

## Endoscopy and polyps-diagnostic and therapeutic advances in management

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### Abstract

Despite multiple efforts aimed at early detection through screening, colon cancer remains the third leading cause

of cancer-related deaths in the United States, with an estimated 51000 deaths during 2013 alone. The goal remains to identify and remove benign neoplastic polyps prior to becoming invasive cancers. Polypoid lesions of the colon vary widely from hyperplastic, hamartomatous and inflammatory to neoplastic adenomatous growths. Although these lesions are all benign, they are common, with up to one-quarter of patients over 60 years old will develop pre-malignant adenomatous polyps. Colonoscopy is the most effective screening tool to detect polyps and colon cancer, although several studies have demonstrated missed polyp rates from 6%-29%, largely due to variations in polyp size. This number can be as high as 40%, even with advanced (> 1 cm) adenomas. Other factors including sub-optimal bowel preparation, experience of the endoscopist, and patient anatomical variations all affect the detection rate. Additional challenges in decision-making exist when dealing with more advanced, and typically larger, polyps that have traditionally required formal resection. In this brief review, we will explore the recent advances in polyp detection and therapeutic options.

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**Key words:** Polyps; Endoscopy; Colonoscopy; Endoscopic submucosal dissection; Endoscopic mucosal resection; Quality; Combined endoscopic-laparoscopic resection; Combined laparoscopic-endoscopic resection; Combined endoscopic-laparoscopic surgery

**Core tip:** Changes in polyp detection including chromoendoscopy and narrow band imaging, as well as reliance on quality indicators such as the 6-min withdrawal time, aim to improve adenoma detection rates. Once identified, novel approaches for large and advanced polyps such as endoscopic submucosal dissection and endoscopic mucosal resection, combined laparoscopic-endoscopic resection along with combined endoscopic-laparoscopic resection are available to surgeons that

may obviate the need for formal resection. Although technical expertise and experience is required, physicians caring for these patients should be familiar with each of these alternative procedures.

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## INTRODUCTION

Endoscopic technology has undergone dramatic improvements since Philipp Bozzini (1773-1809), a urologist from Frankfurt, Germany, developed the lichteiter in 1806 - a light-conducting system that featured a candle and system of prisms to inspect the rectum, bladder and esophagus of patients<sup>[1]</sup>. Since then, multiple different physicians and scientists such as Nitze, Mikulicz, Waye, and Shinya have advanced this technology from a rigid device able to look into the bladder and stomach to a fully flexible endoscope capable of evaluating the entire gastrointestinal tract. Modern endoscopic equipment allows the direct visualization and treatment of many diseases ranging from colorectal polyps, carcinoma, inflammatory bowel disease, intestinal ischemia, diarrhea, diverticular disease, and lower gastrointestinal bleeding. Auxiliary devices ranging from biopsy forceps, snares, injection needles, various knives, baskets and balloon dilators have been developed to expand the ability of surgeons and gastroenterologists alike to manage complex pathology through the use of endoscopes. This update will briefly review some of the emerging advances and evolving parameters as well as their impact on clinical practice.

## QUALITY PARAMETERS

Colon cancer remains the third leading cause of cancer-related deaths in the United States when each gender is considered separately and second when combined, with an estimated 50830 deaths in 2013 alone. This is despite multiple efforts aimed at early detection through screening, as well as evidence that routine screening reduces mortality<sup>[2-5]</sup>. Barriers to screening include patient fear of the exam and results, financial constraints, time off from work, transportation, and (in some regions) access to care. Multiple studies have demonstrated that when compared to flexible sigmoidoscopy and air-contrast barium enemas, colonoscopy is the most effective screening tool to detect colon cancer<sup>[6,7]</sup>. These dramatic results, in part, prompted Medicare in July 2001 to provide coverage for screening colonoscopy; which, along with technological advances, dramatically increased its overall use in the United States<sup>[8]</sup>. Despite the success of optical

colonoscopy to detect and remove polyps, there remains a substantial rate of undetected polyps. In most major series this rate appears to be low, but has not improved over time, suggesting the need for further advances in the technique. Large studies that include physicians with extensive experience have demonstrated missed polyp rates from 6%-29%, with the variation depending primarily on the size of the lesion<sup>[9]</sup>. Not surprisingly, missed polyp detection rates have been significantly lower for larger lesions. Pooled analysis of tandem colonoscopies has revealed a failure to detect polyps of any size in as many as 22% of cases (95%CI: 19%-26%). In this systematic review, when further stratified by size, adenoma miss rates were 2.1% lesions for  $\geq 1$  cm, 13% for those 5-10 mm, and 26% for polyps 1-5 mm<sup>[10]</sup>. Others have reported similar results, with miss rates for all polyps at 28%, adenomas (20%), polyps  $< 5$  mm (12%),  $> 5$  mm (9%) and advanced adenomas (11%)<sup>[11]</sup>. When accounting for other factors such as the concomitant presence of a sub-optimal bowel preparation, these rates have been reported to be higher than 40% for any size polyp, and even up to 36% with advanced adenomas<sup>[12]</sup>. In order to understand how we may potentially be able to lower this missed adenoma detection rate, we will explore these factors and the data behind each of them.

### Time of withdrawal

One factor that has more recently been identified to impact overall polyp detection rates is colonoscopy withdrawal time. In 2002, a United States Multi-Society Task Force on Colorectal Cancer recommended that the withdrawal time for colonoscopies should average 6-10 min. Interestingly, this was based, in part, on a single small series of only 10 consecutive colonoscopies performed by two experienced endoscopists with vastly different withdrawal practices that found different adenoma missed rates<sup>[13]</sup>. Following confirmatory studies, practice guidelines have since recommended that endoscopists spend a minimum of 6-10 min examining the colonic mucosa during the withdrawal phase of colonoscopy to optimize the diagnostic yield of polyps. In many instances, this has evolved to become a metric that is tracked by hospital administrators to assess the quality of colonoscopies<sup>[14]</sup>. The response was initially positive, and adherence to this benchmark was supported by findings in a study by Simmons *et al*<sup>[15]</sup> that included 11000 colonoscopies showing a direct association between longer withdrawal times and higher polyp detection rates ( $r = 0.76$ ;  $P < 0.0001$ ). Although this association was overall strong, it dropped significantly as polyp size increased ( $r = 0.19$  for polyps 6-9 mm,  $r = 0.28$  for polyps 10-19 mm,  $r = 0.02$  for polyps  $\geq 20$  mm). Small variations on this theme were subsequently reported, with others finding overall procedure time (which included the consent and sedation periods and not just withdrawal time) correlated with increased rates of polyp detection ( $r = 0.64$ , OR = 1.4, 95%CI: 1.19-1.64 for polyps  $> 1$  cm; OR = 1.03, 95%CI: 0.74-1.43 for polyps  $> 2$  cm)<sup>[16]</sup>. In one of the sentinel

papers, Barclay and associates published a study in the *NEJM* with 7882 colonoscopies using 6 min as the minimum length of time to allow for “adequate inspection” during withdrawal<sup>[17]</sup>. In this study of 12 gastroenterologists, rates of polyp detection ranged widely when measured either by number (0.1-1.05 mean number per patient) or percentage with adenomas (9.4%-32.7%), as well as times of withdrawal (3.1-16.8 min for procedures with no polyps removed). When specifically using a cutoff of 6 min, those with longer withdrawal times had significantly higher rates of detection for any neoplasia (28.3% *vs* 11.8%,  $P < 0.001$ ), as well as advanced lesions (6.4% *vs* 2.6%,  $P = 0.005$ ). Since then, multiple authors have confirmed average withdrawal times of 6 min or longer to be correlated with increased adenoma detection rates, including a quality assurance review of 15955 patients over 49 ambulatory centers, 17 states and 315 gastroenterologists, where longer withdrawals had a 1.8-fold higher rate of polyp detection<sup>[18]</sup>. In this review, factors that were found to be the strongest predictors of withdrawal time  $\geq 6$  min include the presence of carcinoma (OR = 3.7), adenoma (OR = 2), and number of polyps visualized (OR = 1.7). Whether the study is performed in a private practice or academic environment, the relationship between longer withdrawal times and higher rates of overall polyp detection, or adenomas per patient (0.09-0.82), has been consistent<sup>[19]</sup>.

However, the adoption of this quality indicator has not been uniformly supported nor met with complete agreement. Several authors have demonstrated no difference in polyp detection rates, despite improving the frequency of meeting the  $> 6$  min quality metric from 65% to near 100% of the time<sup>[14]</sup>. Others argue that colonoscopy rarely misses polyps  $> 1$  cm (*i.e.*, the most clinically significant polyps), regardless of the time spent during the withdrawal phase. Still others have agreed that while withdrawal time is associated with higher rates of polyp detection, longer withdrawal times have not been associated with changes in rates of neoplasia discovered at subsequent follow-up colonoscopies, including a recent VA Cooperative Studies Group analysis<sup>[20]</sup>. Similarly, after a monitoring and feedback program was instituted that focused on withdrawal times and polyp detection rates, there was an increase in mean withdrawal time (6.6-8.1 min,  $P < 0.0001$ ) and overall polyp detection rate (33.1%-38.1%,  $P = 0.04$ ). However, this was again observed to *not* be associated with an increase in neoplasia detection rate from the initial to the post-intervention time periods (19.6%-22.7%,  $P = 0.17$ )<sup>[21]</sup>.

Despite this, withdrawal time has evolved into a quality metric indicator in many centers for determining the adequacy of colonoscopy. As such, this has led to some changes in clinical practice - both positive and negative. Some authors have reported improved rates of longer withdrawal times to comply with these guidelines, simply knowing that this quality measure was being recorded, but without using that time to perform the corresponding evaluation. To combat this, practices such as vetting

through bystander observation and video recording have been attempted, though without a significant increase in polyp detection<sup>[22]</sup>. Other authors have shifted their focus in an attempt to further clarify the reasons for variations in polyp detection rate. Factors such as number of procedures, mean patient age, percentage of women, and mean procedure time have all been evaluated (in addition to polyp size) with only procedure time being significantly associated with polyp detection rate in a study of 2665 screening colonoscopies<sup>[23]</sup>. Multiple other patient and physician-related factors have also been identified as causes for higher miss rates including experience of the endoscopist, larger colon folds, morphology of polyp, and polyp location (*i.e.*, blind spots at the flexures)<sup>[11,24]</sup>.

### Physician fatigue

Physician fatigue has been considered another variable that affects colonoscopy quality performance and adenoma detection rates. This was first noted in a study demonstrating that afternoon colonoscopies have higher failure rates than morning colonoscopies, with higher overall incompleteness rates (6.5% *vs* 4.1%,  $P = 0.013$ ) as well as higher rates of inadequate bowel preparation (15.4% in am *vs* 19.7% in pm)<sup>[25]</sup>. When using cecal intubation rates as the endpoint, success was again lower in the afternoon (93.5% *vs* 95%,  $P = 0.02$ ), although gender, age and bowel preparation were felt to play a role in these differences as well<sup>[26]</sup>. Adenoma detection rates have also varied based on the time of day the colonoscopy is performed, with one study reporting rates of 29.3% in the morning *vs* 25.3% in the afternoon ( $P = 0.008$ ), independent of factors such as poor bowel preparation, withdrawal time, or partial evaluation<sup>[27]</sup>. To further clarify this, authors have compared results of providers that perform a full day of colonoscopy with those limited to half-day blocks. Adenoma detection rates in those only working half days have showed no significant difference between early and late procedures within that time period (27.6% *vs* 26.6%, OR = 1.05, 95%CI: 0.88-1.26,  $P = 0.56$ ), while those in the same practice with full-day blocks reporting higher detection rates in the morning (26.1% *vs* 21%,  $P = 0.02$ ), suggesting that the additional time, and subsequent fatigue, plays a role for this difference<sup>[28]</sup>. It appears that provider fatigue culminates in lack of focus or acumen in many cases, and translates into lower rates of “successful” colonoscopies as time progresses. Interestingly, polyp detection rates have also been shown to decline as time passes during an endoscopist’s schedule, regardless of time of day, or number of prior procedures. Each elapsed hour in their work schedule was associated with a 5.6% reduction in polyp detection ( $P = 0.005$ ), suggesting that physician fatigue can progress more rapidly in certain cases<sup>[29]</sup>.

### Training and technique

Regardless of the metric proposed, proper training remains a major factor in becoming and remaining proficient in any endeavor. Historically, intra-procedural quality indicators for colonoscopy have focused primarily on

physician-related factors such as cecal intubation rates, terminal ileal intubation, number of polyps detected, number of polyps retrieved, size of polyps detected, time to reach the cecum, and more recently withdrawal time. Guided by principles such as the United Kingdom Department of Health Global Rating Scale for endoscopy, emphasis has shifted more on defining quality experience through patient-driven metrics including appropriateness of the intervention, proper information/consent, overall safety, patient comfort, and providing timely results<sup>[30]</sup>. Use of colonoscopy-based virtual-simulator models has been one way to supplement inadequate exposure during residency training, and improve both the trainee experience and end result. Multiple studies have demonstrated that following intervention with 3-D simulators, many of these aforementioned traditional metrics such as cecal intubation rates, overall times, and need for further medication interventions significantly improve<sup>[31]</sup>. On the other hand, it remains to be seen how these newer quality metrics will be evaluated, reported and enforced.

## POLYP CLASSIFICATION

In general terms, a polyp refers to the elevation of tissue above the gastrointestinal epithelium. Colon polyp types range widely from hyperplastic, hamartomatous, and inflammatory varieties to neoplastic adenomatous lesions. Although these lesions are all “benign”, up to one-quarter of patients over 60 years old will have “pre-malignant” adenomatous polyps. Traditionally, polyps have been classified most commonly by their histology (*i.e.*, villous, tubular, tubulovillous, *etc.*), location, and physical description - with pedunculated and sessile being the most common descriptive classes. Since their first description in 1985<sup>[32]</sup>, flat adenomas are increasingly more common and represent one of the “high-risk” categories along with adenomas larger than 1 cm, those with high-grade dysplasia, those associated with inflammatory bowel disease, villous or tubulovillous adenomas, and patients with multiple adenomas (typically > 3). Similarly, serrated adenomas represent another high-risk group, and are believed to represent a unique pathway in the adenoma-carcinoma sequence.

### Flat polyps and serrated adenomas

While there has been some controversy regarding the impact and importance of flat adenomas in the United States and Europe, they are more widely believed to be significant in Asia. The Japanese Research Society Classification (Kudo classification of adenomas) describes flat lesions as those with a height that is less than one half the diameter<sup>[33]</sup>; while the Paris classification uses protruding and non-protruding divisions<sup>[34]</sup>. Increasingly, these lesions are recognized for their role in malignancy as well as difficulty with identification<sup>[35]</sup>. Serrated polyps represent another type of lesion that has been reported to be more difficult to diagnosis. Originally described following evaluation of hyperplastic polyposis syndrome

patients, these lesions have a characteristic serrated architecture and can occur either as a traditional serrated adenoma (classically seen as a polypoid lesion), or as a sessile serrated adenoma (flat, slightly raised, right-sided > left). Though historically often diagnosed as a variant of hyperplastic polyps, these lesions are found in about 7% of all colonoscopies, and are now more properly classified as their own distinct entity. They are also believed to have a higher risk of malignancy that occurs apart from the traditional adenoma to carcinoma sequence<sup>[36,37]</sup>.

The traditional polyp-cancer sequence has been established since Muto *et al*<sup>[38]</sup> described it in 1975. Adenocarcinoma of the colon can arise *via* multiple different pathways, with the most common described by genetic alterations that result in micro-satellite stable carcinomas<sup>[39]</sup>. Approximately 1/3<sup>rd</sup>, however, will arise along the serrated pathway, developed from the precursor lesion known as the sessile serrated adenoma (SSA). This is caused from an extensive methylation at the CpG island promoter site, which may demonstrate microsatellite instability. While controversy exists, it has been reported that SSAs are precursor lesions to micro-satellite unstable carcinomas; though limited data on the rate of progression currently exists<sup>[40]</sup>. In their pre-malignant state, these polyps show features between those of hyperplastic polyps and adenomas. On a molecular level, they have a high proportion of the *BRAF* mutation and DNA methylation. *BRAF*, a member of the RAF family of serine/threonine kinases, mediates cellular responses to growth signals, and *BRAF* mutations have been strongly associated with mis-match repair-deficient colorectal cancer<sup>[41]</sup>. Methylation and inactivation of the DNA repair genes *MLH1* and *MGMT* (O6 methylguanine-DNA methyltransferase) similar to that in hereditary non-polyposis colorectal cancer, are felt to be the critical steps that lead to this instability<sup>[42]</sup>. It has also previously been found that patients with micro-satellite unstable cancers demonstrate an increased serrated polyp to adenoma ratio compared to those with stable cancers. Therefore when encountering patients that have more serrated polyps than adenomas during colonoscopy, subsequent cancers in these patients may demonstrate microsatellite instability and should be considered for appropriate testing<sup>[43]</sup>. Risk factors for the development of sessile serrated adenomas include greater than 20 pack-year smoking history (OR = 7.31, 95%CI: 3.9-13.6), and, to a smaller extent, diabetes and obesity<sup>[44]</sup>.

Unfortunately, there continues to be inconsistencies in the literature regarding the ultimate prognosis and malignant potential of both flat polyps and serrated adenomas. Even large series comparing flat lesions with polypoid have found that the size of the lesion confers much greater risk than the morphology for the development of malignancy. Furthermore, the incidence of high-grade dysplasia or cancer in flat neoplasms was found to be similar to that of polypoid neoplasms (5.4% *vs* 4.6%, *P* = 0.36)<sup>[45]</sup>. While still somewhat controversial, what seems increasingly clear is that while further informa-

tion is required to determine the exact malignant risk of these lesions, there is evidence to suggest that they have a higher risk profile and should be followed accordingly.

### Laterally spreading tumors

Another subset of high-risk lesions includes laterally spreading tumors (LSTs). These lesions have been increasingly described over the past 20 years and are characterized by their higher likelihood to spread laterally along the luminal wall rather than vertically<sup>[46]</sup>. By definition, LSTs applies to lesions > 10 mm in diameter<sup>[47]</sup>. Okamoto initially described two clinical and histologic subtypes, which are identified as the granular-type (LST-G) and non-granular (LST-NG)<sup>[48]</sup>. Granular types appear endoscopically as multiple even or uneven nodules with the same color with its surrounding normal mucosa, while the non-granular type (also referred to as flat) appear smooth. These lesions may also be further stratified based on their morphological appearance as LST-G-H (homogenous) and LST-G-M (nodular mixed) type or LST-NG-F (flat elevated) and LST-NG-FD (pseudodepressed)<sup>[49]</sup>.

These lesions have a much higher propensity for being missed *via* standard white light colonoscopy, as well as more advanced techniques such as narrow band imaging (NBI) and chromoendoscopy<sup>[50]</sup>. More importantly, LSTs have an increased rate of submucosal invasion. Rates of invasion, particularly for the LST-NG subtype are as high as 30%-40%<sup>[46]</sup>, whereas the granular subtype are significantly lower (about 5%-10%)<sup>[51]</sup>. While the risk of lymph node metastases is low for early invasion<sup>[52]</sup>, the preferred management is still somewhat controversial, but mostly based on clinical and morphological appearance<sup>[53,54]</sup>. What is clear, however, is that these lesions represent a high-risk group with a substantial rate of concomitant malignancy, and endoscopists need to have an acute awareness of their potential presence and follow-up on them accordingly.

## POLYP DETECTION

There is little doubt that colonoscopy is a highly specific and sensitive test for the detection of colonic lesions, and several factors play a role in the adenoma detection rate (Table 1). However, differentiating early colon cancer from polyps can be more difficult. Factors that are associated with the presence of malignancy in a colonic polyp include villous architecture, increasing size, presence of multiple polyps and sessile lesions<sup>[55]</sup>. To further help in distinguishing benign from cancerous lesions, Kudo *et al*<sup>[56]</sup> in 1994 reported on differences in mucosal pit patterns of various colorectal polyps. In this classification system, staining patterns that are often seen in hyperplastic polyps or normal mucosa differ from the unstructured surface architecture more commonly identified with malignancy. Pit patterns were classified into seven principal types: (1) normal round pit; (2) small round pit; (3) small asteroid pit; (4) large asteroid pit; (5) oval pit; (6) gyrus-like pit; and (7) non-pit. The authors found that there

**Table 1 Factors associated with adenoma detection**

Variable	Association
Withdrawal Time < 6 min	Worse
Sub-optimal bowel preparation	Worse
Patient anatomy	Variable
Experience of endoscopist	Variable (mostly worse with early)
Afternoon endoscopy	Worse
Flat adenomas	Worse
< 1 cm	Worse
Narrow band imaging	Variable data <sup>1</sup>
Chromoendoscopy	Variable data <sup>1</sup>

<sup>1</sup>Compared to traditional white light colonoscopy.

was a correlation between pit patterns and the histology of the cells in the gland. The authors further went on to categorize these seven principle types into 5 pit patterns: (1) normal round pit; (2) small and large asteroid pits; (3) small round pit; (4) oval pit; (5) gyrus-like pit; and (6) non-pit pattern. By using this schema, types I and II are non-neoplastic and III, IV and V are neoplastic, with accuracy rates reported as high as 90%<sup>[57]</sup>. Chromoendoscopy and NBI use these differences in pit pattern to help detect and differentiate polyps.

### Chromoendoscopy

In chromoendoscopy, a dye such as indigo carmine can further enhance the surface structure of epithelial lesions with the aid of magnifying endoscopy<sup>[58]</sup>. Pit patterns become more recognizable, and outlining the borders of polyps is reported to be more accurate. Accuracy rates have been reported as high as 87%-100% and 76%-99.8% in diagnosing non-neoplastic and neoplastic polyps, respectively<sup>[59]</sup>. Furthermore, this technique has been shown to be beneficial for helping detect small lesions and decreasing the missed polyp rate, with diagnostic accuracies of 95% with magnification chromoendoscopy for lesions < 5 mm compared to 76% with traditional colonoscopy<sup>[60,61]</sup>. A recent update of the Cochrane review consisting of 5 studies compared chromoendoscopy *vs* conventional endoscopy for detection of polyps, and showed that chromoendoscopy is more apt to identify patients with at least one neoplastic lesion (OR = 1.67, 95%CI: 1.29-2.15), as well as those with ≥ 3 neoplastic lesions (OR = 2.55, 95%CI: 1.49-4.36) over “white” light endoscopy<sup>[62]</sup>. Although still not widely used, especially in the United States, chromoendoscopy has also been cited to reduce the time, cost and risk with biopsy/polypectomy, once the initial learning curve associated with dye application is complete.

## NARROW BAND IMAGING

NBI is an imaging technique that also relies on better definition of capillary pattern to improve the contrast between adenomas and surrounding normal mucosa. Adenomas, like malignancy, have a characteristic angiogenesis that can be detected using various wavelengths

of light that variably penetrate the colon mucosa<sup>[63]</sup>. The theory behind its efficacy lies in its ability to contrast the “normal” mucosa from that of adenomatous tissue to a greater degree than standard white light colonoscopy by selecting out specific wavelengths through optical filters that “narrow” the bandwidth of light. Developed by Gono *et al*<sup>[63]</sup> (and originally described on the vascular pattern and adjacent mucosa of the underside of the human tongue), it uses the reflected light to visualize the superficial structure and enhance the vasculature within the mucosal layers. Unlike chromoendoscopy, which relies on sprays and specialized equipment, NBI is readily available on many colonoscopy systems and does not require additional imaging. The data supporting its use, however, remains somewhat conflicting. In a pilot study by Machida *et al*<sup>[64]</sup>, NBI had a 93.4% diagnostic accuracy, equivalent to chromoendoscopy with magnification, and higher than that of conventional colonoscopy. In one randomized trial during screening colonoscopies, patients randomized to white light ( $n = 108$ ) and NBI ( $n = 103$ ) had adenoma detection rates of 58.3 and 57.3 ( $P = 0.88$ ), respectively. However, when the authors further evaluated only flat adenomas, a lesion believed to be best defined by NBI, the detection rates were 9.3% for traditional colonoscopy and 21.4% for NBI ( $P = 0.019$ )<sup>[65]</sup>. Other randomized data including 1256 patients comparing NBI technology to white light with associated high definition video found no difference in overall adenoma detection rates (33% *vs* 34%), total number of lesions (200 *vs* 216), or any other subgroups of adenomas to include flat lesions<sup>[66]</sup>. In this study, only hyperplastic polyps were found more commonly in NBI. Several other authors have found NBI did not improve the colorectal neoplasm miss rate compared to traditional methods<sup>[67]</sup>, or even those of small and flat adenomas with the use of high-definition colonoscope<sup>[68]</sup>. A recent Cochrane review identified 11 randomized trials with 3673 patients comparing NBI to standard white light endoscopy for the detection of colorectal polyps. The authors found similar rates of overall polyp detection (6 trials,  $n = 2832$ , RR = 0.97, 95%CI: 0.91-1.04), and adenomas (8 trials,  $n = 3673$ , RR = 0.94, 95%CI: 0.87-1.02), even when stratifying by the number of patients with at least one lesion by size [ $< 5$  mm: RR = 0.95, 95%CI: 0.84-1.08,  $I^2 = 56\%$ ; 6-9 mm: RR = 1.06, 95%CI: 0.81-1.39,  $I^2 = 0\%$ ;  $\geq 10$  mm: RR = 1.06, 95%CI: 0.77-1.45,  $I^2 = 0\%$ ]<sup>[69]</sup>.

On the contrary, there are studies that do report improvements in distinguishing neoplastic from non-neoplastic lesions using NBI, with accuracy rates higher than that of colonoscopy and equivalent to chromoendoscopy (80%-82% low magnification NBI; 85% low magnification chromoendoscopy; 87%-90% high magnification NBI; 82%-92% high magnification chromoendoscopy; standard colonoscopy (67%-68%)<sup>[70]</sup>. Other authors have found sensitivity of 90%-96% and specificity of 85%-89% in differentiation of neoplastic *vs* non-neoplastic lesions, comparable to that of chromoendoscopy. Furthermore, accuracy rates were even higher with the

addition of magnifying endoscopy, up to 94% for neoplastic and 89% for non-neoplastic lesions<sup>[71,72]</sup>. Similar to chromoendoscopy, however, the ultimate role this will have relies on the long-term data, ability to lower costs, and proper training of endoscopists prior to incorporation into everyday and widespread use.

### Endoscopic mucosal resection

Endoscopic mucosal resection (EMR) was first described in 1990 by Inoue and Endo in Japan<sup>[73]</sup>, and subsequently followed by Soehendra *et al*<sup>[74]</sup> in Hamburg, Germany in 1997. In the esophagus and stomach, as well as the colon, EMR allows removal of superficial tumors of the gastrointestinal tract. Unlike polypectomy that removes the tumor at the base of the mucosa, the plane of resection during EMR occurs in the middle or deep submucosal layer. Drawbacks of piecemeal excision include difficulty with proper staging, histological diagnosis, and definitive evaluation of the margins<sup>[46,75]</sup>. Furthermore, unlike the stomach, the colonic wall is much thinner and haustrated, leading to a technically more difficult procedure. Indications for EMR currently include adenomas or small, well-differentiated carcinomas confined to the mucosa or with minimal invasion into the submucosa, those more than 1/3<sup>rd</sup> of the luminal diameter, or flat/depressed polyps. In essence, EMR enables select lesions to be removed endoscopically that would potentially require colectomy<sup>[76]</sup>. It is important that these early carcinomas do not have lymphovascular invasion, due to the increased risk of lymph node metastases. As this technique is currently performed more commonly in Japan, the Japanese Society for Cancer of the Colon and Rectum's current criteria for curative endoscopic resection are: submucosal invasion of less than 1000  $\mu\text{m}$ , moderate or well-differentiated lesion characteristics, and the absence of vascular invasion<sup>[77]</sup>. Moss and colleagues have also identified risk factors for submucosal invasion and failure of successful EMR in a prospective, multi-center cohort of 479 patients and 514 lesions<sup>[78]</sup>. In their collective experience, Paris classification 0-II a+c morphology, nongranular surface, and Kudo pit pattern type V were all risk factors for invasion, with even higher risks (up to 55.5%) when multiple factors were present. EMR was attempted in 464 patients, being successful in 414 (89%), with a prior EMR attempt by the referring endoscopist (OR = 3.75, 95%CI: 1.77-7.94), difficult position (OR = 2.17, 95%CI: 1.14-4.12) and ileocecal valve location (OR = 3.38, 95%CI: 1.20-9.52) all predictors of initial failure.

Local recurrence has been reported in 6.9%-13.4% of cases of EMR, with higher rates reported following piecemeal excision, invasive pathology, and for lesions  $> 2$  cm (rates up to 39%)<sup>[79]</sup>. Median times for recurrence are typically within the first 6 mo, signifying the importance of follow-up endoscopic evaluation between 3 mo and 1 year<sup>[80]</sup>. In patients with larger polyps or those with dysplasia or cancer, it is recommended that they undergo more high intensity surveillance<sup>[81,82]</sup>. Other reported risk factors for recurrence include a granulous appearance of

the lesion and distal rectal lesions. Incomplete (R1) resections and those with deep positive margins should be considered for surgery.

Outcomes for EMR are, in general, very good as most patients are highly selected. When performed by experts, less than 3% of lesions are referred for surgical resection (due to inadequate removal), 44%-60% are performed *en bloc*, and the remaining lesions undergo successful piecemeal removal<sup>[83]</sup>. In sample series, complications involve procedural (10%-13%) and late (0%-1%) bleeding, post-polypectomy syndrome (2%-3%) and perforations (1%-2%)<sup>[84]</sup>. In attempt to identify high risk polyps that contain cancer prior to EMR, several authors have shown malignancy rates are higher with sessile polyps and those > 3 cm<sup>[83,84]</sup>. Although these factors are not absolute contraindications to EMR, it is typically more difficult to remove tumors larger than 2 cm by *en bloc* resection using EMR, with reported rates of about 30%. The decision to perform EMR should be made on an individual basis<sup>[85-87]</sup>.

### Endoscopic submucosal dissection

Endoscopic submucosal dissection (ESD) is primarily used to help with resecting larger tumors and aid in achieving higher rates of en-bloc resection of superficial tumors in the gastrointestinal tract than EMR. While EMR is the current standard in most centers outside of Asia, ESD is a technique that should, in general, be reserved for highly selected lesions by specialized endoscopists skilled and experienced in this technique. Although still primarily performed in select centers and lacking widespread use, the goals of ESD remain: (1) treating mucosal cancer; (2) achieving an R0 resection; (3) meeting quality standards; and (4) ensuring that procedures are performed by endoscopists trained in this technique and under institutional review board approval<sup>[88]</sup>. As a general guideline, ESD is more commonly indicated when a snare is unlikely to enable a successful *en bloc* resection with EMR. ESD is also indicated when tumors are diagnosed as carcinomas with intramucosal to shallow submucosal invasion, as well as lesions with submucosal fibrosis that cannot be removed by EMR, even if less than 20 mm in size. Others have proposed that this technique is suitable for all large polyps, early colorectal cancer, and those lesions that cannot be accessed transanally in patients who wish to avoid major resection.

Similar to other new technology, both EMR and ESD have learning curves that play a large role in determining outcomes. Previous reports out of Asia, where experience tends to be much greater, have demonstrated proficiency for larger lesions occurs at about 80 cases, with generalized avoidance of major complications such as perforation at about 30-40 procedures<sup>[89,90]</sup>. Yet, the learning curve of ESD and its outcome comparison to EMR in centers where endoscopists are not as familiar or experienced is less defined to date. Probst and colleagues evaluated their learning curve in a European study of 82 rectosigmoid lesions, with successful resection using ESD techniques in 76 (93%)<sup>[91]</sup>. Over the 7-year study period,

the authors divided up their experience into three separate phases (1-25, 26-50 and 51-76 years). During this time, both the rates of en-bloc resection (60%, 88% and 96%, respectively) and R0 resection (80%, 86% and 88%) increased, while procedure times significantly decreased (200, 193 and 136 min).

Using different techniques, other authors have reported successful en-bloc resection occurs in up to 85%-89% of cases and piece-meal resection is possible in the remaining 10%-15%<sup>[92-96]</sup>. Clear lateral and deep margins (*i.e.*, complete resections) have been reported in up to 79%-86% of cases<sup>[97,98]</sup>. As previously stated, because it is difficult to perform en-bloc resection by EMR for lesions larger than 20 mm, ESD may be more suitable for these lesions. The ability to predict depth of invasion in an attempt to decide whether to pursue EMR, ESD or formal resection remains somewhat difficult. Similar to EMR studies, predictors of submucosal *vs* mucosal invasion include poor-differentiation and the absence of background adenoma<sup>[83,84]</sup>.

Briefly the technique of ESD involves an initial bowel preparation to remove residual feces. An endoscope with a single channel is used along with a high-frequency electrosurgical generator. After identification of a lesion, one of several types of solutions (including a mixture of 1% hyaluronic acid solution and 10% glycerin solution) is injected around the lesions to elevate the submucosa<sup>[99]</sup>. Specialized knives in various shapes and sizes help to perform the dissection and resection. The border of the tumor is initially marked by indigo carmine dye and with approximately 1 cm margins. Following a mucosal incision, and depending on the physician preference, a partial or circumferential incision is made along with injection of hyaluronic acid solution into the submucosa, and the dissection is carried down to the deep submucosa. This process is continued around the tumor until the entire lesion is resected en bloc, when possible.

Perforation using ESD occurs in 1.4%-10.4% of cases, with the majority of series reporting rates < 2%<sup>[100]</sup>. These rates are classically higher than reported with EMR and are most likely due to the depth of dissection, and in certain cases lesions that are associated with a significant amount of fibrosis<sup>[101]</sup>. When small perforations occur, endoscopic clips have been utilized to close the site when feasible<sup>[102]</sup>. In more severe cases or those that cannot be closed endoscopically, more definitive procedures should be performed either by laparoscopy or laparotomy. Cases of delayed perforation occur in < 1% of cases, and are thought to be a result of thermal injury<sup>[103]</sup>. Postoperative hemorrhage rates are reported between 0%-12%, comparable to that with EMR, and the majority are self-limiting<sup>[96]</sup>. Another not infrequent complication is the inability to complete the procedure secondary to patient restlessness from abdominal distension and pain (12%-32%), requiring additional conscious sedation or even general anesthesia. Additionally, the use of carbon dioxide has been shown to significantly reduce this pain and bloating when deep sedation compared to traditional

air insufflation<sup>[104]</sup>. Other more rare complications include obstruction, fever, and pain<sup>[105]</sup>. Most importantly, residual disease has been reported in 2%-3% with ESD<sup>[106]</sup>. In one of the few series comparing ESD with EMR, 145 colorectal tumors were treated by ESD and another 228 treated by EMR. ESD was associated with a longer procedure time (108 min *vs* 29 min,  $P < 0.0001$ ), higher en bloc resection rate (84% *vs* 33%,  $P < 0.0001$ ) and larger resected specimen size (37 mm *vs* 28 mm,  $P = 0.0006$ )<sup>[86]</sup>. There were three (2%) recurrences in the ESD group and 33 (14%) in the EMR group requiring additional EMR ( $P < 0.0001$ ). Complication rates were similar (perforation 6.2% ESD *vs* 1.3% EMR, delayed bleeding 1.4% ESD *vs* 3.1% EMR;  $P > 0.05$ ). Although both of these techniques are currently only offered in select centers, emerging literature and advances in technology may provide the impetus for more widespread training and utilization.

### Combined laparoscopic-endoscopic resection/combined endoscopic-laparoscopic surgery

It is important to note that most lesions can (and should) be approached through traditional techniques. However, for select more advanced lesions, other methods are available. Combined laparoscopic-endoscopic resection (CLER) or combined endoscopic-laparoscopic surgery offers another approach for the removal of these advanced lesions that are not amenable to traditional endoscopic techniques, and would normally go on to formal resection. Lesions that are identified as being larger or more difficult to remove in the endoscopy suite are marked, and the patient is taken for a procedure under general anesthesia. In the operating room, the subcutaneous layer under the polyp is injected to lift the polyp. After laparoscopic ports are placed, the bowel is manipulated from the outside to expose the base of the lesion, and endoscopic polypectomy is performed. This enables direct evaluation for any full thickness injury, as well as the ability to imbricate or close the bowel wall using full thickness sutures should the need arise. Additionally, a sleeve resection can be performed that removes the lesion along with a full-thickness section of the surrounding wall (*i.e.*, in cecal lesions). A leak test can also be performed by submersion of the staple/suture line under water along with CO<sub>2</sub> or air insufflation. Any concerns regarding the applicability of the lesion for this procedure are alleviated by immediate conversion to a standard laparoscopic-assisted oncological resection<sup>[107]</sup>.

Technical success rates have consistently been reported in 77%-97%, with the remaining requiring conversion to resection<sup>[108,109]</sup>. Common reasons for an inability to perform this procedure include difficult lesion location, poor visualization (which has been aided by CO<sub>2</sub>-insufflation), and concerns for malignancy. Post-operative complications have been generally < 10%, with the majority being minor wound infections, bleeding, and ileus. Major complications are rare, with many reports citing a 0%-3% incidence. Recurrence rates are also low, reported in 10%-15% and typically are benign that may be ap-

proached *via* similar CLER, standard endoscopy or formal resection<sup>[107-109]</sup>. Final pathology ultimately will dictate the need for any subsequent segmental resection, and patients should be counseled about this ahead of time. Novel approaches for large and advanced polyps are available to surgeons that may obviate the need for formal resection. Although technical expertise and experience is required, physicians caring for these patients should be familiar with these alternative procedures.

## CONCLUSION

Our goal remains to identify and intervene on lesions at the polyp stage, prior to invasion. While colonoscopy is the most effective screening tool to detect pre-cancerous polyps and colon cancer, we must focus on the quality indicators such as withdrawal time and adenoma detection rate to ultimately improve our outcomes. Advances such as NBI, chromoendoscopy, endoscopic mucosal resection, endoscopic submucosal dissection, and CLER are tools that may improve the management of benign and early malignant polyps, and physicians performing endoscopy should be well-versed in their applicability and efficacy.

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