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Review Article

Gastrointestinal Applications of Confocal Laser Endomicroscopy

Samuel Han[1]*, Daniel Kaufman[1], Andrew Fischer[2] and Wahid Wassef[1]

[1]*Department of Gastroenterology, University of Massachusetts Medical School, USA*
[2]*Department of Pathology, University of Massachusetts Medical School, USA*

***Corresponding author**
Samuel Han, Department of Gastroenterology, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655, USA. Tel: 617-640-1495; Email: Samuel.Han@umassmemorial.org

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Abstract

Confocal laser endomicroscopy presents a novel method of real-time in vivo histological analysis of tissue that can be easily performed during endoscopy. This review goes over the fundamental principle of the technology and presents its various gastrointestinal applications. With particular focus on dynamic imaging, this review outlines the diagnostic potential of this technology.

ABBREVIATIONS

CLE: Confocal Laser Endomicroscopy; GI: Gastrointestinal; IBD: Inflammatory Bowel Disease; BE: Barrett's Esophagus; CA: Cancer

INTRODUCTION

The importance of microscopic evaluation of tissue in the diagnostic process is increasingly important as therapeutic interventions become more advanced and effective. Flexible endoscopy has long been relied upon for direct visualization and macroscopic evaluation of tissue and as a platform through which samples could be obtained for microscopic evaluation. The diagnosis of malignant and pre-malignant pathology has been traditionally dependent on gross identification of suspicions lesions. The risks inherent to repeated tissue sampling via biopsy, namely infection, bleeding and perforation must be taken into account when formulating a diagnostic approach. The ability to detect suspicious lesions on a macroscopic level is also variable and often dependent on the skill and experience of the operator. Random biopsies continue to be a common practice in the screening for malignant lesions in many patients, including but not limited to those with Inflammatory Bowel Disease (IBD), Barrett's Esophagus and urothelial malignancies. Confocal Laser Endomicroscopy (CLE) is beginning to gain widespread recognition as a diagnostic tool that may be used to avoid many of these issues. Initially described in 2004, CLE provides high-resolution, real time histological analysis of targeted mucosa, often mitigating the need for tissue sampling. At present, there are two primary CLE platforms that have been approved by the FDA for clinical use. Endoscope-based CLE (eCLE; Pentax Corporation, Tokyo, Japan) features a confocal microscope integrated in the tip of an endoscope, through which a fiber-optic cable can transmit blue-laser light (the wavelength of which is typically fixed at 488 nm) [1]. This modality allows for high-resolution, *in vivo* microscopic imaging at varying depths [1]. In an alternative system, probe-based CLE (pCLE Mauna Kea Technologies, Paris, France), an external confocal microscope transmits light through fiber-optic probe which may be passed through the working channel of a standard endoscope [2]. The resolution compared to eCLE is lower and the depth is fixed at certain levels, depending on which mini probe is utilized. Both platforms are dependent on fluorescence. Because tissue auto-fluorescence does not provide sufficient contrast for useful microscopic analysis, pre-procedural administration of an intravenous agent, most commonly fluorescein, is typically utilized. An alternative that has emerged, however, is the topical application of acriflavine or cresyl violet. Although these agents are readily available, there remains concern regarding tissue penetration and evenness of staining.

Very little research has been done to compare the two CLE platforms. Practically speaking, despite the superior resolution and depth variability of the eCLE system, the pCLE system offers the advantage of immediate availability with the use of standard endoscopes. Both platforms require special training for endoscopists and an on-site pathologist. The breadth of clinical applications of CLE continues to broaden as the technology gains traction in an increasing number of clinical centers. Within gastroenterology, CLE is becoming more prevalent in diagnosis and monitoring of Barrett's Esophagus, gastric cancer, inflammatory bowel disease (IBD), colon polyps and pancreatic/biliary pathology. Use of CLE is also extending into bronchoscopic tissue evaluation, intra-operative neurosurgical tissue delineation and urologic and gynecologic malignancies. This review will focus on recent advances and new techniques in the use of CLE in gastrointestinal applications, with a particular focus on dynamic *in vivo* imaging.

BARRETT'S ESOPHAGUS

Barrett's Esophagus (BE) is a condition that has dysplastic potential, and that ultimately can progress to esophageal

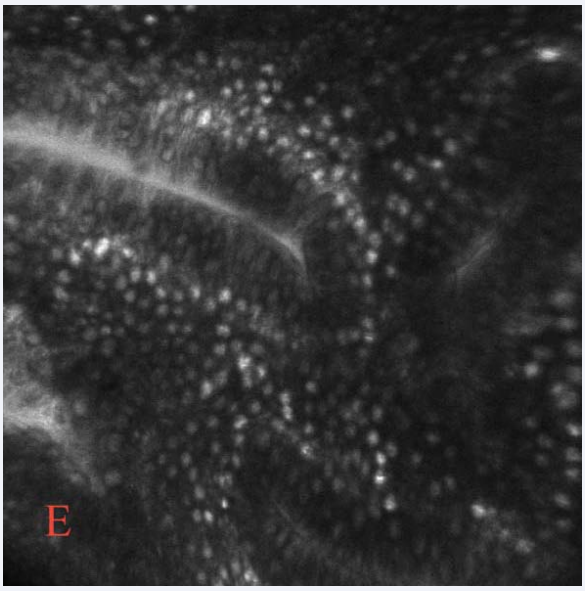

Figure 1 Confocal laser endomicroscopy image showing dilated crypts and fluorescein leakage into lumen [38].

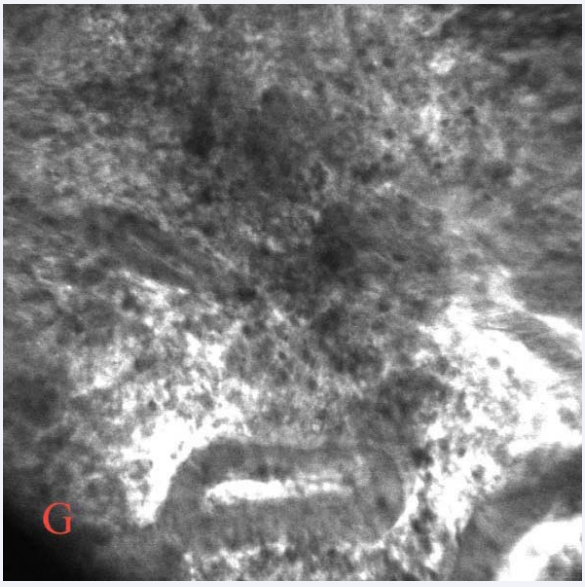

Figure 2 Confocal laser endomicroscopy image showing disruption of epithelium in crypts of colonic mucosa [38].

adenocarcinoma, and therefore necessitates surveillance biopsies. CLE allows for *in vivo* imaging, which may eventually replace endoscopic biopsies. eCLE utilizes the Mainz criteria to identify BE, and has been found to have a sensitivity of 93%, and specificity of 94% in identifying BE-related dysplasia [3]. Use of eCLE can also help target biopsies, as shown by Dunbar et al, who found an improvement in diagnostic yield for high-grade dysplasia to 33.7% compared to 17.2% in standard endoscopy, while also decreasing the number of mucosal biopsies by 60% [4]. An international multi-center trial supported these findings, identifying an improvement in diagnostic yield of BE-related dysplasia from 6% to 22%, while also decreasing the number of biopsies [5]. pCLE incorporates the Miami criteria in detecting BE-related neoplasia with a sensitivity of 88% and specificity of 96% [6]. An *in vivo* evaluation by Bajbouj *et al* found that pCLE was non-inferior to standard biopsy in detecting neoplasia in BE and a multi-center trial (DON'T BIOPCE) comparing pCLE to high-definition endoscopy found a sensitivity and specificity of 88% and 68%, compared to 34 and 93%, respectively in high-definition endoscopy [7,8]. While fluorescein has been the primary contrast agent used in CLE for BE, Gorospe *et al* have examined *ex vivo* use of 2-NDBG (2-[N-(7-nitrobenz-2-oxa-1,3-diaxol-4-yl) amino]-2-deoxyglucose), with dysplasia detection rate of up to 78.6%, compared to 37% and 44.3% in pCLE and eCLE respectively, suggesting promise regarding the potential for improved detection rates of neoplasia in BE [9].

GASTRIC CANCER

Given the increasing worldwide prevalence of Gastric Cancer (CA), CLE has been extensively studied for its diagnostic capabilities. With a sensitivity of 89.2%, specificity of 95.7%, and accuracy of 92.8%, eCLE has shown promise in detecting *Helicobacter pylori*, a key organism in the development of Gastric CA [10,11]. In addition, CLE allows for the detection of gastric pits, enabling classification of gastric metaplasia, with diagnostic accuracy of 97.1% in gastric CA [12]. In comparison with standard endoscopy, Guo *et al* found that eCLE had a much higher sensitivity (98.1% vs. 36.9%) and specificity (95.3% vs. 91.6%) in detecting gastric intestinal metaplasia [13]. eCLE has also been used to differentiate between gastric hyperplastic polyps and adenomas, with an *in vivo* diagnostic accuracy of 90% and overall accuracy of 97% in differentiating between hyperplastic polyps and adenomas [14].

With regards to the identification of superficial cancerous lesions, a large trial by Li *et al* used criteria including irregularity of glandular size and shape, disorganized pits and glands, irregular cells, and loss of cell polarity to diagnose superficial gastric CA/high-grade intraepithelial lesions [15]. Compared to standard endoscopy, CLE had a much higher sensitivity (88.9 % vs. 72.2%), specificity (99.3 vs. 95.1), and accuracy (98.8% vs. 94.1%).

Fluorescein does have shortcomings related to differentiating the degree of dysplasia due to its inability to accurately measure the nuclear-cytoplasmic ratio and hyperchromatism, as shown by Li *et al* who found only a 79.8% diagnostic accuracy for gastric intraepithelial neoplasia and a sensitivity of 66.7% in distinguishing between low- and high-grade intraepithelial neoplasia [16]. However, Ji *et al* found that fluorescein leakage from capillaries into tissue signals a disruption in the gastric para cellular barrier [17]. This disruption was found in gastric intestinal metaplasia, demonstrating another method of CLE to identify gastric CA.

COLON POLYPS

Screening for colon cancer is frequently performed via colonoscopy, and the identification of polyps remains a fundamental step in identifying and preventing the progression of disease. As there are several types of colonic lesions, *in vivo* differentiation between the lesions via CLE offers crucial advice in terms of management of the lesions. Accurate differentiation

could even allow the endoscopist to resect and discard the lesion, instead of being obligated to perform histopathological evaluation.

Kiesslich *et al* performed the 1st human clinical trial with eCLE in examining colon polyps and developed a classification system incorporating crypt, cellular, and vessel architecture [18]. This system was found to have a very high sensitivity (97.4%), specificity (99.4%) and accuracy (99.2%). Since then, many studies have demonstrated a high sensitivity (average of 93.3%) and specificity (average of 89.9%) for CLE in identifying colorectal neoplasia [19-28]. As expected, small polyps have decreased sensitivity (86%) and specificity (78%), as demonstrated by Shahid *et al* who used pCLE to examine polyps < 10mm [29].

Another application of CLE was shown by Shahid *et al* who examined residual tumor post resection [30]. Sensitivity was found to be 97% in CLE vs. 72% in standard endoscopy, and specificity was 77% in both CLE and standard endoscopy, revealing the potential to perform all necessary endoscopic intervention in one session without needing to wait for biopsy results.

INFLAMMATORY BOWEL DISEASE

Inflammatory Bowel Disease (IBD) represents another pathology for which CLE has the potential to provide great benefit. Initially used as a tool to help perform targeted biopsies and thereby decrease the total number of biopsies by up to 50% [31-33], CLE has also been shown to have a high accuracy in identifying intraepithelial neoplasia in patients with Ulcerative Colitis (UC) [34-36]. These prospective studies have shown an accuracy rate, sensitivity, and specificity of up to 98%, 95%, and 98%, respectively in predicting neoplasia, with excellent agreement between CLE and histopathology.

The role for dynamic imaging *in vivo* has expanded particularly in the field of IBD. A pilot study by Buda *et al* found that examining fluorescence leakage and crypt diameter in Ulcerative Colitis (UC) patients allowed prediction of a flare-up within a 12-month follow-up period [37]. Utilizing a video mosaicing technique, which is an algorithm-based process that compiles a series of consecutive images into a single larger composite image to compensate for the motion introduced by the operator or the subject (eg, diaphragmatic motion or vascular pulsation) and effectively create a larger field of view, Buda *et al* examined crypts throughout the large and small bowel of patients with UC. As patients with active inflammation will have a physiologic increase in vascular permeability, fluorescein will extravasate into avascular areas. Thus, fluorescence intensity was used as a marker for fluorescein leakage, allowing for indirect measurement of inflammation, which the study was able to use to effectively predict disease relapse in a 12-month period. This was corroborated by a Li et al, who were able to perform real-time analysis of active inflammation [38]. Alternatively, Turcotte *et al* examined epithelial gap density using CLE in patients with both Crohn's and UC, and found a correlation between increased gap density and an increased number of flares [39]. Kiesslich *et al* utilized CLE with IV fluorescein IBD patients and found cells to become intensely fluorescent during cell shedding [40]. Examining the process of shedding, they also found fluorescein escaping though the gap in the epithelium left by the shedding cell, demonstrating a loss of barrier function. They were able to confirm this flux by performing *in vivo* CLE in the small intestine of mice. They also followed these IBD patients for a year and found a high correlation of flares with barrier dysfunction. Lastly, Lim *et al* examined patients with IBD, and discovered barrier dysfunction in the duodenum of both groups of patients, with leakage of fluorescein into the duodenal lumen, which may help elucidate the pathogenesis of IBD [41]. In line with this, CLE has also been found to have the potential to predict therapeutic response in Crohn's patients. Atreya *et al* used a fluorescent antibody to membrane-bound Tumor Necrosis Factor (mTNF) to detect intestinal mTNF cells, which correlated with clinical response to anti-TNF therapy [42].

BILIARY

Indeterminate biliary strictures present a challenge to physicians, often prompting Endoscopic Retrograde Cholangio Pancreatography (ERCP), which unfortunately features a relatively low sensitivity of histological diagnosis. The use of pCLE via a Cholangio Flex miniprobe (Mauna Kea Tech, Paris, France) which can be inserted into a standard cholangioscope has proved useful in diagnosing these indeterminate strictures [43-45]. Meining *et al* found a sensitivity and specificity of 98% and 67%, respectively in detecting cancerous strictures with pCLE and found a significantly higher accuracy (90% vs. 73%) than standard ERCP with biopsy [46].

PANCREAS

Endoscopic Ultrasound with Fine Needle Aspiration (EUS-FNA) is a commonly used modality in the examination of pancreatic neoplasms, but is hindered by inadequate diagnostic yield. Konda *et al* has started using needle-based CLE (nCLE), which incorporates a submillimeter probe that can be passed through a 19-gauge EUS-FNA needle [47,48]. Examining cystic neoplasms, they found an association of epithelial villous structures with pancreatic cystic neoplasms with a sensitivity of 59% and specificity of 100% [48].

LIVER

An example of CLE application at the cellular level was demonstrated by Goetz et al, who continuously followed hepatocytes in an intact liver *in vivo* for up to 4 hours to view real-time the process of apoptosis. Using acriflavine as the contrast agent, cellular changes, from the initial vesicle formation to the swelling of the cell to become round and lose hexagonal shape to finally cell shrinkage, were clearly seen. Imaging also revealed nuclear membrane loss, nuclear blebbing, and pykinosis with brightly stained nuclei, further demonstrating the ability to follow individual cells at a subcellular resolution [49].

FUTURE CONSIDERATIONS

Molecular CLE, the use of molecular probes to target specific antibodies or peptides, has recently gained attention for its potential applications, particularly with regards to targeting neoplasms, estimating drug affinities to organs, and improving diagnostic accuracy. First used *in vivo* by Hsiung et al, a specific heptapeptide was conjugated to fluorescein, and CLE was used to

show that the fluorescein-conjugated peptide was more strongly bound to dysplastic colonocytes [50]. Sturm *et al* produced similar results, but with esophageal neoplasia [51]. Subsequent studies have expanded this technology to target specific receptors prominent in neoplasms, such as human epithelial growth factor receptor 2 (HER-2) and epidermal growth factor receptors (EGFR) [52-55]. Neumann *et al* and Cârţână *et al* used fluorescently labeled antibodies for MUC2 and CD31, respectively, to target Barrett's Esophagus and Colorectal adenocarcinoma [56,57]. Future studies are needed to evaluate this application further *in vivo* in humans and hopefully include more cancer-specific antibodies and peptides to ultimately improve patient outcomes.

Another application that may play a prominent role in the future of CLE is the measurement of drug affinity in organs and the subsequent ability to assess uptake and efficacy. Hoetker *et al* and Goetz *et al* studied cetuximab, a monoclonal antibody specifically blocking the extracellular component of the EGFR, in murine xenograft models, and showed that a stronger tumor signal for cetuximab was associated with slower tumor progression in gastric cancer and colorectal cancer, respectively [58,59]. Similarly, Foersch *et al* fluorescently labeled bevacizumab, an anti-VEGF (Vascular Endothelial Growth Factor) medication, to assess its uptake in human tissue from patients with colorectal cancer [60].

LIMITATIONS

While CLE carries the potential to perform targeted biopsies and decrease the total number of biopsies needed for neoplastic detection and surveillance, there remain a number of practical and technical obstacles that currently prohibit the replacement of histopathology with CLE. A key limitation of CLE is that it does not allow for full molecular characterization of tissue, as needed for example in the accurate classification of a poorly differentiated malignancy. As described above, molecular CLE will permit detection of specific antibodies and peptides and thereby help diagnosis of neoplasm, but the cost and labor-intensive methodology involved in each molecular tag will likely prevent full molecular classification comparable to that which is so commonly performed with current histopathology. Add into the scrutiny that each molecular probe will receive from the FDA, it remains doubtful that full molecular characterization will be performed via CLE. In line with this, while CLE diagnostic criteria for Barrett's Esophagus such as the Mainz and Miami criteria have been developed, most neoplasias have no consensus for CLE diagnostic criteria, further clouding the diagnostic potential of CLE.

Another fundamental limitation with CLE lies with its inability to penetrate beyond the mucosal layer of the intended tissue, effectively preventing diagnosis of submucosal invasion. Depth of penetration (250 μm) could be minimally enhanced by 2 photon techniques, especially if new infrared fluorophores are developed and proven to be safe *in vivo*. Increased penetration would correspond to decreased lateral resolution with current technology, which accounts for the differences between eCLE and pCLE.

Lastly, there have not yet been enough human *in vivo* studies performed to reliably determine the overall efficacy and safety profile of CLE. Thus far, there do not appear to be any immediate complications of CLE that differ from standard endoscopy complications, but the number of CLE procedures performed remains low given its relative novelty. Additionally, the effect of molecular probes in terms of safety is unclear at this time, but raises the possibility of triggering systemic immunological side-effects given systemic/topical administration of these agents.

Ultimately, large, prospective, multicenter trials are needed to fully elucidate the diagnostic potential and advantage of CLE in a variety of neoplasias. CLE, for all intents and purpose, has not entered clinical practice yet, but promises the ability to rapidly detect neoplasia at an early stage and facilitate clinical decision-making. It remains to be seen whether CLE will ever be able to fully replace histopathology.

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