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Virtual Colonoscopy : A new tool in the prevention of colorectal cancer

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The burden of colorectal cancer is preventable

In 2005, a total of 386,000 new cases of colorectal cancer are expected in Europe (including Russia). In addition, 212,000 patients will die of the disease during the same year [1]. In subsequent years, the numbers are likely to increase further due to the aging of the population. Preventive measures against colorectal cancer are based on two main pillars: **primary prevention**, through recommendations for a healthy lifestyle (physical activity and diet); and **secondary prevention**, through early detection and treatment of superficial cancer and premalignant precursor lesions. Adenomatous colonic polyps are well-known precursors of colorectal cancer, and the risk of malignant transformation in these lesions is high when their diameter reaches a cut-off value of 10 mm. Superficial cancer and premalignant lesions in the colonic mucosa are found in asymptomatic individuals. The average risk of sporadic colorectal cancer reaches a significant level in individuals of both sexes aged 50 or over. People with a close relative who has had colorectal cancer have a 2–3-fold increase in the level of risk, attributable to shared environmental factors. A determining genetic factor leading to familial cancer syndromes is responsible for approximately 5% of cases. In this situation, individuals who have the mutation have a 100% chance of developing cancer.

Screening is justified for a disease if the incidence is sufficiently high and if the procedures used to detect and treat it have been proved to be effective (as in the case of breast cancer and cervical cancer in women). The justification for carrying out screening for colorectal cancer is now firmly established. Secondary prevention is based on screening asymptomatic persons when they reach the age of 50. Screening can be offered either at the individual level, by a physician advising patients who are aware of the risk and who are willing to undergo examination (opportunistic screening), or using mass-screening measures managed by health-care authorities. In the latter case, the cost-effectiveness of the measures being taken has to be evaluated. The death toll due to colorectal cancer can be significantly reduced through policies designed to achieve early detection and treatment of the disease. Complete cure of this type of cancer is possible with simple procedures (such as polypectomy) [2] when early detection is achieved and the tumor developing in the colonic mucosa is still superficial, with limited invasion into the submucosa. If the tumor advances further into the depth of the digestive-tract wall, the consequent lymph-node involvement produces a transition from localized to regional or distant disease, with a corresponding reduction in curability. The burden of colorectal cancer can also be reduced if the number of new cases (the incidence) is reduced by destroying benign precursor lesions in the colonic mucosa [3].

Virtual colonoscopy is emerging as a screening procedure

Radiographic imaging using the double-contrast barium enema has declined in importance for screening purposes, as it is less sensitive and less specific than colonoscopy. By contrast, the reliability of virtual colonoscopy using two-dimensional and three-dimensional images obtained with computed tomography or magnetic resonance imaging is

increasing, along with the rapid advances being made in digital imaging and dedicated software. Virtual colonoscopy was initially tested in individuals at high risk of colonic neoplasia, and it was found to have a good level of sensitivity for lesions larger than 10 mm. The technique was soon recognized as being a helpful complementary method when colonoscopy is not possible or is incomplete. At the end of 2003, fresh prospects were reported by a group of radiologists and gastroenterologists led by Perry J. Pickhardt, who demonstrated that virtual colonoscopy is capable of detecting polyps and can be used for screening in asymptomatic individuals. Their study, published in the *New England Journal of Medicine* [4], included 1233 asymptomatic individuals in the 50–79 age group, with an average risk of cancer, who were referred for screening colonoscopy.

The strengths of this study lie in the **techniques** used and in **design** of the protocol. Initially, the colon has to be empty; the patient follows a 24-h intestinal preparation regimen (as in optical colonoscopy) and also ingests barium to tag solid food residues and hydrosoluble Gastrografin to tag liquid residues in the colon. Secondly, just before the procedure, the colon is filled with air via a flexible catheter, producing a pneumocolon. Thirdly, radiographic imaging is carried out using a computed tomography (CT) scanner with four to eight channels, and three-dimensional image processing is carried out with commercially available software. The solid and liquid residues are digitally subtracted from the images of the air-filled colon. Fourthly, optical colonoscopy is carried out immediately after the radiographic imaging. As the operator evaluates each segment of the colon, the results of the virtual exploration are displayed, and if there are any discrepancies, the segment is again examined endoscopically. This allows double-checking for false-negative or false-positive results. On average, the examination time for each patient is 14 min for the radiographic tests and 31 min for the endoscopic test. The sensitivity of virtual colonoscopy for polyps compares favorably with that of optical colonoscopy, and even shows slightly higher values for polyps at least 8 mm in diameter.

Virtual colonoscopy with three-dimensional analysis, with digital subtraction of solid and liquid food residues, is thus a viable screening method for neoplastic colorectal lesions. The availability of this new screening test is a welcome innovation. As has been demonstrated with cervical cancer, the effectiveness of screening procedures is mainly dependent on broad coverage of the target disease. The availability of a range of different tests is likely to increase compliance in the population concerned. At the individual level, the best screening test is the one that meets with acceptance and is widely used. The acceptability of a test depends on multiple – often contradictory –behavioral factors [5]. In the study by Pickhardt et al., [4], questionnaires sent to patients after the screening examinations showed that the majority of patients (68%) rated virtual colonoscopy as being more acceptable in terms of overall convenience than optical colonoscopy. However, only 50% stated that they would prefer virtual colonoscopy for a future screening.

Pros and cons of optical colonoscopy

Endoscopy has a unique role in the prevention of colorectal cancer, due to the dual facilities it provides. On the one hand, it allows direct access to neoplastic lesions (superficial malignant and premalignant lesions) for detection, morphological evaluation, and histological control – i.e., it provides **screening**. On the other hand, it also allows simultaneous endoscopic resection of the lesions if they meet appropriate criteria – i.e., it also makes **treatment** possible.

Flexible sigmoidoscopy is a relatively easy procedure; the intestinal preparation is simple, no sedation is required, and the time required for the patient and the operator is minimal. The handling of the instrument can be transferred to trained gastrointestinal nurses without any loss of efficacy. On the other hand, the exploration only covers the distal large bowel (rectum, sigmoid, and part of the ascending colon), so that proximal colonic lesions escape detection. Flexible sigmoidoscopy is a valid procedure for screening colorectal cancer. In the USA and in European countries (such as the United Kingdom and

Scandinavia), it has been adopted in large-scale protocols. Compliance among unselected individuals invited to participate in screening is in the range of 40–45%; the rate is higher in groups belonging to specific insurance programs (56% in the Kaiser medical care program in the USA) [6].

Colonoscopy, as the final examination common to all screening protocols, provides complete exploration of the large bowel. In comparison with flexible sigmoidoscopy, colonoscopy requires a 24-h preparation regimen, which patients often find as unpleasant as the procedure itself. The procedure requires sedation in most cases, and patients are not allowed to drive a car during the following few hours. Colonoscopy is thus more demanding for the patient, and even with optimal organization it requires a minimum of 2–3 hours. In addition, there is a very small, but not negligible, risk of severe complications (such as perforation). This method of thorough and complete exploration of the colon is fully justified in symptomatic patients. The question is whether it should also be offered for screening of asymptomatic individuals, as a one-step procedure that often ensures simultaneous diagnosis and treatment. Evidence is accumulating for a positive answer. In the literature, several analyses have included colonoscopy as a viable option for screening average-risk individuals. In the USA, screening colonoscopy every 10 years has been recommended by the U.S. Preventive Services Task Force, and since 2001, the Health Care Financing Administration has approved coverage of the procedure by Medicare. Finally, compliance among individuals invited to undergo colonoscopy can be high when they belong to specific insurance programs: at the Veterans' Medical Center, 3196 persons accepted among 4659 who met the enrollment criteria [7].

Screening strategy

Screening tests are characterized by their sensitivity (the proportion of negative tests in persons who have the disease) and their specificity (the proportion of positive tests in persons who do not have the disease). Each procedure has advantages and drawbacks in terms of compliance and efficacy.

Selection tests. The fecal occult blood test (FOBT) is easily carried out in the patient's home. However, its sensitivity is only approximately 50% for malignant lesions, and much lower for premalignant lesions. Positive (and false-positive) tests require further examinations, and negative tests are falsely reassuring. Widespread used of the fecal occult blood test can reduce the mortality due to colorectal cancer [7].

Detection tests. Virtual and optical colonoscopy are both unpleasant examinations for the patient. The virtual examination method is more acceptable to the majority of patients, but colonoscopy is still required when there are positive or false-positive findings. Nonneoplastic polyps cause false-positive tests, representing 58% of the positive tests for polyps in the pilot study by Pickhardt et al. [4]. The proportion was lower (37%) if the diameter of the lesion was 10 mm or more. The impact of virtual colonoscopy on the numbers of consecutive screening colonoscopies needed depends on the definition of a positive finding. If the cut-off value is a diameter of 10 mm, colonoscopy is required in only 7.5% of tests; with a cut-off value of 8 mm, colonoscopy is required in 13% of cases, and at 6 mm colonoscopy is required in 29% of cases. Relative to acceptability to patients undergoing screening, the alternative is between offering optical colonoscopy to all patients or virtual colonoscopy for all patients followed by optical colonoscopy in some. In relation to cost-effectiveness, however, most analyses have concluded that virtual colonoscopy is less cost-effective than optical colonoscopy.

It should be noted that this alternative strategy, based only on the detection of **protruding neoplastic lesions**, is being challenged by new concepts of the process of carcinogenesis in the colon. Polyps are not the sole precursors of colorectal cancers, and flat or **nonprotruding neoplastic lesions** (slightly elevated or depressed lesions) also play an important part. Data from Japanese series [8] suggest that at least 40% of early cancers

have a nonprotruding morphology; slightly depressed lesions are associated with an increased risk for malignancy, even when their diameter is less than 10 mm. Lesions of this type have been misdiagnosed in reports from Western countries, and there is growing evidence that they have a similar prevalence. For example, in a recent colonoscopy study conducted in European patients in Sweden [9], the numbers of protruding and nonprotruding superficial cancers observed were 11 and five, respectively. There is no doubt that an optical colonoscopic examination using appropriate techniques is better able to detect flat lesions of this type than virtual colonoscopy.

Future technological developments

With regard to **selection** screening tests, molecular-biological techniques are emerging, and genetic testing for tumor antigens in feces is likely to become a competing technology in the future, with a higher specificity than fecal occult blood testing.

With regard to **detection** screening tests, the technologies used in both virtual and optical colonoscopy are still progressing. In the field of radiography, the rapid development of postprocessing methods for digital images is unlikely to slow down. It can seriously be hoped that digital subtraction of feces from the image in the colonic lumen will make intestinal preparation unnecessary, further increasing compliance with screening examinations using virtual colonoscopy. Magnetic resonance imaging is suitable for tissue characterization and should be capable of tagging neoplastic areas. In the field of endoscopy, parallel developments are taking place – including high-resolution magnification, endoscopic cytoscopy, and the development of image processing methods including structure enhancement, color enhancement, and narrow-band imaging. The analysis of lesions is approaching the level of an optical biopsy, capable of providing support for treatment decisions. During the endoscopy procedure, lesions can be classified as nonneoplastic (no treatment), neoplastic (and suitable for endoscopic resection), or neoplastic (and justifying surgical treatment). Histological checking in the pathology department is of course still necessary for guidance.

Conclusion

A bright future can be expected in the prevention of colorectal cancer, as the following three challenges are met: firstly, substituting simple genetic testing for fecal occult blood testing; secondly, eliminating the need for intestinal preparation for radiographic imaging; and thirdly, improving the effectiveness of optical endoscopy in detecting nonprotruding neoplastic lesions. Optical colonoscopy may become less important as a diagnostic tool, but more important for analyzing and providing endoscopic treatment of the early stages of colorectal neoplasia.

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The texts of all of these references are available at www.esge.com

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