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Chromoendoscopy is better. So why am I not (yet) using it for routine IBD surveillance?

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Long-standing ulcerative colitis (UC) and colonic Crohn's disease (CD) are associated with increased risk of colorectal cancer (CRC) initially estimated at a prevalence of 18% at 30 years after diagnosis.[1] Though recent studies suggest a secular decline in incidence, those with extensive colitis and long-duration of disease remain at an elevated risk[2]. The temporal decline in IBD-related CRC may relate to improved control of inflammation through more effective therapies, but may also be in part due to surveillance programs that can identify dysplasia, leading to endoscopic or surgical treatment before progression to cancer. The most common approach for surveillance is random four-quadrant biopsies every 10 cm (a total of 32 biopsies), an option still endorsed by many clinical society guidelines. Yet this method is widely acknowledged to lack sensitivity as with even the recommended 32 biopsies (though fewer are frequently obtained in practice), the confidence in detecting dysplastic fields involving at least 5% of the surface of the colon is only 80% and to identify dysplastic fields involving 1%, a staggering 160 biopsies may be required[3]. Additionally, with recognition that most dysplasia is endoscopically visible[4], the balance of the scales is tipping away from the random biopsies leading to the question– what to replace it with?

With advances in endoscopic technology, interest turns to contrast-enhanced endoscopy to improve our ability to identify dysplasia. The most common technique, dye-spray chromoendoscopy (CE), involves spraying of indigo carmine or methylene blue dye sequentially in various segments of the colon, to facilitate identification of otherwise invisible flat or subtly raised lesions. This method has long been purported to be the gold-standard for identification of dysplastic lesions in IBD. In a prospective study of 115 IBD patients undergoing surveillance at the Mount Sinai Hospital in New York, Marion *et al.* reported a higher dysplasia detection rate with CE (16 low grade dysplasia (LGD), 1 high

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grade dysplasia (HGD)) than random biopsies with white light endoscopy (WLE) (3 LGD, p=0.001)[5]. Supporting data emerged from other cohorts[6] and summarized in a meta-analysis by Subramanian *et al.* that included six studies and 1277 patients, CE was associated with a 7% greater yield in detecting dysplasia and a 40% lower miss rate compared to WLE[7].

In this issue of *Clinical Gastroenterology and Hepatology*, two studies add to the evidence favoring CE as the most sensitive strategy in patients with long-standing IBD. Marion *et al.* present a follow up of their 2008 study of patients in an IBD surveillance program[8]. The present study included 68 (out of the original 115 patients) with a median disease duration of 21 years who were followed for a five year period from 2006 to 2011. All underwent colonoscopy with random biopsies, targeted WLE and dye-spray CE. After a mean of 3 endoscopies per patient, only 6 dysplastic lesions were detected by random biopsies, compared to 11 and 27 with targeted WLE and CE respectively with CE being superior to both random biopsies (Odds ratio(OR) 5.4, 95% confidence interval (CI) 2.9 – 9.9) and targeted WLE (OR 2.4, 95% CI 1.4 – 4.0). In the second study from the University of Calgary, Fort Gasia and colleagues describe a cohort of 454 IBD patients undergoing surveillance between 2011 and 2014[9]. Just over a quarter each of the patients underwent standard WLE with random biopsies or high definition (HD) colonoscopies with random biopsies; 14% underwent virtual chromoendoscopy while only a small fraction of patients underwent dye-spray CE with random (n=4) or targeted (n=24) biopsies. On follow-up, a total of 243 lesions (including sporadic adenomas and hyperplastic polyps) were detected. All four dysplastic lesions identified were visible on HD WLE and the single case of adenocarcinoma was detected as a visible lesion in a patient undergoing random biopsies for surveillance. No dysplasia was identified from random biopsies alone. In light of this mounting evidence, and with recommendations from the British Society of Gastroenterology[10], European Crohn's and Colitis organization[11], and the recently published SCENIC consensus guidelines[12] favoring chromoendoscopy as the preferred strategy for surveillance, why then has its uptake for routine surveillance of all IBD patients been slow? The answers to this question are manifold.

First, most studies demonstrating the superiority of CE over WLE used standard definition colonoscopies as the comparator. Their findings are in contrast to the Fort Gasia *et al.* study in this issue which found no difference in yield between dye CE, virtual CE, and targeted HD WLE in their cohort of 454 patients. In a large Dutch study by Mooiweer *et al.* that included 401 patients undergoing CE and 772 undergoing WLE, there was no difference in detection of dysplasia between the two groups (11% vs. 10%)[13]. A prior study utilizing narrow-band imaging also similarly found no difference in yield with CE compared to HD WLE[14]. Thus, it remains to be robustly demonstrated that CE with targeted biopsies is superior to a good quality HD WLE for surveillance in IBD. Second, the superiority of CE in the hands of expert endoscopists may not translate into a similar benefit in those performing fewer surveillance examinations or with inadequate training in the method. Indeed, for many emerging endoscopic technologies, there will likely be a learning curve and operator experience will play an important role in determining accuracy of the procedure. Thus, whether CE can be as effectively performed in the community setting as in a referral IBD center remains to be seen.

A third factor is that the natural history of dysplastic lesions identified using CE remains unknown. Superior endoscopic surveillance strategies will result in identification of lesions encompassing a smaller surface area and likely with a less aggressive natural history than those identified on standard definition WLE from which much of our understanding of the natural history of dysplasia in IBD is derived. In a study pooling data from 10 prospective studies and 1225 patients, among those with high grade and low-grade dysplastic lesions, 42% and 19% already had cancer at immediate colectomy[15]. However, these estimates cannot be automatically applied to those with dysplasia identified using HD WLE or CE. Before routinely adopting a test (in this case – CE), it is important to be able to accurately interpret the results of the test (i.e. finding a dysplastic lesion) to make an informed decision with the patient about surveillance or surgery. In both the index and follow-up studies by Marion *et al.*, no synchronous cancers were identified in patients undergoing colectomy for dysplasia identified on CE, further suggesting a less aggressive natural history of lesions identified using these exams.

A fourth, and practical factor, is the logistics associated with CE. Despite the absence of a demonstrable difference in duration of a good quality CE when compared to WLE with random biopsies, anecdotal experience suggests that unless the endoscopy unit including the nurses and the technicians are intimately familiar with the procedure, CE adds some (albeit small) additional time when compared to WLE, particularly if biopsies are obtained. In large IBD practices, this can add up to a significant additional time burden. The costs incurred by this additional time (and consequently lost additional procedures) as well as the equipment needed may also not be appropriately reimbursed. Furthermore, some patients are not candidates for CE because of inadequate bowel preparation or significant visible inflammation. Thus practical challenges also remain, albeit many that can be addressed through education and training of the providers concerned.

In summary, once we gastroenterologists are able to overcome our clinical inertia, it is increasingly clear that the strategy of random biopsies will be abandoned as the best surveillance strategy in patients with long-standing IBD. A few random biopsies may still be necessary to evaluate for histologic healing if this becomes a therapeutic endpoint in the future. In individuals who are very high risk or have prior dysplasia, CE with targeted biopsies should be preferred for routine surveillance. However, in the remaining majority of IBD patients, either HD WLE or dye-spray CE may be appropriate with little data available to show a clear choice between the two. Prospective studies comparing CE to HD WLE, defining the optimal interval between examinations, the natural history of lesions thus identified, as well as the long-term impact of such surveillance on CRC incidence and mortality is essential to accurately inform our practice.

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