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Neoplasia in IBD

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1. Introduction

Longstanding inflammation of the colonic mucosa places patients with ulcerative colitis (UC) at increased risk for the development of colon cancer. As such, there has been significant research over the last 20 years into efforts to understand the natural history of neoplastic lesions in UC in order to modify this risk. This chapter will focus on the epidemiology of neoplasia in UC, the biology of IBD-associated cancer, outcomes after a diagnosis of a dysplastic lesion, as well as strategies for surveillance and chemoprevention.

2. Epidemiology

The majority of studies examining the development of cancer in IBD have demonstrated an increased risk for neoplasia in patients with long-standing UC (1-6). A 2001 meta-analysis involving 116 studies and over 50,000 patients calculated the cumulative risk of CRC in UC as 8.3% at 20 years and 18.4% at 30 years (7). However, two recent population based studies, one from Denmark and the other from Olmstead County in Minnesota, did not find a significant increase in risk (3, 8). The discrepancy in results between these more recent studies and older analyses may be secondary to the effects of newer, more effective anti-inflammatory agents for IBD or the implementation of surveillance programs and removal of colons with dysplastic lesions prior to the development of cancer.

3. Risk factors

It is postulated that cancer develops in patients with IBD secondary to prolonged inflammation. The evidence to support inflammation driving neoplastic transformation stems from studies demonstrating that patients with longer disease duration, extensive colitis, and uncontrolled inflammation are at increased risk for neoplastic changes. Risk of colorectal cancer (CRC) development rises with increased interval from diagnosis of IBD-associated colitis (2, 9). In fact, CRC is uncommon in patients who have had colitis for less than 7 years, and more commonly develops in patients who are diagnosed with IBD at a younger age (5, 7). Several studies have also demonstrated that cancer develops more frequently in those with an increased extent of colitis (2, 4). A Swedish population-based study using barium enemas quantified this risk by standardized incidence ratio as 1.7 for individuals with proctitis, 2.8 for those with left-sided colitis, and 14.8 for those with pancolitis (2).
Two recent publications have established that severity of inflammation is associated with an increased risk for cancer in IBD. In a retrospective cohort from the St. Mark's hospital,

severity of inflammation by histology was significantly associated with neoplasia in patients with extensive colitis (10). Interestingly, in this multivariate analysis only histologic inflammatory activity and not endoscopic inflammation was associated with neoplasia. A second retrospective study from Mt. Sinai hospital in New York confirmed severity of inflammation over time as a risk for neoplasia (11).

Two other well-described risk factors for neoplastic development in IBD include a family history of colorectal cancer and a history of primary sclerosing cholangitis (PSC). Several retrospective analyses have reported that patients with IBD who develop neoplasia have an odds ratio between 2.3 and 5.0 for having a family history of CRC (5, 12-14). A large population-based cohort also demonstrated a relative risk for the development of neoplasia of 2.5 for patients with a family history of colon cancer (15). As in the case of sporadic colon cancer with positive family history, this association was stronger for patients with a first-degree relative with CRC less than 50 years of age (15). Potentially, the most significant risk factor for neoplasia in patients with UC is a concomitant diagnosis of PSC. Although the reported frequency of neoplastic changes in this population varies among studies, patients with UC and PSC have consistently demonstrated a markedly increased risk for the development of both dysplasia and colon cancer compared to patients with UC without PSC (5, 16-20). The overall incidence of CRC in patients with UC and PSC was between 16% and 25% in a Swedish population-based study after 10 years of disease duration (17). This risk of neoplastic changes in UC patients with PSC has also been noted to occur earlier in the disease course than UC patients without PSC.

4. Definition of dysplasia

In UC, the term dysplasia is defined as neoplastic changes confined to the colonic epithelium. Tissue that is positive for dysplasia is most commonly identified as either low grade (LGD) or high grade (HGD) (21). Dysplasia is also characterized based on its endoscopic appearance, and outcomes of progression to cancer are associated with this endoscopic classification. Historically, flat dysplasia has been defined as dysplasia identified only by histological and not endoscopic features. However, recent studies have demonstrated that most lesions classified as flat dysplasia were obtained from targeted biopsies of visible lesions (22, 23). Raised lesions that are not endoscopically resectable are termed dysplasia associated mass or lesion or DALMs. The term ALM (adenoma-like mass) refers to a raised, endoscopically resectable lesion that resembles a sporadic adenoma by endoscopic and histological characteristics.

5. Biology of IBD-associated cancer

Although initiating mechanisms of carcinogenesis in IBD remain unknown, neoplastic lesions likely result from a combination of genetic alterations and inflammatory mediators that activate cell-signaling pathways. These pathways in turn promote deregulations in growth and apoptosis. Several molecular changes occurring in IBD-CRC are similar to those seen in sporadic CRC. In contrast to solitary lesions in sporadic colon cancer, however, neoplastic lesions in IBD are often multifocal. This finding likely reflects the widespread field defects throughout the UC involved mucosa that increase the risk for neoplastic changes. Moreover, expression changes in coding and non-coding (microRNA) genes that

are seen in malignant transformation, also occur in chronic UC, further supporting this hypothesis (24-26).

Genomic instability characterized by either chromosomal instability or microsatellite instability occurs in both sporadic and IBD-associated CRC. In fact, frequencies of these genetic abnormalities (chromosomal instability – 85%, microsatellite instability – 15%) are similar in IBD-CRC and sporadic CRC (27-30).

Genetic changes in the tumor suppressor, p53, are believed to play an important role in the development of IBD-associated neoplasia. Loss of heterozygosity and p53 mutations have both been reported in colons with IBD-associated neoplasia (31-33). It is believed that changes in p53 may occur prior to the development of dysplastic lesions in 'at risk' mucosa (32). Moreover, reactivity of p53 antibodies increase with histologic progression from UC patients without dysplasia to those with dysplasia and CRC (34). Positive p53 immunostaining can also occur prior to the development of dysplasia in chronic UC mucosa (35, 36).

The WNT pathway is deregulated in IBD-associated cancer development as occurs in sporadic colorectal carcinogenesis. Similar to genetic changes in p53, it appears that up-regulation of WNT signaling occurs early in UC-associated neoplastic progression (37). In addition to overexpression of proteins in the WNT signaling cascade, hypermethylation of WNT-suppressor genes in this pathway occur during neoplastic development in IBD (38). Such methylations could lead to silencing of tumor suppressor genes. In contrast to sporadic colon cancer, however, it appears that APC loss of function mutations play a less significant role in initiating WNT signaling (39-41). Increased mutations in the oncogene, *K-ras,* have also been described in IBD-associated colon cancer (31). However, the timing of *K-ras* mutations in neoplastic progression needs to be clarified in larger studies.

In addition to genetic changes, previous studies in animal models of ulcerative colitis and colitis-associated colon cancer have demonstrated involvement of other key signaling pathways including the vitamin D receptor, NFκB, transforming growth factor beta (TGFβ), cyclooxygenase-2 (COX2), toll-like receptor-4 (TLR4), and the epidermal growth factor receptor (EGFR). Several mouse studies have shown that active vitamin D or its analogues inhibit progression in murine models of inflammation-associated colitis (42, 43) Furthermore, one retrospective analysis identified decreased expression of VDR in IBD-associated dysplastic lesions (44). NFκB controls a vast array of functions and is a master regulator of many pro-inflammatory cytokines including TNF-α and IL-1β. NFκB overexpression is known to contribute to both inflammation and malignant transformation in several cancers (45). NFκB has also been demonstrated to contribute to malignant transformation in a mouse model of inflammation-associated cancer (46). In the study by Greten et al, NFκB in epithelial cells was essential for survival signals, allowing mutant clones to expand, whereas NFκB in stromal cells increased cytokines and growth factors required for tumor growth (46). Furthermore, NFκB mediates TNF-α activation of cytidine deaminase in human colonic epithelial cells and colitis-associated cancers. Activation induced cytidine deaminase plays a critical role in physiological antibody diversification, but also contributes to malignant lymphocytic transformation (47). In addition to NFκB up-regulation, TLR4 overexpression occurs in colitis-associated colon cancer that enhances Cox-2 expression via an EGFR-dependent mechanism (48). Recent studies from our laboratory have demonstrated that EGFR signals were required for Cox-2 up-regulation in this model (49).

6. Surveillance for IBD-associated neoplasia

There are no randomized controlled trials investigating the mortality benefit of surveillance colonoscopy in patients with UC. The best evidence to support routine endoscopic surveillance comes from retrospective case-controlled studies. In a retrospective analysis of patients with CRC, Choi et al. reported that patients who underwent surveillance had a carcinoma detected at an earlier Dukes stage and improved 5-year survival rate (50). A second analysis by Lashner and colleagues found that in 186 patients with extensive UC who underwent surveillance, patients had an improved survival and delayed time to colectomy, although the decrease in mortality was not related to cancer free survival (51). A Swedish population-based nested case-control study examining patients who died from CRC reported that two of 40 patients with UC who had died from colon cancer had undergone at least one screening exam, compared to 18 of 102 controls with UC who did not die from colon cancer (52). Similar protective effects of surveillance were seen in a second retrospective cohort (13). In a Cochrane database analysis of these studies published in 2006, the authors concluded that there was indirect evidence that surveillance is likely to show a cost benefit and be effective in reducing the risk of death from IBD-associated CRC (53).

The current standard of care recommended for the prevention of cancer in IBD is regular surveillance colonoscopy. The ability to prevent cancer with this strategy relies on the early detection of precancerous lesions. Most strategies for early detection involve both random biopsies and targeted biopsies of suspicious lesions. The major challenge with this strategy is sampling error. With random biopsies, it has been estimated 33 biopsies are needed to exclude dysplasia with 90% certainty and 64 biopsies are need for a 95% certainty. Most gastroenterologists do not approach such numbers of biopsies during surveillance exams (54, 55). Several recent studies, however, indicate that the yield of targeted biopsies is much greater than random biopsies of the colon. One possible explanation for these findings was suggested by three recent retrospective analyses. These studies concluded that most dysplastic lesions can be visualized with white light colonoscopy (22, 23, 56).

Recent experience with chromoendoscopy, however, has consistently shown superior detection of dysplastic lesions with super vital staining compared to uncontrasted white light examinations (57-61). Chromoendoscopy is typically done with either indigo carmine or methylene blue dye. In a recent meta-analysis of six studies, the difference in proportion of lesions detected by chromoendoscopy vs. white light only was 44% (62). Autofluorescence with narrow band imaging (NBI) has been suggested to improve detection of dysplastic lesions in UC as well, although studies testing the benefit of NBI compared to high definition colonoscopy have been inconclusive (63-65).

Several recommendations have been published to guide surveillance strategies in patients with UC (66-69). The most recent consensus statement was released by the American Gastroenterological Association (AGA) and recommended initiating surveillance no later than 8 years of disease duration for patients with left-sided or pancolitis (69). During surveillance examinations, multiple biopsies should be obtained from each anatomic location in the colon. This statement included chromoendoscopy as a recommended alternative to random biopsies by endoscopists who have expertise with the technique. The AGA recommended repeat examinations every 1-3 years and to decrease the interval to every 1-2 years after 20 years of disease duration. For patients with PSC, surveillance exams should be performed at the time of diagnosis and then yearly thereafter, because of an increased risk earlier in the disease course.

7. Outcome after a diagnosis of dysplasia

After a diagnosis of flat HGD, colectomy has been universally recommended because there is a significant risk of harboring a synchronous CRC. One systematic review calculated this risk as 42% (70). A subsequent prospective analysis from St. Marks Hospital reported a 45% incidence of synchronous carcinomas in patients undergoing immediate colectomy after diagnosis of HGD (9). In this analysis, eight patients underwent surveillance. Of these eight, one developed CRC and seven developed further dysplasia (6 HGD, 1 LGD) (9). There appears to be a similar risk of development of cancer in patients with endoscopically unresectable DALMs (70, 71). Because of the high risk of CRC development, colectomy is warranted for any patient with a DALM or flat HGD.

In contrast to HGD, the management of patients with IBD-associated indeterminate dysplasia (IND) or LGD remains controversial. Previous studies have varied in their reported rates of progression from low-grade lesions to advanced neoplasia from 16% to 54% (9, 70, 72-76). The discrepancy in reported rates of progression to advanced neoplasia is likely secondary to the population heterogeneity of these studies. Within the classification of LGD, outcomes are different for flat dysplastic lesions and adenoma-like dysplastic lesions (ALMs). For patients who have an ALM in the absence of surrounding dysplasia, the risk of development of cancer appears to be minimal (77-79). For this reason, patients with polypoid lesions that resemble a sporadic adenoma without surrounding flat dysplasia can be managed with endoscopic resection and surveillance. Conversely, flat dysplastic lesions carry a higher risk of malignant progression and of harboring a synchronous CRC at the time of diagnosis (72, 74, 78). Total abdominal colectomy should be discussed with patients following a diagnosis of flat LGD. For patients with controlled disease who elect to undergo surveillance of flat LGD lesions, close follow up with endoscopic evaluations, initially at 3 to 6 month intervals is warranted.

Although neoplastic changes may develop in the pouch or in the anal transition zone, the risk of dysplasia appears to be low for patients with UC who undergo a restorative proctocolectomy with ileoanal anastomosis. One large analysis of 23 observational studies and over 2000 patients estimated that only slightly more than 1% of patients have confirmed dysplasia in the pouch or anal transition zone at follow up (80). A more recent analysis of over 3000 patients from the Cleveland Clinic reported the incidence of neoplasia to be 0.9%, 1.3%, 1.9%, 4.2%, and 5.1% at 5, 10, 15, 20, and 25 years after surgery, respectively (81). In both these studies, the risk of neoplastic transformation was significantly higher in patients who had dysplasia or cancer as their indication for initial colectomy. Although there are no published guidelines for surveillance after restorative proctocolectomy, many clinicians recommend a surveillance program because there remains a risk of neoplastic transformation, albeit low. It is postulated that performing a hand-sewn ileoanal anastomosis may decrease the risk of neoplasia. However, published studies have reported no difference between a stapled technique and hand-sewn anastomosis with mucosectomy (81, 82).

8. Chemoprevention

The primary goal of chemoprevention is to decrease the incidence of neoplastic lesions in those at increased risk. An effective chemopreventive agent offers the theoretical advantage over surveillance endoscopy alone by deceasing the frequency, cost, and risk of colonoscopy, as well as reducing need for colectomy.

The majority of studies examining chemopreventive agents in IBD have focused on the use of 5-aminosalicylates (5-ASA). There are several postulated mechanisms by which 5-ASA inhibits malignant transformation. These include inhibition of NFκB, increased apoptosis of mutant clones, decreased proliferation, and prevention of oxygen-radical induced DNA damage (83-85). A meta-analysis of nine case control studies examining the efficacy of 5-ASA in preventing dysplasia or cancer revealed a pooled odds ratio of 0.51 (95% CI, 0.38-0.69) (86). However, several studies that have been published subsequent to this meta-analysis have not found a protective effect of 5-ASA therapy (87-90). Taken together, data to support 5-ASA chemoprevention in IBD is inconclusive, likely due to the heterogeneity of individuals in these studies. Furthermore, it is not known what effect 5-ASA has on CRC risk in patients who have achieved mucosal healing with other therapies.

The bile acid, ursodeoxycholic acid, has been used as a chemopreventive agent in UC patients with PSC. In animal models, UDCA is protective against the development of colon cancer (91-94). The mechanism of UDCA's chemopreventive activity remains uncertain, although it is likely multifactorial (92, 94) There have been two retrospective analyses of UDCA in patients with UC and PSC with conflicting results (93, 95-97). In a randomized placebo-controlled trial of UDCA at the dose of 13-15mg/kg-body wt/day, the relative risk for dysplasia or cancer in the group receiving UDCA was 0.26 (95% CI, 0.06-0.92). However, a more recent randomized placebo-controlled trial examining high dose UDCA (28-30 mg/kg-body wt/day) in UC patients with PSC found that patients taking UDCA had a higher risk of developing colorectal neoplasia (98). Currently, the American Association for the Study of Liver Diseases (AASLD) does not recommend UDCA for chemoprevention in patients with UC and PSC as larger prospective studies of low dose UDCA are needed to further evaluate this potential chemopreventive agent (99).

Other chemopreventive agents that have been studied in IBD-associated colitis include folic acid, immunomodulators, and vitamin D. Although a recent analysis of thiopurines in IBD found their use to be protective, the majority of studies investigating the chemopreventive efficacy of immunomodulators have not shown a benefit (10, 75, 100, 101). While folic acid deficiency is associated with decreased risk of sporadic CRC in epidemiological studies and folic acid is protective of other malignancies, the studies examining folic acid in the chemoprevention of CRC in patients with IBD have not demonstrated a benefit (102-104). The data on chemoprevention with folic acid in IBD comes from small retrospective analyses that have failed to show a statistical difference in the risk of dysplasia (105, 106). Finally, vitamin D has shown chemopreventive efficacy in murine models of sporadic and inflammation-associated colon cancer (42, 43, 107). Although vitamin D supplementation has not been examined in humans with UC, decreased vitamin D receptor expression is seen in cancers of patients with IBD and vitamin D appears to be chemopreventive of human CRC in epidemiological studies (44, 108). For this reason, vitamin D might offer a potential benefit to patients with chronic UC, although there have been no controlled studies in an IBD population.

9. Conclusion

Patients with chronic ulcerative colitis are at increased risk for the development of colon cancer. Because of this risk, colonoscopic surveillance is recommended for early detection of precancerous lesions. Successful implementation of surveillance programs has likely limited the mortality from CRC in this high-risk population. The outcome after detection of

dysplastic lesions needs to be better defined in future studies as endoscopic imaging techniques improve our ability to detect early neoplastic changes. Identification of effective chemopreventive agents against CRC development in UC could decrease the incidence and morbidity of colitis-associated neoplasia. To date, however, there is a lack of data to recommend the use of any specific chemopreventive agents in UC. Because of the cost and morbidity in the detection and treatment of neoplastic lesions in chronic UC, future research is urgently needed to identify efficacious, safe, and cost-effective chemopreventive agents and to establish clinical and biological predictors of dysplasia in order to tailor personalized surveillance strategies.

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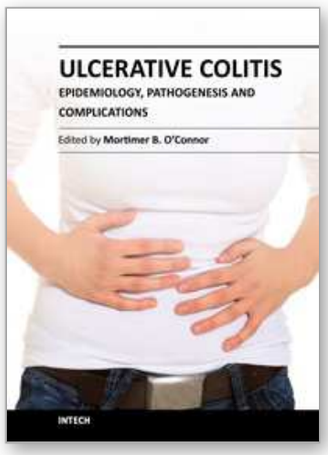

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This book is intended to act as an up-to-date reference point and knowledge developer for all readers interested in the area of gastroenterology and in particular, Ulcerative Colitis. All authors of the chapters are experts in their fields of publication, and deserve individual credit and praise for their contributions to the world of Ulcerative Colitis. We hope that you will find this publication informative, stimulating, and a reference point for the area of Ulcerative colitis as we move forward in our understanding of the field of medicine.

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