Advances in the Diagnosis and Management of Colonic Dysplasia in Patients With Inflammatory Bowel Disease

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Abstract: The prevalence of colorectal cancer (CRC) in inflammatory bowel disease (IBD) is estimated at 3.7%. Risk factors for CRC include more severe disease (as reflected by the extent of disease and the duration of poorly controlled disease), family history of CRC, pseudopolyps, primary sclerosing cholangitis, and male sex. In addition, both early and late onset of IBD have been shown to be risk factors in different studies. Most societal guidelines recommend initiation of surveillance colonoscopy at 8 to 10 years after IBD symptom onset, followed by subsequent surveillance in 1- to 2-year intervals. A recent paradigm shift has led to a focus on targeted biopsies using high-definition colonoscopy or chromoendoscopy rather than traditional white-light endoscopy, as most dysplasia has proven to be visible with these advances in technology. With this shift, endoscopic resection of focal dysplasia, rather than early recommendation for colectomy, has become commonplace. Future studies should focus on newer methods of dysplasia detection, along with comparative effectiveness trials, to determine the optimal approach. Individual risk stratification may also prove beneficial in determining optimal surveillance strategies and intervals.

Patients with inflammatory bowel disease (IBD) carry a higher risk of developing colorectal cancer (CRC) than the general population.[1,2] The risk is similar in Crohn's disease and ulcerative colitis, although CRC seems to present at a later stage in Crohn's disease compared to ulcerative colitis.[3-5] The prevalence of CRC in IBD is estimated at 3.7% according to an early meta-analysis.[1] Incidence rates of 0.2% to 2.0% at 10 years of disease, 1.4% to 8.0% at 20 years, and 3.1% to 18.0% at 30 years have been reported in the literature.[1,6] A more recent prospective study using the CESAME (Cancers et Surrisque Associé aux Maladies Inflammatoires Intestinales en France) cohort confirms the high risk of CRC in IBD with a standardized incidence ratio of 2.2 (95% CI, 1.5-3.0; *P*<.001).[7] An estimated 15% of IBD-related deaths are thought to be related to

CRC, making this an important topic to address in this population.[8]

Retrospective data suggest a higher risk for CRC in the setting of several risk factors.[9,10] Both early and late onset of IBD have been shown to be risk factors in different studies.[11,12] Other risk factors include family history of CRC,[13-15] pseudopolyps,[16,17] primary sclerosing cholangitis (PSC),[18] and male sex.[19,20] In addition, risk of CRC is thought to increase with a longer duration of disease[21] and active inflammation.[22] Extensive disease is also a risk factor, with pancolitis carrying a higher risk of CRC than left-sided colitis.[7] Proctitis, however, does not carry an increased CRC risk compared to the general population. Conversely, 5-aminosalicylic acid (5-ASA) agents appear to be protective against CRC and possibly responsible for the lower incidence of CRC in certain groups, as seen in a Danish cohort study.[8] 5-ASA agents have been shown in studies to prevent CRC with an odds ratio (OR) of 0.51 (95% CI, 0.37-0.69).[16,23] According to a meta-analysis, the number needed to treat to prevent 1 CRC in IBD was reported to be 63 at 10 years of disease and 7 at 30 years of disease.[8] However, a less severe phenotype of IBD may be confounding the difference in CRC in this meta-analysis.[8,24] Thiopurines may prove to be protective as well. In one study, patients on thiopurines were less likely to develop high-grade dysplasia or CRC according to a multivariate analysis.[7] Folic acid has also been studied in chemoprevention, with a trend toward significance. Given its low cost and side-effect profile, folic acid has been recommended by some gastroenterologists to prevent IBD-associated CRC.[25]

Pathogenesis

The pathogenesis of CRC in IBD follows an inflammation-dysplasia-carcinoma sequence.[26] Like sporadic CRC, there are 2 main pathways that play a role in carcinogenesis: the pathway of chromosomal instability and that of microsatellite instability. However, p53 mutations and microsatellite instability tend to occur earlier in colitis-associated dysplasia than in sporadic CRC.[27] Furthermore, molecular alterations occur in the setting of oxidative stress and reactive oxygen species, which are commonly seen in inflamed tissue and contribute to carcinogenesis in IBD.[27] Unlike sporadic CRC, inflammation-associated CRC tends to progress more often from nonpolypoid lesions and present with a higher rate of synchronous CRC.[5]

Timing of Surveillance

Colonoscopic surveillance allows for early detection of cancer or premalignant lesions.[24] Choi and colleagues conducted a retrospective analysis to compare IBD patients who had undergone surveillance to those who had not, and reported less advanced CRC on diagnosis and improved 5-year survival (77.2% vs 36.3%, respectively).[4] Provenzale and colleagues performed a cost-effectiveness analysis using a Markov model to determine whether surveillance colonoscopy is cost-effective compared to no surveillance for patients with ulcerative colitis.[28] The researchers found that surveillance colonoscopy had an incremental cost-effectiveness ratio ranging from $4700 to $250,000 for yearly surveillance.[28]

Current guidelines recommend initiating CRC surveillance at 8 to 10 years after onset of IBD symptoms for all ulcerative colitis patients excluding those with isolated proctitis and for Crohn's disease patients with at least one-third colonic involvement.[29-31] The British Society for Gastroenterology (BSG) recommends starting surveillance 8 to 10 years after symptom onset for pancolitis and 15 to 20 years after symptom onset for left-sided colitis.[31] Further, it recommends shorter surveillance intervals with each subsequent decade of disease duration. The American Gastroenterological Association guidelines are similar except that they recommend fixed interval surveillance every 1 to 2 years.[29] The BSG recommendations differ from other guidelines due to their inclusion of risk stratification in the determination of surveillance intervals.[31,32]

Methods of Surveillance

A comparison of surveillance methods for colonic dysplasia in patients with IBD appears in the Table. Colonic surveillance should occur when IBD is in remission. Numerous biopsies are required to accurately diagnose colonic dysplasia when using the surveillance method of random biopsies.[24] In order to reach a 90% sensitivity for colonic dysplasia, at least 33 random biopsies from around the colon are required.[33] Therefore, the traditional approach has been to take 4-quadrant biopsies every 10 cm throughout the colon, with targeted biopsies of any mucosal abnormalities.

Random biopsies only account for less than 1% of the colonic surface area; thus, a greater focus has been placed on targeted biopsies. Most dysplasia can be visualized on high-definition white-light endoscopy. A study in 2013 compared standard white-light to high-definition colonoscopy in the detection of colonic dysplasia in IBD, with higher dysplasia detection rates using high-definition colonoscopy.[34] In 2016, a retrospective study of patients undergoing surveillance colonoscopy from 2011 to 2014 revealed the superiority of targeted to random biopsies (8.2% vs 19.1%; P<.001), with similar detection rates regardless of whether targeted biopsies were obtained

Table. A Comparison of Surveillance Methods for Colonic Dysplasia in Patients With Inflammatory Bowel Disease

Surveillance Methods Compared	Study Type	Endpoint	Efficacy	Reference
Standard white-light vs high-definition colonoscopy	Retrospective	Dysplastic lesions	Adjusted prevalence ratio, 2.2 (95% CI, 1.1-4.5)	Subramanian et al[34]
Random vs targeted biopsies	Retrospective	Neoplastic lesions	8.2% vs 19.1% (*P*<.001)	Gasia et al[35]
Standard white-light colonoscopy vs chromoendoscopy	Meta-analysis	Dysplastic lesions	RR, 1.8 (95% CI, 1.2-2.6); absolute risk increase, 6% (95% CI, 3%-9%)	Laine et al[41]
Narrow-band imaging vs dye chromoendoscopy	Prospective	Intraepithelial neoplastic lesions	15.4% vs 46.1% (*P*=.2)	Pellisé et al[43]
Chromoendoscopy and endomicroscopy vs conventional colonoscopy	Prospective	Neoplastic lesions	19 vs 4 intraepithelial neoplastic lesions (*P*=.005)	Kiesslich et al[44]

RR, relative risk.

using high-definition colonoscopy, dye chromoendoscopy, or electronic chromoendoscopy.[35]

Targeted biopsies can be enhanced using chromoendoscopy, a surveillance method utilizing colored dye, usually either methylene blue or indigo carmine. The benefit of chromoendoscopy is that it can highlight subtle mucosal irregularities, leading to higher detection rates with a sensitivity of 93% to 97% and a specificity of 93%.[36,37] An early prospective, randomized, controlled trial demonstrated superiority of chromoendoscopy using methylene blue to a random-biopsy approach (12.4% vs 38.0%; *P*=.003).[37] In another study, 9 dysplastic lesions that were not found on random biopsies were detected using chromoendoscopy with indigo carmine solution.[38] Recently, a retrospective cohort study of patients with dysplasia undergoing chromoendoscopy following a positive standard white-light endoscopy revealed new lesions that were not detectable on initial colonoscopy, many of which were amenable to endoscopic resection; some lesions were already differentiated into multifocal dysplasia requiring a surgical resection.[39] The limitations of chromoendoscopy include its operator dependence, need for an adequate bowel preparation, and the concern that it might be too time-consuming.[40] The recently published SCENIC (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations) guidelines recommend chromoendoscopy over white-light endoscopy, whether using standard (strong recommendation) or high-definition (conditional recommendation) colonoscopy.[41] Although guidelines suggest moving toward targeted biopsies, random biopsies remain important as an alternative in the setting of inadequate bowel preparation or inflammation when chromoendoscopy may be limited.[41]

The use of an optical substitute to chromoendoscopy, such as narrow-band imaging (NBI), has also been considered.[40,42] However, a study comparing NBI to conventional colonoscopy did not show a difference in dysplasia detection. This prospective, randomized, controlled trial compared NBI to chromoendoscopy and found NBI to be less time-consuming and not significantly different in detecting CRC.[43] NBI had a lower false-positive rate, but it missed suspicious lesions with a nonsignificant miss rate difference of 30.7% (95% CI, -64.2% to 2.8%).[43] Given the miss rate in NBI as compared to chromoendoscopy, NBI is not considered a substitute for chromoendoscopy. A newer adjunct to chromoendoscopy is confocal laser endomicroscopy, which in combination with chromoendoscopy has shown an increase in diagnostic yield for CRC compared to chromoendoscopy or standard colonoscopy alone.[44] Noninvasive surveillance methods, such as stool DNA, have not been widely used or studied for IBD surveillance specifically, but studies are currently underway.

Diagnosis and Treatment

There are high rates of interobserver variation in the histologic diagnosis of low-grade dysplasia, leading to controversy on how to best manage these patients.[24] In a small retrospective study, 50% of patients with low-grade dysplasia developed advanced neoplasia.[45] In a population-based study of 692 IBD patients, 4.2% developed a flat dysplasia, and none progressed to cancer.[46] A retrospective cohort study evaluated 102 patients with IBD and

low-grade dysplasia and reported a low rate of progression to advanced neoplasia.[47] In this study, 4.9% of patients with low-grade dysplasia developed high-grade dysplasia or adenocarcinoma. Flat distal lesions were more likely to progress (hazard ratio, 3.6; 95% CI, 1.3-10.6).[47] Controversy remains on whether to proceed with colectomy in cases of low-grade dysplasia or continue with serial surveillance. A surveillance strategy of repeat endoscopic surveillance every 6 months with graduation to annual surveillance after 2 studies with negative findings has been proposed.[24] Surgery should be limited to patients with further risk factors for progression to CRC or a multifocal distribution.

Traditionally, the term dysplasia-associated lesion or mass (DALM) was used to describe endoscopically visible, raised lesions. Retrospective studies reported high rates of colorectal adenocarcinoma in patients undergoing colectomy for a nonendoscopically resectable DALM.[48-50] Nevertheless, small studies from the late 1990s have shown that endoscopic resection with subsequent surveillance was not inferior to surgery in patients with adenoma-like lesions.[51,52]

With regard to high-grade dysplasia, concurrent malignancy rates are high and estimated at 42%[48]; therefore, colectomy is recommended. However, with an increase in endoscopic mucosal resection, localized resection may be an option for select patients with localized high-grade dysplasia. A recent case series of endoscopic submucosal dissection demonstrated endoscopic cure without recurrence of dysplasia at 2-year follow-up.[53] A systematic review investigated the risk of CRC after endoscopic resection of a focal dysplastic lesion with a low risk of subsequent CRC with 5.3 cases (95% CI, 2.7-10.1) reported per 1000 patient-years.[54] However, the rate of subsequent dysplasia was significant with 65 cases (95% CI, 54-78) reported per 1000 patient-years.

Special Circumstances

Primary Sclerosing Cholangitis

Patients with PSC are at a particularly high risk for CRC.[55] A Swedish population-based study reported a 33% incidence at 20 years of disease duration.[56] Deoxycholic acid, a bile acid, is thought to possibly play a role in carcinogenesis in PSC. Current recommendations suggest starting colonoscopic surveillance immediately after diagnosis and following with annual surveillance thereafter.[24] Ursodeoxycholic acid has shown some benefit in reducing colonic dysplasia in this population (OR, 0.18; P=.01).[57] This is thought to be related in part to reduced colonic concentration of deoxycholic acid.[58] However, the CRC risk persists after orthotopic liver transplantation.[59]

Early-Onset Colorectal Cancer

Lutgens and colleagues published a retrospective study looking at the incidence of CRC in the IBD population in the Netherlands, with 17% to 22% presenting with CRC prior to the advised surveillance period of 8 to 10 years.[9] In the ENEIDA (Estudio Nacional en Enfermedad Inflamatoria Intestinal Sobre Determinantes Genéticos y Ambientales) registry, 42% of patients with ulcerative colitis and CRC were diagnosed with CRC within 8 years of ulcerative colitis diagnosis.[60] In a third study, Brackmann and colleagues described a 12% rate of CRC within 10 years of symptom onset and a 21% rate of CRC within 10 years of IBD diagnosis in a Norwegian population.[12] Significant rates of early-onset CRC have been reported in multiple populations. Based on these data, the most recent European consensus guidelines recommend initial surveillance at 6 to 8 years after onset of IBD symptoms, as compared to the more widespread recommendation of 8 to 10 years. Furthermore, these guidelines recommend risk-stratifying individuals based on extent of disease, presence of active inflammation, pseudopolyps, and family history.[61]

Ileal Pouch-Anal Anastomosis

No current guidelines exist for the surveillance or management of patients with pouch dysplasia. In a prospective cohort study, 40 patients with pouch dysplasia were identified, of which 22 had low-grade dysplasia.[62] Persistence or progression of low-grade dysplasia was found in 27.3% of these patients. These patients were more likely to have a family history of CRC (P=.029).[62] This is an area that would benefit from further research given the paucity of data in the literature.

Conclusion

Colonic dysplasia and CRC are a significant source of morbidity and mortality for individuals with IBD. Various studies have identified significant factors that may increase CRC risk among IBD patients. In addition, certain protective factors have given hope for chemopreventive strategies, with 5-ASA agents strongest among them. With the increased use of high-definition colonoscopy and chromoendoscopy, there has been a shift in ideology regarding dysplasia surveillance techniques with a focus on targeted rather than random biopsies. Along with this, endoscopic resection with subsequent surveillance has become a mainstay for focal dysplasia, rather than colectomy. The optimal use of confocal laser endomicroscopy, among the newer surveillance techniques, remains to be determined. CRC continues to be a considerable concern among IBD patients and gastroenterologists alike. Further research evaluating how to best individualize colonic

dysplasia surveillance and stratify individual risk by known predictive and protective factors is important to provide the best care to patients with IBD.

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