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Endoscopic evaluation for colon cancer and dysplasia in patients with inflammatory bowel disease

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ABSTRACT

Certain patients with inflammatory bowel disease (IBD) have an increased risk of developing colorectal cancer, and surveillance is recommended to detect dysplasia and early neoplasia. Endoscopic techniques that screen large mucosal surface areas for potential areas of interest that have been studied in IBD surveillance include dye-based surface chromoendoscopy with methylene blue or indigo carmine, dye-less chromoendoscopy including narrow-band imaging, i-scan, Fujinon intelligent chromoendoscopy, and autofluorescence imaging. Literature to date supports the use of surface chromoendoscopy with either methylene blue or indigo carmine to maximize dysplasia detection. Characterization of detected lesions may be further enhanced with optical biopsy technology, including confocal laser endomicroscopy and endocystoscopy, that allows in vivo histologic diagnosis that may guide both diagnosis and therapy of detected dysplastic lesions. Current and future endoscopic approaches for optimizing screening and surveillance of colon cancer and dysplasia in patients with IBD are reviewed.

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1. Introduction

Inflammatory bowel disease (IBD) is associated with a 1.5-2 times increased risk of colorectal cancer (CRC) [1]. Multiple societies endorse surveillance colonoscopy in patients with ulcerative colitis (UC) proximal to the rectum or Crohn's disease involving more than one-third of the colon, in an attempt to detect dysplasia and early neoplasia [2-10]. Case-control and cohort studies have demonstrated that surveillance colonoscopy is associated with a decreased incidence of CRC and an increased CRC-associated 5-year survival rate [11-16]. Risk for CRC is greatest in patients with primary sclerosing cholangitis (PSC), increased disease extent, severity, and duration [17-22]. Herein we review current and potential future endoscopic approaches for optimizing screening and surveillance of colon cancer and dysplasia in patients with IBD.

2. Techniques for dysplasia detection

Surveillance should ideally be performed when in remission [9,10]. Excellent bowel preparation is required to identify subtle lesions [23]. “Red-flag” techniques are endoscopic techniques that screen large mucosal surface areas for potential “areas of interest” [24], and many modalities have been studied in IBD surveillance colonoscopy.

2.1. Standard-definition white light endoscopy

Historically, surveillance guidelines using standard white light endoscopy (WLE) endorsed a random biopsy protocol (4 biopsies obtained at every 10 cm intervals during withdrawal) [5]. The recommendation for random biopsies stemmed from the belief that dysplasia in IBD was often endoscopically invisible. In an attempt to determine whether flow cytometric measurement of DNA content in colonic biopsies could identify patients with UC at increased risk of progression to dysplasia, Rubin et al [25] determined the prevalence and distribution of DNA aneuploidy. High-risk patients without cancer or dysplasia were subsequently enrolled in a prospective surveillance study. In the specimen procurement protocol, samples of flat mucosa were taken from 4 quadrants at 10 cm intervals from the cecum to the anus. Based on the percentage of biopsies with abnormal histology, the authors estimated that if dysplasia is present in 5% of the colonic mucosa, 33 biopsies are required for histologic detection of dysplasia with 90% confidence [25]. Multiple societies endorsed this 33 random biopsy protocol as the standard for IBD surveillance [3,5,26].

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Subsequent studies have demonstrated that most dysplasia is endoscopically visible, and there is a low yield of random biopsies as compared to targeted biopsies [27-30]. A single-center experience of 1010 surveillance colonoscopies in 475 patients with UC during a 10-year period found that 94% of neoplastic lesions were macroscopically visible, with only a 0.2% yield from random biopsy. Random biopsies from normal-appearing colon (no endoscopic features of prior severe inflammation) yielded no dysplasia [30]. Lesion detection is further enhanced with the use of image-enhanced endoscopy (IEE) [27-30]. Several but not all national and international consensus guidelines endorse the use of IEE over standard WLE, with the European Crohn's and Colitis Organization stating that random biopsy is an inferior method of dysplasia detection [6-10,31].

2.2. High-definition white light endoscopy

Standard-definition (SD) endoscopes have image resolutions of approximately 367,000 pixels [32]. High-definition (HD) endoscopes display image resolutions that range from 850,000 pixels to more than 1 million pixels [32]. The higher pixel density and faster line scanning on the monitor produce sharper images [33]. One retrospective observational study of HD ($N = 209$) vs SD ($N = 160$) found that the adjusted prevalence ratio of detecting any dysplastic lesion was 2.21 (95% CI: 1.1-4.5) in the HD group as compared to the SD group [34]. HD endoscopy is recommended rather than SD endoscopy to maximize dysplasia detection [8].

2.3. Magnification

Magnification refers to the ability to optically zoom or magnify images 150-fold, without affecting pixel density [33,35]. Magnification endoscopy, coupled with other endoscopic modalities, can aid in the characterization of detected lesions. Further discussion of the role of magnification endoscopy in the endoscopic evaluation of dysplasia will be detailed in later sections.

2.4. Chromoendoscopy

Chromoendoscopy (CE) refers to enhanced imaging techniques that highlight mucosal architectural abnormalities and submucosal vascular patterns. CE can involve the topical application of dyes (dye-based CE) or use optical or virtual enhancement tools (dye-less CE) [36].

2.4.1. Dye-based CE

Dilute indigo carmine (IC) (0.03%-0.5%) or methylene blue (MB) (0.04%-0.2%) is sprayed via a spray catheter or through the water-jet channel using an automated pump during dye-based CE [8-10,37,38]. Indigo carmine is a contrast agent, whereas MB is an absorptive agent that is variably absorbed or unabsorbed by inflamed or dysplastic mucosa [39]. The colonic mucosa is sprayed on withdrawal either segmentally or every 30 cm, and excess fluid is aspirated [10]. Surface chromoendoscopy highlights the topography of the colonic mucosa [39], aiding in the detection of subtle lesions that might have been missed with WLE alone [38] (Figure). Several organizations have recommended surface chromoendoscopy with IC or MB as the preferred surveillance technique for maximizing dysplasia detection during IBD colonoscopy [7,9,10,31,40] with a 2-3-fold increase in per-patient dysplasia detection and 4-5-fold increase in per-lesion dysplasia detection [10]. A meta-analysis of 8 trials (2 randomized controlled trials, 4 prospective tandem studies, and 2 retrospective studies) demonstrated a significant increase in dysplasia detection with chromoendoscopy compared to standard WLE (relative risk = 1.8, 95% CI: 1.2-2.6]) and an absolute risk increase of 6% (95% CI: 3%-9%) [8]. CE is the recommended technique when compared to standard WLE [8].

There are few studies comparing CE to HD WLE. A prospective, tandem study of the implementation of CE with IC into practice using HD colonoscopes demonstrated an increased yield of CE (21%) vs HD WLE (9%), resulting in a relative increase in yield of 129% per patient, $P = 0.007$ [41]. The increased yield was greatest for the detection of flat lesions: 1 flat lesion was detected with HD WLE vs 7 with CE, resulting in a relative increase in yield of 700% ($P < 0.001$) [41]. Preliminary results from a randomized trial of HD CE (50 patients) compared to HD WLE (53 patients) found a total of 14 dysplastic lesions (1 with high-grade and 13 with low-grade dysplasia) in 11 patients (22%) in the HD CE and 6 dysplastic lesions (all low-grade dysplasia) in 5 patients (9.4%) in the HD WLE arm. HD CE was significantly better ($P = 0.04$) than HD WLE on a per-patient basis for the detection of endoscopically visible dysplastic lesions [42]. As we await more high-quality studies comparing CE to HD WLE, during HD colonoscopy, CE is the suggested technique to maximize dysplasia detection [8].

The technique of CE has previously been described [37,38]. SURFACE guidelines have been proposed to aid in standardization of the technique [43]. Picco et al [41] demonstrated that CE can be successfully implemented into practice after a short training session using images from a teaching file and general instruction on the IC CE technique. Physicians with no prior experience in CE UC surveillance demonstrated a high yield using CE with acceptable withdrawal times (withdrawal time stabilized at a median of 19 minutes after more than 15 procedures had been performed) [41]. In a meta-analysis, CE appears to increase procedure time by 11 minutes compared to WLE [44].

Magnification endoscopy can help characterize lesions detected by CE by differentiating neoplastic from nonneoplastic lesions. Routine application of Kudo pit patterns may not be applicable in colitis, as regenerative mucosa can have pit patterns that become elongated and irregular [45] and can resemble Kudo type IV pit patterns without harboring dysplasia [46]. However, in a study by Hata et al [46], no neoplasia was seen in lesions with type I or II pit patterns. Nishyama et al [47] demonstrated that in neoplastic lesions pit density was greater (89% vs 60%) and pit margins more frequently irregular (63% vs 33%) when compared to nonneoplastic lesions. Larger prospective studies are needed to validate these findings.

Despite the endorsement by multiple societies and international consensus groups, adoption of CE as the standard for surveillance has been slow. Some critics call into question the natural history of CE-detected lesions, stating that the goal of surveillance should be to prevent life-threatening colon cancer [48]. The longitudinal experience with standard WLE vs CE supports CE as tool for cancer prevention. Over a 5-year period from 2006-2011, with a median of 27.8 months of follow-up for the cohort, Marion et al [49] found that CE was superior to targeted WLE (odds ratio = 2.4, 95% CI: 1.4-4.0) for dysplasia detection, and that a negative CE surveillance colonoscopy was the best indicator for a dysplasia-free outcome. In addition, Choi et al [16] recently demonstrated in their St. Mark's Hospital cohort of 1375 patients undergoing 8650 colonoscopies, 1098 of which were performed with CE, that there was a 2-fold higher neoplasia detection rate in the CE group ($n = 92/1098$, 8.4%) compared to the WLE endoscopy group ($n = 175/4,373$, 4.0%; $P < 0.001$). The incidence rate of CRC in patients with at least 1 CE surveillance colonoscopy was significantly lower (2.2 per 1000 patient-years) than in those who never had a CE examination (4.6 per 1000 patient-years; $P = 0.02$). Although not significantly different, there was also a trend toward a lower postcolonoscopy CRC rate in the CE group (1.2 per 1000 patient-years) compared to WLE group (1.8 per

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