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Progress in endoscopic imaging of gastrointestinal tumors

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Abstract. – *State of the Art:* New technologies in the form of high-magnification or "zoom" endoscopy complemented by chromoscopic agents or Narrow Band Imaging permit early detection of neoplastic lesions, particularly flat and depressed types. Detailed characteristics of the mucosal surface can be obtained, enabling an *in vivo* "optical biopsy" to make an instant diagnosis at endoscopy, previously possible only by using histological or cytological analysis. Advances in fiber optics, light sources, detectors, and molecular biology have led to the development of several novel methods for tissue evaluation *in situ*.

***Perspectives:* Promising imaging techniques include fluorescence endoscopy, optical coherence tomography, confocal microendoscopy, molecular imaging, and light scattering and Raman spectroscopy.**

***Conclusions:* These techniques probably are able to replace conventional biopsy in the near future, but the endoscopists should become increasingly more familiar with histopathologic findings.**

Key Words:

Gastrointestinal tumors, Narrow band imaging, Fujjinon intelligent colour enhancement, I-Scan, Autofluorescence imaging, Spectroscopy, Confocal laser endomicroscopy, Endocytoscopy, Optical coherence tomography.

Introduction

The detection of small premalignant lesions is largely dependent upon the experience of the endoscopist and the identification of subtle mucosal changes with standard white light endoscopes. Once the lesion has been detected, visible suspicious areas are targeted biopsied or endoscopically removed to obtain a definitive diagnosis. In addition, in diseases like ulcerative colitis or Barrett's oesophagus (BE) random biopsies are recommended, but it remains questionable whether this time-consuming approach is clinically effective. This need led to intensified efforts to develop an "ideal" technique that could objectively detect the maximum number of cases of cancer with a minimum number of biopsies (Table I).

Red Flag Techniques With "Virtual" Chromoendoscopy

"Red flag" methods involve special techniques that are added to standard white-light endoscopy in order to increase the sensitivity for detecting early neoplasia in a broadfield imaging examination[1,2].

Olympus Narrow Band Imaging (NBI), Fujjinon Intelligent Colour Enhancement system (FICE), and Pentax i-scan are applied to a new generation of high-resolution endoscopes, allowing the endoscopist to easily switch between the "Virtual chromoendoscopy-mode" and the normal "High resolution-mode" with no need for special equipment or dyes.

NBI works through the application of a special optical filter to the white light source, enabling to "narrow" the wavelength of the light and to emphasize both the mucosal "pit-pattern" and the vascular network[3]. The FICE system is based on a computed spectral estimation technology that processes the reflected photons to reconstruct virtual images with a choice of different wavelengths. This leads to enhancement of the tissue microvasculature as a result of the differential optical absorption of light by haemoglobin in the mucosa[4]. I–Scan (Pentax, Tokyo, Japan) is an endoscopic postprocessing light filter technology using sophisticated software algorithms with online image mapping technology embedded in the high-definition EPKi processor. This technology enables resolution above HDTV standard, which can provide detailed analysis based on vessel (V-mode), pattern (P-mode), or surface architecture (SE-mode)[5].

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Table I. Novel imaging techniques in digestive endoscopy.

"Red flag" techniques	Chromoendoscopy – Lugol's Solution – Methylene Blue – Indigo Carmine – Acetic Acid	 Detection of early squamous carcinoma Detection of Barrett's esophagus Detection of gastroduodenal malignancies Detection of Barrett's esophagus
	Virtual chromoendoscopy (NBI, FICE, I-Scan) Fluorescence endoscopy	Enhancement of surface and vascular patterns Wide-area surveillance of gastrointestinal mucosa
Functional imaging	Light-scattering spectroscopy Raman spectroscopy	Subcellular morphological examination Molecular histopathologic examination
Virtual histology	Confocal microscopy Endocytoscopy Optical coherence tomography	Cross-sectional histopathologic examination of mucosal neoplasia Iintracellular changes of mucosal neoplasia Cross-sectional histopathologic examination of mucosal neoplasia

Prior studies have demonstrated the value of virtual chromoendoscopy in the evaluation of patients with upper GI lesions including BE dysplasia[6], and the classification of colorectal lesions[7-9]. However, a few recent studies have shown conflicting results with no improvement in adenoma detection rates[10-12].

Functional Imaging

While NBI, FICE, and i-Scan rely on improved anatomic resolution and contrast, other methods focuses on functional imaging. During progression from normal tissue to neoplasia, tissue undergoes both architectural and biochemical changes which lead to alterations in its interaction with light, producing spectral signatures useful to differentiate between various tissues.

Autofluorescence imaging (AFI) detects subtle changes in the concentration of specific chemicals in tissue that have the ability to fluoresce when activated by specific wavelengths of light. As an example, most changes noted in BE with AFI rely on loss of collagen in dysplastic tissue resulting in reduced green and increased red fluorescence[13].

Raman spectroscopy is based on detecting characteristic spectral "fingerprints" of molecules in the tissue based on the molecular vibrations in response to light energy[14]. Reflectance spectroscopy qualifies the colours and the intensity of reflected light, altered by the tissue through absorption of certain wavelengths such as haemoglobin, thus defining vascularity and oxygenation status. Light scattering spectroscopy uses the variation in scattered light across a full spectrum to measure the size and density of nuclei in the epithelial layer. This is a highly accurate method which correlates directly with histologic changes of dysplasia[15].

Some authors suggest that it may be ideal if AFI and NBI could be used back-to-back in a complimentary fashion with a multi-modal system that incorporate high-resolution videoendoscope (HRE), NBI and AFI: high-resolution imaging should be used for a standard examination, AFI to detect suspicious lesions in selected patients and NBI for a close inspection of these areas[16].

Virtual Histology

In vivo confocal laser endomicroscopy (CLE) is a newly developed diagnostic tool that allows immediate optical histology of the mucosal layer during ongoing endoscopy. The quality of the new, detailed images obtained with CLE might be the start of a new era.

Confocal laser microscope can be integrated into the distal tip of a conventional video endoscope (Pentax EC-3870CIFK; Pentax, Tokyo, Japan), or a miniaturized probe, using a single optical-mode fibre acting as both the illumination point source and the detection pinhole can be used as "baby-scope" (Optiscan Pty. Ltd., Notting Hill, Victoria, Australia, and Cellvizio, MaunaKea Technologies, Fort Washington, PA, USA)[17].

The grey-scale image created is an optical section representing one focal plane within the ex-

amined specimen. Series of confocal images within successive planes can be used to reconstruct three-dimensional structures in a virtual specimen[18].

Several prospective studies have already been published confirming the high level of diagnostic accuracy of CLE. The diagnostic spectrum of CLE is currently expanding from screening and surveillance for colorectal cancer[19] towards Barrett's esophagus[20], Helicobacter pylori-associated gastritis[21], and gastric cancers[22]. Several other clinical applications – such as coeliac disease[23,24], microscopic colitis[25], squamous-cell carcinoma[26], and architectural evaluation of the liver during laparoscopy[27] – have also been proposed.

Endocytoscopy (EC) provides, in combination with chromoagents, in vivo histologic images with the use of an ultra high magnification (450-1125 times) catheter which is passed through the working channel of the endoscope. Unlike CLE, EC provides images in colour but is limited to the most superficial cell layer. Endocytoscopy imaging may correlate closely with histopathology in differentiating between neoplastic and non-neoplastic lesions as well as adenomas and invasive cancer[28], with an estimated sensitivity and specificity of 79 and 90% respectively[29].

Optical coherence tomography (OCT) performs a cross-sectional, high-resolution, tomographic imaging of the microstructure of mucosal tissues by measuring back-scattered or back-reflected infrared light, similar to that of B-mode ultrasound imaging[30]. Most of the so far published studies aimed at evaluating OCT imaging to detect dysplasia and early cancer at different levels of the gastrointestinal tract[31]. Unfortunately, attempts to identify OCT patterns characteristics for dysplasia within BE, especially the high-grade type, have been substantially disappointing[32,33]. Whether no data are currently available about its use in the stomach, small bowel and colon[34,35], more promising are the results regarding the discrimination between non-neoplastic and neoplastic tissue when bilio-pancreatic strictures of unknown etiology are identified during an endoscopic retrograde cholangiopancreatography (ERCP) procedure[36,37].

The ability of OCT imaging to recognize the villous pattern and submucosal inflammatory changes, could be used to identify and stage celiac disease[38], and to differentiate patients with Crohn's disease from those with ulcerative colitis[39].

Conclusions

Current limitations of standard endoscopic practice are rapidly being overcome by advanced methods described in this review. Unfortunately, lack of such studies does not allow clear recommendations about the clinical use of these promising technologies.

At this time, clinicians should resist the temptation to use these very promising, but experimental, technologies in making patient management decisions, and a detailed "japanese-like" evaluations is mandatory in western Countries, to achieve an early diagnosis of all gastrointestinal cancers. In the future, the endoscopists should become increasingly more familiar with histopathologic findings, in order to draw the full potential benefits of these new techniques.

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