Limited applicability of chromoendoscopy-guided confocal laser endomicroscopy as daily-practice surveillance strategy in Crohn's disease

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Background and Aims: Patients with longstanding ulcerative colitis have an increased risk for developing colorectal cancer (CRC). Although the risk for ulcerative colitis is well-established, for Crohn's disease data are contradictory. This study aimed to determine the number of patients with Crohn's disease with dysplasia who are undergoing surveillance and to assess the diagnostic accuracy of chromoendoscopy (CE) combined with integrated confocal laser endomicroscopy (iCLE) for differentiating dysplastic versus nondysplastic lesions.

Methods: Patients with longstanding Crohn's colitis undergoing surveillance colonoscopy were included in this multicenter, prospective, cohort study. Surveillance was performed with CE, and lesions were assessed with iCLE for differentiation. All lesions were removed and sent for pathology as the reference standard.

Results: Between 2010 and 2014, a total of 61 patients with Crohn's colitis were included in 5 centers. Seventy-two lesions, of which 7 were dysplastic, were detected in 6 patients (dysplasia detection rate 9.8%); none included high-grade dysplasia or cancer. Combined CE with iCLE for differentiating neoplastic from nonneoplastic lesions had accuracy of 86.7% (95% confidence interval [CI], 78.1-95.3), sensitivity of 42.9% (95% CI, 11.8-79.8), and specificity of 92.4% (95% CI, 80.9-97.6). For CE alone, this was 80.3% (95% CI, 70.7-89.9), 28.6% (95% CI, 5.1-69.7), and 86.4% (95% CI, 80.9-97.6). The study terminated early because of frequent failure of the endoscopic equipment.

Conclusions: This study shows a low incidence of dysplastic lesions found during surveillance colonoscopy in patients with longstanding extensive Crohn's colitis. The accuracy of both CE alone and CE in combination with iCLE was relatively good, although the sensitivity for both was poor. Because of frequent equipment failure, iCLE has limited applicability in daily practice as a surveillance strategy. (Gastrointest Endosc 2016;83:966-71.)

Longstanding ulcerative colitis (UC) increases a patient's risk of developing colorectal dysplasia and colorectal cancer (CRC). Although this risk is well established for UC, conflicting data exist regarding this risk with extensive colitis in patients with Crohn's disease (CD). The risk estimates in patients with CD differ considerably from no increase in CRC risk to a relative risk of up to 3.3 for developing CRC.[1-3]

A potential explanation for this heterogeneity in CRC risk might be selection bias. Previous studies analyzing

Abbreviations: CD, Crohn's disease; CE, chromoendoscopy; CLE, confocal laser endomicroscopy; CRC, colorectal cancer; IBD, inflammatory bowel disease; iCLE, integrated confocal laser endomicroscopy; UC, ulcerative colitis.

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CRC risk in patients with CD included patients with different disease extents. Studies including patients with CD and colitis showed, however, a significant increase in CRC risk.[2-3] Besides disease extent, several other risk factors, such as disease duration, family history of colon cancer, and concomitant primary sclerosing cholangitis, are known to increase the risk of developing dysplasia and cancer in patients with CD.[4-6]

Colonoscopic surveillance of patients with inflammatory bowel disease (IBD) is associated with early detection of premalignant lesions and subsequently to an improved prognosis.[7] Guidelines therefore recommend surveillance in patients with IBD.[8-10] It is known that dysplasia in patients with IBD can be subtle and flat and therefore more difficult to detect than dysplasia in an average-risk population.[11] In addition, postinflammatory mucosal changes such as scarring and inflammatory pseudopolyps further complicate detection of dysplasia in these patients.

Until recently, surveillance was performed by using white-light endoscopy with 4-quadrant biopsies every 10 cm. However, recent studies have proven that chromoendoscopy (CE) significantly increases lesion detection in IBD surveillance colonoscopies compared with white light endoscopy with quadrant-random biopsies every 10 centimeters.[12] Current guidelines recommend the use of CE in surveillance of patients with longstanding colitis.[8-10]

During CE, a dye spray (eg, methylene blue or indigo carmine) is used to highlight the mucosal surface and to enhance the delineation of (early) dysplastic lesions. Although CE improves detection, it has not yet been proven that CE improves differentiation. Even endoscopists with expertise in IBD show great interobserver variation in differentiating lesions found during IBD surveillance colonoscopy, reflecting the difficulty in distinguishing dysplastic from nondysplastic lesions.[13]

Confocal laser endomicroscopy (CLE) is an advanced imaging technique providing highly magnified images of GI epithelium comparable to histopathology. Because of visualization of a limited surface area, CLE is specifically used for differentiation, rather than for detection. CLE can be integrated into a colonoscope (Pentax, Tokyo, Japan) (integrated confocal laser endomicroscopy [iCLE]) or can be applied as a probe system that passes through the working channel of any endoscope (Mauna Kea Technologies, Paris, France). A recent meta-analysis showed that CLE has the highest accuracy of all commercially available imaging techniques in differentiation of neoplastic from nonneoplastic lesions in an average-risk population, although mainly by experts.[14]

The aim of this study was to determine the number of patients with dysplasia undergoing surveillance colonoscopy for longstanding extensive Crohn's colitis and to assess whether the combination of CE and iCLE improves differentiation of lesions found during surveillance colonoscopy.

METHODS

Patients

This study was performed in 5 academic medical centers. Patients with Crohn's colitis undergoing surveillance colonoscopy were included in the study if they were aged ≥18 years, diagnosed with >50 cm of colon disease, and if they were in clinical remission, based on the Simple Endoscopic Score for Crohn's Disease.[15] Patients were excluded if they had undergone colon resections with <50% of their colons in situ, incomplete colonoscopy because of poor bowel preparation, disease activity or stenosis, contraindications for iCLE (allergy for intravenous fluorescein, pregnancy or breastfeeding, severe cardiopulmonary disease, or pre-existent renal disease), or noncorrectable coagulopathy that precludes taking biopsy specimens. This study was approved by the medical ethics committees of all participating centers (NTR2293).

Endoscopic equipment

For CE and CLE, the endoscope-integrated system, iCLE (Pentax, Tokyo, Japan and Optiscan; Melbourne, Australia), was used. In this system, the confocal laser unit is integrated into the distal tip of a standard video endoscope, enabling iCLE imaging on a second monitor. The diameter of both the distal tip and the insertion tube is 12.8 mm. The iCLE imaging plane depth relative to the mucosal surface (ie, z-axis) can be controlled by using two buttons on the hand piece of the endoscope. During iCLE, a single-line laser beam with an excitation wavelength of 488 nm is delivered at the tissue. Confocal image data are collected at a scan rate of 0.8 frames per second. The CLE images have a lateral resolution of 0.7 μm. The field of view is 500 μm, and the range of the z-axis is 0 to 250 μm below the surface.

Endoscopic procedure

All patients were prepared with either 4 L of polyethylene glycol solution or 2 L of polyethylene glycol solution plus ascorbic acid (Moviprep or Kleanprep, Norgine, Netherlands). The procedures were performed with the patients under conscious sedation by using intravenous midazolam and fentanyl or propofol at the discretion of the endoscopist. At the discretion of the endoscopists, butylscopolamine was given intravenously to reduce colon motility. During withdrawal, the entire colon was stained with a 0.1% methylene blue solution. Bowel preparation was determined as good (100% mucosa visible), moderate (>90% mucosa visible), or poor (<90% mucosa, even after extensive cleaning). Each colon segment was scrutinized for the presence of suspicious areas, mucosal irregularities, unusual ulcers, and strictures. All detected lesions were classified according to the macroscopic classification (Paris Classification[16]) of early GI dysplasia, scored for size, location in the colon, and distance from the anus. All lesions were assessed for Kudo pit pattern.[17] The colon mucosa