Confocal Laser Endomicroscopy

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KEYWORDS

• Confocal laser endoscopy • Endomicroscopy • Fluorescence
• Miniprobe • Barrett's esophagus • Gastritis • Gastric cancer
• Celiac disease • Colorectal cancer • Ulcerative colitis

Confocal laser endomicroscopy (CLE) is a new imaging modality for gastrointestinal (GI) endoscopy. It offers in vivo imaging of the mucosal layer at cellular and even subcellular resolution. Thus, in vivo histology becomes possible during ongoing endoscopy. This new imaging modality provides more than conventional histology, because cellular interaction can be observed over time (physiology), and distinct changes can be identified (pathophysiology).

PRINCIPLES OF CONFOCAL MICROSCOPY

Confocal microscopy allows a better spatial resolution compared with that of conventional fluorescence microscopy, because images are not contaminated by light scattering from other focal planes. A low-power laser is focused to a single point in a defined microscopic field of view, and the same lens is used as both condenser and objective folding optical path. Thus, the point of illumination coincides with the point of detection within the specimen. Light emanating from that point is focused through a pinhole to a detector, and light emanating from outside the illuminated spot is rejected from detection. Illumination and detection systems are at the same focal plane and termed as "confocal." All detected signals from the illuminated spot are captured and measured. The created grayscale image is an optical section representing one focal plane within the examined specimen. The image of a scanned region can now be constructed and digitized by measuring light returning to the detector from successive points.

Series of confocal images within successive planes can be used to observe fine (sub)cellular structures, and three-dimensional structures of specimens can also be created. Confocal microscopy has become a standard method for molecular imaging

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in basic research in conjunction with fluorescence labeling techniques, thereby permitting the localization of specific proteins at distinct cellular locations. However, confocal microscopy has been mainly performed so far on a microscope stage at the bench rather than the bedside.[1]

ENDOSCOPIC CONFOCAL MICROSCOPY

Endoscopic confocal microscopy is an outgrowth of conventional laboratory confocal microscopy. Currently, two confocal imaging systems are available for in vivo detection of GI diseases: confocal imaging relying on tissue reflectance and confocal imaging based on tissue fluorescence. Reflectance endomicroscopy was first reported by Sakashita and colleagues[2] in 2003. However, reflectance endomicroscopy suffers from poor resolution and contrast.

Fluorescence confocal imaging has overcome these limitations. The first publication about an integrated confocal fluorescence microscope into the distal tip of a conventional colonoscope (Pentax EC 3830FK, Tokyo, Japan) was made in 2004,[3] showing that in vivo microscopy at subcellular resolution (0.7 μm) simultaneously displayed to white light endoscopy became possible and achieved high accuracy. This approach, designated CLE, permitted immediate diagnosis of colorectal intraepithelial neoplasias using fluorescein or acriflavine as contrast agents.

Most recently, a probe-based confocal endomicroscope was developed, which can be passed over the working channel of standard endoscopes. This further miniaturization using fiber-bundle technology results in compromise of resolution: lateral resolution 3.5 μm and axial resolution 15 μm; field of view of 600x500 μm, and fixed imaging plane depth (see **Fig. 1**).[4]

CONTRAST AGENTS

Fluorescence confocal imaging is only possible using exogenous fluorescence contrast agents. Potentially suitable agents are fluorescein, acriflavine, or cresyl violet.[1] The most common contrast agents are acriflavine hydrochloride (0.05% in saline; topical use only) or fluorescein sodium (5–10 mL of a 10% solution; intravenous application). Confocal imaging following staining with acriflavine hydrochloride and fluorescein sodium reveals a characteristic morphology of mucosal tissue. Whereas topically used acriflavine hydrochloride strongly labels the superficial epithelial cells including nuclei, intravenously applied fluorescein sodium distributes throughout the entire mucosa with a strong contrast within the connective tissue and the capillary network. Fluorescein binds to serum albumin, and the remaining, unbound dye molecules pass across systemic capillaries and enter the tissue, highlighting the extracellular matrix. Confocal images can be generated simultaneously with endoscopic images and allow identification of typical histologic structures within the upper and lower GI tract.

CLINICAL APPLICATION OF ENDOMICROSCOPY

Endomicroscopy can be used to observe living cells during ongoing endoscopy. A plethora of changes can be identified by the examiner. Thus, a thorough knowledge about mucosal pathology is mandatory to obtain reliable online diagnosis.

Barrett's Esophagus

Barrett's esophagus is known to be a premalignant condition in patients with gastroesophageal reflux disease, and most adenocarcinomas of the distal esophagus have

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