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Detecting and Managing Dysplasia in Inflammatory Bowel Disease: 5 Key Tips



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INTRODUCTION

Colorectal cancer (CRC) is a feared complication of inflammatory bowel disease (IBD). Long-standing inflammation of the colon, a feature of both ulcerative colitis (UC) and Crohn's disease (CD) of the colon, can cause genetic and epigenetic changes that lead to neoplastic transformation called dysplasia. If dysplastic lesions are allowed to continue, they ultimately progress to cancer. It is well known that the risk of CRC is driven primarily by extent and duration of inflammation. Except for histological inflammation at colonoscopy, most other risk factors are not potentially modifiable such as family history of colon cancer, presence of pseudopolyps, primary sclerosing cholangitis and of course extent and duration of disease. Some of these non-modifiable risk factors

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therefore serve as ways of identifying at risk patients who should undergo screening and surveillance colonoscopy.

The field of IBD-related CRC prevention is evolving. Fortunately, important advances in disease management to control inflammation (primary prevention) as well as improved detection of precancerous lesions (secondary prevention) have transformed how we think about colorectal cancer and how we detect and manage dysplasia today even compared to 10 years ago.¹ The following review discusses 5 key tips for detecting and managing dysplasia in patients with IBD today.

1. Look for Dysplasia in the Right Patient

Several published guidelines recommended colon cancer screening and surveillance in patients with inflammatory bowel disease. Although the data demonstrating cancer screening in IBD reduces CRC mortality are limited, they are balanced by data demonstrating reduction

in CRC risk over time in surveillance programs.² Three United States (US) based major gastrointestinal societies, American Gastroenterological Association (AGA),³ American College of Gastroenterology (ACG)⁴ and American Society of Gastrointestinal Endoscopy (ASGE)⁵ all endorse colonoscopy-based screening and surveillance in patients with IBD (Table 1).

The first key thing to note is that while patients with IBD may get frequent colonoscopy, this often occurs in the setting of active disease and work up of symptoms. In contrast, colonoscopy performed for the purpose of screening should occur when disease is quiescent and otherwise would not have been performed. Although obviously “opportunistic screening” can occur during a symptom-indicated colonoscopy, analogous to removing a polyp in the work-up of a non-IBD patient who has diarrhea or abdominal pain, the fact is that these should not be considered pure screening. Symptom-based colonoscopies performed in patients with IBD or those with active inflammation should not be considered strictly screening unless inflammation is minimal as inflammation can obscure the presence of dysplastic lesions.

Regardless of the guideline used, the three US-based guidelines all make a recommendation for a first screening colonoscopy and then a recommendation for subsequent colonoscopies assuming no dysplasia is found. Almost all recommend performing the first screening colonoscopy within 8-10 years after diagnosis or alternatively, symptom onset, in all patients regardless of extent. The exception is in patients diagnosed with primary sclerosing cholangitis where it should occur immediately after the diagnosis of PSC. The latter recommendation is based on epidemiologic data showing a significantly increased colon cancer incidence in patients with PSC and that PSC patients often have occult low-grade clinical inflammation, therefore making assessment of disease duration a challenge. Biopsies should be taken in the right and left colon as well as the rectum, as subsequent intervals should be based on the degree of histological inflammation.

Assuming the colonoscopy did not detect dysplasia, guidelines vary with regard to the next colonoscopy, but they all recommend more frequent colonoscopy than the general population. Patients with isolated proctitis, Crohn’s involving less than one third of the colon, or isolated small bowel Crohn’s, do not need subsequent intense surveillance as their risk of colon cancer approximates that of the general population. For

all other patients, the intervals between colonoscopies for IBD patients vary between one and three years depending on the guideline with wide latitude regarding criteria for the subsequent interval. The British society of Gastroenterology Guidelines, not included in the table, risk stratifies subsequent colonoscopies based on degree of inflammation and other risk features so that patients with the lowest risk features may not need the next colonoscopy for five years. Such an extension to five years for surveillance has not formally entered into US-based guidelines, although not unreasonable for low risk patients with no evidence of pseudopolyps and no symptoms or evidence of inflammation on colonoscopy over many years.

2. Focus on Mucosal Abnormalities, Not Simply Random Biopsies During Colonoscopy

The classic technique for performing screening and surveillance involves taking 33 random biopsies throughout the colon. This approach is quite different to what we do during screening colonoscopies in patients without IBD. This unique approach for screening and surveillance in patients with IBD was based on the common notion nicely summarized in a 1995 review article that 95% of dysplastic foci occurred in patients in flat mucosa and was essentially invisible and only occasionally visible macroscopically.⁶ With improved resolution colonoscopes, cables and monitors over the past decade, this notion has changed. More recent data suggest that most dysplasia is visible, not invisible, and the overall yield of random biopsies is low. Even so, other studies show nearly 25% of dysplasia discovered on colonoscopy is from random biopsies and not visible.⁷ As the need and value of random biopsies is debated, the more relevant question is whether these invisible lesions are truly invisible or simply hard to see. Recent data suggest strategies for enhancing dysplasia detection may be useful for detecting these “invisible” lesions, perhaps obviating the need for random biopsies.

Introduction of enhanced dysplasia detecting techniques such as chromoendoscopy as well as data showing each additional minute of withdrawal time increased the flat dysplasia rate by 3.5% suggests these strategies may help reduce the invisible dysplasia rate even further and potentially eliminate the need for random biopsies. An important take home is that even when the dysplasia is visible, it may not look like a classic polyp. The 1995 review that reported that 95%

Table 1. Society-based Guidelines for Colorectal Cancer Screening in IBD Patients

Society	First Colonoscopy (screening)	Subsequent Colonoscopy Interval
American College of Gastroenterology (2010)	All patients 8-10 years after diagnosis Immediately in PSC	-Every 1-2 years
American Gastroenterological Association (2010)	All patients 8-10 years after symptom onset	-Every 1-2 years after screening -Every 1-3 years after 2 negative examinations
American Society of Gastrointestinal Endoscopy (2015)	All patients at 8 years after diagnosis with restaging biopsies	-Every 1-3 years -Interval can be lengthened in patients with endoscopically and histologically normal mucosa on 2 surveillance colonoscopies

of dysplasia is not visible endoscopically, also noted that when it is seen, it may be subtle, such as an irregularity, discoloration or nodularity that could be obscured by inflammation. This description of what subtle dysplasia looks like is probably still relevant today. What has changed is that likely what we thought was invisible dysplasia is now at least partly visible with better control of inflammation, technologic improvement of scopes and monitors and better appreciation of subtle findings on colonoscopy.

Thus, besides trying to reduce inflammation as much as possible when performing surveillance, it is important to focus and biopsy anything that may look different than its neighbor or catches one's attention. If a lesion looks particularly concerning, marking the area with India Ink will be helpful for finding the lesion in the future should the biopsies show dysplasia. Despite this, we must still recognize that lesions can be missed because they can be subtle and blend easily with the surrounding inflammation.

3. Chromoendoscopy but Not Virtual Chromoendoscopy Improves IBD Dysplasia Detection Rate

Chromoendoscopy involves the application of dilute methylene blue or indigo carmine during colonoscopy to the mucosa of the colon with the goal of improving visualization of dysplasia. This is achieved by enhancing contour differences between the lesion

and the surrounding mucosa as well as differential uptake of stain between normal and dysplastic tissue. Several studies have now shown this strategy improves detection of dysplasia in IBD patients over white light, particularly when using standard definition colonoscopes. So called "virtual chromoendoscopy" on the other hand is alteration of the image by the processor to create a pseudocolored image designed to enhance the detection of subtle colonic lesions. These are often proprietary technologies such as narrow band imaging (Olympus) or iscan (Pentax) to name two. However, despite the utility of these technologies to better define lesions, clinical trials have not shown that they improve the detection of dysplastic lesions over white light colonoscopy. Thus, if one wanted to engage in an evidence-based enhanced dysplasia detection technique that contains the word "chromo", dye needs to be sprayed on the colon.

A recent review on the how to perform chromoendoscopy is a useful reference for those who want to learn the technique.⁸ It is important that the patient is well prepared to perform chromoendoscopy. The dye is diluted and can be applied via spray catheter or foot pump. Recommended is to exchange the water irrigation with contrast solution if using the foot pump once the cecum is reached. The dye should be applied circumferentially while withdrawing, spraying on the anti-gravity side. Typically, the colon is examined

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in 20-30 cm segments, once with white light, then reinserting and applying the dye and examining a second time after the dye has been applied. Suspicious areas should be targeted for biopsies or if resectable, removed endoscopically.

4. Avoid Older Terms like DALM and ALM to Describe and Manage Dysplasia

The traditional description of dysplasia involved such terms such as flat dysplasia, dysplasia associated lesion or mass (DALM), adenoma like lesion or mass (ALM) and adenomatous polyps. The problem with these terms is that the definitions were quite vague. For example, the ALM and adenomatous polyp were often indistinguishable clinically. The difference between the DALM and ALM was a functional one, where the DALM was a lesion that could not be resected endoscopically or biopsies surrounding the lesion showed evidence of dysplasia whereas the ALM could be resected endoscopically or had no dysplasia on biopsies surrounding the lesion. Flat dysplasia also produced semantic problems it was it was not always clear if what was meant was visible lesions that were wider than tall or those not seen visually but detected on random biopsies during colonoscopy. Although there is no formal consensus on the optimal way to describe dysplasia in IBD, consensus is to abandon the use of terms such as DALM, ALM and flat dysplasia

for terminology already in use for patients without IBD.

What has been proposed is to first dichotomize dysplasia into visible or invisible dysplasia (the latter detected solely on random biopsies).⁹ Visible dysplasia should be defined into one of 3 categories of lesions that should be familiar to practicing gastroenterologists: 1) pedunculated (lesion attached to mucosa by a stalk); 2) sessile (lesion not attached to mucosa by stalk, entire based is contiguous); and 3) non-polypoid (lesion <2.5 mm above the mucosa with little or no protrusion above the mucosa. Non-polypoid dysplasia perhaps is the term least used by gastroenterologists but it is easy to define: 2.5mm is the half the height of the cup of a closed biopsy forceps.

Once defined this way, one can apply more standard principles of polyp/dysplasia management that are familiar to most gastroenterologists. For example, when managing dysplastic lesions in patients without IBD (such as a tubular adenoma), the first step in management is to define whether the lesion is discreet and endoscopically resectable either by the gastroenterologist performing the procedure or by someone else employing advanced endoscopic technique. One distinction to note is that in patients with IBD, the disease itself can cause scarring in the underlying mucosa, so lesions may be more difficult to lift and resect than the same lesion in a patient without IBD. If marking the lesion with India Ink, it is helpful to pick the wall opposite the lesion, especially if referring

Table 2. 2010 AGA Guidelines for Dysplasia Management and Reduction in Patients with “Flat” or Invisible Dysplasia Over Time

Question:	Should Colectomy Be Performed for Flat Dysplasia?	Should Colectomy Be Performed for Raised Dysplasia?
	<p>GRADE A: Colectomy for flat HGD (high grade dysplasia)</p> <p>Grade Insufficient: Insufficient data to assess balance of benefits and harms of colectomy for flat LGD (low grade dysplasia)</p>	<p>GRADE A: Colectomy for non-adenoma-like dysplasia lesion or mass (DALM)</p> <p>GRADE A: Polypectomy and continued surveillance for adenoma-like lesion of mass (ALM) and no evidence of flat dysplasia elsewhere in colon</p>
Tytgat 1995	95%	5%
Rutter 2004	23%	77%

to someone else, as the India Ink itself can cause scarring if injected nearby the lesion. This approach of defining management of visible dysplastic lesions in IBD based on the same principles of endoscopic management in patients without IBD represents a further evolution of managing dysplasia in IBD with less surgery that has been occurring over the past 15-20 years. Even so, it is important to note that this strategy, while reasoned and based on experience and some evidence, has not been validated.

5. Most IBD Patients with Dysplasia Do Not Need Surgery, but Some Do

Two seminal studies published in the late 1990s changed our thinking on the need for surgery on most patients with IBD and visible dysplasia. These studies ushered in the term “ALM” and suggested that these discrete polyps called “ALMs” with no surrounding dysplasia can be managed with polypectomy alone and did not need surgery. Another seminal study published in 2004 demonstrating that most dysplasia (roughly 75%) was visible, further moved the needle that perhaps if the lesion could be seen, even more patients could be eligible for polyp resection. This thinking was in contrast to the thinking just a decade before that most (95%) dysplasia in IBD was invisible and even when visible, appeared to be ill-defined lesions that could not be resected (Table 2).

That being said, the decision of how to manage any dysplastic lesions found on colonoscopy in a patient with IBD has to be individualized based on the appearance of the lesion, resectability of the lesion, degree of symptoms and inflammation and cannot be generalized into a single summary as to whether IBD dysplasia is managed surgically or endoscopically. Despite advances in optics and techniques, the fact is that even in the 2004 article that first observed that most IBD dysplasia was visible, one of 25 of the “invisible” dysplastic lesions were actually a cancer. Among the visible lesions, six of 85 were cancers but only one could be confirmed histologically at colectomy. Table 2 shows how the proportion of patients who may need surgery has changed. The management of invisible low-grade dysplasia (previously called flat) has been controversial, with the most recent 2010 AGA guidelines proposing an insufficient data to provide a recommendation regarding surgery vs. ongoing surveillance.³ The 2015 SCENIC consensus statement recommended performing a colonoscopy with chromoendoscopy in these patients

and include extensive random biopsies in the area of interest to at least determine whether the “invisible” lesion can be visualized with dye spray.⁹

CONCLUSION

The field of inflammatory bowel disease dysplasia is changing and studies suggest advances in reducing CRC risk in IBD likely due to improved control of inflammation (primary prevention) and surveillance colonoscopy (secondary prevention). Despite limitations in data, surveillance colonoscopy is a currently practiced strategy for IBD patients to prevent colon cancer. By following these 5 tips (choosing the right patient for surveillance, focusing on mucosal abnormalities not random biopsies, incorporating chromoendoscopy in the right patient, abandoning older terms to describe dysplasia and knowing that most patients do not need surgery when dysplasia is found but some do) the hope is to simplify and improve our ability to detect and manage dysplasia in patients with IBD and prevent mortality from colorectal cancer. ■

References

1. Velayos F, Kathpalia P, Finlayson E. Changing Paradigms in Detection of Dysplasia and Management of Patients With Inflammatory Bowel Disease: Is Colectomy Still Necessary? *Gastroenterology* 2017;152:440-50 e1.
2. Rutter MD, Saunders BP, Wilkinson KH, et al. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. *Gastroenterology* 2006;130:1030-8.
3. Farraye FA, Odze RD, Eaden J, et al. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology* 2010;138:738-45.
4. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010;105:501-23; quiz 24.
5. Shergill AK, Lightdale JR, Bruining DH, et al. The role of endoscopy in inflammatory bowel disease. *Gastrointest Endosc* 2015;81:1101-21 e1-13.
6. Tytgat GN, Dhir V, Gopinath N. Endoscopic appearance of dysplasia and cancer in inflammatory bowel disease. *Eur J Cancer* 1995;31A:1174-7.
7. Rutter MD, Saunders BP, Wilkinson KH, Kamm MA, Williams CB, Forbes A. Most dysplasia in ulcerative colitis is visible at colonoscopy. *Gastrointest Endosc* 2004;60:334-9.
8. Sanduleanu S, Kaltenbach T, Barkun A, et al. A roadmap to the implementation of chromoendoscopy in inflammatory bowel disease colonoscopy surveillance practice. *Gastrointest Endosc* 2016;83:213-22.
9. Laine L, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastrointest Endosc* 2015;81:489-501 e26.