PRO SCREENING : LESSONS FROM THE UK SIGMOIDOSCOPY TRIAL. W. Atkin. Colorectal Cancer Unit, Cancer Research UK, St Mark's Hospital, Northwick Park, Harrow, UK.

Both incidence and mortality from colorectal cancer (CRC) are theoretically preventable by screening since extensive evidence suggests that advanced and frequently fatal CRCs develop during an asymptomatic phase from early, localised and therefore treatable cancers, which in turn develop from benign adenomatous polyps. The average time for an early, asymptomatic cancer to become symptomatic is thought to be around 2-3 years and for an adenoma to progress to carcinoma around 10 years. These lag times offer ample time for a screening intervention.

Flexible sigmoidoscopy (FS) allows direct examination of the mucosa of the sigmoid colon and rectum where 60% of colorectal cancers and adenomas are located. Satisfactory bowel preparation for FS can be achieved with a single enema that can be self-administered at home. Evidence from case-control and cohort studies indicates that screening by sigmoidoscopy reduces incidence and mortality rates of distal CRC. However in the absence of evidence from randomised trials, most countries have been unwilling to introduce endoscopic screening. Four randomised trials are in progress (in UK, Italy, US and Norway 1-4). Although the US recommends a 5 yearly screening interval, the protection afforded by a single FS may last for up to 10 years or even longer depending on the age at which it is undertaken. The UK and Italian trials are examining the effectiveness and duration of protection of a single FS screen undertaken between age 55-64. Both trials have completed recruitment and screening and the participants are being followed up using national cancer registries. It is expected that the first results on incidence rates for both trials will be available in 2008.

The UK Sigmoidoscopy Trial is the largest of the trials and has already yielded important results on the feasibility, safety and acceptability of FS as a screening method. This trial recruited 194,726 men and women, aged 55 to 64 years, who had responded to a questionnaire and expressed an interest in having an FS screen. One third were randomly assigned to the FS screening group of whom 71% underwent screening ; the remainder was assigned to a control group which was not contacted. Small polyps were removed during the screening FS and colonoscopy was performed only if high risk polyps (three or more adenomas, size 1 cm or greater, villous, severely dysplastic or malignant) were found. Of the 40,674 people who had the FS test, 5% were classified as high risk and were offered colonoscopy (94% accepted) ; and the remaining 95% were discharged. 62% of the cancers detected at screening were at Dukes' Stage A (this compares with 40% with the fecal occult blood test (FOBT), suggesting the FS detects cancers early than FOBT. Results of our trial and subsequent research suggest that sigmoidoscopy screening is remarkably safe : there was only a single perforation in the 40,000 participants who had a total of 19,000 polyps removed during screening. It is also highly acceptable, with 67% of an unselected UK population attending for screening. We also demonstrated that it would be feasible to offer a single FS to the whole UK population, probably by having nurses undertake the procedure. We are also examining the possibility that non-medical pathologists would undertake classification of any polyps removed.

If the UK Sigmoidoscopy Trial demonstrates that FS screening is as effective as published evidence would suggest, then it is likely that a single FS screen would be offered to the whole population. This will require an increase in manpower and currently we are addressing training and resource issues.

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Flexible sigmoidoscopy as a screening test for colorectal cancer

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Abstract

Flexible sigmoidoscopy (FS) is one of the screening modalities for colorectal cancer. The rationale for screening with flexible sigmoidoscopy is that it provides direct visualisation of the colon, and suspicious lesions can be biopsied. The most obvious disadvantage is that it examines only the lower third of the colon. The technical aspects of FS are sufficiently clear to enable us to define what FS can and cannot do. From the point of view of screening, FS clearly cannot completely exclude the presence of colon cancer in all asymptomatic people. A distinction must be made between screening the general population and testing the individual seeking screening. For the former, obtaining the greatest mortality benefit safely and at an acceptable cost to the nation is the crux of the matter. Recently published data indicate that FS is a cost-effective screening strategy, although colonoscopy and annual fecal occult blood test avert a greater number of cancer deaths. The results of randomised controlled trials of screening FS and colonoscopy, currently being conducted, will allow us to make a more accurate comparison with the established data regarding fecal occult blood test. In conclusion, flexible sigmoidoscopy every 5 years with or without FOBT is one of the screening methods recommended by major professional organizations. It identifies 50 to 70% of the advanced neoplasms, if any discovery of a distal neoplasia is followed up with a total examination of the colon by colonoscopy. (Acta gastroenterol. belg., **2005**, 68, **248-249**).

Introduction

The rationale for screening with flexible sigmoidoscopy (FS) is that it provides direct visualisation of the colon, and suspicious lesions can be biopsied. The most obvious disadvantage is that it examines only the lower third of the colon (3,4). Unlike colonoscopy, FS is most commonly performed without sedation. Preparation for FS can be achieved with a single enema that can be self-administered at home (1). As with the fecal occult blood test, patients with a positive examination, require further examination by colonoscopy (3,4).

It has been well established that patients with an adenomatous polyp found on sigmoidoscopy have an increased probability of additional lesions located more proximally. Hyperplastic polyps are frequently found in the distal colon. With rare exception, there is no significant risk that a hyperplastic polyp will progress to CRC. In addition, hyperplastic polyps in the distal colon do not appear to give information regarding adenomatous polyps elsewhere in the colon (7,11).

Discussion and literature data

The sensitivity of FS is 96.7% for cancer and large polyps and 73.3% for small polyps. The specificity is 94% for cancer and large polyps with a 92% specificity for small polyps (3,4). In the absence of any distal adenoma, 2%-5% of asymptomatic people screened will have isolated proximal advanced lesions. Even more may have isolated nonadvanced proximal neoplasia (9,10). Whether this is acceptable in the context of cancer screening may become clear from prospective studies. The fact that sigmoidoscopy may also miss lesions within the area of the colon that is examined may have implications for the screening intervals used. It has been shown on repeat FS that polyps may be missed in up to 20% of cases, while with colonoscopy a 6% miss rate for adenomas larger than 1 cm has been reported (9).

Only indirect evidence derived from several case-control studies using either rigid sigmoidoscopy or a combination of rigid with flexible sigmoidoscopy currently exists to support the effectiveness of FS. The best designed trial, by Selby *et al.*, avoided many of the biases inherent in case-control studies. The screening histories of persons who died of colorectal cancer were compared against controls and a 59% reduction in mortality from cancers of the rectum and distal colon was found in individuals who had undergone sigmoidoscopic evaluation (3,4,5). Newcomb *et al.* reported an 80% reduction in mortality from cancer of the rectum and distal colon in persons who had ever undergone sigmoidoscopic examination compared with individuals who had never done so (3,4,5).

Of great interest is the optimal interval for screening sigmoidoscopy. In the study by Selby *et al.* described above, the effectiveness of screening sigmoidoscopy was found to be just as great for patients who had undergone the procedure 9-10 years before as compared to those who had just undergone the examination. A modelling study evaluating the optimal interval for sigmoidoscopic screening found that 90% of the effectiveness of annual screening was preserved with an interval of 10 years. This model assumes that adenomatous polyps take 10-14 years to evolve into invasive cancers (3,4).

The baseline findings of a multicentre randomised trial from the UK have been reported. Out of 354 262 of those aged 55-64 years invited to undergo screening

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with a single FS in 14 UK centres, 194 726 (55%) accepted. Out of these 170 432 eligible individuals were randomised. Attendance among those assigned screening was 71% (40674 of 57254). A total of 2131 (5%) were classified as high risk and referred for colonoscopy. Those with no polyps or only low risk polyps (n = 38 525) were discharged. Distal adenomas were detected in 4931 (12%) and distal cancer in 131 (0.3%). Proximal adenomas were detected in 386 (18.8% of those undergoing colonoscopy) and proximal cancer in nine cases (0.4%). Sixty-two percent of cancers were Dukes'A. There was one perforation after FS and four after colonoscopy (1,2,3,4).

The baseline findings of a multicentre randomised trial in Italy in individuals aged 55-64 years have also been reported. Distal adenomas were detected in 1070 subjects (10.8%). Proximal adenomas were detected in 116 of 747 (15.5%) subjects without cancer at sigmoidoscopy, who then underwent colonoscopy. A total of 54 subjects were found to have colorectal cancer, a rate of 5.4 per 1000 (54% of which were Dukes'A). Two perforations occurred (one in 991 sigmoidoscopies and one in 77 colonoscopies) and one hemorrhage requiring hospitalisation (3,4). Flexible sigmoidoscospy is recommended every 5 years for average-risk individuals, starting at the age of 50. Compliance with FS screening has traditionally been poor. FS is viewed as potentially uncomfortable and embarrassing. Only 15 to 30% of eligible persons regularly undergo FS. After the initial examination, ongoing compliance is also poor, undercutting its utility for colorectal cancer (CRC) prevention. Various efforts to improve adherence generally have failed (7,12).

Many guidelines recommend combing FOBT with sigmoidoscopy (13). The addition of FS to FOBT can increase the yield of neoplasia detection fourfold compared to FOBT alone. However, the clinical utility of the converse – adding FOBT if FS is already being performed - is less clear (7). Lieberman *et al.* found that the addition of FOBT to FS raised neoplasia detection rate from 70% to approximately 75% (7,15). One-time screening of asymptomatic subjects with the fecal occult – blood test plus sigmoidoscopy fails to identify about one quarter of subjects with advanced neoplasia and one half of subjects with advanced proximal neoplasia. Over a 16-year period, a one time flexible sigmoidoscopy and FOBT was not as effective as biennial FOBT in detecting colon or rectal cancers (8).

The technical aspects of FS are sufficiently clear to enable us to define what FS can and cannot do. From the point of view of screening, FS clearly cannot completely exclude the presence of colon cancer in all asymptomatic people. A distinction must be made between screening the general population and testing the individual seeking screening (16). For the former, obtaining the greatest mortality benefit safely and at an acceptable cost to the nation is the crux of the matter. Recently published data indicate that FS is a cost-effective screening strategy, although colonoscopy and annual FOBT avert a greater number of cancer deaths (9,14). The results of randomised controlled trials of screening FS and colonoscopy, currently being conducted, will allow us to make a more accurate comparison with the established data regarding FOBT.

Conclusion

In conclusion, flexible sigmoidoscopy every 5 years with or without FOBT is one of the screening methods recommended by major professional organizations. It identifies 50 to 70% of the advanced neoplasms, if any discovery of a distal neoplasia is followed up with a total examination of the colon by colonoscopy.

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