Application and efficacy of the super-magnifying endoscopy for the lower intestinal tract

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ABSTRACT

Endoscopy plays a significant role in the diagnosis, management, surveillance of colorectal cancer (CRC) and inflammatory bowel diseases (IBD). Moreover, magnifying endoscopy and Image-enhanced endoscopy has a crucial role in the clinical settings. In recent, super-magnifying endoscope has been developed, and two devices are currently available, which allow in vivo microscopic inspection of microstructural mucosal features of the gastrointestinal tract: confocal laser endomicroscopy (CLE) and an endocytoscopy system (ECS). Studies of ECS for CRC were reported by Japanese group. A few study concerning ECS for IBD has been reported. CLE has been shown to reliably assess activity of the disease in inflammatory bowel diseases both in UC and Crohn’s Disease. Various published studies evaluating the use of CLE during colonoscopy for distinguishing colorectal polyp pathology and neoplasia. These studies are heterogeneous. More evidence is necessary to be confirm the efficacy of CLE.

Key words Super-magnifying endoscopy, Endocytoscopy, Confocal laser endomicroscopy, Magnifying endoscopy
Introduction

Endoscopy plays a significant role in the diagnosis, management, surveillance of colorectal cancer (CRC) and inflammatory bowel diseases (IBD). Moreover, magnifying endoscopy \(^1\,^2\) and Image-enhanced endoscopy (IEE) \(^3\) has a crucial role in the clinical settings. In recent, super-magnifying endoscopy has been developed, and two devices are currently available, which allow in vivo microscopic observation of microstructural mucosa of the gastrointestinal tract: confocal laser endomicroscopy (CLE), (Mauna Kea Technologies, Paris, France) (Pentax, Tokyo, Japan) and an endocytoscopy system (ECS) (Olympus, Tokyo, Japan). These devices are actually used in clinical study rather than in clinical practice. In this review article, we focused on the newly developed these devices on the application and efficacy for the lower intestinal tract.

Endocytoscopy

The ECS is based on the principle of contact light microscopy. ECS observation also requires pre-treatment with methylene blue or toluidine blue staining \(^4\). The ECS has two types of endoscope; a probe-based ECS (pECS) or an integrated-scope type ECS (iECS). The iECS which has adjustable scope hardness with an outside diameter of 13.6 mm at the distal end and a working length of 1330 mm \(^5\). The first generation iECS has a dual-charged coupled device (CCD) (XCF-260EC1; prototype, Olympus, Tokyo, Japan). This scope can perform conventional and super-magnifying endoscopic observation consecutively using one-touch switch operation without changing endoscope. In ECS mode, this scope has a magnification capability of \(\times 450\); the depth of field is 50 \(\mu m\) and the field of view is 400 \(\times\) 400 \(\mu m\). The second generation iECS is single-CCD integrated type (CF-Y0020-I; prototype, Olympus, Tokyo, Japan). The second generation iECS has a 380\(\times\) magnification with a focusing depth of 50 \(\mu m\) and a field of view of 700 \(\times\) 600 \(\mu m\), which can obtain super-magnifying with Narrow Band Imaging (NBI) pictures \(^6\).
Application of ECS for Colorectal cancer

Several studies were reported by Japanese group. Kudo et al. created an endocytoscopic (EC) classification for colonic neoplasia by using iECS. They classified into the normal mucosa as EC1a, all hyperplastic polyps as EC1b, dysplasias as EC2, massively invasive submucosal cancers (SMm) or worse as EC3b. In this pilot study, they showed a sensitivity of 100% and a specificity of 100% (P < 0.05) to differentiate nonneoplastic from neoplastic lesions. They also showed a high sensitivity (90.1%) and a high specificity (99.2%) to differentiate “SMm or worse” from other neoplastic lesions. Mori et al. validated EC classification using a randomized, controlled, open-label trial to determine the non-inferiority of the first generation iECS to standard biopsy. They showed that the diagnostic accuracy of iECS for the discrimination of neoplastic lesions was 94.1% (95% confidence interval 87.6% to 97.8%), whereas that of standard biopsy was 96.0% (90.2% to 98.9%). These results were within the noninferiority margin (absolute difference -1.9%, -8.6% to +5.0%). They concluded that iECS was noninferior to standard biopsy for the discrimination of neoplastic lesions. In recent study, Kudo et al. focused on the microvasculature of colonic neoplasia. They evaluated 198 consecutive colonic lesions by using second generation iECS with NBI. They classified the endocytoscopic vascular (EC-V) pattern into three categories, which is EC-V1, obscure surface microvessels; EC-V2, clearly observed surface microvessels of a uniform caliber and arrangement; and EC-V3, dilated surface microvessels of a nonhomogeneous caliber or arrangement. They showed that the sensitivity, specificity, and accuracy of the EC-V1 pattern for diagnosing hyperplastic polyps were 95.5%, 99.4%, and 99.0%, respectively. The sensitivity, specificity, and accuracy of the EC-V3 pattern for diagnosing invasive cancer were 74.6%, 97.2%, and 88.6%, respectively. They concluded that iECS could evaluate the microvasculature of colorectal lesions, and the EC-V pattern diagnosis was highly correlated with the histopathologic diagnoses of the other optical biopsy modalities.
Application of ECS for IBD

A few study concerning ECS for IBD has been reported. An efficacy of ECS for evaluating the colonic inflammation has not been still unconfirmed. We applied ECS to the infectious colitis; Amoebic colitis. We enrolled five patients with amoebic colitis. We directly detected E. histolytica trophozoites in all five cases (100%). In contrast, 3 patients (60%) were positive for serology, and 3 were positive for histology with H&E staining. We also applied ECS to the Ulcerative colitis (UC). We created an ECS score (ECSS) to determine a histopathological activity index of UC. We used first-generation iECS with magnification 450×, and sample biopsies were obtained from the same site. To validate the ECSS, we calculated the correlation between the ECSS and Matts' histopathological grade which was determined by expert the pathologist. The ECSS of UC consists of the sum of the indices for shape (0-3), the distance between crypts (0-2), and the visibility of superficial microvessels (0-1). Scores of ECSS showed a strong correlation with Matts' histopathological grades (ρ = 0.713, P < 0.001). Recently, another group evaluated the clinical usefulness of ECSS for accurately monitoring UC during remission. They classified enrolled patients into two groups: those with an ECSS of 0-2 (Grade A) and those with an ECSS of 3-6 (Grade B). They reported that relapse rate of Grade B was significantly greater than that of Grade A. They concluded that the ECSS might be a predictive indicator for UC relapse.

Confocal Laser Endomicroscopy

CLE has been first reported in 2004. Recently, it can be performed with two devices: one integrated into endoscope (iCLE; Pentax, Tokyo, Japan), and another using a mini-probe through the scope (pCLE; Cellvizio, Mauna Kea Technologies, Paris, France) (Figure 1). The pCLE consists Laser scanning unit (Figure 1a) and mini probe (Figure 1b). Mini probe can be advanced through the working channel of a standard endoscope. CLE is based on tissue illumination with a low-power laser with subsequent detection of the fluorescence of light.
reflected from the tissue. Confocal imaging can be based on tissue reflectance or fluorescence. The fluorescent contrast agents are most commonly used. Fluorescein sodium (fluorescein sodium, AK Fluor; Akorn Pharmaceutical, USA) is administered for CLE observation intravenously, or acriflavine (Sigma Pharmaceuticals, Australia), tetracycline, or cresyl violet (AnaSpec, Inc, San Jose, USA) are topically sprayed.

**Application of CLE for Colorectal cancer and polyp**

Various published studies evaluating the use of CLE during colonoscopy for distinguishing colorectal polyp pathology and neoplasia (Table 1). These studies are heterogeneous. The sensitivity of CLE for colorectal polyp pathology is ranging from 43.4 to 100%. These studies are difficult to compare because of differing primary objectives and the modality of CLE used (iCLE vs pCLE). We need more evidence to confirm the efficacy of CLE.

**Application of CLE for IBD**

CLE has been shown to reliably assess activity of the disease in inflammatory bowel diseases, both in UC and Crohn’s Disease. Neumann et al developed a score named the Crohn’s Disease Endomicroscopic Activity Score (CDEAS) to assess in vivo real-time disease activity. The CDEAS consists of six parameters: crypt number (increased or decreased), crypt distorsion, microerosions, cellular infiltrate, vascularity, and number of goblet cells (increased or decreased). By assignment of one point for each given parameter, the score ranges from 0 to 8. They showed that CDEAS strongly correlated with C-reactive protein level. Li et al assessed the potential of CLE in the grading of UC activity. They focused on three categories; crypt architecture, microvascular alterations, and fluorescein leakage. They classified crypt architecture into 4grade, as A to D: A regular arrangement, B Irregular, C Dilation of crypt openings, D Crypt destruction and/or crypt abscess. They confirmed that crypt architecture
classification was strongly correlate with histological index.

**Future perspective**

Super-magnifying endoscopy; ECS and CLE, are mainly applied upper and lower intestinal disease. Residual feces and/or mucous sometimes disturb optimal super-magnifying observation. A little feces and mucus is in the small intestine, thus, small intestinal circumstance is appropriate for super-magnifying observation. Now, we start pilot study by using single-balloon enteroscopy and CLE to observe small intestinal disease. In the near future, utility of super-magnifying endoscopy would be reported.

**Conclusions**

Super-magnifying endoscopy; ECS and CLE have a potential ability to obtain the real-time in vivo histopathology.

**Conflicts of interest**

No financial relationship relevant to this publication is disclosed.

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Table 1: Performance of Confocal Laser Endomicroscopy for colonic neoplasia

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<th>NPV, %</th>
<th>Accuracy, %</th>
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PPV, positive predictive value; NPV, negative predictive value
Figure legends

Figure1

Probe-based Confocal Laser Endomicroscopy system.

a. Laser scanning unit

b. Mini probe. Mini probe can be advanced through the working channel of a standard endoscope.