Confocal Laser Endomicroscopy: What Can We Do with This?

Sang Kil Lee, M.D., Ph.D.
Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, Seoul, Korea

Introduction

Endoscopy is the essential procedure for the diagnosis of gastrointestinal (GI) disease. Subsequent biopsy and histologic diagnosis was the gold standard for final diagnosis. However, detection of dysplasia in the inflamed stomach and intestine, detection of malignancies and discrimination of inflammatory disease from neoplasia remains not easy to get. In recent years, a range of innovative techniques have entered the endoscopic arena due to their ability to enhance the contrast and magnify in cellular level of diseased tissue regions beyond standard white-light endoscopy equipment.

Confocal laser endomicroscopy (CLE) is a technology that allows the user to get microscopic views of the mucosa in real time during endoscopy. The technology can be used through a single endoscope-based system (CLE) (OptiScan, Notting Hill, Australia) or through a probe-based system known as probe-based confocal laser endomicroscopy (pCLE) (Cellvizio; Mauna Kea Technologies, Paris, France). CLE is one of the newest advancements in diagnostic endoscopy and is a highly promising technique for investigating the mucosal surface together with its immediate subsurface areas. Cell structures and tissue morphological characteristics can be visualized to a maximum depth of 250 μm. Recently, there are efforts to use CLE not only for the means for replacing the biopsy, but also for monitoring and prediction the progression of GI disease. In this review, we will touch the indications of CLE in GI disorders.

Barrett’s Esophagus (BE) and adenocarcinoma of esophagus

The first trial of CLE with eCLE to predict BE and associated neoplasia was done at 2006 Kiesslich R, et al. In this study included 63 patients with BE found that CLE predicted BE and associated neoplasia with a sensitivity of 98.1% and 92.9% and a specificity of 94.1% and 98.4%, respectively. Recently Canto et al. did randomized controlled trial that included 192 study patients with BE compared high-definition WLE alone with random biopsy and high-definition WLE with CLE and targeted biopsy. Adding CLE to high-definition WLE increased the rate of sensitivity from 40% to 96% without significantly compromising the rate of specificity (92%). Generally speaking, pCLE showed improved efficacy compared to WLE or high definition endoscopy. However there is debate that pCLE can replace the standard practice for the diagnosis of BE-associated neoplasia due to
its low positive predictive value and sensitivity.

**Stomach**

CLE was tried to characterize dysplasia or cancer and to find the risk factors of gastric cancer such as intestinal metaplasia and existence of *Helicobacter pylori in vivo*. In Asian country including Korea and Japan, the most of EGC are detected by white light endoscopy, however, identification of EGC is difficult because some lesions are very little to recognize and metaplasia on background make endoscopist difficult to find. In the largest published study on the use of CLE for the detection of gastric superficial cancerous lesions, 182 patients were enrolled in phase I to establish morphologic criteria for gastric superficial cancerous lesions and 1,786 patients were enrolled in phase II for prospective validation. CLE criteria for cancer/high-grade intraepithelial neoplastic lesions were irregularity in glandular size and shape, disorganized or destroyed pits and glands, irregular cells with disordered appearance, severe stratification, loss of cell polarity, and irregular shape and caliber of vessels. Using these criteria, eCLE had higher sensitivity (88.9%), specificity (99.3%), and accuracy (98.8%) for the diagnosis of gastric superficial cancer/high-grade intraepithelial neoplastic lesions than WLE (sensitivity, 72.2%; specificity, 95.1%; and accuracy, 94.1%). Furthermore, there were trials to figure out and grade intestinal metaplasia and atrophic gastritis which were confirmed pre-cancerous lesion of gastric cancer by CLE. CLE showed distinct features of intestinal metaplasia, and CLE with targeted biopsies is superior to WLE with standard biopsies for the detection and surveillance of GIM. Recently, Liu et al. reported a new application of pCLE as grading of atrophic gastritis. In this study pCLE had a higher sensitivity, specificity, and accuracy compared with NBI and CE, which were equivalent for diagnosis of atrophic gastritis.

However there is also some drawbacks of application of CLE in stomach. The performance and interpretation of pCLE for gastric lesions also depended on examiner and reviewer. Also there is no standard criteria to interpret the gastric carcinoma and dysplasia by CLE. Here in Korea, the CLE is not permitted to do in practice.

**Colon**

In the colon, CLE was tested in several clinical applications including differential diagnosis of polyp (neoplastic vs. hyperplastic polyp), detection of dysplastic lesion from background of chronic inflammatory bowel disease, and predicting the relapse of inflammatory bowel disease. In the differential diagnosis of neoplastic vs. hyperplastic polyps in the colon, the pCLE had higher sensitivity compared to virtual chromoendoscopy when considering histopathology as gold standard (91% vs 77%; \( P = .010 \)) and modified gold standard (88% vs 76%; \( P = .037 \)). For the colorectal cancer screening and surveillance in patients with ulcerative colitis, four biopsy specimens are taken randomly at every 10 cm between the rectum and the cecum when there are no obvious lesions. However, even this massive sampling regimen examines less than 1% of the total colonic mucosa surface. There is ultimate need of target biopsy than random biopsy. A study of 161 patients with long-standing UC randomized them to conventional WLE with random biopsies or chromoendoscopy with CLE. By using chromoendoscopy and CLE, 4.75-fold more neoplasia were detected (\( p = .005 \)) with 50% fewer biopsies, as compared with conventional colonoscopy.
Recently, the excessive epithelial cell shedding and barrier loss as defined by leakage of fluorescein into the lumen predicts future relapse in inflammatory bowel disease patients.

Conclusions

Confocal laser endomicroscopy (CLE) is an endoscopic-assisted technique developed to obtain histopathological diagnoses of gastrointestinal and pancreatobiliary diseases in real time. Recent research about CLE have shown clinical application and efficiency in gastrointestinal disease, however there are still limitations to use CLE as standard tool as diagnosis and monitor GI disease. Most seriously, CLE is not available in Korea for clinical aim because the government did not approve it. Further innovation and studies should be carried on to overcome this drawback.

References