VALIDATION OF US EVALUATION OF ULCERATIVE COLITIS ACTIVITY

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Abstract- This study was aimed at validating the inter-rater grading agreement for assessing disease activity in patients with established ulcerative colitis (UC) using transabdominal ultrasonography (US) versus colonoscopy (CS). Fifty-seven patients underwent US and CS at four facilities. UC disease activity was assessed using the original US grading system and CS Matts classification. Initially, the US and CS grades were assessed at each examining facility, and still images and movie clips were re-assessed at the central facility. Grading agreement between the examining and central facilities was evaluated. Grading agreement for US and CS were 0.75 and 0.72 in all segments and 0.82 and 0.70 in the maximum grade of each patient, respectively (all $p < 0.001$). US grading agreement was “almost perfect” for the maximum grade and “moderate” to “substantial” for other assessments. The inter-rater US grading agreement was good and not inferior to that of CS for evaluating UC disease activity.

Keywords: Ultrasound, Colonoscopy, Inter-rater agreement, Ulcerative colitis, Disease activity

INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease of unknown etiology characterized by inflammation of the mucosa and submucosa (Danese and Fiocchi 2011; Ungaro et al. 2017). The inflammation usually involves the rectum and extends proximally in the colon for a variable distance. Additionally, it is characterized by alternating periods of remission and relapse. The incidence of UC has been increasing (Ng SC et al. 2018), and the accurate evaluation of disease extent and activity is necessary for disease monitoring and treatment response. The current UC therapeutic goal is to achieve and sustain mucosal healing evaluated using colonoscopy (CS) (Dignass et al. 2012). However, CS is invasive, and difficult to perform frequently; additionally, the risk of perforation is of concern (Civitelli et al. 2014).

Recently, transabdominal ultrasonography (US) has been identified as a useful diagnostic tool for gastrointestinal diseases, especially UC (Allocca et al. 2018; Parente et al. 2010). US can non-invasively observe the detailed wall layer structure in high resolution, as a result of recent advances in the ultrasound scanner (Kucharzik et al. 2015). We have reported moderate concordance between US and CS for evaluating UC in a multicenter prospective study

(Kinoshita et al. 2018). However, if only US experts can diagnose correctly, US cannot be used widely. Therefore, the diagnostic reliability of US requires validation. This study aimed to assess whether US could be used at different facilities to evaluate UC disease activity. We verified the inter-rater grading agreement of US compared with CS as the reference standard.

METHODS

Patients and study design

From June 2013 to August 2016, established UC patients who had undergone US and CS within 2 d at Tomakomai City Hospital, Sapporo Higashi Tokushukai Hospital, Ohguro Gastroenterological Hospital, and NTT East Japan Sapporo Hospital were enrolled. Patients were excluded if they were younger than 19 y of age or had acute complications such as severe bleeding and toxic megacolon, and histologically proven cytomegalovirus colitis. Clinical disease activity was evaluated using the Rachmilewitz clinical activity index (CAI) and classified as inactive, mild, moderate or severe disease (Rachmilewitz 1989). The variables of this index include bowel frequency, blood in stool, general well-being, abdominal pain, body temperature >38.0˚C, erythrocyte sedimentation rate >50 mm/h and hemoglobin level <10.0 g/dL. Disease severity was originally scored as follows:

0-2, inactive disease; 3-4, mild disease; 5-7, moderate disease; 8, severe disease. This study was approved by the institutional review board in each facility, and written informed consent was obtained from all the patients in accordance with the Declaration of Helsinki.

Transabdominal ultrasonography

Ultrasonography was performed using the PVT-375 BT (center frequency: 3.75 MHz), 674 BT (center frequency: 6 MHz) and 704 AT/BT (center frequency: 7.5 MHz) equipped with Xario and Aplio XV/XG/500 (Canon Medical Systems Corp., Otawara, Japan). Six segments of the colon and rectum were sequentially and individually assessed.

US was performed by 17 sonographers, of whom 5, 4 and 8 had <5, 5-10 and >10 y of experience, respectively. Patients generally remained in the supine position during examinations or were moved to the decubitus position as needed. First, convex transducers (frequency: 3.75/6.0 MHz) were used, followed by a high-frequency linear-array transducer (7.5 MHz) for detailed evaluation. The colon and rectum were sequentially assessed first to identify the hepatic flexure, and then the ascending colon toward the cecum was scanned to recognize the terminal ileum and Bauhin's valve. The examination proceeded to the sagittal

plane of the midline to identify the transverse colon located on the caudal side of the gastric antrum. The probe was then rotated 90˚ to trace the transverse colon from the hepatic to the splenic flexure. The descending colon was identified on the left flank. Finally, the colon was traced from the sigmoid colon to the rectum, which was visualized through the urinary bladder. Convex probes (center frequency: 3.75/ 6 MHz) were used to study the rectum. Patients were not asked to fill their bladders before US.

We divided the colon into six segments, including the cecum, ascending colon (A-colon), right-sided trans- verse colon (right T-colon), left-sided transverse colon (left T-colon), descending colon (D-colon), sigmoid colon (S-colon) and rectum, which were examined. The sonographers at the examination facilities saved still images and movie clips if needed.

The US severity was graded on a scale of 1-4 created according to a previously reported study (Hata et al. 1992). We verified this scale in our preliminary study (Wada et al. 2015) and used it in recently published prospective study (Kinoshita et al. 2018) as follows: grade 1 = normal thickening of the colonic wall, <4 mm (Hagiu and Badea 2007); grade 2 = thickened mucosa and submucosa without hypo-echoic change of the submucosa; grade 3 = bowel wall thickening

with loss of stratification; and grade 4 = bowel wall thickening with loss of stratification and irregular mucosa or hyper-echogenic areas in the mucosa, suggesting ulceration (Fig. 1). Furthermore, colonic segments that were difficult to observe were defined as grade “x”.

Initially, the US grade was assessed at each examining facility. All sonographers were aware of the UC diagnosis but were blinded to the patients’ clinical information and CS findings. Next, still images and movie clips were sent to and re-assessed at the central facility by two affiliated registered medical sonographers (M.N. and S. O.) specialized in gastroenterology and hepatology and having more than 5 y of experience. These sonographers interpreted the US grades via consensus. Central readers were also blinded to the interpretations of the US grades made by examining facilities. The grading agreement between the examining and central facilities was then evaluated. Before study initiation, sonographers at all facilities attended four training sessions to ensure a consistent interpretation of the US techniques and grading severity.

Colonoscopy

Colonoscopy was performed by five expert endoscopists who had conducted at

least 2000 CSs using standard CS tools (PCF-Q260, CF-HQ290 I, CF-H260 AZI, CF-Q240 I; Olympus, Tokyo, Japan) before conducting the study procedures. A polyethylene glycol-based bowel preparation was provided to the patients. For patients with severe UC, CS was performed without bowel preparation to avoid the risk of perforation. Six colonic segments and the rectum were examined by CS.

In each segment, disease activity was assessed according to Matts' endoscopic classification (CS grades1-4) as follows: grade 1 = remission; grade 2 = mild activity; grade 3 = moderate activity; grade 4 = severe activity (Hozumi et al. 2013; Matts 1961; Walsh et al. 2014) (Fig. 2). The physicians performing the endo scopic examinations were aware of the UC diagnosis but were blinded to the results of the US examinations. First, CS grade was assessed at each examining facility. Next, still images were sent to and re-assessed at the central facility. Three endoscopists (K.K, R.O. and T.K) affiliated with the central facility who had more than 4 y of experience in performing CS interpreted CS grading by consensus. They were also blinded to the patients' clinical information.

Statistical analysis

The US and CS visualization rates for each colonic segment were compared using McNemar tests. Grading agreement for US and CS between the examining and central facilities was assessed for each segment and all colonic segments, and the maximum US and CS grades, which represented the disease activity of each patient, were evaluated using weighted k statistics. The k values were interpreted as follows: $k \leq 0.20$, slight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; 0.81-1.00, almost perfect agreement (Landis and Koch 1977). p Values < 0.05 were considered to indicate statistical significance. The statistical analysis was performed using standard statistical software (SPSS Statistics Version 23.0 [IBM, Armonk, NY, USA] and the Bell Curve for Excel Version 2.11 [Social Survey Research Information Corp., Tokyo, Japan]).

RESULTS

During the study period, 72 consecutive UC patients underwent US and CS; of these patients, 14 did not undergo US and CS within 2 d, and 1 was suspected of having Crohn's disease. The characteristics of the remaining 57 patients included in this study are summarized in Table 1. Forty-four patients underwent

US and CS on the same day, and all the patients underwent CS after US. Total CS was achieved in 48 (84.2%) patients; in the remaining 9 (15.8%) patients, CS was incomplete because of disease severity or insufficient preparation of the colon. In 57% and 20.8% of patients, the Rachmilewitz CAI assessment indicated inactive and moderately active disease, respectively (Table 1).

Table 2 outlines the details of the site-specific visualization rates, which were higher with US than with CS. Visualization rates for the A-colon, right T-colon and rectum differed significantly between US and CS. US grading agreement for evaluation of UC disease activity was substantial in the majority of the segments, but moderate in the cecum and rectum. CS grading agreement was substantial except for the rectum (0.43) (Table 3). For the maximum grade in each patient, the US and CS grading agreement values were 0.82 and 0.70, respectively (Table 4). Notably, US achieved almost perfect agreement. Representative US findings are illustrated in Figures 3-5.

DISCUSSION

Reports have described the usefulness of US for assessing disease activity and therapeutic response in patients with UC (Allocca et al. 2018; Parente et al.

2010). However, previous studies were conducted at single centers and excluded patients in whom the disease was localized to the rectum. Other studies have reported that US can be used to observe the ileocecum, sigmoid and descending colon in the majority of patients (Bremner et al. 2006; Panes et al. 2013). However, the present study achieved excellent US visualization rates in each segment (>90%), as well as in the rectum (84%). Recent advances in US equipment have enabled exploration of nearly the entire colon. However, the slightly lower visualization rate for the rectum was likely attributable to its deeper location in the pelvis. In contrast, the CS visualization rate was lower in the right-sided colon, which was attributed to insufficient preparation of the colon to avoid possible risks of perforation or aggravation of disease activity in cases of severe UC. Our results suggest that US might provide a feasible alternative means of evaluating the right-sided colon in these severe cases of UC.

Previous studies reported moderate to substantial inter-observer agreement between computed tomography (Horvat et al. 2016) and/or magnetic resonance imaging (MRI) enterography (AlSabban et al. 2017) intended to image inflammatory bowel diseases. Another study reported inter-observer agreement with k values of 0.22-0.85 for US evaluation of Crohn’s disease and suggested

that the poor reproducibility might be attributable to difficulties in recognizing the layered structure (Fraquelli et al. 2008). Allocca et al. (2018) recently reported almost perfect agreement (k = 0.86) between two physicians who conducted US evaluations of UC activity. In that study, however, US was performed by expert physicians at the same facility.

As previously published reports described US evaluations performed mostly by expert physicians at single centers, this is the first inter-rater validation study involving sonographers with a wide range of US experience at four examining facilities and a central facility. Notably, we achieved good US grading agreement and convergence in the majority of segments (k = 0.72-0.78), as well as moderate grading agreement and convergence in the cecum and rectum (both with k = 0.54). Our results suggest that the use of standardized US procedures and unified interpretations might be necessary to generalize the US grading system for assessing UC activity.

In our study, 20% (n = 9/44) of the cases exhibited inconsistencies in the rectum, which were attributed to an inability to use the high-frequency probes required for a detailed evaluation. Intermediate findings can be difficult to interpret, especially because US grade 2 encompasses a wide range of imaging findings. Therefore,

bowel wall thickness with or without irregular mucosa or a hyper-echogenic shallow concavity in the mucosa were difficult to grade using only still images. In our study, CS grading agreement was substantial (k = 0.68-0.79), with the exception of the rectum. In a previous study, expert endoscopists determined a weighted k value of 0.76 for Matts' activity indices (Osada et al. 2010). Their result was concordant with our findings.

We note that the decreased US and CS concordance rates in our study might be due to the enrollment of mostly patients with inactive to mild disease activity. In a previous review of MRI, Horsthuis et al. (2009) stated that severe disease has more pronounced features and is therefore easier to diagnose than mild disease.

This study had several limitations. First, the study population included a small proportion of patients with moderate to severe disease activity (28.3%). Second, 20 patients did not undergo US and CS on the same day, which may have affected our results. Finally, we compared recorded images rather than repeating the examination for the same patients. There was a difference between repeated examinations and re-assessed recorded images. However, in a multicenter study setting, it would be difficult to repeat both US and CS examinations at four

different facilities during a short interval.

Despite these limitations, this study represents a meaningful contribution with respect to US evaluation of disease activity associated with UC. Our findings suggest that it is possible to apply US not only at expert facilities, but also in trained facilities, if the inspection procedures and US techniques are standardized.

CONCLUSIONS

We achieved good to excellent agreement between the US results obtained at the examining facilities and central facility. These findings suggest that US is not inferior to CS for evaluating UC disease activity. Therefore, US can be used to evaluate UC disease activity at different facilities.

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Figure Captions List

Figure 1. Ultrasonography Grade

(A) Ultrasonography Grade 1: normal thickness of the colonic wall and all wall layers are maintained (arrows). (B) Ultrasonography Grade 2: thickened mucosa and submucosa without hypo-echoic change in the submucosa (arrows). (C) Ultrasonography Grade 3: thickened mucosa and submucosa with loss of stratification (arrows). (D) Ultrasonography Grade 4: bowel wall thickening with loss of stratification (yellow arrows), and irregular mucosa or hyper-echogenic areas in the mucosa (pink arrowhead) suggesting ulceration.

Figure 2. Colonoscopy Grade

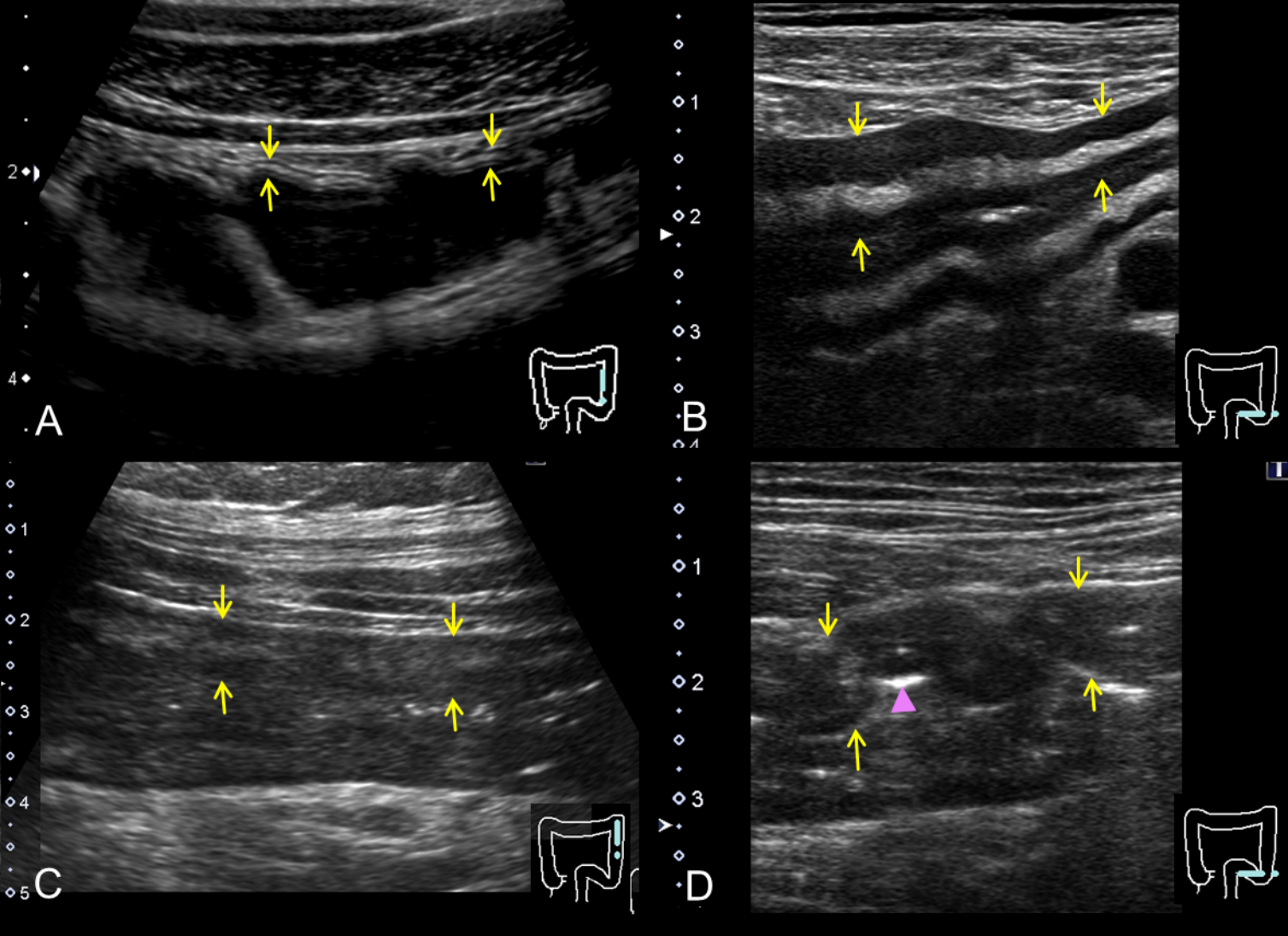
(A) Matts' grade 1: normal. (B) Matts' grade 2: mild granularity of the mucosa with mild contact bleeding. (C) Matts' grade 3: marked granularity and edema of the mucosa, contact bleeding and spontaneous bleeding. (D) Matts' grade 4: severe ulceration of the mucosa with hemorrhaging.

Figure 3. Forty-year-old woman with extensive ulcerative colitis and a Rachmilewitz clinical activity index of 11. Agreement was determined between

the examining and central facilities for the interpretations of US images of the sigmoid colon. (A) Both the central and examining facilities interpreted the ultrasonography image as grade 4; moderate to severe wall thickening, loss of wall layer stratification (hypo-echoic change of submucosa) and disruption of the mucosa or submucosal layer were identified. (B) Both the central and examining facilities interpreted the colonoscopy findings as Matts' grade 4.

Figure 4. Thirty-four-year-old woman with extensive ulcerative colitis and a Rachmilewitz clinical activity index of 13. Disagreement occurred during interpretation of the US image of the cecum. (A) The examining facility interpreted the ultrasonography as grade 4, whereas the central facility interpreted it as grade 2. Wall thickening without hypo-echoic changes in the submucosa was identified by ultrasonography. However, the image was misinterpreted as a loss of layer structure because of the ambiguous muscularis propria layer and serosal border of the posterior wall (yellow arrowhead). (B) The central and examining facilities both interpreted the colonoscopy as Matts' grade 2.

Figure 5. Fifty-seven-year-old man with extensive ulcerative colitis. Disagreement occurred during interpretation of the US image of the left transverse colon. (A) The examining facility interpreted the ultrasonography as grade 1, whereas the central facility interpreted the ultrasonography as grade 2. A very slightly thickened mucosa and submucosa with a layered structure were identified on the ultrasonography image. (B) Interpretation of the colonoscopy was also inconsistent between the facilities. The examining facility interpreted the colonoscopy as Matts' grade 1, whereas the central facility interpreted it as Matts' grade 2.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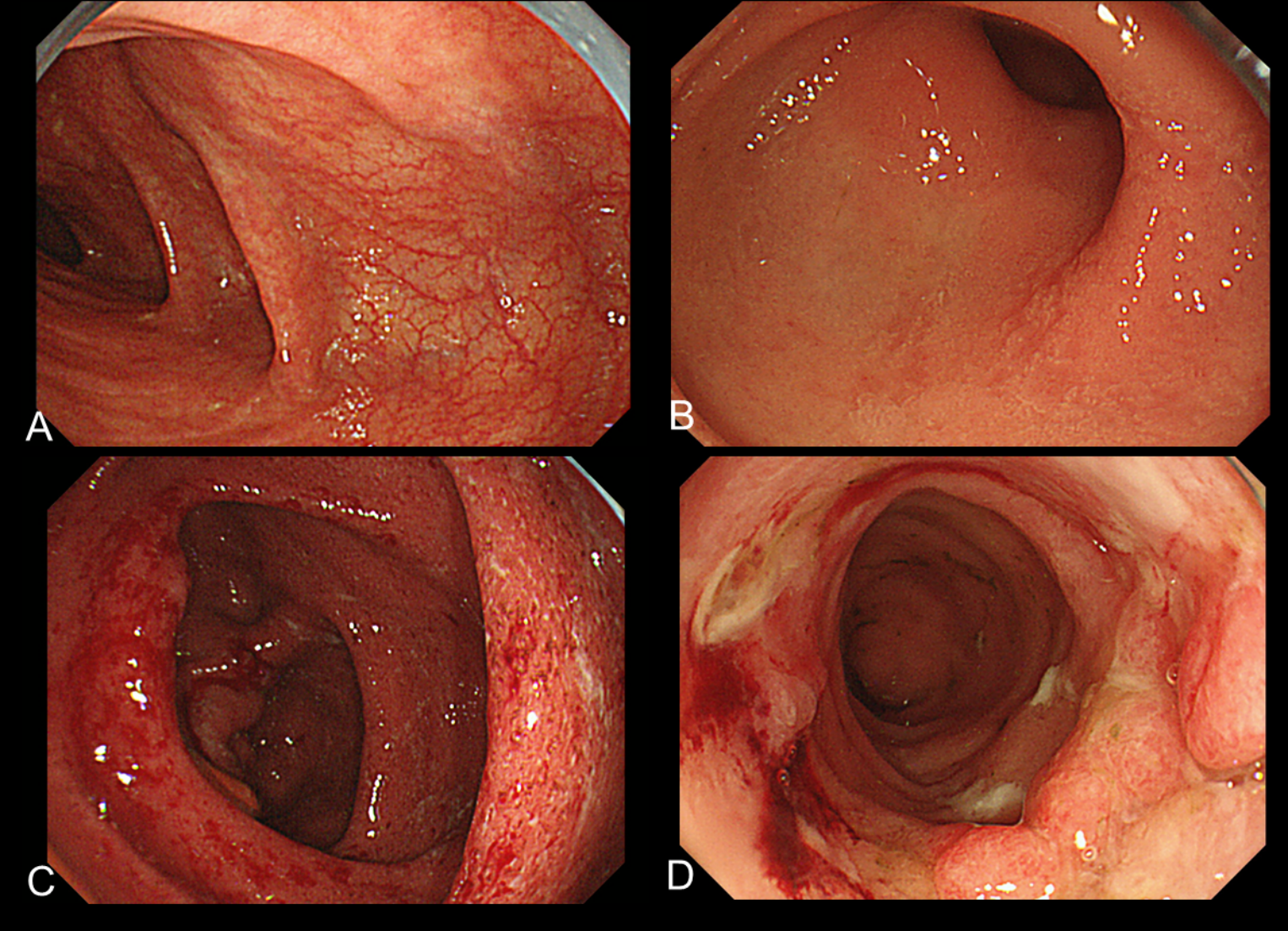
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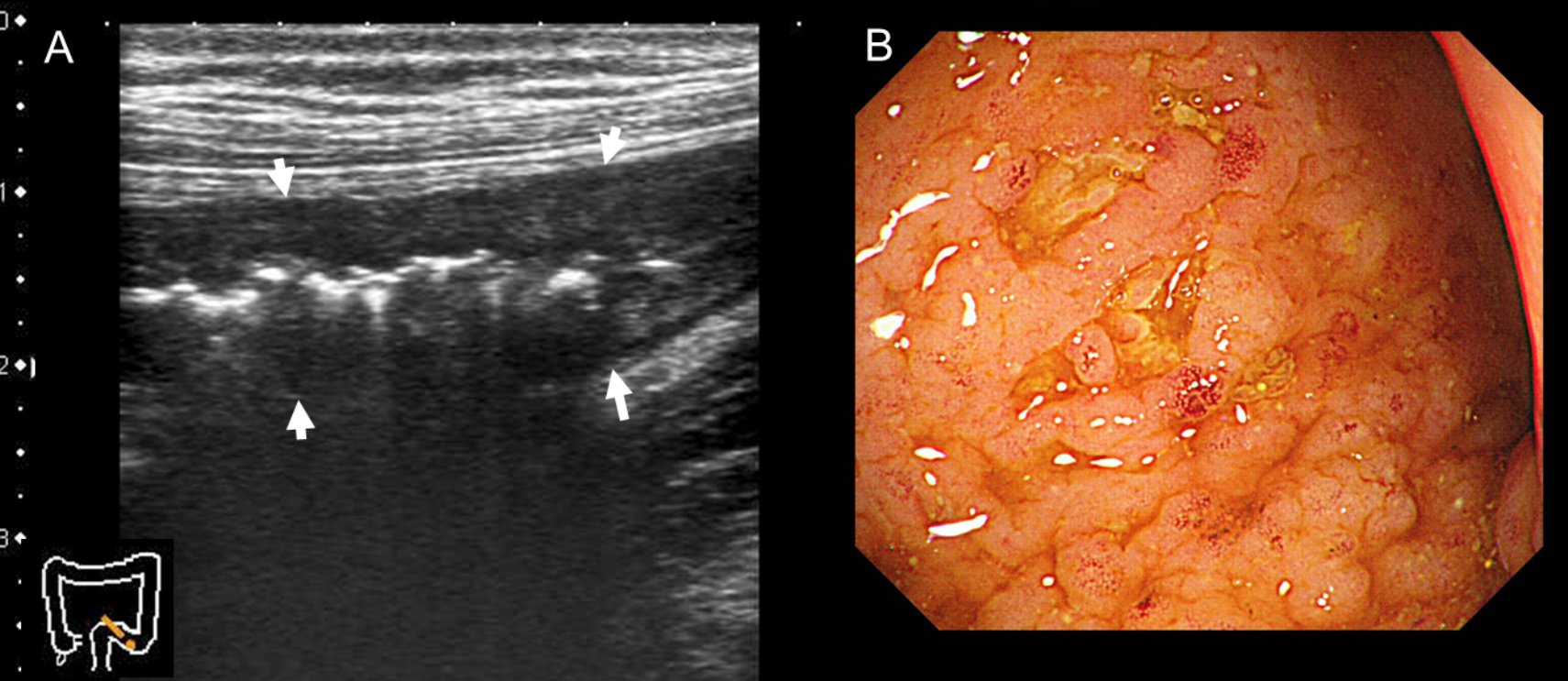
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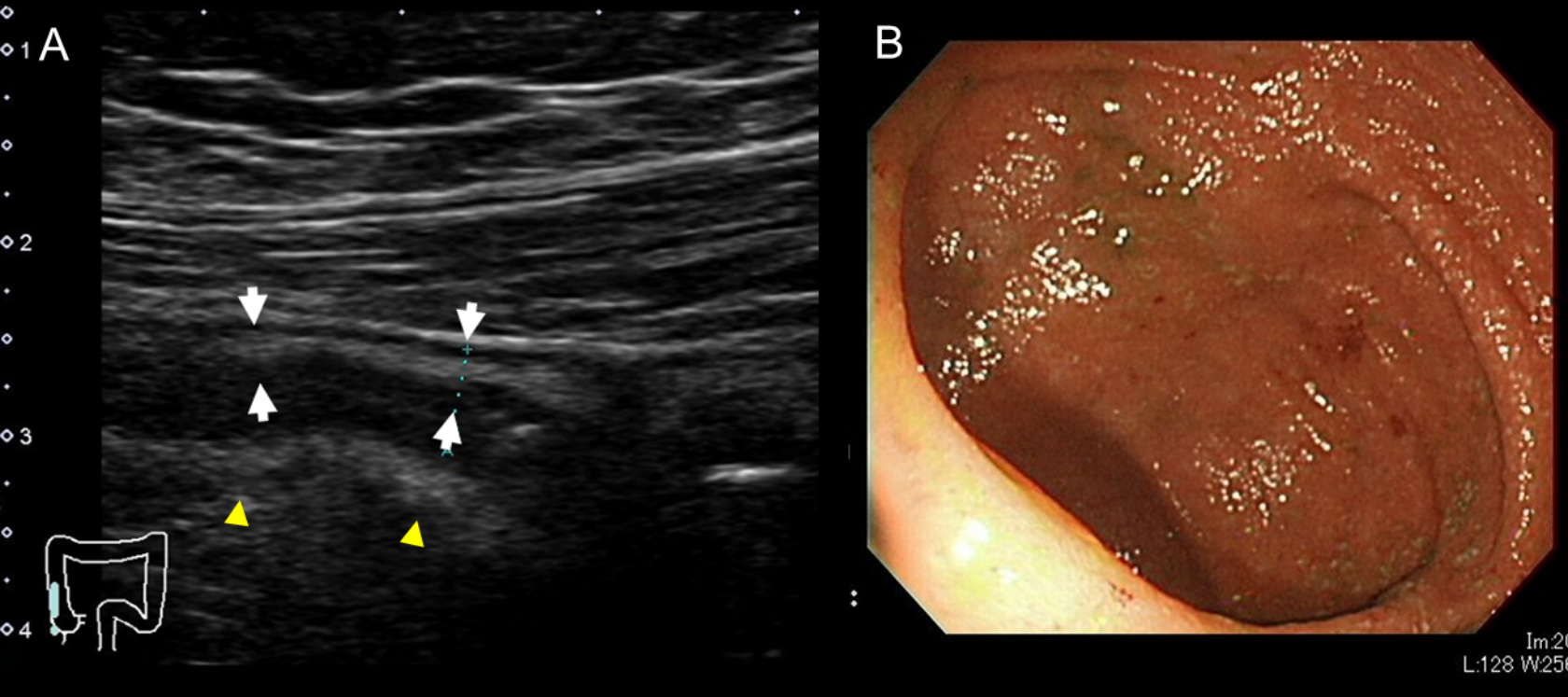
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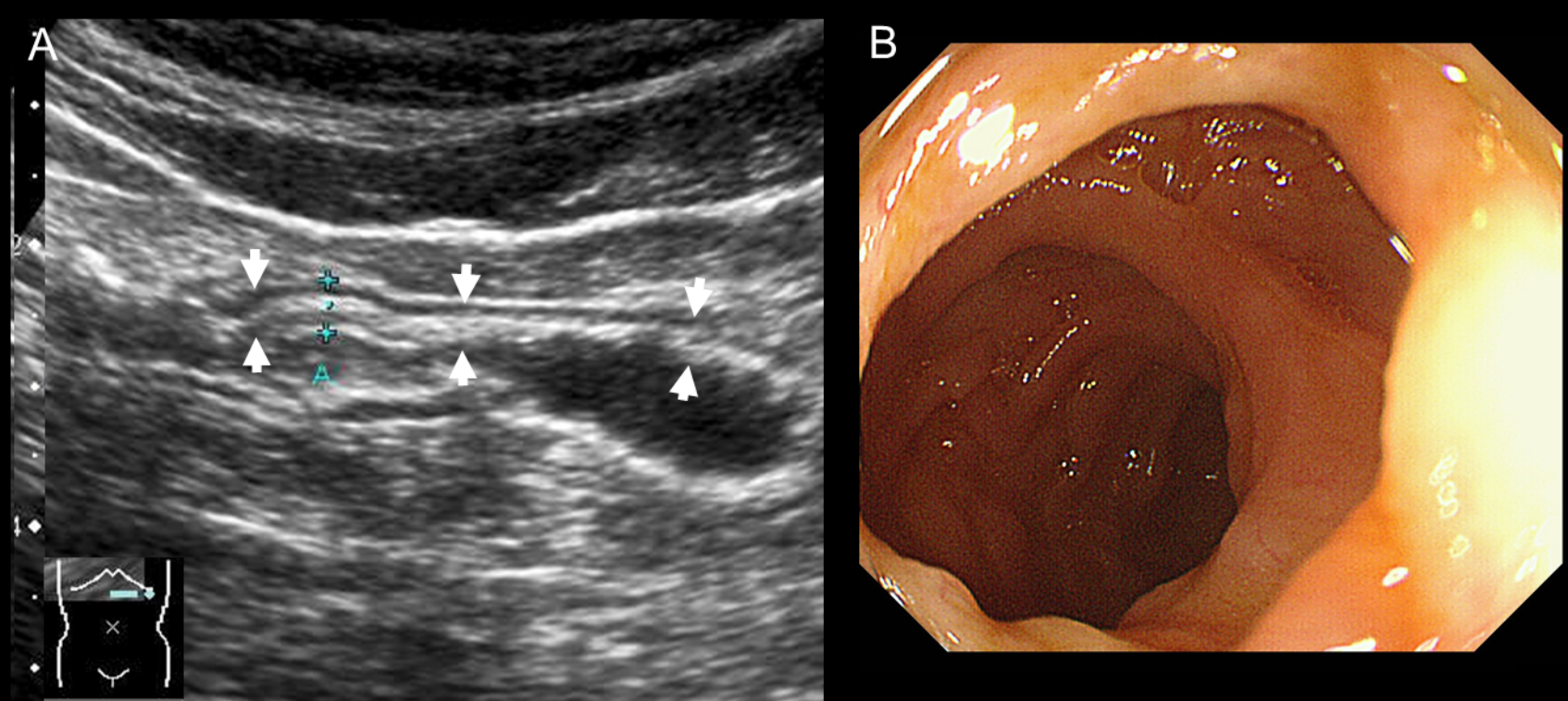
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Table 1. Patient characteristic (n=57)

Median Age (years, range)	48 (19-80)
Male/Female	37/20
Disease duration (years, range)[a]	5.0 (0.1-32.3)
Disease extension	
Proctitis, % (n)	19.3 (11)
Left-sided colitis, % (n)	28.1 (16)
Extensive colitis, % (n)	52.6 (30)
Rachmilewits CAI, median (range)[b]	2.0 (0-14)
Inactive, % (n)	56.6 (30)
Mild, % (n)	15.1 (8)
Moderate, % (n)	20.8 (11)
Severe, % (n)	7.5 (4)
Concomitant medications, % (n)	
Mesalazine	86.0 (49)
Azathioprine/6-mercaptopurine	22.8 (13)
Oral or intravenous corticosteroids	15.8 (9)
Cytoapheresis	7.0 (4)
TNF-α antagonists	5.3 (3)
US maximum grade, median (range)	2 (1-4)
CS maximum grade, median (range)	2 (1-4)
CRP (mg/dL), median (range)[c]	0.04 (0.01-11.82)

Abbreviation: TNF-α, Tumor Necrosis Factor-alpha

[a]Data for the disease duration were missing for 16 patients.

[b]Data for the CAI score were missing for 4 patients.

[c]Data for the CRP were missing for 2 patients.

Table 2. Visualization rate in each colonic segment examined by US and CS

Colonic segment	US, n (%)	CS, n (%)	*P-value*
Cecum	54 (94.7)	48 (84.2)	*0.070*
Ascending colon	56 (98.2)	48 (84.2)	*0.008*
Right t-colon	55 (96.5)	47 (82.5)	*0.008*
Left t-colon	53 (93.0)	49 (86.0)	*0.289*
Descending colon	57 (100)	52 (91.2)	*0.063*
Sigmoid colon	57 (100)	56 (98.2)	*1.000*
Rectum	48 (84.2)	57 (100)	*0.004*
All segments	380 (95.2)	357 (89.5)	*0.001*

Abbreviations: Right t-colon, Right-sided transverse colon; Left t-colon, Left-sided transverse colon

Table 3. Grading agreement of evaluating UC disease activity in US and CS

	US			CS		
Colonic segment	n	kappa	95%CI	n	kappa	95%CI
Cecum	53	0.54†	0.37-0.70	48	0.71†	0.50-0.92
Ascending colon	54	0.74†	0.57-0.92	48	0.73†	0.60-0.86
Right T-colon	55	0.72†	0.58-0.85	47	0.69†	0.53-0.84
Left T-colon	52	0.75†	0.61-0.89	48	0.79†	0.65-0.93
Descending colon	57	0.78†	0.68-0.89	50	0.68†	0.53-0.82
Sigmoid colon	57	0.77†	0.65-0.89	56	0.76†	0.64-0.88
Rectum	44	0.54†	0.34-0.74	57	0.43†	0.15-0.72
All segments	372	0.75†	0.70-0.80	354	0.72†	0.66-0.79
Maximum grade in each patient	57	0.82†	0.73-0.91	57	0.70†	0.53-0.88

Abbreviations: Right T-colon, Right-sided Transverse colon; Left T-colon, Left-sided Transverse colon

†: $p < 0.001$

Table 4. US and CS grading agreement of the maximum grade in each patient (n=57)

		Examining facilities			
US grade		1	2	3	4
Central facility	1	5	1	0	0
	2	6	24	4	0
	3	0	0	9	1
	4	0	0	3	4

		Examining facilities			
CS grade		1	2	3	4
Central facility	1	1	1	0	0
	2	12	17	3	0
	3	0	1	11	0
	4	1	0	3	7