Colorectal cancer screening

Colorectal disease is an extremely common cancer and requires early detection for optimal treatment.

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Colorectal cancer (CRC) is one of the most common cancers in the Western world, with an estimated incidence of 148 810 cases in the USA in 2008, and about 50 000 deaths from this disease. If detected early, patients with disease localised to the colonic wall have a 5-year survival of 90%. The 5-year survival for patients with regional disease is 68%, and a dismal 10% in the presence of distant metastases. Given that most sporadic CRCs develop from adenomatous polyps, it has been shown that CRC risk can be reduced by removal of the precursor lesion, the adenomatous polyp. However, not all polyps will develop into cancers; the polyp size and histology are determining factors for CRC risk.[1] Advanced adenomas are defined as being 10 mm or greater in size, have a villous component, or show features of high-grade dysplasia.

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Risk stratification

It is important to establish the individual patient's risk for CRC in order to advise the appropriate age at which screening should commence, and also the type and frequency of screening procedure.

Important questions to ask are:

- Does the patient have a history of colonic adenomas or CRC?
- Does the patient have a history of any condition that might predispose them to the development of CRC, e.g. inflammatory bowel disease?
- Is there a family history of colonic adenomas or CRC? If so, it is important to establish the number of affected relatives, the degree of relationship and the age at diagnosis.
- This review will focus on those individuals at 'average risk' of CRC. Average-risk persons are individuals aged 50 years or older, with no history of colonic adenomas or CRC, and with no family history of polyps or CRC. The average-risk person has a lifetime risk of developing CRC of 6%. CRC has no gender preference, with males and females being at similar risk.

Several CRC screening guidelines have been published, the latest being a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology.[2] Screening should begin at age 50, or as soon as possible after age 50, to age 75. The latest recommendation from the United States Preventative Services Task Force (USPSTF) advises against screening from age 76 to 85 years and older, as the yield from screening in this population group does not justify the additional colonoscopies performed.[3] This recommendation applies only to screening, and not to patients in whom an indication exists for investigation. In a recently published study, a risk assessment tool has been described for use in white males and females without known susceptibility.[4] Various factors are included in the assessment, including a history of flexible sigmoidoscopy or colonoscopy, body mass index, levels of exercise and dietary history. The assessment can be accessed online (http:/www.cancer.gov/colorectalcancerrisk) and can be useful in patient counselling. A validation study for the risk assessment tool has been performed.[5]

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Screening tests for CRC

The preferred test or tests are those that will prevent CRC, rather than just detect the adenomatous polyp. At present only optical colonoscopy offers this possibility, as the polyp can be removed during the examination. The other tests screen for the presence of the polyp or cancer which, if present, mandates colonoscopy for removal of the polyp or biopsy of the suspected cancer. Screening tests can be divided into stool tests or structural tests.

Stool tests

- Faecal occult blood tests (FOBT)
- Faecal DNA tests.

Structural tests

- Colonoscopy
- Flexible sigmoidoscopy (FSIG)
- Double-contrast barium enema (DCBE)
- Computerised tomography colonography (CTC)
- Capsule colonoscopy (CC).

The stool tests are intended to detect cancers, but may detect larger adenomas. The tests may be used alone or in combination with other tests to improve sensitivity, e.g. FOBT and FSIG, or to follow an incomplete or unsatisfactory examination, e.g. colonoscopy followed by CTC.

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There exist several barriers to screening. Possibly the greatest barrier is a lack of awareness by the general public and many health care providers of the importance of CRC screening. Other barriers include the costs associated with screening, and a lack of screening performance or referral by health care providers.

Faecal occult blood tests

These tests may detect cancers and larger polyps (greater than 1 cm). Polyp and cancer bleeding may be intermittent. FOBT tests thus require multiple samples to be submitted for testing, to improve the yield of the test. Annual FOBT testing is recommended. A positive FOBT must be followed by colonoscopy.

Guaiac-based FOBT (gFOBT). Guaiac FOBT detects peroxidase activity of haeme or haemoglobin. Patients performing gFOBT must restrict certain drugs known to cause gastrointestinal bleeding, e.g. aspirin and NSAIDs, and vitamin C, which may give a false negative result. Certain foods including red meat, poultry and fish, and certain raw vegetables, are to be avoided. Three stool specimens are required. Doctors should not perform gFOBT on stool samples obtained following digital rectal examination. This method of screening has been shown to have a sensitivity of only 5% for advanced neoplasia, and 9% for cancers. The sensitivity of gFOBT used correctly varies from 37% to 79%. Studies using gFOBT have been shown to detect cancers at an earlier stage, with a reduction in mortality of 15 - 33%.[6] A problem often encountered in practice is the failure to ensure colonoscopy after a positive FOBT.

Faecal immunochemical tests (FIT) detect the globin portion of human haemoglobin. Globin is broken down by digestive enzymes in the small intestine. A positive FIT is therefore more likely to indicate a colonic source of blood. The test is not influenced by high-dose vitamin C, and dietary restriction is not necessary, with fewer specimens required. As with gFOBT, annual testing is recommended, and a positive test must be followed by colonoscopy. There are no clear differences in sensitivity between FIT and the newer high-sensitive gFOBT. [7]

Stool DNA (sDNA) screening is based on the shedding of adenoma and carcinoma cells in stool. DNA is stable in stool, and specimens can be sent to the laboratory for testing. A minimum of 30 g stool must be submitted for testing. The adenoma-carcinoma sequence results in multiple gene mutations. Detection of mutations therefore requires a multi-target assay. Among mutations tested are K-ras, adenomatous polyposis gene (APC), P53, BAT-26 and DNA integrity analysis. Sensitivity rates of 52 - 91% have been shown, with specificity rates of 93 - 97%.[8] The sDNA test performs better than Hemoccult II, but is inferior to colonoscopy. Stool DNA testing is more expensive than other faecal-based screening tests. A positive sDNA must be followed by colonoscopy.

Endoscopic CRC screening tests include FSIG and colonoscopy. FSIG is unfairly called 'the poor man's colonoscopy', because it examines only the rectosigmoid colon, or at best examines to the splenic flexure. It has been shown to reduce CRC mortality by 60 - 80% for the area examined, with a protective effect lasting 10 years or longer.[9] FSIG is usually performed without sedation, and can be uncomfortable for the patient. Preparation is usually in the form of a phosphate enema administered prior to the examination. Preparation may be less satisfactory than the colonoscopy prep, resulting in an incomplete examination. The minimum insertion should be 40 cm, but preferably higher. With age more polyps and CRCs are right sided, which will not be detected at FSIG. The finding of an adenoma of any size at FSIG is associated with a two-fold increased risk of proximal neoplasm, and therefore mandates a colonoscopy. The interval between FSIG examinations should be 5 years. To improve sensitivity of screening, FSIG may be combined with a sensitive FOBT performed annually. The perforation rate with FSIG is about 1 in 20 000 examinations.

Colonoscopy has been considered the 'gold standard' test for CRC screening. However, it has become apparent that this is not the case, with an advanced polyp miss rate of 6 - 12%, and a cancer miss rate of up to 5%.[10] Most missed lesions are in the right colon. Colonoscopy does allow examination of the whole colon, with the ability to biopsy suspected lesions and, most importantly, to perform polypectomy. Good colonic preparation is critical for a thorough examination, requiring dietary restriction and laxative intake one or more days prior to the examination. The examination is usually performed under light sedation, seldom requiring general anaesthesia. This requires a day off work, and the patient must be accompanied home by a responsible adult. Colonoscopy is very operator skill dependent.

There are no prospective randomised controlled studies of colonoscopy for reduction of CRC mortality. Indirect evidence exists from FOBT and FSIG trials where patients with positive tests underwent

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colonoscopy, with subsequent reduction in CRC mortality rates. Polypectomy may be ineffective, and can result in CRC occurring in up to 25% of subjects between screening examinations.[11] Complications of colonoscopy include post-polypectomy bleeding up to 14 days after the examination, and perforation in 1/1 000 cases, almost always following polypectomy. Colonoscopy sedation may result in oxygen desaturation, hypotension and arrhythmia. Adequate monitoring is therefore mandatory, with emergency treatment readily available in case of complications.

To ensure the highest standards of colonoscopy, the following endoscopist requirements must be met:

- Appropriate training and experience must be demonstrated.
- Patient risk assessment must be documented.
- A complete examination to the caecum must be performed.
- The operator must have the ability to detect and safely remove polyps.
- The operator must have the ability to document polyps, and the method of removal.
- The operator must be skilled in the management of adverse events.
- The operator must arrange appropriate follow-up of histopathological results.
- The operator must provide appropriate recommendations for follow-up surveillance and screening.

Current guidelines suggest follow-up colonoscopy after 10 years in average-risk individuals with a normal colonoscopy. Patients found to have adenomas or CRC should be followed up as per current surveillance guidelines. The USPSTF recommends that screening be discontinued from age 75. This should however be considered on a case-by-case basis.

Radiological imaging studies

Double-contrast barium enema (DCBE) and computerised tomographic colonoscopy (CTC) are the two radiological modalities used in screening for CRC. DCBE allows visualisation of the entire colon. It has a sensitivity of 48% for adenomas ≤7 mm, and 73% for adenomas >7 mm, and will detect most carcinomas.[12] Patients are required to undergo colonic preparation, and the study is performed without sedation. The risk of perforation is estimated at 1:25 000. Patients found to have polyps >6 mm are advised to undergo colonoscopy and polypectomy. DCBE is operator dependent, and with the declining popularity of the modality, fewer radiologists are skilled in the technique. The present role of DCBE is screening for CRC when CTC is not available and for completion of colonic examination where colonoscopy has been unable to examine the entire colon.

CTC has made great strides due to technological advances in CT imaging. Colonic preparation and air insufflation is required, as in the case of optical colonoscopy. The procedure is performed without sedation, and takes about 10 minutes. Faecal tagging is performed in some centres, allowing for more accurate polyp detection. Patients may experience discomfort due to air insufflation. Recent studies have shown sensitivity of 89% for polyps >6 mm, and 94% sensitivity for large adenomas.[13] Two meta-analyses showed sensitivity for larger polyps (>10 mm) of 85 - 93%, with a specificity of 97%. The sensitivity and specificity for smaller polyps was 76 - 83% and 83 - 97%, respectively. The sensitivity for advanced CRC was 96%, similar to optical colonoscopy.[14]

Patients found to have significant polyps at CTC must undergo colonoscopy and polypectomy. CTC interpretation is highly operator dependent, and adequate training is required. Flat polyps may not be detected at CTC. Although small, the risk of radiation may be important in patients undergoing multiple radiological procedures over several years. Perforation rates of 1:3 600 to 1:7 000 have been reported. Of concern are the number of incidental extracolonic findings at CTC. Clinically significant findings have been reported in 4.5 - 11%. Most findings are of low to moderate importance, e.g. gallstones, kidney stones, etc. The further evaluation of the extracolonic findings can result in increased risk and cost to the patient. Patients with CTC-detected polyps >10 mm in size, or with 3 or more polyps >6 mm in size, should undergo optical colonoscopy and polypectomy. The management of patients with a single polyp 6 - 9 mm in size is controversial. The risk of advanced neoplasia is small (3.4 - 6.6%), and polypectomy is recommended. Patients with polyps <5 mm in size should be followed up.

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There are now sufficient data to recommend CTC as a screening tool for CRC prevention, provided state-of-the-art equipment is used, and with expert radiological evaluation of the images. The interval between screening examinations is currently recommended at 5 years. CTC is useful for patients having had incomplete colonoscopy, often undergoing the procedure on the same day.

Capsule colonoscopy (CC)

The Colon Capsule marketed by Given Imaging is an extension of the small-bowel capsule, which has been used in clinical practice for a number of years. The Colon Capsule has recently been licensed by the FDA for CRC screening, and the first South African studies were recently performed. In the first multicentre trial comparing CC with optical colonoscopy, rates of polyp detection were similar: 80% of significant findings at optical colonoscopy and 70% at CC.[15] Preparation is more intensive than for optical colonoscopy. Advantages of CC over optical colonoscopy are the non-invasive nature of the procedure, patients on anticoagulants such as warfarin and clopidogrel do not have to discontinue these drugs, and no antibiotic prophylaxis is required. The finding of polyps will require patients to undergo colonoscopy and polypectomy.

Conclusions

Colorectal cancer can, in most instances, be prevented by using screening procedures. Screening for CRC should begin at age 50, or later if no screening examinations have been performed. The upper age limit for screening is currently recommended at 76 years. A variety of screening tests are available. The tests of choice are those that can both diagnose polyps and early cancers, and allow the opportunity for therapeutic intervention, i.e. polypectomy and biopsy. Patients found to have polyps discovered with imaging tests or positive stool tests must be referred for colonoscopy and polypectomy. Several of the screening modalities are operator-skill dependent, and the necessary level of training and expertise must be demonstrated. Practices should endeavour to educate the general public regarding the importance of CRC screening. CRC screening tests have been shown to be cost effective; this depends largely on good-quality examinations being performed and follow-up guidelines adhered to. No screening test is perfect and patients need to be aware of this shortcoming.

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In a nutshell

- Colorectal cancer can, in most instances, be prevented by using screening procedures.
- Screening for CRC should begin at age 50, or later if no screening examinations have been performed.
- The upper age limit for screening is currently recommended at 76 years.
- A variety of screening tests are available. The tests of choice are those that can both diagnose polyps and early cancers, and allow the opportunity for therapeutic intervention, i.e. polypectomy and biopsy.
- Patients found to have polyps discovered with imaging tests or positive stool tests must be referred for colonoscopy and polypectomy.
- Several of the screening modalities are operator-skill dependent, and the necessary level of training and expertise must be demonstrated.
- Practices should endeavour to educate the general public regarding the importance of CRC screening.
- CRC screening tests have been shown to be cost effective; this depends largely on good-quality examinations being performed, and follow-up guidelines adhered to.
- No screening test is perfect, and patients need to be aware of this shortcoming