HHS Public Access

Author manuscript

Gastrointest Endosc Clin N Am. Author manuscript; available in PMC 2020 July 11.

Published in final edited form as:

Gastrointest Endosc Clin N Am. 2019 July ; 29(3): 531–548. doi:10.1016/j.giec.2019.02.008.

Management of IBD-Associated Dysplasia in the Modern Era

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Introduction

Colorectal dysplasia and cancer are among the most worrisome complications of inflammatory bowel disease (IBD) that affects the colon.[1–4] While the incidence of colorectal neoplasia (CRN) in the IBD population appears to be decreasing[5,6], there is still an estimated 2-fold higher risk of colorectal cancer (CRC) compared to non-IBD populations in both referral-based and population-based studies.[6] Higher rates depend on disease-related factors, including cumulative inflammatory burden and extent of disease, as well as patient-level risk factors such as concomitant primary sclerosing cholangitis (PSC) and family history of CRC.[6–11] A recent meta-analysis of population-based and referral center studies reported a 2.6% (95% CI: 0.8–4.7) and 6.6% (95% CI: 1.3–13.8) cumulative risk of CRC at 10–20 years and over 20 years of IBD duration, respectively, with as high as 21% cumulative risk of CRC among patients with extensive disease and over 20 years disease duration.[6]

In IBD, CRC develops from a progression that begins with inflammation followed, in some, by development of varying degrees of dysplasia before final malignant transformation to cancer. Despite considerable progress in our understanding of IBD pathogenesis and management, there is still no definitive way to prevent or predict who will develop neoplastic complications. While extensive efforts have been invested in identifying noninvasive biomarkers to risk stratify patients and better predict who will most benefit from tight surveillance and more aggressive management, no molecular or genetic biomarkers have been identified that are reliably sufficient for clinical practice. Instead, risk stratification still hinges on clinical factors, such as PSC, prior dysplasia, endoscopic and histologic disease activity, among others. Likewise, no chemopreventive agents have proven effective. Thus, CRC prevention relies on risk reduction strategies that include enrollment in a CRN colonoscopic surveillance program, smoking cessation, and adherence to medical therapy to achieve deep remission. Adherence to routine surveillance colonoscopy, despite its limitations, cost, inconvenience for patients and minimal but measurable procedural risk, remains the most effective way to diagnosis, prevent, and, in certain circumstances, resect

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colorectal neoplasia, with continued surveillance thereafter.[12,13] The primary goal of dysplasia surveillance is the identification of early neoplasia with implementation of an appropriate treatment strategy if diagnosed. This has been consistently associated with reduced CRC-related mortality.[13–17] Years ago, dysplasia in the setting of IBD colitis was managed surgically with either colectomy or sometimes segmental resection in the case of limited Crohn's colitis. Such an aggressive approach is now less common, presumably due to enhanced endoscopic technology for dysplasia detection, and our ability to successfully manage dysplasia in IBD endoscopically, not to mention improved medical therapies to achieve disease remission.

We will first provide a brief overview of risk factors for CRN in IBD to concretize the approach to risk stratification, and then provide an up-to-date review of the diagnosis and management of dysplasia in IBD, which integrates new and emerging data in the field. This is particularly relevant in an era of increased attention to cost- and resource-containment from the health systems vantage point, coupled with a heightened prioritization of patient quality of life and shared decision-making. We end with a brief discussion of the status of newer therapeutic techniques, namely, endoscopic submucosal dissection (ESD).

The most important takeaway point is that the decision to enter into a dysplasia surveillance program, as opposed to performing colectomy once dysplasia is detected, must be a joint decision between the patient and gastroenterologist that is informed by both patient- and disease-specific factors. A successful surveillance program depends on open communication between both parties with routine office visits, colonoscopies, and most importantly, patient adherence with medical therapy and surveillance exams.

Risk factors for IBD-associated dysplasia and cancer

The endoscopic and histologic characteristics of CRN, when diagnosed, are primary drivers for deciding therapeutic management. That said, it is important to adjunctively consider both patient- and disease-specific factors, particularly when the decision between endoscopic resection versus surgery is not clear-cut. Generally speaking, risk factors for CRN in IBD are well-established and supported by increasingly robust epidemiological literature (Table 1), although some discrepancies, such as male sex as a risk factor, do exist.[8,18,19] Disease-specific risk factors include disease duration, extent, and degree of inflammation, while patient-specific factors include concomitant PSC, prior history of CRN, family history of CRC in a first degree relative, and possibly earlier age of disease onset.[20] Relative and absolute risks of each of these factors vary and most numbers are based on older data prior to the significant increase in use of biologic therapy and enhanced dysplasia detection techniques. Comparison across studies is also challenging because of heterogeneous populations and data sources, study designs and inclusion criteria, and unclear true population-prevalence of some risk factors, such as PSC.[21] Nonetheless, disease extent and duration, as well as concomitant PSC seem to confer the highest and most consistent disease-related risks for developing dysplasia or CRC in IBD. Pancolitis is associated with RR 14.8 (95% CI 11.4–18.9) compared to RR 2.8 (95% CI 1.6–4.4) in left-sided colitis and no increased risk with proctitis. PSC is associated with RR 4.8 (95% CI 3.9–6.4) starting at the time of diagnosis, but might even be higher. In PSC, lesions tend to be right-sided and

risk of progression of low-grade dysplasia (LGD) to high-grade dysplasia (HGD) or CRC is nearly 3-fold higher in patients with IBD colitis and concomitant PSC (8.4 per 100 patient-years) compared to those without PSC (2.0 per 100 patient-years; P=0.01).[22] If there is prior history of LGD, those with IBD and PSC have an even greater risk of subsequent advanced CRN, with our recent multicenter study estimating the rate of advanced CRN following a LGD diagnosis to be 2.8 times higher in patients with versus without PSC.[8] UC disease duration of 10 years is associated with RR 2.4 (95% CI 0.6–6.0), while disease duration of 20 years is associated with RR 2.8 (95% CI 1.91–3.97) for developing colonic neoplasia, although estimates vary.[6,20] Active endoscopic (RR 5.1, 95% CI 2.7–11.1) or histologic (RR 3.0, 95% CI 1.4–6.3) disease also impacts risk of progression to CRN.[8,11] Having a first-degree relative with CRC younger than 50 years old confers a RR 9.2 (95% CI 3.7–23.0) compared to RR 2.5 (95% CI 1.4–4.4) if the first-degree relative is above 50 years old.[20,23] Earlier age of IBD as a risk factor for CRC in IBD is unsettled and there is likely at least some contribution of the non-IBD-related background risk of sporadic CRC after age 40–50 years.[3,24–27]

Structural alterations arising as a consequence of chronic inflammation, such as stricture, pseudopolyps, and shortened tubular colon have long been considered important risk factors for CRC.[20,28–32] The literature regarding strictures in IBD and CRC risk is mixed, and it is likely that the neoplastic implications vary according to IBD type, symptoms, disease duration, and colonic location, with strictures in longstanding UC that are right-sided and symptomatic being the most concerning for harboring neoplasia.[33] Earlier studies suggested that the risk of dysplasia or cancer *associated* with strictures ranged from 0–86%, with up to 40% of strictures themselves harboring cancer [28,29,33,34]; however, these studies were limited by small sample size and lack of detailed clinical and histologic details. A more recent study of 293 patients with colonic strictures (median disease duration at stricture diagnosis, 6–8 years) undergoing surgery for non-neoplastic diagnosis, reported that 3.5% of strictures harbored previously undiagnosed neoplasia within the surgically resected stricture. As comparison, in one center included in this study, intra-stricture neoplasia was the surgical indication in 0.6% of CD colonic strictures and 2.5% of UC colonic strictures.[34] Among colonic strictures without diagnosed neoplasia preoperatively, those with underlying UC/IBD-U (N=45) had LGD in 2%, HGD in 2%, and CRC in 5%, while those with CD (N=245) had LGD in 1%, HGD in 0.4%, and CRC in 0.8%.[34] Interestingly, the only factor associated with neoplasia at the stricture site was *lack* of active disease at the time of surgery (OR 4.9, 1.1–21.3). This and other studies highlight that diagnosing neoplasia on stricture biopsies is imperfect, and there is still a measurable risk of neoplasia within the stricture.[35] The risk of malignant transformation from dysplasia to CRC in strictures is not known, but is generally thought to be low.[35] Risk factors for progression are similarly not well-described, but older age, right sided location, change in stricture length or diameter over time, appearance of stricture later in the disease course, or symptoms (e.g. obstruction, pain) should be considered higher risk and resection seriously considered.[33] In the absence of symptoms or high risk personal or disease related factors, non-neoplastic strictures particularly in patients with CD, likely can be safely managed with surveillance colonoscopy as long as the stricture is passable and the mucosal surface proximally and within the stricture itself can be interrogated endoscopically and histologically.

Pseudopolyps, on the other hand, are probably not the high risk factor that older literature had suggested, based on emerging data stemming from large cohort studies with more rigorous study designs and analyses that specifically control for inflammatory burden.[31] Rather, they should be considered a surrogate marker of more significant cumulative inflammatory burden, which is the driving risk factor. One study reported a low risk of neoplastic transformation of pseudopolyps[31], supporting the current practice of not endoscopically removing pseudopolyps unless there is diagnostic uncertainty or other concerning features (such as abnormal pit pattern by enhanced imaging techniques). So long as the mucosal surface can be adequately visualized for neoplasia surveillance, pseudopolyps alone need not be considered a reason for shortened surveillance intervals, as some societal guidelines suggest.[36] If quality of surveillance is compromised due to impaired visualization from multiple pseudopolyps, colectomy is should be considered.[20] Given the not insignificant risk of metachronous or synchronous neoplasia, the presence of several of the above factors should lower threshold to recommend definitive total proctocolectomy when dysplasia that is otherwise resectable is diagnosed (see below).

Pathophysiology of CRC

The pathophysiology of CRC in IBD is distinct from sporadic CRC (although sporadic CRC can certainly occur in cases of IBD colitis). These differences are reflected in different molecular and phenotypic features. Generally speaking, the development of CRC in IBD colitis is thought to follow the inflammation-dysplasia-carcinoma sequence that is seen in other (luminal and nonluminal) GI cancers, with cancers occurring in areas of active or prior inflammation and influenced by immune and inflammatory pathways.[20] At least in UC (and perhaps segmental Crohn's colitis), chronic inflammation of the colon creates a "field effect", whereby any part of the colon that is currently, or was previously, inflamed, is at risk for neoplastic transformation,[11,28] thus justifying continued surveillance. Alterations in the microenvironment with dysregulated chemokine and cytokine pathways lead to direct DNA damage, immortalization of cells through proliferation, growth and inhibited apoptosis, and also migration potential. Differences in the molecular and genetic features between IBD-associated and sporadic CRC have been described for decades. For example, IBD-associated CRCs less often have APC and KRAS mutations and more often have TP53, IDH1, and MYC mutations compared to sporadic tumors.[37,38] Additionally, while primary carcinogenic pathways appear conserved (e.g. chromosomal instability (CIN) and microsatellite instability (MSI)), the timing and sequence of some pathways might be distinct (e.g. early loss of p53 in IBD-associated CRC).[39,40] To date, molecular and genotypic differences between IBD-associated and sporadic CRC have yet to be successfully leveraged for personalization of therapeutic or surveillance options.

Dysplasia Diagnosis and Surveillance Technique

Currently, there is no molecular biomarker or panel of biomarkers with adequate test characteristics for neoplasia surveillance and diagnosis in IBD, although some stool-based surveillance tests show preliminary promise in discriminating between IBD neoplasia and lack thereof.[41–43] Accordingly, neoplasia diagnosis still relies on a careful colonoscopic exam that meets adequate quality metrics. The interval for surveillance varies according to

the GI society, with some recommending specific intervals based on risk stratification (high-, intermediate-, low-risk according to patient- and disease-related clinical characteristics)[36,44], while others (namely, the United States Societies) offer a relatively nonstratified approach. A more comprehensive discussion of surveillance intervals in the absence of a neoplasia diagnosis is outside of the scope of this review, which is focused on the management of neoplasia once diagnosed.

As noted, a careful colonoscopic surveillance exam that meets adequate quality metrics and adheres to guideline recommendations[36,44–48]remains the gold standard for diagnosing early neoplasia and the only way to decrease CRC-related mortality. Quality metrics for colonoscopic surveillance in IBD mirror CRC screening/surveillance recommendations for the most part, with some nuances.[47] It is recommended that surveillance examinations be performed by a gastroenterologist experienced in IBD management and preferably at an IBD center, when disease is in remission, with adequate bowel preparation. Cecal (or neo-terminal ileum) intubation is imperative, as is sufficient duration of withdrawal time. Active disease should not preclude performing the surveillance exam, but the extent and severity of disease activity should be clearly documented (especially if there are visible lesions) and the pathologist should be informed. Once medically optimized, consideration should be given to performing a repeat short-interval surveillance examination if in fact active inflammation made it difficult to discern neoplastic lesions. Even in quiescent disease, luminal abnormalities such as pseudopolyps and scars may compromise the dysplasia surveillance exam. If this is the case, or if there is an impassable stricture that precludes more proximal interrogations, colectomy should be discussed. Unfortunately, there is marked practice pattern variability and surprisingly low rates of adherence to recommended surveillance techniques.[49–52] Although multifactorial, this might explain, at least in part, why the rate of early/missed CRC following colonoscopy is as high as 15–30% in patients with IBD, 3–6 fold higher than the general non-IBD population.[53,54]

Standard of care for surveillance includes high-definition white light colonoscopy (HD-WLE) with two-four nontargeted random biopsies taken every 10cm from the cecum to the rectum (minimum 32 biopsies), placed in separate jars, along with targeted biopsies as appropriate. For any lesion identified, biopsies should be taken from the surrounding “normal”-appearing mucosa and placed in a separate jar to evaluate for invisible dysplasia or inflammation. Non-targeted and targeted biopsies have been the recommended technique for decades and reflects an era when dysplasia was difficult to identify endoscopically with the unassisted eye, due in large part to lower resolution optics and also a more restricted therapeutic armamentarium in the pre-biologics era when deep mucosal healing was difficult to achieve and distinction between inflammation and dysplasia was challenging.

Standard definition white light endoscopy (SD-WLE) is no longer acceptable for surveillance.[47,55] Over the past two decades, new technologies and image-enhancing techniques have emerged, which, collectively, have greatly improved dysplasia detection. As discussed below, the vast majority of neoplasia is now accepted to be visible neoplasia.[56–58] Indeed, hand-in-hand with, and as a direct result of, these technological advancements, there has a been a paradigm shift in the definitions and classifications of dysplasia, which is now

functionally described as “visible versus invisible” and “resectable versus nonresectable” in its most minimalistic form.

The main image-enhancing technique is dye chromoendoscopy (CE) with indigo carmine or methylene blue, which similarly necessitates adequate mucosal visualization (e.g. adequate bowel preparation, minimal pseudopolyps) and endoscopically quiescent disease. CE is recommended by the Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in IBD Patients: International Consensus (SCENIC) and is also considered standard of care for surveillance in IBD. However, the role of CE in the era of HD-WLE is unsettled and controversial, particularly since the procedural time for CE is often longer and superiority over HD-WLE not established.[59] Current evidence suggests that both HD-WLE and CE techniques are comparable, although CE might detect non-statistically significantly more dysplasia versus HD-WLE.[47,55] A recent meta-analysis[60] of 3 RCTs and 3 observational studies which included 1358 patients with IBD undergoing surveillance (670 CE, 688 HD-WLE) found that more dysplasia was found on CE versus HD-WLE (18.8% vs. 9 %, P=0.08); a similar trend was reported on sensitivity analyses of just the 3 RCTs (242 CE, 151 HD-WLE), (12.4% vs. 10.4%) and also parallels the findings of the SCENIC consensus.[47] There remain several unanswered questions regarding the optimal positioning of CE for surveillance from a practical and cost/resource utilization vantage point, including whether or not nontargeted biopsies are still beneficial, particularly given the additional cost implications. Despite high-definition colonoscopy, chromoendoscopy and other enhanced detection modalities, 10% of dysplasia is still diagnosed on random biopsy and may relate to the less-experienced eye or suboptimal surveillance milieu. Data support random biopsies in CE for those at highest risk, including patients with PSC, personal history of neoplasia, or tubular appearing colon (sign of cumulative inflammatory burden).[56] Updated surveillance guidelines should take into consideration CE vs HD-WLE data, but further investigations are needed to identify which subgroups might benefit most from CE vs HD-WLE.

So-called ‘virtual chromoendoscopy’ (VCE) might bypass some of the shortcomings of CE, specifically those related to procedural time and cost. VCE is an adjunct to HD-WLE and provides instant on-demand mucosal contrast enhancement without needing to spray dye as in CE. Some options include Fuji Intelligent Chomo Endoscopy (FICE) and iSCAN (Pentax). Narrow band imaging has also been evaluated, but this does not increase the yield of dysplasia detection and is thus not currently recommended.[35,47,61,62] VCE is a rapidly evolving and exciting area; however, data are still emerging and its role in CRC surveillance in IBD is not yet established. Furthermore, these technologies are not universally available in the United States. We certainly look forward to more data and head-to-head trails, especially since several of these technologies (and others in the pipeline) have the resolution and magnification to optically diagnose dysplasia without the need for biopsies.

Definitions of Dysplasia and Categorization

The appropriate management of IBD-associated dysplasia is predicated on consistent definitions. As alluded to, the nomenclature and terminology used to describe dysplasia has transformed in parallel with improved endoscopic optics and chromoendoscopy. Terms such as dysplasia-associated lesion or mass (DALM) and adenoma-associated lesion or mass

(ALM), both of which are now obsolete, flat versus raised dysplasia, among others, are a source of confusion given their inconsistent definitions between the IBD and general endoscopy literature, and also within the IBD literature alone. For example, in the IBD literature, a “flat” lesion was historically used to describe any lesion not seen grossly, while in the general endoscopy literature a “flat” lesion refers to a slightly raised lesion (less than 2.5mm in height).[63]

To address this confusion and move towards standardization (and simplification) of nomenclature, the SCENIC consensus statement recommended broad categorization of dysplasia as “visible” (dysplastic lesion seen on endoscopy) versus “invisible” (dysplasia diagnosed histologically from random biopsies without an associated discrete lesion). While the majority of dysplasia is visible dysplasia in the modern era of HD-WLE and CE, an estimated 10% of dysplasia is invisible and is reflected in the iterative recommendation that segmental random biopsies still be performed even if chromoendoscopy is used, and both targeted biopsies and biopsies from the mucosa surrounding a lesion be taken. It is likely that these recommendations may change as more contemporary data accumulate regarding the actual yield of biopsies from mucosa that appears grossly normal on HD-WLE. For example, a recent single center study reported that among 302 polypoid lesions biopsied or resected from 131 patients with IBD in whom lesion-adjacent biopsies were obtained, the yield for invisible dysplasia was 0%.[64]

The newer nomenclature for visible dysplasia proposed by the SCENIC group is based on the Paris classification [63], which has both therapeutic and prognostic implications. At a minimum, descriptors of lesions should include size, morphology (polypoid versus nonpolypoid), border (distinct versus indistinct), and features that might be concerning for submucosal invasion and malignancy (e.g. depression, ulceration, nonlifting of lesion with submucosal injection)..[47] Chromoendoscopy is an adjunct to HD-WLE that might better delineate lesion border. Polypoid lesions (pedunculated, sessile) are defined as those protruding at least 2.5mm into the lumen while nonpolypoid lesions (slightly elevated, flat, depressed) may range from superficially elevated (less than 2.5mm) lesions to depressed lesions.[63] Gross and histologic characteristics of the surrounding mucosa should be noted. Appropriate reporting of these descriptors is critical for deciding whether lesions are amenable to endoscopic resection and, when endoscopic resection is performed, the likelihood that resection will be complete with low to negligible risk of recurrence at the site.

Management of Visible Dysplasia: Endoscopic versus Surgical Resection

The management of visible dysplasia is multimodal and encompasses therapeutic resection (endoscopic versus surgical), ongoing medical management to achieve/maintain disease quiescence, risk factor modification where appropriate (e.g. smoking cessation) and continued close interval colonoscopic surveillance (in the absence of total proctocolectomy). Criteria for what constitutes endoscopically resectable lesions are not clearly delineated in published guidelines and depend largely on the comfort level and expertise of the individual endoscopist. Endoscopic resection includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), although the latter is, practically-speaking, not yet

a viable option in the United States (see below). The goal of endoscopic resection is en bloc resection, with negative lateral and vertical margins. If this cannot be reliably achieved (or is not confirmed following endoscopic resection), then surgery is indicated. Compared to non-IBD patients, en bloc resection can be uniquely challenging because recurrent cycles of inflammation and healing increase the likelihood of submucosal fibrosis, and, consequently, higher risk of incomplete resection and complications (e.g. perforation, bleeding, recurrence). Because ESD dissects through the submucosal plane, it is tempting as an option that allows full en bloc resection of dysplastic lesions in carefully selected patients with IBD. CD might present additional challenges for endoscopic resection because of the potential for transmural involvement and more frequent fibrosis.[65]

Patient selection: Patient Preference and Lesion Characteristics

First and foremost, the decision of endoscopic resection versus surgical resection (colectomy or, potentially, segmental resection in Crohn's colitis) must follow a comprehensive and realistic discussion with the patient that specifically includes discussion of: 1. risks of endoscopic resection; 2. risk of incomplete resection and need for surgery anyway; 3. risk of missed synchronous lesion; 4. ongoing need for continued aggressive colonoscopic surveillance (+/− future therapeutic intervention) due to a high risk of metachronous lesions. This latter point is an important nuance for IBD dysplasia compared to sporadic polyps/neoplasia in patients without IBD, and needs to be highlighted for its potential cost and patient convenience/quality of life implications. If the patient does not accept these risks or is unable to commit to continued surveillance, then she or he should be referred for surgery. Patients with PSC, history of CRC, severe pseudopolyposis or stricture limiting adequate quality surveillance, multifocal dysplasia (some exceptions), or first-degree relative with early CRC should be referred for surgery. Although early CRC without submucosal invasion (T1) arising in patients without IBD are increasingly being removed by ESD in experienced centers, particularly in the East, the data for patients with IBD are limited[66–68] and is not recommended in the United States.

Generally speaking, the assessment of endoscopic resectability of visible lesions should follow the same considerations in patients with IBD patients as in patients without IBD, with some additional key considerations. Well-demarcated, non-multifocal lesions without features suggestive of invasion, should be completely resected by an endoscopist with appropriate expertise regardless of grade of dysplasia. The absence of dysplasia in the surrounding mucosa must be ruled out prior to endoscopic resection. If dysplasia is identified in the surrounding mucosa, the lesion is considered unresectable and the patient should be referred for surgery. Ideally, the surrounding mucosa should be endoscopically/histologically quiescent, although the impact of active inflammation on outcomes of endoscopic resection in this population is not quantified. The activity of the surrounding mucosa might also impact the assessment for submucosal invasion, as areas of active inflammation might have a positive non-lifting sign and overlying ulceration. In patients without IBD, lesions with depression, ulcerations, irregular contours, deformity, mass-like appearance, or non-lifting sign raise concern for the presence of invasive malignancy. But, these features are more difficult to assess in patients with IBD particularly in the face of active disease, and thus do not necessarily carry the same tenacious association with

malignant transformation. Whether the lesion was found in a background of quiescent disease, active colitis, or other mucosal abnormalities such pseudopolyposis should be noted in the procedure report.

For well-demarcated lesions distinction should be made between polypoid and nonpolypoid lesions, not only because methods for endoscopic resection and post-resection surveillance vary, but because the risk of progression to cancer is higher in non-polypoid lesions.[69,70] Whether the more benign course of polypoid lesions reflects the underlying biology of the lesions, or that polypoid lesions are generally more amenable to en bloc removal with less risk of piecemeal and incomplete resection, remains to be clarified, but it is likely a combination of these factors. While a larger proportion of nonpolypoid lesions are being detected as a result of improved technology, this may also represent a true shift in natural history of dysplasia in IBD.

Polypoid, well-circumscribed lesions, in principle, should be amenable to en-bloc resection by standard snare polypectomy or mucosectomy. The mucosa surrounding the polyp should be biopsied and a tattoo should be placed 1–2 folds distal to the resection site. While there is no set size threshold for endoscopic resection of polypoid lesions, 1–2cm is often cited for purposes of guiding subsequent surveillance recommendations and reflects the threshold above which piecemeal resection is often needed. If both the resection margins from the lesion and the surrounding mucosa are negative and no additional dysplasia is detected in the colon, then continued endoscopic surveillance according to a modified schedule may be adequate. For lesions removed piecemeal or lesions >1cm, there is a significantly higher risk of retained neoplastic tissue and recurrence. Thus, SCENIC recommendations are that surveillance colonoscopy should be performed within 3–6 months (earlier threshold if endoscopist-specific concerns) with biopsies at the site of the resection and, if negative, annual surveillance with adherence to quality metrics continued thereafter. For patients with en bloc resection of polypoid lesions <1cm and confirmed negative margins, surveillance colonoscopy is recommended at 12 months.[47] If incomplete resection or recurrence is confirmed histologically, then surgical referral is indicated. These surveillance intervals are based on pooled analyses by the SCENIC international group, who reported a 6% (2–13%) incidence of CRC on follow up between 36–82 months. A meta-analysis by Wander et al. underscored the importance of ongoing surveillance, as the risk of subsequent dysplasia following endoscopic resection of polypoid dysplasia is high at 65 cases per 1000 patient years; however, the clinical implications are unclear as the risk of CRC was low at 5.3 per 1000 patient years.[69] Histologic grade of the resected neoplastic lesion and also focality (unifocal versus multifocal) impacts prognosis. Recent studies reporting longer-term follow up completely resected unifocal LGD are reassuring, as low rates of progression following complete resection were reported even up to three years.[22,71–73] In a study of 18 patients with resected multifocal LGD, 50% were subsequently diagnosed with HGD or CRC at median 32 months.[74] The management following complete resection of a visible lesion confirmed to be HGD is controversial, and the decision of continuing shorter interval surveillance versus colectomy should be individualized.[47,48,75] The safety of lengthening the interval after consecutive colonoscopies with quiescent disease confirmed histologically where no dysplasia is identified is not known, but emerging data suggest that it might be safe to lengthen the interval in the absence of other high risk features like PSC and family history

of CRC, but more data are certainly needed before any recommendation can be made for this high-risk group.[76]

Non-polypoid lesions are more challenging and multiple patient-, provider-, and lesion-specific factors must be considered when determining optimal course of management. Patient-specific factors are those already discussed which relate to the probability of synchronous and/or metachronous neoplasia, patient preference, comorbidities, or presence of an additional surgical indication (e.g. medically refractory disease, impassable stricture, etc). Provider factors relate to level of experience and comfort, and nonpolypoid lesions should be managed by advanced endoscopists with appropriate expertise. For lesions located within strictures, poorly circumscribed, with irregular surface, indistinct borders, or endoscopically inaccessible, endoscopic resection should be deferred in favor of referring for surgery. As compared with polypoid lesions, the natural history of non-polypoid lesions following endoscopic resection is not as well-defined and a lower threshold for surgical referral is warranted particularly given the higher risk of incomplete resection, the higher rate of recurrence and over 8-fold higher rate of progression of LGD to HGD/CRC compared to polypoid lesions.[77] As with all endoscopically resected lesions, a tattoo should be placed 1–2 folds distally and the resection site/surrounding mucosa biopsied adequately on subsequent surveillance examinations. For nonpolypoid lesions with confirmed complete endoscopic removal, surveillance recommendations are based on expert opinion and mirror those for polypoid lesions >1cm or removed piecemeal.

ESD: Is the West there yet?

The primary goal of endoscopic resection for dysplasia in patients with IBD is to minimize the risk of recurrence or progression to cancer and avoid the need for surgery. If this cannot be reliably achieved, then surgical referral is recommended. Borrowing from the non-IBD literature, in appropriately selected patients, appropriately selected lesions, and appropriate provider expertise, endoscopic mucosal resection (EMR) is safe and effective if en bloc resection can be achieved.[78,79] However, incomplete resection and recurrence are major considerations if en bloc resection cannot be achieved with EMR, as this is necessary to evaluate for curative resection. En bloc resection is oftentimes difficult if not impossible for larger lesions (typically ≥ 20mm) and also for lesions in areas of chronic intestinal inflammation where there might be submucosal fibrosis in the absence of invasive dysplasia. Piecemeal resection is associated with high local recurrence rates (10–25%) and potentially inaccurate histopathological assessment.[80] If high-grade dysplasia and most certainly carcinoma are identified, surgical resection is recommended. At least in patients without IBD, ESD of colonic neoplasia is a major advance and allows for higher rates of en bloc resection for larger lesions when performed in experienced hands. ESD involves direct visualization and dissection through the submucosal plane using a special electrocautery knife. ESD was born initially in East Asia in the early-mid 1990s as a noninvasive technique to remove early gastric neoplasia. Screening and surveillance programs in some East Asian countries (e.g. Japan, Korea) enabled detection of gastric cancer in the early stage prior to submucosal invasion where resection via ESD could be curative. With continued refinement of ESD techniques and instruments since its introduction, ESD is now commonly performed for non-IBD associated colorectal neoplasia in East Asia. Colonic ESD is more technically

difficult than gastric ESD due to the significantly thinner lining of the colonic mucosa and colonoscope maneuverability, both of which are particularly problematic for right sided lesions. A recent meta-analysis of 97 studies (71 from Asia) with 17,483 patients—none with a mention of IBD—reported an overall 91% en bloc resection rate (82.9% negative vertical and horizontal margins, "R0"), which was significantly lower in non-Asian (71.3% R0, 81.2% en bloc) versus Asian (85.6% R0; 93% en bloc) countries for the standard ESD technique;[81] the frequency of ESD-related adverse events was nearly 4-fold higher in non-Asian vs Asian countries (3.1% vs. 0.8%). Hybrid ESD, which combines a snaring technique, was associated with poorer outcomes, including higher complication rate.[81] Only 2 of the 26 studies from Western countries originated from the United States, and these were limited to abstracts[82,83], as no full text studies from the United States were identified.

However, as discussed above, endoscopic resection in patients with IBD presents several unique challenges, including the downstream effect of relapsing and remitting inflammation on mucosal and submucosal remodeling due to fibrosis and scarring (and not necessarily malignant invasion). ESD is particularly attractive in patients with IBD for this reason. Unfortunately, the data regarding safety and long-term outcomes of ESD for colonic neoplasia in patients with IBD are limited to three case-series with 65 patients total (Japan, United Kingdom, Italy).[66–68] All patients among these studies were in clinical remission and had a single lesion that was well-demarcated with favorable histology. Even though all lesions were removed by an identified expert in ESD, en bloc resection ranged from 60–100%, with noncurative resection in 21–30%. With respect to complications, bleeding ranged from 0%[67] to 10%[66], while perforation rate ranged from 0%[66,68] to 4%[67]. The first United States experience was only recently published as a brief letter, and reported on a total of 7 patients with IBD (71% UC, 29% CD) who had colonic ESD performed between 2014–2017 at a single center by a single endoscopist.[84] En bloc resection was achieved in 86%, as one patient needed colectomy due to inadequate lifting of a polyp. No patients had clinically significant perforation or bleeding that required hospitalization. The final resected pathology specimen confirmed HGD in 43% (3/7), LGD in 43% (3/7), and no dysplasia in 14.2% (1/7, sessile serrated adenoma).[84] The authors reported that on surveillance colonoscopy at 6-month follow up, there was no dysplasia.

ESD is certainly a very attractive option for a select group of patients, but the need for advanced endoscopists with adequate training and adequate case volume (limited further by few cases of early gastric cancer eligible for ESD) is a major barrier to the safe introduction of ESD in the armamentarium of therapeutic options for IBD-associated colonic neoplasia. Also limiting its primetime appearance are reimbursement considerations, since there is no associated CPT code for ESD, and overall cost-effectiveness when considering the likely longer procedure time and the higher rate of complications and recurrence that might necessitate surgery regardless. Indeed, it would be premature to extrapolate the promising safety profile reported in the Eastern experience to the West and, more specifically, the United States. We certainly welcome and support the enthusiasm for developing training programs in ESD for GI neoplasia in the West and look forward to additional safety and outcomes data to help guide positioning of ESD for the management of colorectal neoplasia in IBD.

Management of Endoscopically “Invisible” Dysplasia

The vast majority of dysplasia can be seen on endoscopy in the current era of HD-WLE and/or chromoendoscopy. As much as one-third of dysplasia initially considered to be “invisible” is actually visible and may be amenable to endoscopic resection.[85] If dysplasia is identified by random biopsies (presumably invisible dysplasia), the pathologic diagnosis of dysplasia should first be confirmed by an expert pathologist with particular expertise in IBD. If confirmed, a repeat colonoscopy with enhanced detection capabilities (e.g. high definition, chromoendoscopy) should be performed by a gastroenterologist with adequate experience in IBD dysplasia surveillance exams. If no lesions are identified despite careful examination and adequate mucosal visualization, random biopsies should be again taken every 10cm and placed in separate jars (minimum 32 biopsies total). If invisible dysplasia is again confirmed, subsequent management should also take into consideration the individual patient and disease-related risk factors for CRC as described previously. If LGD is detected on random biopsy, the surveillance interval should be shortened to every 3–6 months. The idea of colectomy should be discussed with the patient, as well as documentation of their understanding that although biopsies revealed LGD, they are at significant risk of progressing to HGD and cancer, and may even harbor such pathology currently.[77] If HGD is detected on random biopsy the histological interpretation should be confirmed by an expert GI pathologist. If confirmed, a repeat colonoscopy in expert hands using enhanced imaging techniques should see whether there may have in fact been a visible lesion that could be endoscopically resected. If that is not the case, colectomy should be strongly considered

In UC, the presence of dysplasia is assumed to be a field defect placing the entire colon at risk of harboring neoplasia, thus justifying total colectomy; whether this is true in the segmentally affected Crohn’s colon remains to be clarified. The safest approach would be total proctocolectomy, but this should be thoroughly discussed with the patient and referral to an experienced IBD gastroenterologist and surgeon with review of all pathology by an expert is recommended. It remains to be clarified, though, whether patients with segmental Crohn’s colitis found to have HGD (and/or cancer) in the affected colitis segment have similar outcomes if they undergo segmental resection for localized CRN, as opposed to total colectomy. Current data favor total proctocolectomy in these patients due to the high risk of synchronous dysplasia or even cancer, as well as later development of metachronous neoplasia.[86] A retrospective study of 75 patients with Crohn’s disease and localized colon cancer undergoing segmental resection or subtotal colectomy found that 39% had at least one metachronous cancer despite the majority having annual screening colonoscopy; the mean time to new dysplasia and cancer was 5 and 6.8 years, respectively.[86]

Conclusion

The optimal management of IBD-associated colorectal neoplasia is one that is individualized and considers patient-, disease-, and endoscopy-specific factors, in conjunction with the expertise of the treating gastroenterologists and advanced endoscopists. While investigators continue to work in parallel for ways to definitively identify who will develop neoplastic complications of IBD and for ways to prevent the development of neoplasia from the outset (apart from simply controlling inflammation), we are at least in a dynamic era of expanding

therapeutic endoscopic options for IBD-associated neoplasia when diagnosed. Hand-in-hand is an expanding body of literature on outcomes of non-operative management of IBD-associated neoplasia to guide appropriate determination of patient and lesion candidacy for endoscopic resection and ongoing surveillance, as opposed to surgical management. As a counter, though, with increasing access and availability of new technologies and techniques, we need to take care to balance cost and resource utilization, as well as first and foremost ensure shared decision making and appropriate counseling of risks versus benefits of endoscopic versus surgical management of IBD-associated neoplasia.

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Table 1:

Risk factors for IBD-associated colorectal neoplasia *

Patient-specific Factors	Disease-specific Factors	Endoscopic Features
Primary sclerosing cholangitis	Disease duration	Stricture (UC, longer disease duration, proximal location, symptoms)
History of colorectal neoplasia	Disease extent	Shortened tubular colon
Family history of colorectal cancer in first-degree relative	Cumulative inflammatory burden	(Pseudopolyps)
Smoking	Active inflammation endoscopically or histologically	
(+/−) early age of disease onset		
(+/−) male sex		

* See text for full details