



Confocal laser endomicroscopy for gastric neoplasm

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Abstract

Confocal laser endomicroscopy (CLE) is a novel endoscopic modality that provides real-time histological information *via* high-resolution magnified view of the mucosa. CLE has a higher sensitivity, specificity, and diagnostic accuracy in detecting atrophic gastritis as compared to chromoendoscopy and narrow-band imaging. It can even predict low-grade and high-grade intraepithelial neoplasia by analyzing gastric pit patterns. CLE may have some advantages over the standard biopsy protocol, such as higher diagnostic yield and fewer biopsy requirements. Its diagnostic accuracy in detecting superficial gastric cancer is higher than that of white-light endoscopy. Inherent limitations, such as a narrow field of vision, can be surpassed by technological advancements and integration with other detection methods. Artificial intelligence holds promise in automated analysis of histopathological images. Thus, CLE can be helpful in screening for early gastric cancer and may help reduce the risk of complications from repeated biopsies, such as mucosal damage, bleeding, and infection.

Key Words: Confocal laser endomicroscopy; Gastric cancer; Narrow band imaging; Diagnostic yield

Core Tip: Confocal laser endomicroscopy is a new imaging technique used during endoscopy procedures to evaluate the mucosa *in vivo*. Diagnosing and monitoring early cancer in the upper gastrointestinal tract can be effectively achieved through the use of this tool. Minimizing the number of biopsies required is one of the main benefits of this technology, while still maintaining a high diagnostic sensitivity rate. This helps to reduce the risk of complications, such as mucosal damage, bleeding, and infection, that may be caused by repeated biopsies.

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TO THE EDITOR

Confocal laser endomicroscopy (CLE) is a novel endoscopic modality that provides real-time histological information *via* high-resolution magnified view of the mucosa. CLE is based on the principle of confocal microscopy, wherein a low-power laser beam is focused at a specific plane in the tissue and the fluorescence emitted is detected, enabling the functional reconstruction of an image. Since CLE relies upon tissue fluorescence, intravenous and/or topical contrast agents are utilized. There are two kinds of CLE systems that can be used for gastrointestinal (GI) endoscopy. The first one is endoscope-based CLE (eCLE), which is a combination of a miniature confocal scanner and a unique flexible endoscope tip. However, this system is not frequently utilized in clinical practice. The other system is known as probe-based CLE (pCLE), which has a flexible confocal microprobe that can easily pass through the working channels of most traditional endoscopes. In comparison to eCLE, pCLE can capture images more quickly. However, its resolution and preset fixed plane depth are limited[1,2].

COMPARISON OF CLE WITH ENDOCYTOSCOPY

Both CLE and endocytoscopy are high-definition imaging modalities that are designed to provide *in vivo* histological information of GI mucosa and have endoscope-integrated as well as probe-based devices. However, the latter is based on white-light microscopy by using tissue stains (such as methylene blue, crystal violet, or toluidine blue), meaning that visualization and magnification of subepithelial layers is not possible with endocytoscopy[2]. There are few studies comparing the diagnostic accuracies of CLE and endocytoscopy; Zhou *et al*[3] and Pirogov *et al*[4] showed that CLE had a sensitivity, specificity, and diagnostic accuracy of 90%, 87%, and 95.6%, respectively, in detecting early gastric cancer, while Abad *et al*[5] found that endocytoscopy had a sensitivity, specificity, and accuracy of 84.8%, 90%, and 87.2%, respectively, in diagnosing early gastric cancer.

CLINICAL DATA

Gastric cancer has various stages of progression, including chronic gastritis, chronic atrophic gastritis (AG), gastric intestinal metaplasia, gastric intraepithelial neoplasia, and early gastric carcinoma (EGC). A study by Zhang *et al*[6] used eCLE to classify the morphology of gastric pits into seven types based on different pathological conditions. They performed eCLE on 132 consecutive patients and 10 gastric samples and found that the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of type E gastric pit pattern for predicting AG were 83.6%, 99.6%, 96.6%, and 97.6%, respectively[6]. Another study by Wallace *et al*[7] presented the Miami classification for pathological conditions using pCLE.

Li *et al*[8] improved this classification by adding an index of vascular structure, which allows for a more valuable and complete assessment of gastric mucosa. It includes three types of pit patterns and seven subtypes with three kinds of vessel architecture. By combining vascular changes in neoplastic gastric mucosa with gastric pit patterns, this classification has the ability to predict high-grade intraepithelial neoplasia (HGIN) as well as low-grade intraepithelial neoplasia (LGIN). The study results support this statement, with sensitivity, specificity, and diagnostic accuracy for LGIN being 84%, 99.78%, and 99.57%, respectively, and for HGIN being 88.89%, 99.89%, and 99.84%, respectively[8].

Liu *et al*[9] did a study that compared the effectiveness of narrow-band imaging (NBI), CLE, and chromoendoscopy (CE) in detecting AG. NBI and CE are both effective techniques for visualizing precancerous lesions, but they differ significantly from CLE in terms of their working principles. The vascular structures and mucosal features are enhanced by both NBI and CE *via* different mechanisms; NBI utilizes blue and green wavelengths of light, and CE employs staining agents to detect dysplastic and malignant lesions in the GI tract. Both NBI and CE provide visualization of the superficial

mucosal details and vasculature, whereas CLE constructs images at the cellular and subcellular levels, detecting different grades of cellular atypia with a high accuracy[10]. While the diagnostic accuracies of CE and NBI were comparable, the sensitivity, specificity, and accuracy of CLE (92.31%, 86.18%, and 89.33%, respectively) were significantly higher than CE (83.85%, 78.86%, and 81.42%, respectively). The research discovered that CLE has effective sensitivity (91.94%), specificity (96.86%), and NPV (97.37%) in detecting metaplastic AG. This type of AG has unique features, including goblet cells, brush borders, columnar absorptive cells, and villiform foveolar epithelium[11]. These results underline the benefits of using CLE to differentiate between metaplastic AG and non-metaplastic AG.

The biopsy protocol recommended by the Sydney System comprises five parts. Two parts are taken from the antrum, located 3 cm from the pylorus at the greater or lesser curvature. Another two parts are taken from the corpus, one from the lesser curvature, which is located 4 cm proximal to the incisura, and one from the middle of the greater curvature. The final part is taken from the incisura[12]. CLE has some advantages over the standard biopsy protocol, such as higher diagnostic yield and fewer biopsy requirements. Large-scale studies, including multicentric randomized trials, are required for validation of CLE as a potential alternative to standard biopsy protocols.

EGC is detected primarily through histological examination, but this method has limitations. One such area for improvement is the consistency of results from biopsies taken before and after surgery, which can lead to erroneous clinical decision-making[13]. In addition, repeated biopsy can cause mucosal fibrosis, leading to complications like perforation, bleeding, and partial removal of affected mucosa[14,15].

Li *et al*[16] carried out a study to address some of the limitations of the Miami classification. They examined the eCLE images of 182 patients with stomach disease in the first phase and developed a new two-tiered CLE classification for superficial gastric cancer. This classification categorizes gastric mucosa into non-cancerous or cancer/HGIN lesions based on various characteristics such as their cells, architecture, and microvessels. For cancer, glands become irregular in shape and size, pits and glands become disorganized or destroyed, and cells become disordered and lose polarity. The microvessels also exhibit irregular shape and calibre[16]. Lou *et al*[17] used CLE and pathological results to arrive at a diagnosis of poorly differentiated adenocarcinoma of the small curvature of the stomach. The second phase of the study involved examining the effectiveness of that classification in diagnosing gastric lesions, with histological results serving as the benchmark. Compared to white-light endoscopy (WLE), eCLE was found to have higher sensitivity, specificity, PPV, NPV, and accuracy in detecting EGC/HGIN lesions using the two-tiered CLE classification. Specifically, eCLE had a sensitivity of 88.9% compared to 72.2% for WLE and a specificity of 99.3% compared to 95.1% for WLE. The PPV for eCLE was 85.3% compared to 41.6% for WLE, while the NPV was 99.5% compared to 98.6% for WLE. Lastly, the accuracy of eCLE was 98.8% compared to 94.1% for WLE[17].

LIMITATIONS OF CLE

Despite providing high-resolution functional imaging of the GI mucosa, CLE has certain limitations. The primary limitation is the narrow field of vision, due to which the entire GI mucosa cannot be visualised[18]. Although fluorescein is safe to use, there is limited data on the safety profiles of other contrast agents such as acriflavin and cresyl violet[1]. As fluorescent dyes do not stain the nuclei, the nuclear structures cannot be assessed by CLE, making it a distant possibility as a standalone screening test for cancer[18]. Scanning systems at the proximal end of the instrument are often bulky and limit the ability to control the focus. Instead, miniature distal scanning mechanisms, such as the microelectromechanical systems (MEMS) scanner, offer more flexibility in controlling the focus and provide comprehensive assessment of the mucosa with aberration-free scanning over a large field-of-view[19]. Other limitations hindering the widespread adoption of CLE are the requirement of high capital investment and specialized training. Despite its limitations, CLE exhibits substantial potential as an imaging technique for detecting tumors in the upper digestive tract. By making further technological advancements and integrating it with other detection methods, we can overcome its inherent limitations[1].

FUTURE INTEGRATION WITH ARTIFICIAL INTELLIGENCE

Artificial intelligence (AI), which has shown promise in analyzing histologic images such as hematoxylin and eosin images and immunohistochemical staining images, may be useful in evaluating images obtained by CLE[20]. Since diagnosis relies on good-quality histopathological images, which are often difficult to obtain in clinical practice, AI models can assist in real-time, automated interpretation of histopathological images and can supplement the pathologist's interpretation[1,20].

CONCLUSION

CLE is a new imaging technique used during endoscopy procedures to evaluate the mucosa *in vivo*. Diagnosing and monitoring early cancer in the upper GI tract can be effectively achieved through the use of this tool. Minimizing the number of biopsies required is one of the main benefits of this technology, while still maintaining a high diagnostic sensitivity rate. This helps to reduce the risk of complications, such as mucosal damage, bleeding, and infection, that may be caused by repeated biopsies. The inherent limitations of CLE can be surpassed by integrating it with other imaging modalities. AI has a promising role in real-time automated interpretations of histopathological images obtained by CLE.

Multicentric randomized trials are required for validation of CLE as a screening test for gastric cancer and as a potential alternative to standard histological diagnoses *via* biopsies.

FOOTNOTES

Author contributions: Dhali A conceptualized the article, conducted literature review and wrote the primary manuscript; Maity R conducted literature review and wrote the primary manuscript; Rathna R conducted literature review and wrote the primary manuscript; Biswas J conducted literature review and wrote the primary manuscript. All authors agreed with the final version of the manuscript.

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