Communication from the ASGE Publications Committee

LEADING EDGE

The use of chromoendoscopy for surveillance of inflammatory bowel disease

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Note: *For debate purposes, the pro and con positions for patient management will be taken by the invited authors. However, actual decisions regarding patient care must involve discussion of the risks and benefits of each treatment considered.*

CASE PRESENTATION

Case Presenter
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A 73-year-old white man with pancolonic ulcerative colitis diagnosed 22 years ago was referred for a second opinion. He is currently taking mesalamine 1.5 grams twice daily and is asymptomatic. At routine outpatient follow-up 1 month ago, he had a simple clinical colitis activity index of zero.

His last surveillance colonoscopy 1 year ago was a high-definition (HD) white-light examination without chromoendoscopy. The colon preparation was deemed adequate, with a Boston Bowel Preparation Scale of 8. The result of this examination was significant for mild friability, erythema, and a decrease in vascularity noted in a contiguous pattern extending to 20 cm proximal to the anal verge, with a Mayo endoscopic subscore of 1. There were also 2 polyps, which were resected. The first polyp was a 20-mm sessile polyp surrounded by normal-appearing mucosa 50 cm from the entry site, which pathologic analysis revealed to be a tubular adenoma. The second polyp, located at 25 cm from the entry site, measured 10 mm, which pathologic analysis identified as an inflammatory polyp. The patient underwent 4-quadrant surveillance biopsies at 10-cm intervals, with 1 biopsy specimen at 40 cm being suggestive of low-grade dysplasia on pathologic review.

He had undergone no prior abdominal surgeries and had no family history of colon cancer. The patient is a nonsmoker. Laboratory testing revealed normal red blood cell indices and a normal basic metabolic panel.

The patient is reluctant to undergo any major operation and was referred to you to consider performing a repeated colonoscopy with chromoendoscopy for further evaluation of the incidental finding of low-grade dysplasia on his last examination.

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PRO
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Proceed with chromoendoscopy after dysplasia confirmed by a second pathologist

Chromoendoscopy is an exciting technique that can improve dysplasia detection in ulcerative colitis. It is simple, is easy to learn, and can increase dysplasia detection rates up to 4-fold. However, despite its advantages, I cannot recommend chromoendoscopy for all patients who undergo dysplasia surveillance for ulcerative colitis or Crohn's colitis. We just do not yet have adequate long-term follow-up of all patients in whom dysplasia is detected to determine whether colorectal cancer risk is decreased.

I limit chromoendoscopy to high-risk patients with ulcerative colitis or Crohn's colitis only, in whom the likelihood of finding a clinically meaningful lesion would be high. This includes patients with a history of dysplastic lesions/adenomas, those with a strong family history of colorectal cancer, or those who have primary sclerosing cholangitis. In this setting, chromoendoscopy not only enhances lesion detection but also allows for better assessment of endoscopic resectability. For lesions with distinct margins and no overt signs of malignancy, endoscopic resection with follow-up at close intervals appears to be safe, with avoidance of colectomy.

CON
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There is not a compelling case for using chromoendoscopy on this patient

To demonstrate the benefit of chromoendoscopy to patients, it is necessary to show its superiority over conventional HD white-light endoscopy in an appropriately controlled fashion. In conventional colonoscopy, several factors have been demonstrated to affect the adenoma detection rate, including endoscopic withdrawal time, adequacy of the preparation, and maneuvers with the endoscope (including second view and retroflexion), among others. To date there have been no appropriately controlled trials in which chromoendoscopy has been demonstrated to be superior to conventional HD white-light endoscopy.

Question 1: Does dye spray chromoendoscopy offer any added advantage in surveillance of inflammatory bowel disease (IBD) compared with a routine white-light, HD examination, and would you offer it to this patient?

PRO
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Chromoendoscopy is the preferred method for dysplasia surveillance in chronic ulcerative colitis based on the Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Irritable Bowel Disease (SCENIC) guidelines[1] because of its superiority to white-light colonoscopy.[2,3] Unfortunately, the majority of studies that demonstrated its superiority compared it with standard-definition (SD) white-light colonoscopy. Whereas the findings at SD chromoendoscopy predicted dysplasia-free outcome or colectomy in nearly 28 months of follow-up in 1 study,[4] overall longitudinal data are scarce, and HD colonoscopy is the new norm.

High-definition colonoscopy increases dysplasia detection in ulcerative colitis nearly 3-fold compared with SD.[5] The SCENIC guidelines only "suggested" but not "recommended" that chromoendoscopy be used with HD colonoscopy for surveillance of all ulcerative colitis patients. This is based on 1 observational study we published in which dysplasia detection was increased more than 2-fold.[6] Unfortunately, subsequent observational studies[7-9] and randomized trials[10,11] have presented conflicting results. Given this controversy, we perform HD chromoendoscopy only on high-risk patients because we believe they are most likely to benefit from the procedure. We define high risk as having a history of dysplasia or being otherwise at high risk for colorectal cancer. These include patients with history of primary sclerosing cholangitis, strong family history of colorectal cancer, or who have multiple pseudopolyps where dysplasia would be difficult to detect.

We know dysplasia can be multifocal based on the St. Marks experience, where one third of patients with colorectal cancer had a synchronous colorectal cancer or dysplasia at a different colon location at colectomy.[9] For the patient described in this case presentation, even in the absence of dysplasia found on random biopsy, we would perform chromoendoscopy because of the prior large adenoma found.

Surveillance recommendations do not apply to this patient because dysplasia was already found on random biopsy ("invisible dysplasia") after white-light colonoscopy without chromoendoscopy. Regardless of whether it was found with SD or HD, the finding of low-grade dysplasia should be confirmed by a second pathologist, and the patient should not be referred for colectomy. He should undergo HD chromoendoscopy by an endoscopist with experience in the technique. This would provide, with use of the best technology available, a higher likelihood of finding a discrete lesion that can be safely removed and avoiding surgery. If a lesion is found and then removed, his prognosis is excellent. He has a very low likelihood of the

development of colorectal cancer with ongoing surveillance. If no lesion is found, then continued, more intensive surveillance with chromoendoscopy is reasonable, based on the finding of unifocal "invisible" dysplasia on the previous examination. However, unlike unifocal invisible dysplasia, multifocal invisible dysplasia would be an indication for colectomy.

1. Laine L, Kaltenbach T, Barkin A, et al. SCENIC International consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastroenterology 2015;148:639-51.
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To demonstrate the benefit of chromoendoscopy to patients, it is necessary to show its superiority over conventional HD white-light endoscopy in an appropriately controlled fashion. In conventional colonoscopy, several factors have been demonstrated to affect the adenoma detection rate, including endoscopic withdrawal time, adequacy of the preparation, and maneuvers with the endoscope (including second view and retroflexion), among others.[1] To date there have been no appropriately controlled trials in which chromoendoscopy has been demonstrated to be superior to conventional HD white-light endoscopy. Every trial that has evaluated chromoendoscopy thus far has involved the same endoscopist initially performing a conventional colonoscopy and then subsequently completing the colonoscopy with dye spray. Several, but not all, of these studies have reported a higher sensitivity of lesion detection in patients with chromoendoscopy.[2]

It remains unclear whether the increase in detection rates is related to the performance of a second colonoscopic evaluation and whether a repeated colonoscopy without dye spray chromoendoscopy would have yielded a similar increase in detection rates. In other words, a critique of these studies is that they fail to discern whether the increased detection rates are a result of an inherent advantage of chromoendoscopy or a manifestation of the increased amount of time that the endoscopic observer spends looking for lesions. This concept is supported by several tandem or consecutive colonoscopy studies demonstrating that the miss rate of polyps on a single examination is reported to be 16.8% to 28%.[3-7] A recent systematic review demonstrated that chromoendoscopy was superior to SD white-light endoscopy for lesion detection, but chromoendoscopy did not enable increased lesion detection when compared with HD white-light endoscopy.[2]

It is also important to distinguish clinically meaningful from clinically insignificant lesions. The act of just seeing more lesions is not necessarily relevant. Enhanced endoscopic imaging techniques, such as dye spray chromoendoscopy, should be proved to enhance the detection of lesions that change patient treatment and outcomes, specifically the prevention of all-cause cancer-specific mortality or time to interval cancer. The systematic review demonstrated no direct evidence of effect on these outcomes.[2]

In light of the lack of any demonstrated benefit of chromoendoscopy over the use of HD white-light endoscopy, I would not feel compelled to offer chromoendoscopy to this patient.

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Question 2: Comparing methylene blue with indigo carmine, which is your preferred dye chromoendoscopy agent? Are there any specific technical pearls?

PRO
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Methylene blue and indigo carmine are the most common dyes used for chromoendoscopy.[1] Methylene blue is an absorptive dye, meaning that it is taken up by the mucosa. One needs to wait about 60 seconds before visualization is optimal. Indigo carmine simply coats the mucosa, allowing for immediate visualization. Although these dyes have never been compared head to head, dysplasia detection rates are similar. Both dyes are safe, although there was 1 report of DNA damage with methylene blue when it was used in Barrett's surveillance,[2] but no conclusive evidence of harm has been found. Methylene blue is taken up less by the mucosa in areas of chronic colitis, allowing for assessment of disease extent,[3] but this is of little value in practice.

The dyes are mixed in water with concentrations that vary from 0.03% to 0.3% in the literature. We prefer indigo carmine at a concentration of 0.1% because of its ease of use. There have been reported supply shortages of the dye marketed as indigo carmine. We use FD&C Blue No. 2 sterile powder, which is chemically identical to indigo carmine, because it is readily available.

Patient selection and method of chromoendoscopy are most important in enhancing dysplasia detection. Patients must be in endoscopic remission (no mucosal erosion or ulceration present) and have an adequate colon preparation. The colon should be cleaned throughout insertion to the cecum with water wash (water pump) to remove any remaining material. Many endoscopists will use a spray catheter[1] to allow for even segmental spraying, but this adds significantly to the cost of the procedure. We have shown that using the standard foot pump is just as effective.[4] We mix 0.5 g of FD&C Blue No. 2 in 500 mL of sterile water and directly attach this to the foot pump. We then spray the dye in the colon wall opposite the gravity-dependent area, suction the air out to allow for better dye coating, reinflate, and then suction the excess dye.

Although we do not have a separate consent form, we do discuss the chromoendoscopy intent, limitations, and method with the patient. It is important to let patients know that they will be passing blue dye rectally after the procedure and that they should not be alarmed. In addition, the dye will stain clothing. Whereas all this may seem obvious, failure to have this discussion may lead to panicked phone calls and unhappy patients.

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The use of chromoendoscopy has 2 primary goals: (1) to enable the endoscopist to visualize subtle lesions more readily, increasing the sensitivity of lesions; and (2) to help the endoscopist better characterize the lesion that was identified (primarily lesion extent and histologic features), thus improving lesion specificity. In general, there are 3 classes of dyes (absorptive, contrast, and reactive), of which the first 2 are the most commonly used to perform chromoendoscopy in patients with IBD.

Methylene blue (also known as methylthioninium chloride) is an absorptive dye, which is absorbed by certain cells, specifically noninflamed mucosa, but is poorly absorbed in areas of active inflammation and areas of intraepithelial neoplasia. The absorption typically takes up to 60 seconds to occur and persists for approximately 20 minutes.

Indigo carmine (sodium indigotindisulfonate) is a blue contrast dye (used as a food dye) that acts to coat the colonic mucosal surface and highlight tissue architecture. Indigo carmine (in typical concentrations of 0.2% to 0.4%) is sprayed on the colonic mucosa. The pit pattern of the colonic surface becomes highlighted, and disruption, indicating inflammation or changes of the normal pattern resulting from hyperplasia or intraepithelial neoplasia, can be readily identified. The contrast staining persists for only a few minutes.

These 2 agents have never been compared to each other prospectively in a randomized, appropriately controlled fashion in IBD patients. The disadvantages of methylene blue are that it takes somewhat longer to use because at least 60 seconds need to pass before the dye

can be viewed, and its use should be avoided in patients deficient in glucose-6-phosphate-dehydrogenase because it can cause methemoglobinemia in this patient population. In addition, methylene blue is a potent monoamine oxidase-A inhibitor. Serotonin syndrome has been described in patients using long-term serotonin reuptake inhibitor therapy who have received methylene blue. Last, methylene blue stains more than indigo carmine and is difficult to clean off skin if contact occurs.

Given the aforementioned issues, indigo carmine has become my preferred agent for chromoendoscopy. When used in the intravenous formulation, it possesses vasopressor properties; however, this has not been described in patients undergoing chromoendoscopy. With either agent, I usually use an initial diluted formulation; if a lesion of concern is found, a more concentrated formulation is then used to better define and characterize the lesion.

Question 3: When do you perform simultaneous dye spray chromoendoscopy with targeted biopsies in addition to 4-quadrant every 10-cm biopsies, or is it sufficient to perform only 1 modality?

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The practice of random 4-quadrant biopsies has long been the standard of care for ulcerative colitis dysplasia surveillance. The hope was that the use of chromoendoscopy would eliminate this requirement, given the very low yield of random nontargeted biopsies. Unfortunately, no consensus has been reached with different recommendations across national and international societies.[1]

Avoiding random biopsies would decrease the pathology cost and also make up for the additional time required to perform chromoendoscopy. The additional time is a serious impediment to the adoption of this technique across all practice settings. Unfortunately, the SCENIC group did not achieve a consensus on recommending against nontargeted biopsies after review of the literature, citing that 10% of patients who receive a diagnosis of dysplasia have it found on random biopsy. Again, this is based largely on studies with SD colonoscopy. Even with HD chromoendoscopy, a small but important rate of dysplasia detection on random biopsy was found.[2] However, the importance of finding dysplasia on random biopsy has been questioned.

In a Dutch ulcerative colitis surveillance program, only 4 patients with invisible dysplasia were identified from more than 1000 SD colonoscopies.[3] In these 4 patients, 1 had unifocal dysplasia and 2 had visible dysplasia on previous colonoscopies; we would have performed chromoendoscopy for follow-up. One patient required colectomy because of multifocal dysplasia and suggestive ulcerated areas on colonoscopy. In our practice, given that we perform HD chromoendoscopy only on high-risk patients, we do standard random biopsies because of the higher anticipated yield of dysplasia in this population. Although the long-term outcome of the finding of "invisible dysplasia" is not known, we will continue this practice until provided conclusive evidence to the contrary.

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2. Subramanian V, Ramappa V, Telakis E, et al. Comparison of high definition to standard white light for the detection of dysplastic lesions during surveillance colonoscopy in patients with colonic inflammatory bowel disease. Inflamm Bowel Dis 2013;19:350-5.
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The question as to what magnitude of risk (the dysplasia miss rate) is considered acceptable to patients remains the crux of this question. It has been estimated that 1088 to 2707 random biopsies are required to detect 1 specimen with dysplasia. This is based on retrospective post hoc data. In light of these data, and after discussion with the patient, I typically forgo random biopsies when doing chromoendoscopy. Additionally, it is important to recognize that when random biopsies are done, more specimens are taken overall. It has been suggested that taking a large number of specimens distracts the endoscopist from performing an examination as carefully as he or she should. This might cause failure of the endoscopist to focus on an important lesion that should have been a key focus. This last point remains conjecture, although it seems plausible.

Question 4: Are there any disadvantages or risks to the use of dye spray chromoendoscopy and any situations in which it may be contraindicated?

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The disadvantage of dye spraying is added time. Unfortunately, the failure of SCENIC to endorse abandoning random biopsies when using chromoendoscopy has made this technique less attractive to busy endoscopy practices. Overall, about 11 minutes are added to the procedure when chromoendoscopy is performed by experienced hands.[1] The learning curve is more about reducing the time needed for the procedure than it is about dysplasia detection.

We have found that it takes an endoscopist about 15 procedures to become proficient, as measured by withdrawal time from the cecum.[2] Others have shown that even among inexperienced endoscopists, there was no learning curve for dysplasia detection, and this should not be a barrier to implementation.[3,4] These studies start with a library of images presented to the endoscopist learning the technique, which is essential. I would also suggest some supervision by an experienced endoscopist to assure optimal technique for efficiency and dysplasia detection, but this is not absolutely required. Those who perform this technique should track their dysplasia/polyp detection rate to assure quality.

Dye spray would be strictly contraindicated for patients with true allergies or sensitivities to a particular dye. This is a potential issue with methylene blue because it is an absorptive dye, but allergy or sensitivity is rarely seen in practice. Adverse reactions to methylene blue have been described when it is given intravenously for other indications, but not when sprayed over GI mucosal surfaces. It should be avoided in patients with prior sensitivity. Methylene blue was also associated with DNA damage in 1 report when it was used for Barrett's surveillance. The meaning of this finding was not clear, and no harm has been demonstrated.[5] Indigo carmine is not absorbed and is quite safe; adverse reactions are extremely rare. Overall, both dyes are considered equally safe for topical application within the colon.

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The disadvantages of methylene blue are that it takes somewhat longer to use because at least 60 seconds need to pass before the dye can be viewed, and its use should be avoided in patients deficient in glucose-6-phosphate-dehydrogenase because it can cause methemoglobinemia in this patient population. In addition, methylene blue is a potent monoamine oxidase-A inhibitor. Serotonin syndrome has been described in patients using long-term serotonin reuptake inhibitor therapy who have received methylene blue.

Question 5: What is the role of digital chromoendoscopy (such as narrow-band imaging) with or without dye spray chromoendoscopy in IBD surveillance?

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Narrow-band imaging is a very attractive in-scope method that highlights blood vessel architecture and mucosal surface characteristics. Studies in ulcerative colitis surveillance, unfortunately, have not found it to be useful in dysplasia detection in comparison with SD[1] and HD.[2,3] This is due to the background of chronic colitis with altered vasculature and abnormal surface characteristics. Lesion detection overall (dysplastic and nondysplastic) was significantly higher when chromoendoscopy was compared directly with narrow-band imaging in 2 studies. However, although numerically HD chromoendoscopy detected more dysplasia (on both a per-lesion and a per-patient basis), its superiority could not be demonstrated, likely because of a small sample size.[4,5] We find narrow-band imaging difficult to use in ulcerative colitis patients because of all of the background distortion, and on the basis of current evidence, we do not use it for dysplasia detection. Other technologies such as i-scan (Pentax; Medical, Montvale, NJ) and Fujifilm Intelligent Chromoendoscopy (Medical Systems USA, Inc, Wayne, NJ) have not been sufficiently studied in dysplasia surveillance, and we also do not use them as part of our surveillance program.

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At present, there is no established role for digital chromoendoscopy in IBD surveillance. The use of digital chromoendoscopy has not been demonstrated to add any benefit to HD white-light endoscopy in this setting. Several different chromoendoscopy techniques exist. (1) Narrow-band imaging (Olympus; Corporation of the Americas, Center Valley, Pa) accentuates the vascular and mucosal architecture but has not demonstrated improvement in the recognition of dysplasia in comparison with white-light colonoscopy. A recent study demonstrated similar efficacy of narrow-band imaging to chromoendoscopy.[1] (2) Flexible spectral imaging color enhancement (FICE, Fujifilm) and (3) i-scan (Pentax) both use a computer algorithm to alter the white-light image; however, these last 2 modalities have not been prospectively studied in patients with IBD.

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Question 6: In cases of isolated polyps with normal-appearing surrounding mucosa, does dye spray chromoendoscopy provide any additional information, and do we need to take biopsy specimens around the polyp to identify field defects?

PRO
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In cases of isolated polyps with normal surrounding mucosa, the addition of dye spray chromoendoscopy does assist in clearly defining the borders of the lesion. This is more important in SD, but I would argue that it is also important in HD colonoscopy. Although the surrounding mucosa may appear normal, dye spraying will delineate the borders better and reveal subtle characteristics that might suggest chronic inflammation that otherwise may not be apparent.

There has been a paradigm shift in the description of lesions in ulcerative colitis to assess endoscopic resectability.[1,2] The older terms "dysplasia-associated lesion or mass" (DALM), with its ominous connotation, and "adenoma-like mass" (ALM), with its benign connotation, have been abandoned. Lesions should now be described as polypoid or nonpolypoid and whether they are endoscopically resectable. Polypoid lesions are those that are sessile or pedunculated and can be removed by most endoscopists. Nonpolypoid lesions are those that are minimally elevated, flat, or depressed and may need an endoscopist with advanced skills in EMR. The borders of these lesions are more difficult to delineate without chromoendoscopy. Ulceration within a lesion suggests unresectability, but in its absence, the indistinct margins also suggest unresectability.

Delineation of lesion borders is essential because patients with unresectable lesions are referred for colectomy. Lesions that would previously be considered unresectable can now be better visualized through chromoendoscopy and can be safely removed with continued, more intensive surveillance. Given the consequences of a decision regarding resectability, we do perform HD chromoendoscopy as the best way to delineate lesion margins. Even when chromoendoscopy is performed, biopsies around the area of the polyp are recommended.[1,2] This is particularly important in nonpolypoid lesions. Whereas we do perform biopsies around the polyp, in our experience it is rare to find dysplasia (or tissue suggesting inadequate polyp removal), and evidence for this practice has not been demonstrated.

1. Soetikno R, Subramanian V, Kaltenbach T, et al. The detection of non-polypoid (flat and depressed) colorectal neoplasms in patients with inflammatory bowel disease. Gastroenterology 2013;144:1349-52.
2. Laine L, Kaltenbach T, Barkin A, et al. SCENIC International consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastroenterology 2015;148:639-51.

CON
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Although Society guidelines (European Crohn's and Colitis Organisation (ECCO), 2013)[1] and the 2015 SCENIC consensus statement (American Gastroenterological Association [AGA] and American Society for Gastrointestinal Endoscopy [ASGE])[2] advocate that mucosal biopsy specimens should be obtained from the area immediately surrounding the resected polyp to help identify whether there is adjacent dysplasia, the evidence supporting this suggestion in the era of HD white-light endoscopy is lacking. Although this possibility has not been formally tested in a prospective fashion, a recent retrospective analysis of 302 polyps in 131 patients with IBD demonstrated that dysplasia in adjacent biopsy specimens was detected in 2 patients (0.7%) and was endoscopically visible in both cases. The authors noted that the proportion of endoscopically unsuspected dysplasia revealed by adjacent biopsy specimens was 0/300 (0%; 95% confidence interval, 0% to 1.6%). The authors emphasized that the diagnostic yield for "polyp adjacent" biopsy specimens in patients with IBD is negligible, and they suggest that "with contemporary use of high-definition technology and chromoendoscopy, it is no longer necessary to biopsy endoscopically normal adjacent tissue to detect invisible dysplasia."[3] Further evaluation will be needed to confirm these preliminary

findings before the implementation of changes in practice.

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DISCLOSURE

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Abbreviations: AGA, American Gastroenterological Association; ALM, adenoma-like mass; ASGE, American Society for Gastrointestinal Endoscopy; DALM, dysplasia-associated lesion or mass; ECCO, European Crohn's and Colitis Organisation; HD, high-definition; IBD, inflammatory bowel disease; SCENIC, Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Irritable Bowel Disease; SD, standard-definition.