Endocytoscopy

The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee provides reviews of new or emerging endoscopic technologies that have the potential to have an impact on the practice of GI endoscopy. Evidence-based methodology is used, using a MEDLINE literature search to identify pertinent preclinical and clinical studies on the topic, and a MAUDE (U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported complications of a given technology. Both are supplemented by accessing the "related articles" feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases, data from randomized, controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors. For this review, the MEDLINE database was searched through February 2009 by using the keyword "endocytoscopy."

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INTRODUCTION

Recent technological advances in endoscopic imaging have resulted in devices, such as confocal endoscopy and endocytoscopy, that enable visualization of mucosal features at image resolutions rivaling those of histology [inoue 05]. These recent technological advances offer the potential for real-time optical biopsy and lesion characterization and/or differentiation. Endocytoscopy (EC) is an ultra-high magnification technique that provides images of surface epithelial structures at cellular resolution.[1,2] The instrumental aspects and potential applications of EC in the GI tract are outlined in this document.

EMERGING TECHNOLOGY

EC is based on the principle of contact light microscopy. EC enables real-time visualization of the cellular structures of the superficial epithelial layer in a plane parallel to the mucosal surface. The technology uses a fixed-focus, high-power objective lens that projects highly magnified images from a minute sampling site (<0.5-mm diameter) onto a charge-coupled device). EC instruments include probe-based and endoscope-based systems and are currently available only as prototype devices (Table 1).

Probe-based instruments consist of 2 flexible catheter-type devices that provide ultra-high magnification imaging of the epithelial surface at ×570 or ×1400 on a 19-inch monitor (or ×450 and ×1125 on a 14-inch monitor). Both EC probes are designed to fit through therapeutic channel endoscopes (≥ 3.7 mm) and necessitate contact with the tissue surface for imaging. A soft plastic cap affixed at the tip of the endoscope is generally used and apposed against the mucosa to maintain endoscope stability, provide a working distance for the EC probe, and minimize motion artifact during endocytoscopic imaging [kumagai 04]. Endoscope-based instruments integrate the EC component within the endoscope. Both the upper (103 cm long) and lower (133 cm long) prototype endoscopes provide an image magnification of ×580 on a 19-inch monitor, in addition to having conventional optical magnification and narrow-band imaging capabilities. The tip of the endoscope is placed in contact with the tissue surface for endocytoscopic imaging [inoue 06].

Endocytoscopic visualization of subcellular structures (eg, nuclei) necessitates prestaining of the mucosa with an absorptive contrast agent, such as 0.5% to 1% methylene blue or 0.25% toluidine blue.[3] Excess contrast is washed off before imaging. For extended visualization (>5 minutes), repeat staining may be needed. The mucosal surface is generally treated with a mucolytic

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TABLE 1. Endocytoscopes

	Probe-based systems*		Integrated endoscope systems†	
Manufactured by Olympus (Tokyo, Japan)	XEC-300	XEC-120	XGIF-Q260EC1	XCF-Q260EC1
Conventional endoscope image magnification‡	N/A	N/A	Up to ×85	Up to ×110
Endocytoscope imaging magnification‡	×570	×1400	×580	×580
Field of view (μm)	300 × 300	120 × 120	400 × 400	400 × 400
Depth of field (μm)	0-30	0-5	0-50	0-50
Horizontal resolution (μm)	4.2	1.7	4.0	4.0
Endoscope outer diameter (mm)	3.2	3.2	11.6	13.6
Endoscope working channel diameter (mm)	N/A	N/A	2.8	3.2
Endoscope working length (cm)	240	240	103	133

N/A, Not applicable.
*Use CLV-180 light source and CV-180 videoprocessor.
†Use CLV-260SL light source and CV-260SL videoprocessor.
‡Based on a 19-inch monitor.

agent, such as *N*-acetylcysteine, before tissue staining. Endocytoscopic diagnosis is based on the assessment of several cytological and architectural features, such as the density, size, and arrangement of cells; the size and shape of nuclei; the nucleus-to-cytoplasm ratio; and the staining pattern (Fig. 1).[2-8] In the esophagus, for example, malignant squamous epithelium is endocytoscopically characterized by an increase in cellular density and marked heterogeneity in nuclear staining and size, as opposed to the orderly cellular arrangement and homogeneous staining pattern of normal squamous epithelium.[9] EC-based image criteria for tissue diagnosis and/or classification in the esophagus, stomach, and colon have been described, but not yet validated prospectively.[8-10]

POTENTIAL APPLICATIONS

Promising applications of EC include the characterization of dysplastic or early cancerous lesions in premalignant conditions of the GI tract and the histologic differentiation of colon polyps. Given its restrictive sampling area, EC is not a practical tool for wide-field screening of the mucosa but may be useful as an adjunctive technique for targeted assessment of lesions identified by conventional or other imaging (eg, electronically enhanced imaging, chromoendoscopy).

The in vivo potential of EC has been demonstrated in several feasibility studies, with the differentiation of neoplastic from non-neoplastic mucosa as its primary application.[4,8-11] Most studies to date have assessed the use of the probe-based devices. A limited amount of data suggests that the higher magnification probe (×1125) provides superior image quality[11] and potentially better diagnostic sensitivity.[10] In the esophagus, EC achieved 81% sensitivity and 100% specificity in identifying neoplasia based on the blinded evaluation of endocytoscopic images of macroscopically visible lesions in one study.[10] Unlike its promising application in identifying squamous cell cancer,[2,4] the diagnostic performance of EC for the differentiation of Barrett's epithelia has been suboptimal. In a recent study, the application of EC in Barrett's esophagus resulted in a high proportion of unusable images because of suboptimal image quality, fair interobserver agreement, and poor diagnostic specificity.[11] These limitations are translatable to the stomach where gastric mucous secretion hinders visualization of the mucosa by EC.[10] In the colon, interpretation of EC images obtained from 75 colorectal lesions by a pathologist blinded to clinical data resulted in an overall diagnostic accuracy of 93%.[8] In another study, pathologist interpretation of EC images achieved 79% sensitivity and 90% specificity for distinguishing neoplastic from non-neoplastic colonic lesions.[10]

The reported experience on the use of the endoscope-based EC system is limited. This instrument was evaluated in a small study of 29 patients with esophageal lesions, whereby an accuracy of 82% was achieved for differentiating malignant from nonmalignant tissue.[9] Other EC applications have been described, including identification of dysplasia in aberrant crypt foci,[12] visualization of *Helicobacter pylori* organisms in an ex vivo setting,[13] and real-time monitoring of blood flow in rectal mucosal microvasculature.[14]

There are several challenges that may hinder the widespread use of this technology in endoscopic practice. Unlike cross-sectional imaging and histology, EC

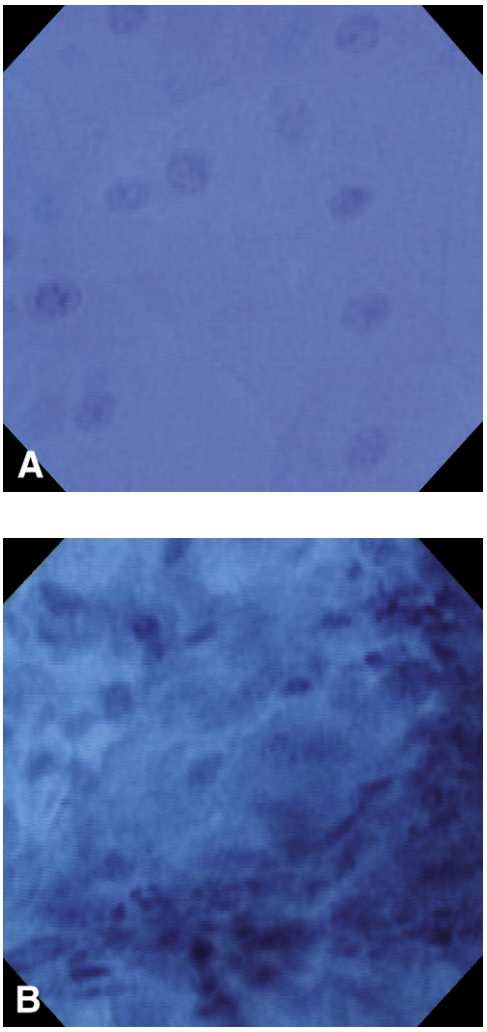

Figure 1. Endocytoscopy images (1400×) in the esophagus. **A,** Small, rounded, and regularly arranged nuclei of normal esophageal mucosa. **B,** Densely packed, darkly stained, and enlarged nuclei of squamous cell cancer.

provides images of the very superficial layer of the mucosa along a horizontal plane. It is, therefore, not a useful technique for depth staging of early neoplastic lesions. The procedure can be time-consuming and labor-intensive because it involves a multistep process of mucosal washing, staining, and imaging, compounded by limitations of visual interference by the presence of mucus or blood, inconsistent image quality, and image degradation from motion artifacts. In addition, diagnosis based on endocytoscopic imaging is subject to interpretation, and there are as yet no validated EC-based criteria regarding tissue diagnosis and/or differentiation for various GI conditions. Once validated criteria are developed, proficiency as an endocytologist will require specific training in the technique and image pattern recognition.

RESEARCH AGENDA

Several aspects of EC deserve further study, including optimizing the staining technique, assessing the relative merits of the different ultra-high magnification instruments, assessing for observer agreement and standardizing image criteria via universal consensus for specific GI conditions, and validating the reproducibility and diagnostic performance of EC in prospective, controlled trials. Ultimately, the impact of EC and competing imaging technologies, such as confocal endoscopy, as tools for targeted biopsies and perhaps as replacement techniques for conventional histology will need to be analyzed from a cost-effectiveness perspective.

SUMMARY

Endocytoscopy is a promising development in advanced endoscopic imaging. The ability to obtain cellular images in real-time has several potential clinical benefits, but further studies are needed to better define the utility of this technology relative to standard endoscopic biopsy.

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