Value of endoscopic ultrasound in prediction of dysplasia in ulcerative colitis

Amr M. Elrabat[a], Neveen F. Ibraheem[a], Maha M. Maher[a], Fatma A. Abozeid[a], Maha A. Abelrahman[b]

Departments of [a]Internal Medicine, [b]Pathology, Mansoura University, Mansoura, Egypt

Correspondence to Amr M. Elrabat, Department of Internal Medicine, Mansoura University, Mansoura, Egypt.
Tel: +20 111 825 3050;
e-mail: amr.rabat@yahoo.com

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Background
Ulcerative colitis (UC) is one of the most common forms of chronic inflammatory bowel disease. Its diagnosis is based on history, clinical, radiological, laboratory, endoscopic, and histological examinations. Endoscopic ultrasound (EUS) is a highly accurate diagnostic endoscopic and radiological modality for assessing of rectal pathology. However, EUS data remain scarce for patients with UC. The aim of this study was to assess the correlation between EUS indices and clinical, endoscopic, and histological scores of inflammation in UC and to evaluate the usefulness of EUS in assessing the activity and dysplasia of UC.

Patients and methods
A total of 57 patients with UC were cross-sectionally evaluated based on clinical (Truelove score), laboratory [complete blood count (CBC), c reactive protein (CRP), erythrocte sedementaion rate (ESR), and fecal calprotectin], and endoscopic (Mayo score) parameters. The patients were divided into three groups: mild UC, moderate UC, and severe UC. They were subjected to EUS at 10, 20, and 30 cm from the anal verge to assess the correlation between severity of UC and histopathological examination results.

Results
Total wall thickness (TWT) at 10 cm from the anal verge was positively and highly significantly correlated to histopathological severity in comparison with 20 and 30 cm from anal verge (P=0.001). TWT at 10 cm by EUS was a significant predictor of the histopathological severity of UC (P=0.007). For TWT of the colon at 10 cm from the anal verge, significant discrimination (P=0.02) between severe UC and mild to moderate UC could be achieved by utilizing a cutoff of 3.5 mm with sensitivity of 60.5% and specificity of 85.7%. In addition, highly significant (P=0.006) discrimination of mucosal dysplasia in UC could be achieved using TWT cutoff of 5.05 mm at 10 cm from the anus with sensitivity of 75% and specificity of 94.3%.

Conclusion
For EUS at 10 cm from the anal verge, TWT cutoff of 3.5 mm can assess histopathological severity of UC, and TWT cutoff of 5.05 mm can predict dysplasia in UC.

Keywords:
dysplasia, endoscopic ultrasound, ulcerative colitis

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Introduction

The term inflammatory bowel disease (IBD) is used to define a set of diseases involving the gastrointestinal tract. It includes mainly Crohn's disease (CD) and ulcerative colitis (UC). IBD is characterized by exacerbations and remissions with long-term complications. Diagnosis of UC is based on history, clinical examination, as well as radiology, laboratory, endoscopy, and histological examination [1]. Endoscopic ultrasound (EUS) is a highly accurate diagnostic endoscopic and radiological modality for the assessment of rectal pathology. It is useful in the assessment of rectal and perianal lesions by measuring colon wall thickness and the surrounding structures [2]. However, such data are still scarce in patients with UC. The aim of this study was to detect the correlation between EUS indices and clinical, endoscopic, and histological scores of inflammation in UC and evaluate the usefulness of EUS in assessing the activity and dysplasia of UC.

Patients and methods

A total of 57 patients with UC were cross-sectionally evaluated by clinical (Truelove score [3]), laboratory

[complete blood count (CBC), c reactive protein (CRP), erythrocte sedementaion rate (ESR), and fecal calprotectin], endoscopy (Mayo score [4]), and histopathology. Patients who attended the outpatient IBD clinic or admitted at Mansoura Specialized Medical hospital were observed during a 1-year period from June 2016 till June 2017. They were divided into three groups: mild, moderate, and severe UC. They were subjected to colonoscopy, after good preparation of colon, in the Endoscopy Unit of Mansoura University Hospital using colonoscope Pentax PK 100 Video scope. Extent of inflammation was detected either proctosigmoiditis, left-sided colitis, pancolitis, and pancolitis with backwash ileitis. Mayo score [4] was applied for detection of severity of UC. Preparation for colonoscopy was done by 2–4 l of hypertonic polyethylene glycol. The cleaning procedure started 24 h before the procedure. Propofol was used for sedation at the patient's request. Each patient was monitored throughout the procedure and supplied with oxygen if needed.

Four biopsies were taken from the sigmoid colon in the area where a suspected lesion was found. All biopsies were examined by a pathologist, from Department of Pathology, Mansoura Faculty of Medicine, blinded to the results of endoscopy. Biopsies were fixed in 10% formalin solution and embedded in paraffin for subsequent analyses. After staining with hematoxylin and eosin, the degree of activity of the inflammation was classified using Geboes scoring system [5]. EUS was done (in the same day or next day) using Endoscopic Ultrasound EG-3870UTK Linear array-Pentax. EUS was introduced till 10, 20, and 30 cm from anal verge to assess the severity of UC through measuring mucosa, submucosa, musculosa, and total wall thickness (TWT) of the colon at four different areas in correlation to endoscopical and histopathological examination. The study was approved by the Ethical Committee in Faculty of Medicine, Mansoura University.

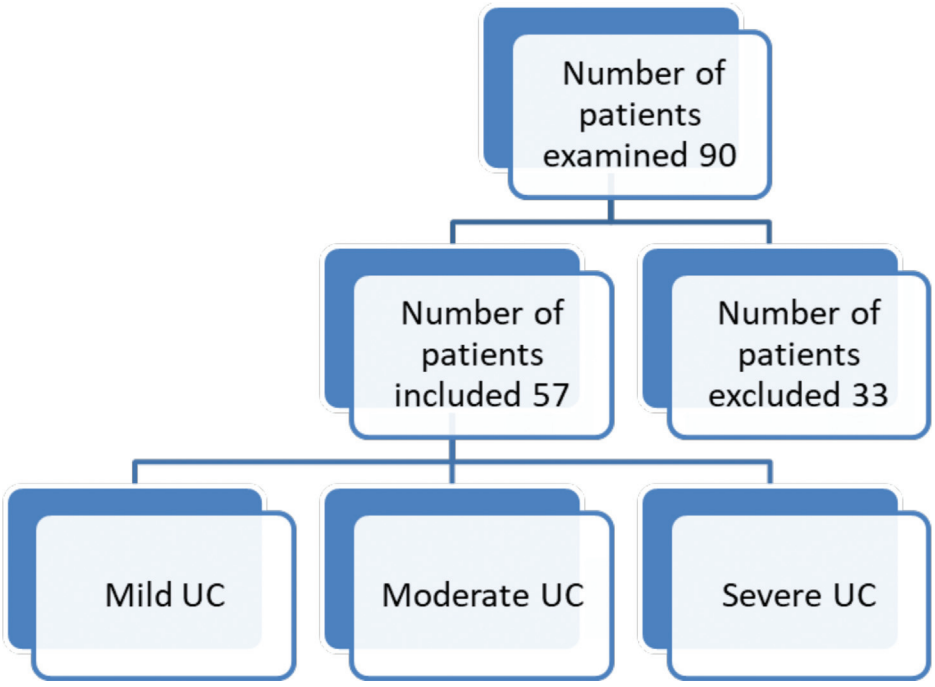
Inclusion criteria

Patients with a confirmed diagnosis of UC (either active or inactive) aged more than 18 years were included. Patients may be treatment naive (i.e. new diagnosis) or on existing therapy including 5-amino salicylic acid (ASA) (oral or topical), azathioprine (AZA), corticosteroids, or biological treatment.

Exclusion criteria

Patients with inability to or unwillingness to undergo flexible sigmoidoscopy or colonoscopy, patients with irritable bowel syndrome or infectious colitis, patients with bleeding tendency (hemophilia, chronic kidney disease, and liver cell failure), patients with surgical local causes of bleeding per rectum (piles, fissures, sinuses, etc.), and patients with a history of cancer colon or surgical resection of colon were excluded. The study was approved by the Ethical Committee in Faculty of Medicine, Mansoura University (Fig. 1).

Figure 1



Classification of patients involved.

Statistics

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for nonparametric variables and mean and SD for parametric variables after testing normality using Kolmogorov–Smirnov test. Significance of the obtained results was judged at the 5% level. All tests were two-tailed.

The Student *t*-test was used to compare continuous data, and the χ^2-test was used for categorical data. Mann–Whitney *U*-test was used for quantitative non parametric variables, to compare between two groups, whereas, Kruskal–Wallis test or also post-hoc test was used to detect any significance among more than two groups concerning all variables.

Relations between variables were done by Spearman correlation coefficient. *P* values of less than 0.05 were considered statistically significant. Diagnostic accuracy of qualitative tests was obtained using receiver operating characteristics curve to detect the cutoff with best sensitivity and specificity.

Discussion

The EUS scan has been used since the early 80s. It was used in the assessment of the rectum after people were familiar with its usage in the management of upper gastrointestinal tract problems. It was used for evaluation of malignancies and later on for assessment of benign disorders including IBD.

IBD including UC was used to be considered a disease of the superficial mucosa. Recently, there is increasing evidence that transmural inflammation exists in many patients, resulting in structural and functional consequences that may affect the function and motility of the rectum and colon [6,7].

EUS has an important role in differention between UC and CD, as patients with UC have thicker mucosal layer, whereas patients with CD exhibit thicker submucosal layer [8].

It can assess the activity of UC, as well as the severity of inflammation through measuring rectal wall thickness (TWT) [9]. It can provide information independent of clinical symptoms, endoscopy, and histology if its inflammatory process extends beyond the superficial mucosa [10].

In this study, 57 patients with UC were enrolled, comprising 30 female and 27 male. The mean age was 35.8±11.1 years. By applying Truelove and Witts' clinical criteria, there were 14 (24.6%) patients with mild, 13 (22.8%) with moderate, and 30 (52.6%) with severe UC. By applying Mayo endoscopic score, there were seven (12.3%) patients with mild, 15 (26.3%) moderate, and 35 (61.4%) severe UC. Most of the patients (71.1%) had proctosigmoiditis (28.1%) and

Table 1 Endoscopic ultrasound indices among studied cases (*n*=57)

	Median (minimum–maximum) (mm)
TWT at 10 cm	3.4 (2.1–7.8)
Mucosa at 10 cm	2.0 (1.1–4.2)
Musculosa at 10 cm	1.05 (0.5–3.4)
TWT at 20 cm	3.1 (1.5–6.7)
Mucosa at 20 cm	1.85 (0.7–3.5)
Musculosa at 20 cm	0.8 (0.4–7.0)
TWT at 30 cm	3.0 (1.3–5.7)

TWT, total wall thickness.

Table 3 Correlations between total wall thickness and histopathogical severity

EUS INDICES	Correlation coefficient (rs)	*P* value
TWT10cm	0.442	0.001**
TWT 20 cm	–0.056	0.723
TWT30cm	–0.016	0.925

P, probability; rs, spearman correlation coefficient; TWT, total wall thickness.

Table 2 Association between histopathology, Truelove score and appearance by Mayo score

		Histopathology				Test of significance
		Mild *N*=4 (%)	Moderate *N*=10(%)	Severe *N*=39(%)	Severe with dysplasia*N*=4(%)	
Truelove score	Remission	1(25.0)	2(50.0)	1(25.0)	0(0.0)	MC
	Mild	2(50.0)^{A}	2(20.0)	5(12.8)^{A}	1(25.0)	*P*=0.04*
	Moderate	0 (0.0)	4(40.0)	8(20.5)	1(25.0)	
	Severe	1(25.0)	2(20.0)	25(64.1)	2(50.0)	
MAYO score	Mild	4(100.0)^{ABC}	1(10.0)^{ADE}	2(5.1)^{BD}	0(0.0)^{CE}	MC
	Moderate	0(0.0)	7(70.0)	8(20.5)	0(0.0)	*P*<0.001**
	Severe	0(0.0)	2(20.0)	29(74.4)	4(100.0)	

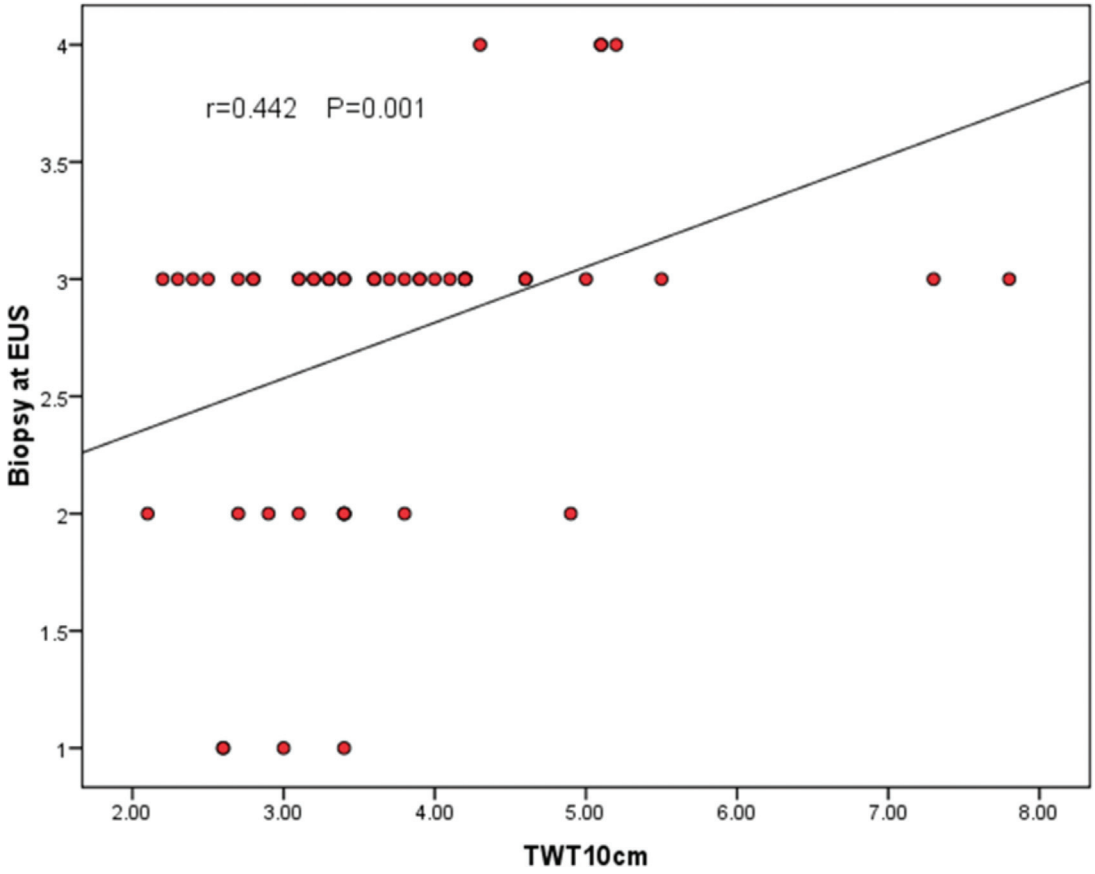
MC, Monte Carlo test; P, probability. *Statistically significant (*P*<0.05). **High statistically significant (*P*<0.01). ABCDE Similar letters denote significant difference between groups by Mann–Whitney *U* test.

Table 4 Validity of EUS indices (TWT at 10 cm) in prediction of severe active cases of UC anddysplasia by biopsy

TWT at 10 cm	AUC (95% C.I)	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Severe UC	0.72(0.58-0.87)	≥3.5	60.5	85.7	92.9	41.4	66.7
Dysplasia	0.92(0.84-0.99)	≥5.05	75.0	94.3	92.9	79	84.6

AUC, area under curve; C.I, confidence interval; NPV, negative predictive value; PPV, positive predictive value; TWT, total wall thickness; UC, ulcerative colitis.

Figure 2



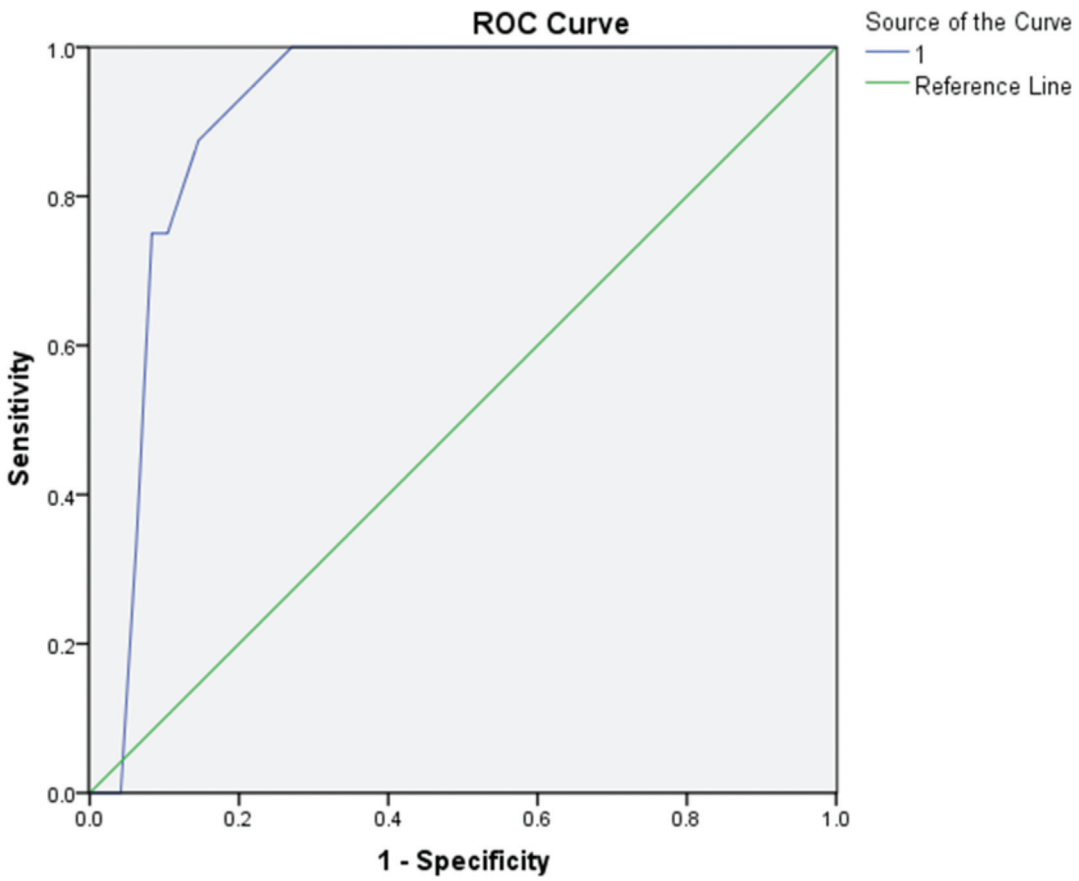
Scatter diagram showing correlation between TWT at 10 cm from anal verge and biopsy at EUS in studied cases. EUS, endoscopic ultrasound; TWT, total wall thickness.

left-sided extension (40.4%) of UC, and the rest of the patients had pancolitis.

The median TWT measured by EUS in this study at 10 cm was 3.4 mm (2.1–7.8) and of mucosa at 10 cm was 2 mm (1.1–4.2). This was similarly proved by Kante *et al.* [11] from India who stated that the mean TWT was 3.59±1.22 mm, whereas mean mucosal thickness was 0.93±0.43 mm in a study of 51 patients with UC (Tables 1–4).

In this study, clinical (Truelove) severity was correlated significantly with increase in TWT at 10 cm from anal verge (P=0.01), and patients with severe endoscopic and histopathological UC were correlated significantly with increase in TWT at 10 cm (P=0.001 and 0.001 respectively; Fig. 2). This was similar to what was proved by Kante *et al.* [11], who stated that patients who were clinically and endoscopically severe had significantly thickened rectal wall as compared with patients with mild disease (P<0.017 and 0.0001, respectively). Moreover, in a study done by Brian *et al.* [10] in more than 58 patients, there was significant increase in TWT for moderate to severe disease but not for mild disease, and the majority of the increased thickness was related to the first three sonographic layers (mucosa, submucosa, and musculosa) (P<0.001). So EUS can provide information independent of clinical symptoms, endoscopy, and histology, if the inflammatory process extends beyond the superficial mucosa.

Figure 3



ROC curve of TWT at 10 cm from anal verge in detection of dysplasia. ROC, receiver operating characteristics; TWT, total wall thickness.

In this study, measurements of TWT at 10 cm were positively correlated with high significance (P=0.001) to histopathological severity of UC in comparison with measurements of TWT at 20 cm and 30 cm from anal verge.

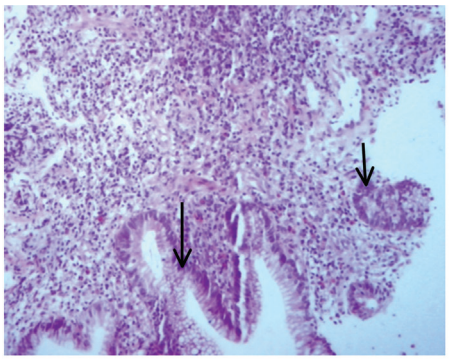
At the cutoff of 3.5 mm, it is possible to discriminate significantly (P=0.02) between severe UC cases and mild to moderate cases from the other side, with sensitivity of 60.5% and specificity of 85.7%. Its positive predictive value (PPV) is 92.9%, negative predictive value (NPV) is 41.4%, and overall accuracy is 66.7%. On the contrary, in a study done by Kibi *et al.* [12] on 56 patients with histopathologically confirmed UC, before being operated, for assessment of the severity by EUS, the sensitivity reached 85.7%, specificity was high to 97.3%, PPV was 88.9%, NPV was 92.4%, and overall accuracy was 95%.

There is a close association between disease duration and the development of colorectal carcinoma. This represents the rationale for recommending regular surveillance endoscopy starting 6–8 years after first manifestation of the disease in the current guidelines [13]. However, dysplasia and intraepithelial neoplasia are frequently missed during routine white-light endoscopic examinations and at the same time, random biopsies have a low yield for dysplasia detection [14]. For this purpose, EUS can have a role in detection and diagnosis of UC-associated invasive carcinoma arising in the rectum [15]. In this study, nine (15.8%) patients were diagnosed with UC for more than 8 years, but only one of them had dysplastic changes by biopsy.

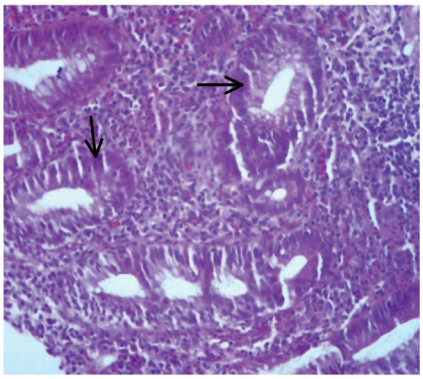
In this study, we have noticed that TWT of 5.05 mm at 10 cm from anus was highly significant (P=0.006) to discriminate mucosal dysplasia in UC with sensitivity of 75%, specificity of 93.7%, PPV of 92.9%, NPV of 79%, and overall accuracy of 84.6%. This has a good effect on the long-term follow-up of severe UC cases that may have high potential to turn to malignancy. This can contribute in diagnosis, follow-up, and treatment of UC by measuring TWT at 10 cm from anal verge (Figs 3–5).

The limitation of this study is that assessment by EUS was limited to a maximum 30 cm from the anal verge, which means it may be possible to miss active disease

Figure 4



A) Ulcerative colitis with dysplasia H&E x10



B) Ulcerative colitis with dysplasia in higher magnification H&E x20

Histopathology pictures of ulcerative colitis (UC) with dysplastic cells: (a) ulcerative colitis with dysplasia hematoxylin and eosin, ×10. (b) Ulcerative colitis with dysplasia in higher magnification hematoxylin and eosin, ×20.

based on rectal EUS alone, espicially in cases of proximal colitis and under treatment. In spite of this, the subepithelial ongoing inflammation can still be visible by EUS better than endoscopy and biopsy alone. Another limitation is the inclusion of a small number of patients (57 patients) with UC and four (7%) patients had dysplasia on top of UC, yet only one of them was diagnosed as UC for more than 8 years, whereas the other three exhibited UC for less than this duration. This has a good effect on the short-term and long-term follow-up of severe UC cases, which may have high potential to turn to malignancy at any time.

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Conflicts of interest
There are no conflicts of interest.

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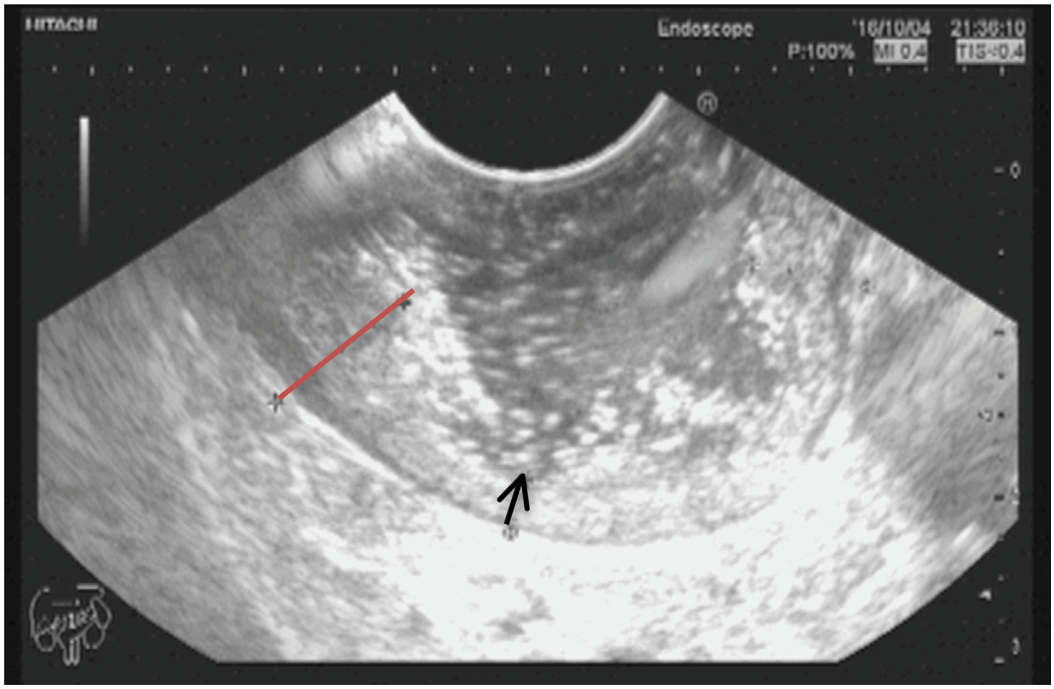
Figure 5



EUS at ulcerating area of rectum in a case of severe UC showing sloughed mucosal layer (black arrows) with increase in TWT=7.7 mm (red line). EUS, endoscopic ultrasound; TWT, total wall thickness; UC, ulcerative colitis.

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