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COLORECTAL NEOPLASIA SURVEILLANCE IN INFLAMMATORY BOWEL DISEASE: UPDATES AND PRACTICAL APPROACHES

Background

Performing colorectal neoplasia surveillance in persons with inflammatory bowel disease (IBD) that is both clinically effective and cost effective is among the greatest challenges facing endoscopists who care for this population. While heightened colorectal cancer (CRC) risk has long been recognized among persons with IBD, this risk has been declining over time, with recent reports suggesting no more than a 1.5–2-fold higher risk compared to age and sex matched members of the general population.[1-4] Nonetheless, given that CRC still occurs at a higher rate in this population, current surveillance strategies are inadequate for some persons. Conversely, 80–90% of persons with IBD had no neoplastic lesions identified during colonoscopy surveillance,[5] suggesting that many persons with IBD are unnecessarily exposed to the risks of colonoscopy, with society bearing these excess costs.

The purpose of colorectal neoplasia surveillance is to reduce the burden of CRC and CRC-related death in the IBD population. Societal guidelines recommend initiating colorectal neoplasia screening with colonoscopy in all persons with colorectal IBD involving at least the rectosigmoid (or at least 1/3 of the colorectum if accompanied by discontinuous inflammation) at 8–10 years following disease diagnosis and continuing lifelong surveillance every 1–5 years.[6-8] Major factors influencing surveillance frequency include historical disease severity, extent of colorectal inflammation, chronic post-inflammatory changes, family history of CRC, history of colorectal neoplasm, primary sclerosing cholangitis, prior colonoscopy findings, and adequacy of prior surveillance (**Table 1**).[6-8] All guidelines further recommend targeted sampling or resection of suspicious visible abnormalities, and some societies continue to recommend extensive non-targeted biopsies to detect

"invisible" neoplasia, particularly if other adjunctive optical modalities, such as dye-spray chromoendoscopy (DCE) or virtual chromoendoscopy (VCE), are not performed, or if the mucosa is poorly visualized, such as in areas of significant inflammation, post-inflammatory polyposis, or poor bowel preparation.[6,9] Most societies now advocate for DCE or VCE as primary screening tools for IBD neoplasia surveillance or, at a minimum, as alternative modalities to traditional white light colonoscopy with non-targeted biopsies where resources and expertise exists.[5-11]

However, there are no prospective studies demonstrating a reduction in the incidence of CRC or of death from CRC with current surveillance strategies in persons with IBD. Furthermore, observations from large retrospective studies are also conflicting.[12,13] A Cochrane analysis of 3 studies in persons with UC did not find a significant mortality benefit for current surveillance strategies.[14] Considering that IBD afflicts many persons at a young age, is rising in prevalence in Canada and globally,[15] and requires intensive lifelong surveillance, the amount of endoscopy resources directed toward IBD surveillance is potentially enormous. Increasing demands on colonoscopy resources from expansion of population-based CRC screening programs and an aging population are likely to challenge the ability to continue to provide intensive surveillance to all persons with IBD. Optimizing delivery of limited colonoscopy resources will thus be essential to maintain effective CRC prevention programs in this population.

Current standards for neoplasia surveillance in IBD have been recently updated.[6,7,10] Shah and Itzkowitz authored a comprehensive review that includes epidemiology, pathogenesis, and management of colorectal neoplasia, along with a chart that compares surveillance recommendations put forward by multiple societies.[16] The present review will highlight new evidence influencing neoplasia surveillance and provide practical approaches for surveillance and management of neoplastic lesions in the IBD population.

Recent Data Influencing Neoplasia Surveillance Strategies

1. *Value of Negative Colonoscopy*: In a multi-centre study conducted across centres in North America and Europe that included 775 persons with long-standing IBD colitis without advanced neoplasia risk factors, Ten Hove et al. demonstrated that having 2 consecutive negative colonoscopies predicted a markedly reduced risk of developing high-grade neoplasia or CRC over a median of 6.1 years of follow-up.[17] A negative colonoscopy was defined as a technically adequate procedure with no post-inflammatory polyps, strictures, active disease, or neoplasia. This observation has led to the American Gastroenterological Association advocating that persons with consecutive negative colonoscopies undergo a 5-year surveillance colonoscopy,[6] in line with recommendations from multiple medical societies for persons without active endoscopic or histologic inflammation and/or who have limited historical colitis extent.[6,7]

2. *Importance of Cumulative Inflammatory Burden*: Choi and colleagues from St. Mark's Hospital in the U.K. conducted a retrospective single-centre study that included 987 persons with extensive UC between 2003 and 2012 who underwent surveillance colonoscopy every 1–2 years from 8–10 years after the onset of disease symptoms, which included 7516 colonoscopies and 13 884 patient-years of follow-up, with segmental random biopsies and targeted biopsies from suspicious areas.[18] They found that a cumulative inflammatory burden score, based on an average histologic inflammation severity score that included multiple surveillance episodes over several years, was significantly associated with future colorectal neoplasia development (hazard ratio [HR] 2.1 per 10-unit increase in cumulative inflammatory burden, 95% confidence interval [CI] 1.4–3.0).[18] Age at colonoscopy, primary sclerosing cholangitis, colonic stricture, and tubular, featureless, or shortened colon were also predictors of future colorectal neoplasia risk, whereas inflammation severity based on the most recent colonoscopy alone was not. These findings were further validated by Yvellez and colleagues at the University of Chicago.[19] While incorporating these findings accurately into clinical practice requires systematic endoscopic and histologic surveillance, clinicians could incorporate these findings into their decision making regarding timing of surveillance colonoscopy by estimating the historical inflammatory burden in their patient population over the preceding 5–10 years rather than focusing on findings from the most recent colonoscopy.

3. *Personalized Risk Model of Neoplasia Progression* In a multi-centre retrospective cohort of 246 persons with UC, Curtius and colleagues evaluated 17 clinicopathological variables for association with time-to-progression of low-grade dysplasia (LGD) to advanced neoplasia, defined as high grade neoplasia or CRC, among participants with UC who had LGD that was identified during index colonoscopy. They derived a model comprising 4 statistically significant variables: LGD >1 cm (HR 2.7; 95% CI 1.2–5.9), unresectable or incomplete endoscopic resection (HR 3.4; 95% CI 1.6–7.4), moderate/severe histological inflammation within 5 years of LGD diagnosis (HR 3.1; 95% CI 1.5–6.7) and multifocality (HR 2.9; 95% CI 1.3–6.2).[20] They went on to validate this model in a retrospective cohort from 3 centres comprising 198 persons with UC and demonstrated excellent discriminatory ability (area under the receiver operating characteristic curve=0.89) and calibration (Observed/Expected of 1.01 [95% CI 0.64-1.52]), and minimal prediction error (Brier score=0.068), for progression to advanced neoplasia over 3 years from the date of LGD diagnosis. While longer term follow-up data and validation in other jurisdictions is required, this group has developed a web-based tool to compute

personalized risk prediction for advanced neoplasia based on their model for use in clinical practice termed UC-CaRE (www.uc-care.uk).

4. *Virtual Chromoendoscopy as a Surveillance Tool*: Pancolonic DCE has shown a benefit over both standard definition and high definition white light endoscopy for the detection of colorectal neoplastic lesions in persons with IBD,[21] and has been recommended as the preferred modality for colorectal neoplasia surveillance in this setting by multiple societies.[5-10] Conversely, VCE technologies, including Olympus' narrow-band imaging and Pentax' *i*scan, had failed to show similar benefits in comparison to white light endoscopy for neoplasia detection.[22] However, several recent randomized controlled trials have shown that pancolonic narrow band imaging performed similarly to DCE for neoplasia detection in persons with IBD.[22-24] Based on these data, several societies now support VCE as an alternate strategy to DCE for colonoscopy surveillance in persons with IBD,[6,11] especially considering the limitations for adoption of DCE in many centres, including inadequate endoscopist training, cost of supplies, and added procedural time. VCE technologies are now routinely available with easy-to-use "flick of a button" formats that are offered in the latest generation endoscopes and can be readily applied during colonoscopy without additional resources or procedure time. Improved brightness and sophistication of VCE technologies have made them more suitable for routine use. Importantly, both DCE and VCE require meticulous bowel preparation for optimal visibility and neither modality is a substitute for careful inspection for visible abnormalities. Furthermore, DCE remains the preferred strategy to unmask suspicious lesions that are poorly delineated during white light endoscopy.[6]

5. *Serrated Epithelial Change:* While tubular, tubulo-villous, and serrated adenomas are well recognized pathological entities in persons with and without IBD, serrated epithelial change (SEC) is a less commonly recognized histologic finding that is most often encountered in nontargeted biopsies of persons with long-standing colitis in their fifth to sixth decade of life.[25-27] SEC is distinct from other serrated colorectal lesions in persons with IBD, including characteristic histologic findings of disorganized crypt architecture, irregular serrations, and goblet cell-rich epithelium.[28] Several studies have reported a higher incidence of colorectal neoplasia among persons identified as having SEC.[27,29] Although the clinical implications, and appropriate diagnosis, and management of SEC are still being defined, a reasonable approach for the clinician would be to endoscopically resect visible circumscribed SEC, and to consider more frequent endoscopic surveillance with targeted and non-targeted sampling in those with widespread SEC.

Practical Approach to Neoplasia Detection, Surveillance, and Management

A putative framework for IBD neoplasia surveillance and management is outlined in **Figure 1**.

1. *Optimized Neoplasia Detection*: Routine surveillance should ideally be conducted with high-definition white light colonoscopy in combination with pancolonic DCE or newer generation VCE. Where resources and/or expertise for chromoendoscopy are not available, or when inflammation or suboptimal bowel preparation limit application of DCE or VCE, a suitable alternate strategy is high-definition colonoscopy in combination with widespread non-targeted biopsies (30-40) throughout the colorectum. Extensive non-targeted biopsies of non-suspicious mucosa should always be obtained in persons with major risk features, such as primary sclerosing cholangitis, mild chronic inflammation, or diffuse post-inflammatory changes (i.e., extensive post-inflammatory polyposis, extensive scarring or foreshortening, or diffuse SEC). Localized non-targeted biopsies should be routinely obtained from areas previously harbouring invisible or high-risk visible neoplasia. In the absence of widespread non-targeted biopsies, 1–2 non-targeted biopsies should be obtained per colonic segment to assess for microscopic inflammation, as this may influence treatment and future neoplasia surveillance. If adequate neoplasia surveillance is not possible because of the presence of significant inflammation, repeat surveillance should be performed following a period of optimized medical therapy.

2. *Surveillance Intervals*: Colonoscopy surveillance frequency should generally be between 1 and 5 years, guided by the risk factors stated previously (**Table 1**). However, as proposed by the American College of Gastroenterology, [10] a rational approach to surveillance frequency should be based on a combination of risk factors and findings from previous colonoscopy. It is the opinion of the author that surveillance frequency should also consider risk factors for CRC that are established in the general population as well as IBD-specific factors recognized more recently to predict neoplasia risk, including consecutive negative colonoscopies, cumulative inflammatory burden, and SEC.

3. *Neoplasia Management*: Persons with pathologically-confirmed neoplastic lesions that are not completely resectable owing to their location or morphology, or because they harbour features of submucosal fibrosis or invasion should be referred for surgery. Persons with high-risk neoplastic lesions that are completely resected and do not harbour features of invasive cancer, but that are either large (i.e., >2 cm), harbour high-grade neoplasia, have highly complex morphology (i.e., laterally spreading tumours with indistinct borders), or are locally recurrent, may be appropriate for either intensified endoscopic surveillance (i.e., every 3–6 months until 2 consecutive

≤ 1 year	≤ 2-3 years	≤ 4-5 years
Macroscopic and/or microscopic moderate to severe colorectal inflammation or extensive mild inflammation (optimize medical therapy) Poor bowel preparation Primary sclerosing cholangitis First degree relative diagnosed with CRC before age 50 or multiple first-degree relatives diagnosed with CRC Extensive/severe post-inflammatory polyposis, scarring or serrated epithelial change History of invisible neoplasia or higher-risk visible neoplasia (high-grade, multifocal, complex morphology, recurrent) within previous 5 years	Macroscopic and/or microscopic limited mild inflammation (optimize medical therapy) First degree relative diagnosed with CRC after age 50 or multiple second-degree relatives diagnosed with CRC Limited/moderate post-inflammatory polyposis, scarring or serrated epithelial change History of invisible neoplasia or higher-risk visible neoplasia (high-grade, multifocal, complex morphology, recurrent) > 5 years ago Low-risk visible neoplasia (single tubular or serrated adenoma, fully resected) within previous 5 years No features meeting criteria for earlier surveillance	Absence of inflammation (endoscopic and histologic) and neoplasia in current examination AND either of: Similar findings on prior colonoscopy Limited historical colitis extent (< 1/3 of colorectum) AND No features meeting criteria for earlier surveillance

Table 1. *Recommended timing of the next surveillance exam where no neoplasia are found at the present colonoscopy*; Adapted from Murthy et al, 2021[6]*
**Exact timing should also consider other factors, such as age, sex, body mass index, co-morbidities, smoking history, and cumulative inflammatory burden over the preceding 5 to 10 years*
Abbreviations: CRC, colorectal cancer

negative colonoscopies) or surgery. In such situations, clinicians should have a risk-benefit discussion with the patient that considers their ability to comply with IBD treatment and endoscopic surveillance as well as factors that may impact surgical risk, such as age, body mass, and comorbid conditions. Persons with lower-risk resectable visible neoplastic lesions are appropriate for continued endoscopic surveillance, with the surveillance intervals dictated by factors such as neoplasia size, number, grade, and resection completeness, wherein shorter intervals (i.e., 3–6 months) are suggested for high-grade or incompletely resected lesions. Where uncertainty exists, referral to an expert centre for a second opinion is appropriate. Additionally, clinicians may consider using the UC-CaRE model to guide timing of surveillance colonoscopy in persons with low-grade neoplastic findings.

Persons with invisible or poorly delineated neoplastic lesions identified during white light endoscopy should be referred for DCE, conducted by an experienced endoscopist, to unmask any potentially resectable lesions. During DCE, non-targeted biopsies of the areas of abnormality identified during white light endoscopy should be performed, in addition to targeted sampling and/or resection. If a fully resectable lesion is identified and removed, or, if no neoplastic lesions are identified during DCE, continued intensified endoscopic surveillance every 3–12 months, guided by other risk factors, until 2 consecutive high-quality exams in which no neoplastic lesions are detected is appropriate. Conversely, the persistence of unresectable high-grade or multifocal neoplasia during DCE should prompt surgery. Unifocal invisible LGD remains an area of uncertainty, wherein the risks and benefits of intensified surveillance versus surgery should be personalized following a discussion with the patient.

Limitations and Future Directions

There are a number of shortcomings to the current approach to neoplasia surveillance in persons with IBD that will need to be addressed in the coming years, including: (i) absence of personalized risk stratification models to guide timing of screening and surveillance that consider the collective predictive value of multiple risk factors and protective factors toward CRC risk; (ii) failure

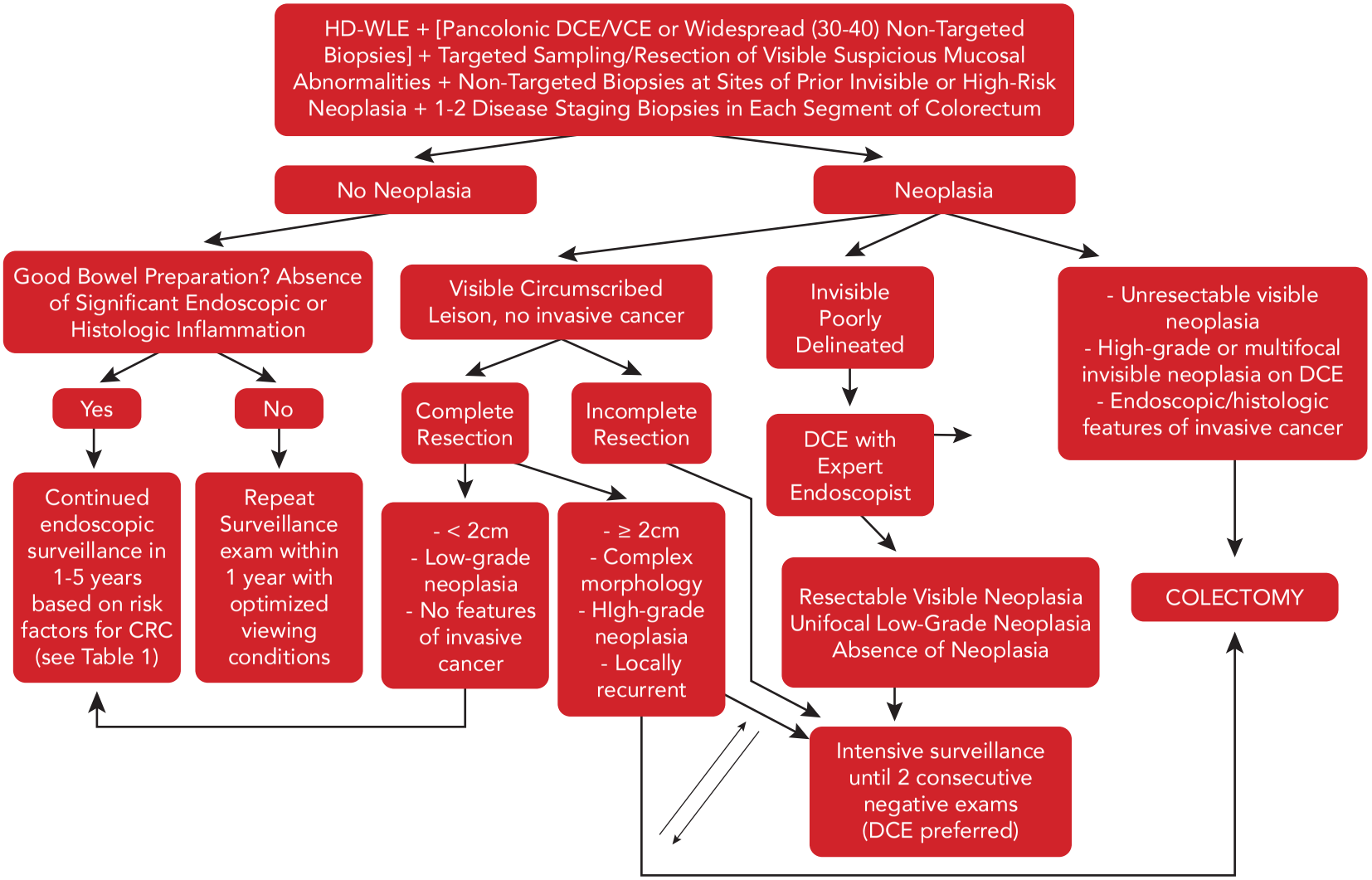

Figure 1. *Putative Framework for Colorectal Neoplasia Detection and Management in Persons with IBD Undergoing Surveillance Colonoscopy; courtesy of Sanjay Murthy, MD, MSc (Epid), FRCPC*

CRC, colorectal cancer; HD-WLE, high-definition white light endoscopy; DCE, Dye-spray chromoendoscopy; VCE, virtual chromoendoscopy

to consider factors such as patient age, sex, body mass index, comorbidities, immunosuppression, smoking history, and prior colonoscopy exposure in current surveillance algorithms; (iii) limited ability to accurately assess the cumulative lifetime contributions of inflammatory burden and neoplastic findings toward CRC risk; (iv) failure to adequately address the importance of traditional neoplastic lesions, such as adenomas and serrated lesions, particularly those outside of the colitis field, toward overall CRC risk and screening/surveillance requirements; (v) absence of a standardized definition of "advanced neoplasia" that considers lesion size, number, morphology, histology, and resectability, as well as limited ability to stratify persons at high risk of harbouring advanced neoplasia for intensive surveillance; and (vi) absence of convincing data regarding the utility of adjunctive modalities, including DCE, VCE, and non-targeted biopsies, in the context of the latest generation endoscopes and practice standards.

Ongoing clinical trials

Multiple Canadian studies are currently being conducted to address some of these important limitations. The IBD-Dysplasia trial is a multi-centre non-inferiority randomized controlled trial designed to assess the utility of widespread non-targeted biopsies as an adjunct to high-definition white light endoscopy for colorectal neoplasia detection in persons with colorectal IBD. This trial started in 2020 and, with more than 40% of participants already recruited, aims to be completed by 2025. Predict IBD Neoplasia is a multi-centre study that aims to develop a multivariable colorectal neoplasia prediction model to guide timing of surveillance colonoscopy in persons with colorectal IBD. This study began in 2022 and aims to be completed by 2027.

Summary

Despite data suggesting a declining risk of CRC and the lack of prospective studies demonstrating a reduction in the incidence of CRC or of death from CRC with current surveillance strategies in persons with IBD, surveillance continues to play an important clinical role for endoscopists who care for this population. Numerous factors may influence colorectal neoplasia risk, with newly recognized factors including cumulative inflammatory burden, sequential normal colonoscopies and SEC. Surveillance frequency and neoplasia detection modalities should be personalized, incorporating the collective contribution of all risk factors and protective factors. A framework for IBD neoplasia surveillance and management is presented here, accepting that many limitations to optimal screening and surveillance strategies in persons with IBD still exist. Ongoing clinical trials are underway in Canada, the results of which hope to address some of these shortcomings.

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Financial Disclosures:
None declared

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