Advances in CRC prevention: screening and surveillance

Running title: "Enhancing detection and resection in colonoscopy"

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ABSTRACT

Colorectal cancer (CRC) is amongst the most commonly diagnosed cancers and causes of death from cancer across the world. CRC can, however, be detected in asymptomatic patients at a curable stage, and several studies have shown lower mortality among patients who undergo screening compared to those who do not. Using colonoscopy in CRC screening also results in the detection of precancerous polyps that can be directly removed during the procedure, thereby reducing the incidence of cancer. In the past decade, convincing evidence has appeared that the effectiveness of colonoscopy as CRC prevention tool is associated with the quality of the procedure. This review aims to provide an up-to-date overview of recent efforts to improve colonoscopy effectiveness of by enhancing detection and improving the completeness and safety of resection of colorectal lesions.

INTRODUCTION

Approximately 50 years after the introduction of diagnostic colonoscopy and polypectomy[1, 2], colonoscopy is firmly entrenched across much of the world as one of the most commonly performed and valuable procedures in clinical medicine. In many countries, colonoscopy is the primary imaging test to evaluate patients with colorectal symptoms, particularly those with bleeding. Colorectal bleeding in its various forms, including hematochezia, iron deficiency anemia, melena with a negative upper endoscopy, and positive fecal blood test, has a substantially higher predictive value for colorectal cancer (CRC) compared to colonoscopy in patients with non-bleeding symptoms or no symptoms [3, 4]. Excellent detection as well as same session biopsy and potentially also treatment have made colonoscopy the test of choice in bleeding patients.

In addition to prevention of colorectal cancer deaths through detection of curable cancers, colonoscopy can also prevent most incident cancers. As CRC develops gradually from premalignant adenomatous and serrated polyps, colonoscopy with polypectomy provides an opportunity to halt this process. Evidence for cancer prevention by colonoscopy is found in a randomized controlled trial of fecal blood testing [5], a surveillance study [6], cohort [7] and case control studies [8-10], and in large trials evaluating variable detection [11, 12]. CRC prevention via colonoscopy is achieved through effective detection and resection of precancerous lesions. No other available imaging technique matches or even approaches the sensitivity of colonoscopy for precancerous lesions, particularly for serrated polyps [13].

Despite its strengths, colonoscopy has certain disadvantages and limitations. Colonoscopy has a relatively long learning curve, and fully trained colonoscopists demonstrate marked variation in polyp detection [14, 15], cancer prevention [11, 12], polyp resection [16], and use of appropriate screening and surveillance intervals [17]. Colonoscopy carries risks associated with bowel preparation, sedation, aspiration, perforation, and splenic injury. Patients subjected to resection of all exposed lesions sometimes suffer post-polypectomy hemorrhage, including from lesions with an extremely low risk of ever causing harm, and which would not have been detected by other imaging or screening modalities.

Delivering high quality colonoscopies should be the aim of all endoscopists. In this review we summarize ongoing efforts to improve the quality of colonoscopy as a detection and resection tool, as well as efforts to improve its safety and cost-effectiveness.

QUALITY IN COLONOSCOPY

Colonoscopy is currently regarded as the reference standard to detect and prevent CRC. It is widely practiced and generally safe and accurate, but not perfect. In the past decade, worldwide awareness on the importance of quality assurance of colonoscopy has emerged. Tandem colonoscopy studies, in which patients undergo colonoscopy twice in the same day, provided the first direct evidence that colonoscopy systematically misses small colorectal polyps, and some larger polyps [18, 19]. Further, there was evidence that some endoscopists missed more polyps than others, and this variable detection was shortly associated with examination technique during withdrawal [20]. An audit study in 2003 in the UK identified a remarkably low adjusted cecal intubation rate of only 56.9%, demonstrating that in some countries poor performance extended to insertion technique and the ability to achieve complete examinations [21]. These findings were the origins of widespread efforts to improve colonoscopy performance and reduce operator dependence in basic colonoscopy outcomes. Subsequently, a vast amount of research on quality and accuracy of this procedure has appeared in literature.

Regarding detection, colonoscopy is not fully protective for the development of post-colonoscopy CRCs, which are disproportionately located in the right-sided colon [8, 22-26]. Post-colonoscopy (interval) CRCs are defined as CRCs diagnosed after a complete negative or clearing colonoscopy and diagnosed before the recommended surveillance or screening interval [27]. The majority of those post-colonoscopy cancers appears to be the result of procedural related factors and not related to patient- or biological factors [27]. This is supported by a study reporting that 23% of patients with a newly diagnosed CRC larger than 2 cm had undergone a colonoscopy within the preceding 30 months [28]. Certainly to achieve optimal effectiveness of this invasive procedure, the procedure should have proper indications, the interval between surveillance intervals should be consistent with guideline recommendations, and the benefits of the procedure should outweigh the complication risk, burden and other disadvantages of an invasive procedure.

In an effort to assess the quality of colonoscopy between endoscopists and practices, various quality indicators have been proposed in guidelines [29-32]. Ideally such indicators are based upon clear evidence, and for several parameters such evidence is available. For each phase of the colonoscopy, i.e. preprocedure, intraprocedure and postprocedure, registration of quality indicators is recommended (TABLE A) [29].

A colonoscopy is only complete and accurate if the whole colon, including the cecum, is visualized. Low cecal intubation rates (CIRs) have been associated with higher rates of proximal post-colonoscopy cancers [33]. Therefore, cecal intubation should be confirmed and photodocumented by endoscopic pictures of the cecal landmarks, ileocecal valve and appendiceal orifice. Effective

endoscopists should achieve cecal intubation rates of at least 90%, and when adjusted for strictures, stenosis and poor bowel preparation or in healthy adults with an indication of screening at least 95% [29-32].

To ensure safe intubation and optimal inspection, adequate bowel preparation is indispensable. Poor bowel cleansing has been associated with incomplete colonoscopy, prolonged procedure time and reduced yield. Studies demonstrating the correlation between bowel prep quality and post-colonoscopy CRCs are, however, not available yet[31]. Assessment of the quality of the bowel preparation is essential and should be documented with a validated scale, for example the Boston Bowel Preparation Score (BBPS)[34]. This score is used after optimal cleaning and rinsing, and thus a judgment of the final situation at which inspection took place. BBPS scores of ≥ 2 in each of three colon segments correlated with adequate bowel cleansing[35], and should allow the colonoscopist to recommend a screening or surveillance interval appropriate to the findings of the examination, without the need to shorten the recommended interval based on preparation quality. Consistent with this conclusion, segmental scores of ≥ 2 predict a lower risk of polyps in that segment at follow up colonoscopy[36].

The bowel-cleansing regimen is regarded as burdensome by many patients. The optimal bowel preparation is effective, tolerable and safe, also for individuals with comorbidities. Multiple regimens exist, which can be roughly divided into high and low volume preparations. The high volume preparations are the 4 liter polyethylene glycol -electrolyte lavage solutions (PEG-ELS), which are suitable for all patients and which, when given in split doses, are likely the gold standard for effectiveness. 4 L PEG-ELS causes less fluid and electrolyte shifts than hyperosmotic preparations, and are often preferred for patients with renal insufficiency, heart failure, and decompensated liver disease. Because of their high level of effectiveness, 4L PEG-ELS preparations are preferred in many units for patients with clinical features that predict difficulty achieving adequate preparation, including those with chronic constipation, obesity, diabetes mellitus, and those on opioids or tricyclics. Patients with a history of ineffective preparation are often given >4L of PEG-ELS. Conversely, high volume is often difficult to tolerate and some patients cannot complete ingestion. For many healthy outpatients, low volume preparations provide high quality preparation and improved tolerance. Hyperosmotic , low volume preparations based on sodium phosphate or sodium sulfate are effective, though rare instances of renal failure from sodium phosphate have markedly reduced its use in the U.S.. Other low volume preparations include combinations of 2L PEG-ELS plus ascorbate, and in the U.S there is substantial use of non-FDA approved regimens based on PEG3350 in sport drinks, or on magnesium citrate, or combinations of these agents. Other low volume preparations include combinations of 2L PEG-ELS plus ascorbate as well as “home-made”

preparations based on PEG3350 in sport drinks, which is often combined with magnesium citrate. Split-dosing, i.e. giving half the regimen the evening before colonoscopy and half on the morning of colonoscopy, improves bowel prep quality and detection compared to evening before regimens. "Same-day" dosing, in which the entire preparation is given the morning of colonoscopy, is also effective. The US Multi-Society Task Force recommended that colonoscopy programs should be able to achieve adequate bowel preparation in at least 85% of outpatient examinations[37]. This document as well as the European guideline can be consulted for best practice[37, 38].

Thorough inspection of the colonic mucosa is crucial to optimize its effectiveness. Most mucosal inspection takes place during withdrawal of the endoscope from cecum to rectum. Taking at least 6 or more minutes to inspect the colonic mucosa is associated with an increase in adenoma detection rate (ADR).[14] The ADR is currently considered one of the most important evidence-based quality indicators for colonoscopy. Two landmark papers have demonstrated that the ADR of individual endoscopists is associated with the risk of post-colonoscopy CRCs [11, 12]. Patients scoped by a colonoscopist with an ADR of <20% had a 10 times higher risk for post-colonoscopy cancer than when scoped by an endoscopist with an ADR >20% [11, 12]. Most guidelines recommend an ADR of at least 20-25% in screening colonoscopies. Although a clear evidence-based quality indicator, ADR also has some inherent limitations. First, the target ADR depends on the population scoped. When colonoscopy is used as a primary screening method, average ADR is expected to be relatively low but above 20-25% [29-32], whereas ADRs in FIT-positive screenees have a much higher median of at least around 50% [39, 40]. Other risk factors like patients' sex also heavily influence target ADRs [41]. Besides, the ADR does not evaluate the total number of adenomas per individual patient, which is especially important in populations with high ADRs like FIT-positive screenees. To measure ADR, the histopathology result must often be manually derived from a pathology database, making it a more complicated parameter for monitoring purposes. However, while conventional adenomas are the clear precursors of the majority of colorectal cancers, some serrated lesions (sessile serrated lesions and traditional serrated adenomas) are precursors for CRC and should also be detected and removed. Those serrated polyps are not included in ADRs. A few recent studies suggested the proximal serrated polyp detection rate as quality parameter for high quality colonoscopy, however the association between a serrated polyp detection rate and post-colonoscopy CRCs has yet to be determined [42, 43]. Further, differentiation of hyperplastic polyps (which are generally considered to not be precancerous) from sessile serrated lesions is still generally subject to large interobserver variation in pathology interpretation [44], which complicates developing an endoscopic quality target for detection of sessile serrated lesions.

Resection is an emerging area for quality measurement. A single center study found that effective eradication of polyps 5-20 mm in size varied 3 fold between endoscopists[16]. A tool developed and validated in Europe to assess polypectomy competency (The Direct Observation of Polypectomy Skills or DOPyS) [45] was recently used to assess 13 high-volume screening colonoscopists [46]. Among all polypectomies observed and scored blindly, only 64% were judged competent, and between endoscopists competent resections varied from 30% to 90% of polypectomies. Specific competencies that varied between endoscopists included achieving the optimal positioning of the polyp, determining the extent of the lesion, maintaining a stable endoscope position, accurately placing the snare, achieving an adequate margin of normal tissue, examining the resection site for residual polyp and removing residual polyp when present. Detection as measured by ADR and competency in polypectomy had little correlation. Thus, a validated tool is now available both for teaching polypectomy and assessing polypectomy competency.

Assessment of patient discomfort and complications of colonoscopy is also essential for quality assurance purposes. Use of carbon dioxide insufflation reduces post procedural pain and hospitalization for observation compared to room air insufflation [47]. Discomfort is also related to the depth of sedation, but deep sedation is associated with an increased risk for complications, particularly aspiration pneumonia[48]. The overall risk of complications after colonoscopy increases when individuals receive anesthesia services [49]. Sedation practice varies across centers, countries and continents and seems to be heavily influenced by expectations and beliefs of doctors and patients. For quality and auditing purposes, doses of sedatives and depth of sedation should also be reported and related to the comfort score. Recently, the composite performance indicator of colonic intubation (PICI), combining cecal intubation rate, comfort, and sedation was proposed [50]. Achieving PICI was significantly associated with the detection of one or more polyps, compared with procedures that did not achieve PICI.

The most ideal quality indicator for colonoscopy, however, is the rate of post-colonoscopy CRCs. To allow comparison, a clear definition on the taxonomy of interval cancers, including post-colonoscopy cancers, is of utmost importance and has been established [27]. However, whenever feasible, post-colonoscopy CRCs should be measured over a long time-span and enabled by accurate detection of those cancers. This requires large numbers of colonoscopy, structured reporting, and reliable coupling to a cancer registry. As post-colonoscopy CRCs are relatively rare, this parameter is less useful as a quality indicator for individual endoscopists, but should rather be used as an indicator at the level of a center or a national screening program.

These and other current quality indicators were gradually developed as new evidence emerged. Ongoing research will allow development of new indicators that are more accurate and comprehensive in their depiction of quality. Assessment and benchmarking of those quality indicators forms the basis for continuous quality improvement. Auditing and benchmarking, including provision of training to underperformers, demonstrated a benefit on CIR, ADR, post-colonoscopy CRCs and sedation-use [51-53]. To facilitate standardized and complete reporting on important quality indicators, structured terminology and colonoscopy reporting systems should be encouraged [54-56].

ADVANCED DETECTION TOOLS FOR COLORECTAL LESIONS

From previous studies it is known that adenomas most prone to be missed at colonoscopy are small (<10 mm), flat and located at the proximal side of haustral folds or the inner curve of the hepatic or splenic flexure. [24, 57, 58] In a systematic review of tandem colonoscopy studies published between 1991 and 2004, a remarkable 22% pooled miss-rate for all polyps was reported [57]. The miss-rate for lesions measuring at least 1cm was 2%, for small polyps 13%, and for diminutive polyps 26% [57]. In line with these results, a simulation study using CT-colonography estimated that 7.8% of the colonic surface is not visualized during standard colonoscopy using current wide-angle colonoscopies (170 degrees) [59].

In the past years, high-definition white light endoscopy has become the standard of care for endoscopy, and guidelines advice their routine use [29, 60, 61]. Besides, several advanced technologies and devices have been developed aiming to improve polyp detection. These techniques include advanced imaging techniques as well as techniques that aim to increase visualisation of the colonic surface (FIGURE A). However, as discussed in the previous paragraph, ascertaining basic quality measures remains of paramount importance.

When assessing clinical studies on new endoscopic detection techniques, it is important to realize that blinding for the technique is impossible in these trials. Therefore, close attention should be given to the quality of such studies, and investigators should try to make the two modalities comparable in terms of patient population, quality of endoscopists, their experience with the new techniques as well as all basic quality indicators.

Most advanced imaging techniques are based on the principle that the mucosal structure of (pre-) malignant lesions differs from the surrounding healthy tissue and consequently differ in their ability to absorb and reflect light. This trait is then used to depict such lesions differently, thereby facilitating their detection. These techniques include virtual chromoendoscopy with narrow band

imaging (NBI), iScan, flexible spectral imaging color enhancement (FICE), blue laser imaging (BLI) and autofluorescence imaging (AFI). However, despite the plausibility of this approach and the early positive outcomes for these techniques as a detection-tool [62-64], the pooled outcomes of these studies suggest that ADRs are not conclusively improved by the use of these imaging techniques [60, 65, 66]. It seems that when endoscopists become acquainted with this new technique and detect lesions they did not see before, this also affects their performance with (high-definition) white light endoscopy [62, 67].

From CT-colonography studies it is known that especially adenomas located at the proximal side of haustral folds or the inner curve of the flexures are more prone to be overlooked at colonoscopy, as they lie outside the regular field of view of colonoscopy. [68] In order to increase visualisation of the colonic surface aiming to improve adenoma detection rates, several surface exposing technologies have been proposed. These surface exposing technologies include cap-fitted colonoscopy, Endocuff or EndoRings assisted colonoscopy, through-the-scope optical devices, full-spectrum endoscopy (FUSE) and (prototype) wide angle view colonoscopies. For these techniques, results on adenoma detection and miss rates have been variable between studies [69-77]. This is also true for the FUSE system: a first study showed large differences in miss rates [71], but this positive result could not be confirmed in a subsequent large comparative randomized trial [72]. This example underlines the fact that large, randomized trials in daily practice are required to determine whether an improved ADR remains true in broader practices and whether the use of these endoscopes and devices is cost-effective and clinically warranted [77].

CHARACTERIZATION OF LESIONS

For decision-making in the management of colorectal lesions, lesion characterization is crucial. First of all, the entire surface should be examined for factors associated with deep (>1000 microns) submucosal invasion of cancer. These factors include morphologic features like ulceration, changes in the pit pattern, and disruption of the surface vessel pattern[78]. Often changes in the pits and vascular patterns that denote deep submucosal invasion are evident only in areas of surface ulceration. Deep submucosal invasion is associated with a higher risk of lymph node metastasis[79, 80], and is generally a contraindication to both EMR and ESD. Such endoscopic features are generally specific for deep submucosal invasion (or even greater depth) but lack sensitivity for submucosal invasion generally[81]. Thus, the modern endoscopist should be familiar with other endoscopic features that are associated with an increased risk of submucosal invasion generally, though the depth of invasion may be superficial (<1000 microns). When superficial submucosal invasion is

present, endoscopic resection may be considered curative in some cases if it was performed en bloc. Thus, when these "other" endoscopic factors are present, en bloc resection by EMR or ESD is often preferred if feasible. These "other" factors associated with submucosal invasion generally include non-granular morphology (particularly if associated with depression), and the presence of a large nodule in an otherwise flat lesion (see below)[81, 82]. Recognition of deep submucosal invasion as well as other features associated with an increased risk of any invasion by non-expert endoscopists can be further improved, and training for endoscopic diagnosis for early invasive cancers is urgently needed to ensure optimal clinical practice for treatment of these lesions [83]. To systematically describe a lesion and assess the risk of deep as well as any submucosal invasion, several morphological classification systems have been developed. These include location, size, Paris classification, lateral spreading tumor classification (if applicable) and evaluation of the mucosal surface pattern with high-definition endoscopes and advanced imaging techniques [84] (FLOWCHART 1).

The size of a lesion is directly related to the chance that the lesion harbors invasive growth into the submucosa. One to five mm ("diminutive") lesions have a very low risk of invasiveness, whereas 6-9 mm ("small") lesions have a tiny risk of 0 to 0.4% [85]. For lesions of 10mm and larger, the risk of cancer gradually increases from 2.4% for 10 to 20 mm lesions to a maximum of 19.4% for polyps measuring more than 20 mm in size [86]. However, measuring polyp size during colonoscopy is subject to inter-observer variability, and a gold standard is not available. A recent proof-of-concept simulation study using a visual grid cue during endoscopy to measure polyp-size showed promising results [87] and should be further explored. As long as objective tools for daily practice are not available, ideally an open snare or biopsy forceps with known size should be used to size a lesion before resecting it.

The Paris classification divides polyps into several categories depending on their morphology: pedunculated (0-1p), sessile (0-1s), slightly elevated (0-IIa), flat (0-IIb), slightly depressed (0-IIc) and excavated (0-III) [88]. Especially recognizing and classifying depressed and excavated morphology seems relevant. While rare, lesions of this specific morphology are associated with an increased risk of invasive growth. The term laterally spreading type (LST) lesion refers to lesions of at least 10mm [89]. For this type of lesions a separate classification is used, dividing these in granular and non-granular types. An increasing size, non-granular type LSTs and LSTs with a large dominant nodule >10mm in size are associated with an increased risk of harboring invasive growth [81, 90-94].

The introduction of high-definition endoscopes allows for precise evaluation of mucosal surface patterns, the most helpful tool to predict histopathology of polyps. For colorectal lesions,

several surface pattern classification systems as the Kudo, NICE, WASP and JNET classification for both chromoendoscopy and virtual chromoendoscopy have been validated [78, 95-100].

Besides assessment of submucosal invasion, accurate characterization could facilitate a "Resect and Discard" strategy, in which diminutive polyps are resected after endoscopic characterization but do not have to be submitted for histopathology. Diminutive polyps in the rectosigmoid endoscopically deemed to be hyperplastic (or at least serrated) at histopathology can be reasonably left in place [101]. Only about 2% of lesions deemed hyperplastic in the rectosigmoid are found to be sessile serrated lesions on histopathology [102]. In 2011, the American Society of Gastrointestinal Endoscopy published the so-called Preservation and Incorporation of Valuable Endoscopic Innovation (PIVI) guideline containing performance thresholds for this purpose [101]. For diminutive polyps that are diagnosed with high confidence, in combination with outcomes of histolopathology assessment of larger polyps and those characterized with low confidence, endoscopists should achieve at least 90% agreement between surveillance intervals that he/she predicted by optical diagnosis and the definitive surveillance intervals that are based on histopathology. Besides, they should achieve at least 90% negative predictive value for neoplastic polyps in the rectum and sigmoid, i.e. at least 90% of polyps they assess as non-neoplastic are indeed not neoplastic at histopathology [101]. However, whereas expert endoscopists are able to achieve the PIVI-thresholds for diminutive polyps [103-105], studies with endoscopists working in daily clinical practice have shown conflicting results [106-111]. This difference could be explained by differences in time and dedication, but also in training and feedback of performance. Recently, the UK national health policy has endorsed the Resect and Discard strategy for implementation in clinical practice [112]. For optimal cost-effectiveness however, studies evaluating the effect of validated training programs and regular feedback on PIVI-tresholds in daily practice are essential and underway. Other potential barriers for implementation of the strategy are acceptability by the public and potential medical-legal risk of Resect and Discard when the policy has been implemented and there is the inevitable occurrence of an interval cancer. In these instances the cause of the interval cancer will likely be a missed lesion nearby in the colon rather than a discarded diminutive lesion. The defense will depend on development of clear society and institutional policies and stored high-quality photographs of discarded lesions.

RESECTION OF LESIONS

The CARE study demonstrated that the problem of variable performance in colonoscopy also extends to polypectomy, identifying a threefold difference between endoscopists in rates of effective polyp resection [16]. Increasing polyp size and serrated histology also predicted ineffective resection [16].

Polyps of all predicted histologic types and sizes identified proximal to the sigmoid colon are typically resected, though the wisdom of resecting diminutive polyps has recently been challenged [113]. Despite the very low risk of cancer in diminutive lesions, available data on the natural history of small and diminutive polyps are in general confined to 2-3 years of observation [85]. These limited data, in combination with uncertainty about patient acceptance of leaving lesions in place for long intervals, means that resection of even diminutive lesions other than distal colon hyperplastic polyps is likely to remain standard for now.

Table B (TABLE B) shows several current and recent trends in endoscopic resection in the colorectum. Several resection techniques are currently available (FIGURE B). First, the use of hot forceps for removal of diminutive polyps has been largely abandoned, both because it is ineffective, leaving residual polyp in place in 17-53% of lesions [114 115] and because it creates thermal injury that is associated with unnecessary risk, especially of perforation. Animal studies show that thermal injury is much harder to control with hot forceps compared to snaring, even with optimal technique [116]. Further, guidelines stipulate that hot forceps should not be used for removal of lesions larger than 5 mm [117]. Currently, the use of hot forceps in colonoscopy has been essentially reduced to the process of avulsion during EMR, in which flat areas (often associated with submucosal fibrosis) that are resistant to snaring, are removed with forceps (either hot or cold) rather than ablated [118].

Second, the use of cold resection techniques rather than hot resection is increasing generally in polyp resection, primarily because it reduces risks. Cold resection has been found histologically to cause less injury to submucosal vessels compared to hot snaring [119]. In a randomized controlled trial comparing cold to hot snaring of small polyps in anticoagulated patients, cold snaring reduced the risk of delayed hemorrhage from 14% to 0% [119]. Similarly, conversion to cold snaring reduced the risk of delayed hemorrhage in an observational study performed in a single practice [120]. Several randomized controlled trials found that rates of complete polyp resection with cold snaring were not different from hot snaring [121-123]. One study found that resection of small polyps with a thin-wire stiff snare made specifically for cold snaring resulted in superior complete resection rates compared to a standard snare [119], but results have been inconsistent [124]. Cold snaring is also considerably more time-efficient that hot snaring in some studies, reducing total procedure time by more than 5 minutes [125, 126]. This is likely because there is no need to set up the cautery and patient grounding equipment before proceeding with resection. Cold snaring of larger lesions, or when mechanical

tension is needed for transection, commonly leaves a cord of white submucosal tissue protruding from the defect, but the cord is devoid of residual polyp and represents submucosal tissue [127]. The cold resection technique has been extended to lesions over 1 cm in size [128] and also to performance of endoscopic mucosal resection (EMR), particularly for serrated lesions, and it appears effective in initial studies [129] and is nearly devoid of complications. Additional data regarding effectiveness of cold EMR are needed.

A third trend is toward cold snare resection of diminutive and small lesions over cold forceps resection. When polyps reach a size of 4mm, snare resection is more effective and efficient compared to cold forceps methods [130]. Forceps methods are particularly inappropriate if piecemeal resection is required. A general rule that seems reasonable is that forceps resection of 1-3mm polyps is appropriate, particularly if it can be accomplished in one bite, and large capacity and jumbo forceps are more effective in this regard compared to standard forceps [131].

A fourth trend is an increasing use of EMR over standard snare polypectomy techniques. EMR has emerged as the treatment as choice for nearly all flat and sessile lesions ≥ 20mm in size in the colorectum. A series of studies performed by multiple groups of expert endoscopists has delineated the effectiveness, safety, and superiority of EMR over surgical resection for lesions in this size group [132-134]. Modern EMR depends closely on advanced imaging and interpretation skills. In the absence of overt endoscopic evidence of deep submucosal invasion, morphologic features such as a nongranular surface, a large sessile component, and depression are predictors of submucosal of invasion [81, 94] that warrant *en bloc* resection when feasible, and appropriate handling of resected specimens by the endoscopist and pathologist. EMR is particularly important for serrated lesions, because submucosal injection of a contrast agent clearly delineates the lesion perimeter during piecemeal removal [135, 136]. The technique is considered appropriate for serrated lesions in the 10-20mm size range [137]. Inclusion of a contrast agent stains the submucosa so that any muscle injury is readily seen (as the target sign) leading to easy repair and prevention of delayed perforation [138]. Submucosal injection fluids that are more viscous than saline create superior submucosal cushions and improve the efficiency of resection [139]. Modern EMR emphasizes resection by snaring, with avulsion as a rescue method, rather than ablation of residual visible polyp tissue [118]. Cold resection or use of microprocessor controlled electrocautery with emphasis on cutting over coagulation current are increasingly utilized [132]. Some experts endorse performance of EMR under water and without submucosal injection. When the lumen is filled with water, the mucosa “floats” away from the muscularis propria, providing a margin of safety for resection in the submucosal plane without submucosal injection. Under water EMR allows en bloc resection of a larger group of lesions [140], because submucosal injection typically increases lesion size. Potential disadvantages include difficulty

identifying muscle injury because of absence of submucosal staining, and peritoneal contamination if perforation occurs.

Endoscopic submucosal dissection (ESD) has advantages compared to EMR including a lower recurrence rate at first follow up. Also, a group of patients with superficial (SM1; upper one-third) submucosal invasion can avoid surgery compared to similar patients after piecemeal EMR [141]. Despite these advantages, the expansion of ESD in western countries is often delayed by low numbers of experienced practitioners, long learning curves for ESD, long procedure times, higher perforation rates compared to EMR, and lack of appropriate reimbursement. Advances in ESD technology, combined with the attractiveness of *en bloc* resection, are likely to increase the utilization of colorectal ESD in western countries over time. However, effective use of ESD depends on the appropriateness of the clinical indication [142]. An emerging area of resection that is receiving increasing attention and bypasses both EMR and ESD is the full thickness resection device [143]. This endoscopic technique has been developed to allow accurate diagnosis and potentially definitive treatment for lesions invading any depth of the submucosal layer of the colonic wall. It combines resection of the entire colonic wall performed after secure closure of the expected defect by the use of a modified over-the-scope-clip mounted on a cap with a preloaded snare.

FUTURE TRENDS

Table C (TABLE C) lists reasonable expectations for developments in colonoscopy relative to cancer prevention and cost-effectiveness of colonoscopy for neoplasia management. Several of the predicted developments constitute major paradigm shifts in colonoscopy application. However, given the steady advances in instrumentation, examination effectiveness, and polypectomy technique, reconsideration of fundamental approaches is appropriate and necessary.

There will be continued challenges to the role of colonoscopy as a primary screening strategy. New screening strategies based on risk stratification [144] may direct screening colonoscopy to the highest prevalence screening populations, while lower prevalence populations are screened with inexpensive, noninvasive, and highly specific tests like FIT. However, the challenges to achieving adherence to repetitive fecal screening outside of organized screening programs will make screening colonoscopy, with its potential for long term protection, continue to be an attractive screening approach in the opportunistic screening setting [145]. Continued progress in combined assays such as FIT-fecal DNA and other molecular markers can be expected to further displace screening colonoscopy, though for programmatic screening lower cost DNA tests are needed [146, 147]. As a

further development, these tests would ideally only detect those premalignant lesions that are close to developing into cancer. If this becomes reality, screening colonoscopies are likely to be replaced by therapeutic colonoscopies in those patients with relevant lesions at a truly high risk for CRC.

Second, there are potential consequences of the quality movement and the trend toward higher ADRs and the detection of increasing numbers of diminutive lesions. One consequence is that patients in the 60-70 year range with negative colonoscopies performed by high ADR colonoscopists would be reasonably expected to have a very low risk of ever developing CRC. Such patients might be advised to either stop screening or have only once or twice in a lifetime a screening colonoscopy. Second, for high ADR colonoscopists, the low-risk cohort of adenoma bearing patients will be expanded. For example, many 5-10 year examination intervals could be expected for 1-4 small tubular adenomas when the colonoscopies are performed by a high ADR examiner [148]. However, we expect that quality assurance, and consistent use of techniques and potentially also devices proven to enhance detection, will reduce the variation between high and low ADR examiners by time.

Also, the application of artificial intelligence (AI) technology will likely change polyp detection and differentiation practice. Detection programs will provide real-time assessment of the adequacy of colonoscope tip deflection and cleaning to expose all mucosa [149], while simultaneously highlighting potential lesions. Strategies such as Resect and Discard, that eliminate the pathologic assessment of diminutive polyps or at least diminutive adenomas, are likely to emerge as accepted clinical strategies [15]. Previously hampered by poor performance among community endoscopists, the application of artificial intelligence (AI) technology to the prediction of colon polyp histologies will make strategies like Resect and Discard universally feasible. These achievements are likely to further reduce operator dependence in colonoscopy.

In the not-too-distant future, the combination of these trends may completely change the face of colonoscopy. Average-risk individuals participating in organized screening programs might be systematically invited to perform a highly selective stool-test at home. Those individuals with colorectal lesions at high-risk for CRC development will be invited to undergo a therapeutic colonoscopy, in which artificial intelligence will help with the detection of these lesions. After detection, polyp histology will be predicted, potentially followed by advice on the optimal resection technique and whether histopathological analysis is recommended. The endoscopist will perform en-bloc resection of the lesion using easier, less laborious, and safer techniques than those currently available. Finally, patient-selection for surveillance colonoscopies may also be based on the outcomes of stool-tests instead of risk-stratification at the time of the last colonoscopy.

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FIGURE LEGENDS:

Figure 1: Top: Proposed systematic approach for structured lesion description including morphological features associated with deep submucosal invasion.
Bottom: Schematic overview of several endoscopic resection methods.

Figure 2: Advanced imaging techniques. a; picture of a pT1sm2 adenocarcinoma using narrow band imaging, b; picture of a tubular adenoma with low-grade dysplasia using autofluorescence imaging, c; picture of a sessile serrated lesion without dysplasia using linked color imaging, d; picture of a tubular adenoma with low-grade dysplasia using blue light imaging.

Table A. Minimum recommended registration of preprocedure, intraprocedure and postprocedure quality indicators based on current prevailing international guidelines [29-32].

Quality requirement	**Description**	**Recommended minimum if applicable**
Preprocedure		
Accreditation and professional registration	Accreditation conforming to the levels proposed by scientific society of gastroenterology and registration with a professional gastroenterology society	-
Number of colonoscopies	Number of (screening) colonoscopies performed per year	≥ 500 (lifetime)
Number of polypectomies	Number of polypectomies performed per year	≥ 50 (lifetime)
Intraprocedure		
Completeness of exam		
(Unadjusted) cecal intubation rate	The percentage of colonoscopies with a complete cecum intubation	≥ 90%
Bowel preparation	The percentage of colonoscopies where the colon is sufficiently clean to be able to inspect the mucosa well (BBPS ≥ 6)	≥ 90%
Withdrawal time	The percentage of negative colonoscopies with an withdrawal time	≥ 6 minutes
Detection rates		
Cancer detection rate	The percentage of colonoscopies where (more than) one cancer has been detected	-
Adenoma detection rate (ADR)	The percentage of colonoscopies where (more than) one adenoma has been detected	≥ 20%
MAP	The mean number of adenomas per procedure (colonoscopy)	-
PSPDR	The percentage of colonoscopies where (more than) one proximal serrated polyp has been detected	≥ 5%

Removal rates			
	Polyp removal rate	The percentage of polyps removed of the total number of detected polyps during the colonoscopy	≥ 90%
	Polyp retrieval rate	The percentage of retrieved polyps for histological evaluation of the total number of polyps detected during the colonoscopy	≥ 90%
Tattoo placement			
	Tattooing	The percentage of suspected cancers given a tattoo, except from cancers located in the cecum and up to 4 cm from the dentate line	100%
Postprocedure			
Patient satisfaction			
	Comfort Score	The percentage of colonoscopies in which the participant experiences moderate or severe discomfort (according to the GCS)	≤ 10%
Wellbeing of patients			
	Complication record	Keeping a complication record	-
	Complications during colonoscopy	The percentage of colonoscopies performed by the endoscopists where a complication occurs (up to 30 days after the procedure)	-
		Perforation rate colonoscopy	The perforation rate for colonoscopies performed by the endoscopist (up to 30 days after the procedure)	-
		Perforation rate polypectomy	The perforation rate for colonoscopies with polypectomy performed by the endoscopist (up to 30 days after the procedure)	-
		Polypectomy bleeding	The percentage of colonoscopies with polypectomy performed by the endoscopist , where complicated bleeding occurs (up to 30 days after the procedure)	-

Table B. Current and recent trends in polyp resection during colonoscopy.

1. Hot forceps are used only for avulsion of flat residual polyp that can't be snared during EMR; hot forceps have no advantage and result in unnecessary risk in the resection of diminutive polyps
2. Cold resection techniques continue to expand to an ever enlarging group of target lesions; including cold EMR
3. Cold snare resection is preferred over cold forceps resection even for diminutive lesions; snaring is more effective and efficient than forceps resection
4. The target set of lesions for EMR over standard polypectomy techniques continues to expand; for serrated lesions the threshold for performance of EMR should be 10-15 mm; all sessile and flat lesions ≥ 20 mm should generally be treated by EMR rather than use of standard techniques
5. Several trends in the technical performance of EMR have emerged
a. Classification schemes based on morphology (e.g. Paris classification and non-granular vs granular) and blood vessel and pit classifications using image enhanced endoscopy allow prediction of cancer risk, appropriateness of endoscopic resection, and the need for en bloc resection
b. High definition instruments allow delineation of residual polyp during resection and at follow-up
c. Several viscous injection solutions perform better than saline
d. Contrast in the injection fluid defines lesion boundaries and stains the submucosa, permitting recognition of muscle injury
e. Microprocessor controlled currents emphasizing cutting over coagulation current reduce thermal injury and may reduce complications
f. Visible polyp that can't be snare resected should be avulsed with forceps rather than ablated

Table C. Predicted future trends in the use of colonoscopy for colorectal cancer detection and prevention

1. Screening colonoscopy in organized screening programs will be progressively reduced in low-risk persons by therapeutic colonoscopies, as inexpensive and highly-selective non-invasive fecal tests will identify patients with colorectal lesions at high-risk for CRC development
2. Patients with one or two negative colonoscopies after age 50 by high level detectors (high ADR endoscopists) will be recommended to forego further colorectal cancer screening based on minimal residual lifetime risk
3. The low risk adenoma bearing cohort recommended to undergo next examination in 5-10 years will, when examination is performed by high ADR colonoscopists, be expanded to include persons with 3-4 small or diminutive tubular adenomas with low-grade dysplasia
4. Operator dependence in colonoscopy performance will be progressively reduced by quality improvement programs and technical improvements
5. Artificial intelligence (deep learning) programs will provide real-time assessment of withdrawal technique, assistance in lesion identification, and prediction of histology

Systematic lesion assessment

1. Record the location of the lesion
2. Size next to reference point of known diameter
3. Paris and LST classification
4. Surface pattern with high-definition electronic chromoendoscopy

Morphology associated with submucosal invasion

1. Paris classification III, O-IIa, or O-IIa+IIc
2. Non granular LSTs or granular LSTs with dominant nodule > 10mm
3. Kudo pit pattern type V and NICE type 3
4. Gross morphological features as spontaneous bleeding, fold convergence, surface redness, sclerous wall change, white spots, and exudates