Screening for colorectal cancer in asymptomatic average risk patients : role of imaging

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Abstract

Early detection of colorectal cancer or advanced adenomas is a public health priority in many industrialized countries. There are various methods of screening average risk individuals for colorectal cancer, and their effectiveness may depend on subjective parameters like local expertise and patient's preferences. This paper reviews these tests with special emphasis regarding imaging techniques that aim to provide less-invasive alternatives to optical colonoscopy (OC) which is the standard of reference. Both Double-Contrast Barium Enema (DCBE) and Virtual Colonoscopy (VC) have >90% sensitivity compared to OC in the detection of clinically relevant colonic lesions. Nevertheless, VC may have an edge over DCBE for technical and reproductivity reasons, as well as greater learning opportunities. Imaging techniques criticisms regarding diminutive and flat lesions, cost, radiation exposure and effects on gastroenterological practice are addressed. (Acta gastroenterol. belg., **2011**, 74, **70-76**).

Key words : virtual colonoscopy, double-contrast barium enema, colorectal cancer, screening tests.

Introduction

In Europe, colorectal cancer (CRC) is the second leading cause of cancer-related death after breast in women and lung in men (1). While the incidence of CRC is increasing, the mortality seems to decrease in the same time in countries where screening is performed (2). As recommended by the joint guidelines from the American Cancer Society, the United States Multi-Society Task Force on CRC, and the American College of Radiology, early detection of CRC and advanced adenomas should be a priority. For this purpose, patients with high or very-high risk should only be screened by optical colonoscopy (OC) while average risk patients could undergo any of the other available screening tests, such as flexible sigmoidoscopy, Double Contrast Barium Enema (DCBE), Virtual Colonoscopy (VC), Fecal Occult Blood Test (FOBT), DNA stool test at appropriate interval (3).

In this paper, the strengths and weaknesses of CRC screening modalities will be reported with particular emphasis on imaging techniques. We will also discuss the place of virtual colonoscopy (VC) as a non invasive option screening for CRC.

Strengths and weaknesses of the colorectal cancer screening tools

Biological tests

Fecal occult blood testing (FOBT) is based on the principle that colonic tumors and adenomas may silently bleed in otherwise asymptomatic patients. Its efficiency in reducing mortality from colorectal cancer has been established, provided it is at least biennially repeated (4). FOBT can be performed either by gaiac (gFOBT) or immunochemical analysis (iFOBT). gFOBT is easy-to-perform and highly automated. It has therefore been elected for mass screening by some countries, including Belgium, because of low cost (~ € 32) (5). Sensitivity and positive predictive values of gFOBT for both cancer and adenomas are respectively 12.9-37.1% and 11.4%, and 9.8-15% and 17.1% (6-8). There are no clear patterns of superior performance in overall test performance between gFOBT and iFOBT (3).

It has recently come to light that CRC causes DNA alteration in excess (9). In a face-to-face comparison, DNA stool test has shown better sensitivity than FOBT for detecting both advanced adenomas (15.1% *vs*. 10.7%) and cancer (51.6% *vs* 12.9%) (9-10), but still requires annual or biennial repetition. The actual cost of this test is a limitation for screening (~ € 250-500).

Optical tests

OC is considered as the standard of reference for colonic study (3). Optimization of OC for colorectal cancer detection requires high-resolution endoscopes and mucosal coloration for better detection of flat lesions (11). OC allows a full colonic study but requires a clean colon. Its global cost is variable, generally increased by anesthesia and temporary hospitalization (~ € 520). One must be aware that there is a 0.01 to 0.2% risk of perforation (12) and that not all procedures are complete, both depending on pelvic adherences and colonic length.

Flexible sigmoidoscopy is a light derivative from OC that only explores approximately 60 cm of the distal colon and can be performed on unprepared colon, after a small water enema**.** It was introduced as a screening test for CRC, basing on the higher prevalence of polyps in the distal colon (13). Nevertheless, a normal distal colon with proximal lesions is not uncommon, especially in older patients (14).

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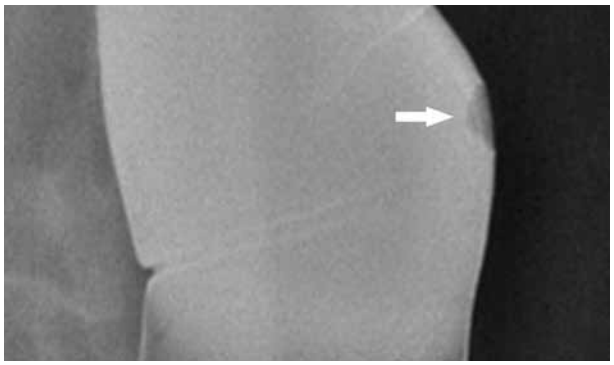

Fig. 1. — Single contrast barium enema : a polyp is seen as a radiolumency into the opaque contrast media filling the bowel lumen (arrow).

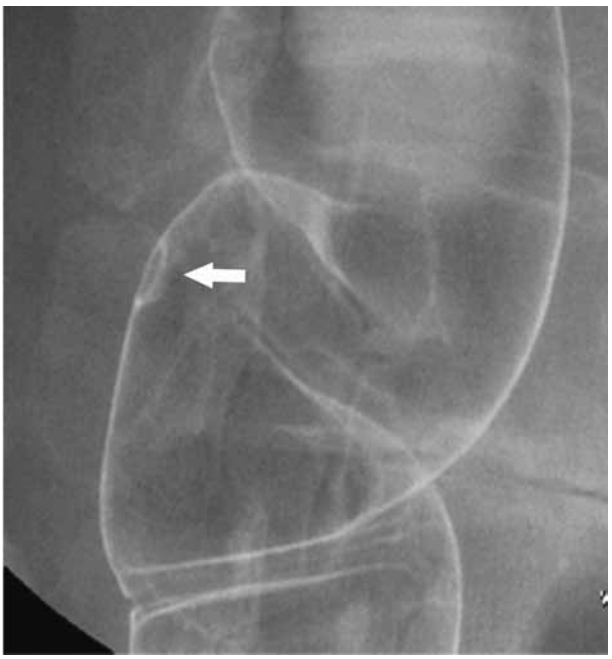

Fig. 2. — Double Contrast Barium Enema : a polyp is seen in profile in the air-distended and barium-coated bowel wall (arrow).

Imaging techniques

The radiological studies of the colon rely on the following requisites to allow detection of endoluminal lesions and stenoses : colonic distension and a contrast between colonic wall and content. Currently, the main techniques are DCBE and VC.

Radiography

Historically, the first way of creating an imaging contrast was to fill the colonic lumen with a contrast agent. The best example for such an approach is the single contrast barium or gastrografin enema in which lesions appear radiolucent within the contrast-filled bowel lumen. This technique has 95% sensitivity for cancer detection, 72% for polyps < 1 cm and 94% for polyps ≥ 1 cm (15-16) (Fig. 1). DCBE represents a more sophisticated approach in which the mucosal surface is coated with a thin layer of high-density barium in a clean air-distended colon. On technical ground, DCBE diagnostic yield depends essentially on 3 quality factors. The first is the quality of the mucosal coating, since with an even slight impairment of the coating, lesions can be missed. The second is the colon distension that should just efface the normal mucosal folds ; both insufficient distension and over-distension can obscure lesions. The third is the precision of the projection as each loop should be projected both free of overlapping loops and in profile. This cannot always be achieved in practice, so that some segments have to be observed through overlapping loops and lesions have to be recognized en face as well (Fig. 2).

Although DCBE technique was first described by the end of the fifties, Sosna *et al*. reported 11 prospective studies in a meta-analysis evaluating its performances compared to OC in the detection of CRC and polyps (17). Across these studies, there is a great variation in per-patient sensitivity and specificity for ≥ 10 mm polyps, with respective ranges of 43-100% and 74-99%.

Cross-sectional imaging

Using cross-sectional imaging, it is possible to enhance the colonic wall by intravenous injection of a contrast agent. Some departments of radiology perform routine abdominal CT after water enema but without any colonic cleansing (Fig. 3). While the technique is not suitable for lesions < 10 mm, Pilleul *et al*. reported a 95.5% sensitivity and a 93.5% specificity for ≥ 10 mm lesions (10).

Magnetic resonance (MR) with intravenous injection of a paramagnetic contrast agent on a water-filled colon also allows to detect colonic lesions (13). Limited access to MR equipments, intravenous contrast cost and study duration time do not allow to routinely perform this study.

VC is also known as Computed Tomographic Colonography, as it uses the simple contrast between the gas-distended clean colon and the wall on CT images to produce computer-generated images representing the mucosa (Fig. 4), although MR images can be used for the same purpose. Examination quality depends upon three technical factors. The first is the cleanliness of the colon, because compact adherent feces and untagged residual fluid may respectively mimic or hide polyps. The second is the colonic distension since lumen cannot be assessed in collapsed or poorly distended segments, causing potential misdiagnoses (18).

The last refers to acquisition parameters that should result in thin and overlapping slices. In a meta-analysis, Halligan *et al*. found respective ranges of sensitivity and specificity as broad as 45%-97% and 26%-97% for VC versus OC (19).

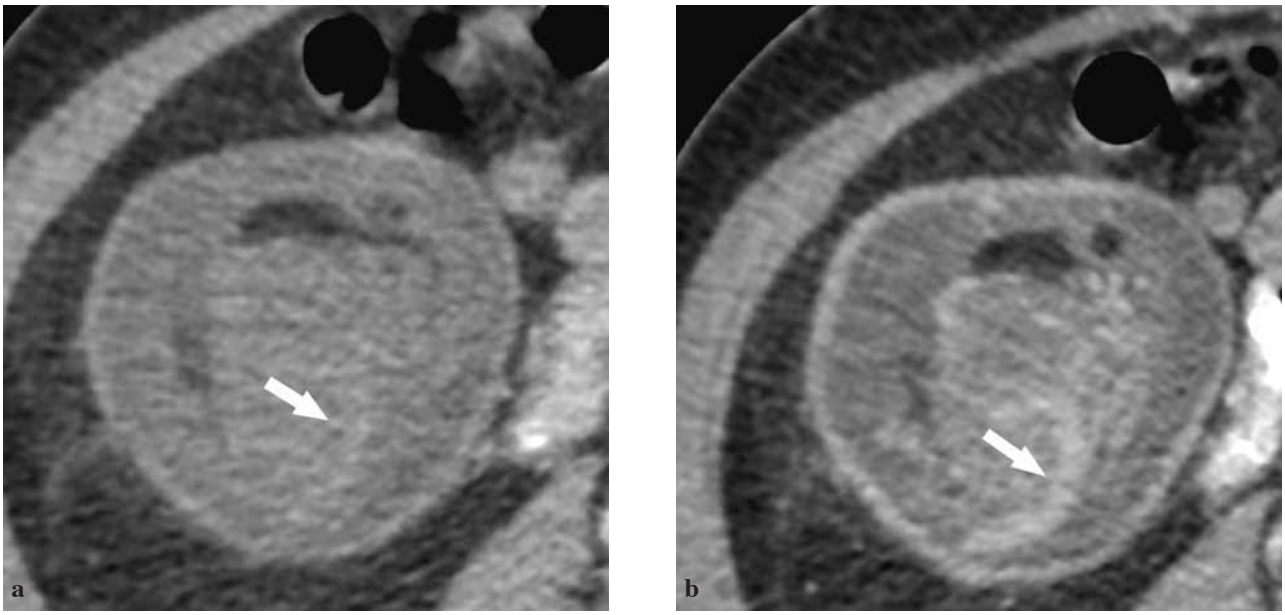

Fig. 3. — Computed tomography with intravenous contrast and water enema, showing a cecal tumor with intussusception into the proximal colon (arrow).
a. arterial phase ; b. venous phase with enhancement of the tumor.

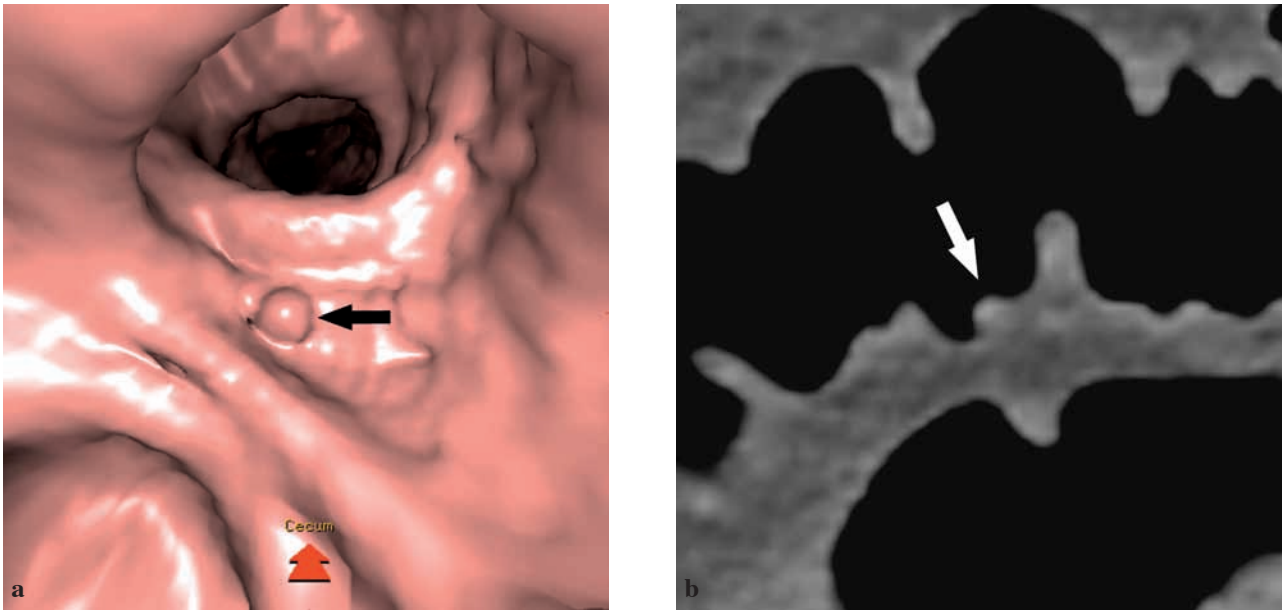

Fig. 4. — Virtual colonoscopy appearance of a polyp.
a. 3D image reconstruction of the bowel lumen to simulate optical colonoscopy (polyp : black arrow) ; b. magnified axial computed tomographic slice showing the polyp (arrow).

Virtual Colonoscopy versus Double Contrast Barium Enema

VC and DCBE are both well-tolerated ambulatory and cost-effective (~ € 215 and € 170 respectively) procedures that provide a complete colonic study. Both share disadvantages in terms of reading difficulties. Some are related to subjective psycho-visual factors because some radiologists are more comfortable with DCBE images than VC and vice-versa. On the other hand, objective specific skills are necessary to extract diagnostic information after every effort has been made to obtain excellent images in both techniques. For this purpose, training and expertise are mandatory as illustrated by the American College of Radiology Imaging Network trial (20). Indeed, even with a requested experience of at least 500 cases or participation at a 1.5 day training course, half of the readers failed the certified examination

consisting in the proper diagnosis of at least 90% of the lesions ≥ 10 mm in 50 consecutive cases.

There are differences in terms of performances between VC and DCBE. In the literature, only 2 studies proceeded to face-to-face comparison of DCBE and VC versus OC. For Johnson *et al*. (15) in 2004, in a series of 837 patients and for Rockey *et al*. (21) in 2005, in a series of 614 patients, the sensitivities of DCBE and VC were respectively of 44 and 72%, and 48 and 59%. Despite the relatively low sensitivity of these 2 techniques in both papers, VC was clearly more accurate than DCBE. The superiority of VC over DCBE can easily be explained by the fact that DCBE analyses the contours while VC studies the lumen. In consequence, VC reading is not compromised by dolichocolon, pelvis locked colonic loops or ileal reflux that may all be responsible for superimpositions. In addition, VC allows the analysis of colonic wall and environment. Therefore, submucosal or subserosal lesions such as carcinoid tumors, endometriosis, peritoneal metastatic seeding or infiltrating tumors are more easily recognized (22).

On a technical point of view, DCBE is more dependent than VC on operator's skills, with each study being different from another one in terms of difficulty.

Reading difficulties are easier to overcome for VC. We have observed a significant improvement of accuracy in beginners after only one course and the reading of 60 cases (23). Numerous training courses are currently available for VC. In contrast, DCBE currently out of fashion, relies for its learning on long-term apprenticeship.

Another important advantage of VC is the possible assistance by an automatic polyp-candidate detection software (CAD) that has a detection level similar to experienced readers (16). In addition and independently of all these considerations, VC is able to detect extracolonic lesions such as aortic aneurysms, lithiasis, ascites or tumors as it provides a full, unenhanced study of the abdomen and the pelvis (18).

VC among the other screening tests

VC is the most recent of the radiological screening tests, and since its beginnings, it faces and addresses progressively criticism regarding its abilities versus other established screening tests.

Screening capabilities

VC was first described in 1994 (24). The first publications, involving small series of symptomatic or high-risk patients, were cheering as the sensitivity reached 90% for ≥ 10 mm lesions (25-26). The question was then to determine to which extend the technique would be suitable for screening average risk patients.

In 2003, Pickhardt *et al*. (25) compared VC and OC, segment by segment, in 1233 average risk patients, and found a better sensitivity for VC versus OC (93.9% vs 88.7%) for significant size lesions (≥ 8 mm). They concluded that "VC is an accurate screening method that compared favorably with OC in terms of detection of clinically relevant lesions". A few months later, in a series of 614 patients, Cotton *et al*. found 39% and 55% sensitivity of VC for the detection of polyps ≥ 6 mm and ≥ 10 mm respectively, and stated that "VC is not ready for widespread clinical application". Technique and training need to be improved" (26). These discrepancies can be explained by the fact that Cotton's study readers were inexperienced and the exams were performed between 2000 and 2001 with both outdated CT scanners and reading software, while Pickhardt's study involved experienced readers using state-of-the-art technique and reading software.

To dispel doubts concerning VC performances, a randomized multi-center study was performed in the US in 2007, using state-of-the-art technology in both academic and non-academic centers (20). In a cohort of 2531 subject, this confirmed similar sensitivities between OC and VC for significant size lesions (≥ 10 mm) (90% sensitivity for VC versus OC).

Diminutive lesions

Low sensitivity (65%) of VC for ≤ 6 mm lesions is a common shortcoming (3). However, 70% of these lesions are simply hyperplasic and advanced histology is demonstrated only in approximately 2% (27-28). The ratio between risk and patient's benefit (in terms of survival) is therefore clearly against the resection of these diminutive lesions. A college of experts, both in the US and in Europe, advised that polyps < 6 mm should not be reported in VC (27-28).

Flat lesions

CRC arises mostly from polypoid adenoma but can also arise from nonpolypoid neoplasms, also known as flat lesions. Their propensity to herald a carcinoma is a matter of debate (29-30). Nonpolypoid lesions were believed to prevail essentially in Japan but recent studies demonstrated their significant prevalence in other parts of the world (29). Their appearances include small depressions, completely flat, less than 3 mm-high carpet-like and a height less than half of their width lesions. Using the last definition, Pickhardt *et al*. found similar sensitivities for flat (82.8%) and polypoid (86.2%) lesions on VC (30). For the other types of lesions, the sensitivity of VC is unknown, but probably poor. Likewise, these lesions are difficult to distinguish from normal mucosa at OC. Their diagnosis is often easier with high-definition endoscopes and mucosal spraying with a diluted indigo carmine solution, which is not routinely performed.

Radiation exposure

Another common concern is the radiation risk. Since its very beginning VC is performed at a low tube current

(50-70 mA) because of the high contrast between the soft-tissue wall and the air attenuation in the colon lumen. Its radiation dose, even with two acquisitions (prone and supine), is approximately one half of that administered by a conventional abdominopelvic CT, and similar to a DCBE (31). During the past decade, substantial reduction of radiation doses has been applied to VC (32-33). With the recent advent of statistical iterative reconstruction methods, the doses administered by VC have been dropped to levels comparable to environmental background radiation whose yearly threshold for individuals of the general population is 1mSv.

Cost

Despite a comparable or even lower cost/exam compared to other techniques evaluating the full colonic lumen, VC not only identifies colorectal polyps and tumors but also increases the diagnostic yield with extracolonic findings. Early diagnosis of extracolonic lesions results in lives saved. A recent paper demonstrated that VC screening discovers nearly as many cancers outside the colon as inside it (34). Unfortunately, low dose acquisitions and lack of intravenous contrast do not always allow full characterization and are responsible of complementary diagnostic procedures with a subsequent increase of cost.

Numerous cost-analysis studies are on their way, taking many factors into account, such as survival, treatment, financial and health consequences of both intra- and extra-colonic findings. In a recent publication Heresbach *et al*. compared cost-effectiveness of CRC screening strategies with VC, gFOBT and iFOBT (35). They found that VC results in substantially less additive optical colonoscopies than iFOBT, and is cost-effective for low values of willingness to pay per life year gained. In another article, the same authors found that VC with a 6 mm threshold for polypectomy is associated to a substantial cost reduction without significant loss of efficacy (36).

Business

We performed in our institution a review of a 4-year experience (2003-2007) after evaluating the impact of VC implementation on both VC and OC business. A total number of 4336 patients underwent VC, and 359 OC during this time-period. A significant yearly rise of the number of both procedures was demonstrated (Fig. 5). While additional data analysis are needed to determine the yearly evolution of the therapeutic/diagnostic OC ratio, a lesson can already be drawn from our experience : Implementation of VC increases the total number of screening procedures by both arithmetical effect and emulation of the other procedures, which is beneficial to both the patients and other procedures' businesses.

Another business effect of VC implementation may be an increase in compliance for screening which is currently around one half of the population in the age to be screened over a period of 10 years (37). Indeed, it has been reported that compliance to screening for CRC raises to 80% when both OC and VC are available, compared to about 70% without the availability of VC (38). Pooler reported a survey of 573 patients who underwent

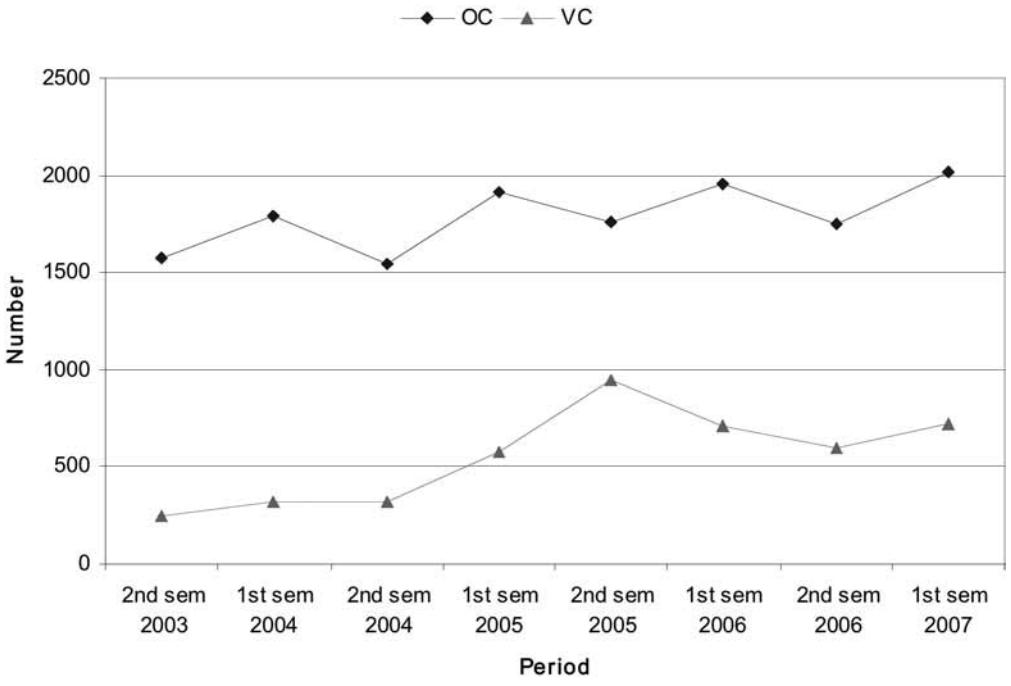

Fig. 5. — Semestrial evolution of the number of optical (—◆—) and virtual (—▲—) colonoscopies in our institution between 2003 and 2007. A constant raise of both procedures is observed.

VC as screening test at University of Wisconsin, of whom one third would not have undergone OC if it had been the only available test (39).

OC and VC should indeed supplement each other with special emphasis on a good cooperation between radiologists and gastroenterologists. In our institution, polyps detected by VC can beneficiate of a same day endoscopic resection, while incomplete optical colonoscopy may be followed by a same day virtual colonoscopy.

Conclusion

Compliance to CRC screening guidelines in the general population is currently low. None of the screening tests is perfect, with each presenting its own unique advantages. Patient's preferences and availability of resources should therefore be taken into account in order to improve adhesion to screening programs and to reduce effectively CRC mortality. VC provides the same advantages as DCBE, but with a better accuracy in lesion detection and (nowadays) a lower radiation dose administration. In addition, VC allows detection of extracolonic anomalies. Its implementation provides finally a high-quality non invasive alternative to diagnostic OC.

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