INFLAMMATORY BOWEL DISEASE: A PRACTICAL APPROACH, SERIES #79

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Management and Surveillance of Dysplasia in Inflammatory Bowel Disease

Patients with inflammatory bowel disease have an increased risk of developing colorectal cancer. Although surveillance is widely practiced, no large controlled trials have shown that it reduces mortality. Patients with longer duration and extent of colitis are at the highest risk. Surveillance for dysplasia and cancer should begin after 8 years of disease. Dysplasia associated with a non-adenoma-like lesion or mass and high grade dysplasia are indications for colectomy while adenoma-like lesions may be managed with complete polypectomy and frequent surveillance colonoscopies. This review will outline epidemiology, pathology, management of colon cancer in ulcerative colitis and Crohn’s disease and the evidence supporting a role for cancer surveillance. Newer techniques for colonoscopic surveillance and chemoprophylaxis will also be discussed though there may not be sufficient evidence to support widespread use of chemopreventive agents.

INTRODUCTION

Inflammatory bowel disease (IBD) places patients at increased risk for colorectal cancer (CRC). The risk is related to the anatomic extent, duration and severity of the disease. Although no large controlled trials have shown that surveillance decreases mortality, surveillance is widely practiced and recommended by all the major gastroenterological societies. This review will outline the epidemiology, pathology, natural history, surveillance and management of dysplasia in the setting of inflammatory bowel disease.

Epidemiology

The risk of colorectal cancer is increased in patients with ulcerative colitis (UC) and Crohn’s disease (CD). A Swedish population-based study estimated that the risk of colorectal cancer in IBD was 95 cases per 100,000 population.1 The trend over the last 40 years has generally been of a decline in incidence of colorectal cancer. It is not clear if a gender difference exists in the risk. In another population-based study, males had a 60% higher risk of colorectal cancer than females though the effect of sex was seen only after ten years of follow-up.2 These gender differences could be explained by differences in the extent of inflammation or patient behavior leading to differences in medication or surveillance.
The risk of CRC in UC has been well-studied and depends on the extent and duration of disease. Patients with disease extending to the hepatic flexure or more proximally have the greatest risk of colorectal cancer. Compared to an age-matched population, the risk begins to increase eight to 10 years following the onset of symptoms. In one series, the absolute risk of CRC in patients with pancolitis was 30% after 35 years of disease. Another study showed the presence of “backwash ileitis” (inflammation of the terminal ileum in the setting of colitis) as a risk factor for CRC, but other studies have not confirmed this relationship. The severity of inflammation may also be an independent risk factor as shown in a case–control study and later confirmed in a cohort study.

While patients with colitis confined to the left colon (i.e. distal to the splenic flexure) also have an increased risk of colorectal cancer, theirs is less so compared to patients with pancolitis. Many studies have shown that the risk of CRC increases after 15 to 20 years in patients with left-sided colitis, though rates of dysplasia are similar to patients with pancolitis. Patients with ulcerative proctitis and proctosigmoiditis are probably not at increased risk for CRC. Patients with UC complicated by primary sclerosing cholangitis do have an increased risk of colorectal cancer, particularly in the right colon. This suggests bile acids may play a role in the development of this cancer.

The risk of dysplasia in CD has been less well-studied than that in ulcerative colitis. It may be similar to that of patients with UC but not all studies have reached this conclusion; the extent of risk is still debated. Most of these studies did not adjust for duration and extent of disease. An American population-based study found a significantly increased risk of small bowel but not colorectal cancer. A Swedish population-based study noted the overall relative risk of colon cancer was 2.5 in patients with CD though increased to 5.6 in those with disease restricted to the colon. The risk was even higher in patients diagnosed before age 30. Colorectal cancer in CD is observed at a similar age as that in UC with a median duration of disease prior to cancer diagnosis of 15 and 18 years, respectively. Despite this increased risk, however, the overall number of patients with CD who develop colorectal cancer is small.

**Pathogenesis**

The pathogenesis of colon cancer in IBD is not well understood but seems to be different than for sporadic CRC. Patients who develop CRC in IBD are usually younger (40s -50s) compared to sporadic CRC, who tend to be in their 60s at diagnosis. Dysplasia in UC is preceded by a long history of chronic inflammation and can be found at sites distant from the cancer. Dysplasia in sporadic colon cancer is usually associated with a polyp without inflammation.
Pathology

As in sporadic colorectal cancer, most cancers in IBD patients are adenocarcinomas. However, poorly differentiated, anaplastic and mucinous carcinomas are more common in colitis-associated CRC than sporadic. Neoplasms may appear polypoid, nodular, ulcerated or plaque-like. Colon cancer associated with UC is most common in the rectum and sigmoid colon whereas neoplasia in Crohn’s disease is evenly distributed between the right colon and the rectosigmoid. Cancer associated with IBD occurs in areas with chronic inflammation. Synchronous tumours occur in 12 percent of CRC in IBD cases compared to 3 to 5 percent in sporadic CRC.

It is generally accepted that colorectal cancer in IBD is preceded by dysplasia. Histologically dysplasia is categorized as negative, indefinite or positive; the positive category is divided into low grade and high grade dysplasia. Dysplastic areas may be difficult to recognize on endoscopy since they can be flat or only slightly elevated. Dysplasia may be difficult to distinguish from changes of chronic inflammation on histology and thus the presence of dysplasia should be confirmed by an experienced GI pathologist. The criteria for dysplasia emphasize the uniform nature of dysplastic changes affecting all parts of the crypt and surface epithelium. Other abnormalities seen in dysplastic epithelium include increased mitoses, back to back gland pattern, increased nuclear size, pleomorphism, and hyperchromaticity.

Detection of Dysplasia

Dysplasia is defined as unequivocal neoplasia of the epithelium confined to the basement membrane without invasion into the lamina propria. Unlike sporadic CRC in which dysplastic adenomas begin as raised polypoid lesions, dysplasia in IBD can arise in mucosa that is indistinct from surrounding mucosa. Flat dysplasia is thought to be endoscopically invisible and is conventionally thought to be detected only on random biopsy specimens. However, these lesions are in fact visible using newer generation colonoscopes with higher optical resolution. Elevated lesions that are endoscopically visible but not amenable to endoscopic resection are referred to as DALMs (dysplasia associated lesion or mass) a term that implies a high rate of synchronous malignant lesions. A newer term ALM (adenoma-like lesion or mass) describes a polypoid lesion resembling a sporadic adenoma found in an area of the colon not involved by chronic colitis and one that can be resected endoscopically. Low grade and high grade dysplasia was established with the presumption that low grade changes are early and less associated with imminent cancer.

Management of Dysplasia

One in 8 patients with UC will have dysplasia or cancer found on their initial screening colonoscopy, but those with a negative initial exam have a 3% chance of developing high grade dysplasia or cancer on subsequent surveillance colonoscopies. Nineteen percent of patients with LGD will already harbor concurrent CRC or HGD and an additional 29%-54% will subsequently develop advanced neoplasia over the next 5 years. HGD carries a 43% risk of synchronous malignancy and is an indication for colectomy.

Risk factors for the development of cancer in UC are duration and extent of colitis, early age of onset of colitis, family history of colorectal cancer and severity of microscopic inflammation. The duration and extent of colitis are well established risk factors for the development of cancer in UC. Patients with greater than 10 years of disease and those with extensive disease are at highest risk. The incidence rate increases with each successive decade of disease activity with approximate cumulative probabilities of 2% at 10 years, 8% at 20 years, and 18% at 30 years although recent data suggest that rates may represent an overestimate.
of the true risk.39

Some patients with ulcerative colitis develop dysplasia associated with a non-adenoma-like lesion or mass (DALM). These DALMs may harbor an underlying invasive carcinoma that may not be detectable by endoscopic biopsy and therefore requires colectomy. In a case-series of 12 patients with DALM that was resected, 60 percent had invasive carcinoma in the resected specimens. Malignancy was not detected prior to resection on multiple endoscopic biopsies.27

Unlike non-adenoma-like lesions, sporadic adenomas do not require colectomy and may be removed endoscopically even if they arise in an area of colitis. As a result, the two need to be distinguished to prevent unnecessary surgery. Patients with a non-adenoma-like DALM are more likely to be younger, have a longer duration of disease, more extensive disease and larger lesions. Lesions that appear endoscopically as pedunculated or sessile adenomas rather than flat, ulcerated or plaque-like even if located in an area of colitis have a favorable prognosis with endoscopic removal and close follow-up.28-30

Polypectomy with close excision and follow up colonoscopic surveillance is adequate treatment of patients with an adenoma-like DALM. A small study compared treatment of UC patients with adenoma-like DALM and non-UC patients with sporadic adenomas with polypectomy combined with surveillance and found no difference in the incidence of polyp formation on follow-up.28

Image 4. Demonstration of Chromoendoscopy

Image 5. Abnormal mucosa well defined by chromoendoscopy

Inflammatory pseudopolyps are islands of residual intact colonic mucosa that result from mucosal ulceration and regeneration in IBD. These polyps are usually found scattered throughout the colon but are not dysplastic. Pseudopolyps are a marker of increased disease activity and neoplasia.18 Their presence can obscure recognition of true adenomas and DALM.27

Adenoma like lesions can be safely managed by polypectomy with biopsies of the surrounding flat mucosa. If the lesion is successfully removed in its entirety and the surrounding mucosa is free of dysplasia, more frequent surveillance colonoscopy is recommended. If surrounding biopsies are found to be dysplastic, colectomy is advised given the likelihood of concurrent cancer or progression to cancer.29-31, 35

Surveillance of Dysplasia

Screening and surveillance for dysplasia and cancer should begin after 8 years of disease. Patients with ulcerative proctitis are not considered at increased risk of CRC. Patients with left sided UC or those with more proximal disease are at higher risk than is the general population. Patients with Crohn’s disease (CD) are also at increased risk of CRC. CD patients with one third or more of the colon involved and with 8 years or more of chronic colitis should receive surveillance endoscopies.30 In Crohn’s colitis there is little data regarding screening and surveillance colonoscopy with biopsy. In one study, 259 patients who underwent examinations at least every 2 years, 16% were found
Management of Dysplasia on Surveillance Colonoscopies in Ulcerative Colitis and Crohn’s of the Colon

<table>
<thead>
<tr>
<th>Society</th>
<th>Low Grade Dysplasia</th>
<th>Indefinite Dysplasia</th>
<th>High grade Dysplasia</th>
<th>Negative</th>
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<tbody>
<tr>
<td>American College of Gastroenterology</td>
<td>1. Confirm with second GI pathologist 2. Colectomy</td>
<td>1. Intensive medical therapy. 2. Repeat surveillance in 3-6 months.</td>
<td>1. Confirm with second GI pathologist 2. Colectomy</td>
<td>1. If disease duration &lt; 20 years, repeat surveillance in 2 years. 2. If disease duration is &gt; 20 years, repeat surveillance annually.</td>
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a. Lower risk – Extensive colitis with no active endoscopic or histologic inflammation, left-sided colitis, or Crohn’s colitis involving less than 50 percent of the colon.

b. Intermediate risk - Extensive colitis with mildly active endoscopic or histologic inflammation, post-inflammatory polyps, or a family history of colorectal cancer in a first-degree relative who was at least 50 years of age.

c. Higher risk - Extensive colitis with moderately active endoscopic or histologic inflammation, a stricture in the preceding five years, dysplasia in the previous five years that was not treated surgically, primary sclerosing cholangitis, or a family history of colorectal cancer in a first-degree relative younger than 50 years of age.

To have abnormal biopsies that comprised indefinite, LGD, HGD, and cancer. 24, 33, 35, 40.

Although surveillance programs remain a popular management strategy in UC, some cancers will develop despite a surveillance program. The benefits of surveillance programs remain controversial particularly in light of estimates that about $200,000 is spent in surveillance programs for every carcinoma found or prevented. 41, 45, 46.

Those who develop UC after the age of 70 may not need surveillance because the increased risk of cancer (continued on page 32)
will not then begin until the eighth decade, an age at which UC confers little or no additional risk above that in the general population.\(^{30,35}\)

In pancolitis the surveillance interval is generally recommended to be 1-2 years. Since the dysplasia-carcinoma sequence likely requires an extended period of time every 2 years would seem appropriate after two consecutive annual colonoscopies at which no dysplasia was detected. Screening is generally recommended to begin 8 years after onset of pancolitis since it is unusual for patients will develop carcinoma before 10 years of disease.\(^{34,41}\)

Left sided colitis is defined as disease distal to the splenic flexure. Colonoscopy with biopsies should begin 12-15 years after onset of disease. Surveillance procedures for dysplasia and carcinoma colonoscopy must be conducted to the ileocecal valve. To maximize the amount of tissue obtained endoscopists procure two to six biopsies per site using jumbo forceps usually from six to ten sites in the colon. Alternatively four quadrant biopsies every 10 cm can be performed. Rubin et al. published a detailed histology assessment of patients with UC who underwent colectomy. They reported that 33 biopsies were required to have a 95% sensitivity for any dysplasia to be present but up to 64 biopsies were required to find the highest degree. Because there is an increased risk of rectosigmoid cancer in UC an increased number of biopsies should be obtained from these sites.\(^{34,41}\)

Biopsy of obvious inflammatory polyps or pseudopolyps is to be avoided since they are less likely to contain dysplasia and are often difficult to interpret. However a lesion greater than 1 cm, or those with abnormal color or configuration from the usual inflammatory polyp should be sampled or removed completely. Strictures in UC are suspicious of carcinoma and should be sampled extensively since malignancy may be present in over one third of cases. Colonic strictures in Crohn’s disease must also be sampled since a significant proportion (5-11%) may be malignant.\(^{25,34,35,39}\)

**Colonoscopy**

Dysplasia in IBD can be flat and multifocal and can be easily overlooked with conventional white light endoscopy. Random sampling throughout the colon has been the mainstay of conventional surveillance practice. However, obtaining at least 33 random biopsies throughout the colon is tedious, expensive and time consuming. There has been increased emphasis on targeted biopsies in surveillance colonoscopies because evidence suggests most dysplasia in UC is associated with visible mucosal abnormalities.\(^{32,33}\) Subramaniam et al. found that high definition colonoscopy was associated with higher dysplasia detection rate in comparison to standard definition colonoscopy.\(^{33}\) There is growing evidence that the yield of surveillance can be improved by addition of newer endoscopic methods such as chromoendoscopy (CE) and autofouresence with narrow-band imaging (NBI)\(^ {38}\) that enhance the detection of subtle mucosal abnormalities. Chromoendoscopy with topically applied dyes such as methylene blue or indigo carmine facilitates the endoscopic detection of flat circumscribed colitis associated neoplastic changes in UC.\(^ {42}\) Five controlled studies showed that the diagnostic yield for the detection of intra-epithelial neoplasia using CE is higher compared with conventional colonoscopy with random biopsy specimens.\(^ {44}\) Although CE allows for identification of mucosal lesions, it is not suitable for accurate endoscopic diagnosis of intra-epithelial neoplasia in UC because of the lack of cellular resolution and subsurface imaging.\(^ {42,44}\) Recently, a miniaturized confocal microscope integrated into the distal tip of the conventional colonoscope was developed.\(^ {33}\) This new diagnostic technology in gastrointestinal endoscopy denoted confocal endomicroscopy enables histologic evaluation of the mucosal layer during colonoscopy. Because of the time required for examination of large surface areas, this technique is not suitable for screening of the entire colonic surface in UC to detect neoplasias in flat mucosa. In a study by Kiesslich, et al., CE was used to identify potential neoplastic lesions and was combined with endomicroscopy for the endoscopic diagnosis of colitis associated intra-epithelial neoplasia in UC. By using such chromoendoscopy-guided endomicroscopy, they were able to diagnose a 4.75 fold greater neoplastic detection rate in UC in comparison with conventional colonoscopy with random biopsy specimens and significantly (50%) fewer biopsy specimens were required. Endomicroscopy and chemoscopy prolonged colonoscopy for about 10 minutes on average, although this was not significantly different from the conventional colonoscopy group.\(^ {42,43}\)

**Chemoprevention in IBD**

Sulfasalazine products have been investigated for their
chemopreventive effects and have yielded conflicting results. While Velayos and colleagues concluded that mesalamine is chemopreventive, other investigators have failed to demonstrate a meaningful protective effect. Given the disparity of results in studies, it remains unknown whether mesalamine-based medications are efficacious chemopreventive agents. However, given their utility in maintaining remission, their use is advocated in patients with UC.  

Data from observational studies suggest that long term use of 5-amino salicylates may reduce the CRC risk by half in patients with long standing IBD while population based studies have been inconsistent and less convincing.

Studies by Lashner et al. failed to prove a significant protective effect of folic acid in IBD. Their data however suggested the possibility of a chemopreventive effect. Given the low cost and low risk of adverse events at conventional doses of 400 mg per day and 1 mg per day, the administration of folic acid remains a common practice.

Ursodeoxycholic acid (UDCA) has been suggested to decrease the risk of colorectal dysplasia in patients with PSC and UC. However, studies involving the usage of UDCA as a chemopreventive agent in patients with PSC and UC have yielded mixed results and are based on retrospective analyses with inherent limitations. Furthermore, high dose UDCA can be problematic in PSC patients. Therefore, UDCA cannot be recommended as a chemopreventive agent in PSC patients given the limited information available.

The utility of immunomodulators in patients with steroid dependent and steroid refractory disease are well established forms of therapy in IBD. A single cohort study did not demonstrate a protective effect of 6-mercaptopurine and azathioprine yet Cesame study revealed a 3.5 time lower risk of CRC with thiopurines. The effect of methotrexate and anti-TNF agents as chemopreventive agents has not been studied.

CONCLUSION

Patients with UC and Crohn’s disease have an increased risk of developing CRC although estimates of CRC risk are varied. Risk factors for development of CRC include younger age at diagnosis, extent and duration of colitis, severity of inflammation, family history of CRC, and coexistent primary sclerosing cholangitis. An initial screening colonoscopy should be performed in UC patients 8-10 years after the onset of symptoms. Thereafter, screening intervals are determined by the extent of colitis. Extensive biopsies should be obtained and the trend is toward targeted biopsies of suspicious lesions using enhanced imaging techniques such as high definition endoscopy and chromoendoscopy. With the exception of strictures screening and surveillance of CRC in patients with Crohn’s disease should be managed similarly to patients with UC. Current literature advocates the use of 5-ASA as a chemopreventive agent, but this remains inconclusive. The overall approach to cancer prevention in IBD includes intensive control of disease activity and close surveillance with colonoscopy.

References

Prospective study of the progression of low-grade dysplasia in ulcerative colitis using current cancer surveillance guidelines. Inflamm Bowel Dis. Epub 2012 April 16.


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