

Insights into the role of gastrointestinal ultrasound in ulcerative colitis

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Abstract: Endoscopic evaluation with histological sampling is the gold standard for the diagnosis and follow-up of patients with inflammatory bowel disease (IBD), but in the past few years, gastrointestinal ultrasound (GIUS) has been gaining ground. Due to the transmural nature of inflammation in Crohn's disease, GIUS has been mainly applied in this context. However, GIUS is now being reported to be accurate also for ulcerative colitis (UC). This review summarizes current knowledge on the use of GIUS in UC, with a focus on clinical practice. The review covers topics such as GIUS parameters, especially bowel wall thickness; the use of GIUS in assessing disease extent and in monitoring disease activity; GIUS indexes and scores; and the combination of GIUS with transperineal ultrasound for a better assessment of the rectum. With the always growing body of evidence supporting the accuracy of GIUS in UC, this diagnostic imaging modality can be expected to play a bigger role in disease flare evaluation, early treatment monitoring, and acute severe disease management.

Keywords: colonoscopy, disease activity, inflammatory bowel disease, ultrasonographic parameters

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Introduction

Ulcerative colitis (UC) is one of the two main forms of inflammatory bowel disease (IBD). Together with Crohn's disease (CD), these chronic illnesses are characterized by an interplay between immune system alterations, genetics, and environmental factors.¹ They often require lifelong therapies and continuous clinical follow-up, with regular laboratory testing and endoscopic and radiological examinations.^{2,3}

UC-related inflammation typically involves only the colonic mucosa; the inflammation spreads continuously from the rectum proximally, to different extents in different patients. According to the Montreal classification,⁴ there are three forms of UC: proctitis (involving only the rectum), left-sided colitis (also involving the sigmoid and descending colons), and pancolitis or extensive colitis (extending over the splenic flexure). On the contrary, in CD, the inflammation is typically

transmural and the whole gastrointestinal tract can be affected, although in most cases the inflammation is limited to the ileum and colon.⁵

Until a few years ago, therapeutic success in IBD was defined as the remission of intestinal symptoms. However, our better comprehension of the natural history of IBD and, especially, of the pathophysiological mechanisms underlying the development and perpetuation of inflammation, has led to the identification of new therapeutic targets.⁶ In turn, the advent of more effective therapies with different mechanisms of action has led to modifications in the overall management of IBD. In particular, more ambitious therapeutic goals in UC, such as endoscopic and even histological healing, appeared as objectives to obtain due to their association with overall better outcomes.⁷ Moreover, these objectives are now becoming not only the key to achieving deep disease control but also the drivers to monitor

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Figure 1. Ulcerative colitis in remission, transverse section: normal wall thickness of the sigma.

therapeutic responses and to guide therapeutic changes.^{3,6,7}

Colonoscopy with histological analysis remains the gold-standard method for the diagnosis and follow-up of UC patients.² However, it is an expensive, invasive diagnostic tool that is generally not well accepted by IBD patients due to the required bowel preparation before the exam and to the discomfort or pain during the procedure.^{8,9} As a consequence, new imaging techniques have been developed. Among these, gastrointestinal ultrasound (GIUS) appears to be one of the best in terms of diagnostic yield, costs, and acceptability.¹⁰ GIUS was first applied in CD, due to the transmural nature of inflammation, and in this context, it is now an essential instrument for assessing disease activity, complications (e.g. abscesses, fistulas, strictures, and bowel enlargement), and therapeutic responses.^{11–13} The usefulness of GIUS in UC has been supposed for more than 20 years,¹⁴ and only recently has this usefulness been widely recognized. This narrative review describes the use of GIUS in the management of patients with UC, with a focus on clinical practice.

How to perform GIUS

To perform GIUS, no specific preparation is required, but the patient should fast for 3 h before the examination. GIUS is performed with the patient in supine position, with standard abdominal probes (3.5–5 MHz) and high-frequency probes (7–11 MHz), with gradual compression. In general, a standard probe is used to get an

initial panoramic view of the abdomen and bowel, while high frequency is necessary to correctly assess bowel wall thickness (BWT), stratification, ulceration, and peristalsis. Although the starting point is not codified, it is recommended that individual operators perform GIUS with the same repeated scheme to allow evaluation of the whole bowel.¹⁵

If colonoscopy is planned on the same day, GIUS should be performed first to avoid the excessive presence of air in the bowel from per-endoscopic insufflation. There is no risk of interference with GIUS from intravenous contrast medium administered for magnetic resonance imaging or computed tomography exams. Colorectal distension by enema or anti-spastic medication is not required.

GIUS parameters for UC

Despite the widespread use of GIUS in UC patients, no standardized parameters have so far been identified. Recently, an expert panel assessed the reliability of GIUS in UC in order to identify reliable parameters.¹⁶ They find, according to another systematic review,¹² that the parameters to be evaluated should be BWT, parietal blood flow, Doppler signal, wall layer stratification, and fatty wrapping.

According to many GIUS studies, BWT is the most important parameter for defining UC disease activity (Figures 1 and 2) and extent.^{17–19} Its performance improves when associated with detection of a Doppler signal.^{20,21} Bowel wall blood flow can also be measured after the intravenous administration of contrast medium, with similar results to the Doppler signal.²² BWT should be measured in longitudinal sections, to ensure reproducibility and interobserver agreement.^{18,23} As BWT is a quantitative measure, it is also the most objective parameter, assuming it is evaluated by a well-trained operator.^{11,13} Maconi *et al.*¹⁴ reported that BWT was significantly higher in patients with active UC than with disease in remission, and it remained altered in patients who did not respond to therapy. Many studies found that 3 mm^{21,23–26} or 4 mm^{14,19,27,28} was a useful threshold for defining active disease. However, some studies found differences between different colonic segments (e.g. >4 mm in the sigmoid colon and >3 mm in the descending, transverse, and right colons¹⁸) and between different

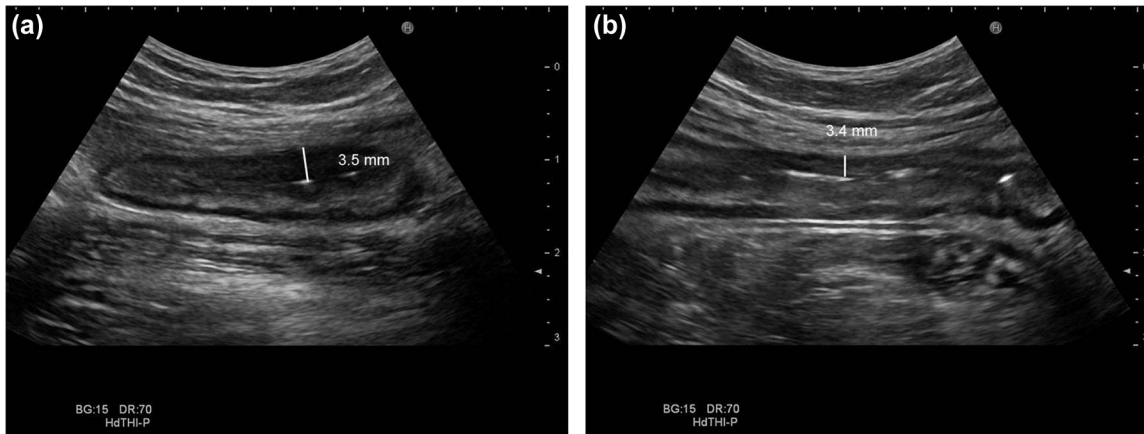


Figure 2. Ulcerative colitis moderately active: (a) transverse section of the sigma and (b) longitudinal section of the sigma.

age groups of patients (e.g. 3 mm in adults and 4 mm in children^{18,29}). Nevertheless, BWT has proven to correlate well with clinical, endoscopic, and histological activity in many studies.^{14,19,25,30–32} Parente *et al.*³⁰ demonstrated a good concordance between GIUS and both the Baron and Truelove scores, at the beginning of a flare and after therapy. In some studies, BWT was also found to correlate with C-reactive protein levels.^{14,25,29}

Other parameters that may help in assessing disease activity are the echogenicity of the submucosal layer, mesenteric fibrofatty proliferation, and loss of colonic haustration.³¹

Evaluation of disease extent

One of the major limitations of colonoscopy in patients with severely active UC is the risk of interruption at the sigmoid colon due to problems of tolerability and concerns about safety.³³ Therefore, it may be difficult to obtain information about the exact extent and features of the disease before starting intravenous steroids or a rescue therapy. In these cases, GIUS has proven to be effective in evaluating the disease extent.^{13,18}

A recent meta-analysis of the use of GIUS in UC³⁴ found good sensitivity and specificity in detecting active disease (when BWT >3 mm) in the right and transverse colons. This accuracy decreased, however, moving toward the rectum, where the diagnostic potential of GIUS is poor due to the rectum's deep position in the pelvis.

Evaluation and monitoring of disease activity

GIUS can be used as a surrogate of colonoscopy in evaluating disease activity.^{14,30} Monitoring of therapeutic responses, especially when a patient is experiencing a disease flare, is crucial for the optimal management of UC patients. Undoubtedly, frequent colonoscopies to assess treatment responses are not practical or cost-effective and are unlikely to be accepted by patients. On the contrary, GIUS does not require bowel preparation, it is readily available in most hospitals, and it is well accepted by most patients.⁸

As shown by the TRUST&UC (TRansabdominal Ultrasonography of the bowel in Subjects with IBD To monitor disease activity in Ulcerative Colitis) study,¹⁸ BWT correlates with disease activity scores both at the beginning of a flare and after 12 weeks of therapy. This prospective multicentric observational study was conducted on 224 patients with UC (excluding those with proctitis) with an active disease score ≥ 5 on the Short Clinical Colitis Activity Index (SCCAI). High BWT (>4 mm in the sigmoid colon and >3 mm in the other segments) and the Doppler signal were evaluated at the time of diagnosis and over a 12-week period (at 2, 6, and 12 weeks). Moreover, additional parameters, including loss of haustration, loss of wall stratification, ascites, lymphadenopathy, and mesenteric fibrofatty proliferation, were evaluated at each visit. During the study period, the percentage of patients with high BWT changed significantly over time: a sigmoid colon

BWT >4mm was found in 89.3% of patients at baseline and in 32.0% at week 12, and a descending colon BWT >3mm was found in 83.0% of patients at baseline and in 37.6% at week 12. Moreover, all additional parameters showed significant reductions from baseline to 12 weeks. Other interesting findings of this study are the correlation between SCCAI and BWT and the fact that BWT at week 2 predicted the response to treatment.

The usefulness of GIUS and especially BWT in monitoring responses to cytapheresis was shown by Yoshida *et al.*³⁵ Their study not only demonstrated that GIUS was accurate in monitoring therapeutic responses, but they also found that a 2.5-mm reduction in BWT was predictive of a sustained response after 1 week. Indeed, of all the patients who achieved a BWT reduction of at least 2.5 mm after cytapheresis, 90% were still in clinical remission after 1 year of follow-up *versus* 40% of patients with a BWT decrease less than 2.5 mm.

Finally, a recent pilot study of 10 patients indicated the potential utility of GIUS in patients admitted to hospital for severe UC.³⁶ In particular, the study found that a BWT >6 mm in any colonic segment at admission was associated with a poor corticosteroid response and with the need for salvage therapy.

GIUS scores and indexes for UC

With the growing importance of GIUS in UC monitoring and management, several ultrasonographic scores and indexes have been developed. Their usefulness, however, is still a matter of debate, especially regarding their relevance and feasibility of use in everyday clinical practice.^{21,37} Here, we summarize the main tools that have been proposed.

In 2014, Civitelli *et al.*³⁸ proposed a score for the pediatric UC population. Ultrasound parameters such as BWT, increased vascularization, loss of stratification, and absence of colonic haustration were compared to the Mayo endoscopic score, and, at multivariate analysis, all these parameters strongly correlated with disease activity.

Another UC score is the Humanitas Ultrasound Criteria, first reported by Allocca *et al.* in 2018.²⁶ Their prospective study of 53 UC patients found that BWT >3 mm, hypoechogenicity, a signal on

power Doppler, and lymphadenopathy correlated with endoscopic disease activity. With this study, they built a score according to which ultrasound UC activity is defined by either a BWT >3 mm plus a power Doppler signal or by BWT >4.43 mm without the signal. This score had a sensitivity of 0.71 and a specificity of 1.00, and interobserver agreement was excellent ($\kappa = 0.86$). This score was recently validated under the new name Milan Ultrasound Criteria.³⁹

Recently, another new index for grading disease activity in UC patients was developed and internally validated on 60 patients, using endoscopy as the reference standard.⁴⁰ According to this index, a BWT >2.1 mm discriminates between remission and mild endoscopic activity. Furthermore, a cutoff of 3.2 mm discriminates between mild and moderate endoscopic activity and a BWT >3.9 mm correlates with severe endoscopic activity. The other parameters included in the index were the presence of a color Doppler signal (which predicted active disease), lack of haustrations (also predictive of active disease), and fat wrapping (predictive of severe disease). There was a strong correlation between the index and endoscopic disease activity.

GIUS and transperineal ultrasound

One of the major limitations in using GIUS in UC is the extreme difficulty in assessing rectal involvement due to the rectum's deep position in the pelvis, not readily reachable by GIUS. One way to improve the accuracy of GIUS in assessing UC rectal involvement could be to combine it with a transperineal evaluation or with the measurement of fecal calprotectin.

On the model of how perianal CD is assessed,⁴¹ transperineal ultrasound (TPUS) has been proposed as a new noninvasive tool for evaluating the rectum in UC. For this purpose, Sagami *et al.*⁴² evaluated GIUS combined with TPUS and fecal calprotectin in 53 patients with active UC requiring colonoscopy (used as the gold standard). At univariate analysis, BWT <4mm predicted endoscopic and histological remission with areas under the curve of 0.90 and 0.89, respectively. This correlation was found to be even better than that between fecal calprotectin and endoscopic findings. So, the authors suggested that TPUS could be used in combination with GIUS to assess the whole colon.

TPUS might also be useful in evaluating the pouch in UC patients who had restorative proctocolectomy with ileo pouch–anal anastomosis (IPAA) for refractory or complicated disease, but so far evidence is lacking. Diagnosing and managing pouchitis and identifying surgical failures are challenging tasks for physicians who care for these patients.⁴³

Discussion

Evidence supporting the use of GIUS in UC patients is still limited. However, considering its noninvasiveness, relatively low costs, lack of need for bowel preparation, and, especially, the growing evidence that supports its accuracy, we predict that GIUS will become increasingly used in clinical practice in the coming years. Indeed, even if scarce data exist about its current use in hospitals, it is known that the lack of GIUS is felt as a relevant unmet need by physicians managing IBD patients.⁴⁴

The most important applications of GIUS appear to be evaluating the response to therapy and completing the study of the colon in patients with acute, severe UC scheduled for proctosigmoidoscopy. Further large, prospective studies are needed to validate the diagnostic accuracy of GIUS in comparison with colonoscopy and to identify reliable prognostic parameters.

Finally, GIUS has some limitations. First, the technique is not standardized and the qualifications of an ‘expert’ GIUS operator remain to be defined;⁴⁵ in this regard, scientific societies dedicated to IBD can play an important role in promoting research and educational programs on GIUS. In practice, other limitations include excessive abdominal fat, low disease activity, and difficulties in evaluating the rectum.⁴⁵ These difficulties may be overcome by associating GIUS with a transperineal evaluation or by measuring biochemical markers such as fecal calprotectin. If this approach is validated, it would represent another strength of ultrasonography over colonoscopy.

Conclusion

The role of endoscopy in UC will remain irreplaceable in some cases (e.g. biopsy at diagnosis, surveillance for dysplasia or colorectal cancer, and exclusion of cytomegalovirus superinfection in steroid-refractoriness). Nonetheless, it is likely

that GIUS will soon demonstrate its undoubted utility in the management algorithm of UC. In the era of the ambitious therapeutic targets and personalized medicine, GIUS will help monitor UC patients, from the early evaluation of therapeutic responses to changes in therapeutic strategies.

However, for the role of GIUS to be fully recognized and its use widespread, several needs should be met. The most important are standardization of the procedure and definition of the learning curve. It is also important to determine whether GIUS or testing of biomarkers (e.g. fecal calprotectin) is better for noninvasive UC monitoring. Currently, GIUS appears to be superior due to its ability to assess disease extent and severity.

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CB and SS: study concept and design; acquisition of data; drafting of the manuscript; MV acquisition of data; drafting of the manuscript; DGR and GM revision of the manuscript for important intellectual content;

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