



TOPIC HIGHLIGHT

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Colorectal cancer and dysplasia in inflammatory bowel disease

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Abstract

Both ulcerative colitis and Crohn's disease carry an increased risk of developing colorectal cancer. Established risk factors for cancer among patients with inflammatory bowel disease (IBD) include the younger age at diagnosis, greater extent and duration of disease, increased severity of inflammation, family history of colorectal cancer and coexisting primary sclerosing cholangitis. Recent evidence suggests that current medical therapies and surgical techniques for inflammatory bowel disease may be reducing the incidence of this complication. Nonetheless heightened vigilance and a careful, comprehensive approach to prevent or minimize the complications of invasive cancer are warranted in this unique cohort of patients. Current guidelines for the prevention and early detection of cancer in this high risk population are grounded in the concept of an inflammation-dysplasia-carcinoma sequence. A thorough understanding of the definition and natural history of dysplasia in IBD, as well as the challenges associated with detection and interpretation of dysplasia are fundamental to developing an effective strategy for surveillance and prevention, and understanding the limitations of the current approach to prevention. This article reviews the current consensus guidelines for screening and surveillance of cancer in IBD, as well as presenting the evidence and rationale for chemoprevention of cancer and a discussion of emerging technologies for the detection of dysplasia.

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Key words: Cancer; Dysplasia; Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Chemo-prevention

INTRODUCTION

Patients with inflammatory bowel disease (IBD) have an increased risk of developing intestinal cancer. The magnitude of that increased risk as well as how best to mitigate it remain a topic of ongoing investigation in the field. Although only 1% of all cases of colorectal cancer (CRC) occur in patients with ulcerative colitis (UC) or Crohn's disease^[1], patients with IBD represent one of the highest risk groups for developing this dreaded complication. Strategies to reduce or prevent the complications associated with invasive cancer are essential in this high-risk population. Current guidelines advocate routine surveillance colonoscopy as the cornerstone of prevention. For patients in whom precancerous dysplastic lesions or early cancer are detected, surgical removal of the colon can be a potentially curative procedure for both the cancer and the colitis. This secondary prevention strategy has several drawbacks, however. Colonoscopy is less sensitive for detecting precancerous dysplasia in IBD patients than in the general population. Unlike in sporadic CRC in which dysplastic adenomas begin as raised polypoid lesions, dysplasia in IBD can arise in mucosa that is indistinct from surrounding mucosa, making it "invisible" to the endoscopist. Consequently many lesions may be missed. Additionally, the molecular biology of cancer in IBD is unique in that the accumulation of molecular and genetic alterations may occur more rapidly or in an unconventional sequence when compared to sporadic CRC. Given the limitations of the current surveillance approach, primary cancer prevention via chemoprevention has been proposed as an alternative or additive strategy. Although such a prospect would be ideal, the effectiveness of medications to mitigate cancer risk in IBD has not been firmly established. Further research is directed toward improving detection of dysplasia during colonoscopy through the use of novel endoscopic imaging techniques.

These exciting and promising developments are hoped to impact the approach to cancer prevention in patients with IBD. This article reviews the epidemiology of cancer and dysplasia in IBD, as well as the evidence and rationale behind consensus guidelines for screening and surveillance.

EPIDEMIOLOGY OF CANCER IN ULCERATIVE COLITIS

The increased risk of colorectal cancer in UC has been recognized for decades, although estimates of the magnitude of that risk vary considerably in the literature. Some authors have described a cumulative probability as high as 60% for developing cancer after 40 years of disease^[2], while others have demonstrated a risk level on par with that of the general population^[3]. Several reasons have been proposed to explain these discrepant results, including a lack of uniformity in study design and case definitions, geographic differences in incidence based on environmental factors, and referral center bias. In an effort to bring clarity to this issue, Eaden and colleagues performed a meta-analysis in 2001 in which they reviewed 116 studies (41 of which were included in the analysis), encompassing 54478 patients with UC and 1698 cases of CRC, to yield an overall prevalence of CRC in UC of 3.7%^[4]. By pooling the results of the studies that reported data on duration of disease by decade the authors were able to calculate a cumulative probability of CRC in UC of 2% after 10 years, 8% after 20 years, and 18% after 30 years of disease. Since this landmark publication, however, several more recent population-based and referral-based studies suggest that this risk may be declining over time or may simply be lower than previously accepted. Bernstein *et al* conducted a large population-based study in Manitoba, Canada, including 19655 person years of follow-up in which they described an increased incidence rate ratio for developing CRC of 2.75 [95% confidence interval (95% CI), 1.91-3.97] compared to the general population^[5]. This estimate of risk is approximately half that reported in the Eaden meta-analysis. These results were replicated in a population-based study in Hungary where the cumulative incidence of CRC was found to be 0.6% after 10 years, 5.4% after 20 years, and 7.5% after 30 years of chronic UC^[6]. A small population study from Olmsted County in the United States followed 378 patients diagnosed with UC between 1940 and 2001^[7]. Only 6 cases of CRC were discovered in 5567 person-years of follow-up, yielding a 30-year cumulative probability of CRC in this cohort of only 2%, not significantly different from the non-IBD patients in this population cohort. Interestingly, no cases of CRC were discovered in patients whose UC was diagnosed after 1980. Although the number of patients in this study was relatively small, these results were reinforced by a much larger study in Denmark involving 22290 person-years of follow-up that demonstrated no increase in CRC risk among UC patients^[3]. The 30-year cumulative probability of CRC was only 2.1% among UC patients in this population. This declining trend in CRC incidence among UC patients holds true at referral centers as well. In 2006, Rutter and colleagues from St. Mark's Hospital in the

United Kingdom reported on their 30 year experience with the longest prospectively collected database on surveillance for dysplasia and cancer in UC^[8]. The cumulative incidence of CRC in this referral population was 2.5% at 20 years, 7.6% at 30 years and 10.8% after 40 years of disease. The reasons for this observed change in incidence may be the more widespread use of surveillance colonoscopy, a chemoprotective effect attributable to the more widespread use of maintenance therapies, more aggressive surgical intervention or dietary or environmental factors. Despite the encouraging finding that CRC in UC appears to be less common than previously believed, one should take caution in interpreting the results of these more recent studies as evidence to relax the practice of routine screening and surveillance. Rather these results may indicate that a comprehensive approach to screening, surveillance and control of disease inflammation is highly effective and that physicians should maintain an appropriate level of vigilance in this high-risk patient population^[9].

RISK FACTORS FOR CRC IN ULCERATIVE COLITIS

Several factors have been identified that increase the risk of CRC in patients with UC. The observation that cumulative cancer risk increases over time^[4,10] establishes that increasing duration of disease is an important risk factor. Consistent with an intuitive understanding of CRC risk as being associated with the cumulative effect of chronic inflammation, the extent of colon involvement in UC is an independent predictor of cancer risk^[10]. A Swedish study reported that the relative risk of CRC was 1.7 for ulcerative proctitis, whereas the risk in left-sided colitis was 2.8 and this risk rose to 14.8 in patients with extensive colitis^[10].

Until relatively recently there was no hard evidence to support the intuitive notion that the degree of inflammation correlates with cancer risk. This may in part be due to the difficulty of demonstrating an independent effect of inflammatory activity while controlling for duration and extent of disease, two factors that are surrogate measures of cumulative inflammation. Three recent studies have confirmed this association, however. In a retrospective analysis from the St. Mark's Hospital in the UK, Rutter and colleagues demonstrated that severity of inflammation on biopsy independently predicted risk of CRC^[11]. This finding was reinforced by studies from the University of Chicago and Mt. Sinai Medical Center in New York in which inflammatory activity was shown to be independently associated with CRC risk^[12,13]. In several studies, a younger age at diagnosis is also associated with an elevated risk of CRC, independent of disease duration^[10]. Although the reason for this association is not known, it may in part be related to the finding that patients with an early age of diagnosis tend to have more severe inflammation^[11]. Several studies have demonstrated that a family history of CRC, independent of a family history of IBD is associated with higher risk of developing cancer^[14-17]. Additionally, coexistent primary sclerosing cholangitis (PSC) confers an elevated risk of CRC in UC

patients, with a meta-analysis by Soetikno *et al* describing an odds ratio of 4.09 (95% CI, 2.89-5.76) when compared to UC patients without PSC^[18]. This finding has led to the recommendation of closer surveillance in this unique high-risk subset of UC patients. The reason for elevated CRC risk in PSC may be that PSC is a marker for longstanding subclinical disease^[19]. However, the finding that treatment with ursodeoxycholic acid (UDCA) can lessen CRC risk suggests that the altered bile acid milieu of PSC may play a role in carcinogenesis^[20,21]. Additionally, one study has demonstrated that backwash ileitis may be an independent predictor of increased CRC risk^[22]. The finding of a stricture or dysplasia during colonoscopy also carries a heightened risk of malignancy^[23,24].

Thus, cancer risk in UC appears to result from the combined effects of chronic inflammation (as estimated by the extent and duration of disease and the degree of histologic inflammation) and an individual's underlying genetic predisposition (as suggested by family history, coexistent PSC and early age of diagnosis). Unfortunately, severity of inflammation appears to be the only modifiable risk factor, underscoring the importance of medical management in mitigating cancer risk, and highlighting the need for a preventive approach to cancer and pre-cancer detection.

CANCER IN CROHN'S DISEASE

While the relationship between UC and CRC has been appreciated for many years, the association between Crohn's disease and CRC has gained increasing recognition recently. Measuring the risk of CRC in Crohn's disease poses several methodological challenges, relating to the heterogeneous nature of the disease, with many patients having no colonic involvement. Even among patients with Crohn's colitis it is difficult to control for the extent of colonic inflammation, given that the disease can involve any area of the colon in a patchy distribution, and many Crohn's patients have undergone partial surgical resection of the colon, removing some of the at-risk tissue. Consequently, there is substantial variation among the articles that attempt to quantify the risk of CRC in Crohn's, in terms of both study design and results.

Several publications offer estimates of CRC risk in colonic Crohn's disease. Gyde and colleagues reported the relative risk of CRC in Crohn's colitis to be 23.8, whereas the risk was 4.3 in the general Crohn's population^[25]. Greenstein and colleagues calculated a relative risk of 6.9 for developing CRC in isolated colonic Crohn's^[26]. A landmark study from Sweden demonstrated a relative risk of CRC of 5.6 for those with exclusively colonic involvement, as compared to a relative risk of 3.2 for patients with ileocolitis and 1.0 for patients with ileal involvement only^[27]. This not only established that Crohn's carries a higher risk of CRC, but also that this risk correlates with the extent of colonic involvement. Additionally, a subset analysis revealed that patients whose IBD was diagnosed prior to age 30 had a higher relative risk than patients diagnosed at an older age, similar to patients with ulcerative colitis.

A meta-analysis of twelve hospital-based and population-

based studies of CRC risk in Crohn's disease revealed an overall relative risk of CRC in all Crohn's patients of 2.5 (95% CI, 1.3-4.7)^[28]. In the subset of patients with colonic disease this risk rose to 4.5 (95% CI, 1.3-14.9), while for patients with ileal disease only the risk was not significantly different from the general population. The cumulative risk of CRC for all patients with Crohn's disease, regardless of disease distribution, was 2.9% after 10 years, 5.6% after 20 years and 8.3% after 30 years of disease. In contrast to the Canavan meta-analysis that included population and referral-based studies, Jess *et al* performed a meta-analysis restricted to population studies of intestinal cancer risk in Crohn's^[29]. Six papers met the inclusion criteria and reported varying estimates of relative risk of CRC ranging from 0.9 to 2.2, with a pooled estimate of 1.9 (95% CI, 1.4-2.5).

The risk of CRC risk in Crohn's is equivalent to that in UC when comparison is controlled for similar extent of disease. In a study by Gillen and colleagues from the UK, patients with extensive Crohn's colitis were compared to patients with extensive ulcerative colitis with regard to CRC risk^[30]. The results were astonishingly similar with a relative risk of developing CRC of 18 for Crohn's colitis and 19 for UC. The cumulative risk of CRC was 8% at 22 years for patients with Crohn's versus 7% at 22 years for patients with UC. A large population-based study in Canada demonstrated increased incidence rate ratio of CRC in Crohn's patients of 2.64 (95% CI, 1.69-4.12) compared to the general population^[5]. This was remarkably similar to the risk of CRC in UC patients in the same study, reinforcing the finding that Crohn's and UC share a similar risk of CRC. In addition to a similar magnitude of risk, Crohn's patients share many of the same risk factors for CRC as UC patients, including younger age at diagnosis, greater extent of colonic involvement and longer duration of disease. In addition it appears that bypassed segments of bowel^[31] and perianal fistulae^[32] in Crohn's disease may also be sites at increased risk for neoplastic transformation and warrant heightened vigilance. Furthermore, bowel strictures in Crohn's disease may harbor dysplasia or cancer^[33] and should be carefully biopsied and resected if a pediatric or upper endoscope cannot traverse them. Different from UC, however, is that benign strictures are considered a possible manifestation of the disease so may not need resection otherwise.

While it is technically difficult to determine the exact risk of CRC in Crohn's disease, it is generally accepted that patients with Crohn's disease of the colon are at increased risk for dysplasia and CRC, and that this risk is related to cumulative effect of colonic inflammation, akin to UC. With the exception of strictures as described above, screening and surveillance of CRC in patients with Crohn's should be handled identically to patients with UC, matched for extent of colonic involvement.

DYSPLASIA IN INFLAMMATORY BOWEL DISEASE

The current approach to surveillance is grounded in the concept of an inflammation-dysplasia-carcinoma sequence, with dysplasia representing a premalignant

phase during which intervention can prevent or minimize the complications associated with invasive cancer. An understanding of the definition, diagnostic challenges and natural history of dysplasia in IBD is, therefore, essential when contemplating complex clinical management decisions.

Dysplasia is defined as unequivocal neoplasia of the epithelium confined to the basement membrane, without invasion into the lamina propria^[34]. Dysplasia can be classified as raised or flat based on its endoscopic appearance. Flat dysplasia is classically thought to be endoscopically invisible and is detected only on random biopsy specimens. At least 2 authors, however, have demonstrated that many of these lesions are in fact visible through standard white light endoscopy using newer generation colonoscopes with higher optical resolution^[35,36]. Elevated lesions that are endoscopically visible, but not amenable to endoscopic resection are often referred to as DALMs (dysplasia associated lesion or mass) a term with ominous connotation attributable to the high rate of synchronous malignancy associated with these lesions^[24,37]. A newer term ALM (adenoma-like lesion or mass) has been introduced to describe the finding of a polypoid lesion resembling a sporadic adenoma that is found in an area of the colon not involved by chronic colitis. Irrespective of the endoscopic appearance of a lesion as raised or flat, pathologists use the same set of criteria to describe the histologic appearance of dysplasia in IBD. A standardized classification system introduced by Riddell and colleagues in 1983 divides dysplasia into categories, including indefinite dysplasia, low grade dysplasia (LGD), high grade dysplasia (HGD) and cancer^[34]. Although this system remains widely employed, it has several acknowledged limitations, including poor inter-observer agreement and intra-observer reliability, even among expert gastrointestinal pathologists^[34,38]. This lack of concordance of biopsy interpretations has led to the routine practice of requiring confirmation of a dysplasia diagnosis by a second expert pathologist prior to making critical treatment decisions.

Management of dysplasia, once diagnosed, relies on an understanding of the natural history. In 1994, two groups published data revealing that approximately one in 8 patients with UC will have dysplasia or cancer found on their initial screening colonoscopy, but that those with a negative initial exam have a low incidence (about 3%) of developing high grade dysplasia or cancer on subsequent surveillance colonoscopies^[24,39]. Among patients with LGD who undergo immediate colectomy 19% will already harbor concurrent CRC or HGD^[24] and an additional 29%-54% will subsequently develop advanced neoplasia over the next 5 years^[24,39,40]. HGD carries a 43% risk of synchronous malignancy and is therefore considered to be an indication for immediate colectomy^[24]. DALMs associated with a similarly high rate of CRC are likewise an indication for total proctocolectomy^[24,37]. In contrast to DALMs, however, adenoma-like lesions can be safely managed by polypectomy with biopsies of the surrounding flat mucosa^[41]. If the lesion is successfully removed in its entirety and the surrounding mucosa is free of dysplasia, a regimen of more frequent surveillance colonoscopy is

recommended. The finding of adjacent dysplasia in the flat mucosa prompts immediate colectomy by most experts, given the likelihood of concurrent cancer or progression to cancer.

MOLECULAR BIOLOGY OF CANCER IN IBD

Several of the molecular alterations that contribute to sporadic CRC are also found in colitis-associated CRC, including loss of APC and p53 tumor suppressor gene function. However, the timing and sequence in which these genetic mutations occur differs from sporadic CRC. Whereas APC loss is considered an early development in the adenoma-carcinoma sequence of sporadic CRC, and p53 represents the final mutation that transforms adenoma into carcinoma, the opposite is often true in IBD-associated CRC. While the description of an inflammation-dysplasia-carcinoma sequence facilitates our understanding of the molecular alterations involved in IBD-associated CRC, it is important to recognize that this process does not necessarily occur in a systematic and sequential progression from inflammation to indefinite dysplasia to LGD to HGD and ultimately to carcinoma. Cancer can develop without any apparent preceding dysplasia, and the natural history of low grade dysplasia has been described to regress or to progress to cancer without evolving first into HGD^[42]. This unpredictable course of dysplasia in IBD complicates efforts to develop molecular or histologic markers of neoplastic progression or future cancer risk. Currently our limited understanding of the molecular biology of IBD-associated cancer is not sufficient to use these markers for clinical management decisions. However, as our knowledge advances, it is possible that such markers will one day complement or supplant histologic evidence of dysplasia in assigning cancer risk in patients with IBD.

CHEMOPREVENTION OF DYSPLASIA AND CANCER

Chemoprevention refers to the use of chemical compounds to prevent, halt, or reverse the development of cancer. One advantage of chemoprevention over the current secondary prevention strategy of routine colonoscopy is the potential to intervene early enough in the carcinogenic sequence to avoid not only cancer, but also the need for colectomy. The goal of chemoprevention should be to reduce CRC risk, allowing for less frequent surveillance exams and a reduction in the number of invasive cancers. The bulk of evidence for chemoprevention in IBD relates to the use of 5-aminosalicylates (5-ASA). Unfortunately, no prospective data exist, and retrospective studies have yielded mixed results with regard to the protective effect of 5-ASA medications. A meta-analysis by Velayos *et al* including 9 case control and cohort studies revealed a pooled odds ratio of 0.51 (95% CI, 0.38-0.69) for the development of dysplasia or cancer in patients with regular use of 5-ASA medications^[43]. Given the substantial heterogeneity of individual study results, this pooled estimate signifies the most accurate estimate of the protective effect of 5-ASA.

The most compelling evidence for chemoprevention

in IBD comes from a prospective randomized placebo-controlled trial of UDCA in the high-risk subset of UC patients with coexisting PSC^[20]. Compared to the placebo group, patients who received UDCA had a relative risk of 0.26 (95% CI, 0.06-0.92) for developing CRC or dysplasia. A retrospective study at the University of Washington of patients with PSC and UC corroborated these results by demonstrating a strong negative association between UDCA use and dysplasia, with an odds ratio of 0.18 ($P = 0.005$)^[21].

While other medications have been explored as potential chemopreventive agents, none have yielded satisfactory results. The adverse effects of corticosteroids and non-steroidal anti-inflammatory drugs preclude their long-term use for chemoprevention in IBD patients, despite some evidence to suggest a protective effect in both IBD and non-IBD patients. The use of folate for chemoprevention has sound rationale and an excellent safety profile, but inadequate evidence of a protective benefit. Likewise despite the rationale of medically controlling inflammation as a potential mechanism of cancer prevention, there are insufficient data to recommend azathioprine or 6-mercaptopurine for chemoprevention.

SURVEILLANCE FOR DYSPLASIA AND CANCER

Periodic surveillance colonoscopy is the foundation of our current approach to cancer prevention in IBD. This strategy relies on the ability to detect CRC at a preclinical phase of dysplasia during which intervention can avert the adverse consequences of invasive cancer. Detection of dysplasia depends on the frequency and technique of surveillance colonoscopy, as well as the quality of pathologic review. Itzkowitz and Harpaz report that a typical biopsy samples less than 0.05% of the colon^[44], highlighting the potential for sampling error associated with nontargeted biopsies to look for flat dysplasia. Rubin *et al* retrospectively determined that 33 biopsies are required to detect dysplasia with 90% sensitivity, and 64 biopsies are needed to achieve 95% sensitivity^[45]. Although consensus guidelines incorporate this finding and recommend 30-40 biopsies, this can be quite cumbersome to perform. Additionally, many gastroenterologists are either not fully aware of these recommendations or intentionally do not adhere to them^[46,47]. Newer imaging technologies such as chromoendoscopy, magnification endoscopy and confocal laser microscopy offer the potential to enhance detection of dysplasia during surveillance colonoscopy, allowing endoscopists to take fewer high-yield biopsies of targeted abnormal mucosa.

The recommendation to perform surveillance in IBD patients comes from consensus expert opinion, supported by solid rationale and an ethical imperative to attempt prevention in an at risk population^[48]. However, hard evidence of efficacy is lacking. A Cochrane review concluded that although there is no clear evidence that surveillance colonoscopy prolongs survival in IBD patients; there are data to suggest that cancers tend to be detected at an earlier stage with a correspondingly more

favorable prognosis^[49]. The authors include the caveat that lead time bias may contribute substantially to these results. Additionally they conclude that indirect evidence supports surveillance as a cost-effective endeavor^[49].

A number of guidelines published over the past decade offer direction to gastroenterologists in their approach to surveillance of dysplasia and cancer in IBD^[23,50-53]. An international panel of experts convened by the Crohn's and Colitis Foundation of America published consensus guidelines in 2005 suggesting that an initial screening colonoscopy be performed in all UC patients 8-10 years after onset of symptoms attributable to UC^[23]. The dual purpose of this initial screening exam is to identify dysplasia or cancer, if present, as well as to evaluate for possible reclassification of disease extent. The extent of disease in a given UC patient should be considered the greatest extent of involvement documented on either gross or histologic exam at the time of diagnosis of UC or at initial screening colonoscopy. Patients with Crohn's disease should be managed in an identical manner to UC patients of comparable extent of colonic involvement. Crohn's patients with at least one third of their colon involved are considered to have extensive colitis. Those patients with left-sided or extensive colitis (UC or Crohn's) who have a negative screening examination should continue periodic surveillance at an interval of every 1 year to 2 years. In light of the increased risk imposed by coexistent PSC, annual surveillance is warranted beginning at the time of PSC diagnosis. The technique of colonoscopy should involve 4 quadrant random biopsies at 10 cm increments throughout the colon in addition to targeted biopsies of suspiciously abnormal mucosa. All abnormal biopsies results should be confirmed through independent review by a second pathologist. A finding of indefinite dysplasia should prompt accelerated surveillance with a repeat exam in 3 to 6 mo. Management of low grade dysplasia is a subject of debate among experts with no clear consensus on optimal management. In the setting of LGD, physicians should initiate an informed discussion with their patients regarding the risks and benefits of immediate surgery versus heightened colonoscopic surveillance. Prophylactic colectomy should be offered due to the about 20% prevalence of concurrent malignancy^[8], with counseling about possible surgical complications including incontinence, adhesions, pouchitis and decreased fertility in female patients. Patients who elect nonoperative management should be informed regarding the drawbacks of surveillance, including limitations with endoscopic detection and sampling and challenges with histologic interpretation. An accelerated program of surveillance colonoscopy every 6 mo should be pursued with adherence to an extensive biopsy protocol.

The finding of high grade dysplasia should prompt referral for immediate total proctocolectomy attributable to the high rate of concurrent or subsequent malignancy^[24]. Raised lesions found within an area of colitis should be removed, and the surrounding mucosa biopsied. If the lesion is amenable to complete endoscopic resection and the adjacent mucosa is free of dysplasia, a regimen of more frequent surveillance colonoscopy is recommended. The

finding of adjacent dysplasia in the flat mucosa warrants referral for colectomy. Raised lesions resembling adenomas that are encountered in areas free of inflammation can be handled in accordance with standard guidelines for management of sporadic adenomas^[23].

Strictures represent a unique circumstance that merits a higher degree of vigilance. Colonic strictures in UC often harbor malignancy and are considered a strong indication for surgery, even if biopsies and brushing of that area are unrevealing^[23]. In Crohn's disease, colonic strictures may be followed with annual surveillance and biopsy if the lesion can be traversed with a standard pediatric colonoscope. In the setting of longstanding Crohn's disease, consideration should be given to surgical resection of a stricture due to the heightened risk of CRC^[23].

NOVEL IMAGING TECHNIQUES

Despite improvements in optical resolution of modern endoscopes, surveillance colonoscopy has suboptimal sensitivity for detecting flat dysplasia. Consequently, a protocol of nontargeted biopsies is still advocated to detect these "invisible" lesions. This approach is time-consuming and cumbersome, however, and adherence to this regimen by physicians is poor^[47]. Endoscopic techniques to improve macroscopic and microscopic visibility of dysplastic lesions are crucial to enhancing the diagnostic yield of surveillance colonoscopy and reducing the number of missed lesions. Chromoendoscopy, magnification endoscopy, narrow band imaging and confocal laser endomicroscopy are evolving technologies that hold promise in this regard.

Chromoendoscopy involves the application of dye during colonoscopy to highlight subtle mucosal changes that cannot be appreciated by standard white light imaging techniques. Indigo carmine is a contrast dye that augments subtle mucosal alterations, whereas methylene blue is an absorptive dye that is avidly taken up by normal mucosa, but does not stain areas of inflammation or dysplasia, thereby creating a contrast gradient that enhances visualization. At least 3 prospective studies have demonstrated that chromoendoscopy improves the sensitivity of detecting neoplasia in UC patients^[54-56]. In addition to this improved sensitivity, chromoendoscopy offers the potential to improve specificity as well, by facilitating enhanced endoscopic characterization of lesions, thereby allowing the endoscopist to perform fewer biopsies that are more targeted. The combination of chromoendoscopy with magnification permits a detailed analysis of the mucosal architecture, and can assist gastroenterologists in differentiating benign from neoplastic lesions during colonoscopy, improving the yield of targeted biopsies^[57].

Narrow band imaging uses specialized light filters to enhance visualization of the tissue microvasculature, facilitating distinction between normal mucosa and neoplasia. Although this novel and innovative technology remains to be thoroughly evaluated in the setting of surveillance in IBD, it holds the potential to offer the same benefits as chromoendoscopy with greater ease of application.

Confocal laser endomicroscopy (CLE) enables real-time histologic evaluation of the colonic mucosa during endoscopy and can be combined with chromoendoscopy. Suspicious lesions identified through application of dye can be subsequently examined with extreme detail at the subcellular level of resolution with CLE prior to targeted biopsy. In a randomized trial in UC patients of chromoendoscopy in conjunction with CLE compared to conventional colonoscopy, the presence of neoplasia could be predicted with 94.7% sensitivity, 98.3% specificity and 97.8% accuracy^[58]. In this study of 153 patients, the mean examination time was 42 min using chromoendoscopy with CLE compared with 31 min in the standard colonoscopy group. This innovative imaging technique has major implications for the future of colonoscopic surveillance in IBD.

Despite the promise and emerging information about these new techniques, factors of cost and training remain far from answered, and chromoendoscopy is not yet considered a standard of care approach to surveillance in the United States.

CONCLUSION

Patients with UC and Crohn's disease have an increased risk of developing CRC. This risk appears to be related to the cumulative effect of chronic inflammation and correlates directly with the extent and duration of disease as well as the severity of inflammatory activity. Additional factors that further increase CRC risk in IBD patients include a younger age at diagnosis, coexistent PSC and a family history of CRC. Despite varying estimates of the magnitude of cancer risk in IBD, it remains widely accepted that patients with IBD represent a high-risk group for developing CRC in whom current therapies and surgical techniques may be affecting the incidence of this complication, so a careful approach to prevention and surveillance is still warranted. The overall approach to cancer prevention in IBD should be a comprehensive strategy, including regular follow-up visits and intensive control of disease activity through medical therapy, in concert with routine surveillance colonoscopy involving extensive biopsies. Despite several acknowledged limitations, periodic surveillance colonoscopy continues to serve as the foundation of a prevention strategy, with colectomy reserved for patients in whom dysplasia or cancer are discovered. Cancer risk reduction through regular use of chemopreventive medications remains an attractive concept, and the most compelling data is in the setting of PSC and IBD, in which UDCA offers substantial benefit. The accumulated data appears to favor 5-ASA as a chemopreventive agent, but this remains inconclusive due to the retrospective nature of these studies. Novel endoscopic imaging technologies to enhance detection of neoplasia are under investigation and hold promise for improving the yield of surveillance colonoscopy.

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