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Best Practices for Dysplasia Detection, Surveillance and Management in IBD

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INTRODUCTION

The epidemiology of inflammatory bowel disease (IBD) related colorectal cancer (CRC) has changed significantly since publication of the first case report nearly a century ago. These changes have only accelerated in the past decade or two due to the widespread use of high-definition scopes to improve detection of dysplasia and advanced therapies to better control damaging and obscuring inflammation. Even so, the risk of colorectal cancer in IBD remains elevated. While strategies for describing, screening for, and managing dysplasia in IBD are much closer to general population screening than in prior years, several IBD-specific nuances exist. This article provides an updated assessment of colorectal cancer risk in IBD and summarizes some of these nuances into ten best practices for the detection, surveillance, and management of colonic dysplasia in inflammatory bowel disease.

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The Biologic Risk of Colorectal Cancer in IBD – Then and Now

Inflammatory bowel disease has historically been a high-risk condition for developing colorectal cancer.[1] Inflammation is a key driver of neoplasia via a cycle of chronic cellular damage and repair.[1] To define the true biologic risk of colorectal cancer it is helpful to look at epidemiologic studies performed before the widespread use of advanced therapies and high definition colonoscopes.

Ekbom et al. published two seminal studies evaluating the risk of colorectal cancer in a

population-based cohort diagnosed with ulcerative colitis or Crohn's disease between 1922 to 1983 and followed through 1984.[2,3] Compared to expected incidence, the incidence of colorectal cancer in ulcerative colitis was increased nearly sixfold (standardized incidence ratio (SIR)= 5.7, 95% confidence interval (CI): 4.6-7.0), with a clear risk gradient based on the extent of inflammation in the colon.[2] In Crohn's disease, the relative risk of colorectal cancer in Crohn's disease of the colon alone was also nearly sixfold (SIR=5.6, 95% CI: 2.1-12.2).[3] Less extensive disease was associated with a lower risk, and ileal disease alone did not harbor any increased risk (SIR= 1.0, 95% CI: 0.1-3.4).[3]

Fortunately, more recent cohorts have shown a reduction in colorectal cancer, although the risk still appears higher than the general population. A community based cohort from Northern California (1998 to 2010) reported an increased incidence of CRC for both ulcerative colitis (SIR=1.6, 95% CI: 1.3-2.0) and Crohn's disease (SIR=1.6, 95% CI: 1.2-2.0).[4] Similar findings were seen in a Scandinavian population-based study (1969-2017) with a numerically comparable risk in UC (Hazard ratio (HR)=1.7, 95% CI: 1.6-1.8) and Crohn's HR=1.4, 95% CI: 1.3-1.5).[5,6] Thus, despite advances in reducing colorectal cancer risk in IBD, IBD-specific CRC screening strategies are still needed. While the strategies for describing,

Table 1. Recommended surveillance intervals in inflammatory bowel disease

Society (Year)	Intervals
British Society of Gastroenterology (2019)[17]	**Annual:** PSC, FH CRC <50, dysplasia or stricture < 5 years, extensive colitis with **severe inflammation** **3 years:** PIP, FH CRC >50 years, extensive colitis with **mild** inflammation **5-year:** Extensive colitis with **no active inflammation** or left-sided colitis or Crohn's colitis <50% colon
American College of Gastroenterology (2019)[14]	**1-3 years:** based on combined risk factors for CRC findings on previous colonoscopy
American Gastroenterology Association (2021)[9]	**Annual:** PSC, FH CRC <50, dense PIP, high-risk dysplasia <5 years, moderate-severe inflammation (any extent) **2 or 3 years:** PIP, extensive mucosal scarring, FH CRC >50, low-risk dysplasia <5 years, prior dysplasia > 5 years, mild inflammation (any extent) **5 years:** continued disease remission, mucosal healing current exam AND • >= 2 consecutive exams without dysplasia OR • Minimal historical colitis (proctitis, < 1/3 colon CD) **Average risk:** isolated small bowel Crohn's
European Crohn's and Colitis Organization (2022)[11]	**Annual:** PSC, FH CRC <50, dysplasia or stricture < 5 years, extensive colitis with **severe inflammation** **2-3 years:** PIP, FH CRC >50 years, extensive colitis with **mild-moderate** inflammation **5-year:** Colon affecting <50%, extensive colitis with minimal inflammation

Abbreviations: PSC- primary sclerosing cholangitis; FH- family history; CRC- colorectal cancer; PIP- post-inflammatory polyp

screening for, and managing dysplasia in IBD are much closer to the general population than in prior years, several IBD-specific nuances exist.

These nuances are relevant because screening, discerning precancerous lesions, and removing them in an inflamed, ulcerated, or scarred colon can be challenging and quite different from general population screening. These nuances are summarized into ten best practices for the detection, surveillance, and management of colonic dysplasia in inflammatory bowel disease and designed to facilitate this endeavor.

Ten Best Practices for Screening and Dysplasia Detection and Management in IBD

1. Use the modified Paris classification to describe dysplasia.

Previously, the characterization of dysplasia in inflammatory bowel disease was quite distinct from general population screening.[7] A consensus guideline workshop from 2014 recommended abandoning this nomenclature, which characterized dysplastic lesions as either adenomatous polyps, adenoma like polyps, dysplastic associated lesions or masses, or flat dysplasia.[8] In its place, a more standard morphologic naming system, the Paris classification, was recommended with slight modifications for use in IBD. The workshop endorsed naming visible dysplastic lesions the same as in general population screening, specifically as either polypoid (subcategories sessile and pedunculated) or non-polypoid (subcategories elevated, flat or depressed). A third category, called invisible dysplasia, was meant to capture the phenomenon unique to IBD whereby dysplasia is unexpectedly detected in what was thought to be non-dysplastic, but inflamed colonic mucosa.[8]

Besides using the modified Paris classification, a best practice is to report when possible other key features of dysplasia, as these features may become relevant for determining feasibility of endoscopic resection at a second opinion.[9] These additional features include size, border clarity, location, if within an area of colitis, if any ulceration present, and any special techniques used to visualize, such as dye spray chromo endoscopy or narrow band imaging. In addition, if a resection is attempted, perceived completeness of resection should be noted.

2. Perform the first surveillance colonoscopy 8 to 10 years after symptom onset and immediately after a diagnosis of primary sclerosing cholangitis.[9]

Historic studies have shown a significant increase in dysplasia and cancer risk beginning around 10 years after disease onset.[10] Most current guidelines recommend a surveillance colonoscopy around 8 to 10 years after symptom or disease onset, depending on the guideline, even in patients with very limited disease.[9,11] Given patients with limited or minimal disease are most likely to not have had a colonoscopy since diagnosis, colonoscopy in these patients can help assess both the degree of current inflammation and whether there has been any progression of colitis. Patients with a diagnosis of primary sclerosing cholangitis should undergo screening immediately, given the association between subclinical inflammation and colon cancer.[9,11]

3. Focus on the fundamentals of dysplasia detection; recall that 90% of dysplasia is visible, even if subtle.[9]

It was only a generation ago, that only 5% of dysplasia in IBD was considered visible.[12] Thus, began the practice of random biopsies in an effort to detect otherwise invisible dysplasia.[7] Over time, enhanced dysplasia detection techniques such as dye spray chromoendoscopy were used to improve detecting subtle or atypical lesions. In fact, a more recent meta-analysis suggested a benefit for chromoendoscopy when using standard definition scopes, though interestingly not when using more modern high-definition scopes.[13]

The most recent American Gastroenterological Association Clinical Practice Updates on this topic emphasized focusing on the fundamentals of dysplasia detection, given that advances in both high-definition scopes, and better control of obscuring inflammation, has made dysplasia more visible, albeit still subtle.[9] These fundamentals include use of a high-definition scope for screening, screening when inflammation is quiescent, washing and carefully inspecting all fully visible mucosa, and taking targeted biopsies of suspicious mucosal abnormalities or sites of prior dysplasia.[9]

4. Enhanced dysplasia detection techniques should have a secondary, not primary role in dysplasia detection.

As a corollary of the above principle, enhanced dysplasia detection techniques, including non-targeted biopsies, dye spray chromoendoscopy, and "virtual chromoendoscopy" (narrow band imaging or iScan) have a complementary role in dysplasia detection, but their use should not be at the expense of the above fundamentals.[9] In fact, the efficacy of these supplementary techniques will likely be low if the above fundamentals are not present (meticulous inspection of the mucosa using a high-definition scope with a good bowel preparation in the setting of quiescent inflammation).

5. Take the randomness out of the random biopsy.

It was just slightly over a decade ago that taking up to 30-40 "random" biopsies throughout the colon was the standard for dysplasia detection in inflammatory bowel disease.[7] More recent guidelines have abandoned the term "random" biopsy for the preferred term "non targeted" biopsy, in part to emphasize the importance of context when interpreting the findings of biopsies.

The most recent AGA Clinical Practice Update on this topic categorized biopsies in IBD patients into three contexts help interpret results.[9] The first is *targeted biopsies*, defined as biopsies of a suspicious mucosal abnormality to rule out subtle dysplasia. The second category is *non-targeted biopsies*, defined as biopsies of non-suspicious areas to rule out invisible dysplasia. The third is *staging biopsies*, defined as biopsies of microscopically inflamed or uninflamed mucosa to assess histologic disease activity and extent. Beyond "forcing" context with these three categories, it is important to reflect and be aware any specific individual biopsy patterns which may give additional information beyond these categories. Thus, when possible, describing the appearance of the underlying mucosa where biopsies are taken can further assist in decision making, should biopsies reveal dysplasia.

6. Proactively look for signs of dysplasia.

Inflammation, ulceration, scarring of the mucosa, and post-inflammatory pseudopolyps can obscure subtle and sometimes not so subtle clues indicating dysplasia. Therefore, it is important to proactively look for findings suggesting possible dysplasia within this background abnormal mucosa. These findings include any inexplicable or ill-defined mucosal irregularity or subtle change in mucosal color, vascularity, nodularity, elevation, or ulceration.[9] This process can be simplified even further by looking for any mucosa that looks different than its neighbor and spending additional time examining it to determine if it merits biopsy.

7. Know that narrow band imaging is among several accepted enhanced dysplasia techniques.

Dye spray chromoendoscopy, the process by which methylene blue or indigo carmine is applied to the mucosa during colonoscopy to better accentuate subtle changes in elevation or pit pattern, has been shown to increase dysplasia detection in inflammatory bowel disease.[13] A recent meta-analysis reported a greater benefit when using older standard definition colonoscopes compared to high-definition scopes.[13] Virtual chromoendoscopy, whereby technologic processing in the scope produces accentuated pictures meant to highlight the same changes as dye spray chromoendoscopy, are often proprietary technologies including Narrow Band Imaging (Olympus) and iScan (Pentax), among others.

While initial studies showed no benefit to "virtual" chromoendoscopy, more recent studies have shown either a benefit of virtual chromoendoscopy over white light colonoscopy or equivalent performance compared to dye spray chromoendoscopy, leading several societies to endorse virtual chromoendoscopy as a reasonable alternative to dye spray chromoendoscopy.[9,11,14] While non-targeted biopsies typically are not recommended when virtual or dye spray chromoendoscopy are used, a French study suggested some additional benefit in the setting of primary sclerosing cholangitis, prior dysplasia, or a tubular colon.[15]

8. Manage visible dysplasia in IBD patients like in the non IBD population with a caveat: Endoscopic resection may be more challenging because of scarring from underlying colitis.

Advances in disease management and experience in removing large and complex lesions using endoscopic mucosal resection or endoscopic

surgical dissection, has changed how most visible dysplastic lesions in IBD are managed.[9,16] Instead of surgery, which was commonly recommended in the past, most lesions can now typically be managed with endoscopic resection, similar to the general population.[8] Even so, depending on the lesion, endoscopic resection may be challenging due to scarring from underlying colitis, thus necessitating consultation from an interventional endoscopist.

Most lesions less than 2 cm in size with clear border, without features of submucosal invasion or fibrosis and no histologic features of invasive cancer can typically undergo endoscopic resection with standard polypectomy techniques, followed by regular surveillance. In contrast, lesions that are larger than 2cm or complex based on a highly regular or indistinct borders or are laterally spreading, may be appropriate for endoscopic resection by an interventional endoscopist or may require surgery. Often this decision is based on local expertise, but it is reasonable to get a second opinion from an interventional endoscopist and IBD specialist. Finally, lesions that appear unresectable due to size, location, or where there are endoscopic features of invasive cancer should be referred for surgery.[9]

9. Treat invisible dysplasia as a special situation in IBD.

Invisible dysplasia, where dysplasia is incidentally diagnosed on biopsies taken from seemingly non-dysplastic mucosa, is a challenging and special situation in inflammatory bowel disease.[9] These situations are best managed by first, confirming the diagnosis of dysplasia with a second pathologist. Then, repeating the colonoscopy using dye spray chromoendoscopy, to unmask subtle dysplasia and determine resectability. If no lesion is found, then extensive biopsies in the area of prior dysplasia are recommended.

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10. Determine surveillance intervals based on 3 factors and avoid yearly surveillance except in those with the highest risk factors.

Determining screening intervals after a normal colonoscopy, regardless of whether someone has IBD or not, can be challenging, however there are three important factors to help guide this decision. The first is the inherent biology and natural history of the underlying condition or findings regarding future cancer risk. The second is the presence of any genetic or environmental modifiers. The third is other factors that can obscure the detection of precancerous lesions at that colonoscopy.

Based on these factors, most surveillance guidelines have categorized follow up into either a 1 year, 2-3 year, and 5 year option.[9,11,14,17] A 5-year surveillance is new to US-based guidelines, but designed for a very select subset of patients with minimal inflammation, evidence of mucosal healing, and a history of exams without dysplasia and minimal colitis. In fact, most patients likely are appropriate for two or three years. Annual colonoscopy is typically reserved for those at highest risk for dysplasia or cancer, such as primary sclerosing cholangitis, recent dysplasia, or evidence of severe inflammation. As a reminder, these are intervals for surveillance. There may be other reasons to perform a colonoscopy before a screening exam is indicated, such as evaluation of symptoms, abnormal biomarkers, or assessment of mucosal healing.

SUMMARY

The epidemiology of inflammatory bowel disease (IBD) related colorectal cancer (CRC) has changed significantly since publication of the first case report nearly a century ago. Despite advances in reducing colorectal cancer risk in IBD, IBD-specific CRC screening strategies are still needed. While the strategies for describing, screening for, and managing dysplasia in IBD are much closer to the general population than in prior years, discerning precancerous lesions, and removing them in an inflamed, ulcerated, or scarred colon can be challenging and thus some differences remain compared to general population screening. ■

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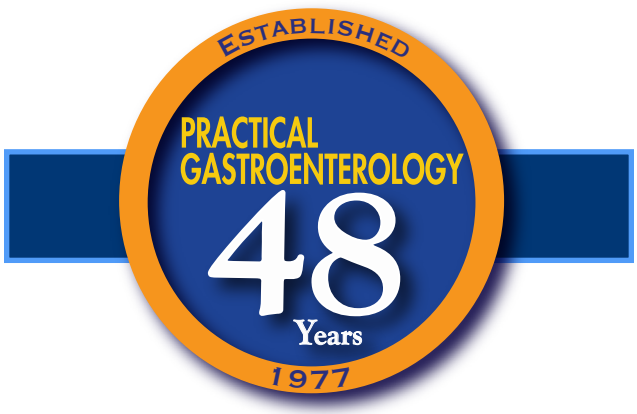

Answers to this month's crossword puzzle:

1 G	L	2 U	C	3 A	G	4 O	N	■	5 C	6 E	L	7 L	S	■
E	■	N	■	L	■	C	■	8 E	■	N	■	O	■	9 A
10 T	R	I	G	L	Y	C	E	R	I	D	E	S	■	N
■	■	T	■	E	■	U	■	G	■	E	■	11 E	12 T	A
13 B	I	■	■	14 R	A	R	E	■	15 U	R	E	S	I	S
I	■	16 S	■	G	■	■	■	17 P	■	M	■	■	18 P	T
19 O	B	E	20 S	E	■	21 D	O	R	22 M	A	N	23 T	■	O
P	■	24 C	A	N	■	E	■	25 E	A	T	■	26 R	I	M
27 T	28 O	R	N	■	29 E	X	O	C	R	I	N	E	■	O
30 E	N	E	■	31 L	■	T	■	E	■	C	■	M	■	S
32 R	E	T	R	O	G	R	33 A	D	E	■	■	34 B	35 M	I
I	■	I	■	N	■	36 A	L	E	■	37 F	38 I	L	E	S
39 N	40 O	N	■	41 G	42 A	L	L	S	43 T	O	N	E	■	■
■	R	■	44 O	■	B	■	A	■	45 U	C	■	46 D	47 I	P
■	48 B	O	R	B	O	R	Y	G	M	I	■	■	D	■