Korean J Gastroenterol Vol. 68 No. 1, 29-35
http://dx.doi.org/10.4166/kjg.2016.68.1.29
pISSN 1598-9992 eISSN 2233-6869

ORIGINAL ARTICLE

KJG

Flexible Spectral Imaging Color Enhancement and Probe-based Confocal Laser Endomicroscopy in Minimal Change Esophageal Reflux Disease

Rapat Pittayanon[1,3], Surasak Aumkaew[1,3], Rungsun Rerknimitr[1,3], Naruemon Wisedopas[2,3], and Pinit Kullavanijaya[1,3]

Division of Gastroenterology, Department of Internal Medicine[1], Department of Pathology[2], Faculty of Medicine, Chulalongkorn University, Thai Red Cross[3], Bangkok, Thailand

Background/Aims: Although flexible spectral imaging color enhancement (FICE) can facilitate the diagnosis of minimal change esophageal reflux disease (MERD), the complicated diagnostic criteria cause suboptimal inter-observer agreement. Confocal laser endomicroscopy (CLE) yields good diagnostic results but its inter-observer agreement has never been explored. This study compares the diagnostic value of magnifying FICE and probe-based CLE (pCLE) for MERD and evaluates the inter-observer agreement of both techniques.

Methods: Thirty-six patients with suspected MERD and 18 asymptomatic controls were recruited. Magnifying FICE was used for evaluation of distal esophagus. pCLE counted the number of intrapapillary capillary loops (IPCLs) using more than five IPCLs in 500×500 micron area as a criterion for MERD diagnosis. The validity scores and interobserever agreement of both FICE and pCLE were assessed.

Results: For FICE *vs.* pCLE, the accuracy was 79% *vs.* 87%, sensitivity 94% *vs.* 97%, specificity 50% *vs.* 66%, positive predictive value 79% *vs.* 85%, and negative predictive value 82% *vs.* 92%. Interobserver agreement of FICE was fair to substantial, whereas pCLE had substantial to almost perfect agreement.

Conclusions: Both FICE and pCLE have good operating characteristics and can facilitate the MERD diagnosis. However, among different observers, pCLE is more consistent on MERD diagnosis. **(Korean J Gastroenterol 2016;68:29-35)**

Key Words: Minimal esophageal reflux disease; Probe-based confocal laser endoscopy; Flexible spectral imaging color enhancement

INTRODUCTION

The prevalence of gastroesophageal reflux disease (GERD) has been increasing across the globe[1] including Asia.[2] GERD is usually diagnosed either by the presence of reflux-associated symptoms[3] or esophagogastroduodenoscopy (EGD), demonstrating the presence of mucosal break at the distal esophagus (so called "erosive esophagitis").[4] More importantly, erosive esophagitis is not only the criterion for GERD diagnosis but is also a good predictor for response to treatment with proton-pump inhibitors (PPIs).[5] Acid exposure can lead to typical GERD symtoms if the epithelium has pre-existing damage.[6] Unfortunately, conventional or white light endoscopy (WLE) fails to detect abnormalities of esophageal mucosa in more than half of symptomatic GERD patients[7] and these patients are categorized as "non-erosive reflux disease (NERD)".[3]

Despite negative WLE findings, symptomatic GERD patients may have subtle changes of the esophageal mucosa. These patients can be categorized as minimal change esophageal reflux disease (MERD). The EGD findings with MERD vary in reading, including whitish or reddish turbidity, edematous change, villiform mucosa, or increased vascularity at the squamo-columnar junction.[8,9] Japanese researchers mod-

Received May 14, 2016. **Revised** July 4, 2016. **Accepted** July 4, 2016.

Correspondence to: Rungsun Rerknimitr, Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University, 1872 Phayathai Road, Pathumwan, Bangkok 10330, Thailand. Tel: +66-22564265, Fax: +66-22527839, E-mail: Cholangiogram@gmail.com

Financial support: This work was supported by the Gastroenterological Association of Thailand. Conflict of interest: None.

ified the Los Angeles classification system of GERD by adding minimal changes of the mucosa such as reddish and/or whitish turbidity and categorized it as minimal erosive reflux disease (grade M; MERD).[10] However, the concept of MERD has not become widely accepted because of its poor inter-observer agreement on MERD reading by conventional WLE.[9,11] Recent evidence suggests that NERD patients can be subcategorized to MERD and functional heartburn although magnifying endoscopy is needed for this subcategorization.[12] There is no standard recommendation on what endoscope techniques and criteria should be used to diagnose MERD.

Image-enhanced endoscopy (IEE) including narrow-band imaging (NBI), flexible spectral imaging color enhancement (FICE), and iScan can increase MERD diagnosis by adding the subtle changes related to esophageal inflammation.[13] The high-definition FICE with magnification (EPX-4450HD; Fujinon Fujifilm Co.) is a commercially available image enhancement technology that provides image quality superior to WLE[14] and this can improve MERD diagnosis. From a FICE study using FICE (EXP-4440; Fujinon Fujifilm Co.) without magnification, the Japanese investigators demonstrated a higher MERD detection rate in NERD patients compared with the conventional WLE (77% *vs.* 48%; p=0.03).[15]

Confocal laser endomicroscopy (CLE) is a novel diagnostic imaging technique with 1,000 magnification. Endoscopic-based CLE (eCLE) provided a high sensitivity (94%) and specificity (85%) for MERD diagnosis with criteria of more than five intrapapillary capillary loops (IPCLs)/500 square micron or dilated intercellular space more than 7 micron.[16] Five years later, another eCLE study revealed a perfect specificity (100%) but only a 42% sensitivity for MERD diagnosis because, instead of splitting the two criteria, they used the combination of criteria of more than 6 IPCLs/125 square micron and dilated intercellular space more than 2.4 micron.[17] Unfortunately, both studies did not report the inter-observer agreement. To date, research on probe-based CLE (pCLE) on MERD diagnosis is not available.

The necessity of evaluating diagnostic accuracy for MERD and inter-observer agreement of FICE and pCLE is to emphasize the importance of differentiation between MERD and NERD, in order to manage those patients properly. Therefore, this study compares the diagnostic value of magnifying FICE and pCLE for MERD and evaluates the inter-observer agreement of both techniques.

SUBJECTS AND METHODS

1. Subjects

1) Study group

From June 2011 to February 2012, all patients diagnosed with GERD by positive GerdQ Questionaire (over 7 points) in King Chulalongkorn Memorial Hospital were recruited. All underwent EGD under WLE and magnifying FICE plus pCLE. The inclusion criteria were 1) age more than 18 years, and 2) no PPI therapy during previous two weeks. The exclusion criteria were 1) bleeding tendency including decompensated cirrhosis or chronic kidney disease and 2) on long-term antiplatelets or anticoagulants, 3) history of esophageal tumor, stenosis or surgery, 4) pregnancy, 5) history of fluorescein allergy and 6) those with WLE diagnosed as GERD grade A-D.

2) Control group

The control group consisted of patients who did not have any reflux symptoms (GerdQ=0) and were scheduled for EGD examination as part of EGD/colonoscopy for gastrointestinal cancer screening at our institution .

The research protocol was approved by the Faculty of Medicine, Chulalongkorn University Ethical Committee under ClinicalTrial.gov (NCT02336100). Informed consent was given by all patients.

2. Study design

This study was a single-centre, nonrandomised, cross-sectional trial on the discrimination performance of FICE and pCLE for MERD diagnosis. FICE was performed first, followed by pCLE to examine the esophagus. Inter-observer agreement of both FICE and pCLE were also assessed.

3. Instrument and criteria to diagnose minimal change esophageal reflux disease

FICE with magnification (EPX-4450HD) was performed in all paticipants at ×1, ×50 and ×100 magnification with station 0 (RGB 525,495,495), 1 (RGB 550,500,470), 5 (RGB 560,500,475), and 8 (RGB 540,505,420). The criteria for positive FICE were adopted from our previous study[18]: A) triangular indentation, B) punctuate erythema, C) villiform mucosa, and D) increased number of IPCLs (Fig. 1).

At the same session, the Cellvizio gastroflex (Mauna Kea Technology, Paris, France) was applied to evaluate the number of IPCLs by using more than 5/ 500×500 microns (four

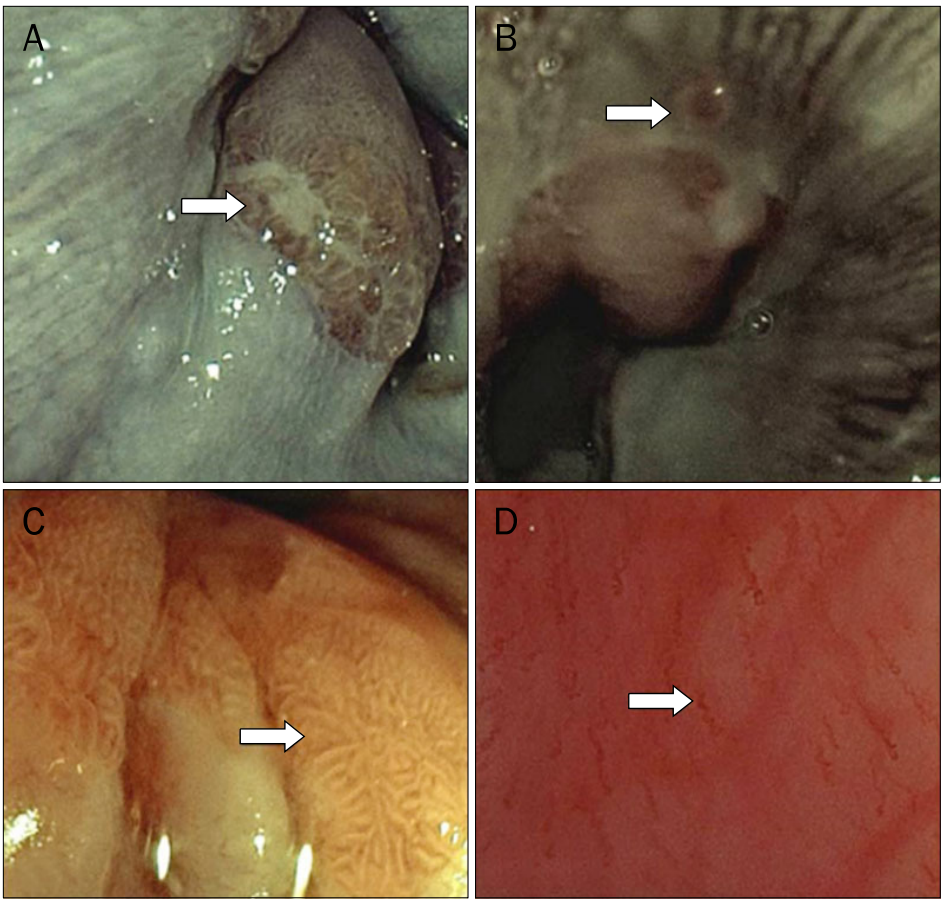

Fig. 1. Flexible spectral imaging color enhancement criteria for minimal change esophageal reflux disease diagnosis. (A) Triangular indentation (non-magnification) (arrow). (B) Punctuate erythema (arrow; ×50). (C) Viliform mucosa (arrow; ×50). (D) Increased number of capillary vessel (arrow; ×100).

sets of pCLE view) as a criterion for MERD diagnosis (Fig. 2).[16]

1) Procedure

EGD was performed under conscious sedation with meperidine and midazolam with an additional 10% lidocaine oral spray. Ten milligrams of hyoscine were also prescribed to decrease esophageal movement to obtain satisfactory visualization. The initial standard WLE with transparent cap was performed first to exclude GERD (Los Angeles grade A-D). Simethicone and N-acetyl-cysteine were used to reduce mucus in the distal esophagus. In those negative WLE for GERD, magnifying FICE (EPX-4450HD) was switched on and the squamocolumnar junction was evaluated by an experienced endoscopist (SA). The endoscopist performed ×1, ×50 and ×100 magnification with the three FICE stations. For the final diagnosis, the recorded images were reviewed off-line later, and the interpreter (SA) was blinded to the GerdQ results and patients' context. Subsequently, pCLE was applied by the same endoscopist (SA) at two centimeters above the esophagogastric junction (EGJ) after intravenous administration of 2.5 mL of 10% fluorescein sodium. Endoscopic findings by

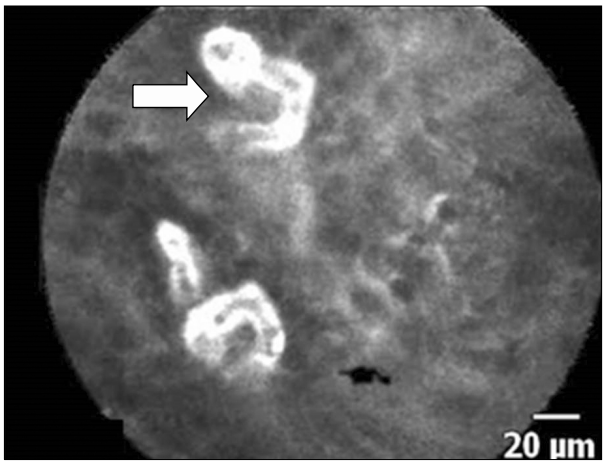

Fig. 2. Probe-based confocal laser endomicroscopy criteria for minimal change esophageal reflux disease diagnosis diagnosis showed one set of the probe-based confocal laser endomicroscopy image demonstrated intrapapillary capillary loops (arrow; ×1,000).

pCLE were recorded in video recorder for an off-line interpretation four weeks later by the other endoscopist who has experience in pCLE reading (RP) and was blinded to the WLE and FICE results. Esophageal biopsy was done at the EGJ and

two centimeters above the EGJ for pathologic evaluation. All histologies were examined by an experienced pathologist (NW) who was blinded to the clinical and endoscopic findings. The criteria for GERD diagnosis by pathology are described elsewhere as 1) basal zone hyperplasia (>15% of epithelial thickness) plus 2) presence of papillary zone elongation (>67%); and 3) density of neutrophil and eosinophil infiltration.[19]

4. Inter-observer agreement

The off-line interpretation by an experienced reader was referred to as the final reading because this reader was blinded to the patient's clinical context. The authors assigned ten gastrointestinal trainees who were not experienced in FICE and pCLE images of the esophagus to study a set of 10 FICE and pCLE images of MERD and non-MERD until they were able to interpret all 10 pictures correctly. Then they were asked to interpret different sets of FICE (n=10) and pCLE (n=12) images of MERD and non-MERD from the study group (n=36) over one week for four sessions in order to assess their learning curve and the inter-observer agreement.

5. Statistical analysis

The baseline descriptive data were analysed and reported as means and standard deviations for continuous variables, and percentage and frequency for categorical variables. All endoscopic readings from FICE, pCLE and matched histology were compared with the GerdQ questionaire. The comparison of FICE and pCLE accuracy was evaluated by McNemar test. Accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of FICE, pCLE, and histology were evaluated by using GerdQ results as a gold standard. Cohen's kappa (κ) was used to analyze the agreement between FICE and pCLE for MERD diagnosis and inter-observer agreement. The value of kappa (κ) for agreement were graded as slight agreement for 0.01 to 0.20, fair for 0.21 to 0.40, moderate for 0.41 to 0.60, substantial for 0.61 to 0.80, and almost perfect for 0.81 to 1.00. The SPSS software version 17.0 (SPSS Thailand Co., Ltd., Bangkok, Thailand) for Windows system was selected for statistical analysis.

RESULTS

There were 42 patients diagnosed with GERD and another 18 diagnosed with non-GERD by GerdQ questionaire in the present study. Of those 42 GERD patients, six patients were excluded because reflux esophagitis (Los Angeles classification grade A or B) was diagnosed by WLE. Therefore, only 36 GERD patients were left for the final evaluation (Fig. 3). The majority of patients in this study were female (72.2% in the GERD group and 66.7% in the control group). The mean age was 53 years in the GERD and 55 in the control group. Other baseline characteristics including height, body weight, BMI, percent of alcohol consumption and smoking, and duration of upright position after meals were not different between groups (Table 1). In the GerdQ positive group, the mean duration of GERD symptoms was 17±14.2 months. Eighty-nine percent had moderate to severe symptoms disturbing daily life activity. The average total GerdQ score was 11.67±1.88.

The standard WLE could detect MERD only in 17/36 (47.2%) whereas FICE and pCLE diagnosed a higher proportion of MERD (34/36, 94.4%). The mean number of IPCLs

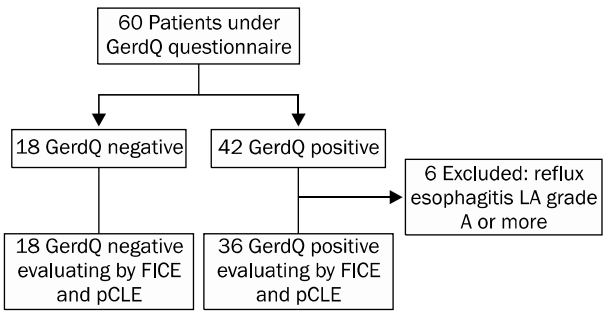

Fig. 3. Study flow chart.
FICE, flexible spectral imaging color enhancement; pCLE, probe-based confocal laser endomicroscopy; LA, Los Angeles classification.

Table 1. Baseline Characteristic of Study Groups

Characteristic	GerdQ positive (n=36)	Normal (n=18)	p-value
Sex (female)	72.2	66.7	0.75
Age (yr)	53.11±10.80	55.83±12.72	0.41
Height (m)	1.59±0.08	1.61±0.07	0.41
Body weight (kg)	60.78±16.14	58.31±8.86	0.47
BMI (kg/m^2)	23.92±5.64	22.48±2.81	0.31
Alcohol consumption	5.6	16.7	0.32
Smoking	0	0	1
Duration of up-right position after meal (hr)	2.86±1.35	2.89±1.18	0.94

Values are presented as % only or mean±SD.

in GerdQ positive patients was 9.47±3.18, and 4.72±1.41 in the control group. Pathology was able to diagnose MERD in only 11 patients (30.6%) (Table 2). For FICE *vs.* pCLE, the accuracy was 79% *vs.* 87%, sensitivity 94% *vs.* 97%, specificity 50% *vs.* 66%, PPV 79% *vs.* 85%, and NPV 82% *vs.* 92%. Pathology showed a good specificity (88%) and PPV (84%) for diagnosing MERD but a poor sensitivity and NPV (less than 50%) (Table 3).

pCLE and FICE revealed an excellent sensitivity (>90%) for MERD diagnosis. However, other validity scores for FICE tended to be lower than pCLE in off-line diagnosis. Moreover, the results of the off-line pCLE interpretation were not different from real-time reading (Table 4).

The inter-observer agreement for MERD diagnosis by FICE was fair to substantial (κ 0.29-0.62) whereas pCLE provided substantial to almost perfect level (κ 0.75-0.96). For pCLE training, all beginners could achieve more than 80% in reading accuracy within the first round of test and they were able to maintain excellent reading skill (>80%) in the three following sessions. The diagnosis of MERD by trainees with FICE was suboptimal and inconsistent (the accuracy varied from 71% to 88%) (Table 5).

Table 2. Endoscopic Findings and Pathology of GerdQ Positive Patients with MERD or NERD and Normal Control

Endoscopic findings/pathology	Presence of GerdQ with MERD or NERD by endoscopy (n=36)	Normal control (n=18)
White light endoscopy		
Normal	19	17
Minimal change	17	1
Erythema without sharp demarcation	13	1
Whitish turbidity	4	0
Invisible of vessles	0	0
FICE		
Positive	34	9
Triagular indentation	20	6
Increased IPCLs	31	3
Punctate erythema	10	3
Villous mucosa	8	1
Negative	2	9
Confocal (pCLE)		
Positive (ICPLs >5/500 μm^2)	34	6
Mean±SE	9.47±3.18	4.72±1.41
Median (range)	8 (3-16)	4 (3-8)
Negative	2	12
Pathology		
Reflux esophagitis	11	2
No reflux esophagitis	25	16

Values are presented as n only, mean±standard error (SE), or median (range).
MERD, minimal change esophageal reflux disease; NERD, non-erosive reflux disease; pCLE, probe-based confocal laser endomicroscopy; IPCLs, intrapapillary capillary loops.

DISCUSSION

To our knowledge, this is the first study comparing FICE and pCLE as the tools to enhance the diagnostic yield of MERD. Our study demonstrated the benefit of both techniques for MERD diagnosis with high validity scores, but pCLE technique was proven to be much easier as the learning curve was short with almost perfect agreement by the beginners. In addition, the real-time and off-line pCLE diagnosis was the same, which represent the consistency of pCLE reading. Moreover, pCLE technique is simple as it does not need a red-flag technique to target the lesion first, and the probe can be directly applied onto the distal esophagus because MERD

Table 4. Sensitivity, Specificity, PPV, NPV and Accuracy of Off-line and Real-time pCLE in MERD Diagnosis

Diagnostic value	Off-line reading	Real-time reading	p-value
Sensitivity (%)	97	95	>0.10
Specificity (%)	66	63	>0.10
PPV (%)	85	83	>0.10
NPP (%)	92	94	>0.10
Accuracy (%)	87	83	>0.10

PPV, positive predictive value; NPV, negative predictive value; pCLE, probe-based confocal laser endomicroscopy; MERD, minimal change esophageal reflux disease.

Table 3. Sensitivity, Specificity, PPV, NPV and Accuracy of pCLE, FICE and Pathology in MERD Diagnosis

Instrument	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
FICE	94	50	79	82	79
pCLE	97	66	85	92	87
Pathology	33	88	84	41	52

PPV, positive predictive value; NPV, negative predictive value; FICE, flexible spectral imaging color enhancement; pCLE, probe-based confocal laser endomicroscopy; MERD, minimal change esophageal reflux disease.

Table 5. Reading Skill and Interobserver Agreement in MERD Diagnosis by FICE and pCLE

MERD reading skill	First test		Second test		Third test		Fourth test	
	FICE	pCLE	FICE	pCLE	FICE	pCLE	FICE	pCLE
Sensitivity	71.4 (57.1-100)	86.1 (50-100)	83.3 (55.6-100)	100	92.5 (75-100)	97.5 (75-100)	91.2 (75-100)	83.3 (33.3-100)
Specificity	70 (33.3-100)	88.3 (66.7-100)	100	94.4 (77.8-100)	70 (50-100)	98.8 (87.5-100)	35 (0-50)	93.3 (77.8-100)
PPV	84.7 (57.1-100)	86.9 (66.7-100)	100	100	92.5 (85.7-100)	97.5 (88.9-100)	84.8 (75-88.9)	94.4 (81.8-100)
NPV	51.2 (25-100)	88.1 (66.7-100)	40 (20-100)	85.7 (60-100)	70 (33.3-100)	98.8 (80-100)	50 (0-100)	80.6 (60-100)
Accuracy	71 (60-90)	88.3 (66.7-100)	85 (60-100)	95.8 (83.3-100)	88 (70-100)	98.3 (91.7-100)	80 (60-90)	90.8 (83.3-100)
Inter-observer agreement (κ)	0.37 (fair)	0.75 (substantial)	0.50 (moderate)	0.89 (almost perfect)	0.62 (substantial)	0.96 (almost perfect)	0.29 (fair)	0.75 (substantial)

Values are presented as % (range).
MERD, minimal change esophageal reflux disease; FICE, flexible spectral imaging color enhancement; pCLE, probe-based confocal laser endomicroscopy; PPV, positive predictive value; NPV, negative predictive value.

always involves the distal esophagus circumferentially.

The present study showed excellent sensitivity of both FICE (94%) and pCLE (97%) for MERD diagnosis. Moreover, pCLE provided good accuracy (87%) whereas FICE showed acceptable accuracy (79%) for MERD diagnosis. Although the specificity of FICE alone is close to flipping a coin, by adding pCLE the specificity increased to 66%, and this could help us selecting the proper treatment in the two thirds of patients with reflux symptoms who truly have MERD. Theoretically, confirmed MERD patients respond to PPIs better than NERD and functional heartburn patients.[6,8] Unfortunately, the poor inter-observer agreement by FICE criteria in the present study reminds us about the requirement of systematic training with enough experience before these endoscopists could perform this IEE to diagnose MERD adopting these FICE criteria. These results emphasize that pCLE is more practical for clinical practice, especially for the beginner.

In our experience, the dilated intercellular space criterion is subjective and may be very difficult to evaluate in clinical practice. In contrast, a criterion using an increase in the number of IPCLs seems more promising because it is simple, very accurate, and easy to learn, as we demonstrated in our training evaluation. All of our beginners could achieve more than 80% in reading accuracy within the first round of test and their reading skills were consistently high in those three sessions. In addition, we demonstrated that the beginners could achieve the substantial level of inter-observer agreement after a short session of training. Although the increase in IPCLs number could also be observed in dysplastic epithelium,[20] fortunately this is not considered a factor because almost all targeted patients for MERD diagnosis are at low risk to develop esophageal neoplasm.

The current study has certain limitations. Firstly, the sample size was small, as the number was not enough to demonstrate a significant difference between pCLE and FICE in MERD diagnosis. However, this is the initial study in MERD diagnosis by pCLE. Secondly, FICE has lower market share than NBI or i-scan. However, FICE is an IEE that many endoscopists use in their daily practice, and the image quality from FICE is comparable to NBI.[21] Thirdly, we did not cross the patients over between the two methods, because it was impossible to do a crossover in this setting as pCLE technique requires direct contact by pCLE probe, and the minute injury to the esophageal mucosa by the probe could alter FICE reading on the esophageal mucosa. Therefore, pCLE had to come later in our study sequence. Fourthly, the endoscopist was not blinded to the result of GerdQ. However, we demonstrated that the off-line interpretation by the experienced endoscopist who was blinded to the GerdQ reults was not different from the real-time readings by the performing endoscopist. Fifthly, although GERD treatment is usually guided by patients' GERD-consistent symptoms, not by endoscopic findings, the correct diagnosis by endoscopy may predict PPI response and guide long-term management. Finally, the present study was not designed to evaluate the cost-effectiveness of pCLE to diagnose MERD. Currently, the pCLE probe

is considered non-reimbursable item in our country and used only for research. Therefore, the implication of this modality requires further evaluation in a larger scale of population that includes cost-effectiveness analysis. However, the only limitation is cost, whereas the pCLE procedure is easy to perform with a short learning curve, and has substantial to almost perfect inter-observer agreement. Moreover, the new generation of pCLE, which is less expensive than the present model, has been developed.[22]

FICE and pCLE are both useful for MERD diagnosis but pCLE is superior in providing a higher level of interobserever agreement and easy reading by novice endoscopists. This implies the more practical use of pCLE over FICE, although the cost-effectiveness of this approach needs a further confirmation study.

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