Reliability of EUS indices to detect inflammation in ulcerative colitis

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Background and Aims: EUS is a potentially useful modality to assess severity of inflammation in ulcerative colitis (UC). We assessed the reliability of existing EUS indices and correlated them with endoscopic and histologic scores.

Methods: Four blinded endosonographers assessed 58 endoscopic and EUS videos in triplicate, from patients with UC. Intrarater and interrater reliability of the hyperemia and Tsuga scores were estimated by using intra-class correlation coefficients (ICCs). Correlation with the Mayo endoscopy score, modified Baron score (MBS), Ulcerative Colitis Endoscopic Index of Severity (UCEIS), and Geboes histopathology score (GHS) were calculated by using bootstrapping methods. A RAND consensus process led to development of standardized definitions and a revised EUS-UC score.

Results: ICCs for intrarater reliability were 0.76 (95% confidence interval [CI], 0.71-0.80) for the hyperemia score and 0.85 (95% CI, 0.79-0.89) for the Tsuga score. Corresponding values for interrater reliability were 0.34 (95% CI, 0.25-0.42) and 0.36 (95% CI, 0.24-0.46). Correlation between hyperemia and Tsuga scores to Mayo scoring system, MBS, UCEIS, and the GHS were 0.39 (95% CI, 0.15-0.61) and 0.28 (95% CI, 0.04-0.51), 0.38 (95% CI, 0.16-0.57) and 0.25 (95% CI, -0.01-0.48), 0.41 (95% CI, 0.16-0.62) and 0.27 (95% CI, 0.01-0.50), 0.37 (95% CI, -0.01-0.48) and 0.24 (95% CI, 0.13-0.57), respectively. The revised EUS-UC score included bowel wall thickening, depth of inflammation, and hyperemia.

Conclusions: Although *substantial* to *almost perfect* intrarater agreement existed for EUS indices in UC, interrater agreement was fair. Standardization of item definitions with development of a revised evaluative instrument has potential application as an evaluative and prognostic tool for UC. (Clinical trial registration number: NCT01852760.) (Gastrointest Endosc 2017;86:1079-87.)

Ulcerative colitis (UC) is a chronic inflammatory bowel disease of unknown etiology characterized by diffuse colon inflammation. Goals of therapy for UC have evolved from control of bleeding and diarrhea to improvement in more objective measures of inflammation. Although biomarkers such as fecal calprotectin and serum C-reactive

Abbreviations: CIMS, Central Imaging Management System; GHS, Geboes histopathology score; ICC, intra-class correlation; MBS, modified Baron score; MES, Mayo endoscopic score; RAND, research and development; UC, ulcerative colitis; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

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0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2017.07.035

Received April 25, 2017. Accepted July 20, 2017.

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protein are widely used as noninvasive markers of disease activity, endoscopy remains the criterion standard for evaluation of inflammation.[1-6] Accordingly, guidelines on the management of UC have identified endoscopic remission, defined as the presence of normal mucosa or vascular blurring without friability, as a preferred treatment target in clinical practice.[7] The rationale for this approach is that mucosal healing is associated with lower risk of relapse, need for corticosteroids, hospitalization, and colectomy.[8-11] Furthermore, it has been recognized that histologic inflammation, which may persist even in patients with complete resolution of symptoms and endoscopic healing, provides additional prognostic value.[12-16]

Although UC is generally considered to be a superficial process restricted to the mucosa, in more severe cases inflammation extends to deeper layers of the bowel wall that cannot be evaluated by endoscopy or endoscopically procured biopsies. In contrast, EUS can examine all layers of the bowel wall. Accordingly, EUS is a highly accurate diagnostic and prognostic modality for the assessment of many diseases of the rectum. Experience with EUS in UC is limited, and its potential role as a prognostic tool in UC remains undefined.[17] Studies in patients with active UC who have correlated rectal wall thickness and depth of inflammatory changes with severity of mucosal disease have demonstrated relatively similar results of increased wall thickening and deeper layer involvement with increasing severity of disease. However, interpretation of the studies is limited because of weaknesses in methodology including lack of blinding, small sample sizes, variations regarding which EUS findings were compared, and differences in the definitions of what constituted normal and abnormal.[17-20] Alternatively, in patients with quiescent disease, deep disease activity, as specified by increased thickness of the first 3 layers of the bowel wall, may have prognostic value.[21] In keeping with this notion, Yoshizawa et al[22] demonstrated that ultrasonographically defined involvement of the muscularis propria or deeper was associated with an increased risk of colectomy. Of those failing medical (intravenous corticosteroid) therapy requiring surgery, 67% (10 of 15 patients) demonstrated inflammation to the muscularis propria or beyond, whereas in those who responded to medical management, only 19% (5 of 27) showed deep inflammation.[22] Although anti–tumor necrosis factor salvage therapy was not used in the study, this observation holds out the possibility that EUS may provide additional prognostic information than other modalities. Finally, EUS may help evaluate and predict response to therapy. In a small study by Watanabe et al,[23] patients with steroid-refractory severe UC who responded to cyclosporine A demonstrated reduction in wall thickness on EUS compared with nonresponders, who had no significant sonographic change.

Before its potential can be realized, the operating properties of EUS in UC must be rigorously evaluated. Evaluation of an index involves assessment of reproducibility, validity, and then responsiveness. Reproducibility is the degree to which repeated measures produce similar results, which is typically determined by measuring agreement or reliability. Reliability is defined as the extent to which raters are able to consistently distinguish between study participants, and agreement is defined as the extent of how similar responses appear from multiple assessments.[24] Validity is defined as the extent to which a score measures what it is intended to measure, and this is often assessed by correlation with a criterion standard. Finally, the responsiveness of an index is its ability to detect the treatment effect of a proven effective medical therapy via a change of its score. Furthermore, an ideal prognostic index should have the ability early in a disease state to discriminate individuals at low risk versus high risk for a given outcome, be easy to measure, and have an acceptable cost profile.

In this study, we assessed the reliability of EUS indices of inflammation and correlated them with validated clinical, endoscopic, and histologic indices of UC inflammation.

METHODS

Study population

Consecutive patients with a documented history of UC who were undergoing colonoscopy as part of routine clinical care were potentially eligible to participate in the study, irrespective of disease extent (proctitis, left sided, and pancolitis), clinical disease activity (remission, mild, moderate, and severe disease), or concomitant therapies (aminosalicylates, steroids, azathioprine, tumor necrosis factor antagonists, topical therapy, and combinations thereof). Patients were not eligible if they were unable or unwilling to undergo flexible sigmoidoscopy or colonoscopy, unable to provide informed consent, had Crohn's disease, or had an ileoanal pouch. All patients provided written informed consent. The study was approved by the institutional scientific research ethics board of Western University.

Endoscopic procedures

Flexible sigmoidoscopy, colonoscopy, and rectal EUS were performed according to standard procedures by a single endosonographer (B.Y.). EUS was performed first with a dedicated radial echoendoscope (Olympus GF-UE160-AL5; Olympus America Inc, 3500 Corporate Parkway, Center Valley, Pa) by using the Aloka ProSound SSD Alpha 10 processor (Hitachi Aloka Medical America Inc, Wallingford, CT, USA). Water insufflation was used to enhance acoustic coupling; sufficient enough to separate the mucosa from the transducer to allow focused imaging but not so much as to cause profound rectal distension. EUS was performed in the rectum by using frequencies between 7.5 and 10 MHz and indices measured at the area of greatest endoscopic and sonographic abnormality. Total wall thickness and thickness of the first 3 sonographic layers (superficial mucosa, deep mucosa, and submucosa) were measured at 4 different