World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v5.i4.174

*World J Gastrointest Endosc* 2013 April 16; 5(4): 174-179
ISSN 1948-5190 (online)


BRIEF ARTICLE

# Endocytoscopic visualization of squamous cell islands within Barrett's epithelium

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Received: May 24, 2012 Revised: March 11, 2013
Accepted: March 15, 2013
Published online: April 16, 2013

## Abstract

**AIM:** To study the endocytoscopic visualization of squamous cell islands within Barrett's epithelium.

**METHODS:** Endocytoscopy (ECS) has been studied in the surveillance of Barrett's esophagus, with controversial results. In initial studies, however, a soft catheter type endocytoscope was used, while only methylene blue dye was used for the staining of Barrett's mucosa. Integrated type endocytoscopes (GIF-Q260 EC, Olympus Corp, Tokyo, Japan) have been recently developed, with the incorporation of a high-power magnifying endocytoscope into a standard endoscope together with narrow-band imaging (NBI). Moreover, double staining with a mixture of 0.05% crystal violet and 0.1% of methylene blue (CM) during ECS enables higher quality images comparable to conventional hematoxylin eosin histopathological images.

**RESULTS:** *In vivo* endocytoscopic visualization of papillary squamous cell islands within glandular Barrett's epithelium in a patient with long-segment Barrett's esophagus is reported. Conventional white light endoscopy showed typical long-segment Barrett's esophagus, with small squamous cell islands within normal Barrett's mucosa, which were better visualized by NBI endoscopy. ECS after double CM staining showed regular Barrett's esophagus, while higher magnification (× 480) revealed the orifices of glandular structures better. Furthermore, typical squamous cell papillary protrusion, classified as endocytoscopic atypia classification (ECA) 2 according to ECA, was identified within regular glandular Barrett's mucosa. Histological examination of biopsies taken from the same area showed squamous epithelium within glandular Barrett's mucosa, corresponding well to endocytoscopic findings.

**CONCLUSION:** To our knowledge, this is the first report of *in vivo* visualization of esophageal papillary squamous cell islands surrounded by glandular Barrett's epithelium.



**Key words:** Endocytoscopy; Barrett's esophagus; Surveillance; Endocytoscopic atypia classification; Crystal violet; Methylene blue; Hematoxylin eosin stain

**Core tip:** Endocytoscopy has been also studied in surveillance of Barrett's esophagus, with controversial results. In initial studies, however, a soft catheter type endocytoscope was used, while only methylene blue dye was used for staining of Barrett's mucosa. In the present study, *in vivo* endocytoscopic visualization of papillary squamous cell islands within glandular Barrett's epithelium in a patient with long-segment Barrett's esophagus is reported.

Eleftheriadis N, Inoue H, Ikeda H, Onimaru M, Yoshida A, Hosoya T, Maselli R, Kudo S. Endocytoscopic visualization of squamous cell islands within Barrett's epithelium. *World J Gastrointest Endosc* 2013; 5(4): 174-179 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i4/174.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i4.174

## INTRODUCTION

Endocytoscopy (ECS) with ultra-high magnification (× 400-1100) represents the most recent innovation in endoscopic imaging, permitting *in vivo* cellular imaging of gastrointestinal (GI) mucosa and visualization of nuclear atypia in neoplastic lesions during routine endoscopic examination[1-5]. Not only structural atypia, but also cellular atypia, with observation of lumens and nuclei, is achieved by recent advances in ECS[5-9].

Two different integrated type endocytoscopes (GIF-Q260, Olympus Medical Systems Corp, Tokyo, Japan) have been recently developed[2,6]. The first is a dual charged couple device (CCD) integrated type (CIF-Y0001, EC1 Olympus, Tokyo, Japan) and the other is a single CCD integrated type (CIF-Y0002, EC2 Olympus).

The dual CCD prototype carries both conventional magnification (× 80) and ultra-high magnification (× 480) abilities, which can be easily interchanged by pushing a button on the endocytoscope[2,6].

The single CCD prototype endocytoscope (CIF-Y0002, EC2 Olympus) has only one lens that can consecutively increase the magnification power from the conventional magnification power to × 380 using a hand lever. The video processor (prototype, Olympus CV-260X) with a light source (Olympus CLV-260) allows narrow-band imaging (NBI)[2].

Methylene blue or toluidine blue single staining was initially used for endocytoscopic evaluation of esophageal lesions[6,10,11]. Recently, however double staining with a mixture of 0.05% crystal violet and 0.1% methylene blue (CM) has been also proposed during ECS[2,3]. Crystal violet alone effectively stains the cytoplasm, while methylene blue single staining dyes both nuclei and cytoplasm, revealing details of cell structure[11,12]. Double CM staining enables well balanced staining of both cytoplasm and nuclei, resulting in improved endocytoscopic visualization of GI lesions, comparable to conventional hematoxylin eosin histopathological images[1].

Minami *et al*[2] has recently described a five type endocytoscopic atypia classification (ECA) of esophageal squamous cell lesions based on size and uniformity of nuclei, number of cells and regularity of cellular arrangement. ECA-1 to ECA-3 lesions correspond to histological categories 1 to 3, according to the revised Vienna[13,14] histological classification of gastrointestinal epithelial neoplasia, while ECA-4 to ECA-5 lesions correspond to Vienna categories 4 to 5 (Table 1). According to the results of Minami *et al*[2], overall accuracy of ECS in evaluation of esophageal squamous cell lesions was 91.3%, providing images similar to conventional hematoxylin and eosin staining[2]. Other endocytoscopic atypia classification systems of esophageal lesions based on "nuclear density" and "nuclear abnormality" have also been studied, with promising results[15].

Endocytoscopy has also been studied in surveillance of Barrett's esophagus, with controversial results[16,17]. In initial studies, however, a soft catheter type endocytoscope was used, while only methylene blue dye was used for staining of Barrett's mucosa[16,17]. Although a standardized endocytoscopic atypia classification system for Barrett's esophageal glandular lesions has not been yet described, endocytoscopically, dysplasia was diagnosed on the basis of polarity of cells and nuclei (spacing, orientation); size, shape and uniformity of nuclei; chromatin; nucleoli; and nucleus to cytoplasm ratio[17].

In the present study, *in vivo* endocytoscopic visualization of papillary squamous cell islands within glandular Barrett's epithelium in a patient with long-segment Barrett's esophagus is reported.

## MATERIALS AND METHODS

The dual CCD integrated prototype endocytoscope (CIF-Y0001, EC1 Olympus, Tokyo, Japan) was used for evaluation of long-segment Barrett's esophagus in the present study. In order to compare endocytoscopic images to histological images, biopsies were taken from the same area of ECS by an experienced endoscopist.

Conventional magnifying endoscopy and ECS was performed under conscious sedation with intravenous pethidine hydrochloride (35 mg; Opystan, Mitsubishi Tanabe Pharma Corporation, Osaka, Japan), supplemented with diazepam (5-10 mg, Takeda Pharmaceutical Co., Osaka, Japan). In order to suppress esophageal peristalsis, scopolamine butylbromide (20 mg; Buscopan, Boeringer Ingelhei, GmbH, Ingelheim, Germany) was also administered intravenously. Conventional and ultra-high magnification examination was performed simultaneously. Flushing with water containing a small amount of simethicone was carried out to eliminate gas and foamy mucus from the esophagus before the procedure.

Conventional white light endoscopy (WLE) showed typical long-segment Barrett's esophagus, without visible lesions (Figure 1A). NBI clearly visualized small squamous cell islands within normal Barrett's mucosa, which were also identified by WLE with difficulty (Figure 1B).

After double CM staining, ECS with gradual magnification followed. A total amount of 10 mL CM mixture was directly injected through the working channel with a 5 mL syringe to esophageal Barrett's mucosa. No catheter spray was necessary. The CM mixture is routinely prepared for ECS use, from 0.05% crystal violet and 0.1% methylene blue due solutions. After waiting 60 s to stain nuclei and cytoplasm, ECS followed.

## RESULTS

Initially, detailed endocytoscopic observation on the back-

**Table 1 Revised Vienna classification of gastrointestinal epithelial neoplasia**

| Category | Diagnosis |
|---|---|
| Group 1 | Negative for neoplasia |
| Group 2 | Indefinite for neoplasia |
| Group 3 | Mucosal low grade neoplasia |
| | Low grade adenoma |
| | Low grade dysplasia |
| Group 4 | Mucosal high grade neoplasia |
| Subgroup 4.1 | High grade adenoma/dysplasia |
| Subgroup 4.2 | Non-invasive carcinoma (carcinoma *in situ*) |
| Subgroup 4.3 | Suspicious for invasive carcinoma |
| Subgroup 4.4 | Intramucosal carcinoma |
| Group 5 | Submucosal invasion by carcinoma |

The Endocytoscopic Atypia (ECA) Classification[10] for superficial esophageal squamous cell lesions is as follow: ECA 1: Large, cytoplasm-rich cells with a rhomboid shape are found in a regular arrangement. Small nuclei are located at their center. This appearance corresponds to healthy squamous epithelium in the esophagus; ECA 2: The cell margin often becomes round. Different-sized small nuclei are observed. The image often shows inflammatory or reactive changes; ECA 3: The cell becomes smaller in size but the nuclei are still compact. This appearance is often observed in borderline lesions; ECA 4: The number of cells increases with an increased nucleus-cytoplasm ratio. This appearance strongly suggests a malignant lesion; ECA 5: Cells of various sizes are arranged irregularly with a high nucleus-cytoplasm ratio. This appearance is recognized endoscopically as a definitely malignant lesion. All images were categorized according to size and uniformity of nuclei, number of cells and regularity of cellular arrangement. Higher ECA category is associated with stronger atypia. ECA 1 to ECA 3 corresponds to Vienna categories 1 to 3; ECA 4 to ECA 5 corresponds to Vienna categories 4 to 5. The data was quoted from the references of 13, 14.

ground mucosa showed regular Barrett's esophagus, without endocytoscopic signs of dysplasia (Figure 1C), while with higher magnification the adenomatous Barrett's glandular orifices were better visualized (Figure 1D). Particularly, high quality endocytoscopic images revealed normal cellular structures, with cells similar in size and shape, without crowding or overlapping and an equal uptake of methylene blue, uniformly oriented in a glandular structure. Furthermore, nuclei were uniform, regular in shape, small in size with normal nucleus/cytoplasm ratio.

Subsequently, ECS focused on the largest squamous cell island surrounded by regular Barrett's epithelium, which was previous identified by NBI. A typical squamous papillary protrusion was clearly identified within regular glandular Barrett's mucosa (Figure 2A). Endocytoscopic findings revealed combined round-shaped cytoplasm-rich cells in an almost regular arrangement, while different sized small nuclei were observed, corresponding to ECA2 according to endocytoscopic atypia classification[2] (Figure 2A). These findings were suggestive of mild inflammatory changes of esophageal squamous epithelium (DVD).

After detailed observation, biopsies were taken from the same area in order to obtain a pathological diagnosis. The location of endocytoscopic images were matched to histological images and complete correspondence of endocytoscopic images with histopathological images was obtained (Figure 2) based on the records of endocytoscopic examination (DVD).

Histological examination showed squamous epithelium within non-dysplastic columnar Barrett's epithelium (Figure 2B). No dysplasia or atypia was found in histopathology of both squamous cell islands and adenomatous Barrett's epithelium, which was in accordance with endocytoscopic images.

## DISCUSSION

Barrett's esophagus is the transformation of the normal squamous esophageal mucosa into columnar epithelium and is considered a premalignant condition with high risk of esophageal adenocarcinoma[18-21]. Traditionally, the diagnosis of Barrett's esophagus is based on histology of biopsy specimens and hematoxylin eosin stain, revealing glandular structures combined with goblet cells[22,23]. The presence of goblet cells is the sine qua non of Barrett's esophagus[24,25].

Long-term endoscopic surveillance with multiple and repeated sets of biopsies are the standard recommended practice in Barrett's esophagus in an attempt to detect dysplasia or carcinoma at an early and potentially curable stage[26-29]. The Seattle multiple biopsy protocol (4 quadrant jumbo biopsies every 1 cm with additional biopsies of mucosal abnormalities), is considered to be the optimal method for surveillance of Barrett's esophagus, although it has never been validated[27,30]. However, even the most intensive biopsy protocols are associated with significant sampling errors[31,32].

By convention, there are four broad categories used by pathologists to describe the dysplastic process in Barrett's: (1) no dysplasia; (2) indefinite for dysplasia; (3) low-grade dysplasia; and (4) high-grade dysplasia; which corresponds to groups 1 to 4 according to the revised Vienna[14] classification for gastrointestinal epithelial neoplasia. The most significant category, high-grade dysplasia, is characterized by carcinoma *in situ* with malignant cells that do not invade the lamina propria. Category (5) corresponds to submucosal invasion by carcinoma[14,18].

However, the ability to grade dysplasia remains a subjective endeavor, particularly outside specialized centers with expert gastrointestinal pathologists[33]. Even among focused gastrointestinal pathologists there is discordance, particularly with regard to the presence of low-grade dysplasia[34]. This lack of precision inherent in histopathological grading has stimulated efforts to identify alternative methods of surveillance in patients with Barrett's esophagus, including more objective molecular and biochemical indicators of an increased risk for progression[18].

ECS is a revolutionized endoscopic imaging technique aiming to replace the histological examination of biopsy specimens, making "optical biopsy" possible while facilitating real time decision-making[8].

ECS after double CM staining using modern integrated type endocytoscopes enables *in vivo* visualization of living cells and evaluation of tissue atypia by approximating the tip of the endoscope onto the mucosal surface[10].

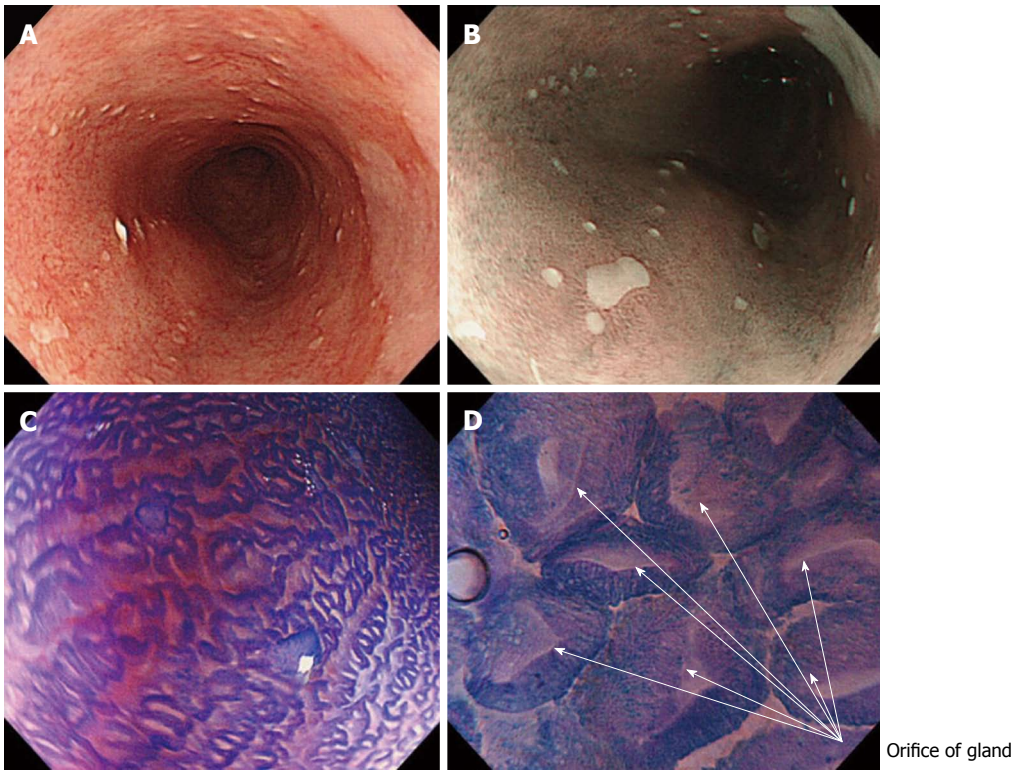


**Figure 1 White light endoscopy, narrow-band imaging and endocytoscopy examination of long segment Barrett's esophagus.** A: Long segment Barrett's esophagus under white light endoscopy (WLE); B: Narrow-band imaging with low magnification clearly visualized small squamous cell islands within regular columnar Barrett's epithelium, which are also identified by WLE with difficulty; C: Endocytoscopy (ECS) examination after crystal violet and methylene blue (CM) double staining; D: ECS examination under higher magnification (× 480) shows the glandular orifices of regular Barrett's epithelium.

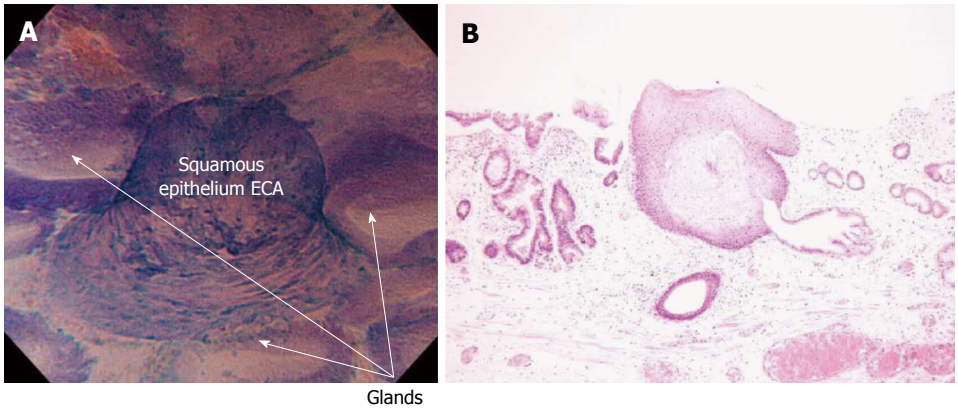


**Figure 2 Endocytoscopy examination of histologically confirmed squamous cell islands within Barrett's esophagus.** A: Endocytoscopy (ECS) examination shows squamous cell islands, within regular glandular structures of Barrett's esophagus. According to ECS examination, squamous papillary structure is classified as ECA2, (round-shaped cells with different-sized small nuclei, suggestive of inflammatory changes); B: Histological examination (hematoxylin and eosin stain magnification) of biopsies from the same area as in Figure (A) confirmed the presence of a squamous papillary structure surrounded by Barrett's glandular epithelium.

No serious complications of ECS have been reported yet[6].

At present, a standardized endocytoscopic atypia classification system has been described for esophageal squamous cell lesions[2] and colorectal[5] adenomatous lesions. ECS has been also applied for Barrett's esophagus[16,17,35,36], with controversial results, however, and without a standardized endocytoscopic classification system.

In contrast to previous endocytoscopic studies in Barrett's esophagus[16,17] where a soft catheter type endocytoscope was used, endocytoscopic evaluation of long-segment Barrett's esophagus in the present study was performed by a dual CCD integrated endocytoscope[2]. This scope has the advantage of gradual magnification at the center of the monitor, ensuring biopsies from the same area of ECS. This is important to compare endocytoscopic images to histological images. Standard endoscopy, supplemented by NBI and conventional magnification endoscopy was also performed by the same endoscope[2].

Another interesting finding of the present study is the

use of the double CM staining technique, which provided higher quality endocytoscopic images of both Barrett's metaplastic epithelium and esophageal squamous cell islands. Although double CM staining has been used in ECS of esophageal squamous cell lesions, to our knowledge, it has not been previously reported in endocytoscopic evaluation of Barrett's esophagus.

ECS may further allow target biopsy, as in the presented case, which is extremely important in surveillance of Barrett's esophagus where random biopsy protocols are currently in use. In the present case, ECS permitted *in vivo* high quality images of squamous cell islands within long-segment Barrett's epithelium comparable to histology. To our knowledge, this is the first report of *in vivo* visualization of typical esophageal squamous cell islands surrounded by glandular Barrett's epithelium. According to the positive results of the present study, although from only one case, endocytoscopic evaluation of Barrett's mucosa is promising. However, further studies and expertise are necessary.

## COMMENTS

### Background

Barrett's esophagus is the transformation of the normal squamous esophageal mucosa into columnar epithelium and is considered a premalignant condition with high risk of esophageal adenocarcinoma. Multiple biopsy protocols are currently the optimal practice in surveillance of Barrett's esophagus, with significant sampling errors, however. Moreover, there is discordance regarding the ability to grade dysplasia in Barrett's esophagus even among focused gastrointestinal pathologists. This lack of precision inherent in histopathological grading has stimulated efforts to identify alternative methods of surveillance in patients with Barrett's esophagus.

### Research frontiers

Endocytoscopy (ECS) has emerged as a novel method of *in vivo* diagnosis of gastrointestinal mucosal lesions aimed at replacing the histological examination of biopsy specimens while facilitating real time decision-making.

### Innovations and breakthroughs

ECS has been studied in surveillance of Barrett's esophagus, with controversial results. In contrast to previous studies in which a soft catheter type endocytoscope was used after single methylene blue dye for staining of Barrett's mucosa, in the present study, a novel integrated type endocytoscope after double crystal violet and methylene blue (CM) staining resulted in higher quality endocytoscopic images, corresponding to hematoxylin eosin histopathological images. To the knowledge, this is the first report of *in vivo* endocytoscopic visualization of typical esophageal squamous cell islands within regular glandular Barrett's epithelium.

### Applications

Based on the encouraging results of the present study, ECS, according to the technique described in this article, would be reliably used for real time, *in vivo* diagnosis of Barrett's esophagus as an alternative to histological examination of biopsy specimens. ECS may allow target biopsy, as in the presented case, which is extremely important in surveillance of Barrett's esophagus where random biopsy protocols are currently in use. However, further studies and expertise are necessary, while a standardized endocytoscopic atypia classification system, similar to that described for esophageal squamous cell lesions and colorectal adenomatous lesions, is necessary and awaited.

### Terminology

CCD: charged couple device; ECS is a novel endoscopic imaging of gastrointestinal mucosa, with ultra-high magnification (× 400-1100), permitting *in vivo* cellular imaging and observation of lumens and nuclei during routine endoscopic examination; The dual CCD integrated prototype (CIF-Y0001, EC1, Olympus, Tokyo, Japan) endocytoscope (× 480) carries both conventional magnification (× 80) and ultra-high magnification (× 480) abilities, which can be easily interchanged by pushing a button on the endocytoscope; The single CCD prototype (CIF-Y0002, EC2 Olympus) endocytoscope (× 380) has only one lens that can consecutively increase the magnification power from the conventional magnification power to × 380 using a hand lever; The revised Vienna classification of gastrointestinal epithelial neoplasia, which is based on the severity of cytological and architectural changes and on invasion status, has to some extent, resolved the differences between Western and Japanese pathologists in the diagnostic classification of gastrointestinal epithelial neoplastic lesions, especially in the use of the terminology of dysplasia, adenoma, early cancer and advanced cancer.

### Peer review

It is very interesting brief report. Superb images and careful description of the technique are the strong points of the paper.

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