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Mucosal imaging advanced technologies in the gastrointestinal tract

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ABSTRACT

The use of advanced imaging technologies to enhance visualization the gastrointestinal mucosa has evolved from being an experimental tool to a valuable adjunct in diagnostic and therapeutic endoscopy. Digital chromoendoscopy including narrow band imaging (NBI) has been incorporated into standard endoscopy systems as a practical instrument used to enhance the mucosal surface and microvasculature. NBI is now routinely used to evaluate mucosal irregularities associated with Barrett's esophagus dysplasia. A recent review of the literature suggests that NBI can be used to evaluate colorectal polyps and its use may even change our clinical management of diminutive polyps. Other technologies, such as confocal laser endomicroscopy (CLE) and optical coherence tomography require independent imaging systems with probes that can be deployed through an endoscope's instrument channel. The incorporation of these technologies into clinical practice has been limited by cost and need for expertise in image interpretation. High-magnification imaging with CLE can evaluate mucosal changes that are both sensitive and specific to various disease processes. CLE probes have a small field of view that makes evaluation of large areas of the gastrointestinal tract time consuming. A second-generation optical coherence tomography system also known as volumetric laser endomicroscopy is capable of wide-field cross-sectional imaging of the human esophagus. New technologies, including second-generation digital chromoendoscopy blue-laser imaging are currently under study. Development and utilization of advanced imaging technologies has been critical in the rapid pace of advances in diagnostic and therapeutic endoscopy in the past decade.

1. Introduction

Diagnostic imaging of the gastrointestinal tract with white-light endoscopy is limited to the mucosal surface. Advanced imaging technologies are valuable endoscopic tools that enhance our ability to examine the mucosa either focally or in a wide-field fashion. Several of these technologies are now commercially available. Digital chromoendoscopy is useful when examining alternations in mucosal microvasculature and mucosal patterns that may provide insight into the presence of dysplasia or early neoplasia. The optical magnification of confocal laser endomicroscopy (CLE) is comparable to histology and allows direct observation of disease processes at a cellular level. Optical coherence tomography (OCT) is a high-resolution imaging technology useful in defining microscopic changes in the mucosa and submucosa. In this review, we provide an overview of the technical aspects of these technologies and their clinical application in gastrointestinal disease.

2. Digital chromoendoscopy

Traditional dye-based chromoendoscopy uses stains that are either absorbed by epithelial cells or help highlight the mucosal surface. In contrast, digital chromoendoscopy uses optical band-pass filters or imaging processing algorithms to generate images that highlight salient mucosal features. One of the advantages of digital chromoendoscopy over dye-based chromoendoscopy is that the user can toggle between high-definition white-light endoscopy and chromoendoscopy using an assigned endoscopic button. It is also more user-friendly without the need for spraying and suctioning dyes from the mucosa.

2.1. Narrow band imaging

Narrow band imaging (NBI) (Olympus Medical Systems, Japan) is the most commonly used digital chromoendoscopy system in

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Western countries. NBI employs optical principles of absorption to highlight mucosal vasculature and surface mucosal detail. The peak absorption of hemoglobin occurs at wavelengths (λ) of 440-460 nm (blue) and 540-560 nm (green). Filtering or narrowing the light spectrum to these wavelengths ($\lambda = 415$ nm and $\lambda = 540$ nm) makes blood vessels appear dark compared with the surrounding mucosa. The highlighted vasculature is useful in delineating subtle mucosal irregularities. The Evis Exera III (Olympus Medical Systems, Japan) is the latest generation of endoscopes with an NBI platform that allows image acquisition without compromising brightness by providing additional illumination. It also provides a "near field focus" feature that allows better definition of the mucosal and vascular pattern at shorter focal lengths.

2.2. Flexible spectral imaging color enhancement and iSCAN

The flexible spectral imaging color enhancement (FICE) (Fujinon Inc, Japan) system and iSCAN systems (Pentax, Japan) use the entire spectrum of white light during image capture and perform image processing through various digital software algorithms that enhance visualization of the mucosal surface. In contrast to NBI, these systems do not employ optical filters.

3. Confocal laser endomicroscopy

CLE uses a laser source ($\lambda = 488$ nm) that passes through a pinhole aperture and is focused at a point of interest. Reflected light from this point is focused on a second pinhole aperture positioned in front of a photodetector. This setup allows for high-resolution imaging of a discrete point by rejecting light that is out of focus (Figure 1). A grayscale image is generated by scanning the focused beam at various planes within the tissue. CLE can achieve a magnification of a 1000-fold with axial and lateral resolutions in the micrometer range.

CLE systems are either endoscope-based (Pentax Medical Corporation, Tokyo, Japan) or probe-based (Mauna Kea Technologies, Paris, France). The endoscope-based CLE (eCLE) system is a standard-definition white-light endoscope with a confocal imaging aperture and instrument channel. Endomicroscopy images are acquired by placing the imaging aperture directly in contact with the mucosa of the gastrointestinal tract. The endoscopic field of view is 475 by 475 μm. Imaging depth can be varied from surface to 250 μm deep. Image resolution is dependent on acquisition rate and can be changed from 1.6 images/s (1024 × 512 pixels) to 0.8 images/s (1024 × 1024 pixels). This system is unfortunately not clinically available anymore.

The probe-based CLE (pCLE) system uses endomicroscopy miniprobes that can be inserted through the working channel of a standard endoscope. This system and its processor are separate from the endoscopic imaging system. Images are acquired by placing the probe in contact with the mucosa of the gastrointestinal tract. A rapid image acquisition rate of 12 images/s generates videos of the mucosa. Under the mosaic function, acquired images are reconstructed and stitched together and can expand the effective field of view. The lateral resolution and field of view vary depending on the miniprobe used with higher resolution probes having narrower fields of view.

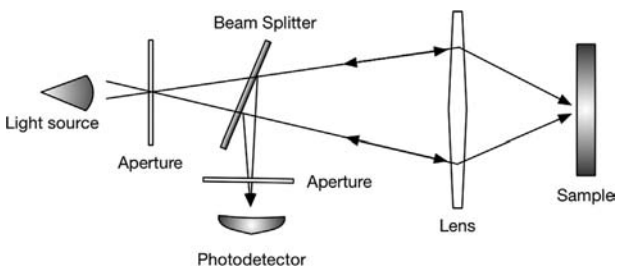

Fig. 1. Schematic diagram showing basic optical principals of confocal laser endomicroscopy. A laser source ($\lambda = 488$ nm) passes through a pinhole aperture and is focused at a point of interest. Reflected light from this point is focused on a second pinhole aperture positioned in front of a photodetector.

3.1. Contrast agents

CLE requires the use of a fluorescent contrast agent to enhance visualization of cells. Contrast agents can be administered intravenously or topically. Intravenous fluorescein sodium is the most widely used contrast agent in endomicroscopy.

CLE can be performed shortly following injection of fluorescein (2.5-5.0 mL) with fluorescence lasting approximately 30 minutes. Fluorescein highlights mucosal capillaries as well as the extracellular space and lamina propria but does not penetrate the nucleus. Intravenous fluorescein has been shown to be safe with minimal adverse effects [1]. The topical agent acriflavine hydrochloride can be used independently or in conjunction with fluorescein to highlight the cell nucleus. The use of acriflavine has fallen out of favor, however, over the concern with its carcinogenic potential. Another topical agent, cresyl violet is a cytoplasmic stain used to outline the nucleus. Both acriflavine and cresyl violet are limited in terms of depth of penetration of the mucosa.

4. Optical coherence tomography

OCT is analogous in many ways to endoscopic ultrasonography, which measures the physical properties of tissue using ultrasonic echo. OCT uses infrared light ($\lambda = 750$-1300 nm) rather than sound waves and measures reflected or backscattered light. The high velocity of light compared with sound, however, does not allow direct electronic measurement of reflected light. To do so, an interferometer is employed to compare the phase difference of 2 light paths or "arms"—a sample arm (tissue) and a reference arm (mirror). Light reflected from the tissue specimen is combined with light that has traveled a known distance through the reference arm and focused onto a photodetector. The combined light waves generate an interference profile (Figure 2).

In time-domain OCT, the reference mirror is scanned across a range of positions that match different depths in the sample tissue. Image acquisition speed is therefore dependent on the scanning speed of the reference mirror. Fourier-domain OCT refers to second-generation OCT imaging that measures the interference

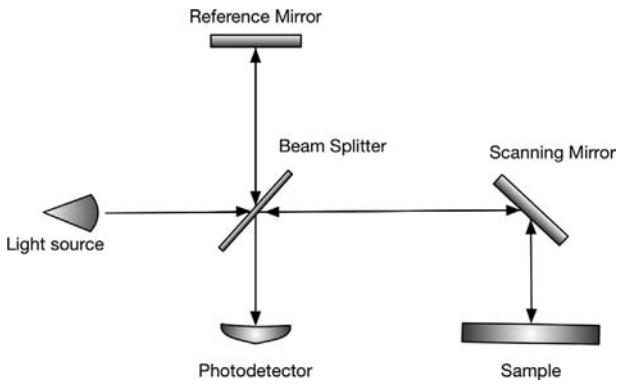

Fig. 2. Schematic diagram showing basic optical principles of optical coherence tomography. Infrared light ($\lambda = 750$-1300 nm) reflected from a scanning mirror (sample) is combined with light reflected from a reference mirror and known to have traveled a set distance. The combined light waves are captured by a photodetector and generate an interference intensity profile.