Usefulness of texture and color enhancement imaging in assessing mucosal healing in patients with ulcerative colitis

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Background and aims: Endoscopic remission is known to be defined as a Mayo endoscopic subscore (MES) of ≤1 in patients with ulcerative colitis (UC). However, some individuals experience relapse even after showing endoscopic remission under white-light imaging (WLI), and no tool exists that can detect these individuals. The aim of this study was to clarify the usefulness of texture and color enhancement imaging (TXI) in the assessment of inflammation in patients with UC.

Methods: This was a prospective, single-arm, observational study conducted at a university hospital. From January 2021 to December 2021, 146 UC patients with endoscopic remission were enrolled. Images were evaluated by WLI, TXI, and pathologic evaluation, followed by prognostic studies. The primary endpoint of the study was the cumulative relapse of UC in each TXI score. The secondary endpoints were the association between TXI and pathologic scores, predictors of relapse, and interobserver agreement between the MES and TXI scores.

Results: Patients with TXI score 2 had significantly lower UC relapse-free rates than did those with TXI scores 0-1 (log-rank test, $P < .01$). When pathologic remission was defined as Matts grade ≤2, the rate of pathologic remission decreased significantly with higher TXI scores ($P = .01$). In multivariate analysis, TXI score 2 was the only risk factor for UC relapse ($P < .01$; hazard ratio, 4.16; 95% confidence interval, 1.72-10.04). Interobserver agreement on the TXI score was good ($\kappa = 0.597$-0.823).

Conclusion: TXI can be used to identify populations with poor prognosis in MES 1, for whom treatment intensification has been controversial. (Gastrointest Endosc 2023;97:759-66.)

Ulcerative colitis (UC) is a diffuse, nonspecific, inflammatory disease of the colorectum with an unknown cause that leads to erosions and ulcers. UC has a reported cumulative relapse risk of 70% to 80% and a cumulative colectomy risk of 10% to 15% 10 years after diagnosis.[1] Recently, clinical remission and mucosal healing have been proposed as an important therapeutic goal for patients with UC. In fact, achieving mucosal healing has been reported to reduce the risk of relapse, surgery, and colorectal tumors.[2-4]

Although endoscopic remission is often defined as Mayo endoscopic subscore (MES) ≤1 in the evaluation of endoscopic remission in UC,[5,6] several recent reports have

Abbreviations: MES, Mayo endoscopic subscore; TXI, texture and color enhancement imaging; UC, ulcerative colitis; WLI, white-light imaging.

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suggested that MES 1 has a higher relapse rate than MES 0.[7-9] Therefore, whether MES 1 should be included in endoscopic remission is controversial. In other words, MES 1 includes patients with and without a risk of relapse, which is difficult to determine by only ordinary endoscopic observation techniques. Therefore, the evaluation of endoscopic remission must be subdivided to distinguish between patients who are more likely and those who are less likely to experience relapse; however, no such novel tool exists.

In 2020, a novel image-enhanced endoscopic approach—texture and color enhancement imaging (TXI) (Olympus, Tokyo, Japan)—was launched, which optimizes the structure, color tone, and brightness of mucosal surfaces under normal light observation. It is expected to improve lesion observation by enhancing slight changes in color tone and structure on images that are difficult to observe with white-light imaging (WLI). Additionally, TXI is available at the push of a single button and at no additional cost. To date, the usefulness of TXI in the detection of early cancers of the pharynx and esophagus,[10] stomach,[11] and colorectum[12] have been reported. We hypothesized that different imaging technologies might be useful in the evaluation of inflammation in UC patients and also in cancer detection.

If the characteristics of TXI can be used to evaluate the mucosa below MES 1, conventionally referred to as endoscopic remission, with detailed segmentation the identification of patients who are at risk of relapse will be possible. Therefore, this study was designed to demonstrate the usefulness of TXI in evaluating inflammation in UC patients who have been identified by WLI to be in endoscopic remission.

METHODS

Study design

This was a prospective, single-arm, observational study conducted at a university hospital. The study complied with the Declaration of Helsinki, and the study protocol (approval ID 20200228) was approved by the Institutional Review Board of Keio University on November 30, 2020. The study was registered at the University Hospital Medical Network Clinical Trials Registry as UMIN000042730. All authors had access to the study data and reviewed and approved the final manuscript.

Patients

Patients with UC who underwent colonoscopy at Keio University Hospital between January 2021 and December 2021 were included in the study. The inclusion criterion was a confirmed diagnosis of UC before the index colonoscopy. The exclusion criteria were as follows: (1) no TXI images; (2) poor bowel preparation (Boston Bowel Preparation Scale = 0 (inadequate) or 1 (poor)[13]; (3) suspected bowel obstruction, stenosis, or fistula; (4) active colonic bleeding; (5) history of colectomy; (6) history of radiation therapy to the abdomen or pelvis; (7) inability to undergo biopsies because of chronic blood diseases or oral anticoagulant platelet medications; and (8) refusal to participate in the study. Inasmuch as this study included patients in endoscopic and clinical remission, we further excluded patients with MES $\geq$2, those with partial Mayo score $\geq$2, and those with insufficient imaging data.

Endpoints

The primary endpoint of this study was the cumulative relapse of UC in each subgroup categorized according to the TXI score as described below. UC relapse was defined as the worsening of clinical symptoms (increase in partial Mayo score $\geq$2) or as endoscopic findings (increase in MES) that necessitated more aggressive medical therapies for UC. The secondary endpoints were the association between TXI and pathologic scores, predictors of relapse, and interobserver agreement between the MES and the TXI scores.

Colonoscopy

All patients underwent conventional bowel preparation with oral polyethylene glycol (Moviprep; EA Pharma, Tokyo, Japan). Five inflammatory bowel disease experts performed total colonoscopy on all patients. All examinations were performed with a PCF-H290ZI endoscope connected to an EVIS X1 system (Olympus, Tokyo, Japan). The 3 sites (right side of colon, left side of colon, and rectum), including the most active site, were imaged by high-definition WLI and TXI, and biopsy samples were taken from the same sites. In cases of low inflammation throughout the colon, biopsy samples were obtained from the rectum only.

Evaluation of endoscopic images and TXI scores

The recorded images were stored as digital data on a hard disk and evaluated by 3 endoscopists. None of the evaluators performed endoscopy on the patients, and the endoscopists were blinded to the clinical and pathologic information. The severity of endoscopic inflammation was determined by the use of MES[14] as follows: 0 = normal mucosa or inactive disease; 1 = erythema, decreased vascular pattern, and mild friability; 2 = marked erythema, lack of a vascular pattern, friability, and erosions; 3 = spontaneous bleeding and large ulcerations as seen on WLI.

Given that TXI is an image-enhancement technique that optimizes structure, color tone, and brightness, we expected that TXI would enhance redness caused by UC inflammation and poor vascular visibility associated with mucosal edema. Therefore, the TXI scores were defined as follows: score 0 = no accentuated redness; score 1 = accentuated redness; score 2 = accentuated redness and

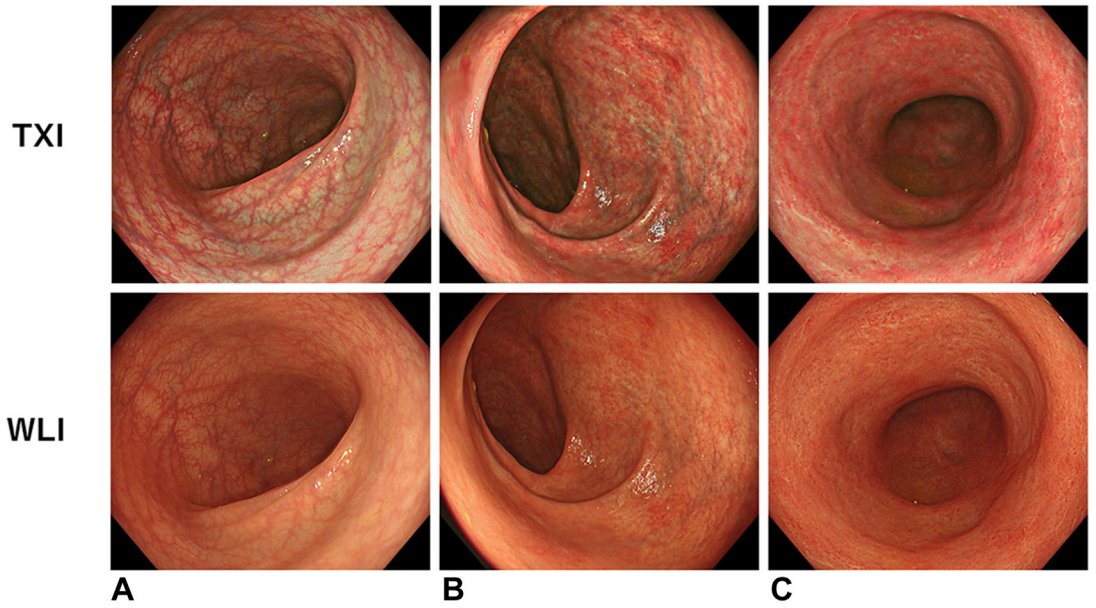

Figure 1. Representative images of each texture and color enhancement imaging (TXI) score. Mucosal images of ulcerative colitis on white-light imaging (WLI) and TXI. **A,** TXI score 0 = no accentuated redness. **B,** TXI score 1 = accentuated redness. **C,** TXI score 2 = accentuated redness and poor visibility of deep vessels.

poor visibility of deep vessels (Fig. 1). The TXI score for each patient was defined as the score of the most severely affected site.

Histologic assessment

Expert pathologists evaluated inflammation in the biopsy specimens using Matts histopathologic grades[15] as follows: 1 = normal appearance; 2 = some infiltration of round cells or polymorphs in the mucosa or lamina propria; 3 = much cellular infiltration of the mucosa, lamina propria, and submucosa; 4 = presence of crypt abscesses, with much infiltration of all layers of the mucosa; 5 = ulceration, erosion, or necrosis of the mucosa, with cellular infiltration to some or all layers. In this study, Matts histopathologic grades $\leq$2 were defined as pathologic remission. The pathologists were blinded to clinical information.

Sample size calculation

On the basis of historical data from our hospital, we estimated the annual relapse rate for patients with MES 0 to 1 as approximately 15%. Inasmuch as final relapse in 30 patients was necessary for us to perform a multivariate analysis including at least 3 variables as risk factors for relapse, we decided to use a sample size of 200 patients.

Statistical analyses

Continuous variables are expressed as mean $\pm$ standard deviation. The Fisher exact test was used to test categoric variables. Kaplan-Meier analysis and log-rank test were used to analyze the cumulative relapse-free rate. Bonferroni correction was performed when multiple evaluations were performed. Univariate Cox proportional hazard regression was used to identify the risk factors for relapse. Multivariate Cox proportional hazard regression analysis was used for the variables that were significant in the univariate analysis. Interobserver agreement was calculated by weighted κ values; κ values of <0.20, 0.21 to 0.40, 0.41 to 0.60, 0.61 to 0.80, and >0.80 indicated poor, fair, moderate, good, and excellent agreement, respectively. P values of $< .05$ were considered statistically significant. JMP (version 14.0; SAS Institute, Cary, NC, USA) was used for all statistical analyses.

RESULTS

Patient characteristics

Between January 2021 and December 2021, 995 patients with UC underwent colonoscopy at Keio University Hospital. Of those, 200 patients met the inclusion criterion. Additionally, 46 patients with MES $\geq$2, 1 with insufficient data, and 7 with partial Mayo score $\geq$2 were excluded, resulting in 146 patients being included in the final analysis (Fig. 2).

The clinical characteristics of the 146 patients included in this study are shown in Table 1. From these patients, 263 biopsy specimens were evaluated. Forty-four patients (30.1%) were classified as MES 0 and 102 (69.9%) as MES 1.

Cumulative relapse of UC in each subgroup according to the TXI score

The cumulative relapse of UC in each subgroup divided according to TXI score is shown in Figure 3. Twenty-three patients experienced clinical relapse during the observation period (average 232.0 $\pm$ 91.9 days). Finally, patients with TXI

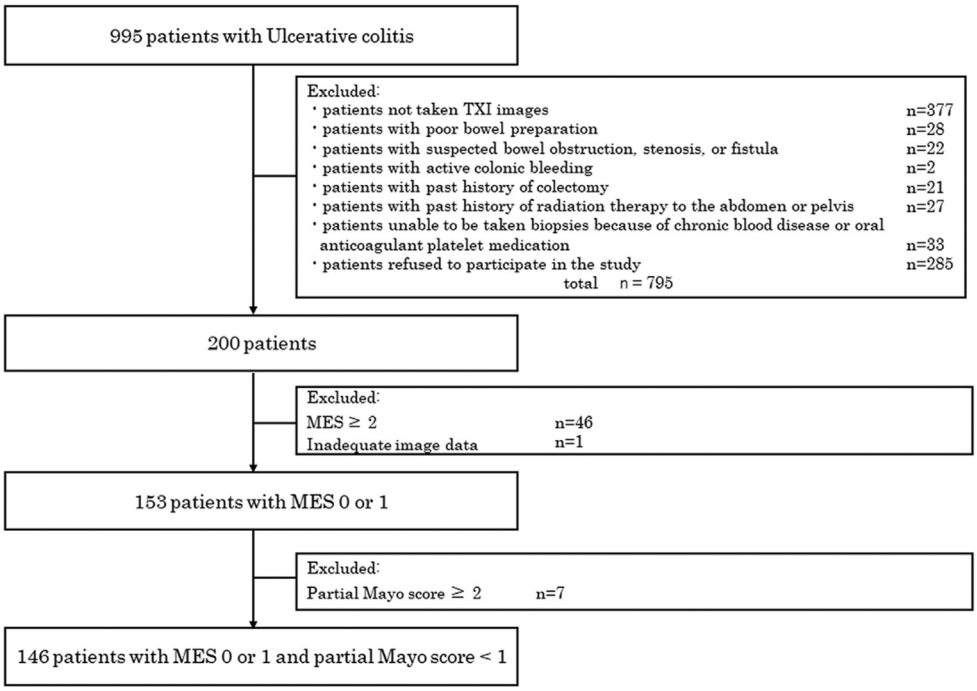

Figure 2. Study flowchart. *MES,* Mayo endoscopic subscore; *TXI,* texture and color enhancement imaging.

TABLE 1. Clinical characteristics of the patients under study

Characteristic	Value
Number of patients	146
Number of sites undergoing biopsy	263
Sex	
Male	99 (67.8%)
Female	47 (32.2%)
Age, y	47.2 ± 14.7
Disease duration, y	13.6 ± 8.7
Extent of disease	
Total colitis	88 (60.3%)
Left-sided colitis	37 (25.3%)
Proctitis	21 (14.4%)
Mayo endoscopic subscore	
0	44 (30.1%)
1	102 (69.9%)
Albumin (g/dL)	4.37 ± 0.51
C-reactive protein (mg/dL)	0.12 ± 0.20
Current medical treatment	
5-ASA	129
5-ASA suppository/enema	28
Corticosteroid	2
Corticosteroid enema/foam	8
Immunomodulator	28
Biologics	27
Observation period (days)	232.0 ± 91.9

5-ASA, 5-aminosalicylic acid.

score 2 had significantly lower UC relapse-free rates than did those with TXI scores 0 to 1 (log-rank test; $P < .01$).

Association between MES and TXI score

The association between MES and TXI scores for 263 sites where biopsy and endoscopic evaluation could be performed is presented in Figure 4. Approximately 80% of MES 0 mucosa sites were classified as TXI score 0, whereas MES 1 mucosa was subdivided into TXI scores 0, 1, and 2. TXI score 2 was found only in the MES 1 group, not in the MES 0 group.

Association between TXI score and Matts histopathologic grades

Figure 5 illustrates the relationship between TXI score and pathologic inflammation assessment by presenting the relationship between TXI score and Matts histopathologic grades. Most sites with TXI score 0 (95.2%) were grade 2 according to Matts grades. For TXI scores 1 and 2, the percentage of grade 2 according to Matts grades decreased as the scores increased (TXI score 1, 67.8%; TXI score 2, 40.0%).

Analysis of factors predicting relapse

A risk factor analysis for UC relapse is presented in Table 2. In univariate analysis, MES 1 ($P = .04$) and TXI score 2 ($P < .01$) were identified as risk factors for UC relapse. Furthermore, when the 2 factors were subjected to multivariate analysis, only TXI score 2 was determined to be significantly involved in UC relapse ($P < .01$; hazard ratio, 4.16; 95% confidence interval [CI], 1.72-10.04).

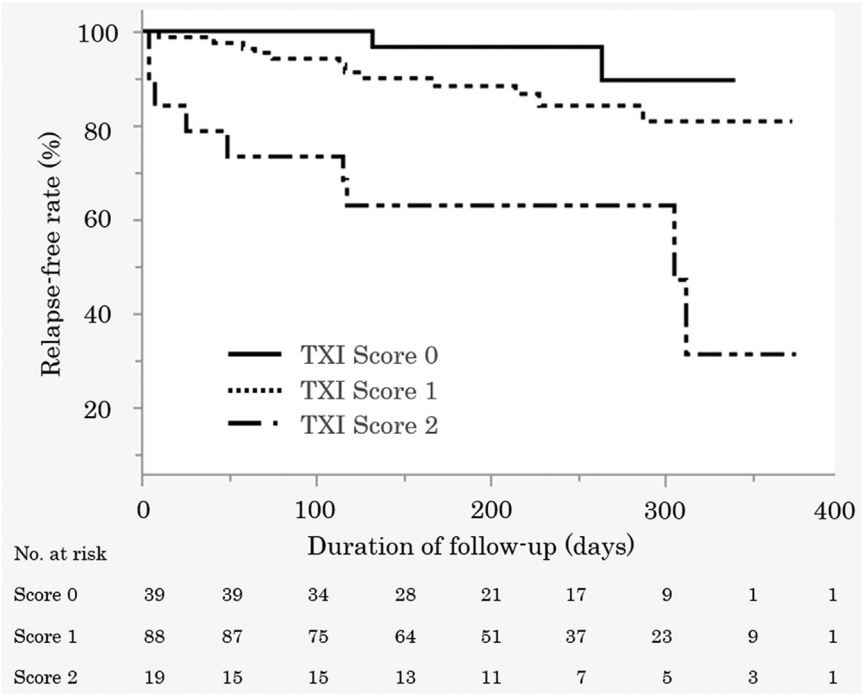

Figure 3. Relapse-free rate of each texture and color enhancement imaging (TXI) score. TXI score 2 had a significantly lower relapse-free rate than TXI scores 0 and 1 ($P < .01$); P values were calculated by the log-rank test.

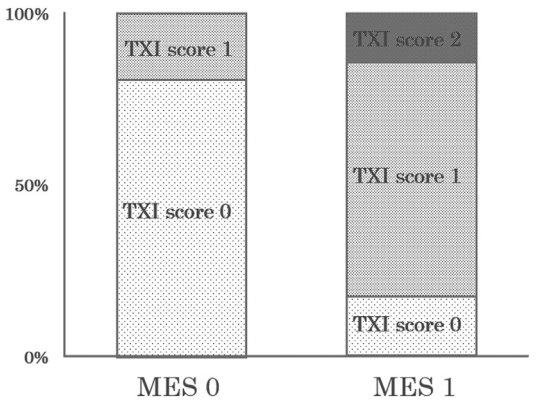

Figure 4. Proportion of texture and color enhancement imaging (TXI) score for each Mayo endoscopic subscore (MES). There was no TXI score 2 in MES 0, and MES 1 was subdivided into TXI scores 0, 1, and 2.

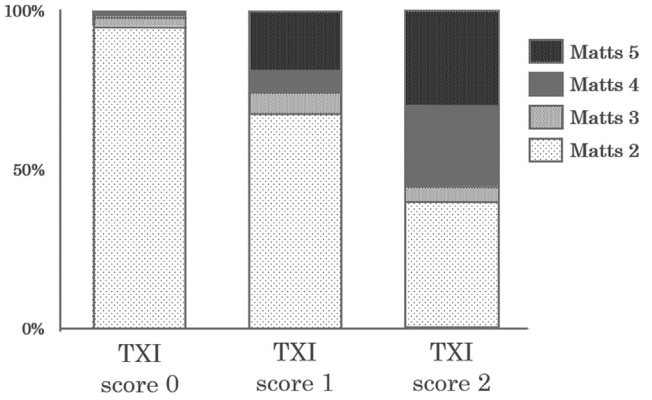

Figure 5. Proportion of Matts histopathologic grades for each texture and color enhancement imaging (TXI) score. The percentage of Matts histopathologic grade ≥3 increased with each increase in the TXI score.

Therefore, the relapse-free rate was again subjected to Kaplan–Meier analysis for patients with MES 0, MES 1 with TXI score 0 to 1, and MES 1 with TXI score 2 (Fig. 6). The relapse-free rate was significantly lower in MES 1 with TXI score 2 than in the others.

Interobserver agreement in TXI score

Supplementary Table 1 (available online at www.giejournal.org) presents the interobserver agreement in MES and TXI scores. No good results were obtained for MES, with κ values of 0.340 to 0.521. However, for the TXI score the κ values ranged from 0.597 to 0.823, all of which showed good to excellent agreement.

DISCUSSION

To the best of our knowledge, this is the first study to demonstrate the usefulness of TXI as a new image-enhancement system to assess inflammation in UC during remission. TXI allowed for a more segmented assessment of the mucosa in endoscopic remission. Patients with TXI score 2 had significantly lower UC relapse-free rates than

TABLE 2. Analyses of factors affecting relapse

Factor		Univariable Cox regression		Multivariable Cox regression	
		Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Sex	Male	1.00	ref		
	Female	1.04 (.43-2.57)	.92		
Age (≤65 y)		3.82 (.51-28.4)	.10		
Disease duration (≥10 y)		0.76 (.33-1.71)	.50		
Total colitis		1.32 (.56-3.12)	.52		
Albumin (≤4 g/dL)		1.25 (.37-4.25)	.73		
C-reactive protein (≥1.0 mg/dL)		1.52 (.66-3.52)	.34		
Corticosteroid enema/foam		2. (.63-7.24)	.27		
Immunomodulator		0.56 (.17-1.88)	.31		
Biologics		1.12 (.42-3.05)	.83		
MES	0	1.00	ref		
	1	2.96 (.88-9.96)	.04	1.95 (.54-6.98)	.28
TXI score	0-1	1.00	ref		
	2	5.00 (2.16-11.57)	< .01	4.16 (1.72-10.04)	< .01

CI, Confidence interval; *MES,* Mayo endoscopic subscore; *TXI,* texture and color enhancement imaging.

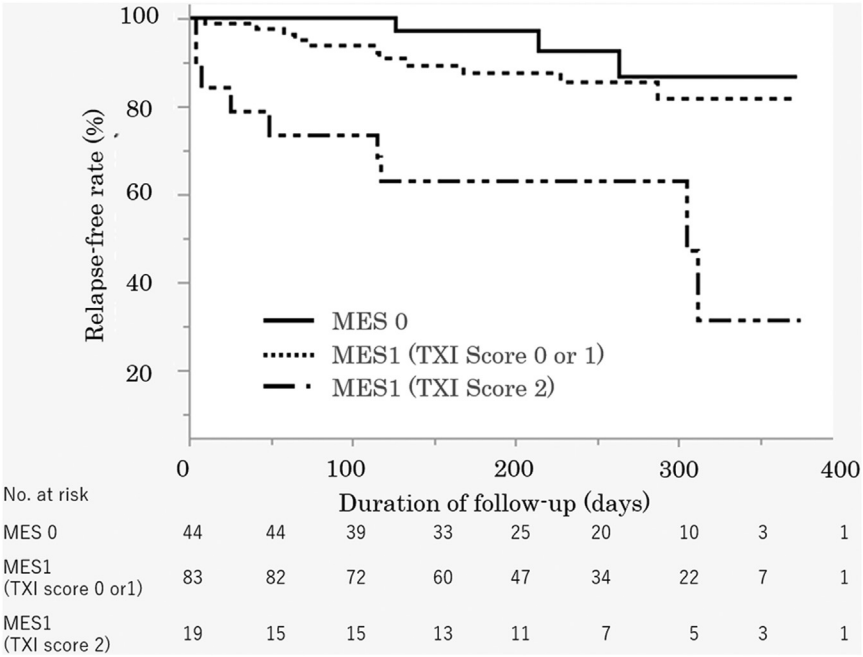

Figure 6. Relapse-free rate of Mayo endoscopic subscore (MES) 0 and MES 1 (texture and color enhancement imaging [TXI] scores 0-1 and TXI score 2). MES 1 (TXI score 2) had a significantly lower relapse-free rate than MES 0 and MES 1 (TXI scores 0-1) ($P < .01$); *P* values were calculated with the log-rank test.

did those with TXI score 0 to 1 (hazard ratio, 4.16; 95% CI, 1.72-10.04).

Endoscopic observation can evaluate a broad surface, not merely a point, less invasively and thus has long been considered the criterion standard for assessing the degree of intestinal inflammation. MES was developed in 1987 to evaluate the efficacy and safety of oral 5-aminosalicylic acid therapy and has long been used in UC.[14] Currently, the treatment goal in UC is not only clinical remission but also mucosal healing.[16] To date, clinical studies have considered endoscopic remission to have MES 0 to 1,[4,5] whereas MES ≥2 indicates eligibility for treatment. However, recently it has been reported that there is a difference of relapse risk between MES 0 and MES 1, both traditionally considered to

be in endoscopic remission. In fact, a meta-analysis by Viscido et al[9] reported lower clinical relapse rates for MES 0 than for MES 1, suggesting that further detailed inflammation assessment is needed for patients with MES 0 to 1. This study reveals that MES 1, which has traditionally been considered to indicate remission with WLI, includes a population at high risk of relapse. Although there have been reports of differences in long-term prognosis between patients with MES 0 and those with MES 1,[7,8] to our knowledge there are no reports of prospective trials indicating that patients with MES 1 had improved prognosis with intensified treatment. Therefore, whether to intensify treatment for patients with UC and MES 1 without clinical symptoms has been a controversial issue, with the decision being left to the discretion of the physician. In this study, patients in endoscopic remission were subdivided according to their TXI scores to determine individuals with an exceptionally low relapse-free rate. Surprisingly, more than half of the patients with TXI score 2 experienced relapse during the observation period (Fig. 3); this rate is remarkably high compared with those reported in previous studies, and the TXI score 2 population is likely to have an extremely poor prognosis and may require intensified treatment. In other words, it may be possible by the use of TXI to detect individuals in need of treatment intensification.

This study was designed to subdivide cases of UC in remission. As shown in Figure 4, most MES 0 mucosa was classified under TXI score 0 and could not be further subdivided; however, MES 1 mucosa could be subdivided into TXI scores 0 to 2. TXI score 2 was included only in MES 1 and was associated with Matts pathologic grades (Fig. 5). In fact, when pathologic remission was defined as Matts grade ≤ 2, a significant difference in the pathologic remission percentage was observed between TXI scores 0 and 1 ($P < .01$) and between TXI scores 1 and 2 ($P = .01$). Additionally, in diagnosing histologic remission, the accuracy of the TXI score was significantly higher than that of the MES (80% vs 62%; $P < .01$) (Supplementary Table 2, available online at www.giejournal.org). To date, it has been reported that endoscopic and histologic assessments of inflammation do not always correlate and that histologic assessment rather than endoscopic assessment can better assess subsequent relapse and the need for corticosteroids.[17,18] This study suggests that a higher TXI score indicates a higher degree of pathologic inflammation. In other words, TXI may allow us to evaluate "deep" endoscopic remission, which is closer to histologic remission.

This study has several limitations. First, the research was conducted in a single center. Second, image evaluation was not performed during the examination; only the images taken by the endoscopist were evaluated. However, all examinations were performed by inflammatory bowel disease specialists and included images of the most intensely inflamed areas; therefore, there was no confusion in the assessment of the association with relapse. Third, it was unclear as to what was indicated by the areas of redness accentuated by TXI. We discussed with the pathologist the difference between redness-accentuated areas and other areas; however, the underlying reason for this remains unclear because TXI does not use a particular wavelength of light. Fourth, interobserver validation was not performed with respect to assessment of pathologic inflammation. Fifth, because this was an exploratory study, no validity assessment of the TXI score was conducted. Based on the results of this study, future validation studies of the TXI score should be carried out.

In conclusion, in patients determined to be in endoscopic remission by the use of WLI, the degree of inflammation can be subdivided and evaluated with TXI. Furthermore, TXI can be used to diagnose MES 1 in individuals with a poor prognosis, for whom treatment intensification has been controversial. Randomized controlled trials of therapeutic interventions for populations with poor prognosis are warranted in the future.

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SUPPLEMENTARY TABLE 1. Interobserver agreement for Mayo endoscopic subscore and texture and color enhancement imaging score

Mayo endoscopic subscore		
	A	B
B	0.340	-
C	0.521	0.449
Texture and color enhancement imaging score		
	A	B
B	0.823	-
C	0.664	0.597

SUPPLEMENTARY TABLE 2. Diagnostic yield of TXI score and MES for histologic remission

Instrument	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
TXI score	96	21	81	60	80*
MES	56	85	93	35	62

Matts histopathologic grade $\leq$2 was defined as histologic remission.
For TXI score, scores 0-1 were considered positive and score 2 was considered negative. For MES, MES 0 was considered positive and MES 1 was considered negative.
MES, Mayo endoscopic subscore; *TXI,* texture and color enhancement imaging; *PPV*, positive predictive value; *NPV*, negative predictive value.
**P* .01 (McNemer test).