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Endoscopic Confocal Microscopy: Imaging to Facilitate the Dawn of Endoluminal Surgery

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Endoscopic confocal microscopy is a new imaging modality that rapidly is gaining applicability in gastrointestinal endoscopy. Confocal microscopy has been used in the biological sciences since 1961 when the concept of optical sectioning of a biological specimen was introduced. Rather than a composite 2-dimensional view of a cell, one could obtain a horizontal section of the cell in a specific x–y plane. This has found application in laboratories where the technology often is combined with fluorescence imaging to resolve the intracellular location of fluorescent markers. In this issue of *Clinical Gastroenterology and Hepatology*, 2 articles highlight the 2 applications that this technology can bring to gastroenterologists.^{1,2} Several features of endoscopic confocal microscopy are being developed. The practicing gastroenterologist should be aware of the different approaches utilized.³

Scope Versus Probe

Unlike prior endoscopic confocal microscopy, the current articles use a probe unit instead of a specialized endoscope system.⁴ The first descriptions of a true endoscopic confocal microscope used a dedicated endoscope that had a confocal instrument built into the system. The confocal system was designed in Australia by a company that had created a fiber-coupled confocal microscope device for laboratory use (Optiscan, Victoria, Australia).⁵ This miniaturized system controls the focus of the lens along the z-axis (depth) of the tissue as well as in the x–y plane. The image is formed by scanning along the x–y axis at a specific depth to form a rasterized (composite) image. An image stack can be formed by scanning again at a different depth in the same x–y plane as the first image to recreate a 3-dimensional view of the target tissue. Illumination of the tissue is performed using a 488-nm laser to achieve this imaging. This dedicated confocal microscopy endoscope has been applied in vivo in the upper and lower gastrointestinal tract for the purpose of diagnosis of neoplastic lesions.

One challenge has been the image-acquisition rate of this endoscope device, which can acquire a 1024 × 512 pixel image in 0.7 seconds or a 1024 × 1024 image in 1.2 seconds. This is relatively slow given that video imaging has a frame acquisition rate of 30 frames per second. The images in the gastrointestinal tract can be blurred by motion artifact caused by respiration and cardiac impulses. The device in the studies reported in this issue is probe-based and has the advantage of acquiring images at 12 frames a second with a field of view of 600 × 500 μm. Thus, the probe system can image about half the field of view but it can acquire images at a rate 8–10 times faster than the endoscope-based systems. This increase in the image-acquisition rate allows physiologic studies to be conducted as described by Wang et al.¹ In this study, the intravenously administered fluorescein can have its fluorescence measured and the rate of uptake calculated. However, variable depth information cannot be obtained with these probes because they scan specifically at a single depth because they have no z-axis motion. Nevertheless, different probes are available that can scan at fixed depths from the surface.

All of these techniques require the administration of a fluorescent contrast agent. Fluorescein is widely used intravenously and was approved by the Food and Drug Administration primarily for retinal imaging. It is well tolerated, although it can change urine color to bright yellow for the 24 hours after administration. Intravenous fluorescein cannot provide cellular details because the nucleus is not stained. However, topically applied fluorescent agents, such as acridine orange, will stain the nucleus, although further assessment of risk-benefit is necessary because acridine orange potentially is carcinogenic. Whether a scope or probe is used at this time, the confocal imaging is performed by a processor that is separate from that used in the endoscope and this requires more equipment to be brought into the endoscopy room.

Physical Versus Physiologic Imaging

The most obvious difference between the 2 articles presented in this issue is the approach taken to tissue characterization. In the article from Meining et al,² lesions from the upper and lower gastrointestinal tract were imaged using a topical contrast agent, 0.25% cresyl violet, which enhances mucosal features and provides fluorescent contrast. Table 1 in the article by Meining et al nicely outlines the features used by the investigators to distinguish benign from neoplastic changes in the mucosa. All of these features are morphologic, and they follow traditional pathologic interpretations, specifically the regularity of glandular structure, the appearance of cells, and loss of specific cell types. These investigators acquired outstanding interpretive skills and performed as well (if not better) than pathologists in assessing tissue histology, with an accuracy of 92% in images that could be interpreted.

In contrast, the article by Wang et al¹ took a physiologic approach using a similar device but with an intravenous contrast agent, fluorescein (3 mL of 5 mg/mL), in patients undergoing screening colonoscopy. Rather than just relying on morphology, the investigators measured the rate of uptake of fluorescein in the tissue, and showed that adenomatous tissue was much slower than normal or hyperplastic tissue to take up the fluorescein. This property could be used to discriminate between histologic types with a sensitivity of 100%, a specificity of 92%, and an accuracy of 93%.

These 2 approaches highlight one question of this next-generation of imaging: will this new technology require additional training to interpret microscopic images or will the imaging be able to generate a discriminant value and tell the endoscopist the tissue type? It should be noted that the physiologic imaging was somewhat time consuming, requiring image acquisition of 1–2 minutes for each site assessed. It is also unclear whether the assessment of multiple sites could be equally investigated because fluorescein would have to clear from the tissues before it could be administered again.

Endoscopist or Pathologist, Looking From the Top or From the Side?

Because much of endoscopic confocal microscopy does involve morphologic imaging, it also is important to determine who should interpret this type of imaging. The endoscopic microscopic classification system for tissues such as Barrett's esophagus is discussed in the article by Meining et al,² who place this in perspective relative to prior publications on endoscopic confocal microscopy. However, these rely on similar features to histology such as black cells with irregular borders and darker periphery, which are thought to be indicative of neoplasia. It has been well established that histologic assessments are fraught with issues of interpretation even among expert pathologists.⁶ It is reasonable to assume that gastroenterologists also would have difficulty with interpretation. However, it must be kept in mind that the imaging being performed takes sections tangential to the probe or endoscope rather than orthogonal sections (into the plane of the tissue) as in standard histology. This is not the typical view seen by the pathologist, although the latter may obtain tangential views at times, as a result of difficulties in sectioning of endoscopic biopsy specimens.

Insight into the issue of orthogonal or tangential views is provided by the study by Meining et al² because they actually compared the ability of the endoscopist to interpret the confocal images vs a pathologist. The investigators found very good agreement between the confocal microscopy images and eventual pathologic interpretation with a κ value of 0.817, even with a gastroenterologist performing the interpretation. Interestingly, the variation between a pathologist and a gastroenterologist performing the interpretation was very small with accuracies of 81.5% for the gastroenterologist and 73.9% for the pathologist. In fact, the gastroenterologist was able to use more confocal images than the pathologist, presumably because the gastroenterologist was more familiar with interpreting images that were out of focus.

There will need to be a resolution as to whether endoscopists can be trained to provide reasonable tissue interpretation, much like when endoscopists learned how to interpret cholangiograms or endoscopic ultrasound images. Many hurdles await the development of this new frontier, including the teaching of this skill, which will need to be developed for fellowship training. Establishment of reimbursement (Current Procedural Terminology) codes for gastroenterologist interpretation of tissue histology also will be needed. Both of these issues will need to be resolved before this technology can be made acceptable to clinical practice. Regardless, the development of this technology seems to be opening another frontier for endoscopy that enhances endoscopic real-time identification of mucosal lesions for optimizing and selecting patients for immediate therapy during the same endoscopy session. The ultimate goal should be that the gastroenterologist-endoscopist be in the driver's seat in the management of patients presenting with mucosal lesions that are appraised thoroughly with endoscopic procedures including histologic characterization, assessment of depth of invasion and surrounding tissues and lymph nodes, and, ultimately, resection in toto using submucosal dissection if necessary.^{7,8} As the wave of diagnostic endoscopy wanes, the gastroenterologist has the opportunity to serve all the needs of the patient presenting with premalignant or malignant localized mucosal diseases. This is the dawning of the age of the endoluminal gastroenterologic surgeon.

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