Advances in diagnostic and therapeutic colonoscopy

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Purpose of review
We review current studies on endoscopic and technologic advances for the detection and treatment of colorectal neoplasia.

Recent findings
Improvements in adenoma detection have been shown to be possible with the use of high definition white light as well as water-related methods such as water exchange. Use of cap assist colonoscopy, when combined with water-related methods, has recently been shown to also improve the detection of adenomas. Narrow band imaging and confocal laser endomicroscopy may have an advantage of offering endoscopists the ability to make an ‘optical diagnosis’ with the possibility of discarding nonadenomatous tissue. Furthermore, educational interventions aimed at improving adenoma detection may have lasting effects on endoscopists’ adenoma detection rates. Lastly, endoscopic mucosal resection and endoscopic submucosal dissection are being applied for the treatment of large colorectal polyps, obviating the need for surgery in most instances. However, further studies are needed to establish the optimal methods for polyp resection.

Summary
Advances in endoscopic technology are being shown to enhance the detection of early cancers and precancerous lesions. However, these tools may be supplementary to a high-quality colonoscopy using excellent techniques, factors that are now being implemented in training programs.

Keywords
colonoscopy, colorectal cancer

INTRODUCTION
The advent of colonoscopy has revolutionized the way we evaluate luminal diseases of the colon. With colorectal cancer being the third most commonly diagnosed cancer, as well as the third major cause of cancer-related mortality in both men and women, colonoscopy offers an advantage of detecting cancer and removal of precancerous lesions [1]. Since its first successful use in 1966 by Overholt and Pollard [2], colonoscopy has undergone several makeovers, with improvements in scope design, imaging acquisition, and accessories for polyp sampling and retrieval. However, even with these technological advancements, the protective effect of colonoscopy is variable and is greater for the distal colon compared with the proximal colon [3–5]. Neoplastic lesions can still be missed, even in the presence of a good bowel preparation, careful inspection of the mucosa, and extended withdrawal time. Between 2 and 25% of adenomas may be missed during colonoscopy, with the miss rate increasing significantly for smaller sized polyps (particularly polyps < 5 mm) [6]. Furthermore, we now recognize that flat or subtle adenomas, particularly sessile serrated adenomas/polyps, can often be missed on colonoscopy, even with standard white-light imaging, and harbor potential for progression to invasive carcinoma via different pathways of carcinogenesis [7–11]. In this article, we review some of the most recent and noteworthy studies addressing the issues related to developments in diagnostic and therapeutic colonoscopy.
ADVANCES IN DIAGNOSTIC COLONOSCOPY

The true goal of a screening colonoscopy is to detect precancerous lesions and early malignancy, and thus prevent death from colorectal cancer. Several techniques and technologies have been studied with the goal to improve diagnosis of neoplastic lesions.

High-definition white light (HDWL) endoscopy allows more detailed, quality images on endoscopy, improving the discrimination of two closely located points [12]. Several studies have investigated the superiority of HDWL endoscopy compared with standard definition white light (SDWL) endoscopy. In a meta-analysis by Subramanian et al. [13], five studies involving 4422 patients demonstrated that HDWL increased adenoma detection by an absolute 3.5% compared with standard video endoscopy (SVE). There were no differences between HDWL endoscopy and SVE in the detection of high-risk adenomas (incremental yield of −0.1%). When grouped according to the overall adenoma detection rate of the studies (>50% or <50%), the pooled weighted mean difference in small adenoma detection was better with HDWL colonoscopy ($P = 0.035$).

Narrow band imaging (NBI) is a technology that filters the light to limit the illumination to narrow bands of blue and green light [14–16]. These wavelengths are absorbed by hemoglobin, and therefore can enhance the visualization of vascular-rich polyps. In a recent meta-analysis by Dinesen et al. [17*], when evaluating seven studies with over 2,900 patients that used NBI for adenoma detection, no statistically significant difference was found in the overall adenoma detection rate or in polyp detection rate with the use of NBI or white light colonoscopy (36% vs. 34%; $P = 0.413$ and 37 vs. 35%; 0.289, respectively). These findings are similar to the previous systematic review by van den Broek et al. [18], which did not show a statistically significant pooled odds ratio (OR 1.23) of detecting adenomas using NBI compared with SDWL endoscopy (95% confidence interval, CI = 0.93–1.61). When used in combination, however, wide-angle HDWL endoscopy and NBI have been associated with increased adenoma detection rates (ADR) [19].

NBI has also been suggested to be very accurate for in-vivo optical prediction of colon polyps, as well as for predicting surveillance intervals. This was demonstrated most recently in a systematic review by McGill et al. [20*]. Twenty-eight studies including 4,053 patients with 6,280 polyps concluded that NBI diagnosis of colon polyps has a very high accuracy, with a less than 90% sensitivity and negative predictive value, as well as 92.6% agreement between endoscopic diagnosis and disease for surveillance intervals. Based on the guidelines set by the American Society for Gastrointestinal Endoscopy (ASGE), in which a greater than 90% negative predictive value for adenomas and a greater than 90% accuracy rate for predicting surveillance intervals need be achieved to consider a ‘resect and discard’ approach [21], the findings in this large systematic review support such a strategy. Most recently, Singh et al. [22*] demonstrated that, by holding didactic learning sessions and providing feedback on performance, NBI was as accurate as HDWL endoscopy for predicting histology of diminutive colorectal polyps. Furthermore, studies are needed to confirm what was demonstrated in this meta-analysis.

Confocal laser endomicroscopy, either endoscope-based or probe-based (pCLE), is a technique that allows imaging of surface epithelium in vivo during endoscopy, with a 1000-fold magnification [23,24]. Unlike conventional colonoscopy, chro-moendoscopy, and NBI, it offers direct microscopic visualization of individual cells, lamina propria, extracellular matrix, and capillaries [23,24]. It has been previously demonstrated that pCLE is more sensitive than NBI or Fujinon Intelligent Color Enhancement imaging for correct classification of colorectal polyps, but overall specificity and accuracy were similar [25,26]. However, when combined, pCLE and NBI reached an overall accuracy of greater than 94%, which would meet the ASGE criteria of a greater than 90% accuracy in polyp histology prediction in order to apply a ‘resect and discard’ approach on colonoscopy [25]. However, the limitations of confocal laser endomicroscopy are well known, and include extra cost in the equipment, the time associated with using an extra device, and the need for an exogenous fluorophore, typically intravenous sodium fluorescein. Studies evaluating the combination of pCLE and other techniques and technologies have been studied with the goal to improve diagnosis of neoplastic lesions.

**KEY POINTS**

- Improving adenoma detection and early cancer detection may be possible with enhanced imaging modalities and accessories, in addition to a high-quality colonoscopic examination.
- Optical diagnosis of colorectal lesions may be possible with high accuracy with NBI and CLE, but further studies are needed to determine whether a ‘diagnose and discard’ strategy will be able to replace histopathology.
- The management of diminutive, small, and large colorectal polyps continues to be studied, with the ultimate goal being to completely resect all adenomatous tissues.
imaging modalities in targeted populations (e.g., patients at higher risk of colorectal neoplasia) will be helpful to determine in which setting pCLE should be routinely implemented.

More recently, i-Scan (Pentax, Tokyo, Japan) has been introduced as a diagnostic tool for colonic polyp detection and differentiation, enhancing the visibility of vessels and mucosal surface structures [27,28]. In a study by Pigo et al. [29], real-time assessment of polyp histology during colonoscopy was carried out among a group of five endoscopists. Correct histology was predicted in 138/150 cases, with an accuracy of 92%, and moderate inter-observer agreement. Furthermore, studies are needed to assess its use in polyp histology prediction.

Chromoendoscopy, a dye–spray-based technique that enhances the visualization of slight mucosal abnormalities, has also been studied in the setting of various colonic diseases [30]. Randomized studies have shown conflicting data with increases in overall ADR [31,32]. A practical clinical limitation to this technique is the extended time needed to apply the dye. This drawback is currently being investigated by studying the use of an oral colon-release formulation of methylene blue in the form of a tablet (Methylene Blue MMX) [33]. Preliminary data have shown an increase in polyp detection rate of 63.5% in a cohort of 96 patients [33]. Larger studies are being currently conducted.

Chromoendoscopy has been shown to be effective for the detection of flat dysplastic lesions in patients with inflammatory bowel disease, a high-risk population. Currently, chromoendoscopy is performed by using either a solution of indigo carmine or methylene blue and targeted biopsies are taken. In a meta-analysis by Subramanian et al. [30], in which six studies involving 1277 patients were studied, chromoendoscopy resulted in a significantly higher yield of flat dysplastic lesions (27%) compared with standard white light endoscopy, and a 44% increase in the proportion of lesions detected by targeted biopsies. Targeted biopsies with chromoendoscopy in the hands of an experienced endoscopist is now supported by several gastroenterologic associations, including the Crohn’s Colitis Foundation of America, European Crohn’s and Colitis Organization, and American Gastroenterological Association [34–36].

With its ability to deflect colonic folds while maintaining a clear view, cap-assisted colonoscopy (CAC) consists of attaching a 4-mm clear cap to the end of a colonoscope. It is now routinely used in the setting of endoscopic mucosal resection (EMR), and, more recently, being used to flatten mucosal folds and potentially improve adenoma detection. In a recent meta-analysis of randomized controlled trial by Ng et al. [37**], 16 randomized controlled clinical trials consisting of 8991 individuals were included. CAC demonstrated a marginal benefit in polyp detection over standard colonoscopy (response rates, RR: 1.08; 95% CI: 1.00–1.17) and reduced the time to cecal intubation (mean difference: −0.64 min; 95% CI: −1.19 to −0.10). However, there was no significant difference in the adenoma detection rate between the two groups (46.8 vs. 45.3% respectively; RR: 1.04; 95% CI: 0.90–1.19). Most recently, in another systematic review and meta-analysis by He et al. [38*], five abstracts and 14 full articles with a total of 9235 participants were studied. Pooled results showed that lesion detection rate per patient was greater for the CAC group (OR = 1.12; 95% CI, 1.02–1.22; P = 0.016). However, these effects appear to be minor, and thus future studies comparing CAC with advanced imaging modalities or in combination are needed.

**IMPROVING ADENOMA DETECTION THROUGH TRAINING AND EDUCATION**

There has been significant heterogeneity of studies showing inconclusive evidence that increasing withdrawal time and periodic review of individual outcomes improve adenoma detection rate. Most recently, Coe et al. [39**] conducted a prospective educational intervention with the aim to increase ADR by conducting an endoscopist training program. The Mayo Endoscopic Quality Improvement Program (EQUIP) training consisted of two training sessions. During the first one, measures of high-quality colonoscopy were reviewed, and during the second session, measures used to identify neoplastic lesions were reviewed. ADR increased from 36% at baseline to 47% in the group that was randomized to EQUIP training, whereas no improvement was seen in the group that did not undergo training. Preliminary analysis showed that this effect in improved ADR persisted at 6 months post-EQUIP training [40].

**IMPROVING TOLERANCE TO COLONOSCOPY AND CECAL INTUBATION**

Many water-related methods for colonoscopy have shown improvement in the outcomes in colonoscopy [41]. Water immersion, in which the removal of water is performed during withdrawal, and water exchange, in which residual feces is removed during the insertion phase of colonoscopy, are two methods that have been shown to be advantageous in reducing overall patient discomfort during colonoscopy [41,42***,43] in many observation and retrospective studies. Most recently, Leung et al.
[42**] performed a systematic review of all randomized, controlled trials (RCTs) that compared water-aided methods and air insufflation during colonoscopy. In 11 RCTs, both water-related methods were associated with reductions in pain score, with a higher reduction of qualitative pain scores seen with the water exchange method compared with water immersion. In nine published reports, a mixed pattern of increases and decreases in ADR was observed with water immersion compared with air insufflation (combined overall ADR 32.9 vs. 34.8%; P = not significant), whereas a higher ADR was observed with use of the water exchange method compared with air insufflation (50.6 vs. 40.9%; P = 0.026). Furthermore, in three studies, a higher ADR proximal to the splenic flexure was observed with the water exchange method when compared with air insufflation (combined proximal overall ADR 45.8 vs. 35.1%; P = 0.0072). Future studies comparing these two water-related methods and air insufflation are warranted.

CAC has also been combined with the water exchange method. Most recently, in a retrospective, single-center, single-endoscopist study by Yen et al. [44*], 100 consecutive patients who underwent CAC combined with water exchange colonoscopy were compared with 101 patients who underwent standard air insufflation colonoscopy. The combined method group had a higher polyp detection rate and ADR, as well as proximal colon ADR and proximal colon serrated polyp detection rate. The number of adenomas and mean number of proximal colon serrated polyps per colonoscopy were also significantly higher. Furthermore, prospective studies are needed, but, nevertheless, this provocative study does raise the question of whether more endoscopists should be using combination methods of water exchange and CAC to improve quality outcomes in colonoscopy.

**OPTIMIZING POLYP RESECTION: FORCEPS, MUCOSAL RESECTIONS, AND SUBMUCOSAL DISSECTIONS**

‘Interval cancers’, or colorectal cancers that are detected after colonoscopy, are thought to be because of prior missed lesions, lesions with a rapid progression to adenocarcinoma (based on more aggressive genetic features), and/or incompletely resected lesions [45**].

The optimal method for the removal of polyps less than 1 cm is unknown. A previous study by Eththymiou et al. [46] demonstrated an astonishing 39% complete polypectomy resection rate using cold biopsy forceps for diminutive polyps (≤ 5 mm). However, a major drawback to this study was the evaluation of only diminutive polyps, which did not reflect a true practice setting. In a recent study by Pohl et al. [45**] 346 neoplastic polyps between 5 and 20 mm were removed by 11 gastroenterologists, and 10.1% lesions were incompletely resected. Incomplete resection rate (IRR) increased with polyp size, being significantly higher for large (10–20 mm) than small (5–9 mm) neoplastic polyps, as well as for sessile serrated adenomas/polyps than for conventional adenomas. This study also found a 3.4-fold difference between the highest and lowest IRR (6.5–22.7%) among the endoscopists. This study raises several issues for future studies. First, randomized studies are needed to determine the most effective method for the resection of polyps less than 1–2 cm. Second, these proposed findings will need to be implemented across practices, which will ultimately require re-training endoscopists, and furthermore raise issues of cost and time management.

EMR and endoscopic submucosal dissection (ESD) are techniques that are now being used with more frequency to resect larger colon polyps (≥ 2 cm), including carcinoma with minimal invasion. When successful, these techniques can allow avoidance of a surgical operation, reducing the overall morbidity associated with polyp resection [47**]. EMR and ESD techniques are still evolving, and one of the most important issues involves determining the optimal techniques and equipment to obtain a well-tolerated and complete (en bloc) resection and removal of all neoplastic tissue. In a retrospective study by Woodward et al. [47*], 423 colonic lesions (size range 1.2–8.0 cm) removed by EMR (with either isotonic saline or hydroxypropylmethylcellulose) in 313 patients were studied, revealing a 12% rate of residual neoplasia at first follow-up endoscopy. The use of piecemeal resection method was independently associated with residual neoplasia, and thus additional procedures were needed to completely resect all neoplastic tissue. Furthermore, because of the concern of residual tissue, many endoscopists use argon plasma coagulation (APC) to the margins of the lesion. However, the data is mixed, with some studies showing APC to be effective in ablating residual tissue, but other studies demonstrating it to be an independent predictor of adenoma recurrence [47*,48,49]. In contrast, ESD provides a greater likelihood for en-bloc resection with the use of an ESD knife and liberal submucosal injection [50,51]. When compared with EMR, ESD has been shown to result in higher en-bloc resection (84 vs. 33%; P < 0.0001) and curative rates (2 vs. 14%; P < 0.0001); however, drawbacks include longer procedure time and increased perforation rate [52]. Prospective studies are needed to
determine the optimal tools and techniques to achieve the safest and most complete resection.

CONCLUSION

Several methods for the improvement in adenoma and early carcinoma detection in colonoscopy have been identified that involve enhancement in imaging technology as well as technique. Management of colorectal lesions continues to be investigated, with the optimal methods for the resection of small and larger polyps still not yet completely defined but, nevertheless, recent data showing promising findings.

Acknowledgements

The authors would like to acknowledge the contributions of Kelly Viola in the Department of Academic and Research Support at the Mayo Clinic in Jacksonville, FL for her help with preparing this manuscript.

Conflicts of interest

Dr Gómez has no conflicts of interest. Dr Wallace receives research funding from Olympus and is a consultant to Cosmo Pharmaceuticals.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest
■■ of outstanding interest

23. Prospective study demonstrating that, through the use of training sessions and performance feedback, NBI may be a superior imaging modality for differentiating diminutive colorectal lesions, supporting the use of a ‘diagnose and discard’ strategy.
38. Pooling 16 randomized controlled studies, this meta-analysis demonstrated that CAC may not necessarily improve the detection of adenomas, but did reduce time to caecal intubation.
40. Similarly to the previous study by Ng et al. [37], this review indicates a marginal benefit of using CAC for poly detection, but, similarly to the other study, there was no significant improvement in adenoma detection with only use of a cap attached to the end of the colonoscope.
39. Coe SG, Crook JE, Diehl NN, et al. An endoscopic quality improvement program improves detection of colorectal adenomas. Am J Gastroenterol 2013; 108:219–226. Excellent original study demonstrating the positive effects of didactic learning sessions and performance feedback on improvement in adenoma detection. This study is being used as a model for future educational interventions across academic and private gastroenterology practices.


42. Leung FW, Amato A, Ell C, et al. Water-aided colonoscopy: a systematic review. Gastrointest Endosc 2012; 76:657–666. This systematic review demonstrated that, overall, water-aided colonoscopy may not necessarily improve adenoma detection compared with conventional air insufflation; however, the water-exchange method, compared with the water immersion method, may be slightly advantageous in detecting more adenoma compared with air insufflation alone.


44. Yen AW, Leung JW, Leung FW. A novel method with significant impact on adenoma detection: combined water-exchange and cap-assisted colonoscopy. Gastrointest Endosc 2013; 77:944–948. When used alone, both cap-assist colonoscopy and water-aided colonoscopy may not improve adenoma detection. However, when used in combination, this single center study did show very promising results of increased adenoma detection.

45. Pohl H, Srivastava A, Bensen SP, et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. Gastroenterology 2013; 144:74–80. This study raises an important issue on factors related to interval colorectal cancers, with emphasis on incomplete polypectomy. The investigators demonstrated that at least 10% of neoplasms were incompletely resected, with a higher risk for larger polyps and sessile serrated adenomas.


