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OBSERVATION

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Surveillance for colitis-associated colon neoplasia

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Abstract

The risk of developing colon cancer is increased in colitis patients, particularly if the disease is extensive and its duration long-standing. Endoscopic guidelines have been developed with the goal of detecting early neoplastic changes prior to development of advanced malignancy. Unfortunately, the natural history of this superimposed neoplastic process in colitis appears to be very heterogeneous and poorly understood. Moreover, there are numerous confounding variables in colitis patients that limit accurate assessment of the surveillance effectiveness of colonoscopy and multi-site biopsy protocols. Although the clinical challenge posed to even the most experienced clinicians remains significant, evolving methods of endoscopic imaging may facilitate better evaluation of this highly select group of patients.

Key words: Ulcerative colitis; Crohn's disease; Colon cancer; Surveillance colonoscopy; Colon biopsies

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INTRODUCTION

In long-standing and extensive colitis, the risk of colon cancer is increased[1]. Supportive evidence for this increased colon cancer risk in colitis initially came from observational studies in tertiary centers in the United Kingdom and the United States during the pre-surveillance era. In these tertiary centers, more severe disease, some already complicated by carcinoma, would have influenced risk estimates. Later, studies using data from different community-based clinical practices or population-based studies suggested that this risk was increased, but the magnitude of this risk was less. Recent data estimates from a referral-based population in a long-standing and uniform program of colonoscopy surveillance in the United Kingdom noted that the overall cumulative incidence of colitis-associated colon cancer was about 2.5% after 20 years of disease, 7.6% after 30 years, and 10.8% after 40 years[2].

Risk factors that may contribute to the eventual development of colorectal cancer in colitis have become increasingly apparent. Some of these risk factors are listed in Table 1, although precise risk estimates for each factor have only been defined to a limited extent. Overall, the underlying cause for this increased cancer risk has been hypothesized to be the ongoing chronic and persistent colonic mucosal inflammatory process[6], but the actual molecular mechanisms involved still require definition. In recent years, a novel, but still hypothetical "inflammation to carcinoma sequence" has been conceptualized to more

precisely separate this process from the well enunciated "adenoma-carcinoma sequence" proposed for sporadic colon cancer[16-18]. A number of differences in the molecular changes of sporadic compared to colitic cancer have been noted[19]. APC loss of function appears to be less frequent in colitis-associated colon cancer, while p53 mutations seem to occur earlier[19]. Finally, CpG-island methylation also appears to be accelerated in colitis[20].

RATIONALE FOR COLONOSCOPY SURVEILLANCE FOR NEOPLASIA

In the past, prophylactic proctocolectomy was sometimes performed in selected cases to reduce subsequent risk of colorectal cancer. Although this undoubtedly reduced colon cancer risk in this setting, most colon resections were not required, and, in themselves, probably resulted in reduced quality of life and created significant morbidity, and likely, some mortality. Although this approach may still have merit in some selected situations, a different clinical approach based on surveillance has emerged in recent decades; in part, owing to the increased availability of colonoscopy to permit detection of neoplasia. In the setting of inflammatory bowel disease, the goal to detect either precancerous changes or early stage invasive carcinoma has been pursued to permit curative colon resection. Although there are no randomized controlled clinical trials to show that surveillance colonoscopy is an effective approach, 3 case-control studies have appeared[21-23]. As a result, enthusiasm exists for development of surveillance programs in chronic colitis, but surveillance colonoscopy *per se* may not actually prolong survival, even in extensive colitis[24]. Possibly, cancers are detected at an earlier stage with a resulting better prognosis, but it has been suggested that this likely reflects, in large part, the phenomenon of lead-time bias[24]. Guidelines for surveillance have been developed based on the rationale that detection of these early neoplastic changes in the colon could result in a significant reduction or elimination of the morbidity and mortality from colon cancer in selected high risk patients with inflammatory bowel disease[25,26]. These guidelines suggest that colonoscopy should be carried out on a regular basis (for some, on an annual basis) and also urge that biopsies be performed throughout the colon to include "flat" areas of mucosa as well as visibly abnormal mucosa (or macroscopically-defined lesions). It has also been emphasized that the optimal surveillance interval has not been defined and that there are no prospective studies on the optimal number of biopsy specimens from different sites in the colon[25].

CONFOUNDING VARIABLES IN SURVEILLANCE PRACTICE

Studies have also shown that patient and physician compliance to published surveillance colonoscopy guidelines or recommendations varies. In part, this likely reflects the presence of many other confounding issues. For example, pre-scheduled procedures may be completed during periods of active inflammatory disease which, from a pathological perspective for histological evaluation, may not be optimal. Guidelines do not clearly define the duration that surveillance studies should be delayed, if moderate to severe symptomatic disease is present. Differences in methodology are also evident and include (but are not limited to): biopsy site, size and numbers; forceps type (e.g. "jumbo"); biopsy methods (i.e. "multiple-bite single pass" biopsies *vs* "single-bite multiple pass" biopsies); and, fixation methods (i.e. formalin *vs* picric acid or mercury-based fixatives, such as Bouin's or Hollande's). Some of these fixatives, for example, may significantly impact on cellular (particularly nuclear/nucleolar) detail in a colonic biopsy section and the resultant histological appreciation and interpretation of neoplastic changes. Studies have also shown that much of the benefit attributed to colonoscopy in a surveillance population may be due, in part, to the intensified degree of follow-up (compared to a no-surveillance population) rather than the precise frequency of procedures (annual or otherwise) or numbers of colonoscopic biopsies *per se*. Assuming similar biological behavior of the disease (which may not be appropriate in an essentially heterogeneous population), patients with inflammatory bowel disease who are followed frequently and regularly are thought to more likely have a positive outcome than those not followed in a defined protocol. Guidelines suggested for long-standing and extensive ulcerative colitis have also been extended to Crohn's disease[25,26] since prolonged disease duration in extensive Crohn's colitis appears to result in increased colon cancer risk[27,28], but data supporting a role for a program of surveillance colonoscopy in Crohn's disease are still needed. Finally, the development of sporadic or "non-colitic" colon cancers in patients with inflammatory bowel disease may also be critically influenced by other underlying genetic, geographic and environmental factors. Some of these factors may confound data analysis and prevent direct translation of published data to immediate clinical practice.

Table 1 Risk factors for cancer in colitis

Epithelial cell dysplasia (high-grade > low-grade)
Extent of mucosal involvement (pancolitis > distal colitis > proctitis)[3,4]
Extended duration of ongoing disease (> 8-10 yr)[1,2,5]
Severity of histologic inflammation (?linked to compliant 5-ASA use)[6,7]
Onset in childhood (?linked to underlying duration of disease)[3,4,8]
Primary sclerosing cholangitis[9,10]
Liver transplantation, usually for primary sclerosing cholangitis[11-13]
Underlying familial colon cancer risk[14,15]
Other (?immunosuppression, ?biologic agents)

EPITHELIAL DYSPLASIA

The key histopathological lesion in bowel disease surveillance categorized by standard classification is epithelial dysplasia[29]. An alternative classification has also been more recently devised[30]. Dysplasia (from the Greek,

translated roughly as "bad formation") is a pathological term used to describe a neoplastic process that is hypothesized to be restricted to epithelial cells, not other mucosal cell types, and occurring in this case in the colon. These epithelial cells display features of both delayed maturation and differentiation, but have not invaded through the underlying basement membrane. From a practical perspective, dysplasia is considered the earliest recognizable form of the neoplastic process with the potential for invasive cancer. Eventual development of cancer has been hypothesized to be related to the degree or grade of dysplasia. Essentially, dysplasia represents a histopathologically-defined risk marker for carcinoma. However, the precise risk for an individual focus of low-grade epithelial dysplasia to ultimately transform into a focus of high-grade dysplasia, and eventually into an invasive carcinoma, is not known although it is probably low. Nevertheless, from a clinical perspective, the detection of dysplasia, an unequivocal neoplastic lesion, is thought to represent a histopathological marker of increased risk for eventual development of invasive cancer, or even concurrent cancer elsewhere in the colon. Importantly, colon cancer may also occur in colitis even if dysplasia is not detected[26].

Indeed, the long-term natural history of epithelial dysplasia is poorly understood, especially in the setting of colitis. Additionally, there are many considerations that might influence this hypothetical biological process. Specifically, it is not known if a tiny focus of epithelial dysplasia in the colonic mucosa remains irreversibly present or if a focus of dysplasia can spontaneously regress, or even disappear. Furthermore, it is not known if a persistent focus of dysplasia, if given enough time, inevitably reaches a higher grade or remains static. Moreover, it is not known if there is a biological qualitative difference between a tiny single focus of dysplasia in flat mucosa compared to a larger "field change" in flat mucosa. Also, it is not precisely known if dysplasia in flat mucosa differs from dysplasia in visibly abnormal mucosa. If dysplasia is associated with a mass lesion, the presence of an associated cancer is thought to be higher, particularly in the mass *per se*. Indeed, underlying malignancy (below the overlying mucosa) has been detected in patients with mucosal biopsies that show dysplasia but no invasive carcinoma. Finally, it is conceivable that dietary, pharmacological or other therapeutic variables, including biological agents, used to treat the colonic inflammatory process may positively or negatively affect this histologically-defined biological change in the epithelial cell.

CLASSIFICATION OF DYSPLASIA

Dysplasia may occur in flat or elevated mucosa. Evaluation of a colonic biopsy for dysplasia results in 3 possible pathological conclusions: negative, indefinite or positive. Changes negative for dysplasia include normal mucosa, regenerative changes and mucosa with active inflammatory change. Changes indefinite for dysplasia include epithelial changes too aberrant to be classified as negative, but insufficient to fulfill criteria for positive. Positive refers to nuclear, cellular and architectural epithelial changes (Table 2). Positive for dysplasia may be further subdivided into low-grade and high-grade dysplasia depending on the predominant location of the nuclei in the epithelial cell layer. In low-grade dysplasia, the nuclei occupy the basal half of the cell. In high-grade dysplasia, the nuclei extend into the luminal half of the cell or the nuclei simply appear in a particularly disorganized pattern. Most pathologists define the degree of dysplasia (low-grade, high-grade) based on the most severe changes detected. Finally, adenomatous polyps with varying degrees of epithelial dysplasia may be seen in colitis. If these are sessile, it may be particularly difficult to distinguish these from other visible lesions, such as the so-called dysplasia-associated lesion or mass.

Table 2 Changes positive for dysplasia[1]

Nuclear changes	Nuclear enlargement
	Pleomorphism
	Hyperchromatism
	Chromatin fragmentation
	Increased mitotic numbers
	Nuclear stratification
Cellular changes	High nuclear to cytoplasm ratios
	Enlarged nuclei
	Reduced or absent mucus production
Architectural changes	Gland-like arrangement of epithelial cells

[1]Dysplasia may be subdivided into low-grade dysplasia and high-grade dysplasia based largely on the nuclear localization in the cells of the epithelial layer. Based on Riddell *et al*[29].

INTERPRETATION ISSUES IN DYSPLASIA

Unfortunately, expert gastrointestinal pathologists may not agree in defining dysplasia or its severity or grade[29,31-34]. Early studies demonstrated good inter-observer agreement for "negative" but limited agreement for grading the "positive" category. Later studies have shown limited agreement for low-grade "positive" compared to the "indefinite" category, compared to high-grade "positive" and "negative" categories. For histological definition of dysplasia, review by a second expert pathologist has also been recommended. In this situation, a second opinion that confirms the initial assessment may be helpful, but the impact of disagreement on the clinical decision-making process has not been thoroughly evaluated. Finally, many clinicians feel that the definition of a single focus of low-grade dysplasia may not be sufficient to recommend colectomy and may increase the frequency of surveillance to confirm the presence of dysplasia or seek an additional site of dysplastic change.

OTHER METHODS FOR PREDICTION OF DYSPLASIA

Other methods have been reported to have potential value in predicting or corroborating dysplasia. For example,

flow cytometry showing DNA aneuploidy in a group of high risk patients without detectable dysplasia prospectively predicted an increased rate of dysplasia development later in the same group (although not in specific individuals within the same group). In addition, use of immunohistochemical staining methods have been advocated as another approach to support the pathological definition of dysplasia (p53, Ki-67, β-catenin). Indeed, a mutation of the p53 tumor suppressor gene, often detected in colon cancer, has been reported in some patients with inflammatory bowel disease before dysplasia is detected[35,36]. α-methylacyl-CoA racemase may also be a useful marker of dysplasia[37] and further confirmatory studies to evaluate its specificity and sensitivity are needed.

ANEUPLOIDY STUDIES AND MATHEMATICAL MODELING

While it is believed that surveillance colonoscopy and biopsy sampling *per se* may either categorize the degree of risk (i.e. low-grade or high-grade dysplasia) for cancer or define an early cancer, it is hoped that this process might actually reduce the morbidity and mortality associated with delayed recognition of a late stage colon cancer. It has been hypothesized that programs of surveillance colonoscopy with defined biopsy protocols might permit accomplishment of this goal. Unfortunately, there are no controlled studies available. Some published guidelines have been based, in part, on an approach taken in an earlier research study[38] largely designed for the different purpose of detection of DNA aneuploidy prior to or during development of dysplasia in ulcerative colitis. In that study, "jumbo" forceps biopsies were obtained from 4 quadrants at 10 cm intervals for an average of 40 separate biopsies for each procedure, in those with disease extending beyond the rectosigmoid region. In addition, visible lesions other than inflammatory polyps were also removed. The biopsies were each estimated to approximate 5 mm in size. Similar studies were performed on colectomy specimens, although the samples were larger (up to 1 cm in diameter) and removed every 3 cm for an average of 100 specimens per colon. A portion of some, but not all, biopsies were used for DNA aneuploidy studies. The study concluded that aneuploidy correlated with histological grade and might define a patient subset without dysplasia potentially at higher risk for later development of dysplasia. Although not designed to determine an optimal biopsy protocol, detection of neoplasia, either dysplasia or cancer, was mathematically estimated to require 18 biopsy samples, possibly obtained during 2 or more colonoscopies over 4 to 6 years, a time estimated for progression to high-grade dysplasia or cancer in ulcerative colitis. Although there are guidelines that have appeared to suggest annual or biannual colonoscopies with multiple biopsies taken in 4 quadrants every 10 cm in extensive colitis, evidence for this approach is not available. Indeed, most biopsies taken with standard forceps measure only about 2 mm × 2 mm. Not surprisingly, a recent study confirmed that jumbo forceps were superior to standard, although large-capacity, forceps in obtaining diagnostically adequate surveillance specimens[39]. If anything, random biopsy sampling only serves to emphasize the potentially high miss rate for focal areas of dysplasia since the total colonic surface area has been estimated, on average, to be about 1600 cm^2. As a result, it is not surprising to find that specialist endoscopists differ substantially in the actual practice of surveillance, including the number of biopsies obtained during a surveillance procedure for dysplasia detection. Recent evidence suggests that evolving technology, including chromoendoscopy with magnification[40], narrow band imaging or confocal endomicroscopy[41,42], autofluorescence imaging[43] and other emerging refinements using new molecular markers[44], may permit more precise definition of neoplastic change in long-standing and extensive colitis, rather than labor-intensive (and time-intensive) procurement of "blind" biopsies from multiple areas of otherwise flat mucosa. It is likely that these newer methods for cancer surveillance (e.g. chromoendoscopy for biopsy targeting) will eventually be incorporated into emerging guidelines[45]. These newer methods of enhancement, however, raise fresh issues underlined by recent mathematical modeling studies suggesting that enhanced endoscopic methods may not necessarily translate into improved patient outcomes[46].

OTHER LIMITATIONS IN NEOPLASIA SURVEILLANCE

Although dysplasia surveillance may be regularly performed, other confounding variables may make evaluation of surveillance programs difficult. The operator may be less experienced and the potential for missing lesions, particularly flat lesions, proximal to the hepatic flexure has been noted. Fortunately, in patients with long-standing chronic colitis, complete evaluation to include the cecum may be more readily accomplished (compared to screening non-colitic colons for polyps); in part, because the colon is often more tubular, fibrotic and foreshortened. Other factors may play a role. Firstly, the biological behavior of a neoplastic lesion in the setting of an extensive and chronic inflammatory process may differ substantially from a neoplastic lesion that develops without a background of inflammatory disease, or may biologically differ depending on the site within the colon (right *vs* left). Secondly, some neoplastic lesions that occur in patients with inflammatory bowel disease, such as neuroendocrine carcinomas, may have rapidly progressive growth. Even though these are very rare, some have been detected within months of surveillance studies that failed to define dysplasia[47,48]. Since colon cancers in this setting of inflammatory bowel disease may be very heterogeneous, detection of dysplasia only suggests increased risk, but cannot predict rate of progression to cancer. Thirdly, neoplastic lesions may also initially develop insidiously in "hidden sites", such as the appendix, where surveillance biopsies cannot normally be procured[49,50]. Fourthly, other underlying diseases followed

by concomitant or new treatments may significantly influence the immunological status of patients in surveillance programs. For example, increased colon cancer rates appear to develop after liver transplantation for sclerosing cholangitis[12,13].

PRACTICAL EVALUATION

Recognizing these inherent limitations, surveillance with multiple site biopsies, at least in well documented extensive disease, has merit as a potentially powerful tool for prevention of colonic neoplasia. Although guidelines have appeared, data to support a precise evaluative approach related to procedural frequency and numbers of biopsies performed during each procedure remain difficult to define, even after 8 to 10 years of ongoing disease. If colonic disease is extensive and long-standing, but the patient has entered clinical remission, then colonoscopic evaluation might reasonably be carried out every 3 years with biopsies from different sites, particularly from macroscopically abnormal mucosa. Part of the value of surveillance, however, also relates to increased frequency of clinical review, especially in those with few or no symptoms. Paradoxically, clinically well patients are often those most likely to become relaxed regarding their ongoing medical care and surveillance. Conversely, patients who remain continuously (or intermittently) symptomatic, especially if relapses are frequent, are more likely to require more significant medical therapy (and more intensive clinical evaluation) for disease control. In these, frequent procedural re-evaluation may become a significant element in their management, and so surveillance will essentially be accomplished. In those with the most clinically significant disease, colectomy should result, reducing (or removing) the colon cancer risk. In time, this approach will evolve as improvements in technology occur and their effectiveness continues to be evaluated.

CONCLUSION

Surveillance colonoscopy in inflammatory bowel disease, particularly in extensive long-standing ulcerative colitis, represents a challenge for the clinician. Assessment of its effectiveness is especially difficult and has been limited because there are numerous confounding variables that play a role in the individual patient. Finally, there is an evolving appreciation that inflammatory bowel disease *per se* represents a truly heterogeneous inflammatory process, even in those classified with long-standing and extensive disease.

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