Surveillance for neoplasia in colitis is the most challenging diagnostic colonoscopic procedure. The detection and treatment of colorectal dysplasia in inflammatory bowel disease remain problematic to the point that unsuspected colorectal cancers (CRCs) are still identified. Excellent bowel preparation and use of high-resolution colonoscopes with chromoendoscopy facilitate the detection and characterization of subtle neoplasia. This approach is superior to taking random biopsy specimens and should be the standard of care for surveillance but requires adequate training. Suspicious lesions should be assessed carefully and described using objective terminology. The terms dysplasia-associated lesions/masses and flat dysplasia are best avoided because they may be open to misinterpretation. Most suspicious lesions detected during surveillance can be removed endoscopically, precluding the need for surgery. Nevertheless, endotherapy in colitis can be difficult as a result of underlying inflammation and scarring. Lesions that are not endoscopically resectable need to be removed surgically, although the possibility that some lesions might be amenable to local resection (including lymphadenectomy) rather than subtotal colectomy may need to be re-evaluated. Despite surveillance programs, patients still present clinically with CRC. This may occur because lesions are missed (possibly because of the failure to use optimal techniques), lesions are not adequately removed, patients fail to return for colonoscopy, or CRCs arise rapidly in mucosa that is minimally dysplastic and the CRCs are not recognized as being potentially invasive even on biopsy. Future advances in, for example, stool DNA assays, use of confocal endomicroscopy, or use of endoscopic ultrasound, may help in the identification of high-risk patients and the assessment of dysplastic lesions.

**Lesion Detection**

The aim of surveillance is to detect neoplastic tissue at a pre-invasive stage (dysplasia) or when a cancer is early, asymptomatic, and potentially curable.

**Random Biopsy Specimens**

In noncolitic patients the dominant premalignant lesions, the sporadic adenoma, along with less common premalignant serrated lesions, are visible endoscopically and usually are well circumscribed. However, in colitis, although identical sporadic lesions can occur, dysplasia also can be difficult to discriminate from inflammatory and postinflammatory changes. Before the reclassification of colitis-associated dysplasia in 1983, it also was believed that dysplasia often occurred as a field effect. However, these data were accrued largely from patients presenting with CRC, rather than in patients with dysplasia on biopsy. The low yield of random biopsy specimens described later supports this observation. It is now recognized that the vast majority of colitic dysplasia is visible endoscopically, thus the recommendation to take multiple random biopsy specimens of mucosa is becoming less tenable. It was
estimated that 33 biopsy specimens were required to have a 90% chance of finding the highest degree of dysplasia present. However, this policy is poorly adhered to, costly, and time consuming. In addition, the detection of a 2-cm-diameter (radius, 1 cm) patch of dysplasia in a large bowel nominally 100 cm in length and 10 cm in circumference (ie, 1000 cm²), would need around 320 biopsy specimens, which is clearly an absurd notion. This also challenges the plausibility of going back to confirm the diagnosis of dysplasia, even if one knows the approximate region from where the biopsy specimen came.

Over the past decade, 10 prospective studies taking per protocol quadrantic random biopsy specimens every 10 cm from the colorectum have been published, allowing us to assess the value of random biopsy specimens: on average, 1 episode of dysplasia is detected for every 1505 random biopsy specimens taken. Assuming 30 random biopsy specimens per colonoscopy, dysplasia would be found in only 2% of patients. A time-consuming random biopsy policy also distracts the endoscopist from meticulous inspection, targeting biopsy specimens now has been adopted as the preferred option in many national guidelines.

**High-Quality Examination**

With improvements in endoscopic equipment and technique, it is now recognized that the majority of colitic neoplastic lesions are visible endoscopically, although a variety of factors affect the ability to detect them. A high-quality bowel preparation incorporating altered diet and split-dosing of bowel purgatives is important to improve mucosal visualization and thus dysplasia detection. This is particularly pertinent during colonoscopy of patients with colitis, in whom the bowel preparation is worse (odds ratio, 0.63; 95% confidence interval [CI], 0.40–0.98) and lesion detection is more difficult. Studies in noncolitic patients have shown higher dysplasia yields with a slower inspection phase of examination. In colitis surveillance, the retrospective study by Toruner et al showed a significant association between longer procedure duration and increased dysplasia detection (R² = 0.12; P = .0066). Position shifts, particularly a supine position during transverse colon inspection, also may aid in lesion detection, as may the routine use of intravenous hyoscine-N-butylbromide, an antispasmodic, although not all studies have confirmed this.

**High-Definition Endoscopes**

Endoscopic image definition has been enhanced with the introduction of high-definition (HD) endoscopic equipment. It is logical to use HD equipment to improve the sensitivity and specificity of dysplastic lesion detection. This was supported by a retrospective cohort study in colitis surveillance, which reported an adjusted prevalence ratio of detecting any dysplastic lesion on a targeted biopsy specimen as 2.21 (95% CI, 1.09–4.45) and 2.99 (95% CI, 1.16–7.79), for HD colonoscopy compared with standard-definition colonoscopy, respectively.

**Chromoendoscopy**

Chromoendoscopy (CE; endoscopic dye-spraying) further enhances the detection of subtle dysplasia, increasing surveillance sensitivity. CE also can aid in differentiation between neoplastic and non-neoplastic lesions by categorizing the crypt architecture using the Kudo et al pit pattern classification. The 2 main stains are indigo carmine, a contrast dye that highlights subtle colonic contour irregularities, and methylene blue, which also is absorbed by noninflamed mucosa, but less well absorbed by neoplasia and active inflammation. One study found in vitro evidence of DNA damage with methylene blue at the concentration used in the colon, raising concern about its safety. Whether this is of any clinical significance is unclear.

Pancolonic CE is currently the gold standard modality for colonic surveillance in colitis: 6 controlled trials showed an increased dysplasia yield of CE with standard white-light endoscopy (WLE) for colitis surveillance of between 2.2 and 4.75 times. A recent meta-analysis confirmed that CE is significantly better than WLE in detecting dysplasia in patients with colonic inflammatory bowel disease. The technique is inexpensive, relatively quick and easy to perform (adding only a few minutes to the colonoscopy compared with random biopsy sampling), and safe. CE without random biopsy specimens now has been adopted as the preferred option in many national guidelines.

**Narrow-Band Imaging**

With narrow-band imaging (NBI), the colon is illuminated with blue/green wavelength light at the push of a button, preferentially enhancing the mucosal vascular pattern, which is altered in dysplastic tissue. Three colitis surveillance studies have compared NBI with WLE. In the prospective randomized cross-over study of 42 patients by Dekker et al, neoplasia was found in 11 patients, in whom first-generation NBI and standard-definition WLE both detected neoplasia in 4 patients, NBI alone detected neoplasia in 4 patients, and WLE alone detected neoplasia in 3 patients (P = .705). In a prospective randomized cross-over study of 48 patients comparing HD WLE with NBI by van den Broek et al, neoplasia was found in 16 patients, in whom NBI detected 13, and HD WLE detected 11 (P = .727). In a randomized controlled trial of 112 patients comparing NBI with WLE by Ignjatovic et al, 5 patients had at least 1 dysplastic lesion in each group (odds ratio, 1.00; 95% CI, 0.27–3.67; P = 1.00). One practical issue with NBI is that the intensity of light illuminating the mucosa is greatly decreased, reducing the depth of field and hampering lesion detection. Thus, evidence suggests that the current
generation of NBI is not superior to WLE when using either standard-definition or HD endoscopes, although its use may be complementary.

One study has been published comparing HD NBI with CE. In a prospective randomized cross-over study of 60 patients by Pellisé et al., CE missed 3 of 22 lesions in 2 of 13 patients, whereas NBI missed 7 of 22 lesions in 6 of 13 patients ($P = .036$). No study has yet assessed the technique against pancolonic dye spraying.

Confocal Laser Endomicroscopy for Lesion Detection

Confocal laser endomicroscopy produces real-time in vivo images of the cellular structure of the mucosa, with 1500-fold magnification. However, although confocal laser endomicroscopy improves lesion characterization, it is not a technology for lesion detection per se.

Lesion Categorization and Terminology

Dysplasia in Noncolitic Mucosa

Polypoid dysplastic lesions that occur proximal to the extent of inflammation in ulcerative colitis, or in an area that has not been affected by inflammation, can be assumed to be sporadic adenomas and can be resected endoscopically. Endoscopic features indicative of previous inflammation include scarring and postinflammatory polyps.

Dysplasia Within Colitic Mucosa

Dysplastic lesions in inflamed or previously inflamed mucosa are important because they may progress more rapidly than adenomas in noninflamed mucosa. Thus, all lesions should be removed promptly.

Endoscopically/Macroscopically Invisible Colitis-Associated Dysplasia

To avoid confusion, we recommend that the clinician should refrain from using the term flat to describe endoscopically unapparent (invisible) dysplasia because this term now commonly is used among endoscopists to describe macroscopically visible but minimally elevated ($<2.5$ mm) lesions in the gastrointestinal tract

A descriptive term such as macroscopically invisible is preferable.

Historical retrospective series and reviews have indicated that when endoscopically invisible high-grade dysplasia (HGD) is detected, colectomy is appropriate owing to high rates either of synchronous or metachronous cancer in $32\%$ to $42\%$ of patients. Care must be taken with these data, however, because none of the studies was designed to answer that question. In addition, CRC does not need to go through HGD to develop invasion, a concept embraced in the original diagnosis of dysplasia.

Where endoscopically invisible low-grade dysplasia (LGD) is detected, management is fraught with controversy because reported rates of progression to HGD or cancer vary from as low as $0\%$ to more than $50\%$. Part of this variability relates to the difficulty a histopathologist has in discriminating neoplastic changes from regenerative inflammatory changes, resulting in low levels of interobserver agreement. If there is any doubt about the histologic diagnosis of dysplasia, the histology should be double-reported by an expert gastrointestinal pathologist. Expertise is difficult to define but includes seeing a lot of biopsy specimens with good agreement (however defined) when compared with peers and resected specimens. There are data suggesting that LGD in particular is overdiagnosed by nonexpert pathologists. In a study of Barrett’s esophagus, when 2 experts evaluated all diagnoses of LGD made over a 6-year period, 85% of biopsy specimens were downstaged to nondysplastic Barrett esophagus or to indefinite for dysplasia, and in only 15% was the initial diagnosis of LGD upheld. On endoscopic follow-up evaluation, 85.0% of patients with a consensus diagnosis of LGD progressed to HGD or carcinoma, compared with 4.6% for patients whose biopsy specimens were downstaged ($P < .0001$). Whether this is similar in colitis is not clear, but because both diseases have much in common it is perhaps likely to be the case.

Management strategies including either colectomy or intensified surveillance need to be discussed frankly with the patient, taking into account other risk factors. However, before any decision is made, the colonoscopy should be repeated by a colonoscopist experienced in the use of CE and interpretation of colonoscopic findings. This is to ensure that an endoscopically visible and resectable lesion is not present, particularly because many apparently random biopsy specimens actually may
have been taken from an area of mucosal irregularity, which can be detected endoscopically. HD equipment should be used wherever possible. In this situation an argument can be made for taking multiple random biopsy specimens as well because this ensures that any decision for surgery/ongoing surveillance has been based on the most comprehensive information possible. Nevertheless, the utility of this has yet to be assessed and, as noted previously, in a patient in whom dysplasia has been detected on a random biopsy, the chance of resampling it is small if localized. This also highlights the importance of carefully labeling all specimens according to colorectal location and also whether they were targeted or random, making it easier to return specifically to that site to identify a potential lesion that might not have been detected at the initial colonoscopy.

The cost of processing multiple biopsy specimens also can be an issue and also may be dependent on the block-embedding technique and whether pathology is charged per block or per specimen. Shifting to chromoendoscopic surveillance helps address this issue.

**Endoscopically Visible Colitis-Associated Dysplasia**

Most dysplastic lesions are visible endoscopically. Raised neoplastic lesions arising within an area of current or previous inflammation have been termed *dysplasia-associated lesions/masses* (DALMs) and early studies showed high cancer incidences in such patients. The original description of DALMs in 1981 espoused the notion that CRCs do not need to go through a spectrum of changes. At that time these were called mild, moderate, and severe dysplasia, *in situ* cancer, and invasive cancer, whereas the current terms are low-grade dysplasia (synonymous with low-grade intraepithelial or noninvasive neoplasia; LGNIN), high-grade dysplasia (synonymous with high grade intraepithelial or noninvasive neoplasia; HGNIN), and invasive cancer. This notion, incorporated into the original definition of dysplasia, remains a limiting factor for a small proportion of patients in whom the features of CRC or dysplasia may pass unrecognized.

The term *DALM* has evolved over time and more recently the term *adenoma-like mass* (ALM) has been used to describe polyps containing dysplasia within an area of colitis and judged to be endoscopically similar to sporadic adenomas. Endoscopic resection of so-called ALMs carries a good prognosis, but these need prompt, careful, and complete removal because there appears to be an increased risk of both HGD and invasive CRC if this is not performed.

Many clinicians and pathologists do not appreciate that there are no clear-cut endoscopic, histologic, or immunohistochemical discriminators between so-called DALMs, ALMs, or sporadic adenomas, although some endoscopic and histologic lesions are more common in colitic than noncolitic patients. One of the pitfalls of using the term *DALM* therefore is that a patient may undergo colectomy irrespective of whether it is the optimal management. Thus, a case can be made that the term should be abandoned. Endoscopically visible dysplasia in colitis may have a varied macroscopic appearance (Figures 1 and 2). A lesion’s morphology is best described by the standardized terminology of the Paris classification, either in shorthand (eg, 0–IIa) or long-hand form (eg, flat, minimally elevated lesion), although some irregular or ill-defined lesions may not be categorized easily. A clear endoscopic description of morphology, pit pattern, whether the lesion is well...
circumscribed, and whether there is background inflammation is preferable. Together with photographs or videos, this permits more objective discussion of optimal lesion management.

Some lesions look identical to conventional sporadic adenomas except that they occur in colitic mucosa, and readily are treated as such. Nevertheless, one should consider if the patient is within the usual adenoma-bearing age range (eg, $45^\circ$ y), because in younger colitic patients, the notion that the colitis has potentiated adenoma development should be considered. If there is a suspicion that the patient has a family history of Lynch syndrome, immunohistochemistry on the polyp may show loss of the appropriate protein in about 70% to 80% of larger polyps.\textsuperscript{45,46} This is best confirmed by performing immunohistochemistry on a tissue block from a CRC of a first-degree relative.

However, the principal determinant of appropriate management remains whether a lesion is endoscopically resectable, as described later.

Dysplasia is not a single spectrum of changes: there are multiple pathways that may intermingle. One alternative pathway is serrated dysplasia,\textsuperscript{47,48} which increasingly has become recognized with greater awareness of serrated lesions in the past decade. The lesions typically mature at the surface, although conventional dysplasia may do so as well. Some prefer to call these changes “indefinite for dysplasia,” following a suggestion originally made in the interpretation of Barrett’s esophagus.\textsuperscript{49} However, the lack of reproducibility between pathologists in that study was such that indefinite for dysplasia was combined with LGD for management purposes. Some diagnoses of LGD are rock solid, primarily because they so closely resemble large-bowel adenomas that there is virtually no interobserver disagreement. Nevertheless, both also can extend to the surface and there also may be overt junctions between dysplastic and adjacent nondysplastic mucosa, a feature that usually denotes that one of them is neoplastic.

Some variants of dysplasia are overtly villous, sometimes with LGD limited to the crypt base, these should be treated with caution because they have a tendency to be accompanied by underlying invasive CRC, frequently with a colloid component.\textsuperscript{50} Some histologic features such as dystrophic goblet cells resembling in situ signet ring cells, or the changes seen grossly and histologically in Figure 3, rarely are seen in sporadic changes but are quite common in colitis.

It should be recognized that CRCs still occur in which the architecture and nuclei are virtually normal, and therefore may be unable to be diagnosed (Figure 4). Although these tubuloglandular carcinomas tend to be low grade, and therefore may not metastasize, they can invade extensively. They remain one of the limiting factors in using surveillance to prevent colitic carcinomas of the large bowel. Those arising in the small bowel in Crohn’s disease or in fistulous tracts may elude detection until they present with symptoms unresponsive to usual therapies. Some carcinomas may have a completely abnormal aberrant crypt pattern of dysplastic crypts that is not seen in adenomas and may be very low grade cytologically. This little-recognized variant is invariably the superficial part of an invasive CRC (Figure 3D). Although not used commonly in the colon, endoscopic ultrasound may aid in vivo assessment of such lesions and help determine appropriate management.

Figure 3. Typical colitic carcinoma of the tubuloglandular type. (A) Superficial villous mucosa with underlying invasion and numerous mucin pools. (B) Detail of carcinoma with mucin pool containing very small bland nuclei identical to those in panel D. (C) Detail of nodule in panel A that could have been biopsied. Note crypts meandering in all directions. (D) Detail of panel C shows very low-grade nuclei; the diagnosis of carcinoma is easy to miss. The architectural features with aberrant crypts in a pattern not seen in adenomas is the only suspicion of an underlying invasive component.
Endoscopic analysis of the pit pattern of a lesion can help discriminate neoplastic from non-neoplastic lesions in vivo with high sensitivity and specificity, and high intra-observer and interobserver agreement. Pit pattern characterization requires training and experience. Moreover, in colitic mucosa these lesions do not always conform and dysplasia even can be found occasionally in otherwise unremarkable inflammatory polyps (sometimes also called pseudopolyps, although there is nothing pseudo about them). Conversely, sometimes a nondysplastic inflammatory polyp may show pit pattern IV (adenoma-like) features. However, these exceptions are sufficiently rare, and inflammatory polyps are so common, that unless there is an overtly dysplastic pit pattern it is advisable only to biopsy or remove inflammatory polyps with atypical features or a neoplastic pit pattern.

Confocal laser endomicroscopy also appears to be an accurate means to determine whether a detected lesion is neoplastic or non-neoplastic, and also can determine the amount of inflammation in the lamina propria. Confocal laser endomicroscopy also appears to be an accurate means to determine whether a detected lesion is neoplastic or non-neoplastic, and also can determine the amount of inflammation in the lamina propria.8,52

Colitis polyposa, in which myriad inflammatory polyps adorn segments of the large bowel often with mucosal bridges, may preclude effective screening and can harbor invasive adenocarcinoma, especially of the tubuloglandular variety. The threshold for surgical resection therefore should be low and this should be discussed with the patient.

**Dysplasia Management**

**Endoscopic Management**

The increasing ability to remove dysplastic lesions endoscopically has changed the management of dysplasia in colitis. Management of endoscopically visible dysplastic lesions within colitic mucosa is best determined by endoscopic resectability: if the lesion is well circumscribed and can be removed fully, it is usually not necessary to recommend surgery even for HGD.

Endotherapy in a colitic colon can be challenging: the mucosa often is friable and active inflammation, ulceration, and scarring all can prevent adequate submucosal lift. Endotherapy therefore should be performed only by colonoscopists who are trained and experienced in advanced endotherapy. Where there is concern that a lesion may be malignant, it is preferable to use an en bloc resection technique because this aids histologic interpretation regarding completeness of excision. Suspicious lesions should be tattooed to permit easy site identification during subsequent procedures. If the lesion is distal this also can be performed using a transanal surgical approach.

After endoscopic resection, biopsy specimens should be taken from the surrounding mucosa to ensure there is no residual neoplasia, unless endoscopic mucosal resection has extended into normal mucosa so that the adequacy of excision can be assessed histologically (Figure 5). However, in the era of high-definition endoscopes, particularly using CE or digital enhancement, it is rare not to be able to delineate the lateral margin of a lesion after careful inspection, although underlying inflammation may make this more challenging.

After piecemeal endoscopic excision of well-circumscribed colitis-associated dysplasia, and after excluding synchronous dysplastic lesions, the site of resection should be rechecked at approximately 3 months, at which time the polypectomy scar should be identified, photographed, and biopsied. This also provides the endoscopists with a further opportunity to ensure that there are no synchronous lesions. Thereafter, annual surveillance for the next 5 years is recommended.28

**Surgical Management**

Although most lesions can be managed endoscopically, surgical resection may be required in the following circumstances. First, in endoscopically unresectable lesions, for example, if a lesion does not lift after submucosal injection. Although this may be secondary to underlying submucosal fibrosis, it also may indicate the presence of an underlying invasive CRC. Encountering mucin pools invariably indicates underlying colloid carcinoma. Second, if dysplasia is found in colitis polyposa, a forest of inflammatory polyps that can harbor an underlying CRC, especially the tubuloglandular type. Third, if HGD is found without an associated endoscopically visible lesion. Fourth, if risk factors indicate that the patient’s lifetime risk of CRC is very high, for example, a young patient with primary sclerosing cholangitis and multifocal dysplasia.

In an era in which lesions can be removed endoscopically and surveillance continued, one can question when local surgical excision may become a viable option...
as opposed to total colectomy in patients with quiescent disease. The notion that patients develop acute flares in the residual mucosa after resection may not be evidence-based. The observation that endotherapy does not appear to trigger colitis flare-ups also suggests that local resection sometimes may be reasonable.

When planning for surgery, a particular problem arises if the dysplastic biopsy is in a container simply labeled "rectum," as if a pouch is performed, inevitably 1 or 2 cm of rectal cuff remains in the patient. Presurgical re-examination of the rectum, specifically taking carefully labeled circumferential biopsy specimens in the 2 or 3 cm above the dentate line, can help reduce the risk of leaving dysplasia in the rectal cuff mucosa.

**Current and Future Challenges**

Whenever colitis surveillance is performed, it should be performed to a high standard, incorporating outstanding bowel preparation, routine use of CE, and careful description and documentation of areas of dysplasia, which can be resected endoscopically or biopsied and tattooed if they cannot be removed.

There are numerous reasons why this may not be standard practice in many centers. This may relate to billing practices for CE: in some regions there may be no billing code. Other considerations may include the initial outlay on high-resolution endoscopes or an unwillingness to learn the technique. Teaching CE should become standard during gastrointestinal fellowship training, but many teaching institutions may lack the necessary expertise.

Increasingly at least one person in each practice group should have the expertise to use these techniques: if surveillance is to be performed, it should be performed well. If these techniques cannot be used in an institution, consideration should be given to referring patients to clinics that can; otherwise the patient should be informed that a suboptimal technique is being used.

The role of molecular pathology remains unclear. There are no molecular pathways that are seen specifically in colitic mucosa; rather, they use conventional pathways: aneuploidy and the wnt signaling pathway or microsatellite stability. The latter is usually part of hypermethylation of gene promoter regions, resulting in their silencing, especially those associated with DNA repair, or mutations in commonly affected genes such as TP53. However, the notion that there still may be focal, multifocal, or field changes at the molecular level that can be detected readily with next-generation and whole-gene sequencing remains possible. It is quite feasible to look for these: for example, a study comparing a patient’s normal DNA with that found in an endoscopically resected lesion, and then determining if those changes are present more diffusely throughout the mucosa. Although finding these abnormalities might not be grounds for colectomy, they could identify patients at increased risk of developing more lesions.

Another potentially attractive future technology is stool DNA testing for colorectal neoplasia. If corroborated by further studies, this may prove an attractive noninvasive test, permitting extension of colonoscopic surveillance intervals or even replacing surveillance as the first-line screening tool.
Conclusions

There have been 2 paradigm shifts in colitis surveillance in the past decade: better recognition of dysplastic lesions using CE and endoscopic resection of colitis-associated dysplasia.

Colitis surveillance is the most challenging diagnostic colonoscopic procedure and should be performed by an experienced and appropriately trained colonoscopist who understands the complexity of dysplasia detection, the techniques to maximize dysplasia yield, and the management of the lesions detected. CE is the current gold standard for colitis surveillance and patients should be offered this technique, which also precludes the need for numerous random biopsies. If CE is not available, quadratic random biopsy specimens from every 10 cm of colorectum should be taken, along with targeted biopsy specimens of any mucosal irregularities, but the patient should likely be informed that this is an inferior technique, and efforts should be made to ensure that each institution that performs surveillance can use these techniques.

Most colitis-associated dysplasia will be visible endoscopically and well circumscribed. Prompt endoscopic resection of such lesions usually is appropriate, taking care to ensure that no dysplasia is left in situ and that there are no synchronous lesions. Resection of lesions can be technically challenging because of inflammation or scarring, and should be deferred to experienced therapeutic colonoscopists.

References

25. Davies J, Burke D, Olliver JR, et al. Methylene blue but not indigo carmine causes DNA damage to colonicocytes in vitro and


