Endomicroscopy and Targeted Imaging of Gastric Neoplasia

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KEYWORDS

• Endomicroscopy • Gastric cancer • Helicobacter pylori • Gastric adenoma
• Intestinal metaplasia • Molecular imaging

KEY POINTS

- Confocal laser endomicroscopy (CLE) is an endoscopic ultrahigh magnification technique that allows microscopic analysis of the mucosa during ongoing endoscopy.
- Multiple studies have demonstrated the ability of gastroenterologists to obtain microscopic tissue analysis of gastric pathologies in real time by CLE.
- Intravital analysis by CLE is used to target biopsies in large or diffuse lesions ("smart biopsies") and to guide and survey endoscopic resection.
- Translational research and molecular imaging with CLE enables visualization of microscopic events in their natural micromilieu virtually free of artifact.

INTRODUCTION

Confocal laser endoscopy (CLE) enables the endoscopist to obtain an in vivo microscopic evaluation of the mucosa. The first studies using CLE in gastrointestinal (GI) endoscopy established the feasibility of such an approach, demonstrating that endoscopists are able to read microscopic images by relying on simplified classification systems. These initial studies more or less followed a proof-of-principle strategy in different GI indications, but the advantage of obtaining in vivo microscopy over ex vivo histology after biopsy sampling was not clearly defined. However, follow-up trials used CLE in a more precise and complementary fashion to random biopsy protocol. This included *targeting* real biopsies by using multiple optical biopsies in conditions in which white light endoscopy alone was unreliable to identify the areas of interest, such as in intestinal metaplasia of the stomach. This "smart biopsy" concept was soon supplemented by using CLE to guide endoscopic resection. This is of advantage for mucosal alterations that are difficult to relocate macroscopically when detected by random biopsies (such as intraepithelial neoplasia in Barrett's esophagus). In such a situation, diagnosis by CLE can be followed by immediate endoscopic resection within the same endoscopic session without the time lag of

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waiting for histopathology results.[1] Guidance of endoscopic therapy is also important before endoscopic resection, where multiple biopsies may induce fibrosis and interfere with subsequent resection, or after endoscopic resection when margins cannot be completely surveyed with real biopsies, but with multiple optical biopsies, to guide re-resection. In a next step, it was shown that CLE did not only imitate histopathology in real time, but it was appreciated that CLE, by its intravital nature, could provide information that was both *complementary* and *different* from histopathology. CLE is virtually free of artifacts, such as from sampling, fixation, cutting, or staining. This offers a unique option to observe (sub)cellular mechanisms in real time and allows functional imaging instead of a static snapshot. Last, because CLE relies on fluorescent imaging, molecular targets have been labeled in experimental settings. Such molecular imaging is currently studied in 2 main indications, the first being detection of lesions (which may not be a major domain of a microscopic point technique, such as CLE), and the second being exact intravital characterization for prediction of response to molecular targeted therapy.

TECHNIQUE OF ENDOMICROSCOPY

For CLE, 2 systems are currently available for clinical use[2–4] that use monochrome blue laser light at 488 nm for excitation. The first system uses a miniaturized confocal scanner integrated into the tip of an otherwise conventional endoscope (endoscope-integrated CLE [eCLE]; Pentax, Tokyo, Japan). Imaging plane depth is adaptable from surface to 250 μm in 4-μm steps. Image acquisition rate is about 1 frame per second at high resolution. The other system in clinical use is probe-based (pCLE; MaunaKea-Technology, Paris, France) and has the advantage of compatibility with most conventional endoscopes. Frame-rate is faster, but with the compromise of a somewhat lower resolution and a fixed imaging plane depth. Optical biopsies by both systems represent optical sections parallel to the mucosal surface (ie, 90° to histopathological sections). A formal head-to-head comparison between the 2 systems has not been performed. For animal and bench-top research, confocal systems are available with similar scanners as for in-patient use that significantly ease translational approaches.

CLE relies on the application of fluorescent contrast agents. Most studies have used fluorescein, which shows a favorable safety profile.[5] Fluorescein is injected intravenously at 5 mL 10%, and imaging becomes possible after a few seconds and lasts for up to 60 minutes. Patients notice a slight yellowish discoloration of their skin for about 1 hour, and a discoloration of the urine (predominant renal clearance of fluorescein). Fluorescein does not result in a staining of cell nuclei; therefore, other contrast options have been evaluated, such as acriflavine[6] or cresyl violet,[7,8] which yield direct or indirect nuclear visualization after topical application. For CLE, the confocal imaging window that is protruding from the distal tip in eCLE, or the probe, has to be in direct contact with the tissue of interest. In the stomach, mucus sometimes has to be cleared off to provide good contact, and peristalsis may be reduced using butylscopolamine. Tissue sampling should be performed only after CLE imaging because blood (containing fluorescein) may blur the microscopic view.

As in every advanced endoscopy technique, CLE has a learning curve. Both handling of the endoscope (positioning, motion artifacts) and image interpretation require training. For Barrett's esophagus and associated neoplasia it has been demonstrated that adequate diagnosis can be obtained after initial training and 100 cases of CLE.[9] For gastric pathology, experienced endoscopists in CLE had greater accuracy in the diagnosis of intestinal metaplasia.[10] In early clinical applications of CLE, close collaboration with an expert GI pathologist should be sought for feedback.