

Review Article

Colorectal Cancer Screening: Future Perspective

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Abstract

Colorectal cancer is the 3rd most commonly diagnosed cancer within the United States and the 2nd leading cause of cancer-related deaths in the US in 2008. The survival rate for patients suffering from CRC is directly proportional to the stage of detection. Timely and accurate detection of CRC is only possible through an organised screening programme. The evidence for currently used CRC screening methods including faecal tests (gFOBT and FIT) and complete structural exams (FSIG, colonoscopy, and DCBE) are reviewed in detail. Furthermore strategies for increasing screening rate and newer technologies including Computerized Tomographic Colongraphy (CTC) and Confocal Laser Endomicroscopy (CME) are also discussed.

Keywords

- Colorectal cancer
- Future
- Techniques
- Cancer
- gFOBT

INTRODUCTION

Colorectal cancer (CRC) is the 3rd most frequently diagnosed malignancy in the United States and accounts for the 2nd leading cause of cancer-related deaths [1]. The natural progression of the tumour from the adenoma to carcinoma sequence allows for the early detection of the condition through various screening modalities currently available. Despite the innovative and ground-breaking screening techniques that have been developed within the last decade, we are lacking behind in adequate survival rate for patients with advanced stages of CRC. In 2008, in the United States (US) alone, ~150,000 patients were diagnosed with CRC out of which a third succumbed to the disease. These deaths are directly proportional to the stage of disease. Patients with lymph node involvement or distant metastasis have only 5 year survival rate of 68% and 10% respectively compared to 90% of patients with localised disease will survive beyond this term [2].

Numerous randomized trials and observational studies, carried out by the US Multi-Society Task Force on CRC, have demonstrated significant effects of early detection on survival rates. Early detection subsequently allows for the removal of adenomatous polyps [3-8]. It is recommended that any CRC screening test showing a positive result, be immediately followed up with a colonoscopy [9-11].

It is of vital importance that healthcare professionals as well as the public understand that CRC screening tests are classified into 2 different categories. The first category contains tests that are first-line in large population cohorts to detect CRC, namely the faecal tests; stool DNA test (sDNA), Guaiac Faecal Occult Blood Test (gFOBT) and faecal blood test (FIT). The principal goal of these tests is to identify CRC cells or blood and as a result

prevention is often inadequate and supplementary. The second category contains invasive tests that have the sole purpose of detecting anatomical abnormalities. These tests are complete structural exams; flexible sigmoidoscopy (FSIG), colonoscopy, Double Contrast Barium Enema (DCBE), and Computerized Tomographic Colongraphy (CTC) [12].

In this review, we will focus primarily on the faecal occult blood tests, as these appear to have the highest potential in regards to the future of CRC screening due to recent technological improvements, followed by a brief description of a few novel technologies in the second category.

Faecal Occult Blood Test (FOBT)

FOBTs have been developed to detect traces or large amounts of occult blood in stool samples. Based on the analyte detected, FOBT are divided into 2 categories: gFOBT (Guaiac Faecal Occult Blood Tests) and FIT (Faecal Immunochemical Test). The detection of blood in stool samples can be applied to numerous conditions, therefore it is of great importance that stool blood tests be carried out annually consisting of abundant stool samples, in order to increase the rate of cancer detection [13-16].

Guaiac Faecal Occult Blood Test (gFOBT)

The most frequently used stool sample test in population cohorts are gFOBT tests [17]. Previously, this test required 2 stool samples from the patient from each of 3 consecutive bowel movements. However, recent evidence shows that an additional stool sample increases the test's sensitivity significantly and therefore it is not recommended to collect three stool samples [18]. Before the patient is tested with a guaiac-based test, protocol suggests they avoid Aspirin and any other NSAIDs,

alongside with avoiding fish, red meat, poultry, Vitamin C, and certain vegetables as these may increase the chance of false-positive or false-negative results [19].

Efficacy and Test Performance: gFOBT has shown that screened patients are provided with an earlier and more curable detection of CRC than those who remained unscreened. Numerous trials, conducted in the United Kingdom, over many years proved reduced mortality rates in CRC in the range of 15-33% [20-22]. In one trial, an incidence reduction of 20% was shown after 18-years worth of follow up [23].

Sensitivity and Specificity: The sensitivity of a test refers to how likely it will pick up a condition when the patient actually has the condition. Essentially, if a test is highly sensitive and the test results shows up as positive – the patient can be quite certain they have the disease. The specificity of a test refers to how often the test will be negative when the patient does not have the disease. Essentially, if a test shows a negative result for a disease – the patient can be quite certain they do not have the disease. For both sensitivity and specificity a rate closer to 100 means a perfect test.

The sensitivity and specificity of gFOBT are proven to be very variable in the literature and are based on factors such as; the specific variant of the test, technique of specimen collection, number of samples collected the hydration of the stool sample, and numerous other factors [24]. Evidence suggests that the sensitivity of a gFOBT test can vary from 37.1% for un-hydrated samples to roughly 79% for rehydrated samples [25]. Recently a study conducted by Allison et al. . Examined high-sensitivity gFOBT for CRC malignancies at different stages. Results showed 64% sensitivity for cancerous polyps and 41% for advanced adenomas for gFOBT [26].

Specificity also varies greatly with gFOBT tests. In the same study (Allison et al.), results showed specificity for cancer and advanced adenomas to be 97.7% & 98.1% respectively [27]. However, it is important to note that commercial companies fund many studies investigating the sensitivity and specificity and therefore caution should be taken into account while interpreting the results. The specificity of gFOBT is variable, with low-test sensitivity gFOBT (such as Hemoccult II) tending to have very high specificities. High-test sensitivity gFOBT (such as Hemoccult SENS) tend to have lower specificity. For Hemoccult SENS, which had greater sensitivity for cancer and advanced adenomas compared with Hemoccult II, specificity for cancer and advanced adenomas was 86.7% and 87.5%, respectively, with a combined specificity for cancer and advanced adenomas of 87.5%.

To conclude, for those patients aged 50-and over, annual screenings with gFOBT have been shown to detect a majority of CRC with a moderate to high sensitivity.

Faecal Immunochemical Test (FIT)

A method primarily used in the UK [28], the concept behind FIT involves applying an immunochemical test to stools for blood [29]. Due to the high price associated with FIT, compared to other screening methods (such as gFOBT), FIT is not very commonly used in the US. However, Medicare has recently approved the use of this test in their patients and their uses have become more widespread [30].

FIT has certain advantages over gFOBT testing. Whilst gFOBT mostly relies on the detection of peroxidase and consumption of peroxidase containing dietary products can influence results, the FIT test is more specific to detect human blood [31]. Moreover, high levels of Vitamin C has been shown to prevent peroxidase formation in patients and this can lead to false-negative test results in gFOBT testing and the mechanism by which FIT works is unaffected [32]. Due to the degradation of globin by digestive enzymes in the upper GI tract, FIT is more specific than FOBT in the screening of CRC.

Finally, the high degree of sanitation associated with FIT is of benefit as it requires less immediate handling of stool itself by the patient?

Efficacy and Test Performance: Many new FIT techniques have entered the worldwide medical market. Diagnostic accuracy studies have been conducted for these new FIT methods in patients who have all undergone colonoscopies to rule out the presence of a neoplasia. Numerous studies have been conducted within the last 20 years comparing FIT with gFOBT. Six studies comparing the performance between FIT with Hemoccult SENS, which is the most sensitive of all marketed gFOBT [33-37], have shown no difference in the cancer detection rates. Therefore, in terms of detection rates, FIT and gFOBT are both equally viable options.

To conclude, patients having an annual screening using FIT have been shown to detect the majority of CRC in a population consisting of average-risk adults aged 50 or over.

DNA Methylation

The preliminary analysis of the use of non-invasive methods such as DNA methylation has shown promise for diagnosis of CRC [38]. . Specific epigenetic biomarkers have been identified that have the potential to diagnose CRC with relative good sensitivity and specificity. The aberrant methylation of DNA promoters in CRC appear to interact together with genetic alterations to drive the initiation and progression of colon polyps to CRC [39]. More recently, biomarker panels are being explored as they are showing excellent potential in CRC diagnosis by combining several successful biomarkers, rather than using a single biomarker [40]. Early results of research in methylation-sensitive microRNAs (miRNAs) suggest there might be a role for these as alternative biomarkers [41].

According to the American Association of Cancer Research, investigative DNA methylation detected 64% of colorectal pre-cancers and roughly 85% of cancers on a patient population of nearly 1,100. This method works by analysing stool samples and its attempt to identify “tumour-related DNA alterations” that are often shed into stool by cancerous or pre-cancerous polyps [42]. The non-invasive character of this test makes it patient-friendly and it can be done in the comfort of a patient’s home [43]. . although this methodology has shown promising results, the results still need to be replicated in further clinical trials. However, routine clinical application of this non-invasive test is eagerly awaited by health professionals as the major advantage is the ability to detect precancerous and cancerous polyps both sides of the colon with equal efficiency [44].

INVASIVE TECHNIQUES

Flexible Sigmoidoscopy (FSIG)

FSIG is a CRC screening method that involves scanning the lumen of the lower half of the colon with an endoscope. It is a relatively quicker and safer procedure than colonoscopy as it does not require sedation of the patient and requires less preparation of the bowel.

FSIG – Efficacy and Test Performance: FSIG is a very common worldwide screening method [45]. Two major case studies were carried out regarding the efficacy of FSIG that showed a 60% to 80% reduction in CRC mortality [46-47]. Four major studies are still being conducted in the United States and Europe to further increase our knowledge of the benefits and disadvantages associated with FSIG [48-51]. Additional studies, which show the effectiveness of FSIG derived from colonoscopy studies, show FSIG is 60-70% as sensitive for detecting advanced adenomas/cancers in the colon in comparison with colonoscopy [52-53]. FSIG is seen to be a more effective detection method in men than women due to the differences in distribution of colonic neoplasia [49]. Numerous studies have shown that FSIG may be less sensitive in African-Americans than in Whites [54-55]. Other studies have also been carried out on the effectiveness of FSIG with other races, and as a result we can see that some demographic differences have been shown to influence sensitivity [56-57].

FSIG – Limitations: The primary limitation with FSIG is that it does not scan the entire colon, focusing mainly on the rectum, descending colon, and sigmoid [58]. FSIG has relatively few complications in comparison with other screening methods; however it is vital to recognize them. The primary complication of FSIG is colonic perforation, which occurs in less than one in 20,000 investigations [59-60]. Another limitation of FSIG is that it may miss right-sided tumours. Recent studies have reported an increased mortality for right-sided colon cancers. Atkins et al. argue the case for a FSIG at age 65 as being effective [61].

Global CRC screening programs

As of most recent statistics, 25 countries currently have an active bowel-screening programme including the United States, Canada, Australia, and the United Kingdom [62-63]. However, recent results show that as many as a third of patients eligible for CRC screening in the United States have not been screened [Centres for Disease Control and Prevention. Vital signs: colorectal cancer screening test use—United States, 2012. *MMWR Morb Mortal Wkly Rep* 5 Nov 2013.]. It is due to financial reasons that screening rates are not higher.

The Future of CRC Screening: Today new, more innovative screening methods are being implemented into the modern healthcare setting. Any new methods are thoroughly assessed using clinical studies to determine whether factors such as detection rates, cost [64] and safety profiles are acceptable. All new screening methods must go through FDA testing. It is currently believed that Colonoscopy is the most accurate method of CRC screening [65] despite the fact that it is the screening method associated with the most risk [66].

Computerized Tomographic Colongraphy (CTC)

Computed Tomographic Colonography (CTC) is also being explored as a more accurate method for CRC diagnosis. Halligan et al. compared CTC to barium enema testing in a study and concluded that CTC was a more sensitive method [67].

CTC- Sensitivity & Specificity: CTC has shown a particularly high sensitivity for detecting polyps of the colon. According to Pickard et al. a sample of 1,233 patients demonstrated a sensitivity of roughly 94% for polyps greater than 10mm in size, a similar 94% for polyps greater than 8 mm in size, and roughly 89% for polyps greater than 6mm in size [68]. This study demonstrated a specificity of 96% for CTC. A later study was conducted which only showed a sensitivity of 55% and a specificity of 91% [69]. The large discrepancies between these 2 studies ultimately led to the American College of Radiology Imaging Network (ACRIN) National CT Colonography Trial, which is a community-based study that determines the accuracy of Computed Tomographic Colongraphy [70]. This study demonstrated a sensitivity of 90% and a specificity of 86% for CTC [71]. These support the use of CTC as a legitimate CRC screening technique. It is important to note that in these studies, an increased polyp size directly correlated with increased sensitivities.

CTC - Benefits, Limitations, & Recommendations: CTC is now seen as an improved screening alternative for CRC. It has the benefit of being less invasive and as a result is associated with less morbidity than colonoscopies; as a result it is the preferred method in elderly patients who have comorbidities. Other benefits include completely removing the risks of cardiorespiratory events and bleeding [72-78]. CTC is not a sensitive method for detecting polyps less than 10mm in size and therefore the clinician needs to exercise caution while interpreting the results of a negative CTC. In addition, CTC requires administration of intravenous contrast; this may worsen the renal function of patients with renal insufficiency. However, in the near future a method by the name of "Faecal Tagging" will remove the need for bowel preparation, making CTC an even more appealing screening technique [79]. The use of CTC as a sole screening module for CRC is, however, highly unlikely as direct mucosal examination is thought to be the gold standard [80-82].

Confocal Laser Endomicroscopy (CLE)

Confocal laser endomicroscopy (CLE) is a novel-imaging tool that allows the endoscopist to visualize tissue morphology *in situ* at cellular resolution during endoscopy. Recent studies have shown that CLE has the ability to differentiate neoplastic (adenomatous) from non-neoplastic (non-adenomatous) lesions in the colon and rectum with an overall accuracy of 82-92% [83-84].

More interestingly, there is a short learning curve for CLE image interpretation for endoscopists. Both gastroenterologists and surgeons were able to interpret CLE images with an overall accuracy of over 90% following pattern recognition training [85-86].

Given that conventional endoscopy has limited ability to discriminate neoplastic from non-neoplastic colorectal polyps and lesions, CLE might have the potential to promote targeted

Table 1: Comparison of CRC screening methods to show sensitivity, specificity, and limitations.

Test	Sensitivity	Specificity	Limitations
gFOBT	37.1 – 79% (varies based on degree of hydration of sample) [25-26]	97.7-98.1% [27]	<ul style="list-style-type: none"> Frequent stool collection Patient must avoid NSAIDs and a wide range of foods
FIT	92% [90]	88% [90]	High cost
DNA Methylation	64% [42]	85% [42]	<ul style="list-style-type: none"> No significant disadvantages *method still in infancy
FSIG	95% [89]	83% [89]	<ul style="list-style-type: none"> More effective in men than in women Less sensitive in patients of African descent Does not scan entire colon – often misses right sided tumors Colonic perforation
CTC	90% [71]	86% [71]	Requires a substantial degree of bowel preparation
CLE [Su et al. 88]	95% [88]	95% [88]	Small field of view - only allow point assessment of a lesion/polyp. Relies on another 'red flag' technique to identify these abnormalities

biopsies during surveillance colonoscopy for ulcerative colitis, where large numbers of biopsies are routinely performed. This could potentially reduce endoscopic workload, histopathology costs and reduce the cumulative risk of complications associated with multiple biopsies.

CONCLUSION

There are currently many options available for CRC screening. Therefore, it is necessary for clinicians and policy makers to choose the methods with the greatest evidence base. The most appropriate screening method should be part of a cancer care pathway in which a positive finding should be streamlined economically for definitive management. It is also important to note that there are many barriers to cancer screening such as; limited access to healthcare, lack of education, physician unawareness, etc. There is a need for global CRC screening. As mentioned previously, currently there are only 25 countries that have active bowel screening programs (including the United States, Canada, Australia, the United Kingdom, etc.) However, there are many countries still underserved in this area. This will include the provision of a sensitive screening tool for low-income countries where CRC is often detected in its latter stages. In middle to high-income countries the barriers to screening are less likely to be due to cost. However there is a need to encourage screening through more innovative methods. Behaviour change through commitments and incentives may be a potential solution to this problem [87-91] (table 1). It is important to find less invasive methods to screen for CRC, which could have many advantages for patients and our overburdened healthcare systems, such as testing in the primary care setting. It is an exciting time for cancer screening and colorectal cancer is amidst the forefront of such innovation making it rather exciting times for those involved in the care of cancer patients.

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