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PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Colorectal Dysplasia in Inflammatory Bowel Disease: A Clinicopathologic Perspective

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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.

Keywords: Colorectal Cancer; Surveillance; Dysplasia; Inflammatory Bowel Disease; Colonoscopy.

Patients with ulcerative or Crohn's colitis have an increased risk of colorectal cancer (CRC), which often develops more rapidly and earlier than sporadic carcinomas. Most specialist societies recommend colonoscopic surveillance to address this risk.

When dysplasia is detected, its management remains challenging for clinicians, pathologists, and patients alike. The gravity of the decision cannot be underestimated, weighing the risk of future (or synchronous) CRC after colonoscopic resection of dysplasia against the mortality and long-term morbidity of colectomy.

Here, we discuss the clinicopathologic diagnosis, prognosis, and management of colorectal dysplasia, drawing on the best available data from this challenging area of care.

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.[1] Before the reclassification of colitis-associated dysplasia in 1983,[2] it also was believed that dysplasia often occurred as a field effect.[3] 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

Abbreviations used in this paper: **AFI, autofluorescence imaging; ALM, adenoma-like mass; CE, chromoendoscopy; CI, confidence interval; CRC, colorectal cancer; DALM, dysplasia-associated lesions/masses; HD, high-definition; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NBI, narrow-band imaging; WLE, white-light endoscopy.**

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estimated that 33 biopsy specimens were required to have a 90% chance of finding the highest degree of dysplasia present.[4] However, this policy is poorly adhered to, costly, and time consuming.[5] 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 cm^2), 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,[6–15] 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 toward mucosal irregularities.

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.[16] A high-quality bowel preparation incorporating altered diet and split-dosing of bowel purgatives is important to improve mucosal visualization and thus dysplasia detection.[17] 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),[18] and lesion detection is more difficult. Studies in noncolitic patients have shown higher dysplasia yields with a slower inspection phase of examination.[17] In colitis surveillance, the retrospective study by Toruner et al[19] showed a significant association between longer procedure duration and increased dysplasia detection ($R^2 = 0.12$; $P = .0066$). Position shifts, particularly a supine position during transverse colon inspection, also may aid in lesion detection,[20] as may the routine use of intravenous hyoscine-N-butylbromide,[21] an antispasmodic, although not all studies have confirmed this.[22]

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.[23]

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[24] 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.[25] Whether this is of any clinical significance is unclear.

Pancolonic CE is currently the gold standard modality for colonoscopic 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.[6–8,11,14,26] A recent meta-analysis confirmed that CE is significantly better than WLE in detecting dysplasia in patients with colonic inflammatory bowel disease.[27] 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.[28]

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,[9] 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,[13] 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,[15] 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