

## Should Chromoendoscopy Be the Standard of Care in Ulcerative Colitis Dysplasia Surveillance?

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### G&H Why does ulcerative colitis lead to dysplastic precursor lesions?

**TU** It is not known exactly why or how ulcerative colitis (UC) can give rise to dysplasia and subsequently to carcinoma in a process that is faster than in sporadic colorectal cancer, but there is some evidence indicating potential mechanisms at play. Two studies have shown that increased inflammation is associated with this more accelerated pathway. Other known risk factors, which suggest possible mechanisms, include a family history of colorectal cancer (suggesting a genetic pathway), sclerosing cholangitis (suggesting a genetic, immune, or bile acid mediated pathway), and both duration and extent of disease. However, the precise molecular process linking inflammation and increased dysplasia is largely unknown.

### G&H What is the current standard of care regarding surveillance of UC dysplasia?

**TU** Typically, UC dysplasia surveillance focuses on patients with long-standing and extensive UC and Crohn's colitis, as well as people with colitis and primary sclerosing cholangitis, because these individuals are at the greatest risk for developing colorectal cancer. For approximately the past 20 years, the standard approach has been to examine these patients every 1–2 years, taking multiple—with studies and consensus statements suggesting a minimum of 32—nontargeted biopsies of the colon, scouting the area for the presence of any raised dysplastic lesions, and biopsying or removing them when they are found.

### G&H How did this approach develop?

**TU** The current practice was cobbled together in the absence of guidelines. Basically, endoscopists used the tool we had—the colonoscope—because that was what was available. We began monitoring patients with periodic white light colonoscopy, and because of the possibility of rapid evolution of dysplasia to cancer and studies showing an association between dysplasia and synchronous colorectal cancer in UC, we took nontargeted biopsies throughout the colorectum. Rubin and colleagues in Seattle showed that among a group of colectomy specimens, 33 biopsies per examination was the number of nontargeted biopsies required to exclude dysplasia with 90% confidence. While that threshold may not be reached in day-to-day practice, the Seattle group's finding made clear that more biopsies led to a higher yield of dysplasia detection. If colonoscopic dysplasia surveillance is to be effective in reducing morbidity and mortality from colorectal cancer, then dysplasia needs to be accurately detected so that the highest risk patients in the group can undergo a timely colectomy. It is worth noting that UC and Crohn's disease (CD) dysplasia was not always visible with older colonoscopic equipment, so conducting as many biopsies as possible helped ensure optimal patient outcomes. Even with today's equipment, there are still dysplastic lesions that are not visible with the naked eye using conventional white light endoscopy equipment, although studies have indicated that the majority of dysplasia detected is endoscopically visible in the modern video endoscopic era.

### G&H When did chromoendoscopy enter into UC dysplasia surveillance?

**TU** Because of the limitations of what could be seen with traditional colonoscopies emitting white light, adjunct techniques have been investigated in colitis and sporadic polyp surveillance practices that have the potential to enable endoscopists to better visualize the colorectal mucosa. It became apparent that adding an adjunct technique would enable us to identify more patients with dysplasia. The most common adjunctive technique is chromoendoscopy.

*(Continued on page 619)*

(Continued from page 616)

### G&H How does chromoendoscopy work?

**TU** Chromoendoscopy works by 1 of 2 methods. In one approach, methylene blue is sprayed onto the lining of the colorectum. The uptake of the dye is different for dysplastic (neoplastic) tissue than it is for colitic tissue. This difference enables the endoscopist to detect lesions that may be missed with standard white light techniques. Another technique uses indigo carmine, which details the spaces between colonic crypts, thereby enabling an endoscopist to distinguish dysplastic (neoplastic) tissue from ordinary colitis tissue. Both methods have been evaluated, and multiple studies have reported increased rates of dysplasia detection with these techniques, in the range of 2- to 4-fold higher than with traditional white light colonoscopy alone. The presumption ensuing from this finding is that the increased detection rate enables us to distinguish between higher risk and lower risk patients, and gives us the opportunity to effectively clear the colon of dysplasia by identifying and removing all dysplastic lesions, rather than leaving occult lesions behind to grow and progress to a more threatening process.

### G&H Is there evidence that the addition of chromoendoscopy benefits patients?

**TU** Unfortunately, there are no longitudinal data showing that chromoendoscopy actually lessens either the incidence of dysplasia on follow-up colonoscopy or cancer-related morbidity or mortality. For some endoscopists and gastroenterologists, the fact that the chromoendoscopic approach finds more lesions is sufficient evidence for its inclusion in standard UC dysplasia surveillance. Many would even suggest that if it can perform about as well as the standard approach while requiring fewer biopsies—thereby using fewer resources and lowering costs—then this would be sufficient reason for advocating its use, even in the absence of a morbidity or mortality benefit. This threshold has certainly been met because chromoendoscopy does find more dysplastic lesions per patient compared to standard white light colonoscopy, although follow-up data showing a reduction in the number of biopsies or the frequency of examinations remain lacking.

For some, the lack of evidence that adding chromoendoscopy to the standard of care reduces morbidity and mortality is troubling. Evidence from analogous studies indicates that simply having a better sieve or finding more patients with a particular feature, thereby increasing the diagnostic yield, does not necessarily change outcomes. Finding more dysplastic lesions therefore may not be the

appropriate measure for gauging the success of a surveillance method or shaping guidelines around it.

### G&H Could you give an example of a similar situation?

**TU** The advent of computed tomography (CT) scanning for the diagnosis and staging of lung cancer led to a phenomenon called stage migration. Because CT scans led to the identification of more lesions, patients who were previously considered to be one stage were moved to another stage, and this movement only occurred in one direction. The sickest of the early-stage patients were now characterized as having middle-stage lung cancer. Patients who were previously considered not yet early-stage were now moved into that category. As a result, the survival rates for each stage improved without actually changing the overall outcome for any given patient or a population of patients. This occurrence was dubbed “the Will Rogers phenomenon” in a 1985 paper in the *New England Journal of Medicine*. The fundamental problem is that survival outcomes end up seeming better without actually being better. In the case of chromoendoscopy for UC dysplasia surveillance, finding more lesions lowers the probability that dysplasia at any stage will lead to cancer—we may just be finding more of the less threatening dysplastic lesions. Chromoendoscopy might be improving outcomes, but it might not be—there simply are not any data clearly indicating the added value of this approach.

If chromoendoscopy or any other adjunctive technique is indeed beneficial, however, it could spare patients from colectomies by locating and removing more dysplastic lesions. The hope with this approach is that it could save colons and save lives. Chromoendoscopy could be an improved sieve for determining who is and is not at risk for cancer, but we do not yet have a study confirming this benefit.

### G&H What are potential problems associated with switching to chromoendoscopy alone?

**TU** First, finding more dysplasia could lead to removing more colons without improving cancer survival. Also, if chromoendoscopy becomes the standard of care, training and development will be necessary. Not all healthcare teams caring for patients with UC will be able to integrate chromoendoscopy as the standard of care into their practice. While this approach does not require much training, not all endoscopists and clinicians are prepared to acquire the new skill. Therefore, if chromoendoscopy does become the standard of care, then many patients will be at risk for not receiving it.

(Continued on page 634)

(Advances in IBD, continued from page 619)

**G&H** Are there newer technologies that could supersede both colonoscopy and chromoendoscopy?

**TU** Technology so often outpaces our ability to interpret its value, and that could be the case with chromoendoscopy as it stands in 2010. Confocal endomicroscopy is a new technique that offers more visual value than either chromoendoscopy or colonoscopy. The approach offers endoscopists the potential to perform in situ pathology that can accurately locate the edges of lesions, thereby leading to the removal of abnormal tissue. However, this is an operator-dependent and labor-intensive technique, and it is subject to some of the same limitations that we currently find with chromoendoscopy vis-à-vis lack of follow-up data, issues of training, practicality, and others. Nevertheless, some endoscopists are using this technique as an adjunct to chromoendoscopy, with the latter being used to find the lesions and the former used to better guide their removal.

Other new techniques include autofluorescence and narrow band imaging, both of which have been studied in several different settings. It remains too early to tell whether these methods will be useful for UC dysplasia surveillance.

**G&H** Is chromoendoscopy currently under consideration for inclusion in official guidelines?

**TU** Chromoendoscopy has already been incorporated as an option in the recently published American Gastroenterological Association guidelines for endoscopists experienced in the technique.

**Suggested Reading**

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