ENHANCED IMAGING TECHNOLOGIES IN DETECTING DYSPLASIA IN IBD: NARROWING OR WIDENING OUR OPTIONS?


It is well established that patients with long-standing inflammatory bowel disease (IBD) are at increased risk for dysplasia and colorectal cancer (Cancer 1992;70(Suppl 5):1313–1316; Gastroenterology 1991;100:1241). Detecting dysplasia can be a challenge in the setting of epithelial regeneration, inflammation, and pseudopolyps. The American Gastroenterological Association (AGA) 2010 position statement recommended extensive biopsies of all anatomic segments of colorectal mucosa under standard white light endoscopy (WLE; Gastroenterology 2010;138:738–745). However, there is a lack of prospective studies supporting this practice, and this technique can be time consuming. Because of some of these challenges, new technologies such as chroendoendoscopy (CE) and narrow band imaging (NBI) to improve detection of premalignant lesions have been developed for use in IBD patients. Despite growing evidence supporting the ability of CE to detect dysplasia more accurately than conventional WLE, the training, time, and expense associated with this technique remain formidable challenges to its wide adoption. New technologies such as NBI are attempting to overcome some of these limitations while improving dysplasia detection. One previous randomized trial failed to show the ability of NBI to detect dysplasia over WLE. Furthermore, this study was underpowered and used first-generation NBI (Endoscopy 2007;39:216–221).

The authors of this study conducted a prospective, randomized, crossover study comparing newer generation NBI with CE for early detection of intraepithelial neoplasia (IN) in patients with long-standing colonic IBD. Patients were enrolled from an outpatient academic gastroenterology clinic in Barcelona, Spain, between April 2006 and November 2007. Eligibility criteria included clinically inactive, long-standing ulcerative colitis >8 years involving at least the left colon, or colonic Crohn’s disease affecting at least one third of the colon (>8 years). Exclusion criteria included poor or moderate bowel preparation, endoscopically active disease, prior colorectal cancer, history of surgical resection of any part of the colon, coagulopathy, indigo carmine allergy, or inability to consent. After inclusion and exclusion criteria were met, a total of 60 patients remained part of the final analysis. All patients underwent both high resolution NBI and high resolution CE (with indigo carmine) within 3–8 weeks. All expert endoscopists were blinded to endoscopic and histologic findings obtained during the first procedure. CE was the first procedure performed in 27 patients and NBI was the first procedure performed in 33 patients. Baseline characteristics were similar between both groups except for a slightly greater number of male patients in the group undergoing NBI first.

With each technique, targeted biopsies of colonic lesions were taken. A blinded GI pathologist assessed lesions histologically and all lesions that were low-grade dysplasia, high-grade dysplasia, or carcinoma were collectively classified as IN. For any dysplastic lesions, a second pathologist reviewed these biopsies. If there was a disagreement among the pathologists, a consensus opinion was reached. The primary outcomes of this study were the number of false positives, defined as biopsied lesions whose histology was not consistent with IN, and true positives, defined as biopsied lesions whose histology was actually IN. Lesions were sampled immediately after detection; therefore, only missed lesions and unresected lesions on second examination could be detected (precluding paired analyses of all lesions). The authors also compared the “miss rates” for NBI and CE colonoscopy. The miss rate was defined as the number of IN lesions...
found on the second examination divided by the total number of IN lesions seen on both examinations.

Thirteen patients (21.7%) had ≥1 IN lesion in 1 of 2 explorations. Those patient with pancolitis and those treated with oral mesalamine had a higher percentage of IN, although the number of patients in this study was too small to make conclusions based on these findings. When comparing the paired endoscopic findings of CE and NBI in the 60 patients who completed the study, on a per-patient analysis, there were no differences in the number of patients with suspicious lesions identified (52 in the CE vs 47 in the NBI group; \( P = .17 \)), true-positive IN lesions (11 in the CE vs 12 in the NBI group; \( P = .43 \)), or false-positive IN lesions (41 in the CE vs 35 in the NBI group; \( P = .49 \)). Although there was a greater number of suspicious lesions seen with CE (208 in the CE vs 136 in the NBI group; \( P = .001 \)), the true-positive rate for IN was similar for both techniques. The majority of the suspicious lesions seen under CE were hyperplastic polyps. CE had a higher false-positive rate compared with NBI, but this was largely because of the much higher number of suspicious lesions that were identified on CE; the percentage of false positives between CE and NBI was similar (94% vs 93%).

Additionally, of the 13 patients who had IN detected by 1 of the techniques, 3 additional lesions were with NBI after CE, including 1 new patient with IN. For those patients who underwent NBI first, CE detected 5 additional lesions, including an IN in 4 new patients who were missed by NBI. However, when comparing CE and NBI miss rates, there were no differences in the per-lesion or per-patient analyses. The miss rates calculated by the authors fail to account for the fact that 2 large lesions in 2 patients seen on NBI initially (not resected at the time), were subsequently seen on CE leading to a falsely high NBI miss rate. The mean withdrawal time was significantly longer with CE compared with NBI (27 ± 10 vs 16 ± 6 minutes). Although not recommending NBI as a standard, the authors concluded that NBI is less time consuming and an equally effective alternative to CE for the detection of IN for patients with long-standing IBD. All patients were subsequently followed for 2 years; none of these patients developed cancers or high-grade dysplastic lesions during this time. The authors conclude that NBI seems to be a less time-consuming and equally effective alternative to CE for the detection of IN; however, owing to the NBI lesion and patient miss rates, it cannot be recommended as the standard technique.

**Comment.** Several new technologies in recent years have become available to gastroenterologists to help differentiate normal, nondysplastic, and dysplastic tissue. In addition to standard and high-definition WLE, CE and NBI are 2 additional endoscopic tools that can aid in the detection of dysplastic lesions. NBI is a technique where ambient light of blue and green wavelengths enhances the detail of certain aspects of the mucosal surface. A special filter is activated by a push of a button on the endoscope. The peak light absorption of hemoglobin occurs at these wavelengths, which results in blood vessels appearing very dark, and thus improving the visibility and identification of premalignant or malignant lesions. CE utilizes stains such as indigo carmine or methylene blue, which provide contrast by permeating between irregularities in the mucosa to highlight irregularities (World Journal of Gastroenterology 2011;17:4271–4276). The 2010 AGA Medical Position Statement on the diagnosis and management of colorectal neoplasia in IBD does not specify a requisite number of biopsies for surveillance colonoscopy, but states that representative biopsies from each anatomic section of the colon should be taken. Because of evidence suggesting a higher sensitivity of CE in detecting dysplasia, the AGA recommends CE as an alternative to random extensive biopsies for trained practitioners (Gastroenterology 2010;138:738–745).

WLE with extensive random biopsies remains an acceptable method for colorectal cancer surveillance in IBD patients. Issues with this modality include expense (multiple pathology specimens), increased time, and lack of proper sampling of all mucosa with a chance of missed lesions. Although CE has a higher sensitivity of detecting dysplasia, it is time consuming, costly, and requires additional training. Potential advantages of NBI compared with CE include the ease of use, less expense, less cumbersome, and less training required. NBI has not been shown to be superior to WLE for detecting adenomas (Gastroenterology 2007;133:42–47; Gut 2008;57:1406–1412; Clin Gastroenterol Hepatol 2009;7:1049–1054), but has shown some promise in high-risk populations such as those with hereditary nonpolyposis colorectal cancer (Gut 2008;57:65–70).

There have been several studies comparing standard WLE with CE for colorectal cancer surveillance in long-standing IBD patients. In general, all of these have shown that CE is better at detecting dysplastic lesions compared with standard WLE (Gastroenterology 2003;124:880–888; Gut 2004;53:165–167; Endoscopy 2005;37:1186–1192). NBI as an alternative to CE has been investigated in several studies. Although NBI has shown promise in detecting specific types of esophageal lesions and dysplasia in high-risk populations, it has not been promising for identifying colonic adenomas in the general population (Gastrointest Endosc 2004;59:288–295). A recent meta-analysis evaluating seven prospective, randomized trials (2,936 patients) of NBI versus standard WLE showed no difference in the overall adenoma detection rate with the use of NBI (Gastrointest Endosc. 2012;75:604–611).

This study conducted by Pelliset al is the first prospective, randomized study that compares effectiveness of NBI with CE for IN detection in long-standing colonic IBD. I applaud the authors on the meticulous design of this project with careful attention to study design, including randomization and blinding. They should also be commended given that this is the first clinical trial that compares a commercially available endoscope with high-
resolution and NBI. The large number of patients enrolled also adds merit to the study results.

However, it is important to keep in mind some of the limitations of this study. First and foremost, the authors of this study make an overreaching conclusion in stating that NBI seems to be an equally effective alternative to CE. This study was not powered to detect such differences. Per their own power calculations, the study’s ability to detect any differences was quite low at 39%. The high miss rate with NBI, as pointed out by the authors, certainly makes NBI not advisable as the standard technique to detect dysplasia in patients with long-standing IBD. However, this was the first study to compare these techniques and subsequent investigators may use these data to help power future trials. Tandem design with documentation of lesions on first examination and intraprocedure unblinding on second examination may have allowed for a larger numbers of lesions to be studied; tandem design may also have higher acceptance rates in patients.

The authors provide a useful starting point in the investigation of newer NBI technologies as a possible tool for surveillance practices in IBD patients. Further investigation in the form of larger, appropriately powered studies to detect differences is warranted to fully understand the possible promise and limitations of NBI compared with CE. Although the data for CE seem promising, there are limitations, including the time and training required and the associated expense. Optical coherence tomography, confocal microscopy, and autofluorescence are additional endoscopic tools that should be evaluated in long-standing IBD patients (Gastroenterology 2004;127:706–713; Inflammatory Bowel Dis 2007;13:640–641). As is often the case with technology outpacing our ability to fully interpret its value, we may find that neither NBI nor CE fully penetrate our practices before being supplanted by other more beneficial tools.

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ASPIRIN AND CHEMOPREVENTION OF CANCER: REACHING BEYOND THE COLON


There is little disagreement that aspirin reduces the risk of colorectal neoplasia (Cancer Prev Res (Phila) 2012;5:164–178). Beyond compelling experimental data, the vast majority of cohort and case-control studies have observed inverse associations between aspirin use and colorectal cancer (CRC). Four placebo-controlled, randomized, controlled trials (RCTs) have shown that aspirin reduced the risk of colorectal adenomas among patients with a prior adenoma or CRC (J Natl Cancer Inst 2009;101:256–266). An RCT in patients with familial adenomatous polyposis found a trend of aspirin in protecting against adenoma development (Cancer Prev Res (Phila) 2011;4:655–665). Most recently, long-term results from the Colorectal Adenoma/Carcinoma Prevention Programme 2 RCT of aspirin in carriers of the Lynch syndrome demonstrated that aspirin significantly reduced CRC risk in a prespecified per-protocol analysis (hazard ratio, 0.41; 95% confidence interval, 0.19–0.86; P = .02) and in intention-to-treat analyses accounting for multiple primary CRCs in some individuals (incidence rate ratio, 0.56; 95% confidence interval, 0.32–0.99; P = .05; Lancet 2011;378:2081–2087).

Last, a recent pooled analysis of a long-term post-trial follow-up of nearly 14,000 patients from 4 randomized, cardiovascular disease prevention trials showed that daily aspirin treatment for about 5 years was associated with a 34% reduction in 20-year CRC mortality (Lancet 2010;376:1741–1750).

Although mechanistically it might be expected that aspirin’s chemopreventive effect on CRC should extend to adenocarcinomas of other body sites, convincing data in humans were lacking until Rothwell et al’s earlier pooled analysis of individual-level data from 8 randomized trials of cardiovascular prevention linked to cancer outcomes (Lancet 2011;377:31–41). Daily aspirin use, irrespective of dose, was associated with a 21% reduced risk of cancer death during the trials, with benefit only apparent after 5 years. A reduction in cancer mortality was also observed during post-trial follow-up to 20 years.

Rothwell et al have now extended these findings with analyses including an additional 43 randomized trials of daily aspirin of any treatment duration for the primary or secondary prevention of vascular disease (Lancet 2012;379:1602–1612). Aspirin (at any dose) significantly reduced risk of nonvascular death by 12% and of cancer death by 15%, with benefit accrued within 3 years for high doses (>300 mg/d) and after 5 years for low doses (<300 mg/d). Across several body sites, a lower risk of fatal and nonfatal cancers emerged after 3 years. In an analysis of 12 primary prevention trials, aspirin also reduced nonvascular death by 12%, but not vascular death, leading to a nonsignificant effect on all-cause mortality. Finally, in 6 primary prevention trials, low-dose aspirin reduced risk of incident cancer by 12%. In contrast, aspirin reduced the risk of major vascular events and increased risk of major extracranial bleeds, but only within the first 3 years of follow-up.

Comment. This study is an impressive tour-de-force. Through rigorous systematic reviews of RCTs of aspirin compared with controls in the Antithrombotic Trialists’ (ATT Collaboration) and detailed searches of the literature, the investigators managed to assemble nearly all available RCT data on aspirin in relation to cancer end-