Advanced Endoscopic Imaging to Predict Clinical Outcomes in Inflammatory Bowel Disease

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KEYWORDS

• Confocal laser endomicroscopy • Crohn's disease • Endocytoscopy
• Endoscopic imaging • Inflammatory bowel disease • Ulcerative colitis

KEY POINTS

- Confocal laser endomicroscopy (CLE) is a high-resolution imaging technology that enables imaging of the mucosa in real time during endoscopy.
- CLE enables functional assessment of the integrity of the intestinal barrier, and studies have shown that barrier dysfunction in patients with inflammatory bowel disease (IBD) correlates to clinical disease behavior and long-term disease outcome.
- Barrier healing is associated with decreased risk of disease progression of IBD, with superior predictive performance compared with endoscopic and histologic remission.
- Endocytoscopy and virtual chromoendoscopy are useful in predicting relapse in patients with IBD and appear to be more accurate than the standard endoscopy.

INTRODUCTION

Advanced endoscopic imaging including high-definition endoscopy, confocal laser endomicroscopy (CLE), and endocytoscopy (EC) serve as an adjunct to predict clinical outcomes in inflammatory bowel disease (IBD). CLE provides real-time highly magnified (~10,000 fold) in vivo images of the gastrointestinal mucosa, comparable to histopathology from biopsy.[1–3] CLE uses tissue illumination after the application of topical (acriflavine hydrochloride/cresyl violet) or systemically (fluorescein sodium) administered fluorescein agents with low-power (488 nm) laser. It is integrated into

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standard high-resolution gastroscope/colonoscope (Pentax Medical, Tokyo, Japan) or CLE catheter-based through the working channel of a standard endoscope (Cellvizio; Mauna Kea Technologies, Paris, France). CLE allows the assessment of histologic information in vivo in real time and allows targeted biopsy. CLE has been shown to predict relapse in patients with IBD.[4–6] EC (Olympus, Tokyo, Japan) uses the technique of contact light microscopy and enables in vivo image magnification of the superficial mucosal layer up to 1400 fold, thereby allowing visualization of crypt architecture and microvasculature.[7]

Clinical remission in IBD does not always correlate with endoscopic or histologic remission,[8] and microscopic/histologic changes of inflammation may persist with endoscopic remission.[9,10] CLE and EC have the potential to diagnose microscopic inflammatory changes, especially in patients with IBD with clinical and endoscopic remission, thereby improving diagnosis and predicting relapse. In this review, we focus on the role of CLE, EC, and virtual chromoendoscopy (VCE) in the evaluation of the gastrointestinal epithelial barrier function and predicting clinical outcomes including relapse and monitoring of response to therapy in patients with IBD.

Epithelial Barrier Function

The crypt villous architecture forming the gastrointestinal barrier is constituted by the tight and adherent junction between the intestinal epithelial cells. These cells undergo turnover, and the shed epithelial cells are replaced by the stem cells at the bottom of the crypts.[11] Normal intestinal mucosa consists of a honeycomb-type vascular architecture in the lamina propria underneath the crypts. Cell shedding causes defects in the gut epithelium called gaps.[12] Microerosions occur when more than one adjacent cell is lost from a single site with exposure to lamina propria.[4] Deficiency in the gastrointestinal epithelial barrier function is associated with disease activity in inflammatory conditions.[13–16] Increased permeability of the gut epithelium is also shown to be a prognostic indicator of relapse in IBD.[17] Assessment of the integrity of the epithelial barrier by fluorescein leakage, and microscopic assessment of crypt architecture and microvascular pattern form the basis for the advanced endoscopic techniques in patients with IBD.

Confocal Laser Endomicroscopy

The laser beam from the confocal laser microscope generates an excitation wave of 488 nm, which penetrates the mucosa up to a depth of 250 μm to obtain the optical sections of 7 μm. Topical or intravenous fluorescent dyes are used in addition to aid in further microscopic assessment of the intestinal mucosa.

Confocal Laser Endomicroscopy Scoring Systems in Inflammatory Bowel Disease

Multiple studies have investigated the features of CLE to detect inflammation in IBD. These include crypt architectural abnormalities, microvascular alterations, inflammatory cell infiltration in lamina propria, and increased vascular permeability as evidenced by fluorescein leakage in lamina propria. Additionally, markers of inflammation include evidence of microerosions and a decrease in goblet cells. Several scores have been developed to objectively quantify inflammation by CLE, the widely used ones include the Watson score, Chang-Qing score, endoscopic mucosal healing (eMH) score, and Crohn's Disease Endomicroscopic Activity Score (CDEAS), and confocal laser Endo microscopy for Histologic Healing in Ulcerative colitis index. **Table 1** summarizes the various scores used in patients with IBD for defining inflammation.

Table 1
Detection of inflammation by confocal laser endomicroscopy in inflammatory bowel disease

Study/Author	Type of IBD	CLE Parameters/Grading	Other Defining Parameters
Watson et al,[4] 2012	UC and CD	Grade 1: No leakage of fluorescein (normal) Grade 2: Presence of fluorescein in the lumen but no microerosions Grade 3: Fluorescein in the lumen and microerosions in the epithelium	Microerosion is defined when the lamina propria is exposed to the lumen with multiple cells being shed per site Grade 2 represents functional defect Grade 3 represents structural defect
Neumann et al,[18] 2012 (CDEAS)	CD	Crypt number, crypt distortion, microerosions, cellular infiltrate, vascularity, and number of goblet cells	
Chang-Qing et al,[1] 2014	UC	*A*: Regular shaped and distributed crypts (normal) *B*: Irregular in shape and distribution but intact crypts (chronic inflammation) *C*: More dilated crypts with fluorescein leakage into the lumen, with the epithelium disrupted in some crypts (acute inflammation) *D*: Most of the crypts are disrupted (acute inflammation)	Based on fluorescein leakage into the crypt lumen and crypt architecture Colonic crypts were classified into 4 grades A, B, C, and D
Hundorfean et al,[3] 2017 (eMH score)	UC	1. Crypt number >5/field = 0 $\leq$5/field = 1 2. Crypt lumen deformity Normal appearance, (small, round) = 0 Enlarged, hypertrophic crypt lumen = 1 3. Crypt lumen leakage Absent = 0 Present = 1 4. Perivascular leakage Absent = 0 Present = 1 {Scores 0–4}	An eMH <1 would correspond to complete mucosal healing, whereas a score of 4 would mean a maximum inflammation degree, indicating relapse

Abbreviations: CD, Crohn's disease; CLE, confocal laser endomicroscopy; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Neumann and colleagues[18] proposed a CDEAS (endomicroscopic activity score) score to assess Crohn's disease (CD) activity in vivo by CLE. In this study, 54 patients with CD (both active and quiescent) were compared to controls. They found that a significantly higher proportion of patients with active CD had increased colonic crypt tortuosity, enlarged crypt lumen, microerosions, augmented vascularization, and increased cellular infiltrates within the lamina propria. In quiescent CD, a significant increase in crypt and goblet cell number was detected, when compared to controls. CDEAS score included 6 parameters including crypt number, crypt distortion, microerosions, cellular infiltrate, vascularity, and number of goblet cells.

Confocal Laser Endomicroscopy in Predicting Relapse in Inflammatory Bowel Disease

CLE is also useful in predicting relapse, steroid-free remission, hospitalization, and surgery in patients with IBD. Combining CLE with conventional endoscopy can help in the identification of future relapse, especially in patients with normal conventional endoscopic findings that can have a major clinical impact in management. The studies that analyze the role of CLE in predicting relapse predominantly in quiescent IBD or patients in remission are summarized in **Table 2**.

The Watson score has been studied as a CLE parameter to predict relapse in patients with IBD. The Watson score is based on cell shedding and barrier loss grading as per fluorescein leakage. Watson score has 3 grades: (1) normal, cell shedding confined to single cell per site; (2) functional defect, cell shedding confined to a single cell with fluorescein leakage into the lumen; and (3) structural defect, multiple cell shedding causing exposure of lamina propria to the lumen (microerosion) with fluorescein leakage. In a prospective study, the Watson grade of 2 or 3 was shown to predict relapse in both ulcerative colitis (UC) and CD with a sensitivity, specificity, and accuracy of 62.5%, 91.2%, and 79%, respectively. In this study, patients with IBD (47 UC and 11 CD) in clinical remission were found to have increased cell shedding with fluorescein leakage that predicted future relapse. Interestingly terminal ileum was the site incorporated for the study in these patients.

In a study by Buda and colleagues,[6] both crypt architectural changes and epithelial barrier function loss were found in patients with UC in remission and predictive of relapse during a 12 month follow-up. In this study, 19 patients with UC in clinical and endoscopic remission were compared to 19 controls. Up to one-third of the patients with UC in clinical and endoscopic remission were shown to have changes in microvascular anatomy and function (characterized by tortuous microvessels with irregular distribution and loss of the normal honeycomb pattern, with increased fluorescein leakage by CLE). Seven out of 9 patients with UC (37%) had disease flare during a 12 month follow-up. A composite score using pericrypt fluorescence and crypt diameter was able to predict relapse during a 12 month follow-up.

Turcotte and colleagues[19] prospectively analyzed 21 patients with CD and 20 patients with UC and showed that epithelial gap density assessed by CLE was predictive of the need for hospitalization or surgery. The site of examination was normal-appearing terminal ileum, about 10 cm from the ileocecal valve. The gap density was calculated as the number of epithelial gaps per 100 epithelial cells counted in the adequately imaged villi, normal gap density was defined as 6% or less (using a control population from their previous study). They found that gap density was found to be a significant predictor for severe clinical disease (requiring hospitalization or surgery), with a hazard ratio of 1.10 associated with each increase of 1% in gap density. However, they did not find any significant correlation between gap density and the number of flares.

Table 2
Studies in confocal laser endomicroscopy predicting relapse

Study	Patients Assessed	CLE Parameters	Site Assessed by CLE	Prediction of Relapse	Definition of Relapse or Other Outcomes
Buda et al,[6] 2014	19 UC (in remission) 19 Control	Pericrypt fluorescence and crypt diameter	All colonic segments	Patients with pericrypt fluorescence >3100 pixel and a crypt diameter >90 μm had a significantly increased probability of presenting a disease relapse	Relapse was defined as a clinical activity index (CAI) ≥3 and abnormal mucosa at endoscopy
Watson et al,[4] 2003	47 UC and 11 CD in clinical remission	Watson grading for fluorescein leakage	Terminal ileum	Watson grade of 2 or 3 had a sensitivity of 63% and a specificity of 91% and accuracy of 79% for the prediction of relapse	CDAI >150 or a CAI >3
Chang-Qing et al,[1] 2014	43 UC in remission	Chang-Qing scale	Sigmoid colon and rectum	Higher grades of inflammation (C, D) were found to have higher rates of relapse. The sensitivity, specificity, and accuracy of CLE in predicting relapse were 64%, 88.9%, and 74.4%, respectively Relapse rates among the 4 grades were significantly different ($P < .001$)	A score of 5 or more of on Simple Clinical Colitis Activity Index during follow-up

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Table 2
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Study	Patients Assessed	CLE Parameters	Site Assessed by CLE	Prediction of Relapse	Definition of Relapse or Other Outcomes
Turcotte et al,[19] 2012	21 CD and 20 UC (both active and inactive disease)	Gap density (number of epithelial gaps per 100 epithelial cells) *Normal* $\leq$*6%*	Terminal ileum	Gap density was found to be a significant predictor for risk of events (hospitalization/ surgery), with a hazard ratio of 1.10 associated with each increase of 1% in gap density No significant correlation between gap density and clinical flare in patients without events	IBD-related hospitalization or surgery and symptomatic flares

Abbreviations: CLE, confocal laser endomicroscopy; IBD, inflammatory bowel disease; UC, ulcerative colitis.

In another study,[1] it was shown that CLE is comparable to conventional histology in predicting relapse in UC. In this study, 43 patients with UC were assessed using clinical, histologic, and CLE findings. They used 4 grades (A–D) of inflammation based on CLE assessment of crypts, also referred to as the Chang-Qing scale. The patients with higher grades of inflammation (C and D) were found to have higher rates of relapse during the 12 month follow-up period. The sensitivity, specificity, and accuracy of CLE in predicting relapse were 64%, 88.9%, and 74.4%, respectively. In this study, CLE was assessed in the distal colon, to avoid the terminal ileum intubation failure.

Confocal Laser Endomicroscopy to Assess Response to Therapy in Inflammatory Bowel Disease

In addition to its role in the prediction of relapse in quiescent IBD, CLE has the potential to assess response to therapy in active IBD as demonstrated by the several studies summarized in **Table 3**. Different studies used different parameters to define clinical outcomes, including hospitalization rates, need for surgery, need for steroids or medical escalation in therapy, and incidence of transmural lesions in CD. CLE parameters also varied in the studies; however, most studies employed some features of gut barrier dysfunction.

Hundorfean and colleagues[3] validated an eMH score using CLE to assess response to infliximab in patients with UC. Their study evaluated 30 patients with UC of whom 23 had moderate-to-severe disease activity based on the Mayo score. CLE procedures were done before and 6 to 8 weeks after 3 infusions with infliximab, and the patients were longitudinally followed for 3 years. Their study was very methodical with a comparison of CLE images with regular histopathology acquired from the same sites. The eMH score used 4 indices including crypt numbers, crypt lumen deformity, crypt lumen leakage, and vascular leakage with a score ranging from 0 to 4. The patients were categorized based on the eMH scores as mucosal healing (MH; eMH <1), responders (eMH <2), and nonresponders (eMH ≥ 2) during the follow-up CLE after infliximab. The eMH score showed high values for sensitivity, specificity, and accuracy: 100% (95% confidence interval [CI], 15.81%–100%), 93.75% (95% CI, 69.77%–99.84%), and 94.44%, with a good correlation with the histologic score (Gupta index) as well as endoscopic activity score (endoscopic Mayo subscore). The follow-up at 3 years revealed lower rates of hospitalization, steroid need, and surgery need for responders, with all MH patients (eMH scores <1) having a long-lasting clinical remission and resection-free survival.

In another study, Karstensen and colleagues[20] studied 22 patients with UC and compared baseline CLE features to those who needed medical treatment escalation after 6 to 8 weeks of therapy. Baseline CLE features of fluorescein leakage, microerosions, tortuosity of the crypts, distortion of the crypts openings, presence of inflammatory infiltrates, and decreased crypt density were significantly higher in active UC (than inactive disease and control). About half of the above parameters showed improvement with medical escalation. Interestingly, fluorescein leakage, which is a major determinant of epithelial barrier function, was not one of them.

Tonitini and colleagues,[21] in their multicenter study of 49 patients with CD, found that the CLE parameters of focal cryptitis and crypt architecture abnormality were able to predict increased incidence of medical treatment escalation ($P < .001$; relative risk [RR] = 3.27) and transmural lesions ($P = .025$; RR = 1.70) during 1 year follow-up. Treatment escalation was defined by the use of systemic steroids, thiopurines, methotrexate, or biologic agents. Though they used only 2 CLE parameters in their study, this was more predictive of the clinical outcomes than the CD endoscopic index of severity and CD activity index (CDAI).

Table 3
Studies in confocal laser endomicroscopy for treatment response

Study	Patients Assessed	CLE Parameters	Timing of CLE	Sites Assessed	Treatment Used	Treatment Response and Other Findings
Hundorfean et al,[3] 2017	23 active UC	eMH scores	Before and after 3 anti-TNF therapy sessions	2 colorectal areas with macroscopically significant lesions The follow-up CLE was done in the same 2 localizations	3 infusions with infliximab (5 mg/kg body weight wk 0, 2, 6, and then every 8 wk	The patients were categorized based on the eMH scores as MH (eMH <1), responders (eMH <2), and nonresponders (eMH $\geq$2)—after infliximab eMH score showed high values for sensitivity, specificity, and accuracy: 100%, 93.75%, and 94.44% with good correlation to histologic and endoscopic score All MH patients (eMH <1) having a long-lasting clinical remission and resection-free survival at 3 y
Kartstensen et al,[20] 2016	22 UC patients in clinical relapse	Crypts, fluorescein leak	Baseline and 6–8 wk after medical escalation	4 different colonic sites	Treatment escalation included oral corticosteroids, infliximab, vedolizumab, azathioprine, 5-aminosalicylic acid	Baseline frequency of fluorescein leakage, microerosions, tortuosity of the crypts, distortion of the crypts openings, presence of inflammatory infiltrates, and decreased crypt density were significantly higher in active UC compared with inactive UC and control After medical treatment, significant improvement was noted in crypt tortuosity, distortion, and density

Tonitini et al,[21] 2018	49 CD patients	Focal cryptitis and crypt architecture abnormality	-	Multiple biopsy specimens were taken from both macroscopically normal and abnormal mucosa after confocal examination	Treatment escalation was defined by the use of systemic steroids, thiopurines, methotrexate, or biologic agents	Baseline CLE parameters of focal cryptitis and crypt architecture abnormality were able to predict increased incidence of medical treatment escalation ($P < .001$; RR = 3.27) and transmural lesions ($P = .025$; RR = 1.70)
Auzoux et al,[24] 2019	25 postsurgical CD patients	Watson scoring	Within 6–12 mo postsurgery	Neoterminal ileum (in the 10 cm above the anastomosis)	NA	Watson's score was significantly higher in patients with endoscopic recurrence ($P = .03$); and clinical relapse ($P = .04$), when compared to endoscopic and clinical remission
Atreya et al,[22] 2014	25 active CD	Fluorescence-labeled antibodies	Prior to initiation of adalimumab (baseline)	Most inflamed area on endoscopy	Adalimumab	High numbers ($\geq$20 cells) of mTNF-expressing cells per confocal image demonstrated a higher probability of clinical response to subsequent adalimumab therapy than patients with low numbers of $mTNF^+$ cells (92% vs 15%). The sensitivity, specificity, and accuracy for the prediction of therapeutic responses were 92%, 85%, and 88%, respectively

Abbreviations: CD, Crohn's disease; CLE, confocal laser endomicroscopy; IBD, inflammatory bowel disease; TNF, tumor necrosis factor; UC, ulcerative colitis.

Though most of the studies thus far have assessed the use of CLE in IBD by the gut barrier leakage and alteration in crypt/microvascular architecture, Atreya and colleagues[22] used an objective method to assess disease response using labeled antibodies to tumor necrosis factor (TNF) in active patients with CD undergoing treatment with adalimumab. Here, fluorescein isothiocyanate-labeled adalimumab (sprayed onto the inflamed mucosa during colonoscopy, followed by CLE) was used to identify the expression of membrane bound tumor necrosis factor (mTNF) expressing cells before the initiation of adalimumab therapy. They hypothesized that the identification of such mTNF-expressing cells in the mucosa may be used to identify patients responding to subsequent anti-TNF therapy. Subsequently, after adalimumab therapy, conventional white light endoscopy was used to assess the mucosal lesions, with a median follow-up of 52 weeks. They found that patients with high numbers of mTNF-expressing cells per confocal image (cutoff $\geq$20 cells per confocal image) demonstrated a higher probability of clinical response to subsequent adalimumab therapy than patients with low numbers of $mTNF^+$ cells (92% vs 15%). The sensitivity, specificity, and accuracy for the prediction of therapeutic responses were 92%, 85%, and 88%, respectively. This study findings have suggested the potential use of molecular endoscopy for personalized medicine.

A recent prospective study from Belgium has shown that residual CLE abnormalities persist in all patients with IBD (n = 72, UC and CD) in endoscopic remission (n = 37) while on biologic therapy (anti-TNF and vedolizumab). About 18.9% of patients had a relapse at a median 33.7 months follow-up that was not associated with any clinical, biologic, histologic, or CLE findings. Hence, the importance of residual CLE changes for patients in endoscopic remission on biologic therapy remains uncertain at this point.[23]

The role of CLE in the postsurgical evaluation of IBD is not well established with only limited data in literature. Auzoux and colleagues[24] used the Watson scoring system to evaluate the disease recurrence in postoperative patients with CD. In this pilot study, 25 patients with CD within 6 to 12 months of surgery were assessed using Watson scoring by CLE and standard white-light endoscopy (Rutgeerts scale) and further monitored endoscopically and clinically for a median of 38 months. They found out that Watson's score was significantly higher in patients with endoscopic recurrence (P = .03); and clinical relapse (P = .04), when compared to endoscopic and clinical remission. Though this study seems promising, future prospective trials with longer follow-ups are warranted.

In a prospective trial to systematically study the endomicroscopic barrier healing on IBD disease outcomes, the Endoscopic Remission, Histologic Remission and Barrier Healing for Predicting Disease Behavior in IBD trial, patients with IBD in clinical remission were prospectively included and closely monitored during long-term follow-up for greater than 2 years.[25] At baseline, patients with IBD in clinical remission underwent ileocolonoscopy with the assessment of intestinal barrier function by CLE. During subsequent follow-up, patients were closely monitored for clinical disease activity and the occurrence of major adverse outcomes (MAOs) defined as disease flares, IBD-related hospitalization or surgery, and initiation or dose escalation of systemic steroids, immunosuppressants, small molecules, or biological therapy. During a mean follow-up of 35 (CD) and 25 (UC) months in 100 patients with CD and 81 patients with UC, 73% of patients with CD and 69% of patients with UC experienced at least 1 MAO. The probability of MAO-free survival was significantly higher in patients with IBD with endoscopic remission compared with endoscopically active disease. In addition, histologic remission predicted MAO-free survival in patients with UC but not CD. However, barrier healing on CLE was superior to endoscopic and histologic remission for

predicting MAO-free survival in both UC and CD. To summarize, CLE-based dynamic monitoring of the intestinal barrier appears to be a predictive and risk-stratifying tool for patients with IBD.

Endocytoscopy in Inflammatory Bowel Disease

Technique

Endocytoscope (contact microscope) is usually integrated into a regular endoscope, allowing for ultramagnification of the mucosal layer and providing real-time microscopy. Topical contrast agents like methylene blue and crystal violet that stain the cells are used to acquire images. Magnification up to 1400 fold can be achieved (Fig. 1A–C).

Role of endocytoscopy in inflammatory bowel disease: assessment of inflammation and clinical outcomes

Studies in EC are limited in literature when compared to CLE. Most of the studies[10,26–28] describe a strong correlation of endocytoscopic and histologic findings. Few studies[29–31] have analyzed the clinical outcome prediction based on EC findings. Most of the studies involved patients with UC (Table 4). The most widely used EC scoring system to assess inflammation is the endocytoscopy system score (ECSS).[7] ECSS (score 0–6) is based on crypt shape (0–3), distance between crypts (0–2), and visibility of microvasculature (0–1).

Iacucci and colleagues[10] conducted a prospective study involving 29 patients with UC after medical treatment or for surveillance showing a strong correlation between EC and histology. They found that ECSS correlated strongly with the histologic scoring but poorly with endoscopic scoring. ECSS total score of 3 or less predicted histologic remission with specificity of 86%, sensitivity of 64% and an accuracy of 80%.

In another retrospective study involving 52 patients with UC, Maeda and colleagues[26] utilized EC with narrow-band imaging (NBI) and showed that endocytoscopic narrow-band imaging (EC-NBI) finding of capillaries in the rectal mucosa strongly correlated with histologic inflammation, and similar studies showed strong correlation between histology and EC.[27,28]

Vitali and colleagues[29] validated another endocytoscopic scoring system called ErLangen Endocytoscopy in ColiTis (ELECT; Table 5) and predicted clinical outcomes in their study of 46 patients with UC. After baseline EC patients were followed by periodically every 4 to 8 weeks while on biologics or other therapy to assess MAOs. They found that about 27% (7 out of 26) of the patients classified as having endoscopic remission were noted to have microscopic inflammation by ELECT score, while the correlation between histopathology and EC was strikingly similar to about 96% (22 out of 23). EC using ELECT score was shown to have an accuracy of 67.4% and

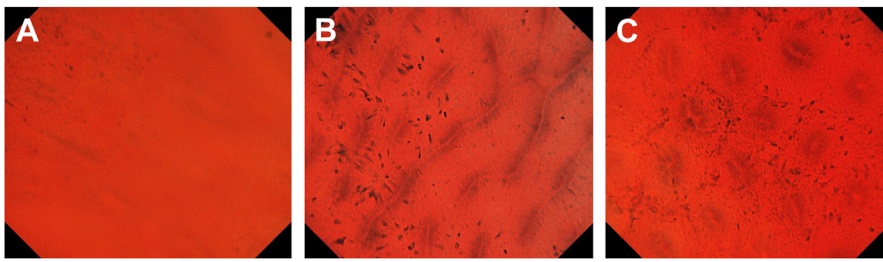

Fig. 1. Endocytoscopy images in UC. (*A*) Infiltration of the cells between the crypts. (*B*) Elongated crypts architecture. (*C*) Irregular crypts. (Image Courtesy of Partha Pal, MD.)

Table 4
Studies of endocytoscopy in inflammatory bowel disease

Study	Patients Assessed	Scoring System	Sites Assessed	Outcomes Measured	Major Findings
Iacucci et al,[10] 2021	29 patients with CD	ECSS	Inflamed sites as marked by white light endoscopy and NBI	Histologic remission defined by Nancy histologic index (NHI) $\leq$1, and Robarts histologic index (RHI) $\leq$3	ECSS had very strong correlation with histologic remission as defined by NHI r = 0.86 (95% CI, 0.42–0.98) and RHI r = 0.89 (95% CI, 0.51–0.98)
Vitali et al,[28] 2023	46 patients with UC	ELECT	Rectum and sigmoid	(1) Disease flare, (2) hospitalization, (3) surgery, and (4) need for initiation or escalation therapy	ELECT score-accuracy of 67.4% and positive and negative predictive values of 66.7% and 68.2%, in predicting clinical outcomes
Maeda et al,[30] 2020	218 patients with UC in remission but risk for relapse (Mayo endoscopic score of 1)	218 patients with UC in remission but risk for relapse (mayo endoscopic score of 1)	Target area based on conventional endoscopy	Clinical relapse-free rates	Endocytoscopic intramucosal capillary network changes and crypt architecture abnormalities can predict relapse
Maeda et al,[25] 2015	52 patients with UC	EC-NBI	Rectal mucosa	Diagnostic ability of EC-NBI	EC-NBI finding of capillaries in the rectal mucosa strongly correlated with histologic inflammation

Ueda et al,[29] 2018	32 UC (mild–moderate disease)	EC-A, B, C, D based on crypt architecture	Rectum	Disease relapse	EC stratification based on crypt architectures in patients with UC can predict disease relapse
Takishima et al,[31] 2022	120 patients with UC in endoscopic remission (Mayo endoscopic score 0)	Goblet appearance	Rectal mucosa under NBI	Clinical relapse	Relapse rate was significantly increased in the depleted goblet group compared to preserved goblet group ($P = .02$)

Abbreviations: CD, Crohn's disease; CE, chromoendoscopy; EC, endocytoscopy; ECSS, endocytoscopy system score; ELECT, ErLangen endocytoscopy in ColiTis; HDE, high-definition endoscopy; IBD, inflammatory bowel disease; NBI, narrow-band imaging; UC, ulcerative colitis.

Table 5
ELECT ErLangen endocytoscopy in ColiTis score

Study/Author	Type of IBD	Score Parameters	Scoring	
Vitali et al,[28] 2023	UC	Crypt shape	Round or oval crypts	0
			Irregular, distorted	1
			Disruption or loss.	2
		Crypt distance	Normal: difference between crypts <2 crypt diameter	0
			Increased (>2 crypt diameter)	1
		Vascular architecture	Round and small-caliber vessels surrounding crypts	0
			Tortuous or crowded vessels, erythrocyte leakage, or vascular dilation	1
		Inflammatory cell infiltrate (in lamina propria)	Absent	0
			Present	1
		Crypt abscess	Absent	0
			Present	1
		Total score	0–6	

Abbreviations: ELECT, ErLangen endocytoscopy in ColiTis; UC, ulcerative colitis.

positive and negative predictive values of 66.7% and 68.2% in predicting major adverse events free course of the disease, better than standard endoscopy.

Ueda and colleagues,[30] in their study of 32 UC patients with mild-to-moderate disease, stratified the EC scores into 4 simple grades EC-A, B, C, and D based on the crypt architecture (regular, irregular, distorted, and disruptive) and compared it with regular histopathology and to predict relapse. They found that their EC stratification was significantly associated with pathognomonic microscopic histologic features for UC. There were significant differences in the remission rate among the EC groups, with 75% relapse occurring in the EC-D group and no relapse in the EC-A group.

Takishima and colleagues,[31] in their retrospective analysis of 120 patients with UC in endoscopic remission, found that the rectal mucosa goblet appearance on EC utilizing NBI was able to predict outcomes. They stratified their patients into 2 groups of preserved and depleted goblet groups, with a finding of a significantly higher cumulative clinical relapse rate in the depleted group, during a median follow-up of 549 days.

Chromoendoscopy for outcome prediction

VCE has demonstrated high accuracy in identifying mucosal inflammation, with a strong correlation with histology. VCE is a simple "push-of-a-button" technique that is readily available during the endoscopic examination. Thus, compared to traditionally used dye-based chromoendoscopy, VCE theoretically offers the advantage of dye-enhanced mucosal imaging without the efforts in time and costs of applying contrast agents during the endoscopic examination. NBI (Olympus, Japan) employs red–green–blue filters to modify white light endoscopy. More recently, Olympus has released 2 new modes, texture and color enhancement imaging (TXI) improving the structure and brightness of the endoscopic images and red dichromatic imaging with the purpose to enhance the blood vessels and bleeding.

Data are available in the literature in patients with UC employing VCE for predicting disease outcomes. The relationship between magnified NBI endoscopy and prognosis

was evaluated in 52 patients with UC in clinical remission with a Mayo endoscopic score of 0 or 1.[32] These patients were assessed with NBI at enrollment and after a 1 year follow-up, the findings were stratified according to vessel appearance. Patients with NBI pattern of bare branches showed a higher risk of relapse (odds ratio 14.2) than those showing a honeycomb pattern.[32] Subsequently, the Paddington International Virtual Chromoendoscopy score (PICaSSO) was developed and it predicted outcomes in UC.[33] A large prospective study evaluating a cohort of 307 patients with UC showed that a PICaSSO score of 3 or less predicted MAOs at 6 and 12 months better than a PICaSSO score greater than 3.[34] In the external validation study, a PICaSSO score of 3 or less was associated with increased relapse-free survival rates than a score greater than 3.[35] The usefulness of TXI was studied recently, and a TXI score of 2 was associated with disease relapse.[36] In this prospective observational study, 146 patients with UC in endoscopic remission were evaluated with white light endoscopy and TXI. Patients with accentuated redness and poor visibility of deep vessels at TXI had significantly lower UC relapse-free rates than patients with no redness or accentuated redness alone, suggesting a possible role of TXI in guiding treatment intensification.[36]

SUMMARY

CLE can complement conventional endoscopy in patients with quiescent IBD to predict future relapse, and in monitoring treatment response in patients with active disease. CLE can identify gut barrier dysfunction (fluorescein dye leakage and microerosions) and other crypt and vascular architectural changes. EC, a promising advanced endoscopic technique has been shown to correlate with histopathological biopsy findings and to predict the clinical outcomes in IBD, though more studies are needed to ascertain its role. VCE is exciting as it is a simple "push-of-a-button" technique that is readily available and, compared to CLE and EC, offers advanced imaging without the efforts and costs of applying contrast agents. These advanced endoscopic imaging techniques have revolutionized the approach to patients with IBD, and the opportunity to integrate with artificial intelligence in the future would likely change outcomes in patients with IBD in the future.

CLINICS CARE POINTS

- If expertise for CLE is available, employ CLE to predict IBD outcomes. CLE-based dynamic monitoring of the intestinal barrier appears to be a predictive and risk-stratifying tool for patients with IBD and more important than endoscopic and histologic healing.
- EC appears to be more of a research tool to evaluate for histologic remission.
- VCE is a simple "push-of-a-button" technique that is readily available during the endoscopic examination. VCE is simple and useful without the efforts in time and costs of applying contrast agents during the endoscopic examination and can predict histologic activity accurately.

DISCLOSURES

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