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Editorial: Clarity and Caution in the Natural History of Low-Grade Dysplasia in Ulcerative Colitis

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Abstract

A substantial body of evidence supports the safety of conservative endoscopic polypectomy for discrete, adenomatous-appearing, colonic polyps in patients with ulcerative colitis. Much less is known about the clinicopathologic factors of low-grade dysplastic lesions at risk for subsequent high-grade dysplasia or colorectal cancer. In this issue of the *American Journal of Gastroenterology*, Choi and colleagues examine the outcome of patients with low-grade dysplasia participating in a surveillance cohort at St. Mark's Hospital, one of the oldest and largest programs of its kind. Long-term follow-up of many, well-phenotyped, low-grade dysplasia cases sheds new light, and raises new questions, on our ulcerative colitis surveillance practice.

In population-based studies, patients with ulcerative colitis (UC) are at increased risk for colorectal cancer (CRC).(1) A recent analysis of almost 7,000 patients with inflammatory bowel disease (IBD) evaluated at two referral centers in Boston showed that having a colonoscopy within the past 3 years was associated with a 35% reduction in CRC risk and a 66% reduction in mortality in IBD patients, even after controlling for other factors.(2) Some of this mortality benefit may be attributable to earlier stage CRC diagnosis in patients participating in a regular colonoscopic surveillance program.(3) Surveillance endoscopy in UC patients aims to identify early cancer and pre-malignant dysplasia, and then select an optimal treatment or prevention strategy.(4)

Recent decades have seen considerable evolution in the management of patients with dysplasia, particularly those of low histologic grade. Given observations of wide heterogeneity in malignant potential among patients with low-grade dysplasia (LGD), considerable study has been devoted to better risk-stratify patients and their lesions in order to recommend either surgery or endoscopic treatment with heightened surveillance.(4) It is increasingly apparent that CRC risk is low after endoscopic therapy for discrete, adenoma-like, polypoid lesions, even when occurring in a background of chronic colitis.(5) A minority will go on to develop high-grade dysplasia (HGD) or CRC, but we know much less about factors which might predict those outcomes.

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We can begin to address this gap with an article in this issue of the *American Journal of Gastroenterology*.⁽⁶⁾ Choi and colleagues studied clinical and pathologic features of patients at index diagnosis of LGD at the St. Mark's Hospital, a large tertiary center in the United Kingdom. This is one of the largest and longest-running surveillance cohorts of UC patients, permitting accrual of a large number of LGD cases; from 1993 to 2012, there were 172 individuals eligible for analysis.⁽⁶⁾ After a median follow-up of 48 months, 33 patients were subsequently diagnosed with CRC (n=20) or HGD (n=13). The impressive number of LGD cases and subsequent events allowed for adequately powered proportional hazards models, which were constructed from a comprehensive list of suspected clinical risk factors. Among these, the authors carefully annotated the characteristics of the index LGD lesions, including endoscopic phenotyping according to the Paris classification scheme. This latter aspect adds greatly to the generalizability of the study findings.

Multivariate analysis revealed four characteristics of LGD which were significantly associated with later diagnosis of HGD or CRC. Non-polypoid lesion appearance, defined as Paris type 0-II (visible, slightly elevated or depressed), type 0-III (excavated), or plaque-like, was the strongest factor (hazard ratio [HR] 8.6; 95% confidence interval [CI], 3 – 24.8), but macroscopically invisible dysplasia (HR, 4.1; 95% CI, 1.3 – 13.4), lesion size ≥ 1 cm (HR, 3.8; 95% CI, 1.5 – 13.4), and previous history of indefinite dysplasia (HR, 2.8; 95% CI, 1.2 – 6.5) were also significant predictors. There was also strong positive correlation between the number of these risk factors present and a subsequent HGD or CRC diagnosis. The strongest risk factor, non-polypoid dysplasia, appears to have been found at significantly greater frequency in those patients who underwent chromoendoscopy rather than a white light colonoscopy (15.8 % vs 7.8%, respectively), although exposure to chromoendoscopy did not lower the risk of HGD or CRC after Bonferroni correction for multiple testing. During the study period, white light colonoscopy was performed with both standard- and high-definition instruments.

Overall, the results support current surveillance guidelines and propose tighter definitions on which lesion characteristics should be considered at highest risk. However, there are several important limitations to the study which should be considered. First, the primary study results included all HGD and CRC events in all patients, including those who went to immediate surgery. Those events found at the time of immediate colectomy, and arguably up to a year after study inclusion, should be considered *prevalent* HGD and CRC, either missed or under-diagnosed as LGD. The cumulative incidence of subsequent HGD or CRC is therefore better represented in the Supplemental Materials (Table S2 and Figure S1), where those who went to immediate surgery were excluded. LGD lesions which were non-polypoid, large or preceded by indefinite dysplasia were still significantly associated with subsequent HGD or CRC, but results for invisible dysplasia were not reported.

The study also relied on the clinical diagnosis of LGD as the index event for the start of the study follow-up period; the histopathology of these lesions was not re-reviewed for research purposes. The authors appropriately remind us that inter-observer agreement on dysplasia diagnosis may be poor, even among experts.⁽⁷⁾ While the magnitude of the present study's findings argue against under-diagnosis of LGD at study inclusion, the lack of a dedicated review calls into question the accuracy of indefinite dysplasia history prior to study entry

and undermines the validity of indefinite dysplasia as an independent predictor of subsequent HGD or CRC.

Taken together with another recent paper in the *American Journal of Gastroenterology*,⁽³⁾ the St. Mark's surveillance cohort experience is generating new questions which provide important directions for future research. These data show that while CRC rates may be decreasing, surveillance colonoscopy appears to be identifying incident CRC at increasingly earlier stages in association with improved CRC survival. Over the same time, colectomy rates for dysplasia have decreased, likely as a result of greater endoscopic management for low-risk lesions. We now must ask ourselves how to build on these apparent gains; how can we further optimize surveillance in UC to safely reduce surgery rates and minimize interval cancers? The risk factors identified in the present study (invisibility, large size and non-polypoid appearance) are collectively hallmarks of colonic neoplasia which either cannot be endoscopically resected or which might be incompletely treated.⁽⁸⁾ It is hoped that chromoendoscopy might improve detection of lesions which can be endoscopically managed while avoiding unnecessary surgery from over-diagnosis; however, we clearly lack effectiveness data on the endoscopic management of non-polypoid lesions, by any modality. (9) Worse, we lack comparative effectiveness data on modern surveillance tools themselves. Chromoendoscopy is clearly superior to *standard*-definition white light colonoscopy for the detection of LGD.⁽⁹⁾ Thus far, preliminary reports of two small, randomized controlled trials comparing high-definition white light colonoscopy to chromoendoscopy have yielded conflicting results.^(10,11)

As we wait for further data to advance this field, the present study can help us better care for our patients with UC. As endoscopists, we should be better prepared to carefully photo-document and measure potentially dysplastic lesions, even if we are confident in our ability to endoscopically treat them. In the clinic, we can better describe the risks and benefits of conservative endoscopic management and better counsel patients at the highest risk, who are undoubtedly disadvantaged by the considerable, yet competing fears posed by elective surgery and cancer.⁽¹²⁾

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