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DISEASES OF THE ESOPHAGUS

Original article

The efficacy of i-SCAN for detecting reflux esophagitis: a prospective randomized controlled trial

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SUMMARY. **New imaging technologies have been applied in endoscopy to improve the detection and differentiation of subtle mucosal changes using a digital contrast method. Among them, i-SCAN technology is the most recently developed image-enhancing technology. We investigated whether i-SCAN could improve the detection rate of reflux esophagitis. Interobserver agreement between endoscopists was compared with conventional white light (WL) endoscopic examination. We performed a prospective randomized controlled trial. A consecutive series of 514 subjects that underwent an esophagogastroduodenoscopy for health inspection were enrolled and randomized into the i-SCAN group ($n = 246$) and WL group ($n = 268$). An esophagogastroduodenoscopy with video recording was used for detecting reflux esophagitis, and reflux esophagitis were categorized by the modified Los Angeles (LA) classification. The total number of reflux esophagitis identified by WL and i-SCAN was 58 (21.7%) and 74 (30.1%), respectively. The diagnostic yield of reflux esophagitis was significantly higher ($P = 0.034$) in the i-SCAN group (30.1%) as compared to the WL group (21.6%). Using the modified LA classification, the detection rate of minimal changes was significantly higher ($P = 0.017$) in the i-SCAN group (11.8%) as compared to the WL group (5.6%), but the detection rates of LA-A and LA-B were not significantly different between the two groups ($P = 0.897$ and $P = 0.311$, respectively). After comparison of the interobserver agreement using randomly selected video clips, the i-SCAN group showed better agreement than the WL group (Kappa value, 0.793 vs. 0.473). Compared to WL endoscopy, applying i-SCAN in daily practice can improve the diagnostic yield of reflux esophagitis by detecting more minimal changes in the squamo-columnar junction of the esophagus and can improve the interobserver agreement of the modified Los Angeles classification.**

KEY WORDS: **GERD, i-SCAN, reflux esophagitis.**

ABBREVIATIONS: FICE, Fuji Intelligent Chromoendoscopy; GERD, Gastroesophageal reflux disease; i-SCAN CE mode, contrast enhancement mode of i-SCAN; i-SCAN SE mode, surface enhancement mode of i-SCAN; i-SCAN TE mode, tone enhancement mode of i-SCAN; LA, Los Angeles classification; NBI, narrow–band imaging; NERD, non-erosive reflux disease; SCJ, squamo-columnar junction of esophagus; WL, white light

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition that develops when a reflux of stomach contents causes troublesome symptoms and/or complications.[1] An endoscopy is a widely used modality for the diagnosis and classification of GERD, and the extent of esophageal mucosal breaks on endoscopy can be assessed.[2–5] However, because over half of patients with GERD reveal no visible abnormality on conventional endoscopy, it is possible that minute mucosal changes are underestimated by conventional endoscopy due to the limitation of visual ability.[6–8] Thus, patients with GERD are subdivided into non-erosive and erosive reflux esophagitis.

In addition of uncertainty in detecting mucosal breaks, the uncertainty in describing the severity of mucosal injury can lead to an inconsistency among interpreters.[9–11] Asian gastroenterologists tend to diagnose endoscopically before they treat patients

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with symptoms suggestive of GERD[12] and use the modified Los Angeles (LA) classification system which includes minimal changes constituting a distinct grade of reflux esophagitis.[4,13] In the modified LA system, a minimal change esophagitis is characterized by mucosa such as erythema and/or whitish turbidity.[4,5,13] However, because a substantial overlap is noted between normal and minimal changes, minimal change and LA-A, and LA-A and LA-B, an interobserver agreement regarding the diagnosis and classification of reflux esophagitis is unsatisfactory for daily practice.[2,10,13]

Currently, new imaging technologies have been applied in endoscopy to improve detecting and differentiating of subtle mucosal changes using digital contrast methods such as narrow-band imaging (NBI), Fuji Intelligent Chromoendoscopy (FICE) and i-SCAN.[14] Among them, i-SCAN technology is the most recently developed image-enhancing technology, which consists of three modes of image enhancement, which include surface enhancement (SE), contrast enhancement (CE), and tone enhancement (TE). SE enhances light–dark contrast, and CE adds blue in relatively dark areas digitally, by obtaining luminance intensity data for each pixel. Applying SE and CE may allow for detailed observation of subtle irregularities around the surface, and TE analyzes the individual RGB components of a normal image and recombines the color frequencies of each component to enhance minute mucosal structures with subtle color changes.[15]

However, there has been a paucity of information that exists regarding the efficacy of i-SCAN for detecting reflux esophagitis. Thus, we investigated the hypothesis that i-SCAN can improve the detection rate of reflux esophagitis and interobserver agreement between endoscopists compared with the conventional white light (WL) endoscopic examination.

MATERIALS AND METHODS

Study design

A prospective randomized controlled trial was performed at Konkuk University Medical Center in Seoul, Korea between June 2010 and September 2010. The study protocol was approved by the Institutional Review Board of Konkuk University Medical Center. Figure 1 shows the flow diagram of the progress through the different phases of the parallel randomized trial.

Study participants

The study participants were recruited to have an esophagogastroduodenoscopy performed for routine

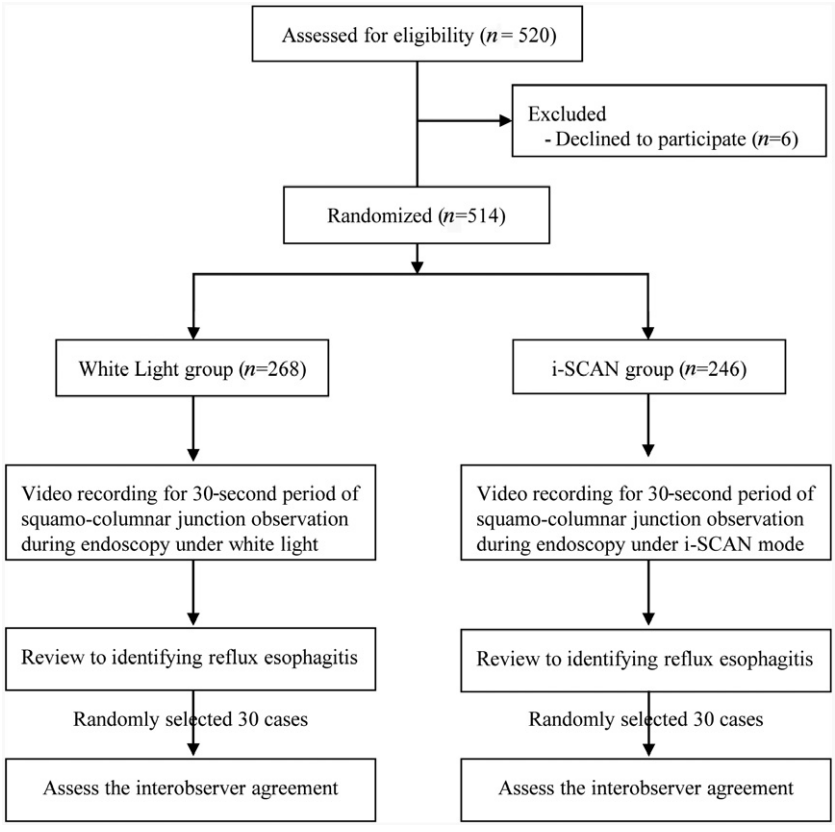

Fig. 1 Flow diagram of the study.

health examination and were assessed for eligibility from June, 2010 to September, 2010. Subjects with a history of gastrointestinal surgery such as a gastrectomy, fundoplication, or distal esophagectomy, those taking a medication for gastrointestinal diseases and symptoms such as H2 receptor blocker and proton pump inhibitors, or those who were not able to record video clips during the examination period of the squamo-columnar junction (SCJ) during an endoscopy were excluded from the study. A consecutive series of 529 subjects aged 18 to 70 years were enrolled. Symptoms were assessed using the GERDQ questionnaire.[16] Demographic data of the study participants as well as the GERDQ questionnaire were collected by two experienced assistant nurses.

Intervention, equipment and endoscopic procedure

For all study procedures, an EPKi processor (Pentax, Tokyo, Japan) and high-resolution adult video endoscopes (EG-2890i; Pentax) were used. The i-SCAN has three modes of image enhancement: surface enhancement (SE; enhancement of the structure through recognition of the edges); contrast enhancement (CE; enhancement of depressed areas and differences in structure through colored presentation of low density areas); and tone enhancement (TE; enhancement tailored to individual organs through the modification of the combination of RGB components for each pixel), and it is possible to apply two or more of these three modes at one time.[15] The staff endoscopists at Konkuk University Medical Center made a consensus that the optimized i-SCAN mode was the combination of 2 + level of CE, 2 + level of SE plus TE-g mode. Thus, the i-SCAN mode was set to the 2 + level of CE, 2 + level of SE plus TE-g mode during study periods. The push button on the endoscope can apply i-SCAN to WL mode or WL to i-SCAN without any time interval.

Table 1 The modified Los Angeles classification system

Grade	Description
LA-N	Normal mucosa
LA-M	Minimal changes to the mucosa, such as erythema and/or whitish turbidity
LA-A	Nonconfluent mucosal breaks <5 mm in length
LA-B	Nonconfluent mucosal breaks >5 mm in length
LA-C	Confluent mucosal breaks <75% circumferential
LA-D	Confluent mucosal breaks >75% circumferential

All subjects were randomized into the WL group and the i-SCAN group via computer-generated random numbers by one experienced assistant nurse. The WL group was examined SCJ under conventional WL only, and the i-SCAN group was subjected to i-SCAN mode through the entire SCJ examination. During the endoscopy, each 30-second period of SCJ observation was recorded. One unedited video clip was made for each subject and collected in an external data storage system.

Diagnosis and classification of esophageal injury

Esophageal injury was diagnosed and classified using video clips at 1 month after the recording of the SCJ examination to minimize the effect of the initial examination. Esophageal injury was classified according to the Los Angeles classification system with Japanese modifications (modified LA classification; Table 1, Fig. 2).[4,5] Grade M was described by three categories; 'Red ones' were defined as erythema without sharp demarcation and/or invisibility of

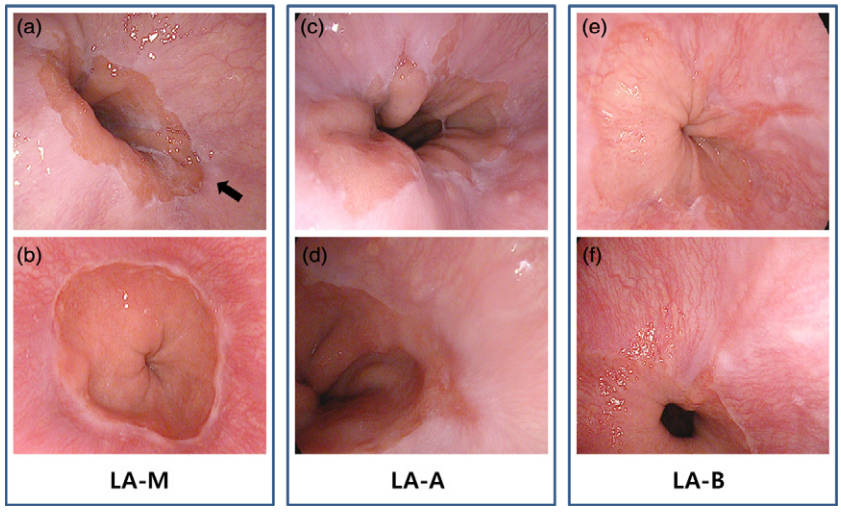

Fig. 2 Examples of modified LA classification In these cases, squamocolumnar junctions were examined by the white light mode of the endoscope (EG-2890i; Pentax). The arrow on (a) shows the mucosal erythematous change without sharp demarcation (LA-M, 'Red ones'). (b) shows the whitish turbidity around SCJ (LA-M, 'White ones'). (c) and (d) are nonconfluent mucosal breaks of less than 5 mm in length (LA-A). (e) and (f) are nonconfluent mucosal breaks of more than 5 mm in length (LA-B).

Table 2 The demographics and symptom characteristics of enrolled participants

	WL group ($n = 268$)	i-scan group ($n = 246$)	P
Age (years)	44.86 ± 10.56	44.80 ± 10.72	0.948
Sex (M/F)	150/118	152/94	0.181
GERDQ questionnaire[16](0 day / 1 day / 2–3 days / 4–7 days)			
How often did you have a burning feeling behind your breastbone (heartburn)?	241/20/7/0	213/24/7/2	0.368
How often did you have a stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)?	225/33/9/1	198/38/8/2	0.676
How often did you have a pain in the center of the upper stomach?	218/3/10/37	194/8/12/32	0.351
How often did you have nausea?	219/3/10/36	193/4/17/32	0.408

vessels due to these findings. 'White ones' were defined as having whitish turbidity and/or invisibility of vessels due to these findings. 'Red & White ones' had both features described for the Red or White categories. After a calibration exercise, video clips were reviewed for the identification of esophageal injury and classification of reflux esophagitis by two reviewers independently (H.S.K and S.N.H). Inter-observer agreement between the two reviewers was high (Kappa, 0.992), and the discrepant cases were made a diagnosis by consensus with a review of video clips.

Interobserver agreement of modified LA classification

A total of six endoscopists (S.I,K, J.H.L, S.Y.K., Y.S.K., B.K.K., H.S.P) participated in this study. The participating endoscopists were instructed beforehand to grade the reflux esophagitis for each case using the modified LA classification. Sixty video clips (30 from the WL group and 30 from the i-SCAN group) were randomly selected by one endoscopist (H.S.K), shown on a single liquid crystal display (LCD) monitor, and watched once under the same conditions. The diagnosis was marked on separate sheets independently to ensure the results were not affected by the other.

Statistical analysis

Assuming an additional reflux esophagitis detection rate of 6% and standard deviation of 20% with WL from the previous data,[8] 260 patients were required in each group (90% power, significance level of 0.05, and 10% dropout rate). Continuous variables were expressed as the mean ± standard deviation, while categorical variables were presented as absolute values and percentages. Differences between continuous variables were analyzed using the unpaired Student's t-test, and differences between categorical variables were analyzed using the $\chi 2$ test and Fisher's exact interobserver agreement for the assessment of esophageal injury. Kappa statistics was used to evaluate interobserver agreement for the assessment of esophageal injury. The strength of agreement was defined as follows: <0.2, poor; 0.2 to 0.4, fair; 0.4 to 0.6, moderate; 0.6 to 0.8, good; >0.8, very good. Analysis was done using SPSS software (v 17.0; SPSS Inc., Chicago, IL).

RESULTS

Characteristics of the study participants

Among the 529 prospectively enrolled patients from June 2010 to September 2010, 15 were excluded due to failure to record video clips during the examination period. A total of 514 patients (mean age 50.6 years, 66.9% male) were included and randomly assigned, 268 to the WL group and 246 to the i-SCAN group. No significant differences were found between the two groups with regards to demographic features and upper gastrointestinal symptoms. (Table 2)

Reflux esophagitis detection rates

Reflux esophagitis were detected in 132 (25.7%) subjects by WL and i-SCAN endoscopies. The minimal changes found in 44 subjects (8.6%), LA-A were 68 subjects (13.2%), LA-B were 16 subjects (3.1%), and LA-C was 1 subject (0.2%). The total number of reflux esophagitis identified by WL and i-SCAN was 58 (21.7%) and 74 (30.1%), respectively. The overall detection rate of reflux esophagitis, the primary outcome parameter, was significantly higher in the i-SCAN group compared to the WL group ($P = 0.034$, Table 3). Although the detection rate of erosive reflux esophagitis showed no statistically significant differences between the techniques (LA-A, 13.4% vs. 13.0%, $P = 0.897$; LA-B, 2.2% vs. 4.1%, $P = 0.331$; LA-C, 0% vs. 0.2%, $P = 0.479$), the detection rate for LA-M with i-SCAN was significantly higher than with WL (5.6% vs. 11.8%, $P = 0.017$; Fig. 3).

We classified the category of mucosal findings of minimal change into 'Red ones', 'White ones', and 'Red and White ones'. The 'Red ones' were more frequently detected in the i-SCAN group (Fig. 4).

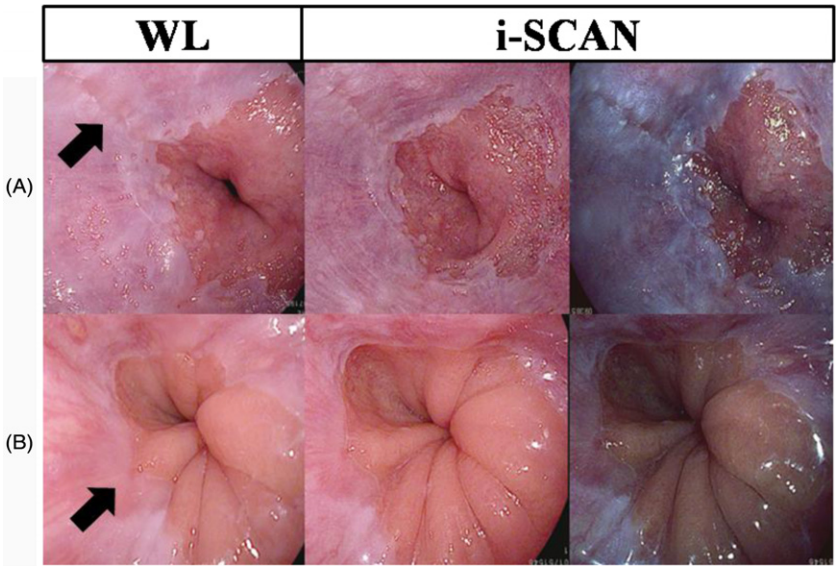

Fig. 3 Images from WL and i-SCAN. A: A mucosal break is not clearly visible in a conventional WL scan, whereas the i-SCAN can depict the mucosal break better. B: The 'Red ones' of minimal change are not clearly visible in conventional WL scan, whereas the i-SCAN can distinguish an inflamed erythematous mucosa better.

Among the 15 LA-M patients in the WL group, 'Red ones', 'White ones', and 'Red and White ones' were 9, 5, and 1, respectively. Interestingly, among the 29 LA-M patients in the i-SCAN group, 'Red ones', 'White ones', and 'Red and White ones' were 20, 3, and 6, respectively. Although these findings were not statistically significant, the erythema mucosal change was more easily detected using i-SCAN.

Interobserver agreement of modified LA classification

The i-SCAN group showed better agreement than the WL group. To determine interobserver variability in terms of classification of esophageal injury, the 60 randomly selected video clips were reviewed by six endoscopists. There was good interobserver agreement for modified LA classification in the i-SCAN group (kappa, 0.793), compared to just moderate interobserver agreement in the WL group (kappa, 0.473). Upon detection of esophageal injury, the i-SCAN group (kappa, 0.631) showed better agreement than the WL group (kappa, 0.414, Table 3).

Table 3 The reflux esophagitis detection rate and interobserver agreement between WL and i-SCAN group

Reflux esophagitis detection rate between WL and i-SCAN group			
	WL (n = 268)	i-SCAN (n = 246)	P
Any reflux esophagitis	58 (21.7%)	74 (30.1%)	0.034
LA-M	15 (5.6%)	29 (11.8%)	0.017
LA-A	36 (13.4%)	32 (13.0%)	0.897
LA-B	6 (2.2%)	10 (4.1%)	0.331
LA-C	0 (0%)	1 (0.2%)	0.479
Interobserver agreement between WL and i-SCAN group			
	WL (n = 30)	i-SCAN (n = 30)	
Kappa value	0.473	0.793	
Cronbach's alpha	0.844	0.958	
95% PI	0.319–0.647	0.690–0.930	

PI, predictive interval.

DISCUSSION

An endoscopy is a widely used diagnostic tool for reflux esophagitis detection. Although its specificity was reported to be excellent, at 90–95%,[17] its sensitivity was only 50%.[16,18] More than half the patients with GERD symptoms were diagnosed as having non-erosive reflux disease (NERD), and this was more common in Asians, ranging between 59% to 87%.[19–21] However, when we performed a careful analysis, the majority of NERD patients did not completely have

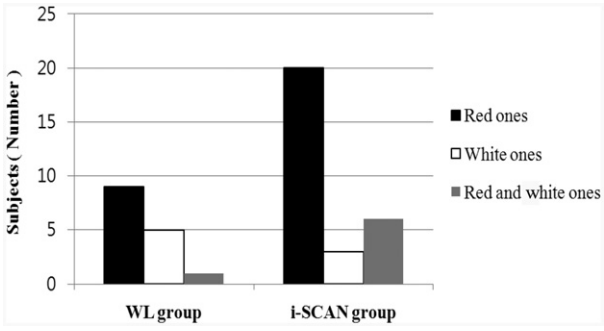

Fig. 4 Detection of the subgroups of minimal change.

normal endoscopic findings, and instead, were found to have subtle distal esophageal mucosal changes from acid refluxate such as reddish or whitish color changes around the SCJ with edema of mucosal folds, blurring with the friability of the mucosal junction, increased vascularity, and micro erosion.[5,22] Unfortunately, it was quite difficult to detect these lesions under conventional WL endoscopy with low interobserver agreement.[2,13,23] Recently, endoscopic technologies have evolved tremendously with the emergence of image-enhancing technologies, and several studies have attempted to overcome the limitation of conventional WL examination using image-enhancing technologies for the detection of minimal esophageal injury. In those trials, the results consistently showed that image-enhancing technologies such as NBI and FICE improved the detection rate of esophageal injury.[15,24,25] However, i-SCAN is a newly developed technology, and its efficacy for detecting reflux esophagitis is uncertain.

Our study showed that the mucosal breaks and erythema at SCJ could be seen more easily and clearly with i-SCAN than with a conventional WL endoscopy, because i-SCAN improved the visualization of the SCJ by enhancing the contrast between the esophageal mucosa and gastric mucosa. It was able to detect the presence of erosive and non-erosive reflux esophagitis caused by acid refluxate at the SCJ not seen in conventional WL endoscopy. For the detection of reflux esophagitis, our results were consistent with one recent study on the use of i-SCAN for the precise detection of mucosal breaks.[8] Hoffman *et al.* reported that i-SCAN improved the detection rate of mucosal breaks (18% with high definition endoscopy vs. 24% with combination of high-definition endoscopy and i-SCAN), but statistical significance could not be achieved with the small sample number.[8] However, unlike the previous study, our study was performed on a much larger set of participants, and the sample size calculation showed significant improvement in the detection of reflux esophagitis.

In our study, the improvement of detection rates resulted from the improved detection of the minimal change in the i-SCAN group compared to the WL group (5.6% vs. 11.8%, $P = 0.017$). In practice, the endoscopists agreed that high-definition endoscopy could provide high-quality images to distinguish mucosal breaks at the distal esophagus.[26] However, high-definition endoscopy without additional image-enhancing technologies showed some limitations in distinguishing color changes without a definite structural abnormality.[4] The application of i-SCAN appeared to improve the detection of minimal change by the intensification of the contrast of inflamed erythematous mucosal change, 'Red ones', against the normal squamous epithelium. Digital chromoendoscopy is an important tool with a high potential for GERD diagnosis particularly for non-erosive reflux disease, since it provides the endoscopist with a simple, safe, and rapid method for better detection of the subtle esophageal lesions.

Evaluation of interobserver variability is important when one is interested in the 'true' differences among observers reporting different values of the same quantity. Minimal changes were considered by the International Working Group for Classification Oesophagitis during the development of the LA classification system.[2] However, the low interobserver agreement for classification criteria including minimal change advocated that minimal changes were excluded from the classification criteria for reflux esophagitis.[4] As shown in our study, interobserver reproducibility in grading reflux esophagitis could be improved when i-SCAN was applied with conventional imaging. The benefits appeared to be derived from better depictions of minimal change and small mucosal breaks. Digital chromoendoscopy, such as i-SCAN, is an important tool with high potential for a GERD diagnosis particularly for minimal change since it provides the endoscopist with a simple, safe, and rapid method for a better detection of the subtle esophageal lesions as well as increased reproducibility.

Minimal changes may be regarded as the starting point in the spectrum of endoscopic findings in reflux disease,[4,5,13] however, the clinical significance of minimal change is still debatable. Tahara *et al.* showed that the pathological conditions of the stomach related to higher gastric acid secretion correlate with minimal changes.[27] However, Kim *et al.* reported that most endoscopic findings indicating minimal changes are not associated with symptoms.[22] As well, Lei *et al.* reported that NERD might exhibit similar disease characteristics in terms of esophageal acid exposure and motor dysfunction, regardless of the presence of minimal change.[28] Using i-SCAN, we were able to double the detection of a minimal change, but the clinical impact of the minimal change detected by i-SCAN might remain uncertain due to the absence of a concurrent pH study or a follow-up endoscopy with i-SCAN after proton-pump inhibitor therapy. Therefore, future studies are required to further the relevance of our findings.

The strength of our study is that the assessment and classification of reflux esophagitis were performed by two endoscopists using recording video of SCJ during an endoscopy. When the endoscopists met cases that were difficult to identify and classify reflux esophagitis, the examination had become more time consuming, and endoscopists had to give careful consideration. In addition, the real-time assessment and classification of reflux esophagitis tended to be depended on the variable of factors related to patients, examiners, and endoscopy. To exclude these biases, we recorded each 30-second period of SCJ

observation during endoscopy and reviewed them for the two experienced endoscopists to identify reflux esophagitis.

We acknowledge the limitations of our study. First, because the participants consisted of volunteers, the asymptomatic participants had a significant portion. Therefore, our study could not show the relationships of reflux esophagitis and NERD. However, a relevant randomization between both groups was performed, and we can conclude the diagnostic efficacy of i-SCAN as compared to WL. Second, this was a single-center study, and further corroborative works are necessary. There were differences in the distribution of upper gastrointestinal symptoms between cases and controls, raising the possibility of confounding factors. Cases and controls were not matched perfectly because we enrolled consecutive subjects who gave informed consent. Nonetheless, there were no significant differences between upper gastrointestinal symptoms by proper randomization.

GERD is the most frequent problem in the upper gastrointestinal tract in outpatient clinics and contributes substantially to morbidity[29,30] which is increasing in prevalence all over the world.[31,32] During the SCJ examination to investigate GERD, compared to conventional WL endoscopy, the i-SCAN application can improve the diagnostic yield of reflux esophagitis by a greater detection of minimal changes and also improve interobserver agreement of esophageal injuries. In our opinion, over the next several years, it may become a useful tool for GERD diagnosis. However, large multicenter randomized controlled studies comparing these new imaging modalities with the conventional WL endoscopy are warranted to validate its accuracy and clinical usefulness.

Acknowledgment

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