Dysplasia and Cancer in Inflammatory Bowel Disease

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KEYWORDS

• Inflammatory bowel disease • Ulcerative colitis • Crohn disease • Dysplasia
• Colorectal cancer • Colitis • Colitis-associated cancer

KEY POINTS

- Improved medical management and endoscopic surveillance of inflammatory bowel disease have reduced the incidence of cancer and its associated mortality.
- Surveillance should begin 6 to 10 years after initial diagnosis. Most societies recommend high-definition colonoscopy with chromoendoscopy and targeted biopsies when available.
- High-grade dysplasia or cancer are indications for surgical resection. Exceptions can be considered for lesions contained in discrete adenomalike polyps that can be removed completely.
- The management of low-grade dysplasia is controversial and the choice between continued surveillance versus colectomy should be discussed with patients.
- Most patients requiring surgery should undergo total proctocolectomy with end ileostomy or reconstruction with or without ileal pouch anal anastomosis.

INTRODUCTION

Inflammatory bowel disease (IBD) is associated with an increased risk of developing dysplasia and cancer.[1–3] Dysplasia and colitis-associated cancer (CAC) develop via a different pathway than sporadic cancer and are secondary to longstanding inflammation; they are linked to the duration and extent of disease.[4] Despite improvements in medical management and endoscopic surveillance, the optimal strategies for surveillance and decision for colectomy remain under debate. Herein we review the current literature regarding the risk of dysplasia and cancer in IBD patients, the

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pathogenesis of dysplasia and cancer, current surveillance guidelines, and best practices for managing these patients.

EPIDEMIOLOGY AND CANCER RISK

Cancer risk is increased in both ulcerative colitis (UC) and Crohn disease (CD) compared with the general population. A previously published population-based study over a 35-year period demonstrated an incidence of CAC to be 95 per 100,000.[5] It is, however, believed that this risk has decreased, particularly in UC. Whether this decrease has been due to improved surveillance techniques and technology or improved medical management of disease is unclear.[5,6]

It is generally believed that the risk of disease is related to the extent and duration of disease; however, reported data vary. Eaden and colleagues[7] performed a metaanalysis of 116 studies examining the risk of CRC in UC patients demonstrated the overall prevalence of CRC to be 3.7%. They reported cumulative incidence rate of 2% at 10 years, 8% at 20 years, and 18% at 30 years. In comparison, an analysis of a colonoscopic surveillance program in patients with UC found the cumulative incidence of CRC in UC to be 2.5% at 20 years, 7.6% at 30 years, and 10.8% at 40 years.[8] Similar findings have been noted in CD, with a reported incidence of 8% at 22 years, and a median duration of disease before a diagnosis of cancer (15 years for CD and 18 years for UC).[9,10]

A population-based study over a 60-year period from Olmsted County, Minnesota, demonstrated no significant increase of CAC in UC patients overall compared with the general population (standardized incidence ratio [SIR], 1.1; 95% confidence interval [CI], 0.4–2.4). However, there did seem to be a trend toward increased risk in those with extensive colitis. This study reported a cumulative incidence of CRC in UC patients of 0% at 5 years, 0.4% at 15 years, and 2% at 25 years after diagnosis of UC.[11] In those patients with CD, there also seemed to be a trend toward an increased incidence of CAC and there was a nearly 40-fold increase in risk of small bowel cancer (SIR, 40.6; 95% CI, 8.4–118). The cumulative risk of CRC in CD was reported as 0.3% at 5 years, 1.6% at 15 years, and 2.4% at 25 years after diagnosis.[11] The CESAME (Cancers Et Surrisque Associé aux Maladies Inflammatoires Intestinales En France) Study Group published an observational study of 19,486 patients with IBD and reported an SIR of 2.2 for all IBD patients. There was no increased risk in patients with limited disease (SIR, 1.1; 95% CI, 0.6–1.8). However, those with extensive colitis (>10 years and >50% of the colon involved) had a far greater risk of CAC (SIR, 7.0; 95% CI, 4.4–10.5).[12] Finally, a Manitoba Health study of 5529 patients observed over a 14-year period demonstrated an increased risk of colon cancer in UC (SIR, 2.8; 95% CI, 1.9–4.0) and CD (SIR, 2.6; 95% CI, 1.7–4.2). A nearly 2-fold increase in risk of rectal cancer was demonstrated only in the UC population and a 17-fold increase in risk of small bowel cancer was noted in the CD population.[13]

Other non–IBD-related risk factors for development of cancer exist, primarily a concomitant diagnosis of primary sclerosing cholangitis and a family history of CRC. Numerous studies have demonstrated an increased risk of CRC in patients with IBD and primary sclerosing cholangitis.[14] A metaanalysis found that the development of carcinoma or dysplasia in patients with UC and primary sclerosing cholangitis was increased (odds ratio [OR], 4.8; 95% CI, 3.6–6.4).[15] This risk has been reported to increase after liver transplantation.[16] Much like the general population, a family history of CRC imparts an increased risk of cancer in IBD. Askling and colleagues[17] reported that IBD patients with a positive family history of CRC had an increased relative risk compared with those with no family history of CRC (SIR, 31 [95% CI, 16–52] vs SIR,

14 [95% CI, 12–16]). This was also significantly greater if the patient was diagnosed before 50 years of age.

PATHOGENESIS

The pathogenesis of CAC seems to follow a different pathway from that of sporadic CRC. Colorectal dysplasia can be classified into 4 histologic criteria: negative for dysplasia, indefinite, low-grade dysplasia (LGD), or high-grade dysplasia (HGD).[18] In sporadic CRC, cancer typically develops within an adenoma and is believed to progress in an orderly fashion from LGD, to HGD, and finally to carcinoma. In contrast, the carcinogenic process in CAC seems to be driven by cellular damage from chronic inflammation and does not necessarily follow such an orderly fashion.[19] IBD patients may develop occult cancers in the absence of dysplasia,[20] or with only indefinite or LGD.[21,22]

Sporadic CRC commonly involves mutations the APC tumor suppressor gene or KRAS oncogene. IBD-related CRC have typically demonstrated early mutations in DCC, p53, IDH1, and MYC genes. Alterations in KRAS and APC seem to arise later if at all.[23,24] Whole-exome sequencing comparing sporadic and IBD-related CRC support these previous models, with sporadic tumors demonstrating altered WNT pathway genes (typically APC) and IBD-related tumors showing SOX9 inactivating mutations (which antagonize WNT/beta-catenin signaling).[23] In summary, the sequence from dysplasia to cancer in IBD patients is less predictable, and may occur at a rate faster than what is seen with the traditional adenoma to carcinoma sequence.

SCREENING AND SURVEILLANCE

Most current guidelines recommend starting surveillance colonoscopy 6 to 10 years after the diagnosis of IBD.[14] Recommended surveillance intervals vary by society, with some accounting for patient risk factors and others leaving it to clinician discretion (**Table 1**). The rate of missed malignancy in IBD patients is not insignificant and underscores the importance of an effective surveillance program, which depends on many factors: patient compliance, adequate bowel preparation, adequate mucosal sampling, and appropriate recognition of abnormal lesions. Wang and colleagues[25] reported a Surveillance, Epidemiology, and End Results database study on missed CRC with and without IBD and found that the rate of missed CRC was 5.8% for non-IBD patients compared with 15.1% for CD and 15.8% for UC ($P<.001$). Given these disparities and the relatively young age that CAC develops, continued efforts to improve surveillance techniques should be pursued.

The most common method of surveillance is traditional white-light endoscopy with random biopsies. General recommendations have been for biopsies in 4 quadrants every 10 cm with additional targeted biopsies of visible mucosal lesions. It has been reported previously that an estimated minimum of 33 biopsies from a single colonoscopy are needed to detect dysplasia with a greater than 90% probability.[26] As improvements in imaging technology have occurred and high-definition endoscopy has become more prevalent, it is believed that most dysplasia is, in fact, endoscopically visible and random biopsy may be low yield and less effective than a more targeted approach.[27,28] A recent retrospective review demonstrated that a median of 29 biopsies (range, 15–36) was obtained during surveillance colonoscopy in a population of UC patients and that only 0.2% of the specimens demonstrated dysplasia. This study also noted that UC-associated neoplasia was visible macroscopically in 94% of colonoscopies.[29] A recently published randomized trial compared the traditional strategy of random biopsies with targeted-only biopsies directly and found

Table 1
Comparison of IBD screening recommendations by society

Society, References	Timing and Indications of First Surveillance	Frequency of Surveillance	Surveillance Technique
American College of Gastroenterology[58,59]	8–10 y UC: Left-sided or extensive colitis; patients with proctitis or proctosigmoiditis alone are not at increased risk of cancer risk CD: Surveillance guidelines not yet determined	Every 1–2 y	Multiple biopsies at regular intervals Routine use of CE in low-risk patients awaits additional information regarding longer term follow-up Consider CE in "higher risk" patients (indefinite or known dysplasia not proceeding to colectomy) and to ensure adequacy of previous resection of polypoid or minimally raised lesions
American Gastroenterological Association[60]	8 y UC: All patients regardless of the extent of disease at initial diagnosis CD: Patients with disease affecting at least one-third of the colon	Extensive or left sided colitis: every 1–2 y After 2 negative examinations: consider every 1–3 y After 20 y of disease: consider every 1–2 y on an individualized based on risk factors PSC: every 1 y History of CRC in first-degree relatives; ongoing active endoscopic or histologic inflammation; anatomic abnormalities such as a foreshortened colon, stricture, or multiple inflammatory pseudopolyps: consider more frequent examinations	Multiple biopsies throughout the colon should be done at the first examination to assess the microscopic extent of inflammation Minimum of 33 biopsy specimens in patients with pancolitis CE with targeted biopsies is recommended if the endoscopist has sufficient experience
American Society of Colon and Rectal Surgeons[61]	8 y UC: All patients CD: No guidelines published	Patients with extensive colitis (disease proximal to the splenic flexure): every 1–2 y Patients with 2 successive negative colonoscopies: consider every 1–3 y PSC: annual	Minimum of 32 random biopsies (2 sets of 4-quadrant in each colonic segment) CE shows some promise but needs more research

American Society for Gastrointestinal Endoscopy[62]	8–10 y UC: Patients with macroscopic or histologic evidence of inflammation within and proximal to the sigmoid colon CD: Patients with >1 segment and/or one-third of colonic involvement	Every 1–3 y High risk (active inflammation, anatomic abnormality, stricture, multiple pseudopolyps), history of dysplasia, family history of CRC in first-degree relative, PSC): annual Patients with $\geq$2 negative colonoscopies, the surveillance interval can be lengthened	Colonoscopy with CE with resection or targeted biopsy of visible lesions is the preferred technique, consider 2 biopsies from each colonic segment for histologic staging Alternatively, random biopsies with targeted biopsies of suspicious lesions is reasonable Patients with pancolitis should have 4-quadrant biopsies every 10 cm, minimum 33 biopsies Patients without pancolitis should have 4 quadrant biopsies every 10 cm limited to greatest extent of involvement documented by any colonoscopy
European Cancer Organisation[63]	8 y UC, CD: onset of colitic symptoms to all patients	Low risk: schedule subsequent examination in 5 y Intermediate risk (extensive colitis with mild or moderate active inflammation; postinflammatory polyps or a family history of CRC in a first-degree relative at $\geq$50 y): schedule next examination in 2–3 y High risk (stricture or dysplasia detected within the past 5 y; PSC; extensive colitis with severe active inflammation; family history of CRC in a first degree relative <50 y): schedule next examination in 1 y	Colonoscopy with CE and targeted biopsies If the appropriate expertise with CE is not available, random biopsies (4 every 10 cm) should be performed; however, this is inferior to CE in the detection rate of neoplastic lesions

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Table 1
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Society, References	Timing and Indications of First Surveillance	Frequency of Surveillance	Surveillance Technique
NHS National Institute for Health and Clinical Excellence[64]	10 y UC: Patients with more involvement than proctitis CD: colitis involving >1 segment of colon	Low risk (extensive but quiescent UC; left-sided UC [but not proctitis alone] or Crohn's colitis of a similar extent): every 5 y Intermediate risk (extensive ulcerative or Crohn's colitis with mild active inflammation confirmed endoscopically or histologically; postinflammatory polyps; family history of CRC in a first-degree relative aged ≥50 y): every 3 y High risk (extensive ulcerative or Crohn's colitis with moderate or severe active inflammation confirmed endoscopically or histologically; PSC [before or after liver transplantation]; colonic stricture in the past 5 y; any grade of dysplasia in the past 5 y; family history of colorectal cancer in a first-degree relative <50 y): annual	Colonoscopy with CE

Abbreviations: CD, Crohn disease; CE, chromoendoscopy; CRC, colorectal cancer; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

Data from Refs.[58–64]

that targeted biopsy was as effective as a random biopsy approach for detecting neoplasia. The proportion of dysplasia was found to be higher in the targeted biopsy arm, causing the authors to suggest that the increased time performing random biopsies may result in suspicious lesions being overlooked owing to bleeding or distraction of the endoscopist.[30]

Chromoendoscopy (CE) uses a dye, such as methylene blue or indigo carmine, to stain the mucosa. This enhances the visualization of the mucosal surface to better detect abnormal areas. A metaanalysis of 6 studies, included 1277 patients comparing white-light endoscopy with CE, found a 7% differential in favor of CE for dysplasia detection, a 44% increase in lesion detection by targeted biopsy, and a 27% increase in proportion of flat dysplastic lesions detected.[31] Given the improved detection rate noted with CE, most societies recommend its use combined with targeted biopsies whenever the technology and expertise are available.[14]

Narrow band imaging uses blue and green wavelength light to better delineate mucosal vasculature. It does not seem to impart any significant increase in neoplasia detection rates when compared with standard or high-definition white-light endoscopy.[32,33]

Another promising technology is confocal laser endomicroscopy (CLE), which uses fluorescent agents to allow in vivo histologic examination. The correlation of CLE with histopathology is very high (κ = 0.91–0.94)[34] and a randomized trial found CE and CLE detected nearly 5 times more dysplasia then conventional colonoscopy with random biopsies.[35] The main limitations of CLE are limited equipment availability and increased procedure times (approximately double that of conventional colonoscopy).[34]

MANAGEMENT OF DYSPLASIA AND CANCER

The management of dysplasia in the setting of IBD is largely predicated on the likelihood for an underlying malignancy and the risk of future progression to malignancy. When patients have biopsies showing HGD, their risk of harboring an invasive malignancy is high (>40% as reported by Bernstein and colleagues[21]), and there is little debate about the seriousness of this situation. However, in patients with LGD, the risk of HGD or cancer is more variable and ranges from 10% to 50%.[21,22,36–38] There is likely minimal difference in the predictive value of dysplasia in patients with CD compared with UC. The presence of synchronous dysplasia in CD patients with CRC is nearly ubiquitous.[39] However, in CD patients without CRC, only 2% of colectomy specimens demonstrated dysplasia.[40]

The optimal management of LGD continues to be debated. Reported rates of progression to HGD or CRC are variable, ranging from zero to greater than 50%.[37,38,41] A metaanalysis of endoscopic surveillance of LGD in a UC population reported a significant increase in the risk of developing CRC (OR, 9.0; 95% CI, 4.0–20.5) or a more advanced lesion, such as HGD or CRC (OR, 11.9; 95% CI, 5.2–27).[42] Befrits and colleagues[41] have reported a lesser risk of progression to more advanced disease. In their study of 60 patients, LGD was found at several endoscopic examinations in various segments of the colon in 73% of patients. However, only 2 patients (both of whom had a dysplasia-associated lesion or mass [DALMs]) progressed to more advanced lesions in 10 years of follow-up.

Although some controversy remains regarding the management of unifocal LGD, some risk factors may exist that predict which of these lesions will progress to a more advanced lesion. Choi and colleagues[43] reported that lesions that are nonpolypoid, endoscopically invisible, 1 cm or larger, or preceded by indefinite dysplasia are

likely at increased risk for progression and should be considered for colectomy. These varied reports underscore the need to counsel patients regarding outcomes of continued surveillance versus surgery in the setting of LGD.[37]

The finding of HGD or CRC usually warrants surgical resection. Patients with UC should undergo total proctocolectomy with end ileostomy or ileal pouch anal anastomosis (IPAA). Approximately 12% to 55% of patients have been found to have an occult or synchronous cancer[21,43,44] and 48% have synchronous dysplasia.[44] Removal of the rectum is generally recommended because the rectum remains at risk, even if the dysplasia or cancer is located in the colon. However, it can be preserved in select patients with a plan for intensive surveillance. Approximately 2% of patients who have a retained rectal stump or who undergo ileorectal anastomoses develop cancer in their rectum.[45]

The type of lesion where the dysplasia is detected may also affect the risk of finding malignancy. Traditionally, lesions have been divided into endoscopically undetectable ("flat") and detectable ("elevated") lesions, with the latter also commonly referred to as DALMs.[2] DALMs are further classified into adenoma-like (polypoid) and nonadenoma-like (nonpolypoid). Adenoma-like DALMs, even those arising in areas of inflammation, behave like sporadic adenomas and can be safely treated with polypectomy and continued surveillance.[2] In contrast, nonadenoma-like DALMs can appear as velvety patches, plaques, irregular bumps and nodules, wartlike thickenings, stricturing lesions, or broad-based masses. Nonadenoma-like DALMs are generally not amenable to endoscopic removal techniques, and thus these patients should be referred for surgical resection.[2]

Patients found to have HGD arising in an adenoma-like DALM that is completely resected may be eligible for close follow-up with colonoscopy in 6 months in lieu of colectomy.[2] This is based on evidence showing that most dysplasia in IBD arises in detectable lesions amenable to endoscopic surveillance.[27] No head-to-head comparisons of polypectomy versus colectomy have been completed, but a small retrospective series found no progression to cancer after polypectomy for HGD with endoscopic follow-up after 6 years.[46] Additionally, a recently published metaanalysis of 10 studies including 376 patients examining endoscopic resection of adenoma-like DALMs found that progression to CRC was low (2.4% of patients after an average follow-up of 54 months). However, there was a 10-fold increased risk of developing dysplasia.[47] **Fig. 1** provides an algorithm for the management of dysplasia in the setting for IBD.[48]

In patients with UC, the presence of dysplasia or cancer is not a contraindication to reconstruction with IPAA. There is generally no impact to performance of restorative proctocolectomy in the setting of colon cancer. However, IPAA in the setting of locally advanced rectal cancer may lead to worse outcome, because preoperative pelvic radiation can impact pouch-related sepsis and long-term pouch function. Postoperative pelvic radiation after IPAA is an even more risky situation, and rarely allows for acceptable pouch function. Taylor and colleagues[49] reported on 17 patients who underwent IPAA in the setting of CRC. These patients had acceptable functional results; however, the use of adjuvant radiation did impact overall function. Another case series reported on 9 patients who underwent IPAA after pelvic radiation, 7 of which were due to rectal cancer,[50] and the pouch failure rate for this small group was 44%. Finally, Merchea and colleagues[51] published a series of UC patients with rectal cancer, including 11 patients undergoing IPAA. Two patients had a failed pouch, one of which was secondary to radiation enteritis. This paper concluded that patients with stage 1 rectal cancer not requiring neoadjuvant chemoradiotherapy can undergo restorative proctocolectomy with good functional results.

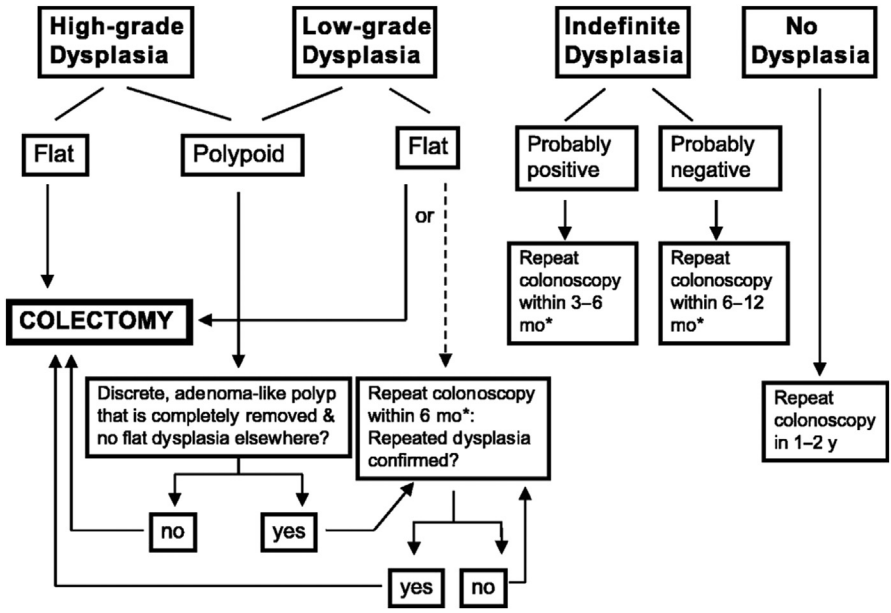

Fig. 1. Algorithm for the management of dysplasia in inflammatory bowel disease. *Duration of short-term surveillance has not been determined. (*From* Itzkowitz SH, Harpaz N. Diagnosis and management of dysplasia in patients with inflammatory bowel diseases. Gastroenterology 2004;126:1642; with permission.)

The most common method of creating IPAA is a double-stapled technique with a distal rectal anastomosis, preserving the anal transition zone. Compared with mucosectomy and a hand-sewn ileoanal anastomosis, a stapled IPAA leaves behind a small rim of at-risk mucosa. It is likely that a double-stapled technique has improved long-term functional outcomes compared with a hand-sewn technique; however, conflicting studies have been published.[52–54] Overall, metachronous cancers within the pouch or the anal transitional zone are rare, with one 2011 review demonstrating 43 known cases, including 30 patients with mucosectomy and 13 with a stapled anastomosis.[54]

Derikx and colleagues[45] reported the incidence of neoplasia after colectomy in IBD and found that, in the setting of IPAA, the prevalence of carcinoma in the pouch to be 0.5%. Limited evidence exists on the need for routine pouch surveillance. However, patients should be counseled to the potential risk of pouch carcinoma and occasional surveillance every few years, or when symptomatic, should be offered.[55]

Patients with CD and HGD, multifocal LGD, or invasive cancer should undergo total proctocolectomy. Approximately 40% of CD patients undergoing segmental resection or subtotal colectomy develop metachronous cancers, with 50% dying from the subsequent disease.[56] Furthermore, it has been reported that up to 44% of the patients with known malignancy will have multifocal disease in the final specimen and 40% may have evidence of dysplasia remote from the cancer site.[57] Because of the poor function associated with CD and IPAA, these patients typically require a permanent end ileostomy. In highly selected patients who are not willing have a permanent end ileostomy, and have "rectal sparing" with no active inflammation or dysplasia within the rectum, a total abdominal colectomy with ileorectal anastomosis can be considered as long as there is intense postoperative surveillance.

SUMMARY

Improvements in the medical management and endoscopic surveillance of IBD have reduced the incidence of cancer and its associated mortality. However, further research is needed to fully understand the molecular and genetic pathways unique to IBD-related dysplasia. Great debate still exists regarding the optimal strategy for determining which patients with early dysplasia can be managed endoscopically and which require radical surgery.

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