INTRODUCTION

Patients with long-standing ulcerative colitis (UC) and Crohn’s disease of the colon are at an increased risk of developing colorectal neoplasia (dysplasia and colorectal carcinoma). The association of UC with colorectal carcinoma was first recognized in the 1920s [1]. In inflammatory bowel disease (IBD) the development of colorectal carcinoma (CRC) occurs through an inflammation-dysplasia-carcinoma pathway [2]. In contrast to patients with sporadic CRC, individuals with IBD-related CRC have an increased incidence of synchronous malignancies, an absence of adenomatous polyps preceding the development of carcinoma, and a more rapid rate of progression of colonic mucosa to dysplasia. In this article we will review the epidemiology, risk factors, detection methods, surveillance and management issues of colorectal neoplasia in IBD patients.
EPIDEMIOLOGY AND RISK FACTORS ASSOCIATED WITH COLORECTAL NEOPLASIA

Several risk factors associated with an increased risk of developing colorectal neoplasia have been described. Multiple studies have demonstrated that the risk of developing colorectal neoplasia is directly related to the extent of colonic involvement in ulcerative colitis as well as Crohn’s colitis [3,4,5]. Patients with subtotal colitis and pancolitis have a higher risk than those with less extensive colitis, while patients with proctitis or distal proctosigmoiditis alone are at no increased risk compared with the general population [6]. Other factors conveying an increased risk include a longer duration of disease (greater than 8–10 years), and a co-morbid diagnosis of primary sclerosing cholangitis (PSC) [7]. A family history of CRC [8], possibly younger age of IBD onset [6], and the severity of both microscopic and endoscopic inflammation are also considered risk factors [9,10]. There is insufficient evidence that “backwash ileitis” (inflammation of the distal ileum in patient with UC) is a risk factor for developing colorectal neoplasia [11,12] (Table 1).

In an often quoted meta-analysis, Eaden reported the risk of developing CRC in patients with ulcerative colitis as 2% at 10 years, 8% at 20 years, and 18% at 30 years [13]. Recent studies suggest that the risk of developing CRC has decreased over time [14,15]. In the 30-year St. Marks prospective surveillance program, the cumulative incidence of developing CRC by colitis duration was 2.5% at 20 years, 7.6% at 30 years, and 10.8% at 40 years [14]. Several epidemiologic population studies have not identified an increased risk of CRC [15]. Nonetheless, it is concluded that patients with IBD have an increased risk of developing colorectal cancer.

When to Initiate a Surveillance Program

The major goal of endoscopic surveillance is to reduce mortality and morbidity related to CRC. Although recommendations are not uniform, the American Gastroenterological Association [16], American College of Gastroenterology [17] American Society of Gastrointestinal Endoscopy, British Society of Gastroenterology [18] as well as the CCFA Consensus Conference [19] recommend that all UC patients undergo a screening colonoscopy between 8 to 10 years after the onset of symptoms with biopsies to assess the extent of disease involvement. The most proximal involvement detected histologically should define the patient’s extent of disease [16]. Patients with extensive UC should then undergo surveillance colonoscopy every 1–3 years. Patients with both PSC and IBD are a notable exception as they confer the highest risk of CRC, and should undergo annual surveillance colonoscopy after the initial diagnosis.

There is no consensus regarding the time to initiate surveillance in patients with left-sided colitis. Some suggest that it be deferred to 12 to 15 years after the onset of symptoms, but the recently published ACG guideline and AGA technical review suggest that surveillance in these patients should be initiated in a similar fashion to patients with pancolitis (i.e. within 1 to 2 years after the initial screening colonoscopy that is performed 8 to 10 years after onset of symptoms). Crohn’s patients with disease involvement in more than one-third of their colon should also undergo an initial screening colonoscopy 8 to 10 years after initial diagnosis.

SURVEILLANCE FOR DYSPLASIA

The association of CRC with dysplasia found in UC patients was first established in 1967, when Morson demonstrated a correlation of synchronous proximal CRC after the detection of dysplasia in random rectal biopsies [20]. Currently colonoscopy remains the most widely used method for detecting dysplasia or CRC, with the goal of surveillance to reduce morbidity and mortality from CRC. Although there are no randomized controlled trials to date comparing endoscopic surveil-

Table 1.
Risk factors for Developing Colorectal Neoplasia in IBD Patients.

- Extensive colonic involvement
- Longer duration of IBD (>10 years)
- Severity of inflammation
- Primary sclerosing cholangitis
- Family history of colorectal cancer
- Younger age of IBD onset (possibly)
- Multiple pseudopolyps and/or colonic strictures
Diagnosis and Management of Colorectal Neoplasia in IBD

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lance, several studies have demonstrated a benefit of surveillance colonoscopy [21,22,23]. The Cochrane group concluded that there was indirect evidence that endoscopic surveillance is effective in reducing morbidity and mortality in colitis-related CRC [23].

Performing high quality colonoscopy during endoscopic surveillance examinations is extremely important in IBD patients. Ideally, colonoscopy should be performed when the patient is in remission because active inflammation may hinder the histological diagnosis of dysplasia. Previous studies have shown that significant under-sampling of colonic mucosa occurs during routine practice [24,25] although more recent studies have demonstrated better understanding of the importance of adequate sampling [26]. It is crucial that endoscopists provide adequate tissue samples for evaluation by pathologists. Multiple samples using the “jumbo” biopsy forceps taken throughout the colon should be obtained, with studies showing that 33 non-targeted biopsies are needed to exclude dysplasia with 90% confidence [27]. Currently an international consensus panel suggests that at least 33 biopsies are needed to detect dysplasia, if present [19]. The current standard for biopsy technique is to perform mucosal sampling via four-quadrant biopsies every 10 cm of the colon (i.e. non-targeted mucosal biopsies), with each set of four samples placed in separate jars. Alternatively six sets of six biopsies can be taken from throughout the colon with increased sampling from the distal colon. For suspicious or raised lesions, endoscopists should take targeted (i.e. lesion-directed) biopsies, which then should be placed in separate jars from the other non-targeted biopsies [19]. It should be noted that with advances in endoscopic imaging and technology (i.e. high-definition screens, newer generation colonoscopies, adjuvant imaging techniques), previously lesions invisible to the endoscopist are being identified more routinely.

Newer imaging techniques The low yield on random biopsies demonstrated on several studies [28,29] during colonoscopic surveillance has led to investigation of newer adjuvant techniques such as chromoendoscopy, narrow-band imaging, and confocal endomicroscopy. These techniques may help improve the overall diagnostic yield by making subtle lesions more visually apparent during endoscopy, thereby facilitating target-based sampling.

Of the various available technologies, chromoendoscopy with methylene blue or indigo carmine appears to be most widely implemented by centers for colitis-related surveillance. Use of this technique involves spraying the entire colon with either methylene blue or indigo carmine, followed by careful inspection of the colon for mucosal changes highlighted by the dye. Studies have demonstrated the ability of chromoendoscopy to improve the sensitivity and specificity in the detection of dysplastic tissue [28–30]. It is possible to evaluate crypt architecture based on pit pattern recognition, which in turn will allow better differentiation between dysplastic and non-dysplastic tissues.

The first published study of chromoendoscopy by Kiesslich et al [28] reported 165 patients with UC randomized to undergo either conventional colonoscopy or colonoscopy with chromoendoscopy (using 0.1% methylene blue). Results from the study showed that there were more targeted biopsies and increased detection rates of dysplasia in the chromoendoscopy group. In a second “back-to-back” study involving 100 patients with UC, the patient first underwent conventional colonoscopy with both random and targeted biopsies [29]. The patients subsequently underwent spraying of the mucosa with 0.1% indigo carmine followed by targeted biopsies. In the first procedure, no dysplasia was found in 2904 non-targeted biopsies, and 43 mucosal abnormalities (of which 2 were dysplastic) were found in 20 patients. After spraying, an additional 114 abnormalities were identified in 55 patients (of which 7 were dysplastic). In a US study, Marion concluded that methylene blue dye-spray targeted biopsies results in improved dysplasia yield compared to conventional random and targeted biopsy methods [30]. These studies suggest that surveillance using chromoendoscopy is more effective in detecting dysplasia in comparison to random non-targeted biopsies via the conventional endoscopic method. The newest recommendations from the AGA [16] and BSG [31] include chromoendoscopy targeted biopsies as an alternative to random biopsies for endoscopists trained in this technique. New imaging techniques being investigated for their ability to detect colorectal neoplasia include confocal endomicroscopy, narrow band imaging and autofluorescence [32].
MANAGEMENT OF DYSPLASIA

The diagnosis of dysplasia depends on the combined efforts of the endoscopist and pathologist. Biopsies obtained at colonoscopy should be graded as 1) negative for dysplasia, 2) positive for dysplasia or 3) indefinite for dysplasia [33]. Biopsies that are positive for dysplasia should be further sub-classified as having 1) low-grade dysplasia, 2) high-grade dysplasia or 3) carcinoma. As there is inter-observer variability among pathologists in classifying dysplasia, confirmation of the diagnosis of dysplasia should always be performed by a second pathologist with expertise in IBD.

Dysplastic mucosa can be flat (endoscopically invisible) or raised. The term DALM (Dysplasia Associated Lesion or Mass) was coined by Blackstone and colleagues in 1981 who described a series of raised dysplastic lesions that were unresectable [34]. In comparison, dysplastic flat lesions are generally invisible via standard endoscopy and usually identified by random biopsies. With the introduction of adjuvant endoscopic imaging techniques (i.e. high-definition colonoscopes, chromoendoscopy), flat dysplastic lesions will likely need to be further sub-classified as they become more easily distinguished from normal mucosa. Patients with no evidence of dysplasia are considered low-risk for CRC, and should have repeat surveillance endoscopy within 1 to 3 years. The management of patients found to have dysplasia will be summarized in the sections below.

DALM (dysplasia associated lesion or mass)

Early studies showed that DALMs are associated with increased incidence of CRC [34], and colectomy is generally recommended following diagnosis. However not all raised dysplastic lesions have the same high association with malignancy. For example, some raised dysplastic lesions resemble sporadic adenomas (termed adenoma-like DALMs) and are easily resectable [Figure 1A]. In contrast, non adenoma-like DALMs [Figure 1B] are unresectable endoscopically, sessile, irregular with indistinct borders and may be ulcerated. Several studies have observed a low risk of developing CRC after complete endoscopic resection of an adenoma-like DALM (mean follow-up period of forty-nine to eighty-two months), assuming that biopsies from around the lesion and elsewhere in the colon show no flat dysplasia [35–37]. An incomplete resec-

Figure 1A. Adenoma-like DALM (courtesy of Jerome Waye, MD)

Figure 1B. Non-adenoma-like DALM
**Flat high-grade dysplasia obtained by random biopsy techniques** The prevalence of synchronous CRC in patients with flat high-grade dysplasia (HGD) approaches 42% in a review of ten prospective surveillance trials of 1225 patients [40]. In this study by Bernstein et al, 32% of the patients not undergoing immediate colectomy were found to have CRC on subsequent evaluation. A cohort study of 600 patients from the United Kingdom undergoing surveillance program over a 30-year period confirmed these findings; 45.5% of patients with HGD undergoing immediate colectomy had evidence of CRC in the specimen and 25% of those undergoing subsequent surveillance developed CRC [14]. These studies indicate the high association of synchronous CRC in patients with flat high-grade dysplasia. In practice, once the diagnosis of high grade dysplasia is confirmed by a second expert GI pathologist, colectomy is indicated.

**Flat low-grade dysplasia obtained by random biopsy techniques** The data for the association of low-grade dysplasia (LGD) with CRC is less robust, and there remains controversy regarding the indications for immediate colectomy. In Bernstein’s 1994 study, 19% of patients with LGD who had immediate colectomy were found to have synchronous CRC, while 8% of patients with LGD who underwent colectomy at a later date had CRC [40]. The UK study by Rutter et al. found similar incidence rates, with 19.6% of patients developing CRC, and 39.1% (18 of 46) of patients with LGD developing either HGD or CRC. In a study by Ullman et al. [41], 23.5% (4 of 17) patients who underwent immediate colectomy for flat LGD had evidence of synchronous advanced dysplasia (in which there were two cases of carcinoma and two cases of HGD). A meta-analysis of studies between 1966 and 2005 concluded that in IBD patients with detected LGD on surveillance, there was a 9-fold risk of developing CRC (OR: 9.0, 95% CI:4.0–20.5) and 12-fold risk of developing any advanced lesion (OR:11.9, 95% CI:5.2–27) [42].

On surveillance, flat LGD can be unifocal or multifocal. In clinical practice, the presence of multifocal LGD is usually an indication for colectomy. If colectomy is not performed for unifocal LGD, the patient needs to be informed of the risk of developing unresectable CRC despite continued surveillance. We recommend that patients with flat LGD who do not undergo immediate colectomy be referred to a center with expertise in chromoendoscopy.

**Indefinite for dysplasia** Pathologists will sometimes categorize biopsies as “indefinite for dysplasia.” These cases usually result from the difficulty of the pathologist to distinguish between true dysplasia and chronic active inflammation. In one study of a group classified as indefinite for dysplasia, the rate of progression to CRC appears to be intermediate between patients with no dysplasia and those with flat LGD [43]. Biopsies confirmed by expert GI pathologists as

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**Table 2. Suggested Performance of Surveillance Colonoscopy**

- All ulcerative colitis patient should undergo an initial screening colonoscopy to determine the extent of colitis (and check for neoplasia) beginning approximately 8 years after the onset of colitis symptoms.
- Crohn’s patients with disease involvement in greater than one-third of their colon should also start a surveillance program approximately 8 years after the onset of colitis symptoms.
- There is no consensus regarding the timing of screening colonoscopy for patients with left-sided colitis although most societies recommend that regular surveillance begin after 8-10 years of disease.
- After the initial screening colonoscopy, surveillance colonoscopy should be performed every 1–3 years taking into consideration patients risk factors.
- In IBD patients with primary sclerosing cholangitis, colonoscopy should begin at the time the biliary tract disease is diagnosed and then yearly.
- During surveillance, 4-quadrant biopsies should be obtained every 10 cm. Each quadruplicate set should be placed in a separate specimen jar. At least 33 biopsy samples should be obtained with increased sampling from the distal colon. Alternatively six sets of six biopsies can be taken from throughout the colon with increased sampling from the distal colon.
- Sample or resect suspicious lesions or polyps and place specimens in separate container jar.
- Chromoendoscopy is as an alternative to random biopsies for endoscopists trained in this technique.
- Ideally, colonoscopy should be performed when the patient is in remission.

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“indefinite for dysplasia” should have a follow-up surveillance colonoscopy within 3–6 months. Figure 2 and Table 2 contain summaries of recommendations for surveillance and the management of dysplastic lesions based on expert opinion.

Non-dysplastic polypoid lesions Inflammatory polyps (pseudopolyps) are polypoid lesions commonly encountered during surveillance [Figure 3]. Their endoscopic appearances vary, and classic-appearing lesions need not to be resected as they have no malignant potential. However the presence of inflammatory polyps is a marker of severe previous colonic injury, and along with the presence of strictures, are both predictors of CRC development [10]. Patients having dysplasia in their colonic biopsies have the lowest rates of progression to cancer, with a reported incidence of 1.1% developing CRC at 5 years.

Adherence to surveillance program Another barrier to adequate dysplasia surveillance involve patient adherence to surveillance programs. More studies are needed to identify which factors contribute to patient non-adherence. The practitioner should carefully counsel the IBD patient on the risk of developing CRC and the potential harm from non-adherence to a surveillance schedule.

CHEMOPREVENTION

Many studies have examined potential chemopreventive agents in IBD. These include mesalamine-based
agents (5-ASA), azathioprine/6MP, folic acid, aspirin, NSAIDs, and ursodeoxycholic acid. In a meta-analysis by Velayos, 5-ASA use was associated with a decreased rate of developing CRC and dysplasia [44]. Regardless, due to their effectiveness in maintaining remission, 5-ASA agents are routinely recommended for all UC patients. A comprehensive review of the data regarding chemoprotective agents in IBD is beyond the scope of this article, and the reader is referred to several recent articles for further information [45,46].

SUMMARY

Certain IBD patients are at increased risk of CRC, in particular UC and Crohn’s disease patients with extensive colitis, longer duration of disease, and a coexisting diagnosis of PSC. All IBD patients should undergo a colonoscopy 8 years after onset of symptoms to assess the extent of disease, with the exception of IBD patients with PSC, who should start surveillance at the time of diagnosis. During surveillance, the endoscopist should routinely perform four-quadrant biopsies every 10 cm for a total of at least 33 samples (or alternatively 6 biopsies in each of 6 bottles) throughout the colon. More biopsies should be taken from the rectosigmoid. Newer adjuvant techniques such as chromoendoscopy show promise in improving diagnostic yield for targeted biopsies and are alternatives to random biopsies for endoscopists trained in this technique.

If no dysplasia is detected, patients with extensive colitis should repeat examinations every 1 to 3 years. The presence of flat high-grade dysplasia is an indication for colectomy due to the high association with synchronous CRC. The management of low-grade dysplasia remains controversial with most authorities recommending colectomy for patients with multifocal flat LGD. Interval cancers will develop in patients who do not undergo immediate colectomy for unifocal flat LGD and the decision to proceed with colectomy need be individualized in this group. If colectomy is not performed, it is recommended that this high-risk group of patients be referred for chromoendoscopy. Patients with biopsies that are indefinite for dysplasia should undergo a repeat surveillance examination within 3–6 months. Patients with polypoid dysplastic lesions that are fully resected and without flat dysplasia elsewhere in the colon can be managed with continued colonoscopic surveillance. There is limited data regarding chemoprotective agents, although the use of 5-ASA is generally recommended given its efficacy in preventing flares in UC patients in remission.

References