Advanced Imaging of the Gastrointestinal Lumen

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“It’s not what you look at that matters, it’s what you see.” Indeed, more than 200 years later, this phrase is still relevant. Gastroenterologists are constantly working to improve luminal imaging diagnosis. Despite these efforts, we struggle with adenoma detection rates in colon and diagnosis of pancreato-biliary malignancies. In the attempt to overcome these limitations, new endoscopic techniques are constantly being introduced. These novel endoscopic imaging techniques now allow for a more detailed analysis of mucosal and submucosal structures and include chromoendoscopy, virtual chromoendoscopy, magnification endoscopy and endocytoscopy. Various studies have shown the usefulness of these imaging techniques for conditions such as Barrett’s esophagus, colon polyps and early neoplasias of the stomach. The recently introduced confocal laser endomicroscopy (CLE) system allows us to analyze structures at the cellular and subcellular layer thereby obtaining an optical biopsy during ongoing endoscopy. CLE has the potential to visualize fluorescence labeled antibodies against specific epitopes in gastrointestinal cancer or inflammatory bowel disease, thus adding molecular imaging to the field of endoscopic imaging revolution.

INTRODUCTION

Endoscopy has been the gold standard for the evaluation and management of a multitude of GI pathologies ranging from premalignant lesions such as Barrett’s esophagus and colonic adenomas to inflammatory conditions such as ulcerative colitis and Crohn’s disease. In recent years there have been significant technological advances that allow the endoscopist to detect and resect a greater number of lesions more accurately with fewer biopsies. These exciting technologies have improved upon standard white light endoscopy (WLE) and include enhancements such as optical magnification and high definition (HD) cameras, dye-based chromoendoscopy, electronic chromoendoscopy, confocal laser endomicroscopy, and nascent technologies such as endocytoscopy and molecular labeling. This review will describe the use of advanced endoscopic technologies, their basic risks and benefits, and their clinical applicability.

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White Light Endoscopy

Traditionally, white-light endoscopy has been used for direct visualization of GI mucosa. Although WLE has the benefit of accurate color representation, it may not offer the most detailed images. In fact, traditional endoscopes are based on the standard definition (SD) television monitors of yesteryear. These are displayed in a 4:3 aspect ratio with approximately 640 pixels in width by 480 pixels in height, producing an image of just under 400,000 pixels. HD televisions are now the norm, and HD endoscopes are also becoming more commonplace. Similar to the 720p HD television format, these endoscopes can have as many as 720 pixels in height, producing an image composed of nearly 1 million pixels. However, unlike the HD television format, which is displayed in a 16:9 widescreen aspect ratio, HD endoscopes are typically shown in a 5:4 aspect ratio to better match the round endoscopic lens. This HD endoscopic image provides increased picture clarity and a recent meta-analysis showed a marginal benefit in detection of both colonic polyps and adenomas when compared to SD endoscopy, with a number needed to treat of 25. Typical high-resolution endoscopes magnify images roughly 30 to 35-fold, but specialized optical zoom endoscopes can magnify the image up to 150-fold. The two types of magnification include optical and digital, with optical magnification employing a movable lens in the tip of the endoscope, allowing a closer image while maintaining the same high resolution. Digital magnification, however, only moves the image closer to the display and is limited by fewer pixels in the same display area, thereby resulting in decreased image fidelity. Moreover, digital magnification typically only allows for a magnification of 1.5 to 2x, given a suitable processor and video equipment. Thus, the best combination is an HD endoscope equipped with an optical zoom, known as high-resolution endoscopy (HRE) with magnification. In one prospective randomized crossover study, HRE with magnification was found to be equally efficacious when compared with both dye-based chromoendoscopy with indigo-carmine or narrow-band imaging (NBI) chromoendoscopy for the detection of high-grade dysplasia or early cancer in Barrett’s esophagus. Moreover, HD colonoscopy was found to detect more adenomas per patient, more right-sided adenomas, and more flat adenomas when compared to SD white light endoscopy in a RCT from 2011. Another study from 2013 showed a 3-fold increase in detection of dysplasia in IBD patients when using HD colonoscopy compared to SD colonoscopy. The downsides to HD colonoscopy with optical magnification include added expense when compared to SD endoscopes and a slightly larger insertion tube diameter and tip, potentially impacting maneuverability during difficult cases.

Dye-Based Chromoendoscopy

Dye-based chromoendoscopy has traditionally used either Lugol’s solution (0.5%-3% potassium iodide...
and iodine in water), methylene blue 0.5% solution, or indigo carmine 0.1-0.4% solution (Figure 1). These dyes can be applied throughout the gastrointestinal mucosa to enhance endoscopic visualization. Images obtained can display the mucosal topography and borders in finer detail, particularly of subtle lesions such as nonpolypoid adenomas.9 Both Lugol’s solution and methylene blue are classified as absorptive stains, as they are actively taken up by epithelial cells. For example, applying Lugol’s solution will result in the normal esophageal mucosa staining intensely greenish brown for 5-8 minutes after spraying, while dysplastic and neoplastic areas will not take up the dye.9 Studies have shown that Lugol’s solution improves visualization of squamous cell cancer in patients at increased risk, such as alcoholic patients and those with head and neck cancers.11

Methylene blue is actively absorbed by intestinal epithelial cells and not squamous epithelium and is thus better suited to enhance detection of the metaplastic columnar epithelium present in Barrett’s esophagus.11 Canto et al showed that using this dye resulted in a more targeted approach to Barrett’s esophagus lesions with fewer biopsies when compared to random sampling, as well as more biopsy specimens containing columnar epithelium.12 Furthermore, in a randomized control trial, Kiesslich et al found that surveillance colonoscopies conducted in patients with ulcerative colitis (UC) using methylene blue dye resulted in significantly more intraepithelial neoplasia found (32 vs 10 lesions) in 165 patients with a sensitivity and specificity of 93% for differentiation between neoplastic and nonneoplastic lesions.13 Thus, the American Gastroenterological Association (AGA) recommends surveillance colonoscopies with image-enhanced endoscopy (such as using dye for contrast) in patients with longstanding UC9 (Figure 3). However, there are some concerns regarding oxidative DNA damage with methylene blue and possible complications such as acute colitis, and thus, this dye is not used as frequently as indigo carmine.14

Indigo carmine is a non-absorptive dye used mainly for its ability to better delineate borders of lesions, which is most helpful to accentuate nonpolypoid lesions. In fact, it is used routinely in Japan to better evaluate for gastric cancer after the completion of a standard white light endoscopic examination.15 It is also well suited to delineate colonic lesions, and studies have shown

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Computerized Virtual Chroendoendoscopy

Virtual chroendoendoscopy can be considered a catchall term for a collection of newer technologies that have recently been able to emphasize various wavelengths of light in order to improve the visualization of abnormal GI mucosa. NBI, flexible imaging color enhancement (FICE), and i-scan technologies will be discussed in this review. NBI technology uses two sets of physical filters placed in front of the endoscopic light source at the 415 nm wavelength (corresponding to blue light) and the 540 nm wavelength (corresponding to green light). The blue light wavelength corresponds to the primary absorption peak of hemoglobin and the green light corresponds to hemoglobin’s secondary absorption peak. This has the effect of emphasizing surface and submucosal capillaries and irregular microstructural capillary patterns, which have been shown to be highly associated with high grade dysplasia and early cancer. This technology can be helpful in characterizing neoplastic colonic polyps, but is prone to error based on the endoscopist’s experience with the technology (Figure 3). Also, NBI technology is unlikely to be routinely used due to its poor light intensity, especially in the stomach and colon.

FICE technology is software-based and does not require the use of physical filters like NBI (Figure 4). The technology uses spectral emission methods to build single-wavelength images, which are then randomly assigned to red, blue, or green channels to create a virtually enhanced color image. The endoscopist can then select preset wavelengths to view (from 400 nm to 695 nm) or manually adjust the viewable wavelength in increments of 5 nm. At any time, a push button can switch the view between a FICE image and standard WLE. This technology, as with NBI, can be coupled with optical magnification to enhance mucosal visualization. Compared with NBI, there are fewer studies evaluating the role of FICE. Although FICE is fairly accurate in the characterization of colorectal polyps, FICE does not improve detection of colonic polyps when compared with either standard WLE or chroendoendoscopy with indigo carmine.

Finally, i-scan is another digital post-processing method that comes with three modes of image enhancement, which are surface enhancement (SE), contrast enhancement (CE), and tone enhancement (TE). Surface enhancement aids in the recognition of edges, contrast enhancement emphasizes depressed areas in view, and tone enhancement modifies the red, green, and blue color balance for the esophagus, stomach, and colon specifically. SE and CE can be adjusted between low, medium, and high, with multiple modes able to be applied together with a simple button push (i.e. low SE and high CE). Similar to NBI, the sensitivity
and specificity of i-scan for the characterization of colorectal polyps are high. However, a randomized colonoscopy trial did not show any increased adenoma yield with i-scan when compared to HD colonoscopy. When compared to WLE images, i-scan images did not differ markedly in brightness or color, unlike NBI images (Figure 5). Thus, both FICE and i-scan appear reasonably accurate for characterization of colorectal lesions, but do not enhance adenoma yield. More studies are required before they can be considered for routine clinical use.

Confocal Laser Endomicroscopy

Confocal laser endomicroscopy (CLE) is a promising new technology that has the ability to deliver microscopic images in real-time during the endoscopic procedure. GI tissue is illuminated by a low-power laser, which then detects reflected fluorescence light through a pinhole. The term confocal denotes that the illumination and collection system are in the same focal plane. The images obtained are sharp and of an extremely high resolution because only the light that is refocused through the pinhole is captured. Intravenous fluorescein (which does not stain nuclei) is generally used for contrast, as topically administered acriflavine (which does stain nuclei) has been found to be a mutagenic dye and potential human carcinogen. Two types of CLE exist, probe-based (pCLE) and endoscope-integrated (eCLE). pCLE passes through the accessory channel of most endoscopes and thus can be used with a bronchoscope, cholangioscope, etc. In addition, pCLE also has the advantage of being able to view video at 12 frames/second and thus, can image capillary flow. The disadvantages include a slightly lower resolution than eCLE and slightly smaller field of view. The eCLE system acquires images at 1.6 frames/second at a 1024x512 pixel resolution or 0.8 frames/second at a 1024x1024 pixel resolution, resulting in approximately 1000-fold magnification. Given this, it is recommended that CLE be used in a targeted fashion for suspicious lesions.

Moreover, CLE can help the endoscopist target the most suspicious area for biopsy by screening multiple areas of metaplasia/dysplasia during the actual procedure (Figure 6 and 7). This technique was applied in clinical practice in a study with 42 patients coming back for surveillance colonoscopy after previous polypectomy. In this study CLE was able to distinguish normal mucosa from regenerative and neoplastic mucosa with 99.2% accuracy. This can help reduce the number of unnecessary biopsies (the single greatest risk factor for major complications of colonoscopy) as well as target truly neoplastic lesions. This was also shown to be the case in a study involving UC patients: the control group was biopsied with just WLE and the experimental group was given panchromoendoscopy with methylene blue and CLE. 21.2 biopsies were needed with the experimental group compared to 42.2 biopsies in the controls, with a negative predictive value.
(NPV) of normal mucosa on CLE of 99.1%. Given these findings, CLE may very well help to abandon the practice of untargeted random biopsies in patients with UC. In Barrett’s esophagus, pCLE was also used to view the mucosa and prevent biopsies on normal-appearing tissue in vivo. This resulted in a 98.8% NPV, thus “allowing nearly risk-free elimination of the random biopsy when pCLE was negative,” saving money for Medicare and mitigating procedure risk in the process. Unfortunately, there is a steep learning curve associated with the use of this technology, and it adds a substantial amount of time to the procedure. Its limited field of view also makes it unsuitable as a red-flag technique, and it needs to be incorporated with HD and dye-based or virtual chromoendoscopy to identify suspicious areas that need endomicroscopic evaluation. Thus, although the technology appears to be safe and accurate in expert hands, additional studies are needed to determine its complete use for routine clinical practice.

Another evolving endomicroscopic technique is nCLE. The principle of needle-based Confocal Laser Endomicroscopy (nCLE) is to image organs within or adjacent to the gastrointestinal by means of a miniprobe inserted through an endoscopic needle placed under endosonographic guidance. The fundamentals of this technology, as well as the principle of operation of nCLE, are substantially similar to pCLE. The AQ-Flex 19 Confocal Miniprobe is compatible with the 19G-type needle only. It is expected to help differentiate the various types of cystic lesions (mucinous versus serous).

Developing Technologies

Endocytoscopy has the potential to deliver even more magnified images than CLE, up to 1400-fold. The technology is currently available in probe-based and endoscope-based forms, yet is still in the prototype phase of development. In essence, it is a high-powered light microscope projecting very highly magnified images that requires contact with the tissue surface. This requires pretreatment with a mucolytic agent such as N-acetyl-cysteine as well as prestaining with a compound such as methylene blue.

Molecular imaging takes biomarkers such as fluorescent dye-labeled monoclonal antibodies against carcinoembryonic antigen (CEA) to help detect cancers and adenomas. The antibody is physically applied via the colonoscope and specific filters pick up the fluorescence on appropriate tissue. Multiple peptides are being tested, including those that target high-grade dysplasia in Barrett’s esophagus as well as cathepsin B, which is upregulated in colorectal cancer.

There is no doubt that existing methods of endoscopy will continue to grow more sophisticated through progressive technological advancement. Key in this progression is the ability to harness their increased sensitivity and individual benefits for the betterment of the patient. As these technologies are further studied some will be more efficacious than others, and those must be fully developed, refined, and possibly combined with others (such as chromoendoscopy with CLE) to
realize their potential. Throughout this process, costs will continue to decline, hopefully to the point where many of the above mentioned technologies become a readily available option for the outpatient endoscopist. The next few years may well prove to be an exciting time in the field of advanced endoscopy.

References