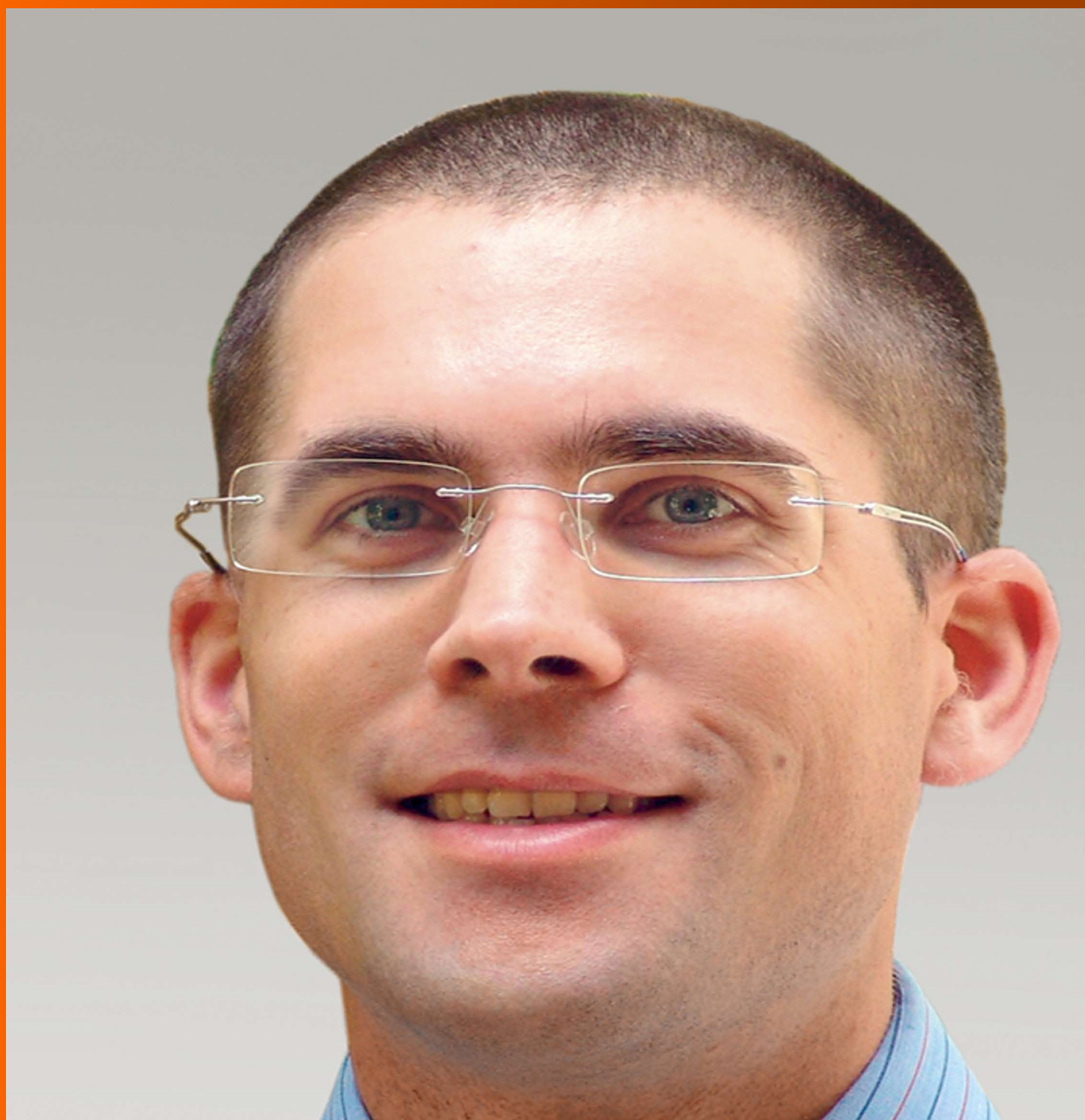


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Use and barriers to chromoendoscopy for dysplasia surveillance in inflammatory bowel disease

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Abstract

Traditionally, patients with inflammatory bowel disease (IBD) have been thought to be at increased risk of developing colitis-associated colorectal cancer. Although there are recent data suggesting that rates of colitis-associated cancer in IBD patients is declining, current guidelines still recommend regular dysplasia surveillance for early detection and prevention of neoplasia in patients with IBD. White-light endoscopy with random biopsies has been the traditional approach for dysplasia detection; however, newer technologies and approaches have emerged. One method, dye-based chromoendoscopy, has the potential to detect more dysplasia. However, longitudinal data to showing a benefit in morbidity or mortality from the use of chromoendoscopy are still lacking. Many societies have included recommendation on the use of chromoendoscopy with targeted biopsies as a method of surveillance for colitis - associated colorectal cancer. This narrative review seeks to outline data on dysplasia detection as well as barriers to the implementation of dye-based chromoendoscopy for the prevention and early detection of colitis-associated colorectal cancer.

Key words: Chromoendoscopy; Inflammatory bowel disease; Dysplasia surveillance

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Core tip: Patients with inflammatory bowel disease (IBD) are at an increased risk of developing colorectal cancer. Current guidelines recommend surveillance for early of neoplasia in patients with IBD. White-light endoscopy with random biopsies has been the traditional approach for dysplasia detection. Dye-based chromoendoscopy has the potential to detect more dysplasia. Many societies have endorsed the use of chromoendoscopy with targeted biopsies as a method of surveillance for colitis associated colorectal cancer. This review seeks to outline

data on dysplasia detection as well as barriers to the implementation of chromoendoscopy for the prevention and early detection of colitis associated colorectal cancer.

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INTRODUCTION

Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory disease of the GI tract. Both ulcerative colitis and Crohn's colitis have historically been thought to be associated with an increased risk of developing colorectal cancer (CRC)^[1-3]. Current guidelines provide various permutations of surveillance colonoscopy to detect and remove precursor lesions at an early stage^[4-7]. Over the last several years, dye-based chromoendoscopy (CE) with targeted biopsies has emerged as an option to improve the ability to detect these early, subtle lesions. CE is a technique using absorptive stains or contrast stains dye such as methylene blue and indigo carmine that can aid in the early detection of malignant changes in the gastrointestinal tract. In this technique, 0.4% indigo carmine or 0.1% methylene blue is sprayed directly onto the colonic mucosa to help detect subtle mucosal irregularities that aid in the detection of changes indicative of dysplasia as well as help in differentiation of neoplastic and non-neoplastic lesions by assessing crypt architecture and modified pit patterns^[8]. The technique of colonic CE was first described by Tada in 1976 with work two decades later indicating a role for CE with high resolution video endoscopy in increasing the detection of small flat neoplastic lesions in UC patients^[9,10]. In this review, we will review current guidelines for the surveillance of colitis-associated colorectal cancer (CAC), barriers to implementation, and areas that require further study.

CRC RISK AMONG PATIENTS WITH IBD

The concept of carcinoma arising as a complication of chronic inflammation from IBD was first described by Crohn and Rosenberg in 1925, with later reports expanding on this observation^[1-3]. A review of the literature in 1961 by Goldgraber and Kirsner^[2] made the observation of increased risk of carcinoma of the colon in patients with UC with pancolonic disease and in those with disease duration greater than 10 years. The presence of dysplastic lesions in the colon of patients with UC was recognized as early as 1949 with the recommendation to search for precancerous lesions

which often were flat (non-polypoid) with rectal biopsies annually as an aid to the detection of early colon cancer being made in 1969^[11,12]. It was not until 1983 that a standardized terminology and grading system were established to help guide surveillance protocols. In the landmark paper by Riddell *et al.*^[13] in 1983, dysplasia was defined as an unequivocal neoplastic alteration of the colonic epithelium that may represent a precursor of carcinoma or itself be malignant and associated with direct invasion into the underlying tissue. The classification for dysplasia was further categorized into either negative, indefinite or positive for dysplasia.

In a landmark meta-analysis conducted by Eaden *et al.*^[14] in 2001, the authors assessed 116 studies and found that the cumulative risk of developing CAC was 2% by 10 years of disease, 8% by 20 years, and 18% by 30 years. Subsequent studies investigating the CAC risk in IBD patients have shown considerable variability, depending on the population studied, with cumulative risk ranging between 2.1% to 33.2%^[15-18]. Remarkably, more recent studies have actually shown that the risk of CAC in IBD patients may actually be declining and nearing the risk of the general population^[19]. In a meta-analysis by Jess *et al.*^[20] assessing 47374 Danish patients with IBD over 30 years, the authors found that the relative risk of developing CAC in UC patients was comparable to non-IBD controls (RR = 1.07, 95%CI: 0.95-1.21) as was the risk of CAC in patients with Crohn's colitis (RR = 0.80, 95%CI: 0.43-1.49). This study also found that the overall risk of CAC was declining in UC patients where the overall RR for CAC decreased from 1.34 (95%CI: 1.13-1.58) in 1979-1988 to 0.57 (95%CI: 0.41-0.80) in 1999-2008. This decline potentially may be attributed to improvement in therapies to reduce intestinal inflammation in IBD or to improved surveillance programs to promote early detection of neoplastic lesions.

Despite the decline in overall risk, there is still consistent information across many studies that there is a particularly higher risk of developing CAC in a subset of patients - those with extensive and long standing UC or CD^[20-22]. Rutter *et al.*^[23] evaluated 68 patients in a case-control study at St. Mark's Hospital in England and found that severity of colonic inflammation is also an important predictor for development of neoplasia. Moreover, in the aforementioned study by Jess *et al.*^[20], despite an overall decline in incidence of CAC in IBD patients, there are particular subsets of patients- those with a diagnosis of UC in childhood or adolescence, those with long standing UC and those with concurrent primary sclerosing cholangitis (PSC)-who were at a notably increased risk of developing CAC during the study period.

CURRENT GUIDELINES FOR CAC SURVEILLANCE

While CAC may only represent a small proportion of

Table 1 Colorectal cancer surveillance guidelines for inflammatory bowel disease patients

Guideline (year of publication)	Timing of initiating surveillance	Surveillance interval	Biopsy protocol
AGA (2003) ^[4]	After 8 yr of disease (pancolitis) After 15 yr of disease (left-sided colitis)	1-2 yr	Random biopsy
BSG (2010) ^[46]	10 yr after onset of colitic symptoms	5 yr (lower risk) ¹ 2-3 yr (intermediate risk) 1 yr (higher risk)	Targeted biopsy with CE (preferred) otherwise random biopsy
ECCO (2013) ^[6]	8 yr after onset of colitic symptoms	5 yr (lower risk) ² 2-3 yr (intermediate risk) 1 yr (higher risk)	Targeted biopsy with CE (preferred), random biopsies if CE expertise unavailable
ASGE (2015) ^[7]	8 yr after symptom onset	1-3 yr (1 yr if any risk factor) ³	Targeted biopsy with CE recommended with SD-WLE (preferred with HD-WLE as well); random biopsies with targeted biopsies of suspicious lesions is alternative

¹Higher risk group: Dysplasia in the past 5 years declining surgery, PSC/liver transplantation for PSC, family history of CRC in a first degree relative < 50 years, or extensive colitis with moderate/severe active endoscopic/histological inflammation; intermediate risk group: Post-inflammatory polyps, family history of CRC in a first degree relative > 50 years, extensive colitis with mild active endoscopic/histologic inflammation; lower risk group: Left sided colitis, Crohn's colitis with less than 50% of the colonic mucosal surface affected by the disease, or extensive colitis with no active endoscopic/histologic inflammation; ²Higher risk group: Stricture or dysplasia in the past 5 years, PSC, extensive colitis with severe active inflammation, or family history of CRC in a first degree relative < 50 years; intermediate risk group: extensive colitis with mild or moderate active inflammation post-inflammatory polyps, or family history of CRC in a first degree relative > 50 years; lower risk group: Patients with neither intermediate nor higher risk features; ³Risk factors: Active inflammation, anatomic abnormality (stricture or multiple pseudopolyps), history of dysplasia, family history of CRC in a first degree relative, PSC. AGA: American gastroenterological association; BSG: British society of gastroenterology; ECCO: European crohn's and colitis organisation; ASGE: American society of gastrointestinal endoscopy; PSC: Primary sclerosing cholangitis; CRC: Colorectal cancer; CE: Chromoendoscopy; SD-WLE: Standard definition white light endoscopy; HD-WLE: High definition white light endoscopy.

all CRC cases (1%-2%), CRC is responsible for one in six deaths of IBD patients^[24]. As such, colonoscopy has been the test of choice for early detection and prevention of CAC in IBD patients. The major United States gastroenterology societies have endorsed colonoscopy for prevention of early CAC^[25-27]. There are limited data on the benefit of the recommended surveillance programs. Some studies have found that patients with IBD undergoing surveillance colonoscopies may have reduced rates of CAC or detection of CAC at an earlier stage^[28].

Choi *et al.*^[29] examined 41 UC patients who developed CAC. The authors found that CAC was detected at a significantly earlier Dukes' stage in patients taking part in an endoscopic surveillance program ($P = 0.039$). Furthermore, the 5-year survival rate was 77.2% for the surveillance group and 36.3% for the no-surveillance group ($P = 0.026$). Though this study is promising evidence in favor of CRC surveillance, other studies have not shown a similar benefit. Lynch *et al.*^[30] prospectively examined 160 UC patients and found no mortality benefit in patients undergoing CRC surveillance. More recently, Ananthakrishnan *et al.*^[31] studied 6823 established patients (following for at least 3 years) with IBD of which 2764 had undergone recent colonoscopy. They found that the incidence of CAC among patients without a recent colonoscopy (2.7%) was significantly higher than among patients with a recent colonoscopy (1.6%) (OR = 0.56, 95%CI: 0.39-0.80). This was one of the few studies which specifically addressed the risk of CAC in IBD patients undergoing surveillance.

Current society guidelines recommend regular dysplasia surveillance in patients with long-standing colitis. Several major GI societies guidelines, including

those published by the American Gastroenterological Association in 2003, recommend initiating a surveillance program to evaluate for dysplasia in patients who have had colitis for at least 8 years^[4,5]. After starting a surveillance program, colonoscopy should continue every 1-2 years. The consensus of the expert panel formulating these guidelines is that random biopsy specimens should be taken every 10 cm in all 4 quadrants and that additional biopsies should be taken of any endoscopically abnormal appearing lesions (strictures, mass lesions, etc.). This results in a minimum of 33 biopsies to meet the threshold for neoplasia detection - a process that can be quite cumbersome and time consuming. Newer society guidelines, such as those issued by the American Society for Gastrointestinal Endoscopy (ASGE) and the European Crohn's and Colitis Organization (ECCO)^[6,7], have now updated their guidelines to incorporate the use of chromoendoscopy for dysplasia surveillance. A summary of the current guidelines from the major GI societies is outlined in Table 1.

There have been many criticisms of the random biopsy strategy as less than 1% of the entire mucosal surface was sampled and low dysplasia detection rates as well as high sampling-error^[32]. There are also no prospective studies that have determined the optimal number of biopsies that should be taken to detect dysplasia reliably though one study has recommended a minimum of 33 biopsy specimens to be taken in patients with pancolitis^[33]. It has also been estimated that this surveillance method provides only 80% confidence that dysplasia involving $\geq 5\%$ of the colon can be detected^[34]. There have also been several studies showing poor adherence of gastroenterologists

in taking the recommended number of biopsies along with practice variability in surveillance^[35-37]. These initial recommendations were made at time prior to high-definition colonoscopy and lesions previously considered “invisible” or flat may be visualized with modern day high-definition equipment. It is now understood that most dysplasia can be visualized endoscopically and have led some to question the added value of random biopsies^[26]. Recent studies have supported the strategy of targeted biopsies of abnormal lesions without random biopsies only when high definition white light endoscopy (HD-WLE) is used. A clinical practice cohort of 454 IBD patients undergoing surveillance colonoscopy between 2011-2014 using standard definition white light endoscopy (SD-WLE), HD-WLE, virtual electronic CE, or CE found that most lesions were visible and of the four dysplastic lesions and one adenocarcinoma identified all were visible with HD-WLE and biopsied in a targeted manner. No dysplasia was identified on random biopsies^[38]. A recent randomized controlled trial of 256 of patients with UC performed in Japan comparing surveillance with either a targeted biopsy protocol vs a random biopsy protocol with white light endoscopy found neoplasia was detected in 11.4% of patients in the targeted biopsy group vs 9.3% in the random biopsy group ($P = 0.617$) with less biopsies specimens being required per neoplasia diagnosis, suggesting a targeted biopsy approach as being more cost-effective and more efficient without missing dysplasia^[39].

SCENIC CONSENSUS STATEMENT

In March of 2015, the SCENIC (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations) consensus statement^[40] regarding use of chromoendoscopy for dysplasia surveillance was released. In this statement, the authors made several updates regarding the approach to dysplasia surveillance among which they suggested that endoscopists consider the use of CE, when utilizing high definition colonoscopy, to enhance dysplasia detection. A commentary by Marion and Sands^[41] accompanying the publication of the SCENIC statement propounded an important argument: The lack of longitudinal data regarding CE limits the ability to accept this as the standard of care in dysplasia surveillance. More specifically, while there is certainly evidence that CE increases dysplasia detection, it remains unclear what the long-term management of these patients should be. While pursuing the goal of cancer prevention, the accompanying risk profile of increased dysplasia detection including onerous surveillance schedules, possibly unnecessary colectomies or post-surgical complications also increases. This risk/benefit profile, along with the limited evidence to support use of CE, must all be considered when deciding to employ this technique.

EVIDENCE FOR CHROMOENDOSCOPY

Two studies increased the attention on CE as a means to more efficiently detect dysplasia in IBD compared to random biopsies. In one study of 100 patients with long-standing UC using a tandem colonoscopy design, random biopsies along with targeted biopsies using standard white light was compared to CE with targeted biopsies only using indigo carmine. This study demonstrated a 3.5-fold increase in diagnostic yield of dysplasia along with a 4.5-fold increase in dysplasia detection, with no dysplasia being detected on random biopsies^[42]. In the first randomized prospective trial using CE for IBD-associated colonic dysplasia, methylene blue was compared to conventional colonoscopy in patients with long-standing UC. Chromoendoscopy was associated with an increased diagnostic yield for total number of detected intraepithelial neoplasia compared to conventional colonoscopy (32 vs 10, $P = 0.003$). The CE group also required less biopsies and using the modified pit pattern demonstrated a sensitivity and specificity for differentiation between neoplastic and non-neoplastic lesions of 93%^[43]. Subsequent studies also have shown an increased detection yield of CE over standard white light endoscopy (WLE), which was highlighted by a meta-analysis evaluating prospective studies comparing CE to WLE. Six prospective studies were included in the analysis and concluded that CE resulted in a 7% higher yield in detection of neoplasia as well as a pooled increase in targeted dysplastic (low or high grade) lesion detection of CE over standard definition WLE of 44% (95%CI: 28.6-59.1)^[44]. Mounting data of the effectiveness in dysplasia detection with CE lead to the 2010 position statement from the American Gastroenterological Association recommending CE as an alternative to analyses of random biopsies for endoscopists experienced with the technique^[45]. The British Society of Gastroenterology also recommended CE with targeted biopsies with a grade A recommendation as the preferred method of surveillance^[46].

Though clinical trials demonstrated a benefit of CE over WLE for dysplasia detection, a large retrospective study covering 13 years did not confirm this conclusion in the clinical practice setting. This multicenter study from the Netherlands including 401 patients undergoing CE and 772 patients undergoing WLE found no difference in the detection of dysplasia between the two groups (11% vs 10%, $P = 0.80$)^[47]. This conclusion was in accordance with a previous study using narrow-band imaging showing no difference in dysplasia yield between CE and HD WLE^[48]. Of note, the authors of this study highlighted that prior studies assessing outcomes in chromoendoscopy had a “back-to-back” design where WLE was performed first followed by CE (as WLE cannot be performed after dye spraying). They postulated that such a design may have overestimated the yield of CE in detecting neoplasia and generated potential bias. To try and fill the discrepancy in the

data, Carballal *et al.*^[49] conducted the first randomized prospective trial evaluating the real-life experience of CE for dysplasia detection in long-standing IBD. In this prospective, multicenter cohort study from Spain, 350 patients with long-standing IBD underwent surveillance using a tandem colonoscopy method with each colonic segment being evaluated with WLE followed by CE using 0.4% indigo carmine with targeted biopsies of suspicious lesions. This study found a 57.4% incremental yield in dysplasia detection with CE vs WLE which was comparable in standard WLE vs HD WLE. The dysplasia miss rate was 40 of 94 lesions for white-light examination. Overall dysplasia detection rate was 15.7% in this real-life setting which is in line with previous estimates^[50]. This study also demonstrated no significant difference in dysplasia detection between CE-expert and non-expert endoscopists with no significant learning curve being observed. Though it has been concluded that CE improves dysplasia detection and is the most effective modality for surveillance, data regarding the effect on patient outcomes and cancer-related morbidity and mortality are still lacking.

BARRIERS TO PERFORMING CHROMOENDOSCOPY

While CE may provide some benefit with regards to increased dysplasia detection, there are several barriers to performing CE that must be considered when deciding whether to implement this technique.

Does expertise affect outcomes?

Much of the existing data, especially data demonstrating positive results, on CE arises from centers where gastroenterologists have particular expertise in performing CE^[42,43,50-53]. In the article by Mooiweer *et al.*^[47], the neoplasia detection rate for CE-based surveillance procedures was 11% compared with an average rate of 14% over several prior randomized trials examining neoplasia detection using CE. The authors of the study postulated that the lower neoplasia detection rate could be due to the inexperience of the endoscopists who had no dedicated training prior to performing the CE procedures. Conversely, Carballal *et al.*^[49] prospectively examined a cohort of IBD patients undergoing dysplasia surveillance between 2012-2014. The study protocol required that each colonic segment was evaluated with white light followed by 0.4% indigo carmine CE. When assessing for differences between expert (endoscopists who had performed > 20 CE-based dysplasia surveillance procedures) and non-expert endoscopists, the dysplasia detection rate was not found to be significantly different between the two groups (18.5% vs 13.1%, $P = 0.20$).

Cost concerns and technical disadvantages associated with CE

The equipment required to perform chromoendoscopy

usually includes one of the absorptive, contrast or reactive stains; these stains are generally inexpensive but have had issues with availability at times. Additionally, when performing chromoendoscopy, a spray catheter may be used to apply a uniform mist of the staining agent. The cost of these spray catheters is between approximately \$50-200. The equipment used to perform chromoendoscopy is compatible with most commonly used colonoscopies and the staining dyes are thought to add no additional risk to the patient^[54]. While the equipment may only add a small amount of cost to the procedure, the cost of additional time to perform high quality chromoendoscopy harder to quantify. The data on cost-effectiveness of this technique is quite limited. One formal cost effectiveness study has been conducted by Konijeti *et al.*^[55]. The authors utilized a Markov model to analyze the cost effectiveness of CE relative to WLE or no endoscopy for CRC surveillance in UC patients. This study design was chosen to better analyze need for surveillance and optimal surveillance intervals given increasing data about decreasing rates of CRC in patients with IBD. CE was found to be more effective and less costly than WLE at all surveillance intervals. However, compared with no surveillance, CE was cost effective only at surveillance intervals of at least 7 years, with an incremental cost-effectiveness ratio of \$77176. While this study suggests that CE may be more cost effective than white-light endoscopy, it only demonstrates a cost benefit over no surveillance if intervals are stretched out to greater than every 7 years. Overall, the question on whether chromoendoscopy offers a cost savings when used in a real-world surveillance program remains unanswered and more studies are required to truly clarify this.

One additional barrier that may prevent gastroenterologists in implementing CE is the additional procedure time. In the meta-analysis conducted by Subramanian *et al.*^[44], taking data from experienced centers, CE increased procedure time by 11 min overall. In the previously mentioned study by Kiesslich *et al.*^[43], procedure time was increased from 35 to 44 min (with CE) overall. However, this procedure time also included time dedicated for random biopsies. If a practice of conducting only targeted biopsies of suspicious lesion were employed, the additional procedure time added by using CE would likely be less. Additionally, increasing experience with CE may translate into shorter procedure times. In an implementation study by Leong *et al.*^[56], the authors observed that withdrawal time decreased with experience, ranging from 31 min for fewer than 5 procedures to 19 min for more than 15 procedures completed.

CLINICAL IMPACT OF CHROMOENDOSCOPY

CE is highlighted as a more effective modality than high definition white light endoscopy for detecting "invisible

dysplasia". However, it is important to consider whether there is truly a significant clinical impact of missed, "invisible" dysplastic lesions on CAC-related outcomes. To answer this question, Rubin *et al.*^[25] conducted a retrospective review of all cases of dysplasia or CRC in UC between November 1994 and October 2004. There were 1339 surveillance examinations in 622 patients with UC; forty-six patients were found to have dysplasia or CRC. seventy-five separate dysplastic or cancerous lesions were identified, 38 of 65 dysplastic lesions (58.5%) and 8 of 10 cancers (80.0%) were visible to the endoscopist as 23 polyps and masses, 1 stricture, and 22 irregular mucosa. Moreover, van den Broek *et al.*^[57] conducted a retrospective analysis of 1010 colonoscopies from 1998-2008. In total, 475 patients with UC were included in the study. Of all colonoscopies, 466 were performed for surveillance (in 167 patients) during which 11772 random biopsies were taken (median 29). Dysplasia was detected in random biopsy specimens alone in 5 colonoscopies (0.5%) in 4 patients (0.8%). Of these 4 patients, 2 had had visible dysplasia in previous colonoscopies, 1 had unifocal low-grade dysplasia that was not confirmed in 3 subsequent colonoscopies, and 1 had multifocal low-grade dysplasia and suspicious appearing ulcerations and underwent proctocolectomy, which confirmed the presence of neoplasia. Thus, dysplasia uncovered *via* random biopsy changed the management of only 1 of 475 patients (0.2%). In comparison, targeted biopsy specimens were positive for neoplasia in 83 colonoscopies (8.2%), and major therapeutic decisions (endoscopic resection or colectomy) were made in 61 of these cases (73%). This data suggests that "invisible dysplasia" detected on random biopsy is infrequent and of unclear clinical relevance. Though recent published data has shown promising results for a targeted biopsy approach to dysplasia surveillance^[38], the issue of invisible dysplasia likely remains an open issue that requires future investigation before eliminating random biopsy protocols altogether.

Does dysplasia detection affect long-term outcomes?

In a meta-analysis by Subramanian *et al.*^[44], the authors assessed the diagnostic yield, for detection of dysplasia between white light endoscopy and CE. In 6 studies involving 1277 patients, the difference in yield of dysplasia between CE and white light endoscopy was 7% (95%CI: 3.2-11.3) with a number needed to treat of 14.3. The difference in proportion of lesions detected by targeted biopsies was 44% (95%CI: 28.6-59.1) and flat lesions was 27% (95%CI: 11.2-41.9) in favor of CE. The aforementioned prospective studies, derived from expert centers, have demonstrated a significant difference in dysplasia detection with the utilization of CE^[42,43,50-53]. It must be noted, however, that most of these studies follow a cross-sectional design in which the number of detected lesions using CE is compared with the number of lesions detected using standard definition white-light endoscopy.

The intended goal of surveillance strategies is to detect early lesions that would lead to decreased colon cancer morbidity and mortality as well as unnecessary colectomies. Although chromoendoscopy may help to increase dysplasia detection compared to white light endoscopy, the clinical implications of this increased detection yield are largely unknown. In a follow-up^[58] to an initial index study^[50] looking at 102 high-risk IBD patients undergoing surveillance comparing CE and SD-WLE with random biopsy, 68 patients were longitudinally followed over a median of 27.8 mo to compare the techniques for dysplasia detection. CE was found to be more likely to detect dysplasia compared to targeted WLE (OR = 2.4, 95%CI: 1.4-4.0) and random biopsy (OR = 5.4, 95%CI: 2.9-9.9) Furthermore, in the 10 patients who underwent colectomy, CE was found to have better overall agreement between endoscopy and colectomy findings regarding the presence or absence of dysplasia which was 80% in CE, 20% for random biopsy and 10% in targeted WLE. Furthermore, a negative result from CE was the best indicator of dysplasia free outcome which may play a role in future decisions regarding recommended screening intervals. There is recent data with conflicting results regarding the impact of lesions detected with CE compared to WLE. In a retrospective study evaluating the implications of LGD found during surveillance in a Dutch cohort, 159/1065 patients evaluated were found to have LGD (133 visible lesions and 26 invisible lesions) for an overall incidence rate of 1.34 per 100 patient-years for all LGD lesions. There was a total of 10 cases which advanced to either HGD (5/10) or CRC (5/10) with no significant difference in the risk of advanced neoplasia during follow-up for index lesions detected with either WLE or CE^[59]. Though there was no difference in advancement in lesions detected by HD-WLE vs CE, this may have been limited by the overall low number of neoplastic lesions.

Finally, these findings are supported by a recent systematic review that demonstrated a superiority of CE over WLE in dysplasia detection when compared to SD-WLE only with no direct evidence of prevention of cancer-related mortality and time to interval cancer in patients who received CE^[60]. As described in this paper, there have been consistent data suggesting increased dysplasia detection with CE, however data showing an impact in cancer related outcomes are still lacking. More longitudinal head to head studies comparing CE with HD-WLE are needed to compare the outcomes of surveillance techniques and to confirm whether the clinical significance of these lesions are indeed comparable.

FUTURE DIRECTIONS

CE appears to increase the rate of colonic dysplasia detection in IBD patients undergoing CAC surveillance. CE with targeted biopsies is now an alternative to random biopsies for CAC surveillance. However, we currently do not have sufficient data to suggest that

there is a clear “real-world” benefit of CE including reduction in cancer rates or improved survival. As such, further studies are required to assess the effect on CAC outcomes, not only dysplasia detection rates. Patients are likely to seek answers from their gastroenterologist regarding the “best” way to prevent CRC. It is important that we are prepared to explain to patients how CE fits into their care.

It is likely that the future of CAC will be increasingly complex as our understanding of dysplasia in IBD and technologies available to detect and treat dysplasia evolve. Risk stratification will likely play a larger role in identifying patients most at risk for CAC who would most likely benefit from aggressive CAC surveillance, including CE.

It is imperative that more studies, particularly longitudinal studies should be done to clarify the role of CE in achieving the ultimate goal of reducing patient morbidity and mortality from CAC while also reducing unnecessary colectomies in patients with clinically insignificant lesions.

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