Review Article

Role of Confocal Laser Endomicroscopy for the Detection of Early Gastrointestinal Malignancy

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ABSTRACT

Presently, detecting early gastrointestinal (GI) malignancy is a challenging strategy. Many new technologies have been developed to detect and characterize tiny mucosal lesion. The advantage of these techniques is not only benefit as an in vivo confirmation on the presence of early cancer but also as the assistance for a targeted biopsy. Recently a confocal laser endoscopy (CLE) has been added as an adjunctive reading tool for precancerous lesion and early GI malignancy.

Key words : Confocal laser endomicroscope, gastric cancer, gastric intestinal metaplasia

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INTRODUCTION

From the recent global report in 2011, gastric and colon cancers are ranged as the second and the third most frequent causes of cancer related death in the world[1]. Usually, patients with early stage of gastrointestinal cancers are asymptomatic, whereas majority of symptomatic patients are found with advanced stage lesions and those usually carry a dismal prognosis. Therefore, the strategy which can detect precancerous lesions or early cancer is very beneficial because they can potentially be cured by an endoscopic resection.

Initially the tools for early cancer detection had started from gastro camera in 1962[2,3] and subsequently progressed to magnify chromoendoscopy. Over a few years, digital chromoendoscopy (DC) including NBI and others optimal band imagings have been developed to detect many GI precancerous lesions such as colonic adenoma and gastric intestinal metaplasia (GIM)[4-10]. Recently, a confocal laser endoscopy (CLE) which provides a higher magnification (X1000) of the GI tract epithelium, has been reported in many studies as an vivo precancerous detecting device for both upper GI[11-14] and lower GI tracts[15-19]. In this review, we summarize the history and possible roles of CLE for GI precancerous lesion and early cancer detection.

Confocal laser endomicroscope (CLE)

Confocal laser endomicroscope (CLE) is the lat-

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est novel endoscopic device which has been commercially available since 2005[20]. CLE is an instrument providing a high-magnification (×1000) of black and white image that comparable to the standard microscopic examination. The principle technique is a summary of display images reconstructed from a pinhole that filtering only a focused light from a reflected plane. Technically, the pin hole reduces scatter light below and above the plane (Figure 1). Therefore, only one single spot in one plane, called "confocal", can be seen at once[21]. During the examination, the confocal system can display a video stream with 1-12 frames/second. In other word, its display resembles a real-time endoscopic picture for histology[11,12, 22-25]. Currently, there are two techniques; a) endoscopic-based confocal laser endomicroscope (eCLE, Pentax-Hoya, Tokyo, Japan) and b) probe-based confocal laser endomicroscope (pCLE, Mauna Kea Technologies, Paris, France). Both require intravenous (IV) contrast injection (Fluorescein) or topical dye spray (eg. acriflavine hydrochloride) to enhance all vascular supplied mucosal structures[21]. The eCLE is an endoscopic-based CLE that integrated a fluorescence microscope into the distal tip of a conventional 12.8-mm diameter flexible endoscope (Hoya cooperation, Tokyo, Japan). The other system called pCLE provided by Mauna Kea Technologies (Paris, France), is a 2.5-mm catheter probe transported 488-nm laser beam with a scanning field of 30,000 pixels[21,25] (Figure 2). With today technology, the quality of confocal image from eCLE is better than pCLE because the eCLE system can provide an adjustable Z-axis focus at different depths. Moreover, eCLE provides a better (0.7 μm) lateral reso-

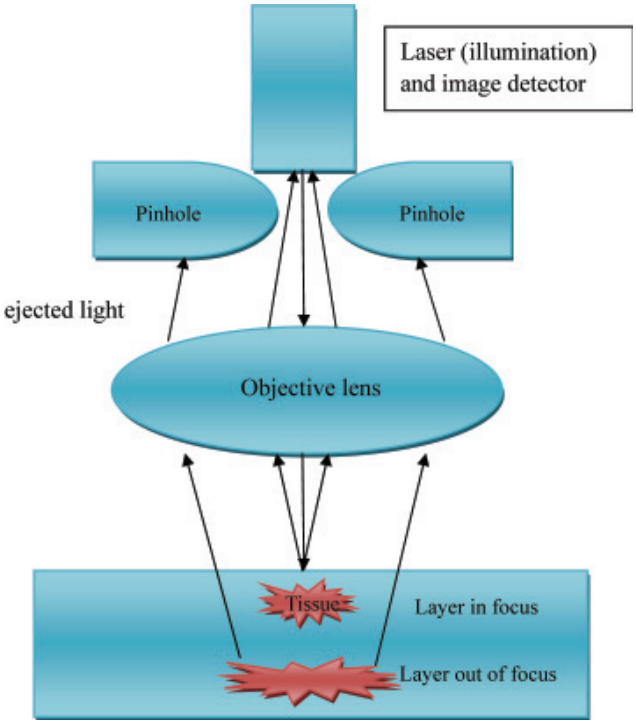
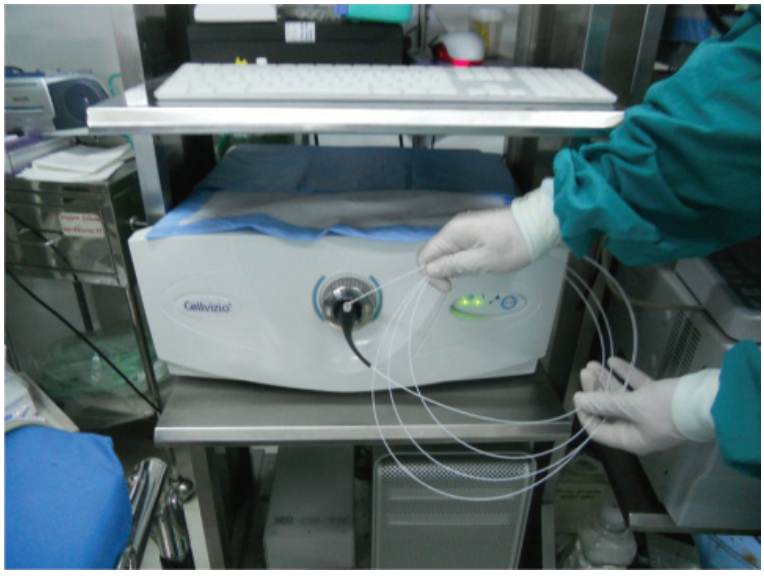


Figure 1. Schematic of confocal laser endomicroscopy (CLE) principle.



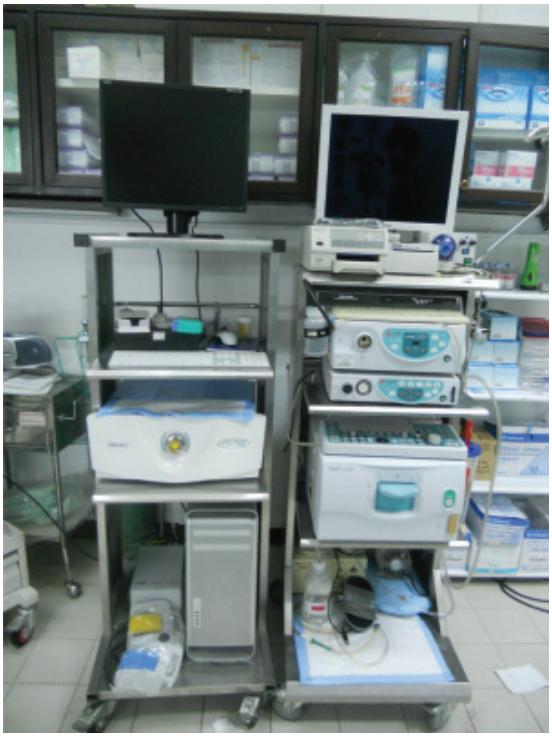


Figure 2. The pCLE probe and syste

lution than pCLE (1 μm)[25,26]. In addition, imaging plane depth of eCLE can be varying up to 250 μm whereas pCLE system has a fixed imaging plane depth at the 200 μm. However, pCLE is more flexible to use because it is more compatible with any endoscope that accept 10 Fr size accessories. Furthermore, pCLE system provides a much faster frame rate (12 images/second) than the current eCLE (± 1 image/second)[27]. Needless to say, the streamline of pCLE images is close to the standard video output (Table 1).

Fluorescein, a slightly acidic and hydrophilic dye, has been used intravenously as a staining substance. Within ten seconds after injection, it distributes through all the surface of epithelial cells. Fluorescein facilitates a real-time histology reading by enhancing structures containing blood vessels including normal gastric epithelium[23,28]. In contrast, any structure that has no vacular supply such as mucin will not be stained by fluorescein. Presently, fluorescein is proven as a very safe contrast agent because less than two percent of patients experienced mild side effects including nausea/vomiting, transient mild degree of low blood pressure, erythema around injected site, diffuse rash and, mild epigastric pain[29].

Another well-known agent called acriflavine hydrochloride, a topical dye, is not currently recommended for early cancer screening because it stains only on the superficial layer of GI tract mucosa[24].

Role of CLE for early GI cancer detection

Esophagus: Using CLE to detect the presence of mucosal abnormalities such as irregular mucosal arrangement, increase diameter of intrapapillary capillary loops (IPCLs), and irregular shape IPCLs can distinguish superficial esophageal squamous cell carcinoma from normal esophageal mucosa with 85-95% accuracy[14,30]. Based on the same criteria, the accuracy will increase to more than 90% for Barrett's epithelium detection[28,30-33]. Subsequently, the latest study[33] proposed six novel pCLE criteria for prediction of high grade/cancer in Barrett's esophagus patient; 1) epithelial surface appears saw-toothed, 2) goblet cells not easily identified, 3) gland are not equidistant, 4) glands are unequal in size and shape, 5) cells are enlarged, and 6) cells are irregular and not equidistant from one another. By following these criteria, experienced endoscopists can perform the examination with 98% accuracy[33]. Furthermore, only a short learning curve is required to train the beginners[33].

Table 1. A comparison between eCLE and pCLE

	eCLE	pCLE
Lateral resolution	0.7 μm	1 μm
Field of view	475 × 475 μm	240 × 240 μm
Z-axis	Yes	No
Versatility	No	Yes
Imaging plane depth	Vary up to 250 μm	Fixed, maximum 200 μm
Image/ second	± 1	12

Stomach: The standard imaging criteria by CLE for early gastric cancer (EGC) detection has not been standardized because the non-structural mitotic glands of the stomach are difficult to recognize. However, the pilot studies read by expert endoscopists reported a high sensitivity near 90%[11,12]. To date, there has been no study focusing on the interobserver agreement by non-experts for EGC reading yet. In contrast, GIM which is a precancerous lesion can be readily recognizable with CLE by demonstrating mucin-containing goblet cell (Figure 3). The sensitivity of eCLE for GIM detection is excellent (98%)[13]. However, the limitation of current technology is the inability of CLE to distinguish between mature and immature GIM[13]. This is very important since the risk of gastric cancer in a patient with immature GIM is much higher than a patient with mature GIM[34,35].

In the authors' opinion, CLE for GIM detection during a routine work is more practical because the globlet cell is easy to be detected by non-experts. In contrast, CLE for EGC screening is not yet recom-

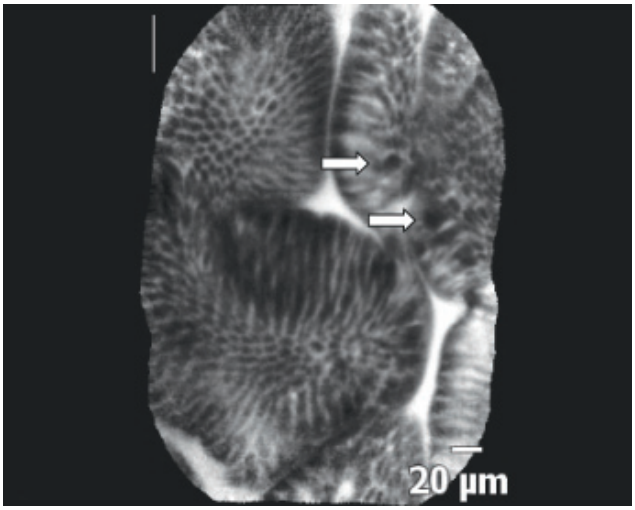


Figure 3. The image of GIM from pCLE (Mucin-containing goblet cells; arrow)

mended in standard practice unless the standardization in EGC reading by CLE is more developed.

Colon: Many studies using CLE showed a very high accuracy (more than 95%) in predicting neoplastic change of colonic polyps[16,18-20]. Unnecessary biopsy can be avoided if CLE confirms hyperplastic change of the polyp. However, this practice is recommended only for a small polyp since in a large polyp the complete examination is impractical. Thus, the incomplete examination can miss the potential malignant histology such as hidden adenoma and serrated histology.

In addition, CLE has been studied to detect other malignant GI diseases such as biliary tract neoplasm[36,37] and many non-malignant GI diseases including H.pylori gastritis[38,39], inflammatory bowel disease[40,41], and celiac disease[42]. However, the current data are insufficient to recommend using CLE as a standard tool for routine endoscopy in those conditions.

CONCLUSION

CLE is the up-to-date revolution of endoscopy practice. Without a need for biopsy CLE can provide a real-time confirmation in many precancerous lesions such as Barrett's esophagus, GIM, and colonic polyp. By contrast, the use of CLE for other malignancy detection is still limited to expert centers due to suboptimal criteria that still too difficult to be adopted by routine endoscopists.

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