

Lecture

Screening for colorectal cancer

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SUMMARY

Screening for bowel cancer really works. The data show that it reduces incidence and mortality. The cost is acceptable and comparable to other screening programs as in breast and cervical cancer. At the present time FOBT is the only modality which balances between effectiveness and safety. The combination of flexible sigmoidoscopy and FOBT is supported by many experts as a good and maybe more effective alternative. Everybody agrees that all men and women should be screened for bowel cancer commencing at the age of 50 years. People in high-risk groups should participate in more intense surveillance and screening programs to prevent CRC as has been shown by many studies. Colorectal cancer can be prevented and that is why all countries should commence screening programs for CRC prevention as soon as possible.

Key Words: Colorectal cancer, screening, colonic tumor

INTRODUCTION

Colorectal cancer (CRC) will develop in about 5.9% of the population over their lifetime.¹ Colorectal cancer is the second most common cause of cancer related death and the third most common cancer in the USA and the UK, with an average survival rate of 40%² ranging from 80 to 90% when the tumor is confined to the bowel wall to <5% in the metastatic disease.³ The vast majority of the cases, more than 80%, are not diagnosed until the cancer has spread through the wall or beyond.

Screening is the term used to describe the investigation of asymptomatic individuals in order to detect disease at an early stage when it is more amenable to treatment, re-

ducing mortality and morbidity and if possible modifying the natural history of the disease. The goal of screening should be to prevent CRC than to diagnose at an earlier stage and this can be achieved by detecting and treating of all adenomas found during screening programs.

According to World Health Organization screening for a disease is justified if a) the disease is frequent and has high mortality and morbidity, b) there is a reliable method detecting the disease at an early stage, with high patient compliance and if clinically applicable, c) post screening treatment improves outcome and prognosis compared to conventional diagnostic methods, d) it is cost effective and benefits outweigh risks.⁴

CRC seems to fulfill many of the above criteria for several reasons: a) it has high incidence, prevalence and cause of death worldwide, b) long period between the development of precancerous lesions (polyps) and invasive cancer which could last up to 20 years, c) adenomatous polyp resection by colonoscopy prevents the progression of the disease to more advanced stages, d) seems to be cost effective in comparison to other frequent cancers like cervical and breast.

The risk of CRC is not the same in all subjects. There is the average population that carries an average risk and the high-risk groups. For this reason guidelines are not uniform to each group.

The guidelines for colorectal cancer screening in high-risk groups can be divided into disease groups and into family group screening. The former consists of patients that have undergone resection of colorectal cancer, polypectomy of adenomatous polyps, long-standing inflammatory bowel disease, acromegaly or ureterosigmoidostomy. The later consists of patients with relatives with colorectal cancer or patients with various inherited polyposis syndromes.

Screening individuals at average risk

People at average risk have no known risk factors and are otherwise healthy people. The aim of screening is to

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prevent and diagnose CRC earlier than the beginning of the 6th decade, when its prevalence is high.

Methods of screening

The various methods of mass screening for CRC include faecal occult blood testing (FOBT), flexible sigmoidoscopy (FS), combination of FOBT and FS and finally total colonoscopy. Recently, the American Cancer Society Colorectal Cancer Advisory Group has reviewed emerging technologies such as: CT colonography, immunochemical FOBT and detection of altered human DNA in stool samples.¹

Faecal Occult Blood testing

It is the most widely investigated screening modality. FOBT has 98% specificity and 50% sensitivity. That means that using this test, 30% of cancers and 75% of polyps will be missed. When using Haemoccult or any similar test, only 2% of the screened population will need further investigation, usually by colonoscopy.⁵ Of these 2% who are investigated, 40% will have pathology found mostly as adenomas a few cancers and rare findings like inflammatory bowel disease.

A metanalysis of four randomized controlled trials and two non-randomized controlled trials of around 443,000 people aged 40 or over in five countries showed 16% reduction in colorectal mortality.⁶

Rehydration of guaiac specimen greatly increases sensitivity and reduces specificity and consequently increases the number of colonoscopies performed. That is why no reduction in CRC incidence has been observed in European trials, which used the unrehydrated FOBT in contrast to US trial of rehydrated FOBT.⁷

Flexible sigmoidoscopy

About half of polyps are detected with a 35 cm flexible sigmoidoscope (FS)⁸. Few case-control studies showed mortality reduction in up to 80% of cases for lesions within the reach of sigmoidoscope.⁹⁻¹¹

The limit of the examination poses the problem of missing half or more lesions depending not only on the length of the large bowel examined but also on the patient discomfort, bowel preparation or endoscopist's skill. It is analogous to mammographic screening of only one breast as Macafee et al¹² mentioned.

Another issue is the proportion of patients who need referral for colonoscopy because of small polyps found on FS. This has been estimated at 5%,¹³ which is more than double the FS referral rate, which is 2%. This extra work-

load needs increased resources in equipment and manpower, which is usually difficult to find.

It has been suggested that 5 years should be the time interval between two sigmoidoscopies. This takes into account that in an average risk population, a polyp probably takes 10-20 years to grow to a size where malignant transformation becomes a possibility.

Combination of FS and FOBT

The combination of FOBT and FS seems scientifically correct despite the increased cost. FOBT can detect possible lesions in the right colon beyond the reach of sigmoidoscopes.

However there is the Norwegian Colorectal Cancer Prevention screening study which randomly enrolled 20,000 subjects aged between 50-64 years to either FS or combination of FS and FOBT.¹⁴ CRC was detected in 0.3% of individuals screened. An adenoma was found in 17% and a high-risk adenoma in 4.2% of subjects. Interestingly there was no difference in CRC and high-risk adenoma detection rate between the two groups.

An accepted CRC screening program that has been suggested, is FS at the age of 50 with biennial FOBT from 60-70 years old.

Colonoscopy

Colonoscopy has the advantage to detect lesions in whole large bowel and remove precancerous lesions, adenomatous polyps, by polypectomy. Colonoscopic examination is the ideal screening method for high-risk populations such as patients with adenomatous polyposis coli and hereditary non-polyposis coli. However Colonoscopic screening would be very expensive both in terms of direct costs and complication rate. It has been calculated that colonoscopic screening of the UK population at age 60 years would probably lead to over 500 severe hemorrhages, over 150 perforations and 50 deaths each year¹². Complication on this scale would rapidly lead to failure of the screening program.

On the other hand, even if colonoscopy was recommended as a screening test, there are no randomized clinical trials that support its use in reducing colorectal cancer mortality. Reports of its effectiveness come from clinical practice, from a case control study¹⁰ and from uncontrolled observational study.¹⁵

It is noteworthy that about half of cases with advanced proximal neoplasia will not have distal adenomas and will not be detected if colonoscopy is not used as a screening method.¹⁶

The ideal interval of CRC screening with colonoscopy seems to be 10 years beginning at the age of 50 years, due to the high incidence of CRC during the 6th decade of life and the long period necessary for an adenoma to progress to invasive cancer (10 to 20 years).

Double –Contrast barium enema

Double contrast barium enema lacks sensitivity and specificity in comparison to colonoscopy. It is insensitive for the detection of small or depressed lesions. It is used as an alternative when colonoscopy cannot be performed or has failed and that is why it is recommended every 5 years.

Emerging Screening Technologies

CT Colonography [Virtual Colonoscopy]

CT colonography is an imaging procedure that uses computer programming to combine multiple, helical CT scans in order to create two- or three-dimensional images of the interior of a patient's colon.¹

In the hands of highly experienced radiologists, polyps greater than 10 mm are detected with sensitivity and specificity that approaches 90%, with sensitivity falling to 50% for polyps less than 5 mm.¹⁷

It has the ability to image the colon proximal to occlusions or redundant loops and it may be the test of choice for completing examination of the colon after failed or incomplete colonoscopy.

Available studies comparing CT colonography in a prospective trial for CRC screening have shown a wide variation in results.¹⁸⁻²⁰ Sensitivity for polyps larger than 10 mm in size varies from 55% to 94%. Reasons for the variability include study populations, relative risk of neoplasia, variation in the technique used to prepare/cleanse patients, differences in technology and experience of operator.

Currently, none of the clinical practice guidelines or societies recommends this technique for CRC screening.

Immunochemical Fecal Occult Blood testing

The immunochemical tests, such as Hemeselect (SmithKline Diagnostics, San Jose, CA), Insure™ (Enterix, Inc., Falmouth, ME) and others employ a more complex reaction that uses monoclonal and/or polyclonal antibodies that detect the intact globin protein portion of human hemoglobin.

Advantages of this test over a guaiac test include, improved specificity and potential increase in patient compliance. However, there is limited clinical experience, because it has not been tested in large screening populations of average-risk individuals.

The Recommendations for Screening and Surveillance for the Early Detection of Adenomatous Polyps and Colorectal Cancer of the American Cancer Society states that “in comparison with guaiac –based tests for the detection of occult blood, immunochemical tests are more patient-friendly, and are likely to be equal or better in sensitivity and specificity”.²¹

Screening Stool for DNA mutations

A stool test for DNA mutations has been produced that targets point mutations at 15 mutational hot spots on *K-ras*, *APC* and *p-53* genes, mutations on *Bat-26* (a micro-satellite instability marker) and long DNA (DNA not degraded by apoptosis). The first version of the test showed a sensitivity of 52% and specificity of 94%. A new version has recently been released that reports sensitivity of 87.5% and specificity of 82%.²²

There is lack of data from screening populations so far and that is why the method is still under investigation.

Cost effectiveness

Health economic data show that FOBT will be as cost effective as either breast or cervical screening. The cost has been estimated from \$ 18,000 to 40,000 per year of life gained.^{23,24}

Compliance rate

A successful screening program demands compliance of more than 50% by the public otherwise the benefits are likely to be outweighed by the costs of implementing the program.¹²

FOBT screening trials achieved population compliance rates of 35-50% in the general population and >60% in clinical trials. People who expressed interest in participating in the trials attended frequently in comparison to the general population.

If FOBT starts at the age of 50 years when CRC incidence is low, it is likely that compliance rates will have fallen by the age of 60 years when cancer incidence is increasing. It seems better to start FOBT after age 60 years to detect cancers (mainly proximal) not prevented by a prior FS screening.²⁵

Flexible sigmoidoscopy compliance rate has been reported from 40% to 60% in the UK population¹². The lower incidence of CRC in USA has been attributed to the higher acceptance of the method as a screening tool by the public and to the high rate of polypectomies performed during the screening test.

The combination of FS and FOBT has caused some

confusion about the need for individual testing and has not been accepted widely.

Colonoscopy compliance rate is rather low even in the most developed countries of Europe. This may have to do with the limited resources in each country demanding massive screening of a large part of the population, especially nowadays with the continuous ageing of the population in Western societies. The complication rate of colonoscopy in a large scale testing is another concern that has not made this method very popular either among governments which fund screening programs or among the public.

Screening individuals at high risk

The guidelines presented below are the summary of the guidelines published by the British Society of Gastroenterology and the Association of Coloproctology in Great Britain and Ireland.²

Follow up after resection of colorectal cancer

There is no evidence that intense follow up for the detection of recurrent disease improves survival. However, it is reasonable to offer liver imaging to asymptomatic patients under the age of 70 in order to detect operable liver metastases once during the first two years after resection, as 80% of recurrences after resection of colorectal cancer occur within the first two years after surgery.²⁶

Although there is no evidence that colonoscopic follow up improves survival, it does produce a yield of treatable tumors. Between 5% and 10% of patients will develop metachronous tumors. It is recommended that a "clean" colon be examined by colonoscopy 6 months after surgery and thereafter at five yearly intervals up to the age of 70 years.

Surveillance after removal of colorectal adenomatous polyps

This group of patients represents the main workload of the Gastroenterology departments worldwide. The risk of CRC in patients with adenomas depends mainly on the number and the size of them. According to the risk three categories can be defined²⁷: *low risk* refers to patients with 1-2 small adenomas (<1 cm), *intermediate risk* refers to patients with 3-4 small adenomas or at least one \geq 1cm and *high risk* refers to patients with 5 or more small adenomas or at least 3 with one of which \geq 1cm.

For the low risk group of patients, available results suggest that the benefits compared with the risks of surveillance colonoscopy are likely to be small in patients with one to two small adenomas and that follow up colonoscopy if undertaken at all, should be delayed at least five years.

Patients, who belong to the intermediate category, can be safely left until three years for the next follow up colonoscopy.

In the high-risk group of patients, the data suggest that an additional colonoscopy at 12 months is warranted in people found at a single colonoscopy to have five or more small adenomas or three or more adenomas, at least one of which is large.

Surveillance can cease following a single negative follow up colonoscopy in lower risk patients, but that two negative examinations are required for higher risk patients.

There is no evidence to suggest that recommendations should differ for patients with a family history who are found to have an adenoma unless it is suspected that they have one of the dominantly inherited syndromes.

The decision to undertake each colonoscopy examination at follow up should depend not only on the number and type of adenomas, but also on the patient's age and wishes and the presence of significant co morbidity.

Screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease

Patients with ulcerative colitis (UC) are at increased risk of colorectal carcinoma. A metaanalysis²⁸ has shown that the risk for any patient with colitis is 2% at 10 years, 8% at 20 years and 18% after 30 years of disease. These figures rise to 9%, 31% and 50% respectively in patients with concomitant primary sclerosing cholangitis (PSC).²⁹

Dysplasia is generally recognized to be premalignant. The development of CRC in patients with UC differs from sporadic cancer. Dysplastic lesions may develop not only from adenomatous polyps but also from flat mucosal.

Surveillance colonoscopies should be performed when disease is in remission²⁷. All patients should have a screening colonoscopy after 8-10 years that will also clarify disease extent. Regular surveillance should begin after 8-10 years (from onset of symptoms) for pancolitis and after 15-20 years for left sided disease. As the risk of cancer increases exponentially with time, there should be a decrease in the screening interval with increasing disease duration. For patients with pancolitis, in the second decade of disease a colonoscopy should be conducted every three years, every two years in the third decade, and yearly by the fourth decade of disease. Two to four random biopsy specimens every 10 cm from the entire colon should be

taken with additional samples of suspicious areas. Patients with PSC (including those with orthotopic liver transplantation) represent a subgroup at higher risk of cancer and they should have annual colonoscopy.

Screening in patients with acromegaly

Acromegaly is a rare disease with increase prevalence of colorectal cancer and adenomas.³⁰ The largest prospective survey comes from St Bartholomew's Hospital that follows up 222 patients, of whom 10 developed carcinoma and 45 adenomas.³¹

Patients with acromegaly should be offered regular colonoscopic screening, starting at the age of 40 years. Total colonoscopy is required. The frequency of repeat colonoscopy should depend on the findings of the original screening and the activity of the underlying acromegaly.

Patients with an adenoma at first screening or increased IGF-1 levels above the maximum age-corrected normal range should be offered screening at three year intervals. Patients with either negative first colonoscopy or a hyperplastic polyp should be offered screening at five-year intervals.

Monitoring patients with ureterosigmoidostomy

Neoplasia at the anastomosis of the ureters and colon in patients with any urinary diversion that mixes urine and stool occurs in about 24% of patients at 20 years of follow up³². The earliest recording is 10 years after formation.

All patients should have a flexible sigmoidoscopy once per year, commencing 10 years after surgery.

In patients who have had an ureterosigmoidostomy but have subsequently been converted to an alternative diversion, flexible sigmoidoscopies should still be done unless it is known that the ureteric anastomosis is removed.

Screening family groups at high risk

Surveillance for people with two first degree relatives with colorectal cancer or one first degree relative diagnosed with colorectal cancer under 45 years

Empiric risk of colorectal cancer can be estimated from family history parameters. These parameters consist of the current age of the patient whose risk is being considered, the age of each affected relative as well as the number and relationship of those affected relatives.

Total colonic assessment is recommended at consultation about family history or between the ages of 35-40 years, whichever is later and repeat colonic assessment at the age of 55 years.³³

People with less family history do not merit surveillance over and above that recommended for the general population.

Surveillance for hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, juvenile polyposis, and Peutz-Jeghers syndrome

The risk of cancer ranges from 10% to 100% in the syndromes that are the focus of this guidance. Observing the specific features of its syndrome can identify affected families, although the identification of the causative genes by molecular analysis is increasing in recent years.

HNPCC

HNPCC is an autosomal dominant genetic disorder resulting from mutation of one of five DNA mismatch repair genes (MMR). One to 2.4% of all cases of CRC fulfill HNPCC criteria. The proportion of CRC cases attributed to DNA mismatch repair genes is 2-3%. The lifetime gastrointestinal cancer risk associated with HNPCC is reported as round 80% for colorectal cancer and 13%-29% for gastric cancer.³⁴⁻³⁵

HNPCC families should be registered in Regional Clinical Genetics Centers and family members offered counseling. Biennial total colonic surveillance should start at age 25 years, or five years less than the first cancer case in the family. Surveillance should continue to 75 years or until the causative mutation in that family has been excluded.³⁶

Patients with an established colorectal malignancy and who are from an HNPCC family or known to carry a mutation in an MMR gene should be counseled and offered a surgical procedure that includes both a cancer control element and prophylaxis. At present there are no data supporting, or against, offering primary prophylactic surgery for patients who do not yet have cancer but are MMR gene carriers.

In families where there are cases of gastric cancer, biennial upper gastrointestinal endoscopy should commence at age 50, or five years less than the first gastric case in the family, whichever is earlier. Surveillance should continue to 75 years or until the causative mutation in that family has been excluded.

FAP

FAP is an autosomal dominant syndrome with near complete penetrance. The syndrome is attributable to mutations of the APC gene on chromosome 5q and this mutation can be identified in 60% of families. Around 25% of all cases are attributed to new (sporadic) mutations of the APC gene. The lifetime gastrointestinal cancer risk asso-

ciated with FAP is almost 100% for colorectal cancer and 7% for cancer from gastroduodenal polyposis.

FAP families should be registered in Regional Clinical Genetics Centers and family members offered counseling. In a minority of FAP families a mutation cannot be identified and so annual flexible sigmoidoscopy should be offered to at risk family members from age 13-15 years until age 30 and at three to five year intervals thereafter until the age of 60 years.³⁶ After colectomy and ileorectal anastomosis, the rectum must be kept under review at least annually for life because the risk of cancer in the retained rectum is 12-29%³⁷.

Patients with FAP should be advised to undergo prophylactic colectomy between the age of 16 and 20 years. The operation of choice is proctocolectomy and ileoanal pouch. However, colectomy and ileorectal anastomosis remains a useful option for many patients with relatively few polyps.

Gastroduodenal and periampullary malignancy account for a small but appreciable number of deaths in FAP patients. The overall lifetime risk of periampullary cancer is 3%-4%. Three-yearly upper gastrointestinal endoscopy is recommended from age 30 years. Patients with a large number of duodenal polyps should undergo surveillance yearly.

PJS

PJS is a rare autosomal dominant syndrome with high penetrance. The risk of colorectal cancer is 10% to 20% and the risk of gastric malignancy 5%-10%.

Large bowel surveillance by colonoscopy is recommended at three-year intervals from the age of 18 years. Upper gastrointestinal surveillance is recommended at three-year intervals commencing from the age of 25 years.³⁶

JP

JP is associated with a colorectal cancer risk of around 10%-38% and a gastric cancer risk of 21%.

Large bowel surveillance for at risk people is recommended at intervals of one to two years from age 15-18 years or even before if the patient has presented with symptoms. Screening intervals could be extended at age 35 years in at risk individuals. However, documented gene carriers or affected cases should be kept under surveillance until age 70 and prophylactic surgery discussed.³⁶

Upper gastrointestinal surveillance is recommended at intervals of one to two years from the age of 25 years.

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