Reliability and accuracy of the endoscopic appearance in the identification of aberrant crypt foci

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Background: Aberrant crypt foci (ACF) have emerged as a putative precursor to colorectal adenoma, with potential use as a biomarker of colorectal cancer. However, there are wide differences in ACF prevalence, dysplasia, and histologic confirmation rates across studies. These differences may, in part, be because of variability in identification of endoscopic criteria.

Objective: To systematically evaluate the accuracy and reliability of various endoscopic criteria used to identify ACF when using magnification chromoendoscopy (MCE).

Design: Images obtained via MCE were shown to participating endoscopists who diagnosed them as ACF or not and who assessed them for the endoscopic characteristics used to identify ACF in the literature.

Main Outcome Measurements: The predictive ability of the endoscopic criteria (crypt number, staining, margin, crypt size, epithelial thickness, and lumen shape) for histologic confirmation of ACF, and their reliability across endoscopists. The accuracy of the examiners in identifying ACF that were histologically confirmed was also assessed.

Results: The interrater agreement rate for all except one of the endoscopic criteria (crypt number) was low and did not improve with training. None of the criteria could significantly predict histologic confirmation of ACF. Despite training exercises, accuracy of endoscopists to correctly identify a histologically proven ACF remained low.

Limitations: Still images with ×40 optical magnification were analyzed rather than real-time endoscopy. All ACF samples were hyperplastic; none were dysplastic.

Conclusions: No endoscopic criteria evaluated by our study predicted histologic confirmation of ACF. MCE had low accuracy and poor reliability. (Gastrointest Endosc 2009;70:322-30.)

Aberrant crypt foci (ACF) have emerged over the last decade as putative precursors to colorectal adenoma. ACF were initially identified as the earliest recognizable lesions on the colonic mucosa of rodents exposed to colorectal carcinogens,[1,2] and animal studies showed ACF to be an important predictor of colorectal cancer development.[3,4] Shortly after the description in animals, ACF were discovered in pathologic specimens of human colonic mucosa.[5] More recently, ACF were identified in human colonic mucosa in vivo via magnification chromoendoscopy (MCE).[6,7]

Results of cross-sectional studies showed that the ACF prevalence and density are greater in patients with colorectal carcinoma and adenoma compared with normal controls,[7-10] which emphasizes the potential use of ACF as a biomarker of colorectal carcinoma. However, there is a significant variability in the criteria and methods used to identify and define ACF on endoscopy. The criterion used most commonly is darker staining[6-8,11] compared with the surrounding normal mucosa. Larger crypt size,[7,11] raised appearance,[6,9,11] thicker epithelial lining,[7] and dilated or slit-like crypt lumen[9] compared with the surrounding normal mucosa are other frequently used criteria. Methylene blue

Abbreviations: ACF, aberrant crypt foci; FSG, flexible sigmoidoscopy; MCE, magnification chromoendoscopy; PLCO, Prostate, Lung, Colon, and Ovarian.

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is the most commonly used dye for mucosal staining; however, indigo carmine has also been used.[8,10]

There is wide variability in the data reported from studies that used MCE.[1] For example, the prevalence of rectal ACF in patients with a normal colon on colonoscopy ranges from 15%[8] to 100%,[11] and the proportion of ACF having dysplastic changes in patients with sporadic colorectal carcinoma ranges from 0%[9] to 61%.[8] The rate of agreement between the endoscopic impression of the presence of an ACF and histologic confirmation is also variable, ranging from 53%[9] to 92%.[7] Because of these widely variable results, the ACF ancillary study of the Prostate, Lung, Colon and Ovarian (PLCO) Cancer Screening Trial was initiated. This large, multicenter study examined ACF prevalence and risk factors and ACF reproducibility across institutions, populations, and endoscopists.[12,13] In the PLCO study, 589 subjects at 4 clinical centers underwent a flexible sigmoidoscopy (FSG) by using high-magnification chromoendoscopy for ACF detection, at year 0 and year 1. During the main phase of the study, images of endoscopic ACF (some of them confirmed by histology and some not) were shown to 5 participating endoscopists, who were blinded to the endoscopic and histologic diagnosis. The interendoscopist agreement rate on whether the image represented ACF was poor (multirater kappa score of 0.2-0.3). The accuracy of the examiners to correctly identify an ACF, based on histology as the criterion standard, was 48% to 66%, and only 60% of ACF identified by endoscopy could be confirmed on histology.[13]

When considering the variability observed in the ACF literature and the levels of accuracy and interrater agreement seen in the PLCO ACF study, we hypothesized that the criteria used to identify ACF are somewhat unreliable across endoscopists and poorly predict histologic confirmation of an ACF. The aims of this study were (1) to identify endoscopic criteria that are the most predictive of histologic ACF and (2) to identify those criteria that are most reliable across endoscopists. We conducted 3 training exercises to standardize the assessment of endoscopic criteria, with the hope that this would improve interrater agreement and concordance of the endoscopic detection of ACF with histology, and then reassessed the reliability and accuracy of ACF detection across endoscopists.

Capsule Summary

What is already known on this topic

- Aberrant crypt foci are putative precursors to colorectal adenoma, but variability in their endoscopic detection may be hampering their use as biomarkers for colorectal cancer.

What this study adds to our knowledge

- The endoscopic criteria used to identify aberrant crypt foci, crypt number, staining, margin, crypt size, epithelial thickness, and lumen shape via magnification chromoendoscopy, are poorly reliable across endoscopists and did not accurately predict histologic confirmation of aberrant crypt foci.

MATERIALS AND METHODS

Population

Methods are presented in the flow diagram in Figure 1. Images were obtained from the PLCO cancer screening trial ancillary study of ACF.[12] Subjects at 4 centers (Georgetown University, Washington University, University of Pittsburgh, and Marshfield Clinic) were eligible if they had an adequate FSG screening examination at the baseline examination of the PLCO trial. All subjects were participants of the PLCO trial, a multicenter randomized clinical trial of cancer screening, which includes FSG.[14] Subjects with abnormal screening FSG results were referred to their personal physicians for evaluation of screen-detected abnormalities and were tracked to determine the results from a subsequent diagnostic workup, eg, colonoscopy. In the ACF study, subjects with advanced and nonadvanced adenoma, hyperplastic polyps, or negative sigmoidoscopy or colonoscopy examinations were included.

ACF examinations

Examiners underwent standardized training, and the ACF examination was performed under a defined protocol by using methylene blue dye (0.2%) and the Fujinon ES-410CE5 sigmoidoscope (Fujinon, Wayne, NJ).[12] The sigmoidoscope was equipped with an optical magnification of $\times 40$ (with an added $\times 80$ electronic magnification) and had a 450,000 charged coupled devices pixel density resolution. ACF in the rectum were assessed and, when detected, removed by biopsy, and the subjects returned in 1 year for a repeated examination. The endoscopic definition of ACF was this: a lesion with crypts larger in diameter than surrounding normal crypts, having thicker epithelium, which may be darker staining, and must be <2 mm raised. Not all criteria were required for identification of ACF. For this study, images, stripped of patient identifying and clinical information, were posted online, in JPEG format, for review.

Training and quality-control measures

All examiners took part in extensive training for the study, which included some examiners personally observing ACF examinations at the Sapporo Medical University School of Medicine in Japan. Before study initiation, a joint conference among examiners with a live demonstration of the ACF examination technique, review of the protocol, and ACF definition was conducted. In addition, a pilot phase was built into the study, which consisted of ACF examinations in 78 subjects, after which the study researchers met and reevaluated the study protocol.