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Review Article

Dysplasia in Inflammatory Bowel Disease-A Journey from the Past to the Present: A Review

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Abstract

Inflammatory bowel disease (IBD) is a relapsing-remitting chronic disorder, consisting of Crohn's disease (CD) and Ulcerative colitis (UC). Colorectal carcinoma (CRC) is the third most common cancer, for which IBD is an independent risk factor. Patients with longstanding IBD are at higher risk for developing CRC. In an effort to minimize mortality from CRC in IBD patients the early detection, recognition and grading of dysplasia is the current standard of care for early detection of CRC. Screening for dysplasia is critical in the detection and prevention of the development of advanced adenoma in long-standing IBD, given the increased risk of colitis-associated cancer. Progress has been made in refining techniques for identifying the presence of visible dysplasia, including chromoendoscopy and the adoption of SCENIC [Surveillance for Colorectal Endoscopic Neoplasia detection and Management in Inflammatory Bowel Disease Patients: International Consensus recommendation] guidelines. There is also controversial evidence to support the use of IBD chemoprevention therapies in the prevention of progression to advanced adenoma; however, maintenance of remission remains paramount. This review will focus on the risk factors, pathogenesis, classification, histological challenges, new endoscopic classification, progression, challenges in detection, management, and prevention of dysplasia in IBD.

Keywords: *Inflammatory Bowel Disease; Dysplasia; Crohn's Disease; Ulcerative Colitis*

Introduction

Inflammatory Bowel Disease (IBD) is a chronic, progressive, remitting-relapsing disorder of the gastrointestinal tract, comprising clinically of Crohn's disease (CD) and Ulcerative colitis (UC). It is thought to arise from a dysregulated mucosal immune response to commensal gut microflora in genetically susceptible individuals. CD and UC though clinically separate entities have a similar goal of therapy, of maintaining a steroid-free deep remission. With ongoing advancements in the natural history of IBD and its disease course, new therapeutic modalities continue to be available. Additionally, treatment focus has shifted to an individualized personalized management approach, including prevention of dysplasia and colitis-associated cancer (CAC). The risk of dysplasia increases with longer disease duration and the presence of advanced adenomas, with chronic inflammation playing a key role in the progression to carcinoma.

Colorectal cancer is currently the third most common cancer, for which IBD, regardless of disease activity status is an independent risk factor. The risk of CAC was initially estimated at being six times higher than the general population, but more recent data reports a rate

of being 2.4 fold higher than the average. This is thought to be due to advances in therapy, use of colectomy in medically refractory cases, and improved surveillance screening [1-12]. Furthermore, there is also a 3-fold higher risk of developing interval cancers, highlighting the importance of surveillance colonoscopy with advanced endoscopic techniques for early detection of flat/advanced adenomas, thereby improving overall prognosis and mortality. Long-term follow-up has shown significant increase in the incidence/*detection* rate of dysplasia when utilizing chromoendoscopy (P = 0.01) [1,2].

Risk factors

Specific risk factors for dysplasia and CRC include co-existing primary sclerosing cholangitis (PSC), duration of IBD, extent of colonic involvement, backwash ileitis, young age of onset, older age of diagnosis, active inflammation endoscopically and histologically, pseudopolyps, stricture formation, and personal/family history of colonic polyps (P = 0.03) [13-28] as summarized in table 1. Disease extent is an independent risk factor. Compared to controls, patients with PSC and UC were significantly more likely to develop dysplasia (P < 0.001) and this risk was cumulative -50% at 25 years of disease duration [20-22]. A study of 3000 patients with UC found a standardized incidence ratio of 1.7 in those with proctitis versus 14.8 with pancolonic involvement. Interval cancers accounted for over 50% of detected lesions [23]. This suggests that dysplastic lesions may be missed during surveillance screening, especially if the lesions are non-polypoid, incompletely resected, or located in the rectum or proximal colon [24]. This highlights the importance of sustained adherence with surveillance screening, especially in the presence of high-risk features [29-32].

Primary sclerosing cholangitis
Extent of colonic involvement by inflammation.
Duration of inflammatory bowel disease.
Younger age of onset of IBD.
Diagnosis of IBD at an older age.
Personal/family history of dysplastic colonic polyps.

Table 1: *Risk factors for the development of dysplasia and colorectal cancer in patients with inflammatory bowel disease.*

Pathogenesis of dysplasia

Sporadic CRC is a multistep process that progresses along the adenoma-carcinoma sequence, with loss of APC tumor suppressor gene as an early event and loss of p53 as a late event. In contrast, p53 mutation with chromosomal instability is an early event and APC gene mutation is identified late. In CAC, initiation and progression of dysplasia also involves multiple stages, but unlike CRC this may not always follow a sequential progression from LGD to HGD to carcinoma. Carcinoma may even occur in patients with no prior evidence of dysplasia. Sporadic CRC usually develops in polypoid adenoma while CAC usually arises from flat dysplasia with indistinct margins. These differences may be due to dysplasia arising in a milieu of inflammation, recurrent injury and repair [33-38]. Colonic mucosa has an inherent high rate of epithelial cell turnover, as well as greater frequency of mitosis and apoptosis specifically in the setting of chronic inflammation. Inflammatory cells and cytokines, directly or indirectly through cellular injury and repair may activate many pathways leading to "field cancerization" and neoplasia.

Longstanding inflammation lead to elevated levels of pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-10, IFN-γ, chemokines, and metabolites of arachidonic acid. IL-6 plays a prominent role in pathogenesis by activating JAK/STAT (Janus kinase/Signal transducer and activator of transcription factor) signaling pathway, a participant in the inflammatory cascade in active IBD. In addition, IL-6 and STAT3 expression is higher in patients with dysplasia/CAC compared to those with inactive IBD or non-IBD controls. Pro-inflammatory cytokines also upregulate COX2 in dysplastic lesions in IBD patients. COX2 upregulates cell proliferation and angiogenesis [39-41]. Inflammation also results in production of reactive oxygen species and oxidative stress-induced DNA damage, leading to activation of pro-

carcinogenic genes and attenuation of tumor-suppressor mechanisms. The role of oxidative stress is enhanced by both reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI). Oxidative stress also damages cellular lipids, proteins, and induces p53 mutations, ultimately leading to recruitment of inflammatory cells and a self-promoting cycle [42]. This provides the necessary environment for sustained DNA damage, aberrant methylation, and chromosomal instability, thereby initiating carcinogenesis. Myers., *et al*. have demonstrated that deposition of Hemoglobin α- chain in colonic mucosa of IBD patients is a mediator of ROS dependent DNA damage [43].

Aberrant methylation of promotor region CpG islands, an epigenetic modification of DNA associated with transcriptional inactivation of tumor suppressor genes has also been identified in non-neoplastic epithelium as an early event in the development of carcinogenesis. There is a progressive increase in methylation of the WNT-signaling pathways genes from normal colonic tissue (4%) to IBD colitis (39%) to IBD associated neoplasia (63.4%) [44]. Other significantly methylated genes in CAC include: APC2, SFRP1, SFRP2, TGFb2, SLIT2, HS3ST2, TMEFF2, p16 and p14. Azura., *et al*. have suggested that hyper methylation screening with TGFb2, SLIT2, HS3ST2 and TMEFF2 genes may predict progression to carcinoma in CAC. Epigenetic silencing of DNA repair genes is less prevalent in the CAC setting as oxidative stress and ROS may cause microsatellite instability (MSI) even in the absence of defects in DNA mismatch repair pathway [45-50]. Promoter hyper methylation of hMLH gene was noted in 9% of CAC cases compared to 15% of sporadic colorectal cancer as summarized in table 2.

Pro- inflammatory cytokines mediators (TNFa, IFN-g, IL-10, IL-6, NF-kB, STAT-3).	Increased levels, early event leading to DNA damage and genetic instability
Aberrant methylation of promoter region CpG island (e.g. Wnt signalling pathway, TGF-b2, SLIT2, HS3ST2, TMEF2).	May predict progression from dysplasia to carcinoma.
Epigenetic silencing of DNA repair genes	Less prevalent in CAC compared to sporadic colon cancer.
P53 mutation	An early event in CAC compared to CRC.
APC tumor suppressor gene.	An late event in CAC compared to CRC.
Altered gut-microbiota	Procarcinogenic role in CAC

Table 2: *Mechanisms and genetic alterations in dysplasia and colitis associated cancer development.*

In addition, aneuploidy (abnormal DNA content), occurs in up to one-third of patients with long- standing UC. It is associated with longer disease duration and has been found in up to 50% of dysplastic lesions and up to 90% of cancers. This may also occur more frequently in HGD lesions [51-54]. Aneuploidy can be present in non-dysplastic colitic epithelium, suggesting a role for chromosomal instability early in the genesis of CAC and thus may be a surrogate marker of chromosomal instability. Recently, Baker., *et al*. using whole genome sequencing demonstrated that copy number alterations (CNA) begin to accrue in non-dysplastic mucosa, and there was a sudden increase in CNA burden at the transition from LGD to HGD [55]. Loss of p53 is specifically seen in biopsies with aneuploidy, implicating itself as a preceding event to the loss of function of p53 [36,37]. However, advanced dysplasia can arise without the presence of aneuploidy, suggesting multiple alternative pathways in the development of neoplasia. Recently, recognition and awareness of the concept of "crypt cell atypia" in inflammatory bowel disease as a dysplastic lesion being a histological marker of neoplastic progression with recommendation of increased endoscopic surveillance, especially if aneuploidy is detected, is gaining momentum [56]. In the future this will need validation across different populations of IBD patients with long term longitudinal studies.

Other less frequently mutated genes in CAC include K-Ras and IDH1. Somatic IDH1 mutations have been identified in 13% of adenocarcinomas in CD and UC. Precursor lesions typically have a serrated morphology [57]. This finding has potential therapeutic implications and are being investigated in phase 1 clinical trials.

Finally, altered gut microbiota potentially plays a role by promoting chronic inflammation. Pro- inflammatory bacterial strains known to be upregulated in IBD have also demonstrated a procarcinogenic effect, including *Bacteroides fragilis* and *Enterococcus faecalis* [58,59].

Fiber-rich foods produce short-chain fatty acids, including butyrate, which has antitumorigenic properties, which is associated with a decreased risk of CRC [60]. Mice models have shown that TGF-b1-deficient mice in an immunodeficient background with inflammation developed colon cancer, but when raised under germ-free conditions, did not develop neoplasia. TGFb1 type II receptors have two microsatellites within its coding region, predisposing them to replication errors in cells that have abnormal DNA MMR. Mutations in TGF-b1 allow colonic cells to be replicated in an uncontrolled fashion. Furthermore, mice that are IL-10 deficient or TCRβ/p53 double knockout do not develop CRC under germfree environmental conditions [61,62]. In summary inflammation, directly or indirectly, play a significant role in initiation of dysplasia and carcinogenesis, which is also evident from association with extent, intensity and duration of inflammation. Thus, inflammation appears to be a primary driver and CAC arises from inflammation-dysplasia carcinoma sequence.

Classification of dysplasia

Dysplasia is defined as non-invasive neoplastic proliferation of the epithelium confined to the mucosal layer, with the ability to progress to carcinoma. Dysplastic lesions are usually flat with indistinct margins but may be polypoid. Histologically, dysplasia classification includes negative for dysplasia, indefinite for dysplasia, low-grade dysplasia (LGD), high-grade dysplasia (HGD), and invasive cancer, as per the Riddell Classification system for dysplasia in inflammatory bowel disease [63]. Much work has been done to standardize the grading of dysplasia and is discussed below [64-67].

Negative for dysplasia is usually noted in areas proximal to the area of involvement in UC, uninvolved skip areas in CD, and in quiescent disease. Histologically, there are parallel and evenly spaced straight tubular crypts, which are perpendicular to the muscularis mucosae. The cells are small and uniform with basal nuclei. In cases of inactive colitis, atrophy is prominent, characterized by crypt loss, or a reduced number of crypts, which can be either distorted or irregularly branched with separation from the muscularis mucosae.

Indefinite for dysplasia is used when reactive and regenerating epithelium that is characterized by mild stratification of the columnar epithelium with vesicular nuclei and prominent nucleoli provide an element of wariness regarding bonafide recognition of dysplasia. Key histological features for indefinite for dysplasia include unexplained nuclear atypia identified by slight stratification and inappropriate cytoplasmic features, such as incomplete maturation and mucin depletion on the background of active inflammation and regeneration. These features overlap with histological features of regenerating epithelium and LGD and are therefore difficult to differentiate. If the epithelial changes appear disproportionate to the inflammation, then it is usually considered indefinite for dysplasia, favoring low grade dysplasia.

Low grade dysplasia in IBD is morphologically similar to sporadic adenomas, with features that include enlarged and hyperchromatic crowded nuclei confined to the basal half of the cell, villous configuration, increased tubule size and number, the presence of some differentiation and maturation including dystrophic goblet cells, and mucin depletion. There is usually an abrupt transition to normal appearing mucosa. One meta- analysis showed that LGD confers a nine-fold increase in risk of developing cancer [68].

HGD is differentiated from LGD primarily by complex morphology and cytology. HGD has full thickness nuclear stratification, nuclear enlargement, hyperchromasia, pleomorphism, and loss of nuclear polarity. Overall, the grade of dysplasia is categorized by the highest grade present. They may also have invasive foci of neoplastic cells in the lamina propria, which are classified as intramucosal carcinoma in this context.

Sessile serrated adenoma/polyp are typically flat and coated with excess mucin material and therefore are difficult to identify in inflamed mucosa. There are very few studies on serrated adenoma/polyp in IBD population. The prevalence rate of serrated lesion appears to be similar to general population. In one study risk of carcinoma development was approximately 20% in SSA/P, similar to non IBD patients [69].

Serrated epithelial change (SEC) is distinct entity and not consistently recognized endoscopically. It is typically found in flat mucosa during routine biopsy in patients with longstanding colitis. It is characterized by hyperplastic mucosal change and flat serrated epithelium

with features of architectural distortion but no definitive features of dysplasia. Architecturally, the crypts undergo loss of orientation to the lumen with epithelial serrations and enlarged goblet cells extending to the base of the crypts. The majority of the lesions were found in the rectum and left colon, and in 55% of cases, no surrounding active inflammation was identified. It is distinguished from SSAs, as it does not follow the typical serrated pathway to advanced adenoma and malignancy. Synchronous dysplasia was seen in 8.0% of cases. The median time to metachronous dysplasia was 34 months. More concerning was a 68% rate of concordant lesions, predominantly located in the sigmoid and descending colon. Those that developed dysplasia were more likely to be older (P = 0.01), male (P = 0.02), and have had at least 1 follow-up SEC lesion (P = 0.001). Further work is needed to delineate the causality of SEC lesions in progression to dysplasia in CAC [70].

Intramucosal tubuloglandular carcinoma usually occurs at younger age in association with synchronous dysplastic lesions in IBD-associated colitis. It usually arises from LGD with well-differentiated mucinous features, co-express CK7 and CK20, with silencing of hMLH. Synchronous carcinoma occurred in 15.6% of patients, attributed to the presence of multifocal dysplasia, which was identified in 37.5% of CRC colectomy specimens [71].

Histologic challenges in dysplasia

Diagnosis of dysplasia can be difficult and certain caveats must be considered. Dysplasia may be present in only part of the biopsy specimen and histologic features may be confounded by histological changes of active inflammation. Dysplasia can also occur in inflammatory polyps, and biopsies from immediately adjacent mucosa is recommended to rule out simultaneous dysplasia and active inflammation. Diagnosis is dependent on cytological, architectural, and maturational abnormalities. Most important feature to differentiate between dysplasia and reactive changes are nuclear features and cytoplasmic maturation. Inter-observer agreement among the subtypes of dysplasia is variable but is the highest for indefinite and LGD. There appears to be interobserver variability for HGD and negative for dysplasia, and thus confirmation of dysplasia with a specialized gastrointestinal pathologist is recommended [72,73]. It also remains critical to document tissue source and completeness of resection, as this can affect histologic interpretation, particularly differentiation of sporadic adenoma and IBD-associated polypoid dysplasia [2,6]. Bowel preparation may cause mucin depletion from crypts, and thus they may appear uniformly eosinophilic. Other causes of mucin depletion include acute inflammation, active regeneration, dysplasia, and enemas.

Certain immunohistochemical markers have been investigated in dysplasia [74-76]. Non-neoplastic flat lesions can be differentiated using molecular markers, such as p53 and ki67. Strong p53/ki67 reactivity and/or presence in the upper third of the surface mucosa is supportive for dysplasia. α-Methylacyl coenzyme A racemase is a mitochondrial and peroxisomal enzyme in fatty acid metabolism that has been identified in 96% LGD, 80% HGD, and in 71% of cancers compared to non-dysplastic epithelium.

Endoscopic classification

Classification of dysplastic endoscopic lesions continues to evolve. Lesions may be raised or flat. “Flat dysplasias” consist of velvety patches, plaques, irregular nodules, stricturing lesions, and broad-based masses, non-amenable to complete resection. These lesions are associated with synchronous and metachronous carcinoma, and retrospective analysis has demonstrated association with malignancy in up to 83% of cases [77].

If raised, in the past, these lesions were considered as dysplasia-associated lesions/mass (DALM), similar to sporadic adenomas in non-IBD patients. In the past, DALM was considered a high risk marker and required colectomy to definitively rule out malignancy as biopsies may not have adequately sampled underlying invasive carcinoma [2,6]. However, IBD associated polypoid dysplasia (DALM) was often endoscopically indistinguishable from adenoma like DALM (sporadic adenoma, unrelated to IBD). Adenoma-like DALMs are less likely to be associated with carcinoma, demonstrated in up to 4.6% of cases. Thus, adenoma-like DALMs identified were managed conservatively with polypectomy and ongoing surveillance if no further dysplasia was detected [3]. Further studies in the present have led to abolition of this term with adoption of SCENIC guidelines, entering into the post-DALM era of dysplasia [6,77].

SCENIC guidelines recommended replacement of DALM with "endoscopically resectable" lesions. These lesions must have distinct margins that can be identified, must be completely removed on visual inspection after endoscopic resection, must have a histological examination of the resected specimen confirming complete removal, and must have biopsy specimens from the mucosa immediately adjacent to the resection site free of dysplasia on histological examination [1]. Lesions are considered visible and polypoid if they protrude into the lumen by greater than 2.5mm; non-polypoid lesions protrude less than 2.5 mm into the lumen [1,77,78].

Endoscopically, neoplastic lesions are described as visible and invisible dysplasia using the terminology adapted from the Paris endoscopic classification as summarized in table 3. Paris endoscopic classification is based on the presence of endoscopic features, such as depression and ulceration. Depression refers to the center of the lesion, indicating that the level of depression is lower than the surface of the adjacent mucosa. Excavated lesions demonstrate discontinuity in the epithelial layer and disruption of the muscularis mucosae [78,79]. Description of visible dysplasia must also consider the margins and ulceration, both of which are associated with submucosal invasion and considered risks for progression to advanced adenomas [77-80]. The Kudo pit pattern has also been used, which examines the surface microstructure of colonic mucosa [81]. However, the pit pattern of regenerative hyperplastic villous mucosa is similar to neoplastic pit patterns, limiting its ability, especially in the setting of UC [81].

Term	Definition
Visible dysplasia	Dysplasia identified on targeted biopsies from a lesion visualized at colonoscopy
Polypoid	Lesion protruding from the mucosa into the lumen > 2.5mm
Pedunculated	Lesion attached to the mucosa by a stalk
Sessile	Lesion not attached to the mucosa by a stalk: entire base is contiguous with mucosa
Nonpolypoid	Lesion with little (< 2.5 mm) or no protrusion above the mucosa
Superficial elevated	Lesion with protrusion but < 2.5 mm above the lumen
Flat	Lesion without protrusion above the mucosa
Depressed	Lesion with at least a portion depressed below the level of the mucosa
Invisible dysplasia	Lesion identified on random biopsy(non-targeted) biopsies of colon mucosa without a visible lesion
General Descriptors	
Ulcerated	Ulceration (fibrinous-appearing base with depth) within the lesion
Border	
Distinct border	Lesion's border is discrete and can be distinguished from surrounding tissues
Indistinct border	Lesion's border is not discrete and cannot be distinguished from surrounding mucosa

Table 3: *Terminology for reporting findings on colonoscopic surveillance of patients with inflammatory bowel disease as adopted by the SCENIC guidelines [Source -Adapted from Laine et al Ref #77].*

Progression of dysplasia

Progression rate of low grade dysplasia to advanced adenoma or CAC varies due to presence of associated risk factors. Risk factors for progression of dysplasia include macroscopic non-polypoid (flat) lesions, invisible dysplasia, lesions > 1 cm, multifocal lesions, history of biopsies indefinite for dysplasia, distal location and PSC [82,83].

Identification of confirmed flat LGD is associated with significant progression to advanced neoplasia while indefinite dysplasia has a lower risk of progression (37 vs 5%), as seen in van Schaik's study of 113 patients with flat LGD and 26 patients with indefinite dysplasia followed for a median of 71 months [84]. LGD lesions were typically unifocal and located in the rectum, while forty patients had multifocal flat LGD, located distal to the splenic flexure (22/40). 16% (18/113) developed advanced neoplasia and 5/11 that initially progressed to

HGD developed subsequent CRC. More concerning is that five patients developed CRC without prior HGD. The median time to progression was 48 months, with an overall 5-year progression rate from LGD to HGD or CRC of 12%. Fumery., *et al.* reported an annual incidence of 0.8% of progression of LGD to CRC in 14 surveillance cohort studies. However, annual incidence of progression to advanced neoplasia was 6.1% in patients with invisible dysplasia [83].

Eluri., *et al*. found that the rate of missed CRC was three times higher in those with IBD versus the general population, emphasizing the importance of early identification and management of dysplasia [2]. No significant differences were found in gender, age of diagnosis, disease type, disease duration, or mean number of previous surveillance colonoscopies. However, there was a significant difference in disease extent, with 55% of the undetected cohort having pancolitis versus 20% in the detected group ($P < 0.01$) [2]. They also identified multifocal dysplasia as a high risk factor for neoplastic progression and significantly identified more often in the undetected group (35% vs 8%, $P = 0.03$) [2]. In addition, the undetected group had a higher rate of rectal lesions, not seen on previous endoscopy. These lesions are thought to have been missed, rather than interval cancers [2].

These studies consistently demonstrate that adherence to a surveillance screening program helps to ensure earlier detection of dysplasia and more timely management, preventing progression to advanced lesions and carcinoma.

Endoscopic detection of dysplastic lesions

Key endoscopic features for dysplasia include elevation, focal friability, attenuated vascular pattern, discoloration, villous mucosa, and irregular nodularity. Long term chronic active inflammation in IBD also induce mucosal changes including scarring, inflammatory polyps, discolouration, altered vascular pattern that overlap with endoscopic features of dysplasia. These overlapping features interfere with accurate identification/visualization of IBD dysplasia and therefore colonoscopy is recommended during disease quiescence [85].

It is critical to optimize techniques for detection. As per the 2015 SCENIC consensus guidelines, if using white-light endoscopy, high-definition white-light endoscopy is superior to standard definition; however, if using standard-definition colonoscopy, chromoendoscopy is recommended versus white-light endoscopy. In addition, SCENIC also recommends chromoendoscopy versus white-light endoscopy when using high- definition colonoscopy [24,77].

Chromoendoscopy significantly enhances detection of abnormalities, and allows for heightened epithelial visualization, using either methylene blue or indigo carmine as contrast enhancers ($P < 0.0001$). Indigo carmine can determine the limit of a lesion, reveal occult neoplasia, and enhance areas of occult depression [7,10,12,15,29,30,79,80,81,86-91]. There was a higher rate of interobserver agreement in polyp detection, increase in detection of non-polypoid dysplasia and negative exam correlated well with dysplasia-free outcome [5,27,87,90]. Kiesslich., *et al*. studied 165 patients with long-standing UC randomized to conventional colonoscopy and chromoendoscopy. Patients in the chromoendoscopy group had a significant increase in detection of intraepithelial neoplasia (32 vs 10; $P = 0.003$) [88]. Carballal., *et al*. showed a dysplasia miss rate of 40/94 with white light endoscopy, and that chromoendoscopy identified an additional 409 lesions in comparison to 188 in those undergoing white light endoscopy. Furthermore, there was no significant difference in detection rate between those with and without expertise in chromoendoscopy [90]. Though the results are promising, further work is required for real-world practice. An unblinded, randomized delayed crossover trial of 48 patients assessing dye-based chromoendoscopy versus virtual chromoendoscopy (VCE) showed that VCE missed fewer lesions but this requires further studies prior to establishing the role of VCE in dysplasia detection [31].

Another alternate surveillance technique includes narrow-band imaging (NBI) which utilizes specific wavelengths of blue and green light to enhance endoscopic images. SCENIC recommends that NBI not be used in place of white-light endoscopy when performing surveillance with standard-definition colonoscopy or high- definition colonoscopy. Furthermore, NBI is not recommended in place of chromoendoscopy when performing surveillance utilizing image-enhanced high-definition colonoscopy (SCENIC) [77]. It has not been proven effective in colitic colons, and in randomized trials fewer lesions were found compared to white-light and high- definition endoscopy [77,80,91-94].

Random biopsies (> 32 random biopsies) were performed for dysplasia surveillance in IBD patients. Several studies have demonstrated that yield from random biopsies are low. Random biopsies sample < 0.1% of the surface mucosa, detect dysplastic lesions in one per 1000 biopsies, and diagnose dysplasia in only 9% of cases. In studies comparing targeted and random biopsies, targeted biopsies had a significantly higher rate of dysplasia detection ($P < 0.001$) and considerably less procedure time ($P < 0.001$) [1,5,27,65,95-97].

Chromoendoscopy with targeted biopsies is the current recommendation as it is a proven and effective technique in improving dysplasia detection, and thereby reducing rates of interval CRC, advanced CRC, and CRC-associated mortality. However, further refinement regarding quality metrics is needed prior to widespread implementation of this technique.

Management of Dysplasia

The management of dysplasia in IBD has undergone changes with knowledge of the natural history of CAC, and adoption of the SCENIC guidelines. Lesions identified in areas without colitis are considered as sporadic adenomas, and managed as such [4]. Currently, if dysplasia is identified on surveillance colonoscopy, and with complete removal of the endoscopically resectable polypoid and nonpolypoid dysplastic lesions, continued surveillance colonoscopy is recommended, rather than colectomy. However, patients with endoscopically 'invisible dysplasia' should be referred to an endoscopist with expertise in IBD surveillance by chromoendoscopy with high-definition colonoscopy. It is imperative that dysplasia also be confirmed by an expert GI pathologist given the marked heterogeneity of these lesions [8,98]. The natural history of polypoid lesions differs from nonpolypoid lesions, and the colorectal cancer risk in IBD from the latter has yet to be determined. Though both are resectable, resection of non-polypoid 'invisible' lesions are more complicated technique-wise and are more difficult to completely excise, yet these may have an inherently higher risk of colon cancer. Prior to endoscopic removal, all the lesion must be assessed for size, location, border, morphology, and surface features including ulceration to determine feasibility for complete resection.

Submucosal injection plays a key role in determining resectabilty of the lesion. Lesions that do not lift, "non-lifting sign" suggest submucosal fibrosis or submucosal involvement by carcinoma. En bloc resection is preferred. If resected in piecemeal fashion with endoscopic mucosal resection, more frequent surveillance is recommended, at 3 - 6 months. In addition, four-quadrant biopsies should be obtained from the area immediately adjacent for residual dysplasia or carcinoma and if present, colectomy is usually recommended. However, recent work has demonstrated that tissue sampling from the immediately adjacent mucosa is low yield and does not aid overall prognostication [87,99,100]. Colectomy is also recommended for invisible dysplastic lesions without distinct borders, as they are associated with dysplasia in the adjacent flat mucosa, as well as with metachronous and synchronous advanced adenomas and carcinoma [4,100]. If the risk of a synchronous lesion is > 73%, colectomy is usually preferred by patients [91,99]. If completely excised, routine surveillance colonoscopy is preferred; however, if the lesion is not amenable to endoscopic resection, colectomy is recommended. Overall, the risk of CRC in IBD has decreased, but the incidence of IBD-associated dysplasia has not; therefore, ongoing surveillance is still required. There is a lack of consensus regarding appropriate interval surveillance in IBD, and an individualized, case by case, personalized approach is recommended.

High grade dysplasia (HGD) usually triggers a recommendation for colectomy and therefore pathological confirmation of the same is imperative. Dysplasia should be demonstrated in a) more than one biopsy specimen obtained during colonoscopy, b) on repeat endoscopy, and c) rebiopsy from the same area. Ideally, this should be confirmed by additional pathologists, preferably with GI expertise. Multifocal dysplasia has been shown to be an independent risk factor for progression to advanced adenomas, and therefore colectomy is advised in this setting [40,102,103]. However, currently, studies are ongoing in endoscopic submucosal dissection and novel colon-sparing techniques [4,104-106].

Low grade dysplasia (LGD) is insufficient to justify immediate colectomy, and surveillance colonoscopy is usually recommended. However, in the case of multifocal LGD, proctocolectomy is recommended, or frequent surveillance every 3 - 6 months, if surgery is declined. LGD has a 5-year 50% rate of progression to advanced neoplasia. The 5-year rate of progression from LGD to HGD is 54% [64]. In a large

study of 600 patients followed for 5932 patient-years, 74 (12.3%) developed advanced adenomas, and specifically 30/74 with CRC, of which 16/30 were interval cancers. There was a significant reduction in CRC incidence over time (P = 0.04). 32/600 (5.3%) had indefinite dysplasia, of which 17 did not progress, 5 developed LGD with a mean interval of 5.1 years and 2 progressed to HGD. 47 patients had LGD and 36 declined colectomy, of which 16 had no further progression. Of those that underwent colectomy for LGD, 20% were found to have CRC in the surgical specimen, and overall 9/46 (19.6%) with LGD developed CRC [27,65]. In those that were found to have HGD, 11 had immediate colectomy, while 8 proceeded with surveillance. Over 19 patient years of follow-up, 7 had ongoing dysplasia and one developed CRC; 5/11 that had colectomy had malignancy identified in the colectomy specimen and overall 3.8% of those with HGD progressed to CRC [27,32]. HGD lesions have demonstrated concurrent CRC in up to 45% of cases. This study highlights the proven clinical benefits of surveillance; however, it raises the complicated issues surrounding management. There is a concern regarding synchronous lesions in the form of advanced adenomas. Further examination is required to better direct management of lesions with LGD. Indefinite for dysplasia requires assessment of risk factors, with further management dependent on risk stratification [82,83,107,108]. Contrary to the past, colectomy is no longer first-line therapy in cases with identification of dysplasia, regardless of degree. However, if multiple high-risk features are present, colectomy is advisable, though as with the paradigm shift of colon sparing procedures in the management of IBD, this remains an individualized personalized case by case decision.

The role of chemoprevention has yet to be definitively proven. The data shows conflicting results, and it remains unclear if there is measurable long term benefit to the natural history of this disease by the suppression of inflammation. Non-steroidal anti-inflammatory medications have demonstrated efficacy in reducing the incidence of sporadic CRC. Mesalamine has been extensively studied in post-hoc, secondary analyses, and systematic review without proven efficacy. The exact mechanism is yet to be determined, but Mesalamine has been shown to scavenge ROS-species by degrading glyceraldehyde-3-phosphate dehydrogenase, and therefore reducing microsatellite instability [40,109]. 5-ASA also decreases epithelial cell turnover caused by inflammation and promotes apoptosis via both inflammatory (COX-dependent) and non-inflammatory pathways, and also inhibits EGFR, NF-kB and Wnt/β-catenin signaling. Systematic review and meta-analysis of nine observational studies found a protective effect in reduced risk of CRC, but not dysplasia, and this was associated with a dose effect of at least 1.2g per day [109-112]. However, there is a lack of consistency in 5-ASA exposure and duration, limiting the validity of the results. In addition, some studies showed a trend towards increased cancer risk, suggesting that there is benefit if given early in disease course [109].

Thiopurines and ursodeoxycholic acid have also been unsuccessfully investigated. A study of 315 patients followed from time of first surveillance colonoscopy until development of LGD, HGD, or CRC or colectomy found that 16% exposed to either 6-mercaptopurine or azathioprine progressed to neoplasia (HGD or CRC) versus 18% of those not exposed to thiopurines. In addition, the thiopurine group had a statistically insignificant higher rate of colectomy (11.5% vs 5.5%, P = 0.6). Meta-analysis of 76,999 patients showed no significant benefit in Crohn's disease, but did in ulcerative colitis, specifically decreased risk of CRC and advanced colorectal neoplasia (both CRC and advanced neoplasia). However, there was no significant reduction in risk of dysplasia alone [93]. Follow-up metanalysis in both case control and cohort studies demonstrated a chemoprotective effect in those with disease duration > 8 years, but not in patients with extensive disease or PSC [113-114]. The data is inconclusive and suggests a protective effect in select patient populations. There is a stronger role for maintenance of remission and adherence with surveillance colonoscopy.

Summary

IBD is a chronic inflammatory disorder of the gastrointestinal tract that comprise of two clinically distinct disease spectrums of CD and UC, that are characterized by the dysregulation of the mucosal immune response to commensal gut microflora in genetically susceptible individuals. The goal of therapy is to induce and maintain a steroid-free long-term remission. This is achieved through significant advancements in understanding the natural history of IBD, as well as the ongoing development of new therapeutic modalities. However, the risk of dysplasia and carcinoma in IBD associated colitis persists. Dysplasia in IBD as a precursor to CRC is an evolving field, complicated by

the lack of a standardized detection technique, as well as the natural risk of sporadic adenoma formation. The pathophysiology of CRC in an IBD bowel appears to differ from the development of sporadic CRC. Though not quite yet understood, they seem related to complex mechanisms that mediate inflammation induced colon carcinogenesis. Newer techniques such as chromoendoscopy has demonstrated significant efficacy in improving early detection of dysplasia with targeted biopsies. The SCENIC guidelines of endoscopic 'visible' and endoscopic 'invisible' dysplasia resulting in *targeted* biopsies have superseded past terminology such as DALM which is no longer in vogue thus marking a new beginning in surveillance and management of dysplasia in IBD. The management of dysplasia and advanced neoplasia is also undergoing a paradigm shift especially in the setting of LGD, with precise lesion characterization by advanced newer refined technologies permitting colon-sparing endoscopic local resections on selected lesions rather than pan proctocolectomy. Management of HGD and cases of multifocal dysplasia remains unchanged, with colectomy as the recommended standard of care. Long-term follow-up has shown that there is a substantial risk for progression to advanced adenoma formation, and that this risk can be significantly mitigated with surveillance screening. Nevertheless, such screening strategies need to be evaluated in balance with efficacy, feasibility, patient compliance and cost effectiveness in daily practice.

Cancer risk stratification in patients with IBD needs to improve for implications in chemoprophylaxis, risk stratification, diagnosis and chemotherapy. Studies in chemoprevention are conflicting, and currently there is no proven benefit for either 5-ASA or immunomodulators; though suppression of inflammation appears to be a key factor in mitigating continued disease progression. The potential for dietary based or drug based clinical interventions in relation to the role of microbiota is another area of research with early promising results. As there is no one size fits all, the goal is for tailored patient assessment with quantification of risks for individualized therapeutic decisions to produce the best health outcomes.

Plans for the future include continued standardization of dysplasia criteria with enhanced optimal improved efficacious surveillance strategy with chromoendoscopy with high definition colonoscopy for early endoscopic detection and management of dysplasia. Understanding dysregulation of cancer related genes, with identification of molecular signatures of dysplasia in colitis-related-dysplasia may offer potential therapeutic interventional targets in the future. As further knowledge is gained in cancer biology, clinical practice, and molecular discoveries, continued clinical and pathobiological investigations are warranted with planned future multicenter trials to produce evidence based robust data for colitis surveillance strategies with impact on patient's cancer free survival, and quality of life. In this context, it is our recommendation that as we move into the future, specialized care in the surveillance and management of dysplasia in IBD is provided with a multidisciplinary team of dedicated expertise of histopathologists, endoscopists, gastroenterologists and colorectal surgeons.

Author Contributions

All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict of Interest Statement

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Volume 6 Issue 10 October 2019