Communication from the ASGE Technology Committee

TECHNOLOGY STATUS EVALUATION REPORT

Confocal laser endomicroscopy

The ASGE Technology Committee provides reviews of existing, new, or emerging endoscopic technologies that have an impact on the practice of GI endoscopy. Evidence-based methodology is used, performing a MEDLINE literature search to identify pertinent clinical studies on the topic and a MAUDE (U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported adverse events of a given technology. Both are supplemented by accessing the "related articles" feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases, data from randomized, controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors. Technology Status Evaluation Reports are drafted by 1 or 2 members of the ASGE Technology Committee, reviewed and edited by the Committee as a whole, and approved by the Governing Board of the ASGE. When financial guidance is indicated, the most recent coding data and list prices at the time of publication are provided. For this review, the MEDLINE database was searched through February 2014 for relevant articles by using the key words "confocal," "confocal and endoscopy," "confocal microscopy," and "confocal laser endomicroscopy." Technology Status Evaluation Reports are scientific reviews provided solely for educational and informational purposes. Technology Status Evaluation Reports are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment or payment for such treatment.

BACKGROUND

Confocal laser endomicroscopy (CLE) is an endoscopic modality developed to obtain very high magnification and resolution images of the mucosal layer of the GI tract. CLE is based on tissue illumination with a low-power laser with subsequent detection of the fluorescence of light reflected from the tissue through a pinhole (Fig. 1).[1] The term *confocal* refers to the alignment of both illumination and collection systems in the same focal plane.[2,3] The laser light is focused at a selected depth in the tissue of interest and reflected light is then refocused onto the detection system by the same lens. Only returning light refocused through the pinhole is detected. The light reflected and scattered at other geometric angles from the illuminated object or refocused out of plane with the pinhole is excluded from detection. This dramatically increases the spatial resolution of CLE allowing cellular imaging and evaluation of tissue architecture at the focal plane during endoscopy.[4,5]

Confocal imaging can be based on tissue reflectance or fluorescence.[6,7] Confocal devices based on tissue reflectance do not require any contrast agents, but current prototypes using 2-photon strategies have relatively low resolution, which significantly compromise in vivo imaging and clinical utility.[6-9] CLE by using topical and/or intravenous fluorescence contrast agents generates images with resolution similar to traditional histological examination.[5,10] CLE systems have included through-the-scope probes or dedicated endoscopes with integrated CLE systems.

Probe-based CLE

The probe-based CLE (pCLE) system comprises a fiberoptic bundle with an integrated distal lens that is connected to a laser scanning unit (Fig. 2). The probe-based system to date has a fixed focal length and so it can only scan in a single plane unlike current microscope systems that can create cross-sectional images at different depths. In pCLE systems, the individual optical fibers function as the pinhole. Cellvizio confocal miniprobes (Mauna Kea Technologies, Paris, France) created for GI tract applications include CholangioFlex, GastroFlex UHD, and ColoFlex UHD (Table 1).

CholangioFlex probes, designed for use during ERCP, require an endoscope accessory channel of at least 1.0 mm, whereas the other probes designed for use in EGD and colonoscopy require a channel of at least 2.8 mm. All probes generate dynamic (9-12 frames/s) images. The depth of imaging from the surface of the confocal lens is 40 to 70 μm for CholangioFlex probes and 55 to 65 μm for both GastroFlex UHD and ColoFlex UHD probes. The maximal field of view for CholangioFlex probes is 325 μm and 240 μm for Gastroflex UHD and ColoFlex UHD probes. The resolution of the CholangioFlex probe is 3.5 μm, whereas for GastroFlex UHD and ColoFlex UHD probes, it is 1 μm (Mauna Kea Technologies). The

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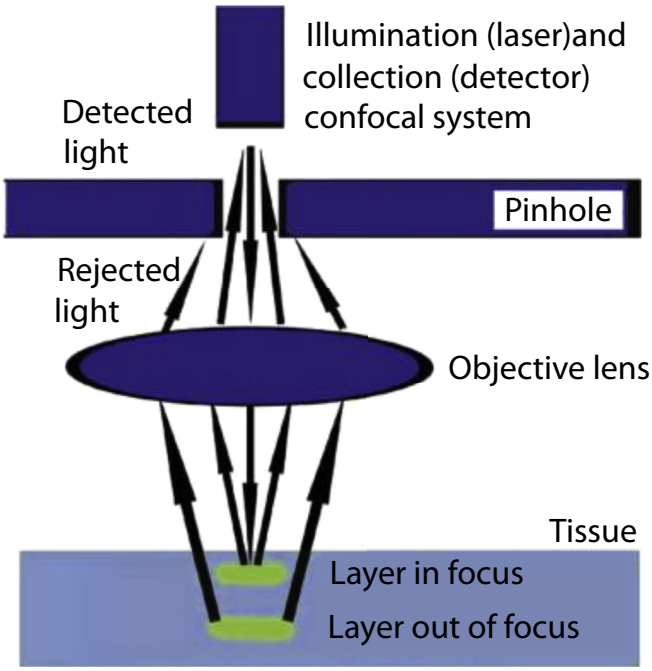

Figure 1. Schematic of confocal laser endomicroscopy principles.

probes can be reused after disinfection for as many as 10 to 20 examinations.

AQ-Flex 19, a probe designed to be advanced through an EUS FNA needle (needle-based CLE [nCLE]), is now available. It requires a 19-gauge needle for passage. The depth of imaging is 40 to 70 μm, the maximal field of view is 325 μm, and resolution is 3.5 μm. The probe can be reused for as many as 10 examinations.

Endoscope-based CLE

Endoscope-based CLE (eCLE) uses a confocal microscope (Optiscan, Victoria, Australia) integrated into the distal tip of a conventional endoscope (Pentax, Tokyo, Japan). The diameter of the eCLE endoscope is 12.8 mm, and the tip length is increased to accommodate the laser microscope so that there is a 5-cm rigid portion (Fig. 3). It can be used for upper and lower GI tract examinations, but is too large for pancreaticobiliary imaging. With this setup, white-light endoscopy and eCLE can be performed simultaneously with images displayed on dual monitors. Images are collected at a scan rate of 1.6 frames/s (1024 × 512 pixels) or 0.8 frames/s (1024 × 1024 pixels) with an adjustable depth of scanning ranging from 0 to 250 μm, a field of view of 475 × 475 μm. The lateral resolution is 0.7 μm, and the axial resolution is 7 μm.[11-16] At the time this report was prepared, this system was no longer commercially available.

The fluorescent contrast agents most commonly used for CLE can be administered intravenously (fluorescein sodium, AK Fluor; Akorn Pharmaceutical, Lake Forest, Ill) or topically (Acriflavin; Sigma Pharmaceuticals, Clayton, Victoria, Australia), tetracycline, or cresyl violet (AnaSpec, Inc, San Jose, Calif) through a spraying catheter.[10,17] Intravenously delivered fluorescein distributes throughout the extracellular matrix of the surface epithelium and lamina propria but does not stain cell nuclei.[2] Topically administered acriflavin stains cell nuclei of the surface epithelium but does not penetrate deeper layers of the GI mucosa.

Fluorescein is usually administered immediately before imaging. Optimal images are obtained within 30 seconds to 8 minutes after injection but can be interpreted for as long as 60 minutes.[17] Doses of as high as 10 mL of 10% fluorescein have been evaluated, with optimal images obtained after administration of 2.5 to 5 mL.[18] After contrast administration, the tip of the confocal endomicroscope or miniprobe is positioned in gentle but firm contact with the area of interest to obtain high-resolution confocal images. Accumulated images can be saved for postprocedural analysis.

EASE OF USE

Key issues regarding the use of CLE include the learning curve of image interpretation, the use of the actual devices (pCLE vs eCLE), and additional time required to perform the procedures. Few studies have evaluated these issues; however, one such study suggested that image acquisition and interpretation are learned rapidly, typically with review of standardized image libraries.[19] Current CLE systems require dedicated equipment. Startup/calibration times with current versions have been shortened to less than 2 to 3 minutes, although total startup including the need for additional equipment, powering, probe insertion, and user interface setup typically takes at least 5 to 10 minutes. pCLE systems allow on-demand use via the accessory channel of any endoscope, whereas eCLE requires the use of a dedicated Pentax endoscope. Both systems allow real-time image acquisition and storage, as well as immediate or offline review capabilities. Images are stored on dedicated image processors using proprietary formats; however, standard video and still images can also be exported into most endoscopic image management systems. However, before CLE can become more widespread, further investigation is needed to determine the practicality of the technology in busy endoscopic practices.

Training in CLE methods is typically done through continuing medical education courses, visitation with experts, and online resources. For pCLE, there is a comprehensive library of case studies and atlases of normal and disease states available online (www.cellvizio.net) as well as on Smartphone applications (currently only available for iPhones at http://itunes.apple.com or download from cellvizio.net). For eCLE, specific training is offered through the expert centers such as the University of Mainz (http://www.unimedizin-mainz.de/uploads/tx_tkveranstaltungen/MEC_Flyer_02.pdf).

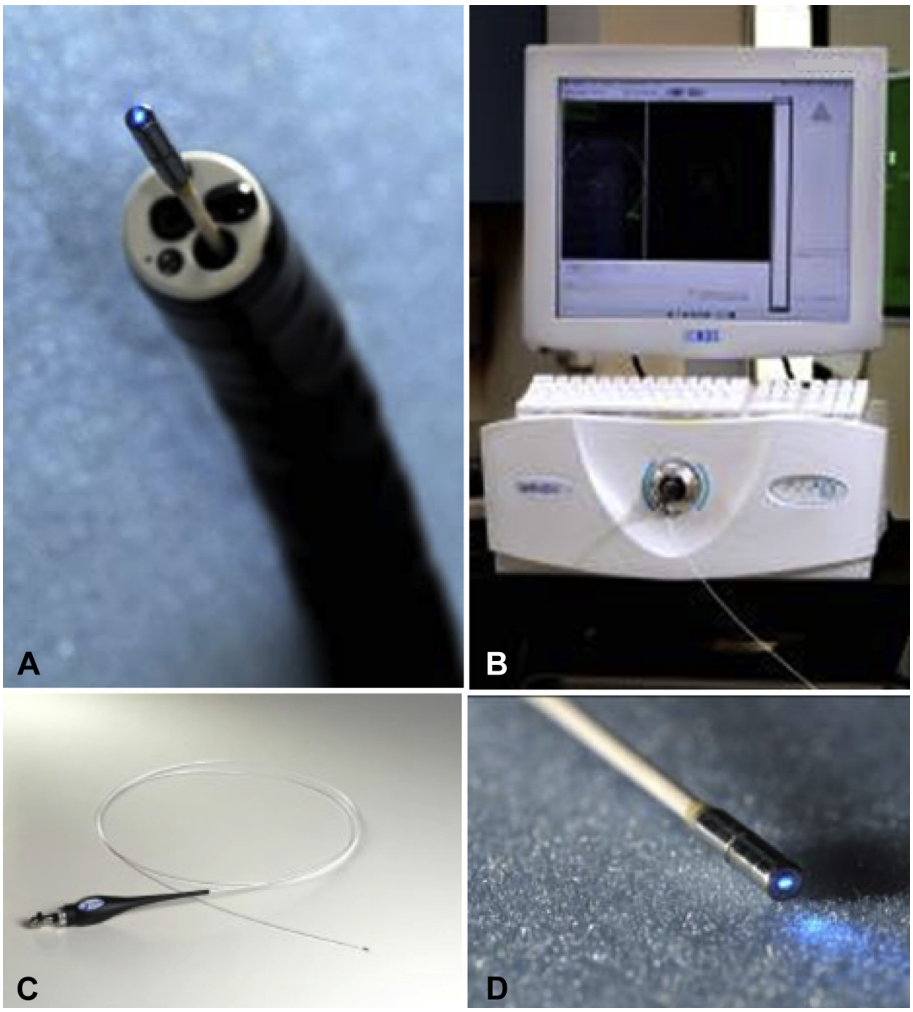

Figure 2. Probe-based confocal laser endomicroscopy (pCLE) system (Cellvizio; Mauna Kea Technologies, Paris, France) showing endoscope with a probe via an accessory channel (**A**), laser scanning unit (**B**), pCLE probe (**C**), and pCLE with laser illumination (**D**).

EFFICACY AND COMPARATIVE STUDIES

A standard classification system has been developed for eCLE, termed the Mainz classification.[13] This classification distinguished neoplastic from hyperplastic polyps of the colon based on a dark, irregularly thickened epithelial layer characteristic of epithelial dysplasia (Fig. 4). The Miami classification was similarly developed for pCLE to distinguish normal and pathological GI conditions (Fig. 4).[20] Because pCLE was fairly new at the time, standards were mainly based on expert opinion and development of consensus. Subsequently, clinical trials with larger sample sizes have assessed the diagnostic accuracy of pCLE by using the Miami classification criteria and have refined the criteria. Experience with pancreaticobiliary imaging with endomicroscopy remains more limited. Comparison of the 2 classification systems seems to indicate that the Mainz classification criteria may be more reproducible.[21]

APPLICATIONS

Current potential applications for CLE in GI endoscopy include Barrett's esophagus (BE) surveillance and treatment, diagnosis of indeterminate biliary strictures (pCLE only), post-resection follow-up of colonic lesions. Evolving applications include differentiation of colorectal polyps, inflammatory bowel diseases, gastric diseases, and pancreatic cysts (nCLE only). Technological advances including miniaturization of probes also offer opportunities to expand the field of indications within and outside the GI tract.

Luminal applications

Barrett's esophagus. In patients with BE, CLE can distinguish between different types of epithelial cells and detect dysplasia and neoplasia.[22-24] Surveillance endoscopy in 63 patients with BE provided in vivo histology of the mucosal layer and was able to diagnose Barrett's epithelium and associated neoplastic changes with 98.1% and

TABLE 1. CELLVIZIO confocal miniprobes

Probes	Compatible operating channel	Length, m	Maximal no. of uses	Field of view diameter, μm	Resolution, μm	Confocal depth, μm
GastroFlex UHD	≥2.8	3	20	240	1.0	55–65
AlveoFlex	≥1.9 mm	3	20	600	3.5	0–50
CholangioFlex	≥1.0 mm	4	10	325	3.5	40–70
AQ-Flex 19	≥0.91 mm (19 gauge)	4	10	325	3.5	40–70
ColoFlex UHD	≥2.8 mm	4	20	240	1.0	55–65
UroFlex B	≥1 mm (3F)	3	10	325	3.5	40–70

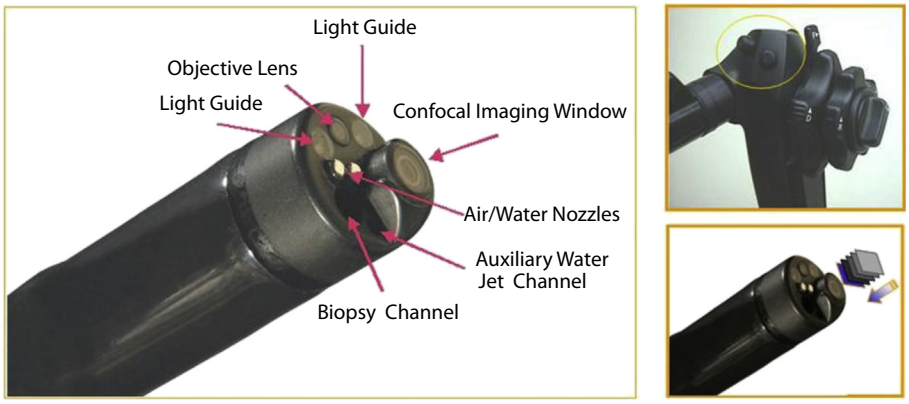

Figure 3. Endoscope-based confocal laser endomicroscope (Optiscan, Nottinghill, Victoria, Australia and PENTAX Medical, Montvale, NJ).

92.9% sensitivity and 94.1% and 98.4% specificity, respectively.[23] The Miami classification for pCLE has been tested and validated in a multicenter, randomized, control trial.[25] Independent endoscopists performed sequential endoscopic imaging to prospectively evaluate the sensitivity and specificity of pCLE compared with white-light endoscopy (WLE) and narrow-band imaging (NBI) for the detection of high-grade dysplasia and early carcinoma in BE. A total of 101 patients with BE presenting for surveillance or endoscopic treatment of high-grade dysplasia or early carcinoma were first examined with both high-definition WLE (HD-WLE) and NBI in random order. Subsequently, suspicious lesions found by both modalities were then targeted by pCLE, and findings were recorded before 874 biopsy samples were obtained. The sensitivity and specificity for HD-WLE alone were 34.2% and 92.7%, respectively, but this improved to 68.3% ($P = .002$) and 87.8% ($P < .001$), respectively, when pCLE was combined with HD-WLE. However, on a per-patient basis, pCLE enabled detection of only 2 additional patients with dysplasia compared with HD-WLE and only 1 additional patient compared with NBI. Although the authors concluded that pCLE combined with HD-WLE significantly improved the ability to detect neoplasia in BE patients, the study had limitations because it was performed at an academic center with an enriched population of patients undergoing procedures by endoscopists with expertise in BE and CLE. Furthermore, the study was not designed to, nor did it demonstrate superiority over commonly available imaging enhancement techniques such as NBI. Hence the applicability of these results in a general population and especially in community-based practices is unknown.

A retrospective study by Gaddam et al[26] attempted to refine the pCLE criteria for dysplastic BE and evaluate accuracy, interobserver variability, and the learning curve in dysplasia prediction. In phase I of the study using 50 pCLE videos, only criteria with more than 70% sensitivity were included in the final set. The authors found that the overall accuracy of pCLE for diagnosing dysplasia was 81.5% and interobserver agreement was substantial ($\kappa = 0.61$). There was no difference in the performance of experts versus nonexperts. If the endoscopist was confident in making a diagnosis, accuracy rates were higher (98% vs 62%).

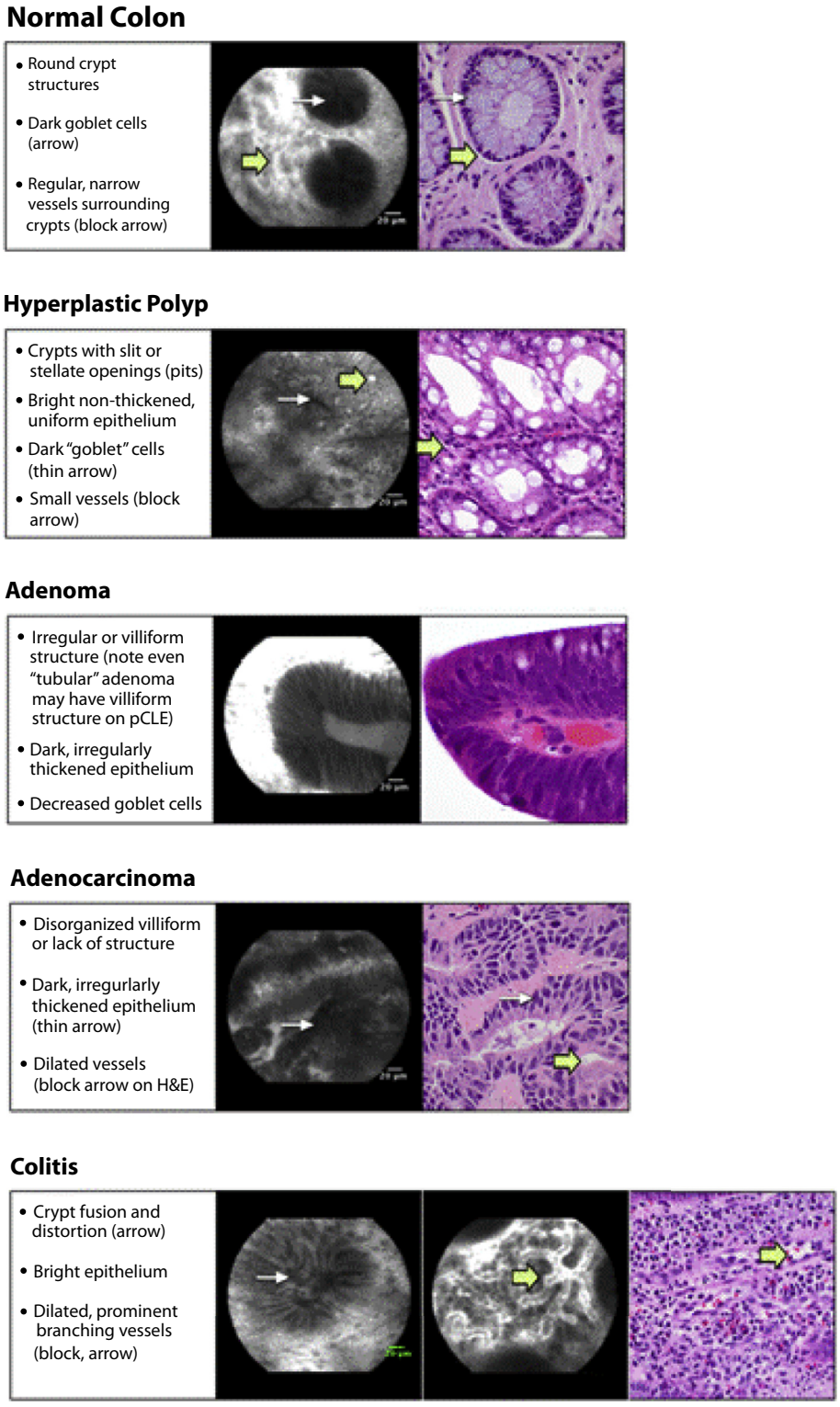

Figure 4. Example of the Miami classification system for probe-based confocal laser endomicroscopy (pCLE). Shown is the classification for colon.

More recently, Canto et al[27] reported a prospective, multicenter, randomized trial comparing HD-WLE plus eCLE with targeted biopsy with HDWLE alone with random biopsy. In 192 patients, eCLE-targeted biopsies had significantly higher yield (34%) for neoplasia compared with random (7%) biopsy and did so with fewer biopsies. Use of eCLE to target biopsy specimens would have eliminated the need for any biopsy in 65% of patients

TABLE 2. Studies evaluating CLE in colorectal polyps

Study	No. of subjects	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy
Kiesslich et al,[13] 2004, Germany	42	97.4	99.4	–	–	99.2
Meining et al,[29] 2007, Germany	13	93	92.0	–	–	–
Hurlstone et al,[30] 2008, United Kingdom	40	97.4	97.4	–	–	99.1
Sanduleanu et al,[31] 2010, the Netherlands	72	97.3	92.8	–	–	95.7
De Palma et al,[32] 2010, Italy	20	100	84.6	90.5	100	92.3
Buchner et al,[33] 2010, U.S.	75	91	76	–	–	–
Shahid et al,[34] 2012, U.S.	65	86	78	76	88	82

CLE, Confocal laser endomicroscopy; *PPV*, positive predictive value; *NPV*, negative predictive value.

with a sensitivity of 96% versus 40% for HD-WLE random biopsy alone. A single patient in the study was missed by eCLE and only detected by random biopsy.

Colorectal diseases. CLE has been used for several indications in the colon including classification of polyps, assessment of resection margins after polypectomy, and evaluation of inflammatory bowel diseases. After identification of a site of interest by standard or enhanced endoscopy, CLE can be applied for further evaluation.

Colorectal polyps. The ability of conventional colonoscopy to differentiate adenomatous from nonadenomatous colorectal polyps in vivo is limited. CLE in this scenario can predict histology intraprocedurally, thereby increasing efficiency and reducing cost. The decision to leave a polyp in situ based on intraprocedural examination would require a test with high accuracy and negative predictive value (NPV). Furthermore, the ASGE PIVI (Preservation and Incorporation of Valuable endoscopic Innovations) initiative has provided guidelines for when it would be acceptable to adopt a "virtual biopsy" approach. Two management strategies that are advocated include the "leave behind" and "resect-and-discard" management. Recommended thresholds for accuracy include 90% or higher NPV for adenomatous polyps and 90% or higher accuracy in predicting correct surveillance interval.[28]

Various published studies evaluating the use of CLE during colonoscopy for distinguishing colorectal polyp pathology and neoplasia are summarized in Table 2.[13,29-34] These studies are heterogeneous and are difficult to compare because of differing primary objectives and the modality of CLE used (eCLE vs pCLE). Nevertheless, these studies suggest that CLE may have the potential to reach ASGE PIVI thresholds; however, the generalizability of the results obtained in academic settings to community practice is unknown.

With regard to the learning curve for CLE, a study by Buchner et al[19] indicated a short learning curve for pCLE for the evaluation of colorectal polyps. In this study involving 11 endoscopists with varied pCLE expertise, accuracy in the analysis of 76 pCLE sequences rose from 63% during interpretation of the first 20 images to 86% during interpretation of the final set of images.

Finally, with regard to sessile-serrated polyps, 2 preliminary studies reported only in the abstract form evaluated the criteria for distinguishing sessile-serrated polyps from hyperplastic polyps.[35,36] The initial results seem promising, but further studies are needed.

Follow-up post-EMR. In a multicenter study, Shahid et al[37] evaluated 129 post-EMR resection sites for recurrent or residual neoplasia within 1 year of intervention. The resection sites were evaluated by high-resolution colonoscopy and electronic chromoendoscopy (ECE), either with NBI or FICE (Fujinon intelligent chromoenoscopy), followed by pCLE. pCLE images were reviewed in real time and later offline, with endoscopists blinded to endoscopic appearance and histology, which was used as the criterion standard. The sensitivity, specificity, positive predictive value, and NPV for ECE was found to be 72%, 77%, 49%, and 91%, respectively, compared with 97%, 77%, 55%, and 99%, respectively, for pCLE. Overall accuracy for ECE was 77% versus 81% for pCLE. When the combination of pCLE and ECE agree, the sensitivity and NPV are 100%, thereby potentially obviating the need for biopsy/histology.

Inflammatory bowel disease. Neumann et al[38] demonstrated a short learning curve for pCLE and high agreement between pCLE and histopathology findings in inflammatory bowel disease (IBD) patients. Li et al[39] assessed the potential of CLE in the grading of colitis. CLE provided information equivalent to that with conventional histology in differentiating between active and quiescent disease based on assessment of crypt and vascular architecture and cellular infiltration. CLE during endoscopic surveillance of IBD patients has shown high agreement with histological findings.[38] In another study, Neumann et al[40] developed a score termed the Crohn's Disease Endomicroscopic Activity Score to assess in vivo activity. The Crohn's

Disease Endomicroscopic Activity Score correlated with C-reactive protein level, thereby having a potential for assessing disease activity.

Taking surveillance biopsies in IBD is time-consuming and carries a low but non-negligible risk. Various studies have examined the role of CLE in surveillance of IBD patients, assessing the extent of disease, targeting biopsies, earlier detection of dysplasia, assessment of mucosal healing, and defining treatment protocols. Kiesslich et al[16] studied patients with ulcerative colitis and classified normal mucosa, regeneration, neoplasia, and inflammation by using crypt and vessel architecture and cellular infiltration. Additionally, in this study, chromoendoscopy was first used to detect flat or suspicious lesions followed by eCLE to further characterize these lesions. In this study of 161 patients, 4.75-fold more neoplastic lesions were detected compared with conventional colonoscopy ($P = .05$). Furthermore, by using chromoendoscopy-directed eCLE, the number of biopsy specimens was reduced by 50% ($P = .08$). eCLE was highly accurate in predicting neoplasia (94.7% sensitivity, 98.3% specificity, and 97.8% accuracy).[16]

A study by De Palma et al[41] used pCLE to diagnose dysplasia-associated lesions or masses. A clear diagnosis by using pCLE could potentially allow selection of patients for immediate EMR versus colectomy.

Gastric diseases. There is no current widely accepted CLE classification for gastric lesions, but precancerous lesions in several stages have been described by using similar criteria of glandular and vascular architecture and cell morphology. In the healthy stomach, both pyloric and fundic glands are characterized by homogeneous epithelial cells in size and height. In intestinal metaplasia, there is a villous architecture, large black goblet cells, tall and bright absorptive cells, and honeycomb-like or coil-shaped vessels with normal caliber. In contrast, in dysplasia the glands vary in size and height, irregular cell arrangement, dilated and distorted vasculature, and hyperdense epithelial cells with increased stratification. Finally, in malignancy, the cells are irregular, glands are disorganized, and vessels are irregular and increased in caliber.

Initial studies of CLE in the stomach allowed direct in vivo identification of *Helicobacter pylori* infection and good visualization of normal and pathological gastric pit patterns.[3,11,42] A study by Wang et al[43] of 118 patients indicated that CLE had a high sensitivity and specificity for the diagnosis of *H pylori*, associated glandular atrophy, and intestinal metaplasia (82.9% and 90.9% for infection, 92.9% and 95.2% for glandular atrophy, and 98.6% and 100% for intestinal metaplasia, respectively). In another study comparing CLE and WLE for detecting gastric intestinal metaplasia (GIM), the sensitivity and specificity were, respectively, 98.1% and 95.3% for CLE versus 36.9% and 91.6% for WLE.[44]

Li et al[45] performed a 2-phase study comparing WLE and CLE in the diagnosis of superficial gastric lesions. In the first phase of the study performed on 182 patients, they defined interpretation criteria for GIM, gastric intraepithelial neoplasia, and cancer. In the next phase, they validated these criteria in 1572 patients. They found that although the specificities of CLE and WLE were similar, CLE was superior to WLE in terms of sensitivity and positive predictive value (PPV) (88.9% and 85.3% vs 72.2% and 41.6%, respectively).

Another study prospectively compared the diagnostic performance of autofluorescence imaging (AFI), magnifying NBI (mNBI), and pCLE with WLE for the diagnosis of GIM by using histology as the criterion standard. A total of 125 sites in 20 patients were examined. For diagnosing GIM, real-time pCLE had better sensitivity (90.9% vs 37.9%, $P < .001$) and accuracy (88.0% vs 64.8%, $P < .001$) compared with WLE. Sensitivity (90.9% vs 68.2%, $P = .001$), specificity (84.7% vs 69.5%, $P = .042$), and accuracy (88% vs 68.8%, $P < .001$) of real-time pCLE were better than AFI. Sensitivity, specificity, and accuracy of real-time pCLE and mNBI for diagnosing GIM were similar. Review of saved pCLE images offline resulted in improved accuracy for diagnosing GIM compared with WLE, AFI, and mNBI. Offline pCLE interpretation had superior specificity (94.9% vs 84.7%, $P = .031$) and accuracy (95.2% vs 88.0%, $P = .012$) compared with real-time pCLE interpretation.[46]

Finally, Pittayanon et al[47] evaluated the learning curve of pCLE. They showed that after a short session of training and quiz on GIM by pCLE, beginners could achieve high reading accuracy and substantial interobserver agreement. Once high reading accuracy is achieved, good reading skills were maintained.

Biliary applications

Despite advances in imaging including high-quality CT and magnetic resonance imaging, EUS, and ERCP with intraductal imaging, management of biliary strictures can be complex. Even with a combination of sampling methods including biopsies, brushing, and aspiration, sensitivities remain low, and improved diagnostic modalities are needed. pCLE allows in vivo real-time visualization of biliary strictures via a dedicated probe passed through a cholangioscope or catheter for ERCP. pCLE can provide real-time microscopic images of the biliary epithelium, thereby providing histological information that is not otherwise available during ERCP.

A prospective, multicenter observation registry was performed in 102 patients with the purpose of determining utility, accuracy, and performance of pCLE compared with histopathology and validating the Miami classification.[48] pCLE obtained higher sensitivity and higher NPV than index pathology (98% sensitivity and 97% NPV for pCLE vs 45% sensitivity and 69% NPV for index pathology, respectively), and higher overall accuracy (81% pCLE vs 75% for index pathology). The combination of ERCP and pCLE was more accurate than ERCP and tissue sampling (90% vs 73%, $P = .001$).

In a subsequent study on the same patient group, the criteria developed during the ERCP registry were tested

by using blinded consensus.[49] A total of 112 pCLE videos from 47 patients were reviewed. Interobserver variability was assessed in 42 patients. The criteria found to be most suggestive of malignant biliary strictures were thick white bands (>20 μm), thick dark bands (>40 μm), dark clumps, epithelial structures, and fluorescein leakage. Combining 2 or more criteria increased sensitivity and predictive values. Moreover, combining all criteria provided a sensitivity, specificity, PPV, and NPV of 97%, 33%, 80%, and 80%, respectively, compared with 48%, 100%, 100%, and 41%, respectively, for standard sampling methods. These criteria have been confirmed by other investigators.[50,51]

In another multicenter study aimed at assessing interobserver agreement in pCLE image interpretation, 25 deidentified pCLE video clips of indeterminate biliary strictures were sent to 6 observers with varying levels of experience at 5 institutions. The Miami classification was used to standardize image interpretation. The authors concluded that the overall interobserver agreement for pCLE images in indeterminate biliary strictures ranged from poor to fair, and further refinement of interpretation criteria and training was required.[52]

Finally, a retrospective study to refine the Miami classification criteria was performed to better characterize inflammatory strictures.[53] By reviewing 60 sequences from the registry, the investigators established new criteria specific to inflammation. Subsequently, they evaluated the diagnostic efficacy of pCLE with these newly developed criteria on 40 additional sequences. They defined reticular strictures, multiple thin white bands, increased spaces between scales (>20 μm), and a dark granular pattern. Further studies are ongoing to validate these criteria.

Pancreatic applications

nCLE allows imaging of organs within or adjacent to the GI tract with a miniprobe passed through an endoscopic needle. In vivo real-time microscopy during EUS may potentially allow for better differentiation of various types of pancreatic lesions.

An initial study using prototype probes demonstrated the technical feasibility, defined a precise imaging protocol, and assessed the safety of the procedure. Images were obtained of pancreatic cysts and solid masses, and typical patterns of pancreatic cysts were observed. It was suggested that there was potential of using this new imaging technology for pancreatic lesions.[54]

A second study of nCLE, INSPECT (In Vivo nCLE Study in the Pancreas with Endosonography of Cystic Tumors), aimed at defining interpretation criteria for the differentiation of mucinous and nonmucinous cysts and assessing safety.[55] Among 65 patients enrolled, the first 27 were evaluated to define a list of descriptive criteria. These defined criteria were subsequently tested in the remaining 38 patients by blinded review of images in consensus fashion. The reference standard used for final diagnosis was surgical pathology of the cyst, if available. Otherwise, the modified reference standard was a consensus diagnosis based on a review of all clinical data for the patient (EUS images, carcinoembryonic antigen level, and cytology) as determined by 5 investigators. The offline review of nCLE images concluded that the presence of 1 criterion, epithelial villous structures, was associated with mucinous cysts ($P = .004$) and had a sensitivity and specificity of 59% and 100%, respectively, for the detection of mucinous cysts.[55]

Another study investigated the combination of direct visualization by using Spyglass, a through-the-needle fiberoptic probe (Boston Scientific, Natick, Mass) and nCLE based on the criteria defined in the INSPECT to differentiate between mucinous and nonmucinous cysts in 21 patients. The sensitivity for mucinous cysts was 88% with Spyglass (by using detection of mucin), 75% with nCLE (by using detection of epithelial structures), and 100% with a combination of the two.[56]

Other applications

Celiac disease. Two preliminary studies suggest that CLE is capable of detecting villous atrophy and increased intraepithelial lymphocytes. In a study of 31 patients, the sensitivity was 94% and the specificity was 92% of CLE with good correlation with the March histology index.[57,58]

Ampullary lesions. One preliminary multicenter study evaluated the interpretation and interobserver agreement of CLE in ampullary lesions. However, the results showed that overall interpersonal agreement of CLE images was poor.[59] Further standardization of CLE image criteria for ampullary lesions is needed.

SAFETY

Adverse events of CLE are primarily related to the allergic properties of contrast agents. Most reported adverse events for intravenous fluorescein are mild, but rare serious adverse events include myocardial infarction, anaphylaxis, seizure, and shock. However, in a study of 2272 GI CLE procedures using intravenous fluorescein, no serious events were reported. Mild adverse events occurred in 1.4% and included nausea/vomiting, transient hypotension, diffuse rash, injection site erythema, and mild epigastric pain.[60] There are limited human data on potential adverse events of topical stains such as acriflavin, proflavin, cresyl violet, gentian (crystal) violet, and methylene blue. Acriflavin is a mutagenic dye and a potential human carcinogen, which limits its clinical utility.[61] In addition, acriflavin and cresyl violet are not approved for human use by the U.S. Food and Drug Administration (FDA).

FINANCIAL CONSIDERATIONS

The pricing for the Cellvizio 100 series system and the confocal miniprobes are listed in Table 3. Applicable

TABLE 3. Pricing (US$)

Cellvizio 100 Series System	175,000
GastroFlex UHD probe	9200
CholangioFlex probe	8900
ColoFlex UHD probe	9900
AQ-Flex probe	9800
AlveoFlex probe	6900
Pentax eCLE scope	Currently not marketed

There are Current Procedural Terminology codes available including 3 category I CPT codes (43206, 43252, and 88375) that became effective January 1, 2013 with Medicare outpatient hospital payments of $927.

Current Procedural Terminology codes at the time of preparation of this report with reimbursement rates are also listed.

RELATED AND FUTURE SYSTEMS

The field of endomicroscopy is now expanding to include other systems for in vivo imaging on a micron scale. One such system recently commercialized and U.S. Food and Drug Administration approved is optical frequency domain imaging, also called needle volumetric laser endomicroscopy (Ninepoint Medical, Cambridge, Mass). This system incorporates a through-the-scope, balloon-centered optical fiber that scans circumferentially a 6-cm segment of the lumen (typically the esophagus). Full-resolution scans can be performed in 90 seconds at a depth of 3 mm (muscularis propria) at 7-μm resolution.[62] The primary application appears to be for the imaging of BE with a potential to detect both surface and subsquamous dysplasia and laser marking for targeted therapy.

Dual-axis CLE is another novel imaging system that is not yet commercially available nor FDA approved. By using dual axes, many of the physical/optical constraints of single-axis systems are overcome, allowing greater depth and wider field-of-view images compared with conventional CLE.[63]

AREAS FOR FUTURE RESEARCH

Several issues pertaining to CLE deserve further investigation:

1. Further studies evaluating the applicability and practicality of CLE, especially in community settings, are needed. Although current studies of CLE seem promising, these have primarily been in academic centers, and their generalizability in nonacademic practices is unknown.
2. More studies evaluating the learning curve of CLE image interpretation, use of CLE devices, and additional time needed to perform the procedure are needed.
3. The clinical efficacy of the technology and its cost-effectiveness compared with other available advanced imaging technologies need to be studied further.
4. Improvements in CLE imaging and image interpretation are needed. Combining CLE imaging with newer molecular markers and the development of computer-based algorithms may be possible avenues for further research in this respect.

SUMMARY

CLE is an emerging technology that has the potential to significantly reduce the number of biopsies in BE and IBD and reduce the need for removal of non-neoplastic colorectal polyps compared with WLE. In the bile duct and within pancreatic cysts, it can provide surrogate real-time histological information that has previously been unavailable. Limitations of CLE include the high cost of the equipment and probes, the lack of proven efficacy compared with other widely available advanced imaging techniques, and the need for either intravenous or topical fluorescent contrast agents. Before the technology can be widely accepted, many further studies are needed to determine its clinical efficacy and evaluate its cost-effectiveness and its utilization in both academic and community settings.

DISCLOSURE

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Abbreviations: AFI, autofluorescence imaging; BE, Barrett's esophagus; CLE, confocal laser endomicroscopy; ECE, electronic chromoendoscopy; eCLE, endoscope-based confocal endomicroscopy; FDA, U.S. Food and Drug Administration; GIM, gastric intestinal metaplasia; HD-WLE, high-definition white-light endoscopy; IBD, inflammatory bowel disease; mNBI, magnifying narrow-band imaging; NBI, narrow-band imaging; nCLE, needle-based confocal laser endomicroscopy; NPV, negative predictive value; pCLE, probe-based confocal laser endomicroscopy; PPV, positive predictive value; WLE, white-light endoscopy.

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