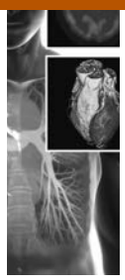

Role of CT colonography in screening programs

Colorectal cancer kills 210,000 persons every year in Europe, its average incidence is 50 in 100,000 people/year, and the average lifetime risk of developing colorectal cancer is 5%. Treatment of colorectal cancer imposes a huge economical burden. The individual direct cost for treating colon cancer early is approximately €20,000. One course of chemotherapy using new combination regimens costs approximately €23,000, and caring for one patient with late-stage colorectal cancer costs approximately €80,000. Prevention of colorectal cancer is possible, and widespread implementation of CT colonography can reduce colorectal cancer incidence and mortality by up to 90%. Advances in technology have provided us with CT colonography, an effective test for imaging the colon, that may represent a formidable prevention tool, and be well accepted owing to its minimal invasiveness. This article gives an outline of the epidemiology and the available prevention strategies for colorectal cancer, illustrates the progress in CT colonography development, and discusses future perspectives.

KEYWORDS: colorectal cancer ▪ computer-aided detection ▪ conventional colonoscopy ▪ CT colonography ▪ fecal occult blood test ▪ flexible sigmoidoscopy ▪ screening

Daniele Regge†, Giovanni Galatola, Cristiana Laudi & Gabriella Iussich
†Author for correspondence: Unit of Radiology, Institute for Cancer Research & Treatment, Candiolo, Turin, Italy
Tel.: +39 011 993 3367
Fax: +39 011 993 3301
dregge@mauriziano.it

Colorectal cancer: epidemiology & rationale for screening

Colorectal cancer (CRC) heavily impacts on public health, being the third most common malignancy diagnosed among men and women in the Western world and having the second highest mortality. CRC accounts for approximately 210,000 deaths each year in Europe [1]. The 5-year survival rate is 90% if the disease is diagnosed while still localized in the submucosa, but only 68% for regional disease and 10% if distant metastases are present [2]. Recent trends in CRC mortality reveal a declining rate in the USA and in other industrialized countries since the mid-1980s, probably due to a combination of reduced exposure to risk factors, effect of screening on early detection and prevention, and improved treatment [3].

Colorectal cancer is a preventable disease. According to large observational and case–control studies, fibers and antioxidants have been shown to be ineffective for primary prevention [4]. Obesity is associated with CRC, but the role of fat and red-meat consumption is still uncertain [4]. Long-term prophylaxis with aspirin, nonsteroidal anti-inflammatory drugs and cox-2 inhibitors are effective for decreasing the risk of CRC, but side effects, such as gastrointestinal bleeding, limit their usefulness [5]. Prophylaxis with oral supplementation of calcium, vitamin D and statins is still under investigation [4]. Finally, follow-up studies since 1970 have supported the association between cigarette smoking and CRC; recent meta-analysis studies have confirmed a positive association between smoking and colorectal adenomas and CRC [6]. An even stronger correlation exists between smoking and non-malignant colorectal polyps – in particular the hyperplastic-serrated types [7,8].

To explain the apparent paradox of smoking increasing the risk of cancer to a lesser extent than that of adenomas, it has been hypothesized that smoking may favor the development of cancer through the alternative hyperplastic-serrated pathway, which may give rise to approximately 15% of CRC [9]. However, more epidemiological studies are needed to clarify such aspects.

Secondary prevention is the most effective way to reduce CRC mortality, through screening programs aimed at reducing the incidence of advanced disease. Approximately 80–90% of CRCs arise in pre-existing adenomatous polyps, following the so-called adenoma-adenocarcinoma sequence, which is considered to a be a slow process spanning more than 10 years [10].

Screening programs are likely to reduce mortality in two ways. First, they allow identification of patients with small localized CRCs, whose treatment is associated with a high probability of long-term survival. Second, they interrupt

future medicine part of fsg

the progression to malignancy by removing premalignant adenomatous lesions. Their removal is indeed associated with a reduction in the incidence of CRC as demonstrated by the National Polyp Study in the USA and by other prospective and retrospective studies [11,12]. However, not all the adenomas have a potential for malignancy; the accumulated evidence has demonstrated that only the advanced adenomas (i.e., those that histologically are either ≥10 mm in size, have a villous component or a high grade of dysplasia) harbor a significant risk of malignant transformation. They are thus considered, together with early CRCs, the target lesions for screening programs, under the definition of advanced neoplasia [13].

Colorectal cancer risk depends not only on the type of adenomas formed, but also on the individual's family and personal history. A total of 75% of new cases of CRC occur in patients considered at an average risk: individuals aged 50 years or older with no personal or family history of colorectal adenoma or CRC are representative of the general population and will benefit from any screening strategy.

The remaining 25% of new cases of CRC are associated with risk factors, which are important to identify in order to stratify patients to appropriate initiation ages for screening and timing intervals for future examinations. Moderate-risk individuals are those with a family or personal history of CRC or adenomas; they can easily be identified by a simple medical interview and be offered screening strategies at an earlier age than the general population [14]. A positive family history of CRC is generally defined as the presence of advanced neoplasia in any first-degree relative aged younger than 60 years, or in at least two first-degree relatives at any age; in such cases, the relative risk is two- to four-fold compared with the general population [14]. A positive personal history is considered in patients who underwent polypectomy of advanced adenomas or resection of CRC with curative intent. A two- to four-fold risk of CRC has been observed in patients whose index adenoma was advanced, and five- to six-fold in those with multiple adenomas [15]. Finally, high-risk individuals are those with hereditary CRC syndromes, such as familial adenomatous polyposis or hereditary nonpolyposis colon cancer; they are carriers of genetic mutations with a risk to CRC ranging between 80 and 100% [16,17]. Patients with long-standing chronic inflammatory bowel disease involving the colon are also included in the increased risk category [18]. The identification of high-risk individuals is possible by a medical interview, and such individuals should be offered genetic counseling and diagnostic tests, including colonoscopy, according to specific guidelines. Although they represent approximately 10% of all CRC patients, emphasis should be given to identify high-risk individuals in order to initiate specific surveillance programs.

In conclusion, CRC is a major public health problem whose burden not only affects the Western world but is also spreading to poor and underdeveloped countries. Mortality can be dramatically reduced by proper prevention programs, but increased awareness and motivation of health providers and the general public is essential to change its epidemiology.

Current status of screening programs in the general population & strategies for the prevention of colorectal cancer

Screening tests that reduce mortality from CRC fall into two categories (Table 1). The first category comprises fecal tests, primarily aimed at the identification of early, asymptomatic, localized CRCs, whose treatment is associated with a high probability of long-term survival. The second category includes imaging tests aimed at identifying and then removing premalignant lesions (adenomas), thus interrupting progression to their malignant transformation.

There is solid evidence from multiple randomized controlled trials that a screening program targeting individuals aged 50 years or older with repeated annual or biennial guaiac fecal occult blood tests (FOBTs) followed by colonoscopy in the positive subjects reduces CRC mortality; the most recent available update shows a 16% reduction (95% CI: 10–22%) after 12–18 years [19]. This figure is less than that observed after 5–10 years, owing to an increase in incident cases in the screened population, likely derived from false-negative results, despite the presence of a developing advanced adenoma.

In order to improve the outcome of the screening strategy and based on extrapolation of data from the literature, it has become clear that tests aimed at visualizating the colon may offer better accuracy than FOBTs do. Thus, flexible sigmoidoscopy, double-contrast barium enema and colonoscopy have been considered as alternative strategies with a longer follow-up interval than FOBTs, which could be efficiently implemented in average-risk individuals over 50 years. This view has been officially endorsed

in the USA by the Preventive Services Task Force (USPSTF) [20]. Although several simulation studies have demonstrated that population-wide use of colonoscopy starting near the age of 50 years may lead to approximately more than a 90% reduction in CRC mortality [21], this approach has not been implemented successfully and nor is there published evidence of mortality reduction using endoscopy-based screening programs, except for pending results from flexible sigmoidoscopy screening studies in Italy, Norway, the UK and the Pittsburgh Cancer Institute (PA, USA) [22–25].

Endoscopic screening tests are indeed biased by several factors, such as potential harms, limited accessibility and scarce compliance by subjects; furthermore, cost–effectiveness analysis has failed to demonstrate the superiority of any one of such tests over screening programs based on FOBTs [26]. As a result, both national guidelines and interventional screening programs recommend that the method for CRC screening should be individualized to patients, practice settings and availability of resources [27], considering that the main hindrance in effectively reducing mortality is not so much due to poor test accuracy but rather to their poor acceptance [28]. However, the somewhat low (16%) reduction in mortality demonstrated by population screening with the guaiac FOBT is indeed partly due to its poor accuracy, thus an effort has been undertaken to develop fecal tests with better diagnostic accuracy. Available evidence has shown that fecal immunochemical occult blood testing and high-sensitivity guaiac FOBT offer better sensitivity and a more or less comparable specificity with the old guaiac test, and an advantage has been postulated in their use in screening programs [29]. Fecal DNA testing has been studied, but the sample size is too limited to recommend its use as a screening test, although it is already commercially available. There are concerns regarding the cost of the fecal DNA test, and the recommendations by the manufacturer to repeat screening at 5-year intervals is not supported by enough evidence [30,31].

Screening strategies identify patients at an increased risk in whom either one or more advanced adenomas or a localized CRC have been removed; they have a genetic predisposition to form further adenomas potentially evolving into cancer [32,33]. Colonoscopy is generally indicated for postpolypectomy and curative cancer resection follow-up, at variable intervals according to the number and histological hallmarks of the removed lesions, age, family history and possibly tobacco smoking [31]. Nonetheless, even when considering patients with the most advanced lesions, adenoma recurrence is only approximately 20%, thus raising the question as to whether a less-invasive test may be performed to avoid colonoscopy in patients who do not have recurrences. FOBT-based strategies are not appropriate for this purpose, whereas there is growing evidence that CT colonography (CTC) may be efficiently used instead.

Table 1. Screening options for colorectal cancer in average-risk adults aged 50 years and older.

Tests	Interval
Tests that primarily detect cancer	
Guaiac FOBT with high sensitivity for cancer	Annual
Immunochemical FOBT with high sensitivity for cancer	Annual
Stool DNA with high sensitivity for cancer	Interval uncertain
Tests that detect adenomatous polyps & cancer	
Flexible sigmoidoscopy (with insertion to splenic flexure)	Every 5 years
Colonoscopy	Every 10 years
Double contrast barium enema	Every 5 years
CT colonography	Every 5 years

FOBT: Fecal occult blood test.
Adapted with permission from [28].

Screening programs in the general population can be implemented either as opportunistic or as organized strategies. In the first setting, primary care physicians and consultant specialists are responsible for informing individuals of the locally available resources for screening, and inviting them to take part. As there are different options of tests, with different profiles of advantages and disadvantages regarding test intervals, accuracy, invasiveness and risk of harm, there is universal agreement recommending that the physician illustrates such options to individuals that meet the age criteria to begin screening. Failure to provide such information and suggestions may also have legal implications. As for the organized setting, several countries have endorsed pilot projects targeting the general population: the key factor for a successful and continuous participation in organized screening programs is unanimously considered the motivated involvement of primary care general practitioners. The Australian National Health and Medical Research Council (NHMRC) recommend organized CRC screening using FOBTs at least every 2 years for asymptomatic people over 50 years of age, and a Pilot Program was conducted between 2002 and 2004 in order to evaluate the acceptability, feasibility and cost–effectiveness involving approximately 57,000 individuals in three sites in Queensland,

Victoria and South Australia (Australia) [34].The Italian SCORE project has involved several regions using an organized approach of sigmoidoscopy and FOBT [35]. In the UK a similar program is on the way [36] and other countries such as Japan [37], Norway [23] and France [38] have developed strong recommendations for screening and organized projects in the effort to reduce CRC mortality. Since 1996, the USPSTF has recommended population-wide screening of CRC, but no organized screening programs are under way.

Compliance to screening programs remains the key factor for reducting mortality that will mostly benefit in absolute terms the screened population. A survey by the CDC in the USA has demonstrated that between 2002 and 2006 the proportion of adults aged 50 years or older who had recently undergone colorectal screening had increased from 54 to 61% overall, but racial and ethnic minorities and those who reported no health insurance coverage, reported a consistently lower prevalence of testing [39].

Despite the various difficulties that are encountered in implementing screening programs, the potential harms that may derive from taking part, the wide variability of test accuracy and operator-dependent endoscopic procedures, and the different choices offered, the age-standardized mortality rates have consistently fallen somewhat in both sexes in the last 20 years in the Western world [3]. This is a result of not only better treatment strategies but also from the continuous spreading of and adherence to screening tests.

The future of CRC screening envisages a rapidly evolving scenario, with novel technologies made available and an ever increasing awareness of the public requesting for accurate, rapid and minimally invasive tests. For screening programs to be effective there is a need for an active involvement of primary care physicians as information providers, a choice of tests of known and proven accuracy, and the development of certified quality standards for the implementation of operator-dependent tests.

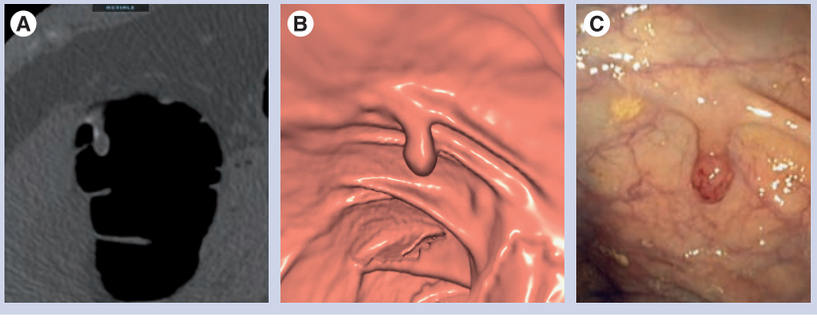

Figure 1. Colon of a 58-year-old, fecal occult blood test positive male.
A 7-mm pedunculated polyp of the transverse colon is visualized at CT colonography on the axial scan **(A)** and at the 3D endoluminal view **(B)**. The finding is confirmed at conventional colonoscopy **(C)**.

Rationale of screening with CTC

Computed tomography colonography is a low-dose abdominal CT study carried out after gently distending the large bowel with either air or CO_2 introduced through a small ballooned rectal tube, in a subject whose colon has been previously cleansed using some form of cathartics. The test is generally completed in a few minutes, and the CT dataset is then sent to a workstation equipped with a dedicated software for postprocessing and visualization. The workstations usually allows both automatic 'navigation' within the colon along the lumen centerline in both directions, and 2D visualization on different planes. Polyps appear as objects protruding within the colon lumen (Figure 1), while cancers may show as masses or wall thickening (Figure 2).

In principle, CTC should make a good and minimally invasive screening test, as it allows detection of premalignant lesions and the visualization of the entire colon mucosa without having to introduce an endoscope within the colon through to the cecum, as in conventional colonoscopy. However, for CTC to be efficiently used as a screening test, sensitivity and specificity need to be verified by screening an asymptomatic population. On the one hand, it is essential that the detection rate of the lesions targeted by screening (i.e., the advanced neoplasia) is adequate, otherwise clinically relevant lesions might be missed, falsely reassuring the individual and delaying diagnosis. On the other hand, specificity must also be high, to avoid referring too many subjects to an unnessecary colonoscopy, negatively affecting costs and the burden to patients. Colonoscopy is an invasive test and carries a major adverse event rate of 3–5 per 1000 examinations [40]; ideally it should be performed as a second-level test only, following a true-positive screening test. An overview on the diagnostic performance of CTC will be presented later in this article. Since last year, as a result of the accumulated evidence, CTC has been considered by the American guidelines for CRC screening as a prevention strategy that can be effectively implemented in the general population [31].

As previously discussed, participation rate is just as important as performance in assessing the effectiveness of a screening program [41].

Participation, or compliance, is mostly affected by the patient's perception of the unpleasantness and invasiveness of the test they are offered. Several factors influence how a screening test for colon cancer is perceived by the individual. Test acceptance is probably the single most important factor influencing participation. In an opportunistic setting, a poorly accepted screening test will cause the individual to either look for an alternative test, or decline screening altogether. In an organized setting, low participation may reduce its cost efficacy, again prompting regulatory agencies to either interrupt programs or seek alternative approaches [42]. Participation is also influenced by demographic and socioeconomic factors, test perception by the primary care physician, promotion and publicity given to the program, and finally the strategies chosen to invite individuals [43].

When considering tests for morphological examination of the colon, low acceptance may be due to poor tolerance, the requirement for bowel preparation, and/or to the test itself, and/or the fact that the test is *a priori* perceived as invasive and unsafe. Bowel preparation is often considered the most critical aspect of CTC [44,45], and efforts have been made to improve exam acceptance by avoiding strong laxatives. The newer fecal-tagging regimens do not require the preparation of a clean stool-free colon; a mild laxative, administered 2–3 days before testing, is used to soften stools so that they can adequately mix with the oral tagging agent, thus making it possible to distinguish these from polyps. Several different tagging protocols have been evaluated in terms of laxative type and dosage, use of iodine and/or barium agents, and administration timing [46–51]. Iodine-based tagging agents are more versatile and effective in marking both the feces and fluid residues homogeneously, at the expenses of a moderate laxative effect [52]. They have, however, in rare instances, caused severe adverse events, and for this reason in-hospital administration may be safer [53,54]. The administration of a mild laxative on the days preceding the exam, followed by an iodine-based solution administered 2 h before scanning are adequate to obtain a good quality CTC study [47,51]. As of today, there are no data on whether minimally invasive preparations, such as that reported previously, will favor compliance to organized screening programs; certainly this approach has made it easier to organize individual access to a CTC service and has made it possible to address safety issues. Fecal tagging can also improve sensitivity of CTC, both by highlighting polyps submerged in the fecal residues and by reducing false-positive findings (Figure 3) [48–50].

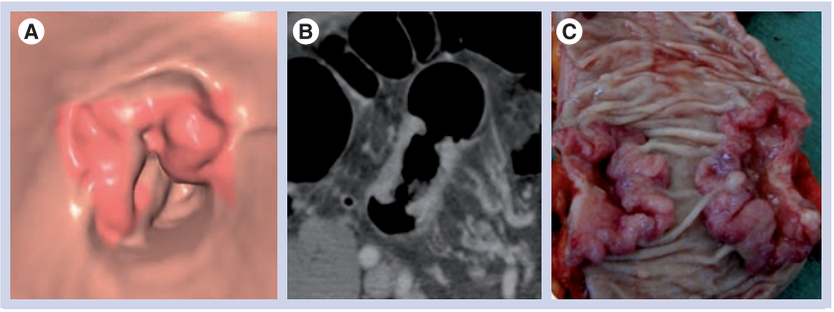

Figure 2. Colon of a 65-year-old male with blood in his stool.
CT colonography shows a stenosing lesion of the sigmoid colon. 3D endoluminal CT colonography view **(A)**, 2D axial CT colonography view **(B)** and surgical specimen **(C)**.

Individuals will comply more readily to a screening test if it is perceived safe and noninvasive [41]. Bowel distension by gas is perceived as the most embarrassing part of CTC [55]. Automatic insufflators are available to regulate pressure during CO_2 administration and improve patient acceptance [56,57]. Colon distension is the most common cause of adverse events at CTC, which include colon perforation, vagal reactions and respiratory distress [56–62]. The risk of perforation is approximately 0.02–0.08%, and it has been described mostly in symptomatic patients. Perforation is rare and usually self-contained in asymptomatic individuals [61]. No CTC-related deaths have been reported to date.

Some recently published articles have expressed concern on the extensive use of CT exams in pediatric- and screening-subjects [63],

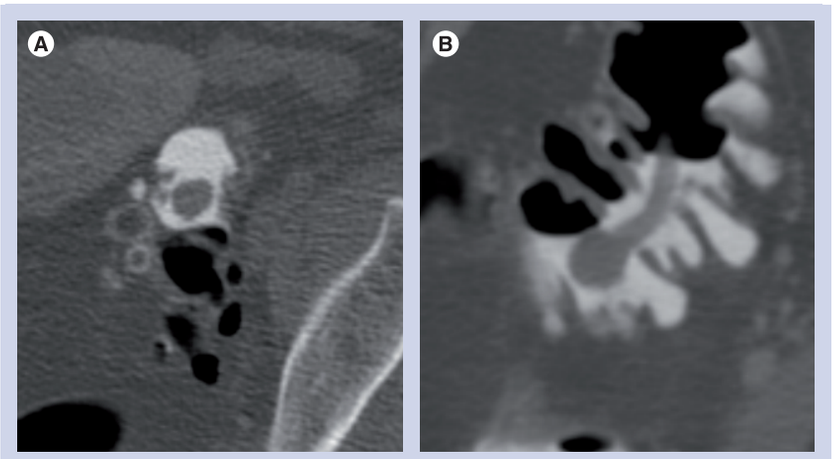

Figure 3. CT colonograph of the colon of a 55-year-old female. Shows a peduncolated polyp in the sigmoid colon. 2D axial CT colonography prone view **(A)** and 2D axial supine view **(B)**. The polyp appears submerged in the tagged iodinated residual fluid.

and these positions may negatively affect both public opinion and policy makers. CTC is now generally performed using low-dose protocols (i.e., an average 4 millisievert per examination, which is less than twice the radiation dose that an individual absorbs yearly from natural radiations). Further evidence supporting this dose as safe derives from the observation that commercial pilots absorb approximately 0.20 microsievert during a long intercontinental flight, for a total of 2–3 millisievert per year, and approximately 80 millisievert for a 30-year long career [64]. Nonetheless, no evidence of radiation-induced cancer has yet been demonstrated in this professional category [65].

Computed tomography colonography also allows assessment of the bowel wall and abdominal cavity, thus conferring peculiar characteristics among the available colon screening test. Extracolonic findings are common, and they may be clinically relevant in only 3–12% of the cases, according the different series and inclusion criteria [66–69]. Relevant findings should be reported and alternative imaging be performed when necessary, taking into consideration, however, that this may add to costs without a demonstrated benefit and be cause for undue anxiety.

Speed is also an advantage of CTC compared with endoscopy, as it requires altogether less than 20 min to be performed, and individuals may go back to their daily activities as soon as they have completed the test, as no premedication is required. If reporting is performed by an experienced radiologist, reading time will be in the order of 10 min.

In conclusion, CTC allows for the assessment of the entire air-to-mucosa interface of the large bowel, and it is well accepted since it is perceived as safe and well tolerated. However, there are some concerns regarding the exposure to low-dose radiation, and the unclear impact on cost:benefit ratio of reporting extra-colonic findings [70–72]. Despite the mounting evidence on the efficacy of using CTC as a screening test, and its inclusion as such in the American guidelines for cancer screening strategies, most primary healthcare physicians still view it with distrust [73].

Results of clinical trials on CTC

Computed tomography colonography has initially been demonstrated to be a valid way to image the colon through a series of studies in patients with known CRC [74–76], and studies on a small series of patients with colorectal polyps [74,77]. Data from these preliminary studies suggest a greater than 75% sensitivity and a greater than 90% specificity for large colorectal polyps (≥10 mm in diameter) and cancers. It was clear that performance was highly dependent on the size of the lesions: the threshold for a reliable detection of small lesions was approximately 5 mm. The rate of detection of larger polyps, and, in particular, adenomatous polyps of at least 6 mm, was very satisfactory and in some series it approached that reported for conventional colonoscopy.

These promising results were confirmed by several single institution prospective studies on polyp detection rate, undertaken between 1996 and 2003, using conventional colonoscopy as the reference standard [78–80]. In each study at least 100 patients were enrolled and the target population comprised of patients at high risk of CRC. For example, patients with rectal bleeding, positive FOBTs results, iron deficiency anemia, family history of CRC or personal history of adenomas. All studies stratified results according to the size (≤5 mm, 6–9 mm and ≥10 mm) and histology type of the polyps. Their results confirmed the findings of previous smaller studies: sensitivity was highly dependent on the size of the polyps, being in the region of 90% or more for polyps at least 6 mm that are considered clinically relevant. Taking all results together, there was evidence that in patients at high risk of colorectal cancer, CTC had similar efficacy to conventional colonoscopy in the detection of polyps of at least 6 mm.

Therefore, the next step was to assess whether CTC could be used as a screening test, and to address this question it was necessary to test CTC performance in asymptomatic individuals. In 2003, Pickhardt *et al.* studied 1233 asymptomatic average-risk subjects aged between 50 and 79 years using double-check colonoscopy as the reference standard (i.e., colonoscopy performed by an endoscopist blinded but in the presence of an assistant aware of the CTC results) and repetition of segmental colon evaluation in case of a false-negative finding [81]. All patients underwent same-day CTC and conventional colonoscopy and the target lesions were adenomatous polyps measuring at least 6 mm. Surprisingly, the per-polyp analysis demonstrated that sensitivity of CTC for advanced adenomas was higher than colonoscopy: 91.5% (54 of 59) versus 88.1% (52 of 59) respectively, although this difference was not significant. All cancers were seen at CTC. Per-patient sensitivity for polyps of at least 10 mm was 93.8%, even higher than colonoscopy sensitivity for

that category of lesions. Overall, specificity was almost 96%. The sensitivity decreased for smaller polyps but remained high, although less than colonoscopy, being 88.7% for polyps of 6 mm or more. In both the per-polyp and per-patient analysis, sensitivity of CTC was slightly higher than that of colonoscopy for adenomatous polyps of 8 mm or larger, but the difference was not statistically significant. Therefore, CTC not only had high sensitivity, but also maintained acceptable specificity for adenomas 6 mm or larger.

Following this encouraging study, a large multicenter trial was designed and performed on asymptomatic subjects – the American College of Radiology Imaging Network (ACRIN) 6664 study [82], carried out in 15 USA medical centers. They enrolled 2531 individuals aged 50 years or older with no known risk factors for CRC, and found a per-patient sensitivity of 90% for polyps larger than 10 mm. Also in this study, CTC sensitivity decreased with the size of the lesions, but still remained between 78 and 90%, for 6 mm or larger and 9 mm or larger lesions, respectively.

The accumulating evidence was fully supportive of the use of CTC in screening patients at average risk of CRC, but there were also two studies [83,84], performed on symptomatic or higher risk patients, which concluded against the use of CTC. However, these studies had many limitations, such as the lack of experience of the radiologists involved in the CTC lecture, the inclusion of centers not very familiar with the CTC technique, the use of a 2D primary reading and the lack of fecal tagging. CTC sensitivity for detecting participants with one or more lesions was only 39% for a threshold of at least 6 mm [83] and 35% in the other study [84]. For a threshold of at least 10 mm the sensitivity was 55 and 64% in the two studies, respectively. Even allowing for some of the studies limitations, such as a lack of reader experience and use of equipment that is not state-of-the-art, those results raised some doubts on CTC performance away from referral centers.

The most recent step taken to prove the accuracy of CTC is represented by the study of Regge *et al.* [85]. Their aim was to assess sensitivity and specificity of CTC in detecting advanced neoplasia sized 6 mm or larger in individuals at an increased risk of developing CRC. They stratified the 934 participants into three groups, those with a family history of advanced neoplasia in first-degree relatives, those with a personal history of adenomas, and those with a positive FOBT. They found an overall per-patient sensitivity for nondiminutive lesions between 85.3 and 90.8%. These figures were comparable with the two large trials on asymptomatic patients [81,82], but definitely higher than the two previously mentioned negative studies on increased risk subjects [83,84]. Taking into account the prevalence of the disease and the accuracy of the test in different groups of patients, this study concluded that CTC could be used instead of colonoscopy in individuals at increased risk of CRC due to a positive family or personal history of colorectal neoplasia. In the FOBT-positive group of patients, the results were not as encouraging. Considering the 50% prevalence of disease in this group, and a 55% rate of referral to colonoscopy owing to a positive CTC, this strategy in FOBT-positive subjects might not be cost effective.

In March, 2008 CTC was added as a screening test in the American Screening Guidelines to test average-risk subjects aged 50 years or older every 5 years, along with the alternatives of a yearly FOBT, flexible sigmoidoscopy every 5 years, conventional colonoscopy every 10 years, or double-contrast barium enema every 5 years [31].

At present there is only one screening program carried out using CTC: the University of Wisconsin (WI, USA) program that began in 2004 [86]. In the first year, 1192 subjects underwent CTC, those in whom at least one lesion 10 mm or larger was identified were sent for colonoscopy, whereas those with 6–9 mm polyps were offered the alternative of a follow up CTC. The overall CTC test-positive rate for 6 mm or larger polyps was 10.8%. Most of the patients with intermediate-size lesions decided to undergo follow-up CTC, thus overall, endoscopic referral rate for patients with positive findings was 6.4%. Concordant lesions were identified in 65 of the 71 patients who underwent subsequent colonoscopy, with a positive predictive value of 91.5%. It was concluded that screening with CTC determines an acceptably low endoscopic referral rate and a high concordance of positive findings registered at colonoscopy.

Further evidence supporting CTC as a valid screening test came from the comparison of the parallel CTC and colonoscopy ongoing screening programs at the University of Wisconsin [87], in which CTC was compared with colonoscopy when applied to the same general screening population. The outcome measured was the detection rate of advanced neoplasia, which, by unanimous agreement, is the target lesion for

strategies to prevent CRC, stratified according to lesion size and overall polypectomy rates. This study indicated that polyps 10 mm or larger at CTC were highly predictive for advanced adenomas, accounting for the great majority of all advanced lesions. Only 0.2% of subcentimeter polyps were histologically advanced, which emphasizes the need of a filtering strategy. The perforation rate of 0.2% (seven of 3163 patients) in the conventional colonoscopy group was within the expected range reported in previous series. The absence of perforation in the CTC screening group was largely due to both the minimally invasive nature of CTC and the decreased numbers of conventional colonoscopy studies and polypectomies as compared with the primary conventional colonoscopy group. The strategy of not reporting diminutive polyps detected during CTC screening is a cost-effective approach that can substantially reduce the rate of polypectomy and complications without negatively affecting efficacy of cancer prevention [70–72].

In 2008, Graser *et al.* published a study comparing CTC against four already-approved screening tests: colonoscopy, flexible sigmoidoscopy, fecal immunological tests and guaiac FOBT [88]. CTC was confirmed as having sensitivities comparable to colonoscopy for polyps larger than 5 mm. The debate of whether CTC may be used in FOBT-positive subjects is still open, as recent data [89] have demonstrated that CTC in this setting had good predictive values and a higher acceptability than colonoscopy. The results of some of the aforementioned screening trials are shown in Table 2.

In conclusion, CTC first gained the role as a clinically accurate test in symptomatic patients, in whom its minimal invasiveness is a great advantage over colonoscopy, particularly for frail and very ill patients, and then as a screening test in subjects both at an average and increased risk. Probably only a small proportion of high-risk patients, such as those with hereditary non-polyposis colon cancer, familial adenomatous polyposis and long-standing ulcerative colitis, remain unlikely candidates for CTC, considering that the narrow test repetition interval of 1–2 years needed in such patients poses serious concerns regarding radiation exposure, and there is a need for frequent biopsies and searches for flat lesions, which are still difficult to identify using CTC.

Future perspective

There is solid evidence supporting CTC as an effective and minimally invasive test for imaging the colon and one that is well accepted by patients. However, several issues need to be resolved before it may be universally perceived as a valid, or even the best possible, CRC screening strategy. Some are test related, others depend on the understanding of the natural history of CRC and the pathological features that affect growth rate and aggressiveness of this tumor [41].

Despite the very high prevalence of premalignant colorectal lesions, their natural history is still not entirely understood, mostly because any polyp that is detected at colonoscopy is now removed, irrespective of its size and macroscopic features [31]; there are no accepted criteria – aside from obvious small hyperplastic rectal polyps – to predict whether a polyp does not have 'advanced' features, or whether it is instead likely to evolve into a malignancy, thus warranting its removal. For decades, polypectomy has been associated with an up to 90% reduction of the risk of developing CRC [11], thus, it would be unethical today not to remove a polyp during colonscopy and

Table 2. Results (per patient) of the most significant clinical trials on CT colonography.

Population	Target lesion	Sensitivity (%)			Specificity (%)	PPV (%)	NPV (%)	Ref.
		≥*5 mm*	≥*10 mm*	*Cancers*	≥*6 mm*			
Asymptomatic	Adenomatous polyps ≥6 mm in diameter	149/168 (89)	45/48 (94)	2/2 (100)	848/1065 (80)	–	604/611 (99)	[77]
Asymptomatic	Adenomas or cancer ≥5 mm in diameter	164/210 (78)	108/120 (90)	108/120 (90)	2042/2321 (88)	169/423 (40)	2066/2108 (98)	[78]
Asymptomatic	Adenoma and advanced adenomas ≥5 mm in diameter	42/46 (91)	23/25 (92)	29/30 (97)	243/261 (93)	42/60 (70)	243/247 (98)	[84]
Increased risk	Advanced neoplasia ≥6 mm in diameter	151/177 (85)	119/131 (91)	39/41 (95)	667/760 (88)	151/244 (62)	667/693 (96)	[81]
Increased risk	Advanced neoplasia ≥6 mm in diameter	192/211 (91)	116/142 (82)	21/22 (95)	63/91 (69)	119/220 (87)	63/82 (77)	[82]

NPV: Negative predictive value; PPV: Positive predictive value.

to just follow it up, considering the unfavorable risk–balance of repeating a colonoscopy versus removing a small polyp. The evidence from few, relatively small observational studies carried out in the era before the introduction of colonoscopy and in the first following decade, shows that the growth rate of polyps depends on their size. Approximately 20% of polyps of 10 mm or larger evolve into an invasive cancer within 5 years [90]; a moderate growth is observed instead in a minority of intermediate size lesions (6–9 mm), whereas the rest (<6 mm) either remain stable or can no longer be found again [91]. There are limitations to these studies: the sample size is small, and estimating the diameter of a small polyp at colonoscopy is a subjective and unreliable method [92,93]. Instead, CTC provides for the first time, an accurate and reproducible minimally invasive way to measure polyp size and volume [94]. It is, therefore, ideal for assessing growth, particularly for polyps smaller than 10 mm, for which the benefit:risk ratio may not be in favor of referral to polypectomy compared with follow-up by CTC.

As previously mentioned, the University of Wisconsin's third-payer screening program is now offering a follow-up alternative to immediate polypectomy for individuals with less than three 'intermediate size' (i.e., 6–9 mm) polyps [86]. When completed, this study will hopefully provide important insights into polyp growth patterns and form the rationale for choosing the safest and more cost-effective approach in the average-risk individual, between CTC surveillance and immediate polypectomy. It is envisaged, however, that an aggressive approach will be warranted in all patients at an increased risk of CRC, irrespective of their polyp size, if a high prevalence of advanced adenomas within the intermediate-size category is confirmed [85].

Another challenging issue concerns the further improvement of CTC accuracy and acceptance. First, it is essential to keep the radiation dose within acceptable limits for a screening test. New CT scanners, with more efficient detectors and reconstruction algorithms, will probably allow us to scan patients using doses lower than 2 millisievert, which is less than the yearly background radiation exposure [95,96]. Second, patient preparation, exam protocols and reader experience are also vital for this issue. In a retrospective review of data from a multicenter study, Doshi *et al.* found that 53% of false-negative CTC interpretations were due to observer errors, and another 26% to technical errors [97]. The authors demonstrated that, following retrospective reconciliation, CTC sensitivity for polyps 6 mm or larger increased by 14%, from 76 to 90%. Technical errors were mainly due to excessive fluid and/or stool, inadequate bowel distension, and movement or streak artifacts, the latter mainly from hip prosthesis. A standard bowel purgation was used in the trial, without using stool tagging [84]. According to the results of a recent meta-analysis, studies performed using fecal tagging yielded a higher sensitivity than those performed without it (88% [95% CI: 84–91] vs 59% [95% CI: 56–63] [98]); this was likely due to an easier detection of polyps that remain 'submerged' in both the supine and prone scans (**Figure 3**). Mistaking polyps for stool residues may also occur.

As previously reported, most lesions are undetected by CTC owing to observer errors, thus, reader experience is probably the most important factor affecting CTC performance [99]. Experienced radiologists fare significantly better than trained radiologists and radiographers in detecting cancer and polyps [100,101]. Experience obviously depends on the number of reported CTC exams; however, it has not been clearly stated how many studies are required to provide sufficient expertise, and the number may also depend on the personal attitude of readers, as talented individuals might become competent after reading as few as 50 validated exams [100].

Reader performance might also be affected by the level of confidence in reporting a lesion. If a reader reports a positive finding, even when the confidence level is low, sensitivity will be privileged over specificity. The opposite occurs for readers who are mainly concerned to provide highest levels of specificity. Reading should probably be adjusted according to the characteristics of the diagnostic setting (e.g., when screening average-risk asymptomatic individuals), specificity should be privileged over sensitivity in order avoid an unnecessarily high colonoscopy referral rate that might increase procedural risks and costs. Conversely, when dealing with high-risk individuals (e.g., those with symptoms or a positive FOBT), in whom the prevalence of clinically relevant lesions exceeds 40% [85], readers should aim at obtaining the highest possible sensitivity.

Performance of CTC might be improved by computer-aided diagnosis (CAD). Several small retrospective studies have demonstrated that detection of colorectal lesions is improved

by CAD [101–103]. However, a gain in sensitivity may be achieved at the expense of a lower specificity; CAD candidates, particularly when they are numerous, might force readers to revise their negative opinion [102]. Specificity is mostly reduced when the number of false-positives is high, and for the less experienced readers [104]. The type of reading paradigm and the number of false-positives also are factors that increase reading time [102,103,105], which might, however, be improved as readers become more confident in using CAD. Prospective studies should assess CAD performance in different realistic environments, such as the daily clinical activity or the implementation of CTC as a screening strategy.

The crucial factor for success and organized screening programs is a high attendance rate [38]. In a large study conducted between 2002 and 2004 in northern Italy, attendance rates for FOBT, flexible sigmoidoscopy and colonoscopy were 32.3, 32.3 and 26.5%, respectively [35]. An attendance rate of 28,4% was reported for CTC in a clinical trial conducted in western Australia on 2000 individuals aged 50–69 years [106], where recruitment was performed by an invitation letter, and a full bowel preparation was performed in all cases; participation was higher in younger individuals and in those with higher socioeconomic standards. A multivariate analysis has shown that individuals who consult their primary care physicians before screening, or have at least one first-degree relative with CRC, have a high probability of participation [43].

Computed tomography colonography may still have a long way to go before being perceived as an effective test by healthcare opinion makers, and this may hinder its implementation in screening programs. In a recent survey completed by 1266 US physicians, only 22.6% perceived CTC as very effective, and as few as 4.8% would routinely recommended it for CRC screening [42]. Randomized trials comparing detection and attendance rate of CTC to other screening modalities might bring some insight on the possible future role of CTC in CRC screening. Two such trials are now starting recruitment. In The Netherlands a trial will compare the participation rate and yield of CTC and colonoscopy in a randomized study involving 7500 asymptomatic individuals aged 50–74 years [201]. In Italy, the randomized trial Protèus will compare participation and detection rate of CTC and flexible sigmoidoscopy in 25,000 asymptomatic individuals aged 58 years or older; all CTC studies will be sent to a single center where they will be interpretted by experienced readers with the aid of a CAD system. Both trials will also perform a cost–effectiveness analysis, as evidence of sustainable costs is essential for public health systems to finance a given screening program.

In conclusion, CTC scores highly as an effective screening modality. It explores the entire colon, there is no need for a strong bowel purgation, it is well tolerated without the need for sedation, severe complications are extremely rare in asymptomatic subjects and its performance is similar to traditional colonoscopy for clinically relevant lesions, being equally effective in asymptomatic individuals both at an average and increased risk of CRC. Owing to this evidence, CTC has now been included in the American Cancer Society Guidelines as a test for opportunistic screening in average-risk individuals, beginning from the age of 50 years [28]. Collaterally, CTC also provides a formidable tool to clarify the natural history of CRC, which is largely unknown. This may heavily affect future strategies for screening and follow-up, providing us with the evidence for deciding whether small- and intermediate-colorectal polyps may be left in place or should be systematically removed. There are, however, gray areas: CTC performance is not likely to be uniform, recent studies have reported low-sensitivity and specificity values, the technique is not yet standardized, reading times are still relatively long and the role of CAD systems is not yet clarified. Efforts will have to be made towards standardization, and efficient training strategies that need be implemented and adjusted to the target population. Healthcare policy makers and primary care physicians are still quite skeptical with regards to the role of CTC in mass-screening programs. In future, large randomized trials should provide answers to important issues, such as attendance rate and cost–effectiveness of screening CTC, hopefully opening the way for its more widespread and confident use.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Colorectal cancer has heavy social & financial costs

- Colorectal cancer is the third most common malignancy in the Western world with the second highest mortality rate and its frequency is also increasing in poor countries.
- The incidence of colorectal cancer is approximately 50 in 100,000 people/year, with a prevalence of 60 individuals in 1000 inhabitants, with an estimated 210,000 deaths yearly in Europe.
- Costs of chemotherapy have increased by over 300-times in the last 5 years, up to €23,000 for a single course. Caring for one patient with late-stage colorectal cancer costs approximately €80,000.

Colorectal cancer is a preventable disease

- The majority of cases arise in pre-existing adenomatous polyps that undergo a slow malignant transformation spanning more than 10 years.
- Advanced adenomas are the most likely premalignant lesions that progress to cancer, and they are defined by size (at least 10 mm in diameter) or histological features (villous component or high-grade dysplasia).
- Identification and removal of advanced adenomas reduces the risk of developing colorectal cancer by more than 90%.
- Early colorectal cancers localized in the submucosa are mostly asymptomatic and their treatment results in a 5-year survival rate of approximately 90%.
- Advanced adenomas and early cancer form the advanced neoplasia that is the best target for screening strategies.

Prevention strategies are mainly hindered by compliance

- No more than 60% of individuals who should benefit from a screening test have actually undertaken one.
- Colonoscopy performed at the age of 55 years is theoretically the most efficient way to identify and treat advanced neoplasia, but it is scarcely accepted by healthy individuals.
- Even compliance to annual or biannual fecal occult blood tests is also suboptimal.

CT colonography is the best candidate for an effective & well accepted screening test

- CT colonography (CTC) allows detection of premalignant lesions and the visualization of the entire colon mucosa.
- CTC is minimally invasive, and prior bowel cleansing can be obtained without using strong laxatives.
- CTC has a sensitivity over 90% for advanced neoplasia and a specificity exceeding 95%.
- CTC has been included as a valid alternative screening test in several guidelines.

Future perspective

- With the help of computer-aided diagnostic systems, CTC may become an easily standardized and widely used test for screening average-risk individuals older than 50–55 years of age.
- There is a valid rationale for avoiding polypectomy in cases where polyps smaller than 10 mm are found at screening CTC, and offering the patient the possibility of CTC follow-up. This may help clarify the natural history of small polyps that are not likely to progress to cancer, thus reducing the costs and risks associated with indiscriminate polypectomies.

Bibliography

Papers of special note have been highlighted as:
- of interest

1 Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P: Estimates of the cancer incidence and mortality in Europe in 2006. *Ann. Oncol.* 18 (3), 581–592 (2007).

2 Ries L, Melbert D, Krapcho M *et al.*: *SEER Cancer Statistics Review 1975–2004*. National Cancer Institute, Bethesda, MD, USA (2007).

3 Boyle P, Ferlay J: Mortality and survival in breast and colorectal cancer. *Nat. Clin. Pract. Oncol.* 2(9), 424–425 (2005).

4 Marshall JR: Prevention of colorectal cancer: diet, chemoprevention, and lifestyle. *Gastroenterol. Clin. North Am.* 37(1), 73–82 (2008).

5 Preventive Services Task Force: Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann. Intern. Med.* 149(9), 627–637 (2008).

6 Liang PS, Chen TY, Giovannucci E: Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. *Int. J. Cancer* 124(10), 2406–2415 (2009).

7 Ji BT, Weissfeld JL, Chow WH, Huang WY, Schoen RE, Hayes RB: Tobacco smoking and colorectal hyperplastic and adenomatous polyps. *Cancer Epidemiol. Biomarkers Prev.* 15 (5), 897–901 (2006).

8 Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P: Smoking and colorectal cancer: a meta-analysis. *JAMA* 300(23), 2765–2778 (2008).

9 East JE, Saunders BP, Jass JR: Sporadic and syndromic hyperplastic polyps and serrated adenomas of the colon: classification, molecular genetics, natural history, and clinical management. *Gastroenterol. Clin. North Am.* 37(1), 25–46 (2008).

10 Winawer SE, Zauber AG, Stewart E, O'Brien MJ: The natural history of colorectal cancer. Opportunities for intervention. *Cancer* 67(Suppl. 4), 1143–1149 (1991).

11 Winawer SJ, Sidney J, Zauber AG *et al.*: Prevention colorectal cancer by colonoscopy polipectomy. The National Polyp Study work group. *N. Engl. J. Med.* 329(27), 1977–1981 (1993).

12 Thiis-Evensen E, Hoff GS, Sauar J *et al.*: Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study I. *Scand. J. Gastroenterol.* 34(4), 414–420 (1999).

13 Winawer SJ, Zauber AG: The advanced adenoma as the primary target of screening. *Gastrointest. Endosc. Clin. N. Am.* 12(1), 1–9 (2002).

14 Winawer SJ, Zauber AG, Gerdes H *et al.*: Risk of colorectal cancer in the families of patients with adenomatous polyps. National Polyp Study Workgroup. *N. Eng. J. Med.* 334(20), 82–87 (1996).

15 Winawer SJ, Zauber AG, Fletcher RH *et al.*: Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-society Task Force on Colorectal Cancer and the American Cancer Society. *CA Cancer J. Clin.* 56(3), 143–159 (2006).

16 Vasen HF, Möslein G, Alonso A *et al.*: Guidelines for the clinical management of familial adenomatous polyposis (FAP). *Gut* 57(5), 704–713 (2008).

17 Vasen HF, Watson P, Mecklin JP, Lynch HT: New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology* 116 (6), 1453–1456 (1999).

18 McConnell BB, Yang VW: The role of inflammation in the pathogenesis of colorectal cancer. *Curr. Colorectal. Cancer Rep.* 5(2), 69–74 (2009).

19 Hewitson P, Glasziou P, Irwig L, Towler B, Watson E: Screening for colorectal cancer using the faecal occult blood test, Hemoccult. *Cochrane Database Syst. Rev.* 24(1), CD001216 (2007).

20 Screening for colorectal cancer. In: *Pocket Guide to Clinical Preventive Services, 2007*: *Recommendations of the U.S. Preventive Services Task Force*. Agency for Healthcare Research and Quality, MD, USA 32–35 (2007).

21 Cappell MS: Reducing the incidence and mortality of colon cancer: mass screening and colonoscopic polypectomy. *Gastroenterol. Clin. North Am.* 37(1), 129–160 (2008).

22 Segnan N, Senore C, Andreoni B *et al.*: SCORE Working Group – Italy: baseline findings of the Italian multicenter randomized controlled trial of "once-only sigmoidoscopy" – SCORE. *J. Natl Cancer Inst.* 94(23), 1763–1772 (2002).

23 Gondal G, Grotmol T, Hofstad B, Bretthauer M, Eide TJ, Hoff G: The Norwegian Colorectal Cancer Prevention (NORCCAP) screening study: baseline findings and implementations for clinical work-up in age groups 50–64 years. *Scand. J. Gastroenterol.* 38(6), 635–642 (2003).

24 UK Flexible Sigmoidoscopy Screening Trial Investigators: single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. *Lancet* 359(9314), 1291–1300 (2002).

25 Weissfeld JL, Schoen RE, Pinsky PF *et al.*; PLCO Project Team: Flexible sigmoidoscopy in the PLCO cancer screening trial: results from the baseline screening examination of a randomized trial. *J. Natl Cancer Inst.* 97(13), 989–997 (2005).

26 Pignone M, Saha S, Hoerger T, Mandelblatt J: Cost–effectiveness analyses of colorectal cancer screening: a systematic review for the U.S. Preventive Services Task Force. *Ann. Intern. Med.* 137(2), 96–104 (2002).

27 U.S. Preventive Services Task Force: Screening for colorectal cancer: recommendation and rationale. *Ann. Intern. Med.* 137(2), 129–131 (2002).

28 Mavranezouli I, East JE, Taylor SA: CT colonography and cost–effectiveness *Eur. Radiol.* 18(11), 2485–2497 (2008).

29 Whitlock EP, Lin JS, Liles E, Beil TL, Fu R: Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. *Ann. Intern. Med.* 149(9), 638–658 (2008).

30 Levin B, Brooks D, Smith RA, Stone A: Emerging technologies in Screening for colorectal cancer: CT colonography, immunochemical fecal occult blood tests, and stool screening using molecular markers. *Cancer J. Clin.* 53, 44–55 (2003).

31 Levin B, Lieberman DA, McFarland B *et al.*: Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 134(5), 1570–1595 (2008).

32 Schmiegel W, Adler G, Fruhmorgen P *et al.*: Colorectal carcinoma: prevention and early detection in patients at high risk-endoscopic diagnosis, therapy and after-care of polyps and carcinomas. German Society of Digestive and Metabolic Diseases/Study Group for Gastrointestinal Oncology. *Z. Gastroenterol.* 38(1), 49–75 (2000).

33 Fornasarig M, Valentini M, Poletti M *et al.*: Evaluation of the risk for metachronous colorectal neoplasms following intestinal polypectomy: a clinical, endoscopic and pathological study. *Hepatogastroenterology* 45(23), 1565–1572 (1998).

34 Foreman L: Bowel cancer screening – a role for general practice. *Aust. Fam. Physician* 38(4), 200–203 (2009).

35 Segnan N, Senore C, Andreoni B *et al.*; SCORE3 Working Group Italy: Comparing attendance and detection rate of colonoscopy with sigmoidoscopy and FIT for colorectal cancer screening. *Gastroenterology* 132(7), 2304–2312 (2007).

36 Goodyear SJ, Stallard N, Gaunt A, Parker R, Williams N, Wong L: UK local impact of the English arm of the UK Bowel Cancer Screening Pilot study. *Br. J. Surg.* 95(9), 1172–1179 (2008).

37 Sung J: Colorectal cancer screening: its time for action in Asia. *Cancer Detect. Prev.* 31(1), 1–2 (2007).

38 Manfredi S, Piette C, Durand G, Plihon G, Mallard G, Bretagne JF: France colonoscopy results of a French regional FOBT-based colorectal cancer screening program, with high compliance. *Endoscopy* 40(5), 422–427 (2008).

39 Centers for Disease Control and Prevention (CDC): Use of colorectal cancer tests – United States, 2002, 2004 and 2006. *Morb. Mortal. Wkly Rep.* 57(10), 253–258 (2008).

40 Lieberman DA: Clinical practice. Screening for colorectal cancer. *N. Engl. J. Med.* 361(12), 1179–1187 (2009).

41 Hassan C, Hunink MG, Laghi A *et al.*: Value-of-information analysis to guide future research in colorectal cancer screening. *Radiology* 253(3), 745–752 (2009).

42 Kablunde CN, Lanier D, Nadel MR, McLeod C, Yuan G, Vernon SW: Colorectal cancer screening by primary care physicians: recommendations and practices, 2006–2007. *Am. J. Prev. Med.* 37(1), 8–16 (2009).

43 Senore C, Armaroli P, Silvani M *et al.*: Comparing different strategies for colorectal cancer screening in Italy: predictors of patients' participation. *Am. J. Gastroenterol.* 105, 188–198 (2009).

44 Ristvedt SL, McFarland EG, Weinstock LB, Thyssen EP: Patient preferences for CT colonography, conventional colonoscopy, and bowel preparation. *Am. J. Gastroenterol.* 98(3), 578–585 (2003).

45 Beebe TJ, Johnson CD, Stoner SM, Anderson KJ, Limburg PJ: Assessing attitudes toward laxative preparation in colorectal cancer screening and effects on future testing: potential receptivity to computed tomographic colonography. *Mayo Clin. Proc.* 82(6), 666–671 (2007).

46 Yoon SH, Kim SH, Kim SG *et al.*: Comparison study of different bowel preparation regimens and different fecal-tagging agents on tagging efficacy, patients' compliance, and diagnostic performance of computed tomographic colonography: preliminary study. *J. Comput. Assist. Tomogr.* 33(5), 657–665 (2009).

47 Campanella D, Morra L, Delsanto S *et al.*: Comparison of three different iodine-based bowel regimens for CT colonography. *Eur. Radiol.* 20(2), 348–358 (2009).

48 Taylor SA, Slater A, Burling DN *et al.*: CT colonography: optimisation, diagnostic performance and patient acceptability of reduced-laxative regimens using barium-based faecal tagging. *Eur. Radiol.* 18(1), 32–42 (2008).

49 Liedenbaum MH, de Vries AH, Gouw CI *et al.*: CT colonography with minimal bowel preparation: evaluation of tagging quality, patient acceptance and diagnostic accuracy in two iodine-based preparation schemes. *Eur. Radiol.* 20(2), 367–376 (2010).

50 Nagata K, Okawa T, Honma A, Endo S, Kudo SE, Yoshida H: Full-laxative versus minimum-laxative fecal-tagging CT colonography using 64-detector row CT: prospective blinded comparison of diagnostic performance, tagging quality, and patient acceptance. *Acad. Radiol.* 16(7), 780–789 (2009).

51 Neri E, Turini F, Cerri F, Vagli P, Bartolozzi C: CT colonography: same-day tagging regimen with iodixanol and reduced cathartic preparation. *Abdom. Imaging* 34(5), 642–647 (2009).

52 Zalis ME, Perumpillichira J, Magee C: Tagging-based, electronically cleansed CT colonography: evaluation of patient comfort and image readability. *Radiology* 239(1), 149–159 (2006).

53 Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K: Adverse reactions to ionic and non ionic contrast media: a report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 175(3), 621–628 (1990).

54 Skucas J: Anaphylactoid reactions with gastrointestinal contrast media. *AJR Am. J. Roentgenol.* 168(4), 962–964 (1997).

55 Iussich G, Laudi C, Della Monica P, Galatola G, Bonelli L, Regge D: Comparing safety and acceptability of same-day CT-colonography and conventional colonoscopy in a multicenter setting. Presented at: *European Society of Gastrointestinal Abdominal Radiology Annual Meeting.* Valencia, Spain, 23–26 June 2009.

56 Burling D, Taylor SA, Halligan S *et al.*: Automated insufflation of carbon dioxide for MDCT colonography: distension and patient experience compared with manual insufflation. *AJR Am. J. Roentgenol.* 186(1), 96–103 (2006).

57 Shinners TJ, Pickhardt PJ, Taylor AJ, Jones DA, Olsen CH: Patient-controlled room air insufflation versus automated carbon dioxide delivery for CT colonography. *AJR Am. J. Roentgenol.* 186(6), 1491–1496 (2006).

58 Neri E, Laghi A, Regge D: Colonic perforation during screening CT colonography using automated CO_2 insufflation in an asymptomatic adult. *Abdom. Imaging* 33(6), 748–749 (2008).

59 Neri E, Caramella D, Vannozzi F, Turini F, Cerri F, Bartolozzi C: Vasovagal reactions in CT colonography. *Abdom. Imaging* 32(5), 552–555 (2007).

60 Sosna J, Blachar A, Amitai M: Colonic perforation at CT colonography: assessment of risk in a multicenter large cohort. *Radiology* 239(2), 457–463 (2006).

61 Burling D, Halligan S, Slater A, Noakes MJ, Taylor SA: Potentially serious adverse events at CT colonography in symptomatic patients: national survey of the United Kingdom. *Radiology* 239(2), 464–471 (2006).

62 Pickhardt PJ: Incidence of colonic perforation at CT colonography: review of existing data and implications for screening of asymptomatic adults. *Radiology* 239(2), 313–316 (2006).

63 Brenner DJ, Hall EJ: Computed tomography – an increasing source of radiation exposure. *N. Engl. J. Med.* 357(22), 2277–2284 (2007).

64 Zeeb H, Blettner M, Langner I *et al.*: Mortality from cancer and other causes among airline cabin attendants in Europe: a collaborative cohort study in eight countries. *Am. J. Epidemiol.* 158(1), 35–46 (2003).

65 Bagshaw M: Cosmic radiation in commercial aviation. *Travel Med. Infect. Dis.* 6(3), 125–127 (2008).

66 Berland LL: Incidental extracolonic findings on CT colonography: the impeding deluge and its implications. *J. Am. Coll. Radiol.* 6(1), 14–20 (2009).

67 Yee J, Kumar NN, Godara S *et al.*: Extracolonic abnormalities discovered incidentally at CT colonography in a male population. *Radiology* 236(2), 519–526 (2005).

68 Gluecker TM, Johnson CD, Wilson LA *et al.*: Extracolonic findings at CT colonography: evaluation of prevalence and cost in a screening population. *Gastroenterology* 124(4), 911–916 (2003).

69 Pickhardt PJ, Hanson ME, Vanness DJ *et al.*: Unsuspected extracolonic findings at screening CT colonography: clinical and economic impact. *Radiology* 249(1), 151–159 (2008).

70 Pickhardt PJ, Hassan C, Laghi A, Zullo A, Kim DH, Morini S: Cost–effectiveness of colorectal cancer screening with computed tomography colonography – the impact of not reporting diminutive lesions. *Cancer* 109(11), 2213–2221 (2007).

71 Vijan S, Hwang I, Inadomi J *et al.*: The cost–effectiveness of CT colonography in screening for colorectal neoplasia. *Am. J. Gastroenterol.* 102(2), 380–390 (2007).

72 Hassan C, Pickhardt P, Laghi A *et al.*: Computed tomographic colonography to screen for colorectal cancer, extracolonic cancer, and aortic aneurysm. *Arch. Intern. Med.* 168, 696–705 (2008).

73 Klabunde CN, Lanier D, Nadel MR, McLeod C, Yuan G, Vernon SW: Colorectal cancer screening by primary care physicians: recommendations and practices, 2006–2007. *Am. J. Prev. Med.* 37(1), 8–16 (2009).

74 Royster AP, Fenlon HM, Clarke PD, Nunes DP, Ferrucci JT: CT colonoscopy of colorectal neoplasms: two-dimensional and three-dimensional virtual-reality techniques with colonoscopic correlation. *AJR Am. J. Roentgenol.* 169(5), 1237–1242 (1997).

75 Fenlon HM, McAneny DB, Nunes DP, Clarke PD, Ferrucci JT: Occlusive colon carcinoma: virtual colonoscopy in the preoperative evaluation of the proximal colon. *Radiology* 210(2), 423–428 (1999).

76 Fenlon HM, Nunes DP, Clarke PD, Ferrucci JT: Colorectal neoplasm detection using virtual colonoscopy: a feasibility study. *Gut* 43(6), 806–811 (1998).

77 Hara AK, Johnson CD, Reed JE *et al.*: Detection of colorectal polyps with CT colography: initial assessment of sensitivity and specificity. *Radiology* 205(1), 59–65 (1997).

78 Yee J, Akerkar GA, Hung RK, Steinauer-Gebauer AM, Wall SD, McQuaid KR: Colorectal neoplasia: performance characteristics of CT colonography for detection in 300 patients. *Radiology* 219(3), 685–692 (2001).

79 Fenlon HM, Nunes DP, Schroy PC 3rd, Barish MA, Clarke PD, Ferrucci JT: A comparison of virtual and conventional colonoscopy for the detection of colorectal polyps. *N. Engl. J. Med.* 341(20), 1496–1503 (1999).

80 Macari M, Bini EJ, Xue X *et al.*: Colorectal neoplasms: pospective comparison of thin-section low-dose multi detector row CT colonography and conventional colonoscopy for detection. *Radiology* 224(2), 383–392 (2002).

81 Pickhardt PJ, Choi JR, Hwang I *et al.*: Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N. Engl. J. Med.* 349(23), 2191–2200 (2003).

▪ **Large prospective study with 1233 asymptomatic participants with intermediate risk of developing colorectal cancer enrolled from three different military facilities.**

82 Johnson CD, Chen MH, Toledano AY *et al.*: Accuracy of CT colonography for detection of large adenomas and cancers. *N. Engl. J. Med.* 359(12), 1207–1217 (2008).

▪ **Prospective study assessing the accuracy of CT colonography (CTC) as a screening tool in 2600 asymptomatic subjects aged over 50 years enrolled in 15 US medical centers.**

83 Cotton PB, Durkalski VL, Pineau BC *et al.*: Computed tomographic colonography (virtual colonoscopy): a multicenter comparison with standard colonoscopy for detection of colorectal neoplasia. *JAMA* 291(14), 1713–1719 (2004).

- **Nonrandomized prospective multicenter study with 608 participants, showing sensitivity for virtual colonoscopy in identifying colorectal polyps ranging from 52% for 10 mm polyps to 23% for 6 mm polyps. This study has been reported by the media as a "total failure for virtual colonoscopy", and prompted a critical analysis of its limitations by many radiology experts.**

84 Rockey DC, Paulson E, Niedzwiecki D *et al.*: Analysis of air contrast barium enema, computed tomographic colonography and colonoscopy: prospective comparison. *Lancet* 365(9456), 305–311 (2005).

85 Regge D, Laudi C, Galatola G *et al.*: Diagnostic accuracy of computer tomographic colonography for the detection of advanced neoplasia in individuals at increased risk of colorectal cancer. *JAMA* 301(23), 2453–2461 (2009).

- **A prospective study assessing the diagnostic accuracy of CTC in the detection of advanced neoplasias in 937 asymptomatic subjects at increased risk of developing colorectal cancer enrolled in 12 medical centers.**

86 Pickhardt PJ, Taylor AJ, Kim DH, Reichelderfer M, Gopal DV, Pfau PR: Screening for colortectal neoplasia with CT colonography: initial experience from the 1st year of coverage by third-party payers. *Radiology* 241(2), 417–425 (2006).

87 Kim DH, Pickhardt PJ, Taylor AJ: CT colonography versus colonoscopy for the detection of advanced neoplasia. *N. Engl. J. Med.* 357(14), 1403–1412 (2007).

- **Compared CTC and conventional colonoscopy as screening techniques for advanced colon neoplasia. The detection rate of advanced neoplasia in both techniques was similar, but the complication rate was lower in the CTC group.**

88 Graser A, Stieber P, Nagel D *et al.*: Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. *Gut* 58(2), 241–248 (2009).

- **Prospective study that compared five different screening techniques for the identification of advanced colorectal neoplasia (CTC, optical colonoscopy, flexible sigmoidoscopy, fecal immunochemical test and fecal occult blood test).**

89 Liedenbaum MH, Van Rijn AF, De Vries AH *et al.*: Using CT colonography technique after a positive faecal occult blood test in colorectal cancer screening. *Gut* 58(9), 1242–1249 (2009).

90 Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL: Natural history of untreated colonic polyps. *Gastroenterology* 93(5), 1009–1013 (1987).

91 Hofstad B, Vatn MH, Andersen SN *et al.*: Growth of colorectal polyps: redetection and evaluation of unresected polyps for a period of three years. *Gut* 39(3), 449–456 (1996).

92 Jeong JY, Kim MJ, Kim SS: Manual and automated polyp measurement comparison of CT colonography with optical colonoscopy. *Acad. Radiol.* 15(2), 231–239 (2008).

93 Park SH, Choi EK, Lee SS *et al.*: Polyp measurement reliability, accuracy, and discrepancy: optical colonoscopy versus CT colonography with pig colonic specimens. *Radiology* 244(1), 157–164 (2007).

94 Yeshwant SC, Summers RM, Yao J, Brickman DS, Choi JR, Pickhardt PJ: Polyps: linear and volumetric measurement at CT colonography. *Radiology* 241(3), 802–811 (2006).

95 Wang G, Yu H, De Man B: An outlook on x-ray CT research and development. *Med. Phys.* 35(3), 1051–1064 (2008).

96 Dachman A, Virmani A, Vannier M: Low dose CT colonography with 256-slice CT: radiation dose reduction and image quality. Presented at: *Radiology Society of North America Annual Meeting*, Chicago, IL, USA, 29 November–4 December 2009.

97 Doshi T, Rusinak D, Halvorsen RA, Rockey DC, Suzuki K, Dachman AH: CT colonography: false-negative interpretations. *Radiology* 244(1), 165–173 (2007).

98 Chaparro M, Gisbert JP, Del Campo L, Cantero J, Maté J: Accuracy of computed tomographic colonography for the detection of polyps and colorectal tumors: a systematic review and meta-analysis. *Digestion* 80(1), 1–17 (2009).

- **Meta-analysis assessing the accuracy of CTC for the detection of colorectal polyps and tumors, evaluating sensitivity, specificity and likelihood ratios for the diagnosis of polyps and colorectal tumors from 47 studies, accounting for a dataset from 10,546 patients.**

99 Pickhardt PJ, Lee AD, Taylor AJ *et al.*: Primary 2D versus primary 3D polyp detection at screening CT colonography. *AJR Am. J. Roentgenol.* 189(6), 1451–1456 (2007).

100 Taylor SA, Halligan S, Burling D *et al.*: CT colonography: effect of experience and training on reader performance. *Eur. Radiol.* 14(6), 1025–1033 (2004).

101 Graser A, Kolligs FT, Mang T *et al.*: Computer-aided detection in CT colonography: initial clinical experience using a prototype system. *Eur. Radiol.* 17(10), 2608–2615 (2007).

102 Petrick N, Haider M, Summers RM *et al.*: CT colonography with computer-aided detection as a second reader: observer performance study. *Radiology* 246(1), 148–156 (2008).

103 Baker ME, Bogoni L, Obuchowski NA *et al.*: Computer-aided detection of colorectal polyps: can it improve sensitivity of less-experienced readers? Preliminary findings. *Radiology* 245(1), 140–149 (2007).

104 Taylor SA, Brittenden J, Lenton J *et al.*: Influence of computer-aided detection false-positives on reader performance and diagnostic confidence for CT colonography. *AJR Am. J. Roentgenol.* 192(6), 1682–1689 (2009).

105 Taylor SA, Greenhalgh R, Ilangovan R *et al.*: CT colonography and computer-aided detection: effect of false-positive results on reader specificity and reading efficiency in a low-prevalence screening population. *Radiology* 247(1), 133–140 (2008).

106 Edwards JT, Mendelson RM, Fritschi L *et al.*: Colorectal neoplasia screening with CT colonography in average-risk asymptomatic subjects: community-based study. *Radiology* 230(2), 459–464 (2004).

■ Website

201 The Netherlands National Trial Register www.trialregister.nl/trialreg/admin/rctview.asp?tc=1829