivo* endoscopic ultrasound guided needle based confocal laser endomicroscopy, *ex vivo* confocal laser endomicroscopy, and histopathology of mucinous cystic neoplasms. Panels A, B, and C are from subject 3 (low grade). Panels D, E, and F are from subject 4 (low grade). Panels G, H, and I are from subject 5 (low to moderate grade). Epithelial bands with incomplete papillary formation are observed in CLE. The *in vivo* CLE demonstrates horizon like bands where *ex vivo* CLE demonstrates better defined epithelial bands. Corresponding histopathology (panel C,  $\times 40$  and panel F,  $\times 20$ ) show low grade dysplasia and panel I ( $\times 40$ ) reveals moderate grade dysplasia. CLE: Confocal laser endomicroscopy.

correlated for the first time, CLE image patterns with surgical histopathology among common PCLs. These promising findings and growing body of literature lend support to further investigation of EUS-nCLE in the management of PCLs.

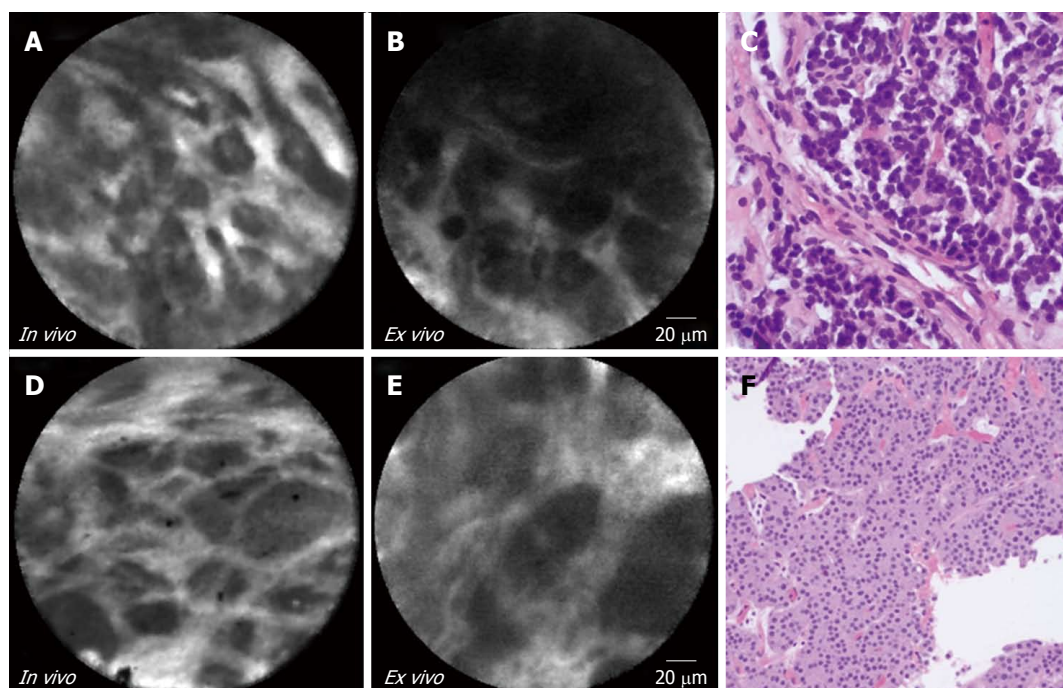
The management of PCLs continues to pose challenges. Suboptimal classification and risk stratification of PCLs can lead to inappropriate surgeries or false reassurances. The current guidelines for management of PCLs are not robust since the diagnostic accuracy of current standard of care (cyst fluid CEA, cytology) is inadequate. There is an increasing need for tools to accurately diagnose PCLs. Over the last 5 years, there is an accumulative body of evidence of applying EUS-nCLE or novel cyst fluid molecular makers in diagnosing PCLs<sup>[6-10,24]</sup>.

Imaging data from three major clinical trials have recognized specific nCLE image patterns for diagnosing

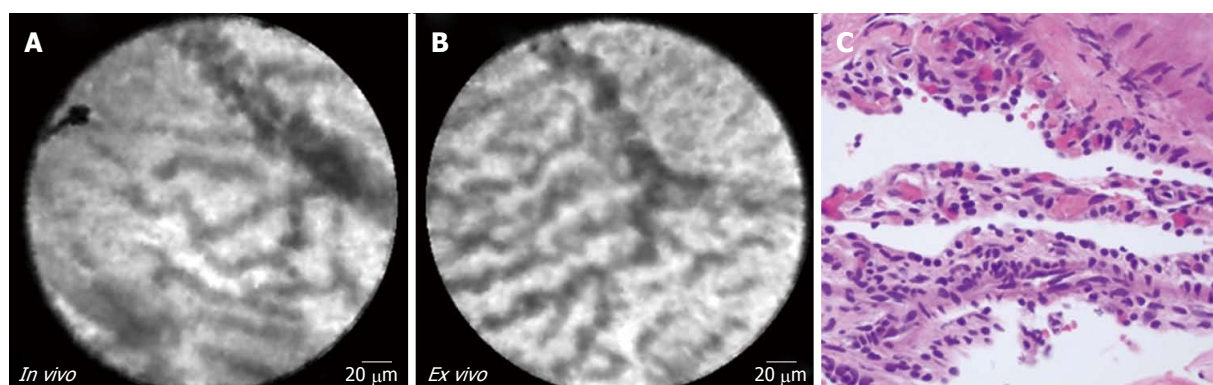
PCLs<sup>[5-8]</sup>. We have recently validated (internally and externally, inter-and intraobserver) nCLE image patterns of common PCLs<sup>[9,10]</sup>. We have also published on the technique of *in vivo* and *ex vivo* CLE imaging of PCLs, and individual nCLE *video reports* of IPMNs, MCNs, SCAs, Cystic-NETs, and squamous lined cysts<sup>[15-18,20]</sup>. In this study, we performed *ex vivo* CLE examination of resected PCLs from subjects enrolled in a prospective study.

For EUS-nCLE aided diagnosis, IPMNs were diagnosed by the presence of finger-like papillae. Although the nCLE image patterns for MCNs were slightly insufficient, they contained a characteristic either single or multiple (layered) band-like epithelium<sup>[8,9]</sup>. Thus, the presence of complete papillae or single/multiple band-like epithelium was diagnostic of a mucinous PCL. The diagnosis of IPMNs tends to be easier than that of MCNs since the latter





**Figure 3** *In vivo* endoscopic ultrasound guided needle based confocal laser endomicroscopy, *ex vivo* confocal laser endomicroscopy, and histopathology of cystic neuroendocrine tumor. Panels A, B, and C are from subject 6. Panels D, E, and F are from subject 7. Circumscribed clusters of cells in a trabecular growth pattern separated by vascular or fibrous cords are observed on confocal laser endomicroscopy examination. Histopathology (panels C, × 40; panel F, × 20) revealed characteristic uniform tumor cells arranged in cords or trabecular fashion.



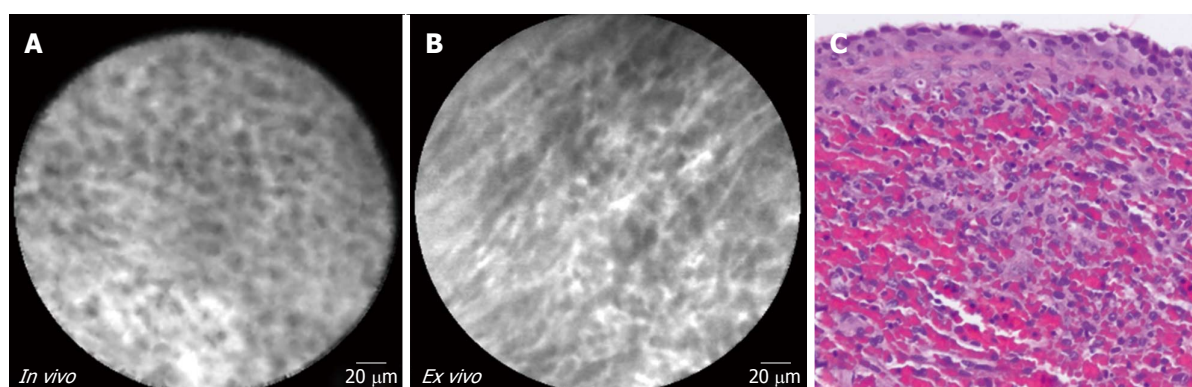
**Figure 4** *In vivo* endoscopic ultrasound guided needle based confocal laser endomicroscopy, *ex vivo* confocal laser endomicroscopy, and histopathology of serous cystadenoma. Confocal laser endomicroscopy images, panels A (*in vivo*) and B (*ex vivo*) depict “fern pattern” of vascularity (subject 8). Histopathology (panel C; HE, × 40) reveals cuboidal to flat epithelial cells with clear cytoplasm lining some cystic spaces.

demonstrate relatively flat or horizon-type epithelium which can be patchy with atrophic areas and foci of inflammation<sup>[25,26]</sup>. We have observed that some MCNs can demonstrate bright inflammatory cells on a dark background suggestive of chronic inflammation similar to pseudocysts<sup>[7,8]</sup>.

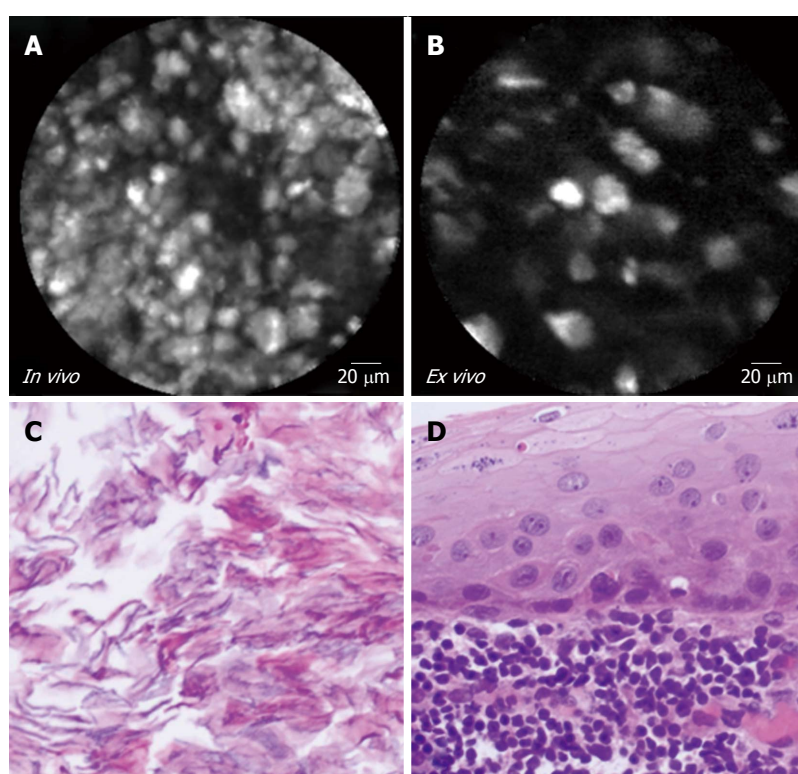
A characteristic “superficial vascular network” or “fern pattern” has been observed in SCAs where the specificity approached 100%<sup>[5-10]</sup>. Comparable image reproduction in *ex vivo* CLE imaging and corresponding histopathological image supports evidence from current studies. The nCLE imaging of cystic-NETs and comparable *ex vivo* image patterns and correlative histopathology confirm published reports<sup>[8,15]</sup>. Some

rare types of PCLs can be difficult to distinguish by cross sectional imaging and are often evaluated for malignant potential<sup>[27]</sup>. Thus, awareness of *in vivo* EUS-nCLE image patterns of rare squamous lined PCLs (lymphoepithelial cyst and epidermoid cyst of IPAS) is useful as it may help avoid unnecessary surgical resection.

The small sample size ( $n = 10$ ) is not suitable for statistical analysis and the images observed in this study may not fully characterize all patients with the examined cyst types. As with other novel diagnostic modalities, we anticipate further refinement of technical aspects and additional characterization of nCLE imaging patterns in the future. Although our



**Figure 5** *In vivo* endoscopic ultrasound guided needle based confocal laser endomicroscopy, *ex vivo* confocal laser endomicroscopy, and histopathology of epidermoid cyst of intra pancreatic accessory spleen. Confocal laser endomicroscopy images, panels A (*in vivo*) and B (*ex vivo*) reveal underlying splenic tissue (panels C, red pulp). Histopathology shows thin epithelial layer (squamous) with underlying ectopic splenic tissue (HE, × 40).



**Figure 6** *In vivo* endoscopic ultrasound guided needle based confocal laser endomicroscopy, *ex vivo* confocal laser endomicroscopy, and histopathology of lymphoepithelial cyst. Confocal laser endomicroscopy images, A (*in vivo*) and B (*ex vivo*) reveal clusters of bright particles representing keratin flakes. Macroscopically the lesion was filled with yellowish pasty material which by microscopy (panel C) demonstrated keratin flakes. The cyst was lined by squamous epithelium surrounded by abundant lymphoid tissue (panel D; HE, × 40).

*ex vivo* nCLE image findings were not externally validated, we have previously performed both internal and external validation of the *in vivo* nCLE image patterns<sup>[9,10]</sup>. Lastly, since surgical resection of pseudocysts rarely performed, we did not perform *ex vivo* imaging of these lesions within the study period.

In conclusion, the evaluation of PCLs continues to pose a challenge. In uncertain clinical situations, a composite approach including clinical features,

imaging characteristics, cyst fluid CEA, cytological examination, and nCLE is necessary. The correlation of histopathology and the reproducibility of *in vivo* and *ex vivo* CLE imaging patterns supports the application of EUS-nCLE as an imaging biomarker in the diagnosis of PCLs. Multicenter prospective studies are needed to confirm whether EUS-nCLE alone or in combination with cyst fluid molecular markers can facilitate desirable outcomes in managing pancreatic cystic lesions.

Table 3 Pancreatic Cystic Lesion Characteristics: Demographics, clinical features, fluid characteristics, and final diagnosis

Subject	Corresponding Figure	Gender	Age	Abdominal symptoms	Size (mm)	Location	MPD communication	MPD dilation	Cyst CEA (ng/dL)	Final diagnosis	Pathological features
1	1A-C	Female	67	Symptomatic	21	Head/uncinate	Yes	Yes	188	IPMN	Gastric subtype
2	1D-F	Male	71	Incidental	40	Head/uncinate	Yes	Yes	Very viscous	IPMN	High grade dysplasia Intestinal subtype
4	2A-C	Female	47	Incidental	28	Neck/body	No	No	6512	Mucinous cystadenoma	High grade dysplasia Low grade
3	2D-F	Female	51	Symptomatic	41	Neck/body	No	Yes	76	Mucinous cystadenoma	Low grade
5	2G-I	Female	45	Symptomatic	24	Neck/body	No	Yes	2400	Mucinous cystadenoma	Low to moderate grade
6	3A-C	Male	44	Symptomatic	57	Tail	No	No	1.5	Cystic-NET	
7	3D-F	Male	30	Incidental	21	Tail	No	No	4.7	Cystic-NET	
8	4A-C	Female	59	Incidental	60	Tail	No	No	0.5	Serous cystadenoma	
9	5A-C	Male	52	Incidental	31	Tail	No	No	Pasty aspirate	Lymphoepithelial cyst	
10	6A-D	Male	62	Incidental	25	Tail	No	No	2664	Epidermoid cyst	

MPD: Main pancreatic duct; CEA: Carcinoembryonic antigen; CEA: Carcinoembryonic antigen; Cystic-NET: Cystic neuroendocrine tumor; IPMN: Intraductal papillary mucinous neoplasm

COMMENTS

Background

Endoscopic ultrasound (EUS) and fine needle aspiration (FNA) are standard of care for evaluation of pancreatic cystic lesions (PCLs). Needle-based CLE (nCLE) is a new technology that offers real-time microscopic imaging of tissue facilitating *in vivo* histopathology. The authors have previously published the technique of *in vivo* and *ex vivo* CLE imaging of PCLs. The aim of this study was to validate the *in vivo* EUS-nCLE image patterns of specific types of PCLs by reproducing identical images in *ex vivo* pCLE examination and correlation with surgical histopathology.

Research frontiers

The current guidelines for management of PCLs are not robust since the diagnostic accuracy of current standard of care is inadequate. There is an increasing need for novel technology to accurately diagnose PCLs. Over the last 5 years, there is an accumulative body of evidence of applying EUS-nCLE in diagnosing PCLs.

Applications

This study confirms the reproducibility of *in vivo* EUS-nCLE image patterns in *ex vivo* pCLE examination of surgically resected PCLs. The histopathology from CLE imaged site-specific biopsies were comparable to CLE patterns. These promising findings lend support to the application of EUS-nCLE in the management of PCLs.

Terminology

Confocal laser endomicroscopy: A novel endoscopic technology that offers real-time microscopic imaging of tissue where the system provides tissue-sequences with high resolution (1-3.5  $\mu$ m) facilitating *in vivo* histopathology.

Peer-review

This new endoscopic technique which is based on confocal microscopy seems very interesting. It allows a pathological diagnosis by acquisition of images that are pathognomonic of the various pancreatic cystic lesions examined by the authors.



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