Chromoendoscopy and Advanced Imaging Technologies for Surveillance of Patients with IBD

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Abstract: Inflammatory bowel disease patients with long-standing colitis have an increased risk of colorectal cancer. The high rate of interval colitis-associated cancers among patients who adhere to a nontargeted, random biopsy surveillance strategy underlies the need for improved methods of early dysplasia detection. Compelling evidence supports the efficacy of chromoendoscopy for increasing the detection rate of dysplasia; however, this technology is currently underutilized in the clinical setting. Other contrast-based technologies—including confocal laser endomicroscopy (Pentax), endocytoscopy, multiband imaging, i-scan (Pentax), and molecular-targeted techniques—show promise in the detection of dysplasia in patients with inflammatory bowel disease. The strategies currently available for identifying patients with dysplasia or colitis-associated cancers remain inadequate and need to demonstrate both cost and time efficiency before they can be adopted in community-based practices.

Although inflammation-mediated cancers comprise only a small subset of colorectal cancers (CRCs), colitis-associated cancers (CACs) can be a dreaded consequence of inflammation and may be life-altering for patients with long-standing colitis. Inflammatory bowel disease (IBD) patients with long-standing colitis have an increased risk of CRC, although the magnitude of this risk is a matter of debate. Patient factors associated with an increased risk of CAC include male gender, young age at ulcerative colitis (UC) diagnosis, and greater colonic extent of inflammation.[1] In patients with pancolitis, the increased CRC risk after 10 years of disease is approximately 0.5–1% per year.[2-7] In a meta-analysis of 8 population-based cohort studies, UC patients had a 2.4-fold increased risk of CRC compared to the general population.[1] Other studies have estimated a higher risk, with up to a 5-fold increased risk of CRC in IBD patients compared to age-matched controls.[8,9] These figures may vary based on patient population factors or, more likely, treatment-related

factors, namely the degree of mucosal healing in patients taking newer medications or the timing of colectomy after detection of dysplasia. Although these figures may fluctuate, the higher-than-expected rate of CRC in IBD patients underlies the importance of screening and surveillance programs for dysplasia in this population.

Dysplasia Surveillance in Patients with Inflammatory Bowel Disease

The approach to dysplasia surveillance in IBD patients has evolved as new technologies and imaging modalities have become available, although, anecdotally, gastroenterologists have been slow to incorporate these innovations into their daily practices. Multiple factors contribute to the difficulty of detecting dysplasia in IBD patients, including the nature of flat dysplasia and the distracting appearance of active colonic inflammation. In addition, endoscopists have for decades had difficulty visualizing dysplastic lesions due to low-definition endoscopic equipment and monitors. Interval detection of CACs has led to the use of a nontargeted, random biopsy surveillance strategy for dysplasia in IBD patients. Intuitively, a greater number of nontargeted biopsies yields more dysplasia detection.[10-12] Currently, the accepted practice for this nontargeted biopsy strategy is to use a jumbo forceps to obtain 4-quadrant biopsies every 10 cm along the colon for a total of at least 32 random biopsies; each quartet of tissue specimens is ideally allocated to an individual biopsy specimen jar for analysis. However, these biopsy benchmark quantities are not routinely met in clinical practice.[10,13-16] Due to the disproportionate number of CACs found in the rectums of UC patients, many practitioners advocate obtaining more than 4 rectal biopsies per 10 cm.[17,18] Mixed results have been reported from studies examining the impact of nontargeted biopsy strategies on early dysplasia detection and CAC mortality.[19-22]

CAC screening guidelines from the American Gastroenterological Association (AGA), American College of Gastroenterology (ACG), Crohn's and Colitis Foundation of America (CCFA), European Crohn's and Colitis Organization (ECCO), and British Society of Gastroenterology (BSG) support the use of random biopsies.[23-30] Nevertheless, random biopsies are limited in their efficacy, as they sample only a small fraction of the mucosa and are time-consuming and costly. The shortcomings of nontargeted biopsies, along with their variable impact on attenuating CAC rates, necessitate the development of new imaging modalities that are inexpensive, easy to learn, time efficient, and tangibly improve patient care. The evidence underlying the importance of chromoendoscopy (CE) and related technologies for addressing these needs are delineated below.

Chromoendoscopy

CE is an enhanced imaging technique in which contrast agents are applied locally to the mucosa during endoscopy to detect mucosal abnormalities. Traditionally, CE is performed via passage of a spray catheter through the working channel of a colonoscope. Prior to contrast application, N-acetylcysteine or acetic acid may be used as a mucolytic agent for mucosal cleansing, and atropine or glucagon may also be used to decrease gut contractions that can cause uneven or misdirected spraying.[31,32] The spray catheter is then advanced to within 1–2 cm of the mucosa, and the contrast agents are applied to segmentally stain the mucosa; excess dye is removed by suction 1 minute after application.[31,33,34] As a time-saving method, some centers advocate the use of a catheter-free washing pump to assist dye spraying.[35] Dysplastic areas may then be identified by observing differences in appearance from the surrounding mucosa, and polypoid lesions can be classified by the Kudo scoring system, which is based on mucosal pit patterns.[36] For polypoid lesions, the Kudo scoring system delineates mucosal pits as normal (round pits, type I), hyperplastic (stellate or papillary pits, type II), or neoplastic (large tubular or roundish pits, type III-L; small tubular or roundish pits, type III-S; branch-like or gyrus-like pits, type IV; or nonstructural pits, type V), as seen in Figure 1.[36,37] Figure 2 demonstrates the ability of CE to enhance the visibility of low-grade colonic dysplastic mucosa in a patient with long-standing UC.

CE agents are divided into 3 categories: contrasting, absorptive, or reactive. The most commonly used contrast agent is indigo carmine, which pools in mucosal grooves to outline intercrypt spaces of the colon, enabling endoscopists to differentiate between dysplastic mucosa and normal or inflamed mucosa. Absorptive dyes include methylene blue, cresyl violet, Lugol's solution, and toluidine blue. It is thought that dysplastic cells have a decreased uptake of these dyes, compared to normal cells, enabling endoscopic distinction of dysplastic areas. However, one concern associated with the use of absorptive agents such as methylene blue is that they can incorporate into the cellular nucleus and may behave like carcinogens.[38,39] Reactive stains, such as Congo red and phenol red, are activated by local differences in pH and have been used to perform CE in the stomach; however, due to the need for pH-dependent reactions, these agents are unlikely to be useful in the colon. The most widely used chromophores for colonic CE are 0.1% methylene blue and 0.1–0.8% indigo carmine.[14,30,31,33]

The first compelling evidence supporting the use of CE in IBD patients was a 2003 study conducted by Kiesslich and colleagues that examined 165 UC patients who were randomized to colonoscopy with methylene-

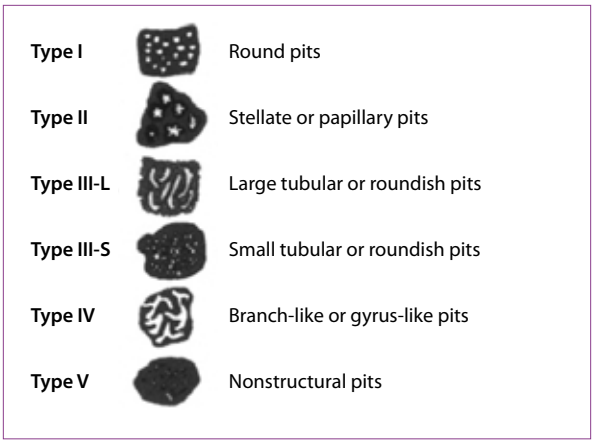

Figure 1. For polypoid lesions, the Kudo scoring system delineates mucosal pits as normal (round pits, type I), hyperplastic (stellate or papillary pits, type II), or neoplastic (large tubular or roundish pits, type III-L; small tubular or roundish pits, type III-S; branch-like or gyrus-like pits, type IV; or nonstructural pits, type V).

Reprinted with permission from Kudo S, et al.[36]

blue CE or conventional white light (WL).[34] CE detected significantly more intraepithelial neoplasia (38% vs 12%; *P*=.003) and significantly more "flat" intraepithelial neoplasia (28.6% vs 4.9%; *P*=.0007) than WL colonoscopy. Additionally, CE was better able to predict the histopathologic degree of colonic inflammation (*P*=.0002) and the extent of active UC (89% vs 52%; *P*<.0001).[34] Other international studies have corroborated an increased dysplasia detection rate associated with the combined use of CE and targeted biopsies.[40,41]

In 2008, Marion and associates conducted a 3-arm study of 102 patients with IBD in which they compared standard surveillance WL colonoscopy with 4 random biopsies every 10 cm, targeted biopsies alone, and methylene-blue CE with targeted biopsies.[42] Due to the technical constraints of performing all 3 procedures in each subject, it was not possible to vary the order of the procedures. During the first pass of the colonoscope, random biopsies were obtained, followed by targeted biopsies; CE was performed during the second pass of the colonoscope. Targeted biopsies with and without dye were associated with significantly higher dysplasia detection rates than traditional random biopsies (9/115 targeted vs 3/115 nontargeted; *P*=.0002). Furthermore, CE-targeted biopsies were associated with a significantly higher rate of dysplasia detection than traditional nontargeted biopsies with WL colonoscopy (*P*=.001), as well as a nonsignificantly increased detection rate compared to WL colonoscopy–targeted biopsies (*P*=.057).[42]

Despite compelling evidence of the efficacy of CE in the surveillance of patients with dysplasia,

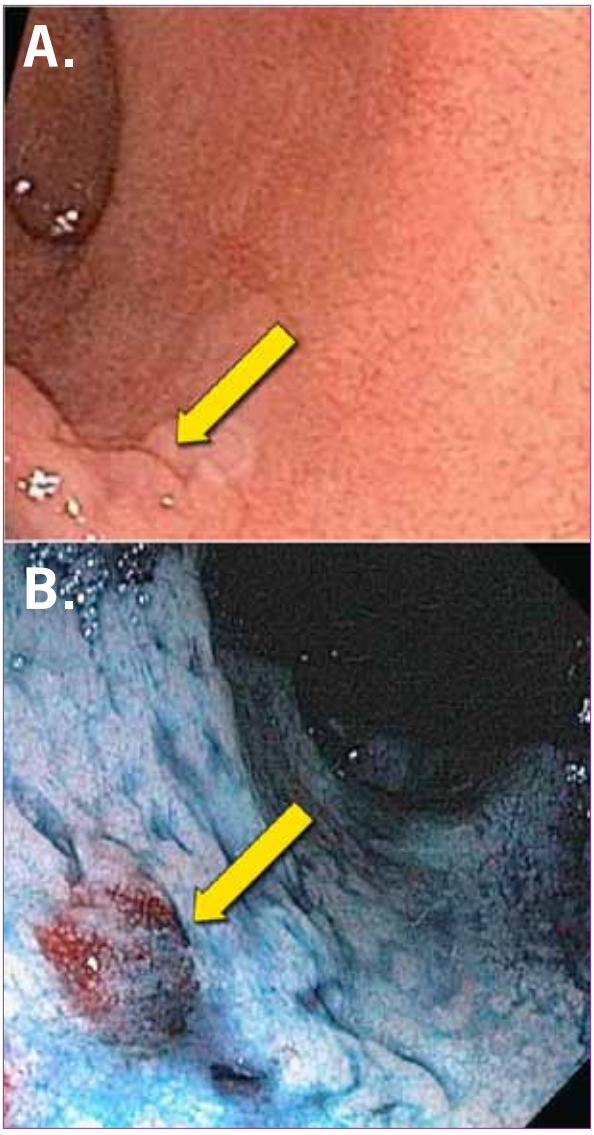

Figure 2. A surveillance colonoscopy in a patient with long-standing ulcerative colitis using high-definition white-light colonoscopy **(A)** and high-definition chromoendoscopy with indigo carmine dye **(B)**. These images depict a focal area of low-grade dysplasia in the rectum. Note the nearly normal endoscopic appearance of the dysplastic lesion when viewed with high-definition white-light colonoscopy **(A)** in contrast to the small, round pit pattern visualized with chromoendoscopy **(B)**, which is consistent with a type III-S Kudo score (ie, neoplasia).

CE is relatively underutilized. According to recent estimates, only approximately 30% of practitioners routinely use CE for the surveillance of IBD patients.[43] These findings raise the question of why CE has not undergone more widespread clinical adoption. One concern preventing widespread adoption of CE for the surveillance of IBD patients is a perceived increase in

procedure duration. Although the overall process of CE may be time-consuming, the withdrawal time associated with CE and targeted biopsies was found to be shorter than that of traditional nontargeted biopsies and WL colonoscopy in a study conducted by Marion and associates.[42] CE is also not perfect; in a study of 900 IBD patients by Moussata and coworkers, random biopsies detected an additional 1% of lesions that were missed by targeted biopsies with CE, suggesting that random biopsies may play a small, albeit inefficient, role in combination with CE for dysplasia surveillance.[44] Furthermore, gastroenterologists may be discouraged from incorporating CE into their clinical practice because approximately 14 IBD surveillance visits are needed to identify each additional case of dysplasia; however, having a number needed to treat of only 14 demonstrates impressive efficacy and should motivate more practitioners to utilize CE.[45]

Roy and associates outlined 5 criteria for evaluating the utility and applicability of new endoscopic imaging modalities: an acceptable level of technical accuracy, patient benefit, affordable cost, test efficiency, and the ability to safely and effectively identify lesions that do not require surgical resection.[46] We believe that CE meets these criteria. The clear advantage of CE over random biopsies with WL colonoscopy for dysplasia detection brings into question the utility of using only the random biopsy method for dysplasia surveillance in IBD patients. CE is low in cost, easy to learn, and efficacious. We believe that the relatively small increase in procedure duration is more than justified by the clinical benefit conferred on this high-risk patient population.

CE has been incorporated into the screening guidelines of several gastroenterology societies, but strong endorsement is still lacking from other societies. The CCFA guidelines from 2005 were the first to endorse the use of CE.[26] In 2008 and 2010, the BSG and ECCO, respectively, recommended the use of CE as an adjunctive imaging technique.[15,28,29] The 2010 AGA guidelines stated that targeted biopsies with CE were an acceptable alternative to traditional, nontargeted biopsy strategies.[30] The 2010 ACG guidelines supported the use of CE in high-risk IBD patients as well as for ensuring the adequacy of previous polypectomy in IBD patients; the guidelines did not make a recommendation regarding the use of CE in low-risk IBD patients.[25] Additional recommendations from these societies likely await further evidence from larger studies of IBD patients, but we believe that the evidence currently available supports the use of CE-targeted biopsies over conventional random biopsies with WL colonoscopy in IBD patients.

However, improvements in high-definition endoscopes will likely enhance the detection of dysplasia without the need for CE. In addition, although CE has shown superiority over WL endoscopy, it remains to be seen whether the increased sensitivity of CE will be maintained outside of research settings with highly trained specialists.

Endomicroscopic Techniques That Use Chromoendoscopy

Other new technologies can also be used to aid in the detection of dysplasia. Confocal laser endomicroscopy (CLE; Pentax) is an endoscopic imaging modality that provides real-time microscopic imaging of the mucosal layer of the gut. CLE illuminates tissue with a low-power laser and detects reflected or fluorescent light through a pinhole.[47,48] CLE can use either reflected WL without a contrast agent or reflected fluorescent light; the latter method requires intravenous or local fluorophores that are administered via a spray catheter.[47,49,50] By focusing a blue laser light source from the distal end of an endoscope onto the tissue of interest, an image is generated using fluorescence and 1,000× magnification, allowing visualization of cell structures at the organelle level. Smaller CLE miniprobe systems have also been studied; these systems are inserted through the accessory channel of the endoscope.[47]

CE was compared to CE-assisted CLE in a 1:1 ratio in a randomized controlled trial of UC patients using targeted or random biopsies for dysplasia screening. CE-assisted CLE with targeted biopsies was found to have a 2.5-fold increase in intraepithelial neoplasia detection (P<.001), as well as increased detection of high-grade dysplasia (P<.001) compared to CE.[51] In a similarly designed study of 153 UC patients in clinical remission, CE-assisted CLE had a 4.75-fold increase in neoplasia detection (P=.005) and required half as many biopsy specimens (P=.008). Also, neoplastic changes were accurately predicted by CLE in 97.8% of cases (sensitivity, 94.7%; specificity, 98.3%).[52]

In addition to dysplasia detection and lesion classification, CLE has been evaluated as a tool for assessing disease activity and relapse in IBD patients. With its layer-by-layer mucosal imaging, CLE has the potential to enhance real-time assessment of disease activity. CLE was evaluated in a case-control study of 54 patients with Crohn's disease (CD) to assess CD activity and mucosal healing. A CD endomicroscopic activity score was developed that described mucosal features of increased colonic crypt tortuosity, enlarged crypt lumen, microerosions, augmented vascularization, and increased cellular infiltrates.[53] Another study of 52 IBD patients used CLE to identify features that were predictive of IBD relapse. In this study, increased width of the luminal crypts and increasing irregularity of the vascular network were predictors of disease relapse, while routine histology was not

a predictor.[54] Due to the small size of these studies, additional and larger studies of CLE in IBD patients should be conducted to evaluate the accuracy of CLE in the prediction of histopathologic diagnoses and to determine the role of CLE in the dysplasia screening algorithm for IBD patients. Currently, the time and training required to perform CLE confine it primarily to research settings, although its clinical implications are promising. If the role of CLE expands, it will most likely be reserved for specialty centers that focus on IBD patients, or it may require real-time interpretation by a pathologist.

Endocytoscopy (ECO) is an emerging modality that uses principles similar to those used in CLE to visualize cellular structures, but ECO uses a fixed-focus lens. ECO can be used with either probe-based or endoscope-based systems that require prestaining of the mucosa.[55] In a small study, ECO was compared to cresyl-violet CE for predicting histology among patients with UC. CE and ECO grading scales showed good correlation, and ECO findings were predictive of the histopathologic diagnosis, which lend credence to ECO and support the need for further investigation of this tool for the real-time identification of dysplasia.[56]

Combining CE with the emerging technology of CLE or ECO has the potential to increase dysplasia detection rates beyond those of both conventional screening and CE. However, potential barriers to the adoption of these modalities include training for the interpretation of histology, increased procedure time, and limited quality of images.[57] The utility of CLE and ECO may lie in real-time lesion classification when potential dysplastic areas are identified by another imaging modality, such as CE.

Narrow-Band Imaging

Narrow-band imaging (NBI; Olympus Medical Systems Corporation) is an optical technique that separates traditional WL into smaller spectrum wavelengths; most commonly, blue light (wavelengths of 415–540 nm) is used, as opposed to the broader spectrum of conventional WL (400–700 nm). Altering the optics and wavelengths of light projected onto the mucosa causes decreased depth of light penetration, which enables maximal absorption by structures containing hemoglobin. This phenomenon outlines mucosal microvascular patterns and surface topography, providing maximal contrast between vascular structures and the surrounding mucosa.[33,58-60] NBI can be activated with a light-filtering switch on the new generation of high-definition endoscopes.[58] A similar technique, multiband imaging (MBI) is used in Fuji intelligent color enhancement (FICE, Fujinon); this approach uses software to digitally process images and restrict light wavelengths, creating a virtual image.

The first randomized, parallel-group, controlled trial of NBI versus high-definition WL colonoscopy for dysplasia detection was conducted in 112 patients with long-standing UC in the United Kingdom. The researchers reported no difference in dysplasia detection rates; they also found an overall low (0.04%) dysplasia detection rate with random biopsies.[61]

Head-to-head comparisons of NBI and CE for dysplasia surveillance have also been conducted. In a randomized controlled trial that compared CE and NBI in 93 patients with long-standing UC, no difference in the detection of neoplasia was noted; however, a 44% increase in withdrawal time was observed with CE.[62] Furthermore, in a recent randomized, prospective, crossover study that compared NBI and CE in 60 patients with IBD, NBI had a higher false-positive biopsy rate (P=.001). CE once again had a significantly longer withdrawal time than NBI (26.87±9.89 minutes vs 15.74±5.62 minutes; P<.01).[63] However, these head-to-head comparisons of NBI and CE involved small sample sizes. In addition, the cost of NBI-equipped endoscopes is markedly greater than the cost of CE contrast agents.[31,58] These observations demonstrate that NBI's role in dysplasia detection in IBD patients is currently limited and that NBI should not be adopted as a primary screening modality. Alternatively, it may be possible to use NBI to help identify inflammatory polyps that present a diagnostic challenge. Better methods for endoscopically discerning inflammatory polyps may also improve the overall accuracy of dysplasia detection in IBD patients.

Technologies on the Horizon

Emerging technologies are trying to obtain the contrast enhancement seen with CE while avoiding the cumbersome use of chromophores or fluorophores; these modalities, such as NBI, use electronic image enhancement to increase blue wavelengths of light while decreasing both red and green wavelengths.[64] MBI, FICE, and i-scan (Pentax) utilize surface, contrast, and tone enhancement via a digital image processing algorithm to better define and outline mucosal structures in real time; similar image filtration occurs with NBI.[65] A randomized, double-blind, controlled study of high-definition WL colonoscopy and i-scan compared the severity and extent of mucosal inflammation in 78 IBD patients, with histologic biopsy as the gold standard. This study showed a significant advantage with i-scan (disease severity, P=.0009; extent of inflammation, P=.011) with no significant difference in the time needed to perform each technique.[66] Because the need to achieve endoscopic mucosal healing is currently controversial, "endomicroscopic" healing will need to prove

its clinical utility by demonstrating an association with improved patient outcomes. To our knowledge, there are no data as of yet on the use of FICE or i-scan in CAC surveillance, although a trial of FICE for the surveillance of IBD patients is registered on Clinicaltrials.gov (identifier NCT00816491).

Other imaging modalities—such as optical coherence tomography and technologies that use autofluorescence—are emerging as possible adjunctive diagnostic techniques for patients with IBD and have the potential to contribute to the identification and classification of dysplastic lesions.[67,68] However, given the limited performance data currently available, these techniques will require more in-depth evaluation on a larger scale to determine their role in IBD dysplasia surveillance regimens.

Molecular-Targeted Chromoendoscopy

Fluorophores that preferentially target dysplastic tissue have also been designed to identify neoplasia during endoscopy. 5-aminolevulinic acid (5-ALA) is converted intracellularly into protoporphyrin IX, which preferentially accumulates in neoplastic tissue and appears as a red spot when viewed under blue light.[69] A small study found high sensitivity for dysplasia detection (ranging from 87% to 100%) in UC patients who received topically administered 5-ALA.[70] Recently, ASYNYDA-FITC, a novel fluorescently labeled heptapeptide that is endoscopically applied to the mucosal surface via a spray catheter, demonstrated efficacy when combined with CLE for detecting high-grade dysplasia or early adenocarcinoma in patients with Barrett esophagus.[71] This peptide marker is intended to remedy the subjectivity inherent in CLE interpretation when only intravenous fluorescein is used. Future versions of endoscopic equipment are also being designed with fluorescent capabilities to accommodate these new strategies.

Conclusion

Traditional WL colonoscopy with nontargeted biopsies is limited in efficacy. Improvements in the optics of endoscopes and the resolution of monitors may increase the ability to detect subtle dysplastic lesions. The data currently available support the use of CE for CAC surveillance in IBD patients, particularly for clinicians who use older-generation endoscopes. Greater awareness and use of CE should strongly impact the identification of dysplasia or early cancers before the development of advanced CAC, but this hypothesis requires definitive confirmation outside of research settings. The strategies currently used to identify patients with dysplasia or CAC remain inadequate; the development of interval cancers continues to stimulate advances in novel, contrast-enhanced imaging methods such as CLE, ECO, and molecularly targeted agents. However, all new technologies will need to be cost-effective and time-effective in order to be adopted in community-based practices.

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