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BRIEF ARTICLE

Assessment of the diagnostic performance and interobserver variability of endocytoscopy in Barrett's esophagus: A pilot *ex-vivo* study

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Abstract

AIM: To investigate a classification of endocytoscopy (ECS) images in Barrett's esophagus (BE) and evaluate its diagnostic performance and interobserver variability.

METHODS: ECS was applied to surveillance endoscopic mucosal resection (EMR) specimens of BE *ex-vivo*. The mucosal surface of specimen was stained with 1% methylene blue and surveyed with a catheter-type endocytoscope. We selected still images that were most representative of the endoscopically suspect lesion and matched with the final histopathological diagnosis to accomplish accurate correlation. The diagnostic performance and inter-observer variability of the new classification scheme were assessed in a blinded fashion by physicians with expertise in both BE and ECS and inexperienced physicians with no prior exposure to ECS.

RESULTS: Three staff physicians and 22 gastroenterology fellows classified eight randomly assigned unknown still ECS pictures (two images per each classification) into one of four histopathologic categories as follows: (1) BEC1-squamous epithelium; (2) BEC2-BE without dysplasia; (3) BEC3-BE with dysplasia; and (4) BEC4-esophageal adenocarcinoma (EAC) in BE. Accuracy of diagnosis in staff physicians and clinical fellows were, respectively, 100% and 99.4% for BEC1, 95.8% and 83.0% for BEC2, 91.7% and 83.0% for BEC3, and 95.8% and 98.3% for BEC4. Interobserver agreement of the faculty physicians and fellows in classifying each category were 0.932 and 0.897, respectively.

CONCLUSION: This is the first study to investigate classification system of ECS in BE. This *ex-vivo* pilot study demonstrated acceptable diagnostic accuracy and excellent interobserver agreement.

Key words: Endocytoscopy; Barrett's esophagus; Dysplasia; Esophageal adenocarcinoma; Interobserver agreement

Core tip: The current gold standard for surveillance of esophageal adenocarcioma in Barretts's esophagus (BE) is endoscopic random biopsy and pathological diagnosis. Endocytoscopy (ECS) has the potential to provide a virtual histological diagnosis *in vivo* and in real-time. However, a major issue relates to that interpretation of cellular and nuclear images may be subject to similar interobserver variability associated with conventional histopathological diagnosis, and there have been no

reliable classification systems for the endocytoscopic diagnosis. We presented the first study to investigate classification system of ECS in BE. This *ex-vivo* pilot study demonstrated acceptable diagnostic accuracy and excellent interobserver agreement.

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INTRODUCTION

Recent advances in endoscopic imaging may lead to improved detection and facilitate therapy of dysplasia and esophageal adenocarcinoma (EAC) in Barrett's esophagus (BE)[1-5]. Histology is regarding as the gold standard for diagnosis of dysplasia and EAC[6,7], but sampling error and interobserver variability among gastrointestinal pathologists have been well described[8-11].

Endocytoscopy (ECS) is a probe-based technique which captures ultra-high magnified images of the epithelial surface, with the capability to discriminate cellular and subcellular features. ECS, thus, has the potential to provide a virtual histological diagnosis *in vivo* and in real-time. ECS has been investigated throughout the gastrointestinal tract for the identification of lesions in the esophagus[12-16], small intestine[17], and colon[18-21]. However, a major issue relates to the fact that interpretation of cellular and nuclear images may be subject to similar interobserver variability associated with conventional histopathological diagnosis[22,23]. To date, there have been no reliable classification systems for the endocytoscopic diagnosis of BE and Barrett's EAC. Accurate diagnosis based on a simple and reproducible classification system is warranted before ECS can be implemented into clinical practice.

Our aim was to develop simplified scheme for the classification of endocytoscopic images in BE and to evaluate its diagnostic performance and interobserver variability among experienced and inexperienced users of ECS in an *ex-vivo* setting.

MATERIALS AND METHODS

Patients and tissue specimens

ECS was performed *ex-vivo* on endoscopic mucosal resection (EMR) specimens obtained from patients undergoing endoscopic surveillance of BE at our institution. All EMR procedures were performed by a single endoscopist using the cap technique (EMR Kit; Olympus America, Center Valley, PA). Lesions targeted for EMR were endoscopically suspect areas, such as nodules or polyps, or dysplastic/neoplastic-appearing mucosa, such as irregular, friable, ulcerated, or villous-appearing mucosa, as seen under high-definition white-light imaging and narrow band imaging[24]. The study was approved by the Institutional Review Board and a written informed consent was obtained from all patients.

Endocytoscopy procedure

As soon as retrieved from the patient, the mucosal surface of each EMR specimen was immediately rinsed with 3-5 mL of 20% N-acetylcysteine to remove excess mucus, followed by the application of 1-1.5 mL of 1% methylene blue solution as contrast agent. *Ex-vivo* ECS imaging was performed using a flexible, catheter-type endocytoscope (XEC120, Olympus Medical Systems Co., Tokyo, Japan) which provides 1100 × magnification at a 120 μm × 120 μm field of view. The stained surface of each specimen was surveyed with the endocytoscope, and the area most representative of the endoscopically suspect lesion was identified. ECS imaging of the lesion was videotaped for approximately one minute.

Histopathology assessment

Histopathological assessment of the EMR specimens was performed according to the protocol in our BE unit, as previously published[25]. Patients had their pathological diagnosis of EMR specimens confirmed by at least two experienced gastrointestinal pathologists with expertise in Barrett-associated neoplasia.

ECS image analysis and classification

Following histopathological diagnoses of EMR specimens, the corresponding ECS videos and images were reviewed by investigators uninvolved in the subsequent blinded image assessment. To accomplish accurate correlation of endocytoscopic images with histological findings, we selected snapshots that were most representative of the histopathological findings for each specimen and matched final histopathological findings with their respective ECS images. With consideration to the previously proposed esophageal endocytoscopic atypia classification by Inoue *et al*[26], we classified the endocytoscopic images as follows (BEC; Barrett's EndoCytoscopy): (1) BEC1 - squamous epithelium; (2) BEC2-BE without dysplasia; (3) BEC3 - BE with dysplasia; and (4) BEC4-BE with EAC.

This classification scheme is based on the interpretation of ECS features (Figure 1): BEC1 images consist of cytoplasm-rich, rhomboid cells in a regular pattern; BEC2 images consist of increased cell numbers and different-sized nuclei/cells; BEC3 images consist of increased nucleus-cytoplasm ratio with dense chromatin and prominent nuclear fission; BEC4 images consist of cells of various sizes that are irregularly arranged, with blurred and enlarged nuclei. Two representative endocytoscopic images for each classification were selected for analysis of diagnostic performance and interobserver variability.

Diagnostic performance and interobserver variability

The diagnostic performance and inter-observer variabil-

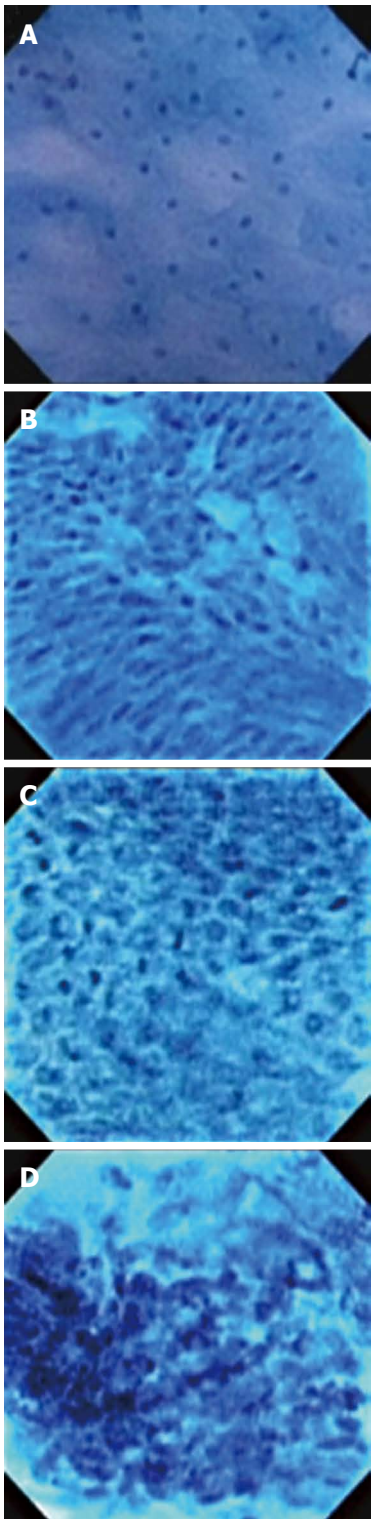

Figure 1 Classification of endocytoscopic images of Barrett's esophagus. A: Squamous epithelium (BEC 1) Cytoplasm-rich, rhomboid cells in a regular pattern; B: Barrett's esophagus without dysplasia (BEC 2) Increased cell number and different-sized nuclei/cells; C: Barrett's esophagus with dysplasia (BEC 3) Increased nucleus-cytoplasm ratio, and dense chromatin and nuclear fission are prominent; D: Esophageal adenocarcinoma (BEC 4) Cells of various sizes, irregularly arranged, with blurred and enlarged nuclei (magnification × 1125).

ity of the new classification scheme were assessed in a blinded fashion. Experienced physicians with expertise in both BE and ECS were provided with a brief 5-min presentation on the new classification, as shown in Figure 1. Inexperienced physicians consisted of clinical fellows (n = 22) in the Division of Gastroenterology and Hepatology with no prior exposure to ECS. They were provided with a 30 min presentation on ECS imaging and the new classification scheme. During the training session, fellows were presented with two non-study sets of pictures representative of each BEC classification for learning purposes. They were given the opportunity to ask questions and review the criteria. The training session and image classification by experienced and inexperienced physicians were conducted separately.

Immediately following the training session, participants were shown the randomly assigned unknown ECS pictures and asked to classify each image as: (1) BEC1; (2) BEC2; (3) BEC3; and (4) BEC4. The participants were blinded to patient history, endoscopic findings, and histopathological diagnoses. During the image classification session, the participants were not allowed to review previously seen images or to change their answers.

Statistical analysis

Data analysis was performed using the SPSS (Chicago, Illinois, United States) statistical software program. Classification accuracy, sensitivity, specificity, and positive and negative predictive values were calculated to assess diagnostic performance. Interobserver agreement was determined using intraclass correlation coefficient (ICC), which assesses agreement beyond chance among investigators. ICC was derived from a 2-way random effects model because both people effects and measures effects were random. An ICC of 0.4-0.75 indicates fair to good reliability, whereas an ICC greater than 0.75 shows excellent reliability.

RESULTS

A total of 20 patients were included in this study: squamous epithelium (n = 2), BE without dysplasia (n = 6), BE with dysplasia (n = 6), and BE with EAC (n = 6). A total of eight representative endocytoscopic images (two images per each classification) from different patients were utilized for this study. The overall classification accuracy for each category among experienced (n = 3) and inexperienced (n = 22) physicians were 100% and 99.4% for BEC1, 95.8% and 83.0% for BEC2, 91.7% and 83.0% for BEC3, and 95.8% and 98.3% for BEC4, respectively. If we combined BEC2 and BEC3 as diagnosis of BE, the classification accuracy would be 95.8%, even in ECS naive observers. The sensitivities, specificities, positive predictive values and negative predictive values for each category are shown in Table 1.

The interobserver agreements for the experienced and inexperienced physicians in classifying each category were 0.932 and 0.897, respectively. When a dichotomized category (BEC 1 and 2 *vs* BEC 3 and 4) was used, interobserver agreements for the experienced and inexpe-

Table 1 Diagnostic performance of endocytoscopy in Barrett's esophagus

	Classification	Sensitivity	Specificity	PPV	NPV
Experienced physicians (staff physician)	BEC 1	1.000%	1.000%	1.000%	1.000%
	BEC 2	1.000%	0.944%	0.857%	1.000%
	BEC 3	0.833%	0.944%	0.833%	0.944%
	BEC 4	0.833%	1.000%	1.000%	0.947%
Inexperienced physicians (clinical fellow)	BEC 1	0.977%	1.000%	1.000%	0.992%
	BEC 2	0.636%	0.894%	0.667%	0.881%
	BEC 3	0.705%	0.871%	0.646%	0.898%
	BEC 4	0.955%	0.992%	0.977%	0.985%
Both experienced and inexperienced (physicians staff physician and clinical fellow)	BEC 1	0.980%	1.000%	1.000%	0.993%
	BEC 2	0.680%	0.900%	0.694%	0.894%
	BEC 3	0.720%	0.880%	0.667%	0.904%
	BEC 4	0.940%	0.993%	0.979%	0.980%

PPV: Positive predictive value; NPV: Negative predictive value.

Table 2 Interobserver agreement of endocytoscopy in Barrett's esophagus

Classification	Staff physician (95%CI)	GI fellow (95%CI)
BEC 1-4	0.932 (0.794-0.985)	0.897 (0.784-0.973)
BEC 1 and 2 *vs* 3 and 4	0.851 (0.593-0.965)	0.581 (0.358-0.856)

GI: Gastrointestinal.

rienced physicians in classifying into this category were 0.851 and 0.581, respectively (Table 2).

DISCUSSION

Barrett's esophagus (BE) is a well-established precursor of esophageal adenocarcinoma (EAC) whose incidence is rising in Western countries. Patients with BE are therefore advised to undergo periodic surveillance to detect dysplastic mucosa and pre-cancerous lesions at an early stage at a time where intervention can be curative. The current gold standard for surveillance is periodic endoscopic random biopsy within the BE segment and pathological diagnosis. Due to inherent limitations of the gold standard, there have been considerable interests in advanced endoscopic imaging techniques to enhance dysplasia and EAC detection. Dysplasia can be patchy in distribution within the BE segment and sampling error can occur with random biopsy techniques. Novel imaging technologies that can reliably detect dysplasia or EAC in real-time would facilitate targeted biopsy and, hence, a reduction in sampling error.

Endocytoscopy (ECS) can provide real-time virtual histological images during endoscopic observation and potentially identify areas that harbor dysplastic or cancerous cells. However, interpretation of ECS images may be subject to similar interobserver variability associated with conventional histopathological diagnosis. A first step is to standardize ECS image criteria for accurate tissue diagnosis. To date, no studies have been conducted on the development and use of a classification system for endocytoscopic images in BE. In this study, we proposed a classification scheme based on ECS cellular and architectural features for categorizing Barrett's tissue, with the aim that the classification remains simple and easy to learn and adopt.

Overall, we had an acceptable classification accuracy for each Barrett tissue category when using our classification system and high accuracy was obtained for the differentiation of BE without dysplasia from dysplastic tissue among experienced observers. Although the number of percentage of accuracy among staff physicians appears low in BE with dysplasia, it is obvious that the small number of denominator is the reason. Our group of inexperienced observers (clinical fellows) classified squamous epithelium and EAC with high accuracy of 99.4% and 98.3%, respectively, and BE with and without dysplasia with acceptable accuracy of 83.0%. These results suggest our classification scheme is reliable and easy to learn. Interobserver agreement regarding both experienced and inexperienced groups was interpreted as excellent (ICC = 0.932 and 0.897, respectively). In classifying into two dichotomized category (BEC 1 and 2 *vs* BEC 3 and 4), interobserver agreement for the experienced physicians was still interpreted as excellent (ICC = 0.851) and interobserver agreement for the fellows showed good reliability (ICC = 0.581).

In this study, all the misdiagnoses of BE with dysplasia (BEC 3) were answered as non-dysplasia (BEC 2). It may imply that our criteria are similar to those of histological diagnosis. Misdiagnosis for non-dysplastic BE occurred in the inexperienced group, and all the misdiagnoses were answered as dysplasia. These facts probably reflect some of the dilemma that exists with pathological interpretation of non-dysplastic and dysplastic BE.

The reported diagnostic accuracy and interobserver agreement of ECS images should be interpreted with caution. In this structured pilot *ex-vivo* study, we intended to show a "classic" unambiguous image for each category and, thus, selected representative images. In BE, the microscopic epithelial changes that represent transition from metaplasia to dysplasia to cancer occur on a continuum. We did not assess how our classification performs near the margins of the transitions. The use of the representative images may maximize diagnostic

accuracy and interobserver agreement and minimize the correlation of the study findings with what will be observed during real-time use *in vivo*. We did not evaluate using "real-time" images correlated with biopsy results using our classification. Further study is warranted in real scanning to validate our classification. An additional study limitation is related to the *ex-vivo* nature of this preliminary study. The performance of *in-vivo* catheter-type ECS is clearly operator dependent. Challenges that lie ahead are the difficulty of maintaining a long, thin, flexible catheter onto the esophageal surface in stable position and in focus. During *in-vivo* observations, gastrointestinal motility may hinder collection of interpretable images. In one *in-vivo* study of ECS in BE[27], 76% of ECS images were recognized as poor quality. The study also had a high false-positive rate of 43%, resulting in both a sensitivity and positive predictive value of 42% in all image sequences. Conversely, an *in-vivo* feasibility ECS study for esophageal cancer conducted in Japan reported that clear and interpretable images were obtained in all cases, with the positive predictive value and the false-positive rate for esophageal malignancy being 94% and 6.3%, respectively[26]. Another *in-vivo* feasibility study also presented high quality images for interpretation[12]. Expertise in handling the ECS device could explain the difference in image quality obtained, and we believe the technical aspects can be overcome as already reported in the previous two *in-vivo* studies. A new endoscope-type ECS (XGIF-Q260EC1 and XCF-Q260EC1; Olympus) has recently been introduced and been reported to obtain more sensitive, ultra-magnified images[28-30]. The new ECS enables easy switch from a conventional endoscopic view to ultra-magnification endocytoscopic view by the press of a button at the top of the endoscope. The new device could reduce the technical burden of maintaining an ECS probe on a moving surface.

Our classification system does not differentiate between low grade (LGD) and high grade (HGD) dysplasia. It is well known the reproducibility of histopathological interpretation of LGD and HGD even among skilled pathologists is a challenge[10]. We still do not have definitive consensus about the management of LGD in BE, and management is individualized. It is clear that surveillance of any dysplastic lesions in BE segment is of importance given the established dysplasia-carcinoma sequence in EAC. In this study, we aimed to assess the potential of ECS in enhancing surveillance of dysplastic lesions in BE. We therefore proposed the two distinct criteria of dysplastic BE *vs* non-dysplastic BE instead of LGD and HGD.

In conclusion, we proposed a simple diagnostic classification system for ECS in BE. In this pilot *ex-vivo* study, acceptable accuracies regarding the diagnosis of squamous epithelium, non-dysplastic BE, dysplastic BE, and EAC were demonstrated. Interobserver agreement in classifying each category was interpreted as excellent, even among observers inexperienced in ECS. The applicability of the proposed classification scheme in the *in-vivo* setting remains to be seen.

ACKNOWLEDGMENTS

We thank Olympus America for providing the catheter-type endocytoscope for this pilot study.

COMMENTS

Background

Barrett's esophagus is a well-established precursor of esophageal adenocarcinoma, therefore it is very important to detect dysplastic pre-cancerous lesions at an early stage at a time where intervention can be curative. The current gold standard of endoscopic random biopsy has inherent limitations. There have been considerable interests in advanced endoscopic imaging techniques to enhance dysplasia detection.

Research frontiers

Novel imaging technologies that can reliably detect dysplasia or early esophageal cancer would facilitate targeted biopsy and, hence, a reduction in sampling error. Endocytoscopy can provide real-time virtual histological images during endoscopic observation and potentially identify areas that harbor dysplastic or cancerous cells and facilitate targeted biopsy.

Innovations and breakthroughs

A major issue relates to the fact that interpretation of cellular and nuclear images by endocytoscopy may be subject to similar interobserver variability associated with conventional histopathological diagnosis. To date, there have been no reliable classification systems for the endocytoscopic diagnosis of Barrett's esophagus and esophageal adenocarcinoma. In this study, the authors proposed a classification scheme based on endocytoscopy cellular and architectural features for categorizing Barrett's tissue, with the aim that the classification remains simple and easy to adopt. This is the first study to investigate classification system of endocytoscopy in Barrett's esophagus. In this study, the diagnostic performance and inter-observer variability of the new classification scheme were assessed in a blinded fashion by physicians with expertise in both Barrett's esophagus and endocytoscopy and inexperienced physicians with no prior exposure to endocytosocpy. Overall, the authors had an acceptable classification accuracy for each Barrett tissue category when using our classification system, and high accuracy was obtained for the differentiation of Barrett' s esophagus without dysplasia from dysplastic tissue among experienced observers. Interobserver agreement in classifying each category was interpreted as excellent among both experienced and inexperienced observers.

Applications

The results of this structured pilot *ex-vivo* study suggest that our classification scheme is reliable and easy to learn.

Peer review

The study to investigate classification system of endocytoscopy in Barrett's esophagus is very interesting. This *ex-vivo* pilot study demonstrated acceptable diagnostic accuracy and excellent interobserver agreement.

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