

Evaluation of New Technologies in Gastrointestinal Endoscopy

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ABSTRACT

Background: Gastrointestinal (GI) tumors are the most commonly diagnosed cancers worldwide and the second leading cause of cancer-related death. Endoscopy is the gold standard for diagnosis of GI cancers. Early diagnosis of GI tumors by endoscopy at the precancerous or early stage may decrease the prevalence and mortality rate of GI cancers. The preventive role of endoscopic interventions and the limitations of conventional white-light endoscopy have given rise to myriad innovations. Chromoendoscopy with dye injection can be used to detect lesions at an early stage. However, the prolonged procedure duration and steep learning curve are disadvantages of chromoendoscopy. Recent technological advances in imaging enhancement have enabled detection of GI lesions without the need for dye injection, using digital chromoendoscopy systems, of which flexible spectral-imaging color enhancement, narrow-band imaging, and I-Scan are the most frequently used. The combination of endoscopic image magnification and high-definition optical systems using digital endoscopic methods has increased the diagnostic value of endoscopy. The development of confocal laser endomicroscopy has also improved in vivo endoscopic diagnosis. This review focuses on the latest technological innovations in endoscopy.

Key Words: Digital chromoendoscopy, Endomicroscopy, Endoscopy.

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INTRODUCTION

Gastrointestinal (GI) cancers are the second leading cause of cancer-related death.¹ Endoscopy is the gold standard for the diagnosis and treatment of GI diseases.² Conventional endoscopy is used to detect mucous puffy lesions, ulceration masses, and stem polyps, but it is inadequate for detecting small polyps and flat lesions and may miss many such lesions.³⁻⁵ For this reason, the diagnostic value of conventional endoscopy is limited.

In recent years, revolutionary developments have occurred in endoscopy. The chromoendoscopy method developed by Kudo et al⁶ has increased the frequency of detection of early-stage cancers and precancerous lesions (**Figure 1**). This dye-based method is time-consuming and requires experience, resulting in the development of new technologies (e.g., digital chromoendoscopy, most commonly, flexible spectral imaging color enhancement [FICE], narrow-band imaging [NBI], and I-Scan) (**Figures 2, 3, 4**). The use of virtual optical filters, magnification, and mobile, high-resolution optical systems and software enables development of the endoscopic lesion images without the need for dyes. One of the most important advantages of these technologies is the traditional white-light endoscopic view option. Generation of chromoendoscopy-like images in a short time, simply by pressing a button on the endoscope, is a considerable advantage without the need for dye usage. Moreover, endoscopists adapt readily to using digital chromoendoscopy, and the learning curve is short.

The confocal laser endomicroscopy (CLE), which uses a laser rather than white light as a light source, represents a marked advance in endoscopy (**Figure 5**). The mucosa can be examined with a miniature microscope placed on top of the endoscope, enabling simultaneous in vivo histologic diagnosis of lesions. This technology has given rise to the concept of optical biopsy.⁷

The use of multiple novel endoscopic technologies has significantly increased the predicted rates of histopathologic diagnosis. However, interpretation of the images generated by these new systems differs among endoscopists, and no consensus has yet been reached. Although numerous classifications have been described in the liter-

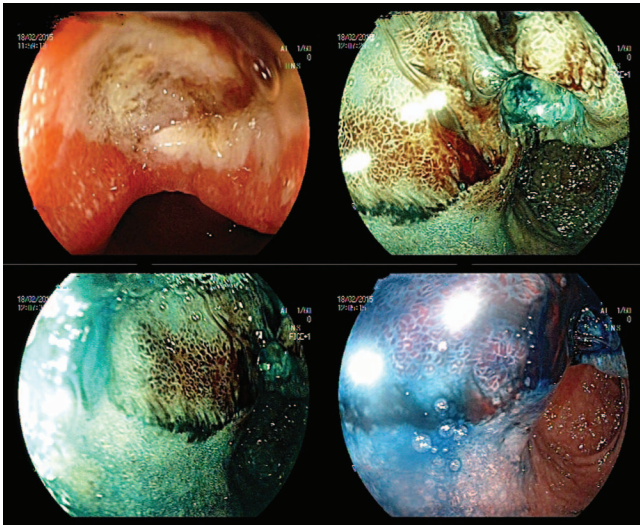


Figure 1. Gastric ulcer. Endoscopic view after administration of *N*-acetyl cysteine and methylene blue dye.

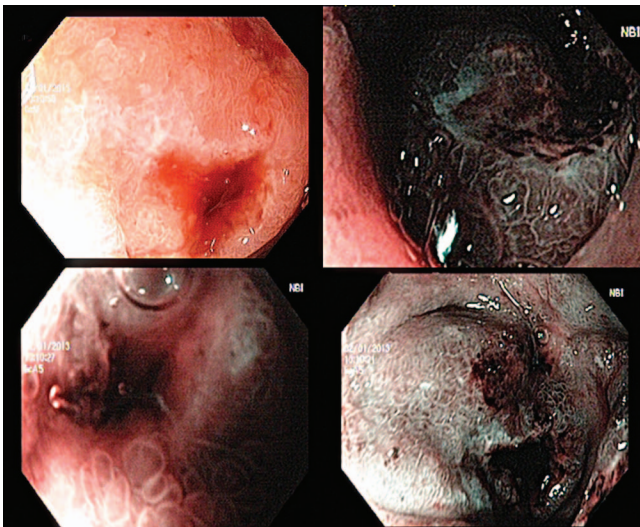


Figure 2. NBI images of gastric ulcer.

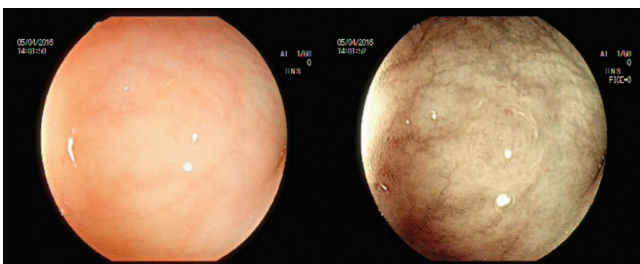


Figure 3. FICE images of colonic flat adenomas.

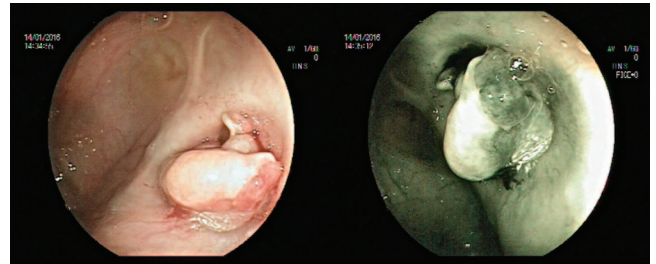


Figure 4. I-Scan images of colonic polyps.

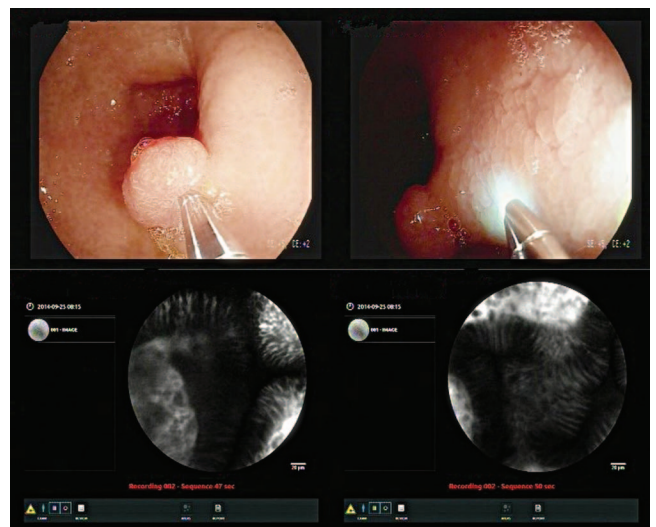


Figure 5. Cellvizio images of a gastric polyp.

Table 1.
The Modified Kudo Pit Pattern Classification⁶

Type	Description
1	Normal round
2	Stellar or papillary
3S	Tubular or round; smaller than pit type 1
3L	Tubular/large
4	Sulcus/gyrus
5	Irregular arrangement, with size equal to grade 3L, 3S, or 4

ature, most are based on the interpretation of superficial lesion patterns and microvasculature architecture. The most widely accepted classification is the pit pattern, which was described by Kudo et al⁶ (**Table 1**).

The use of new endoscopic systems has increased the rate of diagnosis of precancerous lesions and early-stage cancers. The American Society for Gastroenterological Endoscopy, American Gastroenterological Association, American College

of Gastroenterology, European Crohn's and Colitis Organization, British Society of Gastroenterology and the Colitis Foundation of America recommend using these new technologies to detect GI lesions.⁸

Removal of precancerous and early-stage cancers by endoscopic methods, such as polypectomy, endoscopic mucosal resection, and endoscopic submucosal dissection, reduces the frequency of GI cancers and the associated morbidity and mortality rates.^{9,10}

NEW ENDOSCOPIC TECHNIQUES

Chromoendoscopy

Chromoendoscopy offers improved visualization of mucosal lesions by using several dyes and enables histopathologic diagnosis during the procedure. It is often used with magnification and allows a several hundred-fold magnification of images by means of adjustable lenses. Chromoendoscopy contributes to the diagnosis of intestinal metaplasia, dysplasia, early-stage GI cancers, and colorectal polyps.⁸ The major disadvantages of chromoendoscopy include the requirement for operator experience, prolonged procedure duration, and problems related to the use of dyes. Furthermore, there is no consensus among endoscopists regarding interpretation of chromoendoscopic images.

Detailed information on the procedure to be performed is given to all patients beforehand. Adequate sedation of the patients improves image quality and the comfort of the patient and endoscopist during the prolonged procedure. The procedure begins with conventional standard endoscopy followed by narrow-field magnification and chromoendoscopic examination of suspicious lesions. Thus, the procedure time is shortened. Transparent caps attached to the end of the endoscope maintain a 2–3-mm distance from the lesion/mucosa, which is optimal for visualization. The procedure begins with standard endoscopy, and the dye is sprayed onto the suspicious area of the mucosal surface, using a catheter through the study channel of the endoscope and then onto the entire mucosal surface. Excess fluid and dye on the mucosa are aspirated. The image is then magnified several hundred-fold by pressing the magnification key on the endoscope. The surface features of the lesion, fine details, and vascular patterns, are examined in detail and compared with those of normal mucosa; lesion boundaries are examined at the same time. After this histopathologic examination, biopsies are taken from the suspect areas. The surface

inspection must be completed before biopsies can be taken, because hemorrhage caused by the biopsy procedure decreases the quality of the surface inspection. Images obtained after conventional dye application and magnification are recorded.

The dyes used in chromoendoscopy are classified into the following 3 groups: absorptive dyes (methylene blue, toluidine blue, crystal violet, and Lugol's iodine), contrast dyes (indigo carmine), and reactive dyes (Congo red and phenol red).

Chromoendoscopic findings correlate strongly with histopathologic findings in the detection of neoplasms derived from colorectal neoplasia and ulcerative colitis.^{11,12} However, the sensitivity and specificity of this correlation are not 100%, and thus histopathologic examination is necessary. Only a superficial topographic examination can be performed by chromoendoscopy; limited information regarding the deep layers of the mucosa is provided. Chromoendoscopy requires a steep learning curve and advanced experience. However, the procedure is safe, and in experienced hands, it provides important clinical information for the treatment and monitoring of lesions.^{8,11}

Narrow-Band Imaging

The prototype of NBI technology was developed by Olympus (Melville, New York, USA) in the United States. This method can provide up to 1000-fold magnification. The white-light components used in conventional endoscopy are reflected by the mucosal surface in a narrow-band interval and are revealed in such a way that the contrast difference and superficial patterns of the lesions and vascular architecture enable visualization of fine details. GI cancers can invade the mucosa and penetrate the deeper layers. Therefore, details of the submucosal area facilitate histological diagnosis of the lesion. Although deep mucosal structures are visualized by conventional colonoscopy, superficial features are better demonstrated by NBI.

Barrett's esophagus, inflammatory bowel diseases, clonal polyps, and GI cancers can be detected in vivo. NBI is a simple technique that can be performed with a single keystroke with a standard colonoscope, and thus it does not require a long procedure time. In contrast to confocal laser endomicroscopy and chromoendoscopy, lesions can be detected by NBI without the need for dyes.

Conventional endoscopes use white light emitted from a xenon lamp. Shorter wavelengths enable visualization of the superficial regions of the mucosa and longer wavelengths reach the deep regions of the mucosa and sub-

mucosal vascular structures. When blue light hits a mucous membrane, most of the light is reflected, such that superficial patterns and microvascular structures appear black. However, red light is absorbed by the mucosal surface from the mucous membrane to the deeper layers without being reflected, preventing a detailed image of the mucosal surface. Furthermore, light of different wavelengths scatters within tissue differently. As the wavelength of light increases, the degree of scatter increases and reduces the sharpness of the image. Therefore, images obtained with blue and green light are clearer than those obtained with red light. Conventional endoscopy is influenced by the red light component of white light, which provides limited information about the superficial pattern of the mucosa. NBI typically uses blue and green light sources for magnification, accomplished by placing a red-green-blue (RGB) filter in front of a xenon lamp to produce an RGB image at a wavelength range of 400–700 nm (400–430 and 525–555 nm), improving the contrast and enabling conversion of the separately obtained images into a single-color image by a video processor. Another advantage of blue light is better absorption by hemoglobin, enabling imaging of the superficial capillaries and superficial mucosal patterns.

Guelrud et al¹³ reported that NBI is useful for detecting short-segment Barrett's oesophagus. Kaise and colleagues¹⁴ examined microvascular changes, (*e.g.* dilatation of microcapillary vessels, sudden changes in vessel diameters, decreased vascular density in lesions despite increased vascular density up to the lesion border, heterogeneous vascular distribution, and convoluted veins). Regarding mucosal surface changes, mucosal fine details were obscured in certain regions, the environmental mucosal details in the lesion area were reduced by $\geq 50\%$, and the surface details of the lesion were heterogeneous. Therefore, dilatation in the microvascular pattern, sudden diameter irregularities, curving, and heterogeneity are typical changes in gastric cancer. The correlation between pathologic and NBI findings was 85.3%. Machida and colleagues¹⁵ reported that chromoendoscopy and NBI are equally effective for differentiating neoplasia from nonneoplasia, with 100% sensitivity and 75% specificity. Fukuzawa et al¹⁶ showed that NBI is superior to conventional endoscopy for the diagnosis of early-stage colorectal cancer.

Flexible Spectral Imaging Color Enhancement

The prototype of FICE technology was developed by Fujinon (Saitama, Japan). FICE is a software-based system that changes the color of endoscopic images in real time. The original image is processed arithmetically at a specific

wavelength of light. The actual images obtained using 10 preset FICE programs are processed by blue, green, and red filters to generate new images. The colors in the actual image are changed by using the absorption and emission properties of the light, thus revealing fine mucosal details to obtain a clearer image. Ten different new images are obtained by changing the properties of light of different wavelengths comprising the real image by means of virtual electronic filters.

Mouri et al¹⁷ reported that the green light wavelength of 500–530 nm produces the greatest contrast between normal mucosal and neoplastic tissue. Because white light has a broad wavelength range of 400–700 nm, it cannot produce a high contrast between the normal mucosa and early-stage cancer tissue, running the risk of overlooking early-stage neoplasms. FICE technology creates a contrast difference by changing the wavelength of light by means of virtual optical filters and the software creates 10 different images. The contrast difference so created enables detection of early stage cancer.^{18,19}

FICE does not increase the frequency of detection of colorectal polyps,^{20,21} but can determine whether an adenoma is neoplastic.²² The capillary patterns of adenomas are better demonstrated by FICE than by conventional endoscopy.^{23,24}

I-Scan

I-Scan technology increases diagnostic accuracy by revealing fine details of the GI mucosa. Unlike chromoendoscopy, no dye or contrast material is used with I-Scan. Moreover, I-SCAN does not make use of the contrast created by light of different wavelengths, as does NBI. I-Scan is a software-based imaging method.

The prototype of I-Scan technology was developed by Pentax Inc. (Tokyo, Japan). Endoscopic images reveal mucosal details by creating digital contrast.²⁵ This technology involves modification of each image element obtained using white light. More specifically, images obtained by conventional endoscopy are converted into new images simultaneously by processing in the software.^{25–27} Thus, the superficial details and capillary architecture of the mucosa are visualized, enabling detection of previously invisible lesions.²⁶ I-Scan images are developed behind the processor to provide simultaneous presentation. The technology comprises 3 image development elements: surface enhancement, contrast enhancement, and tone enhancement. These image enhancement techniques can be switched to maximize the efficacy of imaging.²⁷

The surface enhancement mode shows mucosal details by revealing the boundaries of small glands and lesions. This mode has 3 levels of image enhancement: low, medium, and high. The contrast enhancement mode displays images obtained using blue light coming through the white light, consisting of blue, green, and red light to the foreground and reveals the superficial pattern and vascular pattern in a way similar to that of NBI. The contrast enhancement mode also has 3 levels and is based on images obtained using blue, green, and red light. Three tone-enhancement options can be used to image the esophagus, stomach, and colon separately.²⁷

According to the pit pattern classification (**Table 1**) proposed by Kudo et al., using I-SCAN for polyps and precancerous lesions, the superficial and vascular pattern can be evaluated. In addition to the pit pattern, information about the extent of the lesion, angiogenesis, and early mucosal changes can be demonstrated by using image enhancement techniques.^{26,27} In a study involving 200 patients, Hoffman and colleagues²⁸ compared I-Scan with conventional colonoscopy and found that the rate of detection of neoplastic lesions by conventional colonoscopy was 13%, compared with 38% by I-Scan. In the same study, I-SCAN was used to differentiate neoplasias and nonneoplasias with a sensitivity of 98.6%.

Anandasabapathy et al²⁷ reported that inflammatory bowel disease lesions with a risk of malignancy are flat rather than morphologically polypoid. Mucosal surface changes can be visualized using I-SCAN-1 and the vascular pattern using I-SCAN-2, enabling prediction of the lesion's malignant potential. I-SCAN-3 provides detailed information regarding the borders of lesions.

Magnifying Endoscopy

In recent years, several diagnostic endoscopic techniques that enable detailed imaging by enlarging the GI mucosa have been developed. These improvements have increased the diagnostic value of endoscopy. One such technique, magnification endoscopy (ME), allows endoscopic images to be magnified several hundred-fold. Minor lesions missed by conventional endoscopy can be visualized by ME. Moreover, it provides a better view of the mucosal and capillary patterns. In addition to better defining upper GI lesions, such as intestinal metaplasia, dysplasia, and early carcinoma, ME is also superior to conventional endoscopy in detecting pattern changes in colon polyps and mucosal changes in inflammatory bowel disease. However, the increased level of detail causes problems in image interpretation. ME facilitates histologic

diagnosis of lesions during the examination. If the area to be magnified and examined is large, then the procedure can be prolonged.

Magnifying endoscopes enlarge the image by using movable lenses, which provide good visualization of mucosal structure and microvascular architecture. Magnifying gastroscopes also have an adjustable focusing system (capable of acquiring close-up and traditional images). MEs have a transparent head attached to the endoscope end that maintains a 2–3-mm distance between the endoscope and mucosa. This transparent head allows the endoscopist to focus on preservation of the image and the correct analysis of mucosal details. At the beginning of the ME procedure, as in conventional endoscopy, the mucosa is examined first; when a suspect lesion is encountered, the image is magnified up to several hundred-fold by pressing the magnification key. ME, in combination with techniques such as chromoendoscopy, FICE, and NBI, enables detailed examination of the superficial pattern and microvascular architecture. After a detailed examination of the demarcation line between the lesion and normal mucosa, biopsies are taken from the suspect areas where the patterns differ. The diagnostic value of this targeted biopsy is higher than that of random biopsies. In addition to ensuring that biopsies are taken from the correct targets, ME avoids unnecessary biopsies.

Confocal Laser Endomicroscopy

CLE has enabled noninvasive assessment of the cellular and molecular properties of tissues in real time, resulting in the concept of optical biopsy. It is rapidly evolving and continues to be developed for new applications.

A conventional endomicroscope is miniaturized and placed on the end of the endoscope. Alternatively, probe-based endomicroscopy involves acquisition of images using probes passed through a conventional endoscope. The image can be magnified several hundred-fold. In addition, contrast media are used to obtain images at the cellular and molecular levels. Two devices are used for endomicroscopy.

Pentax CLE (Pentax [Japan] and Optiscan [Australia]). A miniaturized endomicroscope is placed on the end of a standard 12.8-mm diameter endoscope. Using a blue laser beam of 488 nm wavelength, images are obtained at 0.8 or 1.6 frames/s. This system enables acquisition of cross-sectional optical images with a 500 × 500- μ m field of view, a 7- μ m resolution, and a 250- μ m depth from the mucosal surface. Similar to standard en-

doscopy, a working channel with a diameter of 2.8 mm allows use of air, water, and topical contrast medium. Thus, images are obtained at the cellular level from layers at different mucosal depths in suspect areas by using conventional endoscopy.²⁹

Cellvizio Probe-Based CLE. The Cellvizio system (Mauna Kea, Paris, France) uses probes that are passed through the flexible working channel of the endoscope. Several probes that match the characteristics and diameters of the region of interest in the GI tract are available. These probes provide optical images at depths of 55–130 μm after the endoscopic system is fixed. This system can visualize objects spaced 1.0–3.5 μm apart, which is known as lateral resolution. Because of the small diameter of the probes, this system can also be used in the bile and pancreatic ducts. However, the probes can be reused a maximum of 20 times, which increases the cost. Each probe costs approximately \$5,000. Because it is the only study channel in standard endoscopes, its use in probe passage prevents biopsy and use of topical contrast medium. However, use of a dual-channel endoscope for CLE overcomes these restrictions.

Fluorescent contrast materials are necessary for imaging the mucosa. The 488-nm blue laser beam is absorbed by the contrast agent, which emits light of a different wavelength.³⁰ The emitted light is detected and converted into images by the CLE photosensors. The most commonly used contrast agents are fluorescein and acriflavine.³¹

A confocal laser endoscope can be manipulated as easily as a standard endoscope. The contrast media are applied systemically or topically through the endoscopic study channel according to the properties of the mucosal region examined. To obtain a good image, the endoscope is positioned close to the mucosal region to be examined. Artefacts are removed by gentle aspiration, and the imaging area is fixed. Microscopic images are viewed in real-time on one computer monitor, and the other monitor is used for endoscopic imaging. The system also enables acquisition of horizontal cross-sectional images at various depths. These images can be digitally recorded, stored, and re-examined.³²

Because the pancreatic bifurcation path is difficult to access, diagnosing diseases that involve this pathway can be problematic. If cholangiocarcinomas with a poor prognosis can be detected at an early stage, the patient can undergo surgery or liver transplantation. Histologic examination of the pancreatic bifurcation tract can be achieved using special probes; therefore, in the near future, the use

Endoscopic Technique	Sensitivity (%)	Specificity (%)
Chromoendoscopy	97	81
NBT	97.9	83.8
FICE	91.5	90.9
Magnification Endoscopy	93	95
I-SCAN	28.5	78.4
CLE	80	94

of CLE to diagnose pancreatobiliary stricture is likely to increase.^{33,34} This examination would reduce the need for unnecessary invasive methods such as ERCP and surgical exploration. Wallace and colleagues found that a reticular pattern, irregular epithelium, and no loss of mucosal structure are characteristics of benign strictures. The Miami classification categorizes CLE indications and findings for these strictures.³⁵

CONCLUSIONS

The sensitivity and specificity of the new endoscopic techniques in cancerous and precancerous lesions are shown in **Table 2**.^{15,36–39} The new endoscopic technologies described herein improve the prognosis of GI cancers by enabling their diagnosis and treatment at an early stage. However, these new techniques require experience if they are to be used effectively. The manufacturers are working to improve the ease of use of their products and are increasing the adoption of the new technology by continual innovation. Although these novel techniques are more costly than conventional colonoscopy, this disadvantage is outweighed by their diagnostic advantages, which improve the prognosis of patients with GI cancers.

According to our clinical experience, chromoendoscopy and endomicroscopy remain limited because besides a need for stain use with potential hazards of allergic complications, they have a long learning curve, a long procedure time, and high costs. FICE, NBI, and magnification endoscopy have widespread use because there is no need for use and because of convenience and shorter times of the procedure.

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