AGA Technical Review on the Diagnosis and Management of Colorectal Neoplasia in Inflammatory Bowel Disease

Podcast interview: www.gastro.org/gastropodcast.

Learning Objectives

This article has an accompanying continuing medical education activity on page e12. Upon completetion of reading this article, successful learners will be able to:

1. Understand the predisposing and protective factors for the development of colorectal neoplasia in patients with IBD
2. Understand the natural history of flat and raised dysplasia
3. Review the indications for colectomy in patients with flat and raised dysplasia
4. Review surveillance guidelines in patients with IBD
5. Understand the role of chromoendoscopy in detecting colorectal neoplasia in patients with IBD
6. Review the data on the use of chemopreventive agents to lower the risk of colorectal neoplasia in patients with IBD

Colorectal carcinoma (CRC) complicating ulcerative colitis (UC) was first recognized in 1925 by Crohn and Rosenberg,[1] but it was not until 1948 that Warren and Sommers reported CRC in a patient with Crohn's disease (CD).[2] There has been much dispute regarding the magnitude of risk in both of these conditions. For many years it was believed that the risk in CD was insignificant. However, it is now recognized that the risk of developing CRC is equivalent, in both conditions given a similar extent and duration of disease.

Inflammatory bowel disease (IBD) is relatively rare in the general population. Consequently <1% of all cases of CRC are attributable to IBD. However, it remains 1 of the 3 high-risk conditions predisposing to CRC, along with familial adenomatous polyposis and Lynch Syndrome. Patients have up to a 1 in 5 chance of developing CRC after 30 years of disease.[3] Thus, it is an important issue for both the patient and the physician. The risk is not equivalent for all patients and depends on a number of factors. This necessitates an individualized and sensible approach to surveillance in patients with IBD.

Are Patients With IBD at Increased Risk for Developing CRC?

UC

Patients with long-term UC have an increased risk of CRC, but the magnitude has been difficult to estimate. A number of factors have rendered the magnitude difficult to assess. First, a direct comparison between studies is difficult because of inconsistent methods used to calculate risk. Some studies reported the cumulative risk of developing CRC in a given population of patients with IBD, but unfortunately, many assume that all subjects have the same risk. Other studies have calculated the risk of CRC in IBD cohorts as a standardized incidence ratio (SIR) compared with a control population. These estimates can be adjusted for age and gender but do not provide information on the lifetime risk.

Second, inherent selection biases have affected earlier studies. Most studies were from tertiary referral centers. Case reports and population studies from these centers included patients with more severe recalcitrant disease, and also those who had been referred already with a diagnosis of cancer. In addition, risks were related to the hospital population rather than the population of the host community. More recently, population-based studies that covered defined geographical areas lean more toward conservative, but more accurate, risk estimates. However, some did not distinguish extent of disease, which has led to less informative conclusions. Studies that do stratify the data on key variables should be viewed as the gold standard.

Third, practices regarding treatment of UC differ across continents. Some centers have an aggressive policy with respect to use of aminosalicylates and/or early colectomy. Recent research has emerged that suggests a protective role for aminosalicylates in the prevention of CRC. Centers that adopted this policy of mesalamine prophylaxis long ago may well have modified the risk to their patients. In centers with high colectomy rates, lower cancer incidence rates would be expected because the procedure virtually eliminates the risk. Consequently, it is not surprising that the risk of CRC has been reported to be as low as 1.4% at 18 years in a Scandinavian cohort study of 783 patients,[4] and as high as 34% after 30 years

Abbreviations used in this paper: AMACR, α-methylacyl-CoA racemase; AZA, azathioprine; CI, confidence interval; CRC, colorectal carcinoma; DALM, dysplasia-associated lesion or mass; HGD, high-grade dysplasia; LGD, low-grade dysplasia; 6-MP, 6-mercaptopurine; MSI, microsatellite instability; OR, odds ratio; PSC, primary sclerosing cholangitis; RR, relative risk; SIR, standardized incidence ratio; STn, sialyl-Tn antigen; USPSTF, US Preventive Services Task Force.

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of disease in a tertiary referral center study of 267 patients.[5]

In an attempt to determine the overall risk, a meta-analysis of studies that reported colonic cancer risk in UC has been conducted.[3] Initially, the meta-analysis identified 194 studies. Of these, 116 met the inclusion criteria from which a minimum amount of data (the number of patients and cancers detected) could be extracted. Nineteen of these studies reported stratified data (ie, reported the rates of cancer at 10, 20, and 30 years of disease). The meta-analysis showed that the risk is 2% at 10 years, 8% at 20 years, and 18% at 30 years of disease. The St Mark's group, in the United Kingdom, has since reported further data from their 30-year surveillance program.[6] They have reported similar, although slightly lower, cumulative incidence rates of cancer and dysplasia of 7.7% at 20 years and 15.8% at 30 years. More recent population-based studies, such as data from Jess et al,[7] have suggested that although the risk is increased in patients with extensive colitis (SIR, 2.4; 95% confidence interval [CI], 0.6–6.0), the risk has decreased over time. Several others studies have reported a lower relative risk (RR) of developing CRC (RR ranging from 1.8 to 2.8). These include studies from Canada, Italy, and Hungary and have been summarized in a review article by Loftus.[8]

CD

Until recently, the risk of CRC in CD was unclear. Early studies included patients with colonic resections; some included patients with isolated small bowel disease, and others did not adjust for the duration of disease.[9,10] The risk reported from studies that represent "at-risk populations" (ie, those with long-standing, unresected, and extensive colonic CD) provide estimates of increased risk.[10,11] For instance, in a large population-based survey of 1655 patients by Ekbom et al,[11] a RR of 2.5 (95% CI, 1.3–4.3) for CRC was reported. However, for the 830 patients with Crohn's colitis, the RR was 5.6 (95% CI, 2.1–12.2). A recent study from Denmark provided contradictory results. Jess et al[12] extended the study by Munkholm et al[10] by reexamining the same group of patients with a longer follow-up period (17 years). The risk of CRC was not increased in the total group of patients or in patients with only colonic CD (standardized mortality ratio, 1.64; 95% CI, 0.2–5.92). However, 2 factors need to be considered. The cumulative colectomy rate remained 20% after 20 years of disease, and long-term maintenance therapy with mesalamine drugs has been practiced in this region for decades. These agents are believed to have chemopreventive properties and, thus, may have reduced the incidence of cancer.[13–15] The same group conducted a meta-analysis of 6 studies to estimate the risk of CRC in CD.[16] The pooled SIR for CRC was significantly increased (SIR, 1.9; 95% CI, 1.4–2.5), as was the risk of CRC independently (SIR, 2.5; 95% CI, 1.7–3.5). This was a meta-analysis of population-based studies, and 3 of the 6 reports were performed in Scandinavian countries. A further meta-analysis of 12 studies showed an overall CRC RR in CD patients of 2.5 (95% CI, 1.3–4.7). However, for patients with colonic disease, the RR increased to 4.5 (95% CI, 1.3–14.9).[17]

Comparing the Risk in UC and CD

Without adjusting for potential biases, the largest population-based study, from Manitoba, Canada, demonstrated a risk of CRC in patients with CD (RR, 2.64; 95% CI, 1.69–4.12) equal to patients with UC (RR, 2.75; 95% CI, 1.91–3.97).[18] In fact, absolute cumulative CRC frequencies for CD and UC have been shown to be nearly identical: 8% for UC and 7% for CD after 20 years of disease.[19] The latest data from Olmstead County, Minnesota, did not reach statistical significance.[7] However, this study found a SIR of 2.4 for patients with pancolitis UC (95% CI, 0.6–6.0), and a SIR of 1.9 for those with CD (95% CI, 0.7–4.1).

Therefore, it is now accepted that the risk of cancer is equivalent in both conditions.[11] In a study of 28 patients with CD-associated CRC and 52 with UC-associated CRC, the age at diagnosis of cancer (CD, 54 years; UC, 43 years), the duration of IBD before cancer (CD, 15 years; UC, 18 years), the multiplicity (CD, 11%; UC, 12%) and distribution of cancers, the presence of dysplasia (CD, 73%; UC, 79%), and the overall 5-year survival rates were similar (CD, 46%; UC, 50%).[20] Crohn's colitis should raise the same concerns regarding the risk of developing cancer as does UC.

Are There Well-Substantiated Factors Other Than Dysplasia That Increase or Decrease the Risk of CRC in IBD?

Disease Duration

The increasing risk of CRC with disease duration in patients with UC has been demonstrated in the meta-analysis and surveillance program data previously mentioned.[3,6] An elevated RR is appreciable after 8 to 10 years of disease, which is the time at which regular colonoscopic surveillance should commence. A recent study from The Netherlands has suggested that cancers will be missed if surveillance is commenced at 8 to 10 years for patients with pancolitis, and 15 to 20 years for patients with left-sided disease because 9% to 15% of cancers in their study occurred before this time.[21] However, the vast majority of studies show that the incidence is very low at 10 years of disease, and may be decreasing.[3,6–8] Thus, commencing surveillance prior to 8 years of disease increases the cost of a surveillance program with very little benefit.

Previous guidelines have recommended that the surveillance interval should be shortened commensurate with increasing duration of disease. Recent data suggest that it may not be necessary to intensify surveillance with