Advanced Colonoscopy Techniques and Technologies

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Introduction:

Colonoscopy is the most frequently performed endoscopic procedure in the United States. It is the mainstay of diagnostic and therapeutic options for the practicing gastroenterologist. It plays a fundamental role in colorectal cancer (CRC) prevention, with a dominant position among screening options for CRC and pre-cancerous lesions.(1)

Over the past decade, there have been significant advances in the field of CRC and colonoscopy, including a better understanding of the importance of right-sided lesions, the sessile serrated pathway, and recognition of the significance of operator dependence in colonoscopy. This has been paralleled by an array of technological and technical advances, which have transformed the field of colonoscopy and improved patient care.

This paper addresses the diverse and expanding field of advanced colonoscopy techniques and technologies. It is intended to be a primer on recent and impactful developments in advanced technologies for screening/imaging, mucosal resection techniques, and endoscopic management of CRC (Table 1).

Table 1

Advanced Colonoscopy Techniques and Technologies	
Techniques and Technologies to improve polyp detection • Accessories (transparent cap, EndoRings, Endocuff, ThirdEye Retroscope, NaviAid G-EYE) • Colonoscope technology for	**Mucosal Resection Techniques** • EMR • ESD **Inflammatory Bowel Disease** • Dye-based chromocolonoscopy

increased mucosal visualization (wide angle colonoscopes, FUSE) • High-definition and magnification • Dye-based chromocolonoscopy • Electronic chromocolonoscopy (NBI, FICE, i-SCAN)	• Stricture management **Cancer** • Stenting of malignant obstruction • Dilation of anastomotic stricture

Techniques and Technologies to Improve Polyp Detection

Removal of polyps during colonoscopy decreases the risk of CRC.(2) This paradigm depends on the accurate identification of polyps, which has been shown to vary considerably among different operators.(3, 4) A systematic review and meta-analysis including six tandem colonoscopy studies found an overall miss rate of 22% of polyps in screening colonoscopies.(5) There have been a number of technologies developed to aid mucosal exposure and improve polyp detection.

Accessories:

The use of a transparent cap placed at the distal tip of the colonoscope ("cap-assisted colonoscopy") has been proposed to improve mucosal visualization by allowing flattening of colonic folds. The effect on polyp detection has not been consistent.(6, 7) A meta-analysis from 2012 that included 16 randomized controlled trials of cap-assisted colonoscopy and nearly 9,000 patients showed a small benefit from the use of the transparent cap, with a relative risk (RR) of identifying polyps of 1.08 (95% CI, 1.00-1.17), although adenoma detection was

not significantly increased with cap use.(8) Another meta-analysis showed similar results, with a RR of 1.13.(9)

EndoRings (EndoAid Ltd, Caesarea, Israel) is a mucosal detection aid that fits on the distal tip of the colonoscope, composed of a series of sequentially spaced silicone disks that emanate from the distal tip cuff (Figure 1).(6, 7) The disks are flexible and engage the mucosa to flatten folds through stretching. They also maintain some traction during loop reduction and during interventions.(10) A multi-center tandem colonoscopy cross-over study (currently in abstract form) of 66 patients showed an adenoma miss rate of 15% in the group receiving EndoRings-assisted colonoscopy (followed by standard colonoscopy) vs. a 48% miss rate in the group receiving standard colonoscopy first (followed by EndoRings-assisted colonoscopy, $p < 0.01$).(10)

The Endocuff (Arc Medical Design Ltd, Leeds, UK) is a cylindrical cuff with thin flexible arms, which is placed at the distal tip of the colonoscope (Figure 2). These projections engage the mucosa on withdrawal and allow for manipulation of folds for close interrogation. Similar to the EndoRings device, they maintain a degree of traction to avoid slipping during reduction and interventions.(6, 7) A multicenter randomized trial of standard colonoscopy vs. Endocuff- assisted colonoscopy showed a higher median number of polyps detected per colonoscopy (1 vs. 2, $p = 0.002$).(11) Another randomized trial of standard vs. Endocuff-assisted colonoscopy included 500 patients at 4 centers in Germany, and reported an ADR of 35% in the Endocuff assisted group compared to 21% in the standard colonoscopy group ($p<0.0001$).(12) There have not been any major adverse events associated with its use.

Right-sided mucosal lesions can be missed, due to a propensity for lesions in the right colon to be flat and covered with mucus, the presence of large folds and the slight increased difficulty of maneuvering the colonoscope in the right colon and around the hepatic flexure. “Second-look” examination of the right colon by either forward-viewing or retroflexion can result in increased adenoma detection.(13, 14) A second-look evaluation of the right colon has been demonstrated to identify an additional polyp in 4-10% of cases.(13, 14) The Third Eye Retroscope (Avantis Medical Systems, Inc, Sunnyvale, CA, USA) is a through-the-scope retrograde viewing system composed of an LED light source and camera, which was developed to allow the examination of proximal aspects of folds without the need for retroflexion. One nonrandomized study showed a 15% increase in polyp detection and 16% increase in adenoma detection rate among 298 subjects.(14) A randomized back-to-back study of 349 subjects showed 23% additional adenomas detected on repeat colonoscopy (standard colonoscopy then Third-eye assisted colonoscopy) compared to standard colonoscopy alone.(15) The device has limitations, including cost, decreased ability to suction, and need to remove the device to insert polypectomy tools. To mitigate some of these limitations, the manufacturer is developing a panoramic camera (330 degree visualization) that attaches to the distal tip of the colonoscope. It requires a separate video processing unit. Preliminary feasibility data have described its use in a small number of patients, and the device has recently received FDA clearance.(16)

The NaviAid G-EYE system (Smart Medical Systems Ltd, Ra’anana, Israel) is a system that has a balloon integrated permanently into the distal portion of the colonoscope shaft. The balloon is deflated during insertion, but can be inflated at varying pressures via a foot-pedal control system to assist in minimizing folds during withdrawal. Because it is a permanent component, it undergoes reprocessing along with the colonoscope.(6, 7) A multi-center prospective study

utilizing the G-EYE system demonstrated an ADR of 45%.(17) A randomized trial of tandem colonoscopies showed that the adenoma miss rate was significantly lower for the G-EYE system compared to standard colonoscopy (8% vs. 45%, $p < 0.0002$).(18)

Colonoscope Technology for Increased Mucosal Visualization

Increasing the angle of visualization attainable by colonoscopes has been proposed to increase the examined mucosal surface area. The standard colonoscopes produced by the major endoscope manufacturers have typically had a field of view of 140°. The latest model of colonoscopes by Olympus (CF-HQ190, Olympus America, Center Valley, PA, USA) have incorporated a 170° field of view.(6) A tandem study comparing standard angle and 170° angle colonoscopes showed no differences in adenoma detection rate, although the wider angle colonoscope did reduce insertion and examination time.(19) Two randomized controlled trials compared the standard view colonoscope with the wider-angle (170°) colonoscope. There was no significant difference in adenoma detection rate in either study.(20, 21) A colonoscope by Pentax (Montvale, NJ, USA) called the Retroview has a standard 140° field of view, but has a shortened turning radius which produces a more compact retroflexion and allows easier retroflexed withdrawal in the right colon.(6)

The Fuse endoscopy platform (EndoChoice, Alpharetta, GA, USA) is a full-spectrum endoscopy platform that achieves a 330° field of view by incorporating three individual camera lenses to create three images arranged in panoramic fashion.(6, 7) It is an independent colonoscope and control/processing unit. A multicenter tandem colonoscopy study demonstrated a lower adenoma miss rate in patients initially undergoing the Fuse colonoscopy vs. standard colonoscopy (7% vs. 41%, $p < 0.0001$).(22)

High Definition / Magnification

High definition (HD) imaging has the potential to improve polyp detection during colonoscopy. Chips in high definition colonoscopes produce resolution that currently exceeds 1 million pixels.(23) These endoscopes require distinct HD interface cables and monitors. All three major endoscope manufacturers (Olympus America, Center Valley, PA, US; Pentax Medical, Montvale, NJ, US; Fujinon Inc, Wayne, NJ) produce and market HD/magnifying endoscopes in the US.(23) Standard endoscopes magnify images x30, but the zoom function can lead to optical magnification to x150.(23) HD and magnification endoscopy, in combination with chromoendoscopy, has allowed for the detailed classification of colonic polyps according to pit patterns.(23-27)

Dye-Based Chromocolonoscopy

Dye-based chromocolonoscopy has been shown to achieve slightly higher adenoma detection rates than standard definition or high definition white light colonoscopy, primarily due to increased detection of flat and diminutive polyps.(28) A Cochrane meta-analysis of 5 randomized controlled trials demonstrated that use of chromocolonoscopy was associated with finding 3 or more neoplastic lesions (OR 2.6) and of patients having at least one neoplastic lesion (OR 1.7).(29) Withdrawal times were significantly longer in the chromoendoscopy group.(29)

One study comparing HD white light colonoscopy to chromocolonoscopy included 660 average-risk screening patients, and reported an ADR of 55% for the chromocolonoscopy group versus 48% for the white light group ($p = 0.07$).(30) There were significantly more diminutive polyps, flat polyps and hyperplastic polyps found in the chromocolonoscopy group.(30) Another large randomized

prospective study that included over 1000 patients reported a significantly higher ADR in the chromocolonoscopy group compared to the routine colonoscopy group (46% vs. 36 %, p = 0.002).(31) Concerns about the practicality of dye-based chromoendoscopy and the incremental yield, which is limited to small lesions (and recently, dye supply shortages) have limited its widespread adoption.

Electronic Chromocolonoscopy

Electronic chromocolonoscopy refers to endoscopic imaging technology which creates a distinct contrast of colonic mucosa and blood vessels.(32) Each of the three major endoscope manufacturers has their own proprietary electronic chromoendoscopy platform, as described below. NBI has the most data available.(33)

Narrow-band imaging (NBI, Olympus Medical Systems, Tokyo, Japan), utilizes a filter that produces only 2 “narrow bands” of light (415nm and 540nm) which correspond to the peaks of light absorption for hemoglobin, thus highlighting the vasculature within the mucosa and creating a contrast between the rest of the mucosa and the vasculature.(32) A recent Cochrane review and meta-analysis that included 8 randomized trials and over 3600 patients evaluated the polyp detection rate of NBI assisted colonoscopy and conventional white light endoscopy.(34) Between white light colonoscopy and NBI-assisted colonoscopy, there were no significant differences when considering detection of adenomas, all polyps, or hyperplastic polyps. (34) In 2011, the ASGE published a PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) document regarding the real-time assessment of the histology of diminutive colorectal polyps.(35) A resect-and-discard strategy requires that an endoscopic technology used to determine the histology of polyps ≤ 5mm, when combined with the histopathologic assessment of polyps >_5 mm in size, should provide ≥ 90%

agreement in post-polypectomy surveillance intervals when compared to decisions based on pathology assessment of all identified polyps.(35) Furthermore, a diagnose and leave-behind strategy for diminutive (≤ 5mm) suspected rectosigmoid hyperplastic polyps requires that the technology should provide ≥ 90% negative predictive value for adenomatous histology. (35) A recent systematic review and meta-analysis found that endoscopists who are experts in NBI technology and making assessment with high confidence can attain both PIVI thresholds.(36)

Flexible spectral imaging color enhancement (FICE, Fujinon, Fujifilm Medical Co, Saitama, Japan) is a digital post-processing system that alters white light images to emphasize certain wavelengths more through post-processing algorithms.(32) This is distinct from NBI in that NBI uses a light filter while FICE alters the image at the level of the imaging processor. There are 10 factory preset wavelength combinations that can be brought up by command of the keyboard, while up to three combinations can be programmed into the push button command of the endoscope.(32) Similar to NBI, a large study of over 1300 patients comparing FICE-assisted colonoscopy to HD white light colonoscopy showed no difference in polyp or adenoma detection.(37)

i-SCAN (Pentax Endoscopy, Tokyo, Japan) is also a post-processing image enhancement system. Like FICE, there are pre-set settings that alter the white light image to create increased enhancement of mucosa and vasculature.(32) The three pre-set settings can be accessed by an endoscope push button. A back-to-back study of 389 patients undergoing both i-SCAN assisted colonoscopy and HD colonoscopy found similar adenoma detection rates. There was some improvement of neoplastic vs. non-neoplastic discrimination in the i-SCAN group compared to the standard colonoscopy group (sensitivity 87% vs. 73%,

respectively, p=0.02; specificity 91% vs. 81%, p=0.04, respectively).(38) There was no statistical difference in endoscopists' predictions of the correct surveillance intervals for diminutive polyps with HD white light colonoscopy vs. i-SCAN (95% vs. 97%, respectively).(39)

Mucosal Resection Techniques

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are techniques that were developed to enable the resection of large benign, neoplastic and early malignant lesions.(40, 41) EMR has more widespread adoption than ESD in the West, because of shorter procedure time, lower rate of serious complications and easier learning curve. ESD, however, allows the en bloc removal of large laterally spreading lesions, thus improving the accuracy of pathological evaluation, and some data suggest an improved recurrence rate for large laterally spreading lesions resected with ESD compared to EMR.(42-44)

EMR

There are a number of different techniques that have been developed for endoscopic mucosal resection (EMR), including the injection, cap-assisted, and ligation-assisted techniques.(40) In general, lesions larger than 2cm need to be removed in piecemeal fashion. A meta-analysis that included 25 studies and over 5000 EMRs noted an en bloc resection rate of 59%.(45) The injection-assisted EMR utilizes the injection of a solution such as saline or hydroxyethyl starch often with a colorant added (e.g., methylene blue or indigo carmine) into the submucosal space to create a lift and cushion (Figures 3a and 3b). An electrocautery snare is then deployed to remove the lifted lesion. A large resection bed is often closed with hemoclips to decrease the risk of subsequent bleeding, particularly if the lesion is on the right side of the colon or the patient is on antiplatelet or anticoagulant agents (Figure 3c). The submucosal injection helps to

protect the underlying deeper layers from mechanical or electrocautery damage during resection.(40) The injection is an important part of the procedure, as an inability of the lesion to lift may indicate invasion into the deeper layers.(41) Furthermore, there may be difficulty injecting or canyoning of the lesion if there is fibrosis present, such as from prior biopsy or attempt at polypectomy.(41) The choice of snare depends on lesion size and morphology, but many experts prefer to use large stiff snares for flat laterally spreading tumors (LSTs). A central goal of any EMR technique is to accomplish complete resection of visible polyp tissue using mechanical methods; the use of argon plasma coagulation to ablate raised and visible polyp tissue is associated with higher rates of incomplete resection. For cap-assisted EMR, the lesion is drawn into a transparent plastic distal cap after submucosal injection, followed by snaring. There are single-use devices available that combine the cap and snare in a single mucosectomy device.(40) Ligand-assisted EMR utilizes a variceal band ligator device to suction the lesion into the banding cap. This can be used with or without prior submucosal injection. The ligation band is then deployed over the targeted lesion and then an electrocautery snare is used to remove the captured tissue either below or above the deployed band.(40) Local recurrence of large colorectal lesions removed by EMR ranges from 10% to 30%; however most recurrences (which are likely residual tissue from the original resection) are small and readily treatable using standard endoscopic methods.(46, 47) A surveillance examination is recommended between 3 to 6 months after piecemeal resection, followed by another examination after 1 year. If this examination is unrevealing, then the patient is followed based on current postpolypectomy guidelines.(48)

ESD

Endoscopic submucosal dissection (ESD) is a resection technique that is utilized to achieve en bloc resection of GI epithelial lesions.(41, 49) ESD requires a

submucosal injection, similar to EMR, to create a submucosal cushion. This submucosal space is then dissected using specialized electrosurgical knives that can be deployed through the working channel of the endoscope. Generally, the steps of ESD include: a.) marking of the perimeter of the lesion with coagulation, b.) submucosal injection, c.) circumferential mucosal cutting around the lesion, d.) submucosal dissection e.) specimen retrieval.(41, 49) A clear plastic distal cap is used to assist with traction of the submucosal space. Repeated submucosal injections are often utilized to maintain the submucosal cushion throughout the procedure. Bleeding is commonly encountered, and submucosal vessels are coagulated during the dissection, often with coagulation graspers. After the resection is complete, the resection bed should be interrogated closely for any microscopic perforations or bleeding vessels. It is recommended that the resection bed be closed with a clipping device. There are a number of specialized knives that have been developed for submucosal dissection, some which include an insulated ceramic tip to avoid dissection deep into the muscular layers, angled knives, and features that allow for fluid injection and cutting in the same device.(49)

A meta-analysis of 22 studies of colorectal ESD (20 studies from Asia) included more than 2800 colorectal lesions treated by ESD.(50) Median tumor size was 32mm.(50) The per-lesion summary estimate of an R0 resection was 88% and the rate of surgery secondary to complications per lesion was 1%.(50) Asian retrospective studies show that compared to EMR for lesions greater than 2cm, ESD achieves higher rates of en bloc resection and improved rates of local recurrence.(42-44) Mean follow-up in these studies ranged from 17-26 months, and found local recurrence rate of 12-26% in patients treated with EMR, compared to 0-2% in patients treated with ESD.(42-44, 49) It must be noted, however, that the vast majority of data in colorectal ESD are retrospective and

based on studies conducted in Asia, where the experience with ESD is much more mature. Training and reimbursement continue to be hurdles that Western endoscopists face. Prospective randomized, controlled trials may be helpful to determine the place of ESD compared to more conventional resection approaches.

Bleeding and perforation are the two most important risks of EMR and ESD. Reported significant bleeding rates vary for EMR and ESD, but are approximately 10%.(40) Bleeding during the ESD procedure should be expected, but can be managed intraprocedurally for the vast majority of cases. Perforation rates for EMR (0.3-0.5%) are far lower than for ESD (~5%).(40, 50) Despite the relatively high comparative rate of perforation in ESD, the vast majority are identified during the procedure and amenable to closure with endoscopic clips.(49, 51)

Inflammatory Bowel Disease

Dye-based Chromocolonoscopy in Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) involving the colon increases the risk for CRC. The severity, extent and duration of disease all affect the risk.(28) Colonoscopy has been recommended to detect dysplastic lesions at an early stage. Traditionally, guidelines have recommended four biopsies every 10cm from cecum to anus for surveillance, in addition to biopsies of any suspicious lesions or masses.(52) It has been shown that targeted biopsies have a much higher detection yield than random biopsies.(28, 53)

Several studies have shown no improved detection rate of dysplasia in IBD with digital chromoendoscopy.(54-56)

Dye-based chromocolonoscopy, however, is associated with improved dysplasia detection compared to the traditional approach. One study compared targeted biopsies for surveillance with white light and chromocolonoscopy,(57) and found that chromocolonoscopy detected dysplasia in 8% of cases, while standard colonoscopy detected dysplasia in only 1.6% of cases.(57)

A prospective tandem colonoscopy study of 75 patients showed significantly more dysplasia in the chromocolonoscopy group compared to the high definition white light group (21% vs. 9%, respectively; p= 0.007).(58) Other prospective tandem studies have demonstrated higher rates of dysplasia in targeted biopsies with chromocolonoscopy compared with standard colonoscopy surveillance, although these earlier studies compared chromocolonoscopy to standard-definition white light colonoscopy.(59-62) A meta-analysis of the diagnostic yield of detecting dysplasia with chromocolonoscopy in IBD patients found that there was an increased dysplasia detection rate of 44% compared with white light surveillance colonoscopy.(63)

A recent international multisociety consensus statement reviewed the available literature for the surveillance and management of dysplasia in inflammatory bowel disease.(64) Recommendations included using high definition over standard definition colonoscopy when using white light for surveillance of dysplasia in IBD patients.(64) In addition, when performing HD colonoscopy, chromocolonoscopy was suggested rather than white light colonoscopy. (64)

Stricture Management in IBD

Strictures are commonly encountered in the management of Crohn's disease. Through the scope balloon dilation has been utilized for symptomatic colonic and ileal strictures.(65) In general, balloon dilation may be utilized for relatively short

strictures. The length of the stricture should be known prior to dilation from either a contrasted radiographic examination or endoscopic examination. A guidewire is used to traverse the stricture, through which the balloon catheter is deployed. A pressure or volume-controlled handle dilates the balloon in a controlled manner. After dilation, the dilated stricture is assessed endoscopically.

A retrospective analysis of 38 patients who had attempted hydrostatic balloon dilation for ileo-colonic Crohn's disease-related strictures demonstrated successful initial dilation in 84% of patients.(66) Obstructive symptom recurrence occurred in 36% in 1 year and 60% in 5 years, and there was a 9% complication rate.(66) Another retrospective analysis of 59 patients with 124 dilations (most were anastomotic strictures) with a median stricture length of 3cm and median follow-up time of 29 months demonstrated that 59% of patients required surgery during the follow-up period and a small number (17%) achieved long-term symptom resolution after a single dilation.(67) Thus, stricture dilation in IBD patients can be effective in the short term, but the majority of patients will have symptom recurrence and require either re-dilation or surgery after initial therapy.

Cancer

Patients with CRC may present with obstructive disease. Placement of a stent to restore luminal patency may be considered, either as a palliative measure or as a bridge to surgical resection. Anastomotic stricture can also be encountered post-resection, and endoscopic dilation provides an alternative to surgical revision.

Stenting of Malignant Colorectal Obstruction

Through-the-scope self-expanding metal stents (SEMS) include the WallFlex colonic stent (Boston Scientific, Natick, MA, USA) and the Evolution colonic stent (Wilson Cook Medical, Winston-Salem, NC, USA). The stents are guide-wire

directed, and have markers that can be monitored both endoscopically and fluoroscopically to ensure appropriate deployment. It is recommended that the stents be deployed no farther distally than 2cm from the anal canal or 5cm from the anus to decrease the risk of significant tenesmus or pain. After deployment, the stents are considered a permanent implant.

With the current through the scope stent technology, overall technical success is approximately 85%.(68-70) When stents are used as a bridge to surgical resection, the rate of subsequent single-stage surgery is 60-85%.(68, 71-73) A meta-analysis comparing outcomes of initial colonic stenting and surgery included 10 studies and found a 93% technical success rate for colonic stents.(74) No difference in mortality was found between the stent-first (followed by surgery) group and the emergent surgical group.(74) There were significantly fewer ostomies required in the stent-first group, however.(74) A single study has shown that terminal patients with colonic obstruction had improved GI-related and overall quality of life related to stent placement.(75)

SEMS complications include perforation, bleeding, migration and stent occlusion. . Studies report a 4-10% rate of perforation associated with stent placement.(68, 72, 76) Dilation of malignant strictures prior to stent deployment has been associated with increased perforation risk.(68) Stent migration and obstruction are delayed complications that occur in approximately 10% of cases.(68, 72, 76)

Post-resection Anastomotic Stricture Dilation

Successful dilation of benign anastomotic strictures after surgical resection have been reported in the literature with both fixed diameter bougie dilators and radial expansion balloon dilators.(65) A retrospective analysis of 15 patients treated with Savary bougie dilation of stricture after low anterior resection showed a success

rate of 67%; none of the patients with clinical response required more than 3 dilations and no complications were reported.(77) A single-center retrospective experience of 24 patients undergoing balloon dilation after anterior resection of rectal cancer found dilation to be successful in 92% of cases; the mean number of dilations required was 2.3 and there were no reported complications.(78) A prospective randomized trial of 30 patients with benign post-resection anastomotic strictures comparing an 18-mm through the scope balloon dilator and a 35mm over the wire balloon dilator was successful in all 30 patients and no complications were encountered.(65, 79) In patients undergoing the larger 35mm dilation (device designed for achalasia), there was more durability of response (561 days vs. 245 days, $p = 0.02$) and significantly fewer dilation sessions required.(79)

Conclusion

Several techniques and technologies have been developed for the endoscopic management of colorectal pathology, including advancements in imaging technology to better detect neoplastic lesions and therapy of neoplasms. The colonoscopy landscape has been transformed in the last decade, and disease processes which traditionally required surgical intervention can now be safely and effectively managed by the advanced endoscopist.

Opportunities in development and research abound, including strategies to decrease operator dependence, continued development of techniques and technologies to accurately detect and diagnose polyps and optimize the management of colorectal neoplasia, and measurement of the impact of these advances on CRC prevention.

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