

DYSPLASIA IN IDIOPATHIC INFLAMMATORY BOWEL DISEASE

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Extensive ulcerative colitis or Crohn's disease of 8-10 years' duration or more predisposes to the development of intestinal carcinoma.¹⁻⁶ The coexistence of primary sclerosing cholangitis appears to be an additional important risk factor.⁷⁻⁸ Another more recently defined risk factor is a family history of colorectal cancer, which increases the neoplastic risk in IIBD patients and visa versa.⁹ Management of these patients with life-long risk poses many problems. They are often relatively young and because the acceptable management options are limited to "prophylactic" bowel resection after 8-10 years of disease or lifelong colonoscopic biopsy surveillance for dysplasia or early curable cancer. The rationale for colonoscopic biopsy surveillance derives from the hypothesis, now widely accepted, that cancer in idiopathic inflammatory bowel disease (IIBD) evolves through a premalignant phase of dysplasia that can be detected on biopsy. Such detection of dysplasia identifies the patients who require colectomy for cancer prevention, even if the colitis is clinically asymptomatic.

The numerous problems with dysplasia as the current gold-standard marker for cancer risk in IIBD, including sampling error, distinction from reactive change, observer variability and lack of natural history data are considered further below. The definition and criteria for dysplasia are considered first.

Dysplasia is defined as an unequivocal neoplastic alteration of the colonic epithelium that remains confined within the basement membrane of the gland within which it arises.^{10,11} Histologically, the degree of abnormality (atypia) within dysplastic epithelium forms a continuous spectrum from slight to marked and includes cytologic features of nuclear enlargement, pleomorphism, hyperchromasia, irregular nuclear envelopes and loss of nuclear polarity. Glandular architectural changes of crowding, cribriform formation, angulation, and dilatation with necrotic/apoptotic luminal debris are also important. For purposes of clinical utility, unequivocal dysplasia is divided into low-grade and high-grade dysplasia, based upon its degree of deviation from normal colonic epithelium, as follows:

Diagnostic Criteria for Grading of Dysplasia in IIBD

Negative for dysplasia: The glandular architecture and cellular morphology are free of neoplastic alterations, but may contain reactive or regenerative change from inflammatory injury. The glandular architecture is orderly, not crowded and reveals abundant lamina propria surrounding most glands. The basal-most intestinal glands, which are closest to the muscularis mucosae, make up the regenerative compartment of intestinal mucosa. These deeper glands are characteristically more atypical in intestinal mucosa, especially if it is inflamed, and usually exhibit nuclear enlargement, hyperchromasia, some degree of pleomorphism, and nuclear membrane irregularity. These findings simulate dysplasia except for the critically important fact they are limited to the basal glands and the epithelium matures to a normal cytology as it extends onto the biopsy surface. This baseline deep glandular change that is quite characteristic of intestinal epithelium without dysplasia. It cannot be overemphasized that if it matures, it is virtually always negative for dysplasia.

Care must also be taken at the surface of biopsies not to over interpret tangential sectioning artifact as true nuclear stratification that has not matured and therefore might represent dysplasia. In tangential sectioning artifact, surface nuclear uniformity and simultaneous cytoplasmic elongation as well as nuclear elongation are frequently helpful diagnostic clues that there is no dysplasia. Finally, outside of the deepest regenerative crypt zone, normal epithelial cell nuclear size should be no more than 1-2 times the size of normal lamina propria cell nuclei, such as fibroblasts, endothelial cells or inflammatory cells. This relative measurement takes into account the vagaries of tissue fixation, processing, sectioning and staining by assessing nuclear size in relation to an internally normalized control cell population.

Reactive cytologic alterations in the presence of active inflammation with intraepithelial granulocytes with or without granulation tissue, are also part of the spectrum of changes that are negative for dysplasia, if the cytologic changes mature to the surface of the biopsy and the glandular architecture remains intact. Surface maturation is critical to distinguishing inflammatory reaction from dysplasia. Reactive inflammatory change often also produces a more open (less dark) nuclear chromatin structure and cytoplasmic mucin depletion. Mucin depletion is commonly observed in dysplasia as well, so that care must be taken not to over interpret mucin loss.

Regenerative cytoarchitectural alterations in relation to erosion or ulceration may also be classified as negative for dysplasia. Regenerative change consists of a surface monolayer or near monolayer of cells overlying eroded/ulcerated stroma that is either devoid of deeper glands or shows prominent gland loss with replacement by granulation tissue. The surface regenerative cells may have variably atypical and even bizarre cytologic abnormalities, but in general they maintain a characteristic monolayer growth pattern over stroma devoid of glands and usually have abundant cytoplasm as well as the markedly enlarged nuclei. At times, the monolayer will contain multinucleated cells or will appear to lack cell borders and form a syncytium along the surface. Despite the sometimes extreme cytologic abnormalities, regenerative change is so stereotypical in appearance that it can still be readily diagnosed as negative for dysplasia if it fulfills the above indicated criteria.

Indefinite for dysplasia: The glandular architecture of epithelium that is indefinite for dysplasia is intact or may exhibit mild crowding or mild loss of orderly gland arrangement. The cytologic changes usually show partial but incomplete maturation onto the mucosal surface. Goblet or columnar cell mucin is often diminished and may be absent. So-called “dystrophic” goblet cells, in which the cytoplasmic mucin vacuole is on the basal rather than luminal side of the nucleus, may also be seen. In the presence of pronounced inflammation or erosion/ulceration, the cells may be markedly atypical and lack surface maturation altogether. Numerous mitotic figures may be present.

Crypt-limited dysplasia contradicts the criterion of surface maturation and should only be diagnosed on very rare occasion. At its core, IIBD is an injurious inflammatory disease of the intestines, with a great propensity to mimic dysplasia. Crypt-limited dysplasia therefore poses a serious problem in that it detracts from the importance of surface maturation in the exclusion of dysplasia. While true crypt-limited dysplasia undoubtedly exists, it cannot be overly stressed that it is a very minor exception to the rule that surface maturation excludes dysplasia in the great majority of dysplasia. Thus, the great majority of atypical crypts with surface maturation should be diagnosed as negative for dysplasia, less commonly as indefinite for dysplasia, and only very rarely as crypt-limited dysplasia.

When there is doubt as to the significance of the epithelial abnormalities in a biopsy, the diagnosis of “indefinite for dysplasia” should be made. The singularity of this category falsely creates the impression in clinicians minds that there is only a single basic type of epithelium in this category. In reality there may be hundreds or even thousands of variations on the cytoarchitectural changes that comprise the indefinite for dysplasia category. Pathologists strive to classify the vast array of alterations in this category into the single and utterly limited designation of indefinite for dysplasia. Understandably, therefore, this leads to the highest inter and intra-observer diagnostic variability at this particular part of the diagnostic spectrum of dysplasia.

It is useful to consider four general categories to help organize the possible alterations of changes that are indefinite for dysplasia. Reactive inflammatory in biopsies taken from the edges of ulcers may be indistinguishable from dysplasia. In cases with marked inflammation or ulceration, the atypia may be so severe that not only is dysplasia in contention, but even carcinoma may be suspected. Surface maturation is lacking in this form of indefinite for dysplasia. Cautionary language should be provided to clinicians that repeat biopsies must be obtained after intensive anti-inflammatory therapy; these will often show resolution of the abnormalities. It is also advisable in this, the most highly concerning form of indefinite change, that warning commentary be reported regarding possible advanced neoplasia or carcinoma.

Cases with more mild inflammatory changes and atypia, which are likely negative for dysplasia, form the second major general type of indefinite for dysplasia. This is far less worrisome. The inflammation offers a probable explanation for mild changes but the cytologic abnormalities do not entirely mature onto the surface so that the diagnosis of indefinite for dysplasia is still warranted.

The third major general change that may be classified as indefinite involves *non-inflamed* intestinal epithelium that is not negative for dysplasia, but yet has insufficient alterations for a diagnosis of unequivocal low-grade dysplasia. A common issue again is that the cytologic alterations mature partially but incompletely as the cells extend onto the surface of the biopsy and/or only mild architectural concerns exist. These alterations are presumably on the pathway of neoplastic progression, but have not yet crossed the observer’s threshold for low-grade dysplasia.

Mechanical issues comprise a fourth general type of change that may be classified as indefinite for dysplasia, such as when the biopsy surface is denuded or the biopsy is maloriented and the surface is otherwise unavailable for evaluation. Crush and cautery or other mechanical artifacts as well as poor histologic preparations can also be placed into this category.

Fortunately, the distinction between indefinite and low-grade dysplasia has no practical clinical significance, for both categories are managed the same clinically, namely by conservative continued periodic surveillance and diligent anti-inflammatory therapy to eliminate as much obscuring inflammation as possible. On the other hand, while the distinction between indefinite for dysplasia and low-grade dysplasia is not clinically important, the distinction between indefinite change and negative for dysplasia is a significant concern. Specifically, less surveillance with longer intervals between endoscopies will be applied for the negative category. Furthermore, the great majority, estimated at 90% or greater of IIBD patients should fall within the negative category. As such, even a minimal to modest over diagnosis of the indefinite for dysplasia category will cause unnecessary surveillance, insurance rate increases, and patient anxiety. Thus, pathologists are strongly advised to focus more on distinguishing the negative for dysplasia category from the indefinite category rather than the less important distinction between indefinite change and low-grade dysplasia.

Low-grade dysplasia: The crypt architecture tends to be preserved, and distortion, if present, is mild to moderate. It should be noted that the crypts in low-grade dysplastic epithelium may still be relatively more abnormal cytologically than the surface, but the surface will virtually always have unequivocal dysplastic change as well. Involvement of the surface as well as the crypts in low-grade dysplasia is the major criterion to distinguish low-grade dysplasia from the negative and indefinite categories. The cytologic changes of low-grade dysplasia virtually always extend from the crypts onto the biopsy surface.

Low-grade nuclear cytology usually consists of stratified, elongated or pencillate shaped nuclei that are typically enlarged, measuring more than 2-fold larger than internal control lamina propria nuclei. Low-grade dysplastic nuclei are also usually hyperchromatic, crowded and arranged in an overlapping configuration.

Abnormal mitotic figures may be present but are a soft criterion for diagnosing dysplasia. Mitotic activity alone is unhelpful, even mitoses that extend out of the basal regenerative zone and occur near or at the surface. This is because intestinal mucosa in IIBD has an elevated proliferative rate at baseline and is even more mitotically active with active inflammation.

Goblet or columnar cell mucin is often diminished and may be absent in low-grade dysplasia. Hypermucinous change may, however, accompany a minority of IIBD dysplasias. So-called “dystrophic” goblet cells, as defined above in the indefinite category, may be present in low-grade dysplasia as well. These cytoplasmic mucin-related features are never diagnostic of dysplasia on their own, as dysplasia is diagnosed by nuclear cytology and architectural change; however, the mentioned cytoplasmic findings may be helpful.

Of great importance, nuclear polarity is preserved in low-grade dysplasia, meaning that the long axes of the dysplastic nuclei remain perpendicular to the basement membrane and the nuclei appear orderly and oriented to one another.

High-grade dysplasia: Distortion of crypt architecture usually occurs and is frequently marked, including branching and lateral budding of crypts, asymmetrical gland shapes, marked glandular crowding with little to no intervening lamina propria, villiform configuration at the mucosal surface, and/or intraglandular bridging of epithelium to form cribriform patterns with multiple lumens confined to a single gland. Dilated glands containing necrotic or apoptotic luminal debris are a markedly concerning architectural change in high-grade dysplasia. As a matter of personal opinion, if this feature is seen in more than three glands per biopsy fragment, a warning that intramucosal carcinoma should be considered is appropriate. While nuclear features usually take precedence over architectural change in determining the grade of dysplasia, dilated glands with luminal debris or extremely crowded glands without much if any intervening lamina propria are notable exceptions to this general principle. Such severe architectural changes typically indicate a diagnosis of high-grade dysplasia despite more bland cytology. Extremely crowded high-grade dysplasia without significant intervening stroma and can also border on intramucosal invasion. Where the continuum of high-grade dysplastic alterations end and intramucosal carcinoma begins is difficult, if not impossible to define. Fortunately, in the colon, this distinction is not important and intramucosal colonic neoplasia has never been reported to metastasize and thus is biologically benign.

Cytologically, high-grade dysplasia has greater nuclear enlargement, more irregularity of nuclear membranes, more pleomorphism and more hyperchromasia than low-grade dysplasia. These are all continuous variables, so that unfortunately, precise cutoffs cannot be defined. Pathologists must therefore acquire their own thresholds through high volume experience.

As a rule with virtually no exceptions, nuclear abnormalities extend from the base of the crypts onto the surface epithelium in high-grade dysplasia. It should be noted that the crypts may still be slightly more atypical than the surface in high-grade dysplasia, but if there is any significant degree of maturation in a dysplastic biopsy, low-grade dysplasia is probably more appropriate than high-grade dysplasia.

As in the indefinite and low-grade dysplastic categories, cytoplasmic mucin is *usually* diminished or absent; however, hypermucinous change occurs in all strata of neoplastic change. Similarly, dystrophic goblet cells as defined above may also occur.

Most importantly, high-grade dysplasia will characteristically exhibit loss of nuclear polarity, such that the long axes of the nuclei are no longer oriented perpendicularly to the basement membrane and the orderly orientation of one nucleus to the next is lost. With loss of polarity, the nuclei often also assume a more rounded and less pencillate shape in comparison to low-grade dysplasia. Loss of nuclear polarity is the most objective criterion for distinguishing low and high-grade dysplasia because it is a more dichotomous, yes or no, criterion relative to all of the other continuous variables as discussed above. As such, this author places heavy emphasis on loss of nuclear polarity for high-grade dysplasia. Due to the major consequences of a diagnosis of high-grade dysplasia, prompting aggressive management by colectomy, it should not be established without 100% certainty in the opinion of this author.

Adenocarcinoma: If a well-defined desmoplastic stroma with infiltrating malignant glands can be identified separately from inflammatory stromal changes of scarring and granulation tissue, the diagnosis of at least submucosal invasive adenocarcinoma can be made. These distinctions can be very difficult at times, especially on the basis of endoscopic forceps biopsies. This category is at times impossible to distinguish from high-grade dysplasia.

Natural History of Dysplasia in IIBD

When colectomy has been performed because dysplasia was present in biopsies, a relatively high percentage (around 30-40%) of patients have been reported to harbor a clinically unsuspected carcinoma in the resected colon, especially if a visible mass that was too large to remove endoscopically was present.^{6,12,13} Most of these patients are diagnosed with dysplasia on their first colonoscopy and thus have prevalent dysplasia with its higher risk of unsuspected cancer.^{6,13,14} The prevalence of carcinoma in colectomy specimens appears to be much lower when incident dysplasia is discovered during prospective follow-up surveillance, probably because the neoplastic process in incident dysplasia discovered during surveillance is detected at an earlier stage in its evolution.^{6,13,14}

High-grade dysplasia on biopsy is an accepted indication for colectomy, following diagnostic confirmation by an expert GI pathologist.^{3,15} There are no cohort studies of the actual risk of high-grade dysplasia in IIBD, but the unknown risk is hopefully higher than the risk of colectomy, as this is the standard of care. Short interval follow-up (6 month to 1 year) for patients with biopsies harboring epithelial alterations that are indefinite for dysplasia and for those with low-grade dysplasia is reasonable, although the management of low-grade dysplasia is more controversial.^{3,6,15-17} Colectomy may be appropriate for some patients with low-grade dysplasia, but long term, prospective follow-up data of *adequately sampled patients* are not available to indicate who. Many reported studies in ulcerative colitis claim to provide such natural history data, but in reality there are none that do in the entirety of this body of literature, simply because far too few biopsies were taken to have any degree of confidence that more advanced lesions were not also present.¹⁶⁻¹⁸ Further, virtually no information is available

regarding the natural history of dysplasia of any grade in Crohn's disease. Thus, the entire world's literature to date, to this author's knowledge, on the natural history of low-grade dysplasia in IIBD reports only the outcome of patients undergoing inadequate sampling and therefore undiagnosed colons, rather than the true natural history of rigorously documented patients with only low-grade dysplasia.

A minimum of 33 jumbo-sized and well oriented biopsies are needed to achieve even 90% confidence that dysplasia will be identified on routine colonoscopy.¹⁹ More advanced endoscopic techniques (see later) show great promise for reducing this sampling intensity, but these are all under active investigation and have not yet been applied to any natural history studies of low-grade dysplasia. Thus, from the available literature based only on routine colonoscopy as the current standard of care, if only 10 biopsies are obtained on average in a series purporting to report the natural history of low-grade dysplasia, then there is no confidence that the patient's true and most advanced diagnosis was uncovered, due to inadequate sampling. This practice is inadequate and sheds no light on the true natural history of low-grade dysplasia in the broad surface area of the colonic mucosa. If such inadequately sampled patients then develop cancer, especially if it is diagnosed within only a matter of months of the diagnosis of low-grade dysplasia, this almost certainly represents failure of endoscopic sampling of the cancer that was there and missed at the initial endoscopy. Neoplastic progression from low-grade dysplasia in the colon occurs over years to decades on average, rather than months. The shorter the time interval between dysplasia detection and colectomy, the more true it becomes that the patient had cancer all along. Such data do not teach us about the natural history of low-grade dysplasia and its risk of progression to cancer, they only teach us that bad surveillance does not work and does not adequately prevent cancer. Thus, we still have no information on adequately documented low-grade dysplasia patients and their risk of progression or risk of developing incurable cancer if they remain in surveillance.¹⁶ Despite the lack of evidence, many authorities recommend colectomy for flat low-grade dysplasia, even if it is present at only one site and on one endoscopy.¹⁷ Particularly given the poor reproducibility of the histologic diagnosis of low-grade dysplasia (see below), and the absence of good data on its natural history, an alternative approach in the opinion of this author would be to first ensure that adequate surveillance has been performed, obtaining a minimum of 33 jumbo and well-oriented biopsies.¹⁹ The following additional risk factors may permit a better-informed decision to pursue colectomy: 1) finding more than one site of low-grade dysplasia, 2) finding low-grade dysplasia on more than one endoscopy, and 3) finding low-grade dysplasia in a grossly recognizable lesion that cannot be completely removed in a conservative fashion endoscopically.^{3,15,20}

Polypoid Dysplasia in IIBD

The above discussion applies to endoscopically flat and therefore unrecognizable dysplastic lesion on routine colonoscopy. If a visible lesion arises in a UC patient and is solitary, *and* it can be demonstrably completely removed by endoscopic polypectomy with negative biopsies of adjacent flat mucosa and of the polyp base, *and* there is no evidence of dysplasia anywhere else in the colon, then a conservative approach of continued surveillance, rather than colectomy, may be appropriate.^{3,15,21-23} However, it must be emphasized that in order to achieve adequate assurance that there is no dysplasia elsewhere in the colon, many biopsies must be taken, given the large surface area of the colon.¹⁹ It should also be noted that virtually all of the reported polypoid lesions in IIBD that have been safely followed conservatively by continued surveillance

had *only low-grade dysplasia*.²¹⁻²³ Thus, there are insufficient data on the safety of polypectomy alone for polypoid high-grade dysplasia.

Other Problems with Dysplasia as the Gold Standard Biomarker of Cancer Risk in IIBD

These include sampling error, observer diagnostic variability, and distinguishing it from reactive or inflammatory change.²⁴ Dysplasia may be localized to a single, small area of the mucosa, it may be multifocal, or it may be extensive and involve virtually the entire mucosa.^{19,25} The esteemed Dr. Cyrus Rubin and colleagues at the University of Washington showed that 33 jumbo forceps biopsies are required to achieve 90% confidence that dysplasia will be detected by routine colonoscopy if present.¹⁹ Therefore, it is recommended that at least four-quadrant biopsies be obtained from each 10 cm segment of the colon and every 5 cm within the rectum, based on the higher incidence of distal carcinoma in UC.^{26,27} Specifically, at least one half of colorectal cancers arising in UC occur in the rectum and sigmoid colon.^{26,27} Thus, more intensive sampling of the distal mucosa appears indicated. This surveillance approach has now been endorsed for both UC and Crohn's disease in an official consensus conference practice guideline, sponsored by the Crohn's and Colitis Foundation of America.³

The biopsies from each cross sectional segment of colon can be placed in the same bottle of fixative and made into a single paraffin block. Thus, in a patient with an 80 cm colon, ~36 biopsies would be taken, and 9 blocks would be prepared with two to three step-leveled slides cut from each block.²⁷ Placing more than 6 biopsies in a block limits the amount of biopsy tissue on each section because the histotechnologists have insufficient time to adequately examine and orient biopsies perpendicularly and embed them all at the same approximate level in the continually hardening paraffin. Beyond 4-6 biopsies, the final embedded fragment is at a sufficiently higher level in the ever solidifying wax relative to the pieces embedded earlier, so that a single section or even serial sections will not slice through central core of each biopsy for optimal histologic examination.²⁸ Thus, embedding more than 4-6 biopsies per block is to be discouraged. This practice defeats the purpose of taking extensive biopsy samples by producing unsectioned tissue at highly disparate levels in the paraffin blocks.

New Techniques to Improve Early Detection and Cancer Prevention in IIBD

The problems mentioned in the preceding discussion emphasize the need for more objective markers to identify patients at risk for developing dysplasia or carcinoma. A number of techniques have been explored as potential "markers" for heightened cancer risk, including histochemical, immunohistochemical and molecular assays.^{3,29-31} To date, none of these biomarkers has been validated in long-term prospective trials that obtain adequate numbers of surveillance biopsies to know the true extent of neoplasia over time, but such investigations are ongoing. Biomarkers of genomic instability, in particular, show promise for detecting the at risk subset of IIBD patients. Such genomic instability biomarkers appear to be so widespread that they can even be detected on single rectal biopsies that are negative for dysplasia.²⁹⁻³¹ This latter finding even suggests that full colonoscopy may be eliminated for the low risk majority of IIBD patients, representing as many as 90% of this patient population. Those patients with altered genomic markers who are at highest risk could then have focused and intensive endoscopic surveillance. An NIH-sponsored prospective trial in the USA is now ongoing at the Cleveland Clinic and University of Washington to address the long-term outcome of these promising genomic biomarkers of cancer risk in UC. Preliminary data in Crohn's disease show similar promise.³⁰

Endoscopic detection of dysplasia by means other than conventional endoscopic biopsy and histology are now also under intensive investigation, including such techniques as magnification endoscopy, narrow band imaging, chromoendoscopy, and confocal endomicroscopy.³²⁻³⁴ These technical endoscopic advances may shed further light on our understanding of the natural history of dysplasia in IIBD. More importantly, they show great promise for increasing the sensitivity of dysplasia detection and solving the problem of sampling error, which in the opinion of this author is the greatest problem posed by dysplasia as a gold standard biomarker of cancer risk in IIBD.

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