Advances in endoscopy for colorectal polyp detection and classification

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ABSTRACT

While colonoscopy is considered the gold standard for colon cancer screening, recent advancements in endoscopes have allowed for improved visualization of the colonic mucosa and improved polyp detection rates. Newer technologies also allow for assessment of structural changes for polyp discrimination and determination of histologic type. Classification of polyps prevents the need for a histopathologic report, which requires the additional time and expertise of a pathologist and adds to the overall cost. This review considered advances in endoscopic technologies reported in PubMed over the past 12 years. Technologies that allow for increased visual field of colonic mucosa and may lead to improved colon polyp detection rates include cap-assisted colonoscopy, RetroView, extra-wide-angle view colonoscope, full-spectrum endoscopy, Third Eye Retroscope, NaviAid G-EYE balloon colonoscope, EndoRings, and Endocuff. Image-enhancing methods allow for pit pattern analysis of colorectal lesions, which enables the physician to classify colorectal polyps according to certain polyp characteristics. Image-enhancing methods include chromoendoscopy, autofluorescence, and virtual chromoendoscopy, including narrow band imaging, i-SCAN, flexible spectral imaging chromoendoscopy, and STORZ professional image enhancement systems. In addition, advancements have been made in in vivo microscopic evaluation of colonic epithelium, including confocal laser endomicroscopy, endocytoscopy, optical coherence tomography, spectroscopy, and autofluorescence spectroscopy. Colon capsule endoscopy also has a role in colon polyp detection and classification. The advancements in polyp detection and classification have great promise for earlier detection and removal of advanced adenomas before they advance to colorectal cancer.

KEYWORDS Adenoma detection rates; colorectal polyp classification; colorectal polyp detection; endoscopic advances; in vivo microscopic evaluation; technological advancements

Colorectal cancer (CRC) is the third most common cancer diagnosed in both men and women in the United States. Colonoscopy is the most widely accepted method for colon cancer screening and is currently considered the gold standard. Polypectomy is the most commonly performed therapeutic procedure to prevent progression to CRC. In a systematic review of six studies, the pooled miss rate with colonoscopy was 22% for polyps, 26% for adenomas <5 mm, and 13% for adenomas 5 to 10 mm.¹ There is substantial evidence suggesting that colonoscopy is less effective for right-sided than left-sided CRC.^{2,3} Some reasons include worse bowel preparation in the right colon and the flat, less often

pedunculated nature of polyps in the right colon.² Devices that increase the field of view and the surface area available for inspection may reduce this miss rate. Given that histological assessment of polyps is time consuming and costly, particularly in the case of diminutive polyps, real-time classification of polyps may allow for more timely and cost-effective care. The differentiation of adenomas from hyperplastic polyps can potentially allow for a “resect and discard” strategy for diminutive colon polyps and for a “leaving in” strategy for diminutive hyperplastic polyps in the rectosigmoid colon.⁴ This review addresses advances in endoscopic techniques that improve adenoma detection rates (ADRs) and polyp classification.

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Figure 1. (a) RetroView endoscope with retroflexed tip to allow for full view of the rectum and proximal aspects of interhastral folds on withdrawal. (b) RetroView endoscope retroflexed to assist in visualizing snare for polypectomy. Photos courtesy of Pentax.

METHODS

PubMed was used to search for articles reporting technological advancements in endoscopy for colorectal polyp detection and classification that were published in the past 12 years. All types of articles, including review articles, guidelines, randomized trials, meta-analyses, post hoc analyses, retrospective studies, prospective trials, and simulated pilot studies, were included.

RESULTS

Quality measures

To decrease the number of missed polyps and adenomas and to ensure that colonoscopies are performed optimally, certain intraprocedure quality measures pertaining to the screening of colon cancer are considered, including bowel preparation, cecal intubation rate, withdrawal time (not single best but surrogate indicator), polyp removal if <2 cm, and ADR.⁵ Current recommendations are that individual endoscopists should identify ≥ 1 adenoma in at least 25% of men and 15% of women aged ≥ 50 years undergoing screening colonoscopy.

A study by Corley et al. showed that the ADR was inversely associated with the risk of interval CRC, advanced-stage interval cancers, and fatal interval cancers.⁶ Potentially modifiable factors that may influence ADR can be patient related (proper bowel preparation), endoscopist related (withdrawal time, quality of mucosal inspection including fold examination, additional observers), or procedure related (water infusion, adequate distention, additional examination of right colon, change in position, antispasmodics, colonoscopic equipment, and accessories).⁷ In a retrospective study performed at a Veterans Affairs medical center, the authors analyzed the effect of a quality report card intervention on colonoscopy performance and found that the ADR and cecal intubation rate were both significantly higher with the intervention. Most of the increment in the ADR was related to increased detection of proximal adenomas.⁸

A minimum withdrawal time of 6 minutes was recommended by the US Multi-Society Task Force and was shown to increase the polyp detection rate. This is a surrogate indicator that is ideally targeted when trying to improve ADRs.

High-definition white light colonoscopy

Current high-definition endoscopes have a resolution of 650,000 pixels, allowing for very high resolution. In a large meta-analysis, a marginal increase (3.5%) in the detection of adenomatous polyps with high-definition colonoscopy vs standard video endoscopy was demonstrated.⁹

Increased visual field of colonic mucosa

Advances in endoscopes that allow for increased visualization of the colonic mucosa may provide a means to increase ADRs.

Cap-assisted colonoscopy involves an attachment of a transparent cap to the distal tip of the colonoscope. It is intended to depress colonic folds to improve visualization of their proximal aspects. In a meta-analysis of randomized controlled trials, cap-assisted colonoscopy had a marginal benefit for polyp detection (relative risk 1.08; 95% confidence interval [CI] 1.00–1.17).¹⁰ Another meta-analysis comprising 12 studies concluded that cap-assisted colonoscopy detected significantly more polyps and had a lower average polyp miss rate (12.2% vs 28.6%) than standard colonoscopy.¹¹

RetroView allows for withdrawal in retroflexion, which is a maneuver that is commonly used in the rectum, and can be utilized throughout the colon (*Figure 1*). It allows views of both proximal and distal aspects of interhastral folds simultaneously. Although it is traditionally performed at the rectum to visualize the dentate line, it can also be performed throughout the colon, including the proximal colon. In a study with colon models with 12 simulated polyps hidden behind haustral folds and five placed in easily viewed locations, the RetroView colonoscope detected more polyps overall and more hidden polyps than the conventional colonoscope in standard withdrawal (85% vs 12% and 93% vs 12%, respectively, $P = 0.0001$).¹²

Full-Spectrum Endoscopy Colonoscope (FUSE) is a new endoscopic platform that has imagers on the forward tip of the colonoscope and on both sides of the tip. As shown in *Figure 2*, these three imagers provide a 330° angle of view of the colon displayed to the endoscopist on three side-by-side, contiguous video monitors.^{13,14} This field of view is in contrast to a standard forward-viewing colonoscope, which has a

Figure 2. A full-spectrum endoscopy colonoscope obtains three images (bottom) that provide a 330° view of the colon, compared to the single, 170° field of view provided in traditional colonoscopes (top). Photo courtesy of Endochoice.

field of view of 140° and, with the flexible tip, a field of view of 170°. An international, multicenter, randomized trial of 197 patients yielded a significantly lower adenoma miss rate with FUSE (7%) when compared to a forward-viewing standard colonoscope (41%) ($P < 0.0001$).¹⁴

Third Eye Retroscope is a retroscope that is advanced through a working channel of the colonoscope and retroflexes 180°, allowing for detection of polyps located on the proximal folds and at the anatomical flexures of the colon during colonoscope withdrawal. Studies have shown significant diagnostic yield of detecting adenomas and polyps when using the Third Eye Retroscope.^{15,16} In a multicenter randomized controlled trial including 249 individuals, there was an additional ADR for Third Eye Retroscope of 4.4% for screening, 35.7% for surveillance, 55.4% for diagnostic, and 40.7% for surveillance and diagnostic combined when compared to standard colonoscopy.¹⁵ A next-generation retrograde device, **Third Eye Panoramic**, was developed. It is a single-use video cap containing two side-viewing lenses fitted onto a colonoscope, and it does not require the use of a working channel of the colonoscope.¹⁷

The NaviAid G-EYE balloon colonoscope integrates an inflatable, reusable balloon onto the flexible tip of a standard colonoscope (Figure 3). The balloon can be inflated by the endoscopist upon colonoscope withdrawal, which allows for flattening of the haustral folds and better visualization of hidden areas. Prospective cohort studies have concluded that NaviAid G-EYE is safe, feasible, and has a significantly higher polyp detection rate for both obscured polyps (88.0% vs 25.0%; $P < 0.0001$) and nonobscured polyps (100.0% vs 75.0%; $P < 0.0001$) with balloon-assisted methods vs standard colonoscopy.^{18,19} An increase of ADR of 48.0% with G-EYE compared to 28% in the standard colonoscopy group was demonstrated in an international randomized controlled trial with 1000 patients.²⁰

EndoRings is a silicone rubber device that attaches to the tip of a colonoscope and mechanically stretches the colonic

Figure 3. The NaviAid G-EYE balloon colonoscope attaches a permanent reusable balloon at the flexible tip of the standard colonoscope that is inflated by the endoscopic during withdrawal, which assists in flattening of the haustral folds and stabilizing the endoscopic during intervention. Photo courtesy of Smart Medical Systems.

folds during withdrawal, allowing for visualization of proximal aspects of folds (Figure 4a). In a randomized, multicenter tandem colonoscopy study, there was a statistically significantly lower adenoma and polyp miss rate (10.4% and 9.1%, respectively) in subjects undergoing EndoRings first compared to subjects who underwent standard colonoscopy first (48.3% vs 52.88%, respectively). The cecal intubation times and withdrawal times were not significantly different.²¹

Endocuff is a device mounted on the tip of the colonoscope to help flatten the colonic folds during withdrawal (Figure 4b). A meta-analysis comparing the Endocuff vs conventional colonoscopy demonstrated an increase in ADR, especially in those endoscopists with an ADR $< 35\%$.²² In a randomized prospective multicenter trial of 500 individuals, ADR was significantly increased with the use of the Endocuff compared to standard colonoscopy (35.4% [95% CI 29% to 41%] vs 20.7% [95% CI 15% to 26%], $P < 0.0001$).²³ In another randomized prospective trial involving 498

Figure 4. EndoRings and Endocuff are distal attachments that attach to the tip of the colonoscope to mechanically stretch colonic folds during withdrawal to improve visualization of the proximal aspect of colonic folds. Photo courtesy of US Endoscopy/Arc Medical.

individuals, the polyp detection rate in patients increased by 14% with the use of Endocuff (56% vs 42%, $P = 0.001$), especially in the sigmoid region.²⁴ The Endocuff also improved endoscope tip control, particularly during polypectomy.²⁵

Image-enhancing methods and in vivo microscopic evaluation of colonic epithelium

Image-enhancing methods and in vivo microscopic evaluation of colonic epithelium not only provide a means of increasing the ADR, but they also allow for the assessment of structural changes for polyp discrimination and determination of the histologic type of polyp.

Magnification endoscopy allows for greater visualization of detail and may allow for polyp classification. Pit pattern analysis of colorectal lesions by magnifying colonoscopy is a useful and objective tool for differentiating neoplastic from nonneoplastic lesions of the colon. Characterization and classification of lesion morphology can be based on Kudo's classification criteria, a widely adopted system that classifies colorectal polyps into five types according to their appearance, polyp border and structure, and pit staining pattern. A recent meta-analysis of 20 studies concluded that it is an accurate diagnostic method for the differentiation of neoplastic colorectal lesions.²⁶

Chromoendoscopy utilizes color dyes, usually indigo carmine or methylene blue, to highlight mucosal surface architecture in order to identify colonic polyps or cancer. Chromoendoscopy also facilitates the detection and characterization of flat and depressed colorectal neoplasias. In a two-center prospective, randomized trial, pancolonoscopic chromoendoscopy with simplified, low-volume indigo carmine spraying increased the overall per patient detection rate for adenomas (0.95 vs 0.66), flat adenomas (0.56 vs 0.28), and serrated lesions (1.19 vs 0.49) in an average-risk

population.²⁷ In another study, high-definition chromoendoscopy had a marginal increase in overall ADR and a modest increase in per-patient detection of flat adenomas (0.6 ± 1.2 vs 0.4 ± 0.9 , $P = 0.01$), small adenomas <5 mm (0.8 ± 1.3 vs 0.7 ± 1.1 , $P = 0.03$), and nonneoplastic lesions (1.8 ± 2.3 vs 1.0 ± 1.3 , $P < 0.0001$) compared to high-definition white light colonoscopy.²⁸ A disadvantage to chromoendoscopy is the long procedure times due to dye application. One way to expedite the process is by incorporating methylene blue into a pancolonoscopic application. In a prospective trial of targeted biopsy results in patients with inflammatory bowel disease, chromoendoscopy led to significantly better dysplasia yield than standard colonoscopy.²⁹ In addition, the SCENIC international consensus statement on management of dysplasia in inflammatory bowel disease had a strong recommendation that chromoendoscopy increases the yield of dysplasia compared with standard-definition white-light colonoscopy and is the recommended mode of surveillance when compared to white light alone.³⁰

Virtual chromoendoscopy, also known as filter-aided colonoscopy, utilizes new light filters such as narrow band imaging or postprocessing techniques of reflected light (software-based processing) including i-SCAN, flexible spectral imaging chromoendoscopy, and SPIES. It modulates, by the press of a button and with no loss of time, the spectrum of visible light so that the mucous membranes can be visualized with the filtered light. It is performed much faster and with less effort than chromoendoscopy and virtual chromoendoscopy and can readily be utilized in most procedures. Virtual chromoendoscopy has not been shown to markedly improve detection of polyps or adenomas, but it has the ability to determine polyp pathology and distinguish between normal and neoplastic tissues in real time.

Narrow band imaging (NBI) technology uses rotating filters in front of the light source to narrow the bandwidth of the projected light centered to 30 nm wide spectra of 415 nm (blue) and 549 nm (green) to create a pseudocolored image. As shown in *Figure 5*, the normal mucosa appears green, whereas neoplastic tissue appears brown due to the angiogenesis consistent with adenomatous and neoplastic changes. A meta-analysis of 11 randomized trials comparing white light colonoscopy and NBI in 3673 patients showed no significant difference between white light colonoscopy and NBI for the detection of colorectal polyps, colorectal adenomas, or colorectal hyperplastic polyps.³¹ In randomized controlled trials comparing NBI and white light colonoscopy, NBI did not improve the neoplastic miss rate, adenoma miss rate, or adenoma or advanced ADRs.^{32,33} In a randomized controlled trial that compared the new-generation NBI to high-definition white light colonoscopy, the adenoma and polyp detection rates were significantly higher in the NBI group than the high-definition white light colonoscopy group (adenoma, 48.3% vs 34.4%, $P = 0.01$; polyps, 61.1% vs 48.3%, $P = 0.02$).³⁴

Figure 5. Narrow band imaging technology filters light sources to narrow the bandwidth of the projected light, highlighting neoplastic tissue as brown against green normal mucosa to assist in identifying (a) hyperplastic polyps and (b) adenomatous polyps.

NBI can also be used to improve polyp classification. A systematic review and meta-analysis based on 28 studies concluded that NBI diagnosis of colorectal polyps is highly accurate, with the area under the receiver operating characteristic curve exceeding 0.90. Overall sensitivity was 91.0% (95% CI 87.6% to 93.5%) and specificity was 82.6% (95% CI 79.0% to 85.7%).³⁵ A study using NBI to predict polyp histology found that NBI had a significantly lower diagnostic accuracy for predicting polyp histology in nonpolypoid or diminutive colorectal lesions vs polypoid lesions.³⁶ However, the VALID trial established that the endoscopists were significantly more likely (odds ratio 2.2, 95% CI 1.6–3.0, $P < 0.0001$) to make a high-confidence optical diagnosis with near focus (85.1%) than standard (72.6%) view. The authors concluded that NBI colonoscopy may replace the pathology diagnosis for most diminutive (<5 mm) colorectal polyps.³⁷

i-SCAN, FICE, and STORZ professional image enhancement systems are based on processor-integrated software applications that alter the wavelength ranges of reflected light and offer filter options, unlike NBI. Different filters enable reconstructions of various wavelengths that allow for the visualization of tissue structure and surface in a selective and accentuated manner by an easy switching operation. Studies have reported that i-SCAN and FICE are very similar to chromoendoscopy in differentiating adenomas from nonneoplastic polyps. A systematic review and meta-analysis performed by the American Society for Gastrointestinal Endoscopy established that virtual chromoendoscopy has the ability to meet acceptable performance thresholds outlined by the society's Preservation and Incorporation of Valuable Endoscopic Innovations initiative with high confidence with endoscopists who are experts in using the advanced imaging modality.³⁸

Autofluorescence imaging is based on the phenomenon that when tissue is exposed to light of a short wavelength, some endogenous biological substances are excited, leading to subsequent emission of fluorescence light of a longer wavelength. Autofluorescence imaging is not specific for neoplasia and is therefore associated with a high rate of false-positive diagnoses. To enhance the specificity of this method, it is

usually combined with high-definition endoscopy and NBI for characterization of the detected lesions; this is known as endoscopic trimodal imaging. A meta-analysis of 11 studies identifying the ability to differentiate neoplastic and nonneoplastic lesions showed that autofluorescence imaging had an overall sensitivity of 86.7%, a specificity of 65.9%, and a negative predictive value of 81.5%, which was inferior to the results of virtual chromoendoscopy and confocal endoscopy.³⁹ These data suggest that autofluorescence imaging cannot be used to make a reliable diagnosis, and larger studies are needed to determine its most advantageous use.

In vivo microscopic evaluation of colonic epithelium

Confocal laser endomicroscopy is based on tissue illumination with a low-power laser allowing micron-level spatial resolution with 1000× magnification. As shown in *Figure 6*, this may lead to immediate detection of CRC and premalignant lesions. Confocal laser endomicroscopy may also assist in the differentiation of neoplasms from nonneoplasms, advanced adenomas from nonadvanced adenomas, and adenomatous from nonadenomatous colorectal polyps while predicting histopathology with high sensitivity and accuracy.⁴⁰ In a meta-analysis of 15 studies, Su et al concluded that confocal laser endomicroscopy had high sensitivity (94%, 95% CI 88% to 97%) and specificity (95%, 95% CI 89% to 97%) for discriminating between colorectal neoplasms and nonneoplasms, which was comparable to colonoscopic histopathology.⁴¹ However, it is a time-consuming, highly examiner-dependent technique and has a steep learning curve.

Endocytoscopy involves preparation of the mucosa, including staining, and allows for ultra-high magnification of the colonic mucosa and visualization of cellular details to provide in vivo histologic images. A randomized controlled trial comparing the accuracy of endocytoscopy and standard biopsy for the diagnosis of colorectal neoplasms showed that the diagnostic accuracy of endocytoscopy (94.1%) for the discrimination of neoplastic lesions was noninferior to that of standard biopsy (96%).⁴² The advances made in endocytoscopy allow instant classification among different types of polyps and can be a promising tool for this purpose.⁴³

Figure 6. Confocal laser endomicroscopy images of the colon. **(a)** Normal healthy colonic mucosa with organized colonic crypts and goblet cells. **(b)** Dysplastic colonic mucosa with loss of organized architecture.

Optical coherence tomography uses infrared light to measure the optical reflectivity of tissue as a function of depth. Advances in the optical coherence tomography system have allowed for diagnosis and differentiation between benign and malignant lesions in real time and in vivo, and the system provides an internal microstructural image with high resolution.^{44,45} It may be a promising diagnostic approach for early detection of rectal cancer, diagnosis of polyp tissues, and differentiation of normal and cancerous tissues.

Spectroscopy quantitatively characterizes objects based on their interaction with light in real time. Light scattering can be elastic or nonelastic. The most common type of non-elastic spectroscopy is Raman spectroscopy, which measures vibrational and rotational aspects of molecules and provides insight into the molecular and biochemical composition of the tissues. Raman spectroscopy has shown promising results in detecting adenomatous and cancerous tissues, differentiating normal and precancerous tissues, detecting precancerous and cancerous lesions early, and identifying flat lesions.⁴⁶ In a study assessing the potential of Raman spectroscopy for discriminating between normal tissue and cancerous tissue, two regression methods were used on selected parameters to determine a diagnostic accuracy of 88% and 83% in discriminating between normal and cancerous tissues.⁴⁷

Autofluorescence spectroscopy uses the principle that certain molecules of the gastrointestinal cells called fluorophores emit light when stimulated by light. The modification in biochemical composition of dysplastic tissue can be detected by these techniques.^{48,49} A novel imaging technology called second harmonic generation has the ability to evaluate the amount of extracellular matrix collagen protein and its alignment. It can differentiate malignant from nonmalignant colonic polyp tissue with high sensitivity and specificity and can also distinguish high-grade dysplasia and malignant lesions in an objective, numeric fashion, which makes it a very promising technique to use for early CRC detection.⁵⁰

Endocytoscopy, microscopy, and optical coherence tomography techniques require the gastroenterologist to be trained as a pathologist. Although they allow visualization at a cellular level, nanoarchitectural structure cannot be visualized and chemical composition cannot be determined, unlike

in spectroscopy. Chromoendoscopy and molecular imaging need contrast agents, whereas none is required in spectroscopy. A combination of different techniques in multimodal imaging may enhance the accuracy in differentiating normal and cancerous tissues.

Colon capsule endoscopy

Colon capsule endoscopy was developed in 2006 and has since undergone many major improvements. The second-generation colon capsule has significantly better sensitivity and specificity for the detection of colonic polyps and tumors.⁵¹ In a prospective study in symptomatic patients, capsule colonoscopy identified patients with one or more polyps and adenomas ≥ 6 mm with 81% and 88% sensitivity, respectively, and 81% and 82% specificity, respectively.⁵² Additional studies reported a reasonable sensitivity of 88% to 89% for polyps ≥ 6 mm.^{51,53} Therefore, capsule performance seems adequate for patients who cannot undergo colonoscopy or had incomplete colonoscopies.

Colon capsule endoscopy allows for direct visualization of colonic mucosa. It is sensitive in detection of colorectal polyps; it is easy, comfortable, minimally invasive, and painless and has high patient acceptance. It can be self-administered but requires a more vigorous than usual colon prep. Disadvantages include the reading times of capsule video and the inability to take biopsies or predict histology of polyps. Recent technological advances have allowed for an automatic colorectal polyp detection scheme by using an algorithm,⁵⁴ and a new optical detection method based on the optical properties of immune-conjugated gold nanorods is expected to improve differentiation between cancerous and normal tissues.⁵⁵

DISCUSSION

Better interventions are needed to improve adenoma detection, including the detection of diminutive and flat polyps, in order to have earlier detection and intervention before progression to CRC. The new endoscopic advancements allow for increased visual field of colonic mucosa and enable polyps to be detected behind folds, whereas they may have otherwise been missed. Cameras that allow wider field of views and distal

attachments that increase visualization over folds may be an option to facilitate a lower adenoma miss rate and ideally a higher ADR. These tools may be particularly beneficial to those endoscopists who may have a lower ADR at baseline.

In addition, advancements in colonoscopies also allow for classifications of polyps. Classification allows for fast diagnosis, which alleviates some anxious waiting on the patient's behalf. It can also decrease many costs associated with histopathologic analysis and potential complications that may arise from excessive, unnecessary polypectomy. Advancements in the following technologies have enabled image-enhancing methods and in vivo microscopic evaluation colonic epithelium: chromoendoscopy, virtual chromoendoscopy, autofluorescence, endocytoscopy, confocal laser endomicroscopy, optical coherence tomography, and spectroscopy. Some disadvantages of these techniques are that they require gastroenterologists to be trained to interpret images in order to classify them, and they may require additional time or cost. Further validation and adoption of these classification strategies may support a "resect and discard" or a "diagnose and leave" strategy.

DISCLOSURES

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