

Colonoscopy in Colorectal Cancer Screening: Current Aspects

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Abstract Colonoscopy represents a very important diagnostic modality for screening for colorectal cancer, because it has the ability to both detect and effectively remove pro-malignant and malignant lesions. It is recommended by almost all international and national gastroenterology and cancer societies, as an initial screening modality or, following a positive fecal occult blood test, to be performed every 10 years in individuals of average risk starting from the age of 50. However, a significant problem is the so-called post-screening (interval) polyps and cancers found some years after the index colonoscopy. In order to reduce the rate of interval cancers it is extremely necessary to optimize the quality and effectiveness of colonoscopy. Bowel preparation is of paramount importance for both accurate diagnosis and subsequent treatment of lesions found on colonoscopy. The quality of bowel preparation could be significantly improved by splitting the dose regimens, a strategy that has been shown to be superior to single-dose regimen. A good endoscopic technique and optimal withdrawal time offering adequate time for inspection, would further optimize the rate of cecal intubation and the number of lesions detected. During the last years, sophisticated devices have been introduced that would further facilitate cecal intubation. The percentage of total colonoscopies is now super-passing the level of 95 % allowing the adenoma detection rate to be greater

than the suggestive level of 25 % in men and 15 % in women. This review aims to provide the reader with the current knowledge concerning indications, usefulness, limitations and future perspectives of this probably most important screening technique for colorectal cancer available today.

Keywords Colonoscopy · Colorectal cancer · Screening · flexible Sigmoidoscopy · Colorectal · Polyps

Introduction

Colorectal cancer (CRC) is one of the most common cancers and one of the leading causes of cancer death worldwide. It has been estimated that more than 432,000 new CRC cases and 212,000 CRC deaths occur annually in Europe, corresponding to an age-standardized rate of 29.6 and 12.4 per 100,000, respectively [1]. Worldwide, more than one million new cases of CRC are diagnosed each year killing more than 40 % of the affected individuals. In the USA, roughly 50,000 people die from CRC annually, and the cost of treating advanced CRC exceeds \$250,000 per patient.

CRC consists of easily recognized precursor lesions, a characteristic that makes it an ideal candidate for early detection and treatment. Recent data have shown that patients with CRC identified on screening colonoscopy, suffer not only from a lower-stage disease but they have also better outcomes, independently of their stage [2].

Colonoscopy, despite its risks, inconvenience, and cost, is an endoscopic technique allowing the efficient prevention and early detection of CRC, although there has been an increasing concern about the effectiveness in detecting adenomas and CRC located in the right colon [3].

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The aim of this review is to analyze the indications, usefulness, limitations and future perspectives of colonoscopy, a diagnostic modality probably representing the most important screening technique for CRC.

Screening for Colorectal Cancer: Current Recommendations

A number of national and international societies have released guidelines and recommendations for screening for CRC during the last decade [4]. In more detail:

The European Union guidelines suggest fecal occult blood testing for both men and women from 50 to 74 years. However, there is no preference for this, or any other, screening modality. The European Union provides principles and evidence-based recommendations for fecal occult blood test, sigmoidoscopy and colonoscopy [5, 6].

The U.S. Preventive Services Task Force recommends screening for CRC using high-sensitivity fecal occult blood testing, flexible sigmoidoscopy, or colonoscopy beginning at the age of 50 until the age of 75 [7].

The U.S. Multi-Society Task Force on Colorectal Cancer Screening and Surveillance along with the American Cancer Society recommends one of the following tests for persons aged over 50: an annual fecal occult blood test or flexible sigmoidoscopy every 5 years, or annual fecal blood test plus flexible sigmoidoscopy every 5 years or colonoscopy every 10 years or double contrast barium enema every 5 years.

The American Cancer Society recommends one of the following screening tests starting from the age of 50 for both men and women: flexible sigmoidoscopy every 5 years, colonoscopy every 10 years, Double-contrast barium enema every 5 years, or virtual colonoscopy every 5 years. This society does not specify an upper age limit beyond which CRC screening is no longer recommended [8].

The American College of Physicians recommends that clinicians should screen for CRC all average-risk adults starting from the age of 50. The same society recommends using a stool-based test, flexible sigmoidoscopy, or colonoscopy as a screening test.

The American College of Gastroenterology recommends colonoscopy as the most important screening test. If this cannot be performed, then other modalities, including FOBT or sigmoidoscopy or CT colonography, should be applied. This society does not specify an upper age limit, beyond which CRC screening is no longer recommended [9].

The American Gastroenterological Association, The US Multi-Society Task Force on Colorectal Cancer, and The American College of Radiology recommend a flexible sigmoidoscopy every 5 years, or colonoscopy every 10 years, or double contrast barium enema every 5 years, or virtual colonoscopy every 5 years [10].

The Ontario (Canada) Ministry of Health and Long-Term Care, the Cancer Care Ontario, and the Ontario Guidelines Advisory Committee suggest that all average-risk adults aged over 50 must be screened for CRC using the fecal occult blood test every 2 years or flexible sigmoidoscopy on a 5-year basis [11, 12].

The Canadian Cancer Society recommends that men and women aged over 50 have a fecal occult blood test at least every 2 years. The follow-up for a positive test should include a colonoscopy or double contrast barium enema or flexible sigmoidoscopy [13].

Finally, **the Canadian Association of Gastroenterology** recommends a fecal occult blood test annually or biannually and flexible sigmoidoscopy for all individuals aged over 50. The intervals among normal sigmoidoscopies should be 10 years or longer. Colonoscopy is not recommended for population-based CRC screening. No double contrast barium enema or Computed Tomography is recommended [14].

Other great national gastroenterology societies (e.g., British Society of Gastroenterology) offer guidelines of screening colonoscopy only for moderate or high risk groups of patients.

However, the guidelines concerning screening in general and colonoscopy in particular in Europe and the USA, differ in some way from the above-mentioned guidelines, thus creating some confusion for the general practitioners and other specialists. Practice patterns of screening may differ in some countries. In the USA and other developed parts of the world, surveillance recommendations are generally well correlated with current national guidelines. In a study analyzing the concordance between a tertiary equal access system and national guidelines, recommendations are correlated with established guidelines in 97 % of cases [15].

The guidelines released by the European Union need a broader scope of attention compared with others, as they do not focus on suggesting which method(s) can be recommended for screening for CRC. For example, although the European Union suggests fecal occult blood testing for both men and women from 50 to 74 years, there is no preference for this, or any other, screening modality. Instead, it provides principles and evidence-based recommendations for fecal occult blood test, sigmoidoscopy and colonoscopy [5, 6].

It should be stressed that the prevalence of advanced neoplasia detected during colonoscopic screening might be higher in men than in women suggesting that sex is an independent predictor of the detection of advanced neoplasia. This fact

may warrant a refinement of the screening recommendations to include sex along with age and family history of CRC [16].

Table 1 shows the published guidelines concerning the available (and adopted) screening modalities.

Time Interval Among Screening Colonoscopies

Colonoscopy has become the mainstay for screening and surveillance of CRC. The guidelines for screening and surveillance colonoscopy have been recently updated, particularly in light of a greater recognition of the importance of sessile serrated lesions in the development of cancer [17]. It is important for practitioners to be aware of and understand the recommendations for screening and surveillance, in order to optimize patient safety and to decrease health care use.

Regarding the follow-up recommendations after the initial colonoscopy, the Canadian Association of Gastroenterology recommends a follow-up colonoscopy after 10 years, provided that the index colonoscopy was negative, while in patients with more than 10 adenomas the suggestion is a new colonoscopy after 1 year. In patients with low-risk adenomas on both the index and first follow-up colonoscopy, the suggestion is a second follow-up colonoscopy after 5 or 10 years [18]. However, Przybyla et al. in their study showed that there are a significant number of patients diagnosed with CRC, who fell outside the recommended screening age range. Indeed, they have noticed that one third of patients diagnosed with CRC fell outside of the recommended screening age range of 50 and 75, while 58 % of patients aged less than 50 years had an advanced disease at the time of CRC diagnosis. Consequently, they suggest a re-evaluation of the CRC screening guidelines and risk factor assessment [19].

Lieberman et al. investigated the outcomes of subjects with no polyps at screening colonoscopy who had undergone a repeat colonoscopy during the decade following the initial negative colonoscopy. They found that among individuals who repeated colonoscopy in the year following the initial colonoscopy, 6.5 % had large polyp(s) greater than 9 mm. The incidence of large polyps within 1–5 years after baseline colonoscopy was 3.1 %. They suggest that repeat colonoscopies within 10 years offer no benefit to individuals who had negative and adequate screening colonoscopies, while they are indicated in patients in whom the baseline examination was compromised [20].

Another category concerns patients who have had a poor bowel preparation during the index screening colonoscopy. So far, there are no official guidelines for this kind of individuals. Singhal et al. compared the outcomes of repeat colonoscopy at various time intervals in patients with unsatisfactory preparation on index examination. In all individuals examined, they found a 24 % adenoma detection rate. They, also, noticed that the high risk adenoma and CRC detection rates were 8.4 and

Table 1 Recommendations for screening modalities including colonoscopy by major national and international societies

Society	Starting year	Ending year	Screening modality	Time of repeat examination
U.S. Preventive Services Task Force	50	75	CS or FS or FOBT	High-sensitivity FOBT annually or FS every 5 years combined with high-sensitivity FOBT every 3 years, or colonoscopy at intervals of 10 years
US Multi-Society Task Force on CRC American Cancer Society	>50	?	FOBT, or FS or CS or DCBE	FOBT annually, FS & DCBE every 5 years & CS every 10 years
American College of Physicians	50	?	FS or CS or DCBE or VC	FS, DCBE and VC every 5 years and CS every 10 years
American Gastroenterological Association	50	?	FOBT, or FS or CS	?
American College of Gastroenterology	50	?	FS or CS or DCBE or VC	FS, DCBE and VC every 5 years and CS every 10 years
Ontario Ministry of Health and Long-Term Care, Cancer Care Ontario, and Ontario Guidelines Advisory Committee	50	?	FS	10 years
American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology	50	75	FOBT Every 2 years	FS every 5 years
Canadian Association of Gastroenterology	50	?	FOBT Annu-ally or Biannu-ally FS	If positive CS or DCBE must immediately be performed

FS flexible sigmoidoscopy, CS Colonoscopy, FOBT fecal occult blood test, VC virtual colonoscopy, DCBE double contrast barium enema, CRC colorectal cancer

1.7 %, respectively. Colonoscopies repeated at time interval longer than 3 years showed a significant high-risk adenoma detection rate. Based on these results, they suggest a surveillance interval of no more than 3 years for subjects having an index colonoscopy with suboptimal bowel preparation despite the complete initial colonoscopy [21].

Menees et al. reviewed the colonoscopy reports of average-risk individuals with a normal initial (index) endoscopy. The main outcome parameters were quality of bowel preparation and recommendation for timing of repeat colonoscopy. The quality of bowel preparation was categorized as excellent, good, fair, or poor. They found that recommendations inconsistent with guidelines for 10-year time intervals after a normal initial colonoscopy occurred in more than 20 % of patients. Moreover, patients in the category of “fair preparation” were more likely to have recommendations inconsistent with guidelines compared with individuals with excellent or good preparations. The results of this study suggest that minimizing “fair” bowel preparations may be of help to improve adherence to current recommendations [22].

In conclusion, the international societies must seriously take into account the results of the current publications regarding the time of repeat endoscopic examination in conjunction with the quality of bowel preparation. Screening guidelines must be a continuously adapted topic based on the data of the current literature.

Value of Colonoscopy as a Screening tool for CRC

The risk of developing CRC is quite low in persons aged less than 40, and increases with aging. The incidence of CRC is slightly higher in men than in women. On the other hand, the prevalence of colorectal polyps in the general population is roughly 30 %. A screening colonoscopy is being suggested by a number of societies in all asymptomatic individuals aged 50 or over, especially if they had a positive fecal occult blood test.

The primary goal of screening colonoscopy is the detection of an already existing neoplasia and the subsequent removal by either endoscopic polypectomy or surgery. It must be taken into account that most polyps can be easily detected, but non-polypoid flat lesions may be missed. Not detected flat polyps at the initial (screening) colonoscopy could be responsible for the interval cancers. Therefore, we must continue to ensure quality screenings by providing the best, most cost-effective care to patients [23].

Despite the absence of large randomised controlled trials, observational studies suggest that colonoscopy in the prior 10 years, reduced CRC incidence and mortality by over 60 % [24]. In a population-based case–control study of 3148 patients with a first diagnosis of CRC and 3274 subjects without CRC, Brenner et al. found that a previous colonoscopy was associated with a reduced subsequent risk of CRC,

independently of the indication for the examination. They also noticed that colonoscopy was associated with a reduced risk of cancer in the right colon, regardless of the indication. This population-based study showed that the risk of CRC (including the right colon) was strongly reduced up to 10 years after colonoscopy for any indication [25].

However, even in older people colonoscopy and sigmoidoscopy could reduce the incidence of CRC. A recent case–control study investigated whether sigmoidoscopy or colonoscopy is associated with a decreased incidence of CRC in individuals aged 75 years or over. They showed that lower endoscopy in the preceding 10 years was associated with a significant reduction in CRC incidence, while colonoscopy was associated with significant reduction in distal and proximal CRC [26]. These results support the assumption that both sigmoidoscopy and colonoscopy can reduce CRC incidence in both middle-aged and older asymptomatic individuals.

Barriers to Colonoscopy

A large number of barriers including cost, environment, lack of access to healthcare system, organized or opportunistic screening, provider, psychology as well as inadequate knowledge or awareness and perceived risk of CRC, negative attitudes towards screening and fear of CRC, all have been implicated in the unsatisfactory rate of participation of the population in CRC screening programs.

McLachlan et al. conducted a systematic review of 56 relevant studies in order to characterize patients’ own experience of screening colonoscopy. A number of barriers including bowel preparation (the most burdensome element of colonoscopy), presence of anxiety, and anticipation of pain, vulnerability, inadequate knowledge and fear of cancer, were identified as important obstacles to screening colonoscopy. Physician endorsement, positive family history, and perceived accuracy of the test were identified to be the most significant incentives of performing colonoscopy (irrespective of the reason e.g., positive fecal blood test or regular physician advice). The above-mentioned obstacles and barriers to screening colonoscopy reported by the patients themselves, need to be properly addressed in order to improve subjects’ adherence [27].

Old age represents a significant barrier in CRC screening, and colonoscopy in particular, in many countries. Some national societies, including the U.S. Preventive Services Task Force, recommend against routine screening for CRC in persons over 75 years old. The decision of performing screening colonoscopy in the elders could be difficult and challenging. Most authors agree that such a decision requires the individualized assessment taking into account the risks and benefits for the old person according to his/her overall health [28]. Tran et al. investigated the impact of surveillance colonoscopy in elderly patients compared with a reference cohort. The study

cohort included 4834 patients aged ≥ 75 years and 22,929 individuals in the reference group aged 50–74 years. The incidence of CRC among elderly patients was significantly lower compared with the reference population (0.24/1000 person-years vs 3.61/1000 person-years). Moreover, the age of 75 years and over was independently associated with an increased risk of post-procedure hospitalization. These results suggest that recommendations for surveillance in the elderly population should take into account the impact of co-morbid illnesses and the anticipated risks and benefits of colonoscopy [29].

The unscreened elderly persons represent another category of individuals that must be properly addressed. Van Hees F et al. [30] applied colonoscopy, sigmoidoscopy, and fecal immunochemical test in unscreened persons aged from 76 to 90 years without co-morbid conditions in order to determine the most suitable age and screening modality. They found that CRC screening was cost-effective for patients up to the age of 86 years, screening with colonoscopy was indicated for those up to age of 83 years, while sigmoidoscopy was indicated at the age of 84 years. However, in individuals with moderate or severe co-morbid conditions, screening was cost-effective up to the age of 83 and 80 years, respectively. It seems that in unscreened elderly persons CRC screening should be applied even in subjects below the age of 75 years with colonoscopy as the procedure of choice in most ages [30].

Diverticulosis represents another situation that could create barriers to screening colonoscopy for CRC. Diverticulosis has been associated with interval cancers. In a recent study, Cooper et al. found that diverticulosis was strongly associated with interval CRCs in all parts of the large bowel, a fact that argues against reduced detection of lesions at colonoscopy as the only pathogenic factor of interval cancer development [31]. However, in radiologically proven acute diverticulitis the situation could be different. Sharma et al. have conducted a systematic review and meta-analysis in order to estimate the yield of CRC found at colonoscopy after a radiologically proven acute diverticulitis. Out of 1970 patients CRC was found in 22, and the pooled proportional estimate of malignancy was 1.6 %. Among 1497 patients with uncomplicated diverticulitis, CRC was found in 5 (proportional estimate of risk 0.7 %), while among 79 patients with complicated disease, CRC was found in 6 (proportion estimate of risk 10.8 %). These results suggest that the risk of CRC after a radiologically proven episode of acute uncomplicated diverticulitis is low and that colonoscopy may not be necessary, although patients with complicated disease still have a significant risk of CRC at a subsequent colonoscopy [32].

Technical Improvements in Colonoscopy

Today, flat and small lesions could be successfully recognized by using the so-called high-definition colonoscopes and visual

image enhancement technologies, although the absolute increase in diagnostic yield seems limited. New endoscopic techniques including the cap-assisted colonoscopy (a transparent cap attached to the tip of the colonoscope) and water-exchange colonoscopy can facilitate cecal intubation and increase patients comfort, although they had only a marginal benefit on polyp detection. In a systematic review and meta-analysis, Ng et al. concluded that cap-assisted colonoscopy shortened the cecal intubation time and demonstrated a marginal benefit over colonoscopy for polyp detection [33]. Morgan et al. analyzed 14 randomised controlled trials and showed that transparent cap colonoscopy significantly reduces the cecal intubation time when compared with standard colonoscopy, although there was no difference in the polyp detection between the two groups [34].

Colonoscopy with the Third-Eye Retroscope® generally has lower missing rates compared with standard colonoscopy. A disadvantage of this technique is the fact that it is more time consuming, and is not a suitable modality for a polypectomy.

The Full Spectrum Endoscopy™ colonoscopies have a wider view compared with standard colonoscopes (330 vs 170°). This technique allows the polyp detection rate to considerably increase [35]. The usefulness of a full-spectrum endoscopy colonoscopy in improving the adenoma detection rate compared with standard forward-viewing colonoscopy, was investigated in a multicenter study. It was noticed that the adenoma miss rate was significantly lower in patients in the full-spectrum endoscopy group than in those in the standard forward-viewing colonoscopy group [36]. Although full-spectrum endoscopy represents a technological achievement for colonoscopy that could improve the efficacy of CRC screening, more studies are needed before this device can be used routinely.

Concerning the role of chromoendoscopy in increasing the adenoma detection rate, Leung et al. showed that indigo carmine at concentration of 0.008 % added to the water exchange method could significantly enhance the adenoma detection rate, both overall and in the proximal colon [37].

In conclusion, most of the endoscopic innovations that have been used in the last few years have shown some additional diagnostic yield. However, they are expensive and more time consuming.

Optimal Withdrawal Time in Colonoscopy

Recent studies have shown that increasing colonoscopy withdrawal time (no less than 6 min) could be associated with increasing polyp detection rate [38]. Lee et al. have recently examined this association and found that longer withdrawal times are associated with increasing rate of adenoma detection, although time longer than 10 min offered no additional benefit. Their work confirmed that withdrawal time remains an important quality metric of colonoscopy [39].

Value of Endoscopists' Training and Experience

The endoscopist experience in screening colonoscopy is strongly related to cecal intubation rate, or the complications rate. Therefore, endoscopists performing screening colonoscopies must fulfill the necessary requirements and experience as well as a minimum annual number of endoscopic procedures.

Generally, endoscopists dedicated to CRC screening colonoscopies, have better polyp detection rates and endoscopists with greater than 20 % adenoma detection rate have a significantly lower rate of interval CRC. Endoscopists with a higher polypectomy rate, also, have lower rates on interval CRC. An inverse relationship between endoscopists who classed themselves as gastroenterologists and interval CRC rates has been reported, although others suggest that operator volume and accreditation as bowel cancer screeners, and not the endoscopist's specialty, is related to adenoma detection rate. Training and quality improvement would play a significant role in improving the adenoma detection rate. Screening colonoscopies performed by people other than gastroenterologists, are significantly more often associated with the appearance of interval CRC. The cecal intubation rate, a key quality performance indicator for colonoscopy, is lower in symptomatic patients compared with individuals undergoing CRC screening [40].

Individuals Under Anticoagulation and Antiplatelet Therapy

While diagnostic colonoscopy, with or without biopsy, is considered to be a low-risk procedure, polypectomy is generally categorized as a high-risk endoscopic procedure because of the risk of perforation or bleeding. It is widely accepted that the risk of bleeding after polypectomy does not significantly increase in patients under aspirin or NSAIDs prophylactic treatment at standard doses. Therefore, screening colonoscopy can be performed in subjects under antiplatelet treatment without interrupting these drugs. Also, the risk of bleeding after polypectomy does not seem to increase in subjects with polyps no greater than one centimeter under clopidogrel treatment. However, concomitant use of clopidogrel and aspirin or NSAIDs increases the risk of bleeding after polypectomy and should be avoided. No endoscopic polypectomy is allowed in individuals taking anticoagulants orally.

Bowel Preparation

Bowel preparation is of paramount importance, because the subsequent suboptimal mucosal visualization decreases the adenoma detection rate especially in the proximal colon. On the other hand, effective bowel cleansing is essential for high quality colonoscopy because it improves the detection of

neoplastic lesions and reduces the time of procedure and the rate of complications. Poor bowel preparation is not rare; indeed, up to one third of colonoscopies are compromised by poor bowel preparation, requiring a repeat colonoscopy. It must be stressed that colonic cleansing should be rated as excellent or good in at least 90 % of screening colonoscopies performed.

Among the available cleansing modalities, polyethylene glycol preparations seem to be more efficient and better tolerated compared with a restrictive diet plus laxatives, enemas, or mannitol, while the addition of ascorbic acid improves the taste, while inhibiting the bacterial overgrowth and gas generation [41]. In patients who do not tolerate polyethylene glycol preparations, the combination of magnesium citrate and sodium picosulfate could have similar efficacy to polyethylene glycol preparations and sodium phosphate. It has been reported that Moviprep® (polyethylene glycol plus ascorbic acid) and Phosphoral® (NaP) provided equally efficient bowel cleansing in 90 % of patients, but Moviprep® provided a higher quality of cleansings graded as successful. The two agents were equally tolerated [42].

However, in some cases and in order to avoid dehydration, volume overload, and electrolyte disturbances, polyethylene glycol should be combined with a balanced electrolyte solution. In individuals aged over 65 years, as well as in patients with ischemic cardiac disorder, polyethylene glycol preparation should be avoided due to the increased risk of bowel ischemia. Abnormal electrocardiogram prior or during colonoscopy could be an indication for serum electrolyte concentration assessment.

It must be taken into account that patient compliance and acceptability due to the large volume of polyethylene glycol solution (4 l solution) is poor. It seems that the split-dose of polyethylene glycol regime with regular diet until dinner, represents the most effective cleansing strategy, while splitting the volume of cleansing solution between the day before the test and the day of the examination improves tolerance and security. In a very recently published study, it was noticed that noncompliance with split-dose bowel preparation was the strongest predictor of suboptimal bowel preparation. In this study, it was found that 1 in 7 individuals did not comply with a split dose bowel preparation. A compliance with the split-dose bowel regimen will reduce the risk of a suboptimal bowel preparation [43]. The results of another study, also, revealed that split-dose bowel preparation resulted in better bowel cleansing, and improved patient tolerance [44].

Sodium phosphate-based preparations might be better tolerated, although their use in elderly people or patients with renal impairment could be dangerous. Tolerability of polyethylene glycol solution could also be unsatisfactory especially in elderly people. Careful pre-assessment of the individual examined in order to detect renal or hepatic impairment, heart failure, and use of diuretics must be always kept in mind.

Sodium phosphate preparations and, low-volume hyperosmolar solutions, should not be used in patients with obvious electrolyte disturbances.

It has been suggested that the degree of mucosal cleanliness is optimum if the examination is commenced after some hours of the bowel preparation. Most authors suggest that best results can be obtained if colonoscopy is performed within a few hours of finishing the bowel preparation. The time between the last dose and the start of the examination should be from 2 to 6 h. Patients, who have difficulties in achieving adequate bowel cleansing with standard regimes, represent a difficult to manage group. Although some people suggest the combination of polyethylene glycol with 10 mg of bisacodyl can reduce the volume of solution to two liters, others suggest that the role of bisacodyl should be further investigated [41].

Menees et al. assessed the impact of fair bowel preparation on endoscopists' interval colonoscopy recommendations and miss rates in colonoscopies performed within 3 years of the index screening colonoscopy. They found that fair bowel preparation led to a deviation from the national guidelines. Early repeat colonoscopy follow-up was recommended in 60 % of average-risk patients with normal colonoscopy results [45].

Magnesium-based preparations are widely used in England and a low volume magnesium preparation recently received FDA approve in the USA. Tepeš et al. used magnesium sulphate mineral water (2 L) and low-volume polyethylene glycol plus electrolytes (2 L) for bowel cleansing. Excellent, good, fair and poor bowel preparation was achieved in 82.6, 13.6, 3.2 and 0.6 %, respectively. Better results were achieved in the afternoon colonoscopies and in younger participant groups [46].

In summary, a variety of bowel preparation regimes are available today. The endoscopists must do their best to persuade patients to accurately follow the suggestions in order to achieve excellent bowel preparation. Table 2 shows the cleansing modalities for bowel preparation available today.

Suggestions After an Incomplete Colonoscopy

In case of an incomplete colonoscopy the reasons for this unsuccessful attempt must be carefully reevaluated. If the individual cannot tolerate the procedure or the endoscopist is inexperienced, then the examination must be repeated by an experienced endoscopist using deep sedation. In this case, other endoscopic techniques can be also used, including the use of endoscopes or enteroscopes of variable stiffness.

In case of inadequate colonoscopy, virtual colonoscopy or Pill Cam capsule might also be used. Virtual colonoscopy could also been proposed, if additional risk factors are present, or refusal of optical colonoscopy in high risk patients [47].

Safety of Screening Colonoscopy

Millions and millions of colonoscopies are performed each year worldwide, a fact underlying the importance and safety of this examination. However, because colonoscopy is an invasive procedure and despite the fact that endoscopists are well trained and the current scope technology has made colonoscopy gentler, we do expect some side-effects to occur [48]. Overall, the complication rate is low, not over 1 %, in large series; however, a higher risk occurs in persons from 70 to 80 years old and when there are co-morbid disorders.

Colonic perforation represents one of the most significant complications. Colonoscopy perforation rate should be lower than 1/1000 procedures. The advanced age of the patient, chronic lung or liver disorders, obesity, diverticulosis, previous abdominal surgery, and low experienced endoscopist, all are factors associated with a higher perforation rate [48].

Post-polypectomy bleeding represents the other more significant complication. Post-polypectomy bleeding rate should be lower than 1/200 endoscopic polypectomies. As in the case of perforation, the main risk factors for bleeding include an increased age, concomitant cardiac or renal disorders, anticoagulant therapy, advanced or right-sided polyps, poor bowel cleansing and inexperienced endoscopist.

Finally, there are some other complications related to colonoscopy itself, including colonic lavage requiring a massive rehydration with a risk of renal failure, to sedation and drugs used by the endoscopists or anesthesiologists, bacteremia and infection.

Cost – Benefit of Screening Colonoscopy

It has been previously established that colonoscopy represents a cost-effective screening modality, because it reduces mortality having at the same time a low incremental cost on a population basis [49]. On the other hand, annual screening with fecal occult blood testing costs less than colonoscopy, but it has significantly lower benefit on saving patients' life; and flexible sigmoidoscopy performed every 5 or 10 years is less cost-effective than colonoscopy or fecal occult blood test.

Pyenson et al. estimated that in the USA (in 2010) the average allowed cost for screening colonoscopy was \$2146 for commercial payers and \$1071 for Medicare patients, and that the rate of repeat colonoscopy was higher than what was found in the commercial and Medicare populations [50]. Tangka et al. also reported that the total average clinical cost per individual screened by fecal occult blood test ranged from \$48 in Nebraska to \$149 in Seattle compared with colonoscopy screening ranging from \$654 in St. Louis to \$1600 in Baltimore City [51]. Finally, when screening colonoscopy is performed by non-GI endoscopists, a significant reduction in

Table 2 Proposed bowel preparation modalities

Cleansing modalities	Advantages	Precautions	Remarks
Polyethylene glycol preparations	Very effective cleansing modality	Individuals aged >65 years and patients with ischemic cardiac disorder. Tolerability could be unsatisfactory in elderly people	Split-dose of poly-ethylene glycol regime with regular diet until dinner is an effective cleansing strategy. Splitting the volume of cleansing solution between the day before the test and the day of the exami-nation improves tolerance and security
Polyethylene glycol preparations plus ascorbic acid Magnesium citrate and sodium picosulfate combination Combination of polyethylene glycol with a balanced electrolyte solution. Sodium phosphate-based preparations	Inhibits bacterial overgrowth and gas generation Similar efficacy to polyethylene glycol preparations Avoidance of dehydration, volume overload, and electrolyte disturbances	Use in elderly people or patients with renal impairment could be dangerous. Not be used in patients with electrolyte disturbances	
Combination of polyethylene glycol with 10 mg of bisacodyl Magnesium-based preparations	It could reduce the volume of solution to 2 l Combination of 2 L magnesium sulphate mineral water with low-volume (2 L) polyethylene glycol plus electrolytes		

CRC prevention rate might be anticipated. It has been estimated that in the USA, a 10-year saving of \$2 billion may be expected if all screening colonoscopies are performed by GI endoscopists [52]. These data must be taken into account when the health authorities are planning screening programs for CRC.

Table 3 shows the main quality indicators in colorectal cancer screening [53, 54].

The So-Called “Interval Cancers” and Adenomas

During the last years, it has become clear that some people are diagnosed with CRC relatively soon after a colonoscopy that was characterized as “without abnormal findings”. These ‘interval’ CRCs (cancers diagnosed between serial colonoscopies) have been described in national screening programs, small studies, as well as in studies including administrative data sets.

Baxter et al. among 14,064 patients who have had a colonoscopy performed within 36 months from the index (negative) colonoscopy, 584 (6.8 %) identified with distal and 676 (12.4) with proximal CRC. These interval cancers were significantly associated with the endoscopists’ specialty and the setting. Indeed, a lower rate of interval CRC was noticed among the specialists (gastroenterologists) and if colonoscopy was performed in a hospital setting [55]. Kaminski et al. noticed 42 interval CRCs during a period of 188,788 person-years. They found that the adenoma detection rate was significantly associated with the risk of interval CRC whereas the rate of cecal intubation was not [56]. Robertson et al. discovered 19 interval CRCs among 2915 patients over a mean follow-up of 3.7 years (1.74/1000 person-years). The location of CRCs varied considerably, although most of them

were located at or proximal to the hepatic flexure. Most of CRCs (84 %) were at an early stage, however 2 of patients died because of the cancer [57]. It has been estimated that 1 in 13 CRCs may be an early or missed CRC, diagnosed after an index colonoscopy in usual clinical practice. Women are more likely to have early/missed CRC [58]. Among the causes of the development of these intervals incomplete resection of a previously diagnosed polyp at index colonoscopy, missed cancers or inadequate examination due to difficulties in visualizing polyps at the proximal side of haustral folds, the presence of flat lesions, the poor bowel preparation, and the frequency of colonoscopic examination (as more frequent colonoscopies offer a greater opportunity to detect small asymptomatic CRCs) are probably the most significant. Indeed, Clercq et al. showed that 2.9 % of all CRCs were interval cancers diagnosed on average 26 months after the initial colonoscopy. Most of them (86.4 %) could be explained by procedural factors including missed lesions (57.8 %), inadequate examination/surveillance (19.8 %) or incomplete polypectomy (8.8 %) [59]. These results were confirmed in a recent pooled multi-cohort analysis performed by Robertson et al. The authors underline the importance of the identification and complete removal of neoplastic lesions found at colonoscopy [60].

Many studies raised, also, questions about the magnitude of proximal or right-sided CRC and adenomas. The variation of the outcomes of colonoscopies performed by endoscopists of different experience and ability suggests that a better quality of colonoscopy could lead to better outcome and subsequently, reduced incidence of interval CRC [61].

These interval CRCs could lead to the conclusion that earlier examination (before the suggested 10 years) after a negative initial (index) examination might be of benefit for the

Table 3 Quality indicators in colorectal cancer screening (modified from Rembacken et al. 2012 [53] and Jover et al. 2012 [54])

Quality parameter	Acceptable level
Adenoma detection rate	More than 20 % of cases
Adenoma detection rate after positive fecal occult blood test	More than 40 % of cases
Colonoscopy withdrawal time	Six minutes in at least 90 % of diagnostic examinations
Endoscopist experience	A lifetime colonoscopy experience (at least 400) together with a minimum number of annual screening colonoscopies (at least 200) are required
Cecal intubation rate	In more than 95 % of cases
Use of sedation	In more than 90 % of cases. No more than 1 % of patients should become hypoxic (saturation below 85 % for more than 30 s)
Appropriate bowel cleansing	More than 90 % of colonoscopies should be characterized as “adequate” bowel cleansing
Colon perforation rate	Fewer than 1:1000 examinations should result in a perforation requiring surgical repair
Post-polypectomy bleeding rate	Fewer than 1:20 cases of bleeding should ultimately require surgical intervention
Description of polyp characteristics	The level of 100 % must be achieved

patients. Two recent studies, however, failed to detect any benefit derived from this screening attitude. In the first one, Yang et al. noticed that the magnitude of reduction in the cumulative CRC risk afforded by earlier colonoscopy among elderly individuals, who have had a negative initial colonoscopy, was small, not justifying the risk and cost of subsequent colonoscopies [62]. In the second one, van Hees et al. concluded that screening Medicare beneficiaries more intensively than recommended, was not only inefficient, but also unfavorable for those being screened, thus providing evidence for clinicians and policy makers to discourage this practice [63]. Finally, Corley et al. underlined the importance of quality colonoscopy for CRC prevention. The authors found that compared with the lowest quintile of colonoscopists' adenoma detection rate, the highest quintile was associated with a 52 % reduction in risk for CRC and 62 % reduction in CRC-related death [64]. In our opinion, the frequency of interval colonoscopies must be rigorously examined in the near future.

In conclusion, the adenoma detection rate (the proportion of screening colonoscopies performed by a physician that detect one or more adenomas) is an important recommended quality measure and inversely associated with the whole risk, advanced-stage and fatal interval CRC. Therefore, quality improvements in colonoscopy are clearly needed, with particular emphasis to detection and complete resection of all colorectal polyps.

What is the Role of Flexible Sigmoidoscopy in CRC Screening?

Flexible sigmoidoscopy has been proposed by several societies as an alternative to colonoscopy screening method, because it can decrease CRC incidence and mortality, is easier to perform, has lower rate of complications, and can be performed by non-medical personnel. In a study aiming to explore the comparative effectiveness and cost-effectiveness of colonoscopy compared with sigmoidoscopy, Sharaf et al. performed a cost-utility analysis using a Markov model. Screening strategies included colonoscopy every 10 years, flexible sigmoidoscopy every 5 years, annual fecal occult blood testing, annual fecal immunochemical testing, and a combination of sigmoidoscopy and fecal immunochemical testing. They found that screening colonoscopy could be cost-effective compared with fecal immunochemical testing and sigmoidoscopy, depending on the rates of screening uptake and adherence [65].

A population-based study aiming to estimate the effectiveness of flexible sigmoidoscopy screening on CRC incidence and mortality was conducted in Norway. The study included 100,210 individuals aged 50 to 64. Participants were randomized 1:1 to receive once-only flexible sigmoidoscopy or combination of once-only flexible sigmoidoscopy and fecal occult

blood testing. The control group received no intervention. After a median follow-up of 10.9 years, 71 individuals died of CRC in the screening group vs 330 in the control group. CRC was diagnosed in 253 individuals in the screening group vs 1086 in the control group [66].

So far, three systematic reviews and meta-analyses have been published. In the first one, Elmunze et al. noticed that flexible sigmoidoscopy based screening reduced CRC incidence by 32 % and CRC-related mortality by 50 % in average-risk patients [67]. In the second one, Littlejohn et al. analyzed the data of 24 relevant studies from 14 trials. In these studies, flexible sigmoidoscopy was compared with either no screening or any other alternative screening methods. They found that flexible sigmoidoscopy detected more advanced adenomas and CRCs compared with fecal occult blood test. Flexible sigmoidoscopy also reduced the incidence of and long-term mortality from CRC compared with no screening. However, flexible sigmoidoscopy could be compromised by poorer uptake [68]. Finally, in a systematic review and meta-analysis of 4 randomised controlled trials and 10 observational studies, Brenner et al. found that screening sigmoidoscopy significantly reduced the rate of distal but not proximal CRC incidence and mortality by 31 and 46 % in intention to screen analysis, 42 and 61 % in per protocol analysis of randomized controlled trials, and 64 and 66 % in observational studies, respectively. Screening colonoscopy showed an even stronger reduction in distal CRC incidence and mortality in 6 observational studies, along with a significant reduction in mortality from cancer of the proximal colon [69].

The available data suggest that both, screening sigmoidoscopy and colonoscopy can reduce mortality from CRC in the distal colon, and that colonoscopy compared with flexible sigmoidoscopy can significantly decrease mortality from cancer of the proximal colon.

The role of flexible sigmoidoscopy should be further investigated taking into account the rate of adverse events, the poorer compliance rate compared with stool-based tests and cost, discomfort, complication rates, capacities needed, and differences in compliance rate between sigmoidoscopy and colonoscopy.

Screening Strategies for CRC in Asian Countries

During the last years a significant rise in the CRC incidence in many Asian countries was noticed, a fact making the need for screening of the average population for CRC quite necessary. Until 2008, there were no official screening guidelines concerning CRC in Asian countries. In 2008, the "Asia Pacific Working Group on Colorectal Cancer" with the help of international experts, published the first recommendations for CRC screening based on data regarding incidence, screening modalities available, and feasibility of screening programs, in

these countries [70]. An update of these recommendations was recently released [71].

According to the suggestions of the updated consensus, CRC screening should be started at the age of 50 until the age of 75. Fecal occult blood test, flexible sigmoidoscopy and colonoscopy are the preferred methods for screening for CRC. The working group suggested that immunochemical fecal blood test should be the preferred modality for the average risk individuals. Regarding colonoscopy for subjects of high-risk, a risk-stratified scoring system was suggested by the members of the consensus.

Recently, the cost of screening in Asian countries was also calculated. In a relevant study, Wang et al. evaluated the cost-effectiveness of CRC screening based on screening colonoscopy every 10 years or single colonoscopy, versus no screening, using a Markov model. They noticed that screening colonoscopy could significantly reduce the incidence of CRC and that single colonoscopy was the most cost-effective strategy for the China clinical practice [72]. As Ng and Wong suggested, screening for CRC should be a national health priority in China. On the other hand, studies on the barriers to education of the population for CRC screening and suitable education of the primary care physicians should be a future priority in Asian countries [73].

The incidence of colorectal cancer in India, one of the countries with the largest population in the world, seems to be quite low in both men and women, compared with developed countries in Europe and North America. It is likely that environmental factors concerning mainly dietetic habits (reduced consumption of sugars, and fat-rich food, as well as increased consumption of fruits and vegetables), physical activity while keeping a normal body weight, are responsible for the low incidence rate [73]. To the best of our knowledge, no screening programs for colorectal cancer in India have been so far implemented. However, it seems that the traditional lifestyle is the most important factor for keeping the incidence of colorectal cancer low. A population-based screening program in India may not prove to be cost-effective, given the low burden of colorectal cancer in this country [74].

Future Frontiers in Colonoscopy

New frontiers in screening colonoscopy will focus on improving colonoscopy techniques to ensure that the adenoma detection rate will continuously be improved. Combining high-definition and improved virtual enhancement technology incorporated in ultra-wide colonoscopies and interventional colonoscopes with alternative propulsion mechanisms would enhance the diagnostic yield of colonoscopy in the next few years. These techniques are also expected to reduce patient discomfort during colonoscopy, obviate the need for sedation,

and increase diagnostic yield, thus improving general population access to screening.

So far, numerous studies have focused on quality measures such as withdrawal time. However, better colonoscopic technique is expected to increase the polyp detection rate compared with increased withdrawal time. In the future, we will turn our attention to the ability to accurately detect and remove colorectal polyps. Other modalities could focus on spraying chemical substances in the bowel lumen having the ability to suppress the involuntary constrictions of the bowel muscular layer, thus facilitating the ability of the endoscopist to detect mucosal abnormalities. Finally, there would be efforts to reduce the cost of removing colorectal polyps. A combination of laparoscope and colonoscope could isolate and remove effectively the polyp instead of surgically resecting the bowel part containing the polyp. This would substantially reduce both the hospital stay and the recovery time.

Conclusions

Today, colonoscopy represents the most important diagnostic and therapeutic modality for CRC prevention and treatment. It is recommended by all international and national societies devoted to either gastroenterology or cancer diagnosis and treatment, as an initial screening modality or after a positive fecal occult blood test. Colonoscopy is recommended to be performed every 10 years for individuals of average risk starting from the age of 50. A large number of barriers including cost, environment, lack of access to healthcare system, organized or opportunistic screening, provider, psychological factors as well as limited knowledge or awareness and perceived risk of CRC, negative attitudes towards screening and fear of CRC, all have been implicated in the unsatisfactory rate of the population's participation in CRC screening programs. Significant progresses in some technical characteristics resulted in the improvement of the adenoma detection rate. The estimation of adenoma detection rates should be now considered as a current standard of care for endoscopists and should be benchmarked across national standards. However, technical improvements alone are not enough if they are not accompanied by similar improvement of the skills of the endoscopists. Gastroenterologists must spend more time on withdrawal during colonoscopy in order to achieve better results. There are now enough data supporting the adoption of split dose bowel preparation in order to improve mucosal visualization. Some people suggest that checking a video-recorder might help to detect weaknesses of the previous endoscopic procedure. Missed lesions and incompletely resected lesions seem to account for about 70 % of the so-called "interval colorectal cancers". The current literature emphasizes the extreme importance of performing technically optimal colonoscopic procedures in order to identify and completely

remove all lesions. Moreover, identification and removal of flat lesions when appropriate with chromoendoscopy or high magnification, and high-quality adequate colon cleansing could all improve the results of screening colonoscopy. Concerning new technical achievements, the available data suggest that most of the endoscopic innovations used in the last few years, have indeed shown some additional diagnostic yield. However, they are expensive and more time consuming. Finally, regarding flexible sigmoidoscopy, the available data suggest that screening sigmoidoscopy can reduce mortality from CRC in the distal colon, and colonoscopy compared with flexible sigmoidoscopy can significantly decrease mortality from cancer of the proximal colon. Because the clinical significance of performing an adequate screening colonoscopy is extremely important for the individual screened and the endoscopist as well, we - as gastroenterologists - must apply all the above-mentioned knowledge and guidelines into the routine clinical practice.

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