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Gut published online 13 Oct 2008;
doi:10.1136/gut.2008.156448

Gut Online First, published on October 13, 2008 as 10.1136/gut.2008.156448

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Keywords: CT colonography; colonoscopy; colorectal cancer; screening; sigmoidoscopy; fecal occult blood test; fecal immunochemical test

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Declaration of competing interests, None to declare.

Abstract

Background and Aims: This prospective trial was designed to compare the performance characteristics of five different screening tests in parallel for the detection of advanced colonic neoplasia: computed tomographic colonography (CTC), colonoscopy (OC), flexible sigmoidoscopy (FS), fecal immunochemical stool testing (FIT), and fecal occult blood testing (FOBT).

Methods: Average-risk adults provided stool specimens for FOBT and FIT and underwent same day low-dose 64-multidetector row CTC and OC using segmentally unblinded OC as standard of reference. Sensitivities and specificities were calculated for each single test, and for combinations of FS and stool tests. CTC radiation exposure was measured, and patient comfort levels and preferences were assessed by questionnaire.

Results: 221 adenomas were detected in 307 subjects who completed CTC (mean radiation dose, 4.5 mSv) and OC; 269 patients provided stool samples for both FOBT and FIT. Sensitivities of OC, CTC, FS, FIT, and FOBT for advanced colonic neoplasia were 100% (95% CI 88.4-100), 96.7% (82.8-99.9), 83.3% (95% CI 65.3-94.4), 32% (95% CI 14.9-53.5), and 20% (95% CI 6.8-40.7), respectively. Combination of FS with FOBT or FIT led to no relevant increase in sensitivity. 12 of 45 advanced adenomas were smaller than 10 mm. 46% of patients preferred CTC, 37% OC ($p<0.001$).

Conclusions: High resolution and low dose CTC is feasible for colorectal cancer screening and reaches comparable sensitivities to colonoscopy for polyps >5 mm. For patients who refuse full bowel preparation and OC or CTC, FS should be preferred over stool tests. However, in case stool tests are performed, FIT should be recommended rather than FOBT.

Introduction

Colorectal cancer is one of the major public health issues in industrialized countries. Most colorectal cancers are thought to originate from benign adenomatous polyps that develop over a period of many years (1). Early detection followed by removal of adenomas has been shown to reduce incidence and colorectal cancer related mortality (2, 3). Therefore, screening of the asymptomatic and average risk population is recommended by many organizations and expert panels and is reimbursed by insurance companies in several countries (4-7). Next to colonoscopy, flexible sigmoidoscopy (FS) and guaiac-based fecal occult blood test (FOBT) are widely applied screening procedures which have been compared prospectively to each other. Colonoscopy has been found to be the screening test with highest sensitivity and outperforms FS and FOBT which miss a significant number of relevant adenomas (8). Colonoscopy, however, is not a perfect test in itself, and misses 6-12% of large adenomas (9-11).

Computed tomographic colonography (CTC), also known as virtual colonoscopy, and fecal immunochemical tests (FIT) have been proposed as screening tests for colonic neoplasia (12-14). They have at present not been integrated into screening programmes. Based on recent research, CTC shows heterogeneous results in the detection of colonic polyps: Some studies demonstrated high sensitivity in the detection of relevant colorectal adenomas (8, 13, 15, 16), while other trials showed less encouraging results with reported sensitivities of slightly more than 50% (17, 18). Another important issue of CTC is the theoretical cancer risk associated with the radiation exposure (12, 19). Therefore, if this test shall be acceptable as a mass screening instrument, radiation exposure of a single examination must be kept low, repeated examinations need to be avoided, and sensitivity for relevant lesions must be high. Standard CT colonography will result in radiation doses of 10-12 mSv. Smaller series operating 4-slice scanners with low dose protocols have reported effective doses of 2.1-7.8 mSv (15, 20). With 64-MDCT, increases in dose have been observed in different anatomical regions (21). Recently, a protocol that employs an online dose modulation algorithm that will lead to a 35% decrease in radiation exposure at preserved image quality was developed (22).

Advanced colonic neoplasia comprises the entities invasive cancer and advanced adenoma. Advanced adenoma is defined as a lesion of adenomatous histology that meets at least one of the following criteria: a size of 10 mm or more, the presence of a villous component of at least 25%, or the presence of high-grade dysplasia (23). As these benign lesion are associated with a relatively high risk of progression to cancer, their removal effectively disrupts the adenoma-to-carcinoma pathway that is believed to be responsible for the majority of colorectal cancers (2, 24). The prevalence of advanced adenoma in a screening population lies within a range of 3.7% to 15% and the prevalence of cancer has been reported to be 0.9% (range, 0.5 – 1.3%) (8, 23, 25). While it is not debated that adenoma larger than 1 cm and cancer need to be detected by a screening test, the relevance and handling of diminutive (≤5 mm) and small (6-9 mm) adenomas detected by CTC screening is currently under discussion. Recently, surveillance of polyps of 6 to 9 mm in diameter and non-reporting of diminutive lesions has been advocated (8, 13, 26). Up to now, there is no data to

support that this strategy would lead to an increase in carcinoma incidence in a screening population. However, the prevalence of advanced adenoma in small lesions is about 5%, and the prevalence of cancer in this size group has been reported to be 0.1% (27, 28).

We undertook this study to prospectively compare the performance of the three most commonly applied colorectal cancer screening tests OC, FS and FOBT, to high-resolution low-dose CTC and FIT. For the first time, five different screening tests were compared in the same patients. CT colonography examinations were exclusively carried out using a 64-dector row scanner employing a low dose protocol. We report the sensitivity, specificity, and positive and negative predictive values for the detection of patients with advanced adenoma and adenoma of various sizes for each test. We analyzed the performance according to the polyp of high resolution CTC as a screening instrument compared to OC.

Methods

Study Subjects

The study protocol of this prospective colorectal cancer screening cohort study was approved by the institutional ethical committee, and the study meets all criteria put forth by the Declaration of Helsinki. Participants had to be over 50 years of age and free of symptoms of colonic diseases like melaenic stools, hematochezia, diarrhoea, relevant changes in stool frequency, or abdominal pain. Exclusion criteria also included prior colonoscopy within the last five years, and positive family history for colorectal cancer (one first degree relative diagnosed with CRC before age 60 or two first degree relatives diagnosed with CRC at any age). Persons with a history of or present inflammatory bowel disease, hereditary colorectal cancer syndromes, a body weight >150 kg, or severe cardio-vascular or pulmonary disease were also excluded. All participants provided written informed consent before their participation in the trial.

Study Procedure

For each enrolled patient, a detailed medical history was taken prior to CTC. Patients also completed a questionnaire regarding their personal and family medical history. Patient comfort levels were assessed before and after CTC as well as after OC using standardized questionnaires. Study participants were asked to rate the discomfort related to bowel preparation, CTC and OC on a six-point scale. Complaints were rated as 1=none, 2=very mild, 3=mild, 4=moderate, 5=severe, and 6=unbearable.

Bowel Preparation

A package including instructions and medication for bowel purgation, three FOBT slides, and two 10 ml stool sample containers for FIT was mailed to the participants. Before initiation of bowel lavage, FOBT samples were taken on three consecutive days. The two stool samples for FIT were collected from two different parts from the same stool and stored refrigerated. Bowel preparation was based on a standard “wet prep” regimen including four liters of polyethylene glycol solution (KleanPrep, Norgine Pharmaceuticals, Marburg, Germany) and a commercially available combination of four tablets (5 mg each, for a total of 20 mg) of bisacodyl and 30 ml of sodium phosphate (Prepacol, Guerbet Pharma, Sulzbach, Germany). Study participants were asked to follow a clear liquid diet from 12 am the day before the examinations and ingest the bisacodyl tablets as well as the sodium phosphate solution at 2 pm, and drink three liters of PEG between 5 pm and 8 pm on the day before CTC/OC. The last liter of PEG was drunk in the morning before examinations. To this last liter of PEG, 50 ml of iodinated contrast agent iopamidol (Solutrast 300, BraccoAltana Pharma, Milan, Italy) were added in order to tag residual fluid.

CT Colonography

CTC scans were performed on a 64-channel multidetector row scanner (Siemens Somatom Sensation 64, Siemens Medical Solutions, Forchheim, Germany) at a collimation of 0.6 mm for high-resolution scanning. Images were reconstructed using a standard soft tissue kernel at a slice thickness of 0.75 mm and 0.5 mm reconstruction increment. Tube voltage was 120 kVp, and tube current-time product reference values were 70 mAs in the supine and 30 mAs in the prone position. An online dose modulation technique (Care Dose 4D, Siemens Medical Solutions) was used to automatically adapt the tube current to patient anatomy (22), and dose-length products were recorded for calculation of radiation exposure. Effective patient doses were calculated using appropriately normalized coefficients (29). No intravenous contrast agent was administered. 20 mg of n-butyl scopolamine (Buscopan, Boeringer Ingelheim Pharmaceuticals, Ingelheim, Germany) were administered intravenously for bowel relaxation.

Patients were positioned on the scanner table in right decubitus position and bowel distension was achieved after placement of a rectal tube by manual air insufflation (n=80) or automated CO_2 application (n=227) using a commercially available insufflator (Protocol, E-Z-EM, Lake Success, New York, NY, USA). Adequacy of colonic distension was determined by a radiologist on the CT scout film of the abdomen. Subsequently, the first set of images was obtained in 7-9 s breath-hold with the patient in supine position. After repositioning, the prone dataset was obtained. Datasets were automatically sent to a 3D workstation (Syngo Workplace 2006 version VB 30, Siemens Medical Solutions). All scans were read by one of three experienced abdominal radiologists who had read more than 300 CTC examinations prior to the study using a primary 3D approach with 2D for problem solving. Immediately after CTC, patients were transferred to the endoscopy suite.

Optical Colonoscopy and Flexible Sigmoidoscopy

Video colonoscopy was performed by one of six experienced gastroenterologists who had performed more than 1,000 colonoscopies each before the start of the trial using video endoscopy (CF-Q 160 series, Olympus Medical Systems, Hamburg, Germany). If desired, Disoprivan (Propofol®, B. Braun Melsungen AG, Germany) was administered intravenously. Lesions were measured by comparison of their size to an open biopsy forceps. All polyps were resected or biopsied and retrieved at colonoscopy, and sent to histopathology for analysis. Sigmoidoscopy was defined as endoscopic examination of the rectum and sigmoid colon. FS results were deducted from OC results, no separate endoscopy was performed.

Documentation and Matching of Findings

All findings were documented on a standardized report form. For each of six colonic segments (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum) the absence or presence of polyps was determined and lesion sizes were coded as diminutive (≤5 mm); small (6-9 mm); or large (≥10 mm). These size categories were based on previous research and the consensus statements of the European Society of Gastrointestinal and Abdominal Radiology and the Working Group on Virtual Colonoscopy (26, 30). In the endoscopy suite, the report form containing the CTC results was provided to one of the endoscopy nurses who revealed the results to the endoscopist after withdrawal of the endoscope from each colonic segment. This technique, known as “segmental unblinding”, allows for exact correlation of CTC and OC findings and can therefore be considered an enhanced gold standard. In case of a discrepancy between CTC and OC first look findings, an immediate colonscopic reexamination (“second look”) of the respective colonic segment has to be performed (13, 17); if results were discrepant after 2nd look, the

radiologist was contacted and described the exact localization of the lesion to the endoscopist who subsequently re-examined the segment. First and second look detections at OC were documented separately. In case of concordance of CTC and OC findings, no second look examination was performed. A lesion was rated a true positive detection if colonoscopy and CT colonography detected a polyp in the same or adjacent segment of the colon, and if the measured size of the lesion was within the same size category or if there was a deviation of no more than one size category (13). Only polyps detected in the rectum and sigmoid colon were included for analysis of the performance of flexible sigmoidoscopy (4).

Stool tests

FOBT tests were performed immediately, and stool samples were deep frozen at -80° C. The FOBT test was judged to be positive if one of the 3 samples per patient yielded a positive test reaction.

For FIT the provided stool samples were extracted by means of a stool sampling device (Sentinel Diagnostics, Milan, Italy) shaped like a standard analyzer test tube filled with haemoglobin (Hb) extracting buffer solution. The sample probe of the device has a serrated tip, which was poked into the stool at 3 different positions and pushed back into the tube through a tight membrane removing most of the excess stool leaving a quantitative amount of 10 mg stool in the serrations. Test reproducibility of quantitative stool transfer was shown to be 6.1 % at a Hb mean concentration of 198 ng/mL and 5.2 % at a Hb mean concentration of 600 ng/mL (homogenized stool sample, 11 different positions, 2 replicates each). After 30 minutes of mixing on a head-over-head rotator, the sampling device was de-capped, transferred onto Architect® c8000 Clinical Chemistry Analyzer (Abbott Diagnostics, Abbott Park, USA) and Hb concentration measured by means of the FOB Gold immunoturbitrimetric latex assay (Sentinel Diagnostics, Milan, Italy). The FOB Gold assay is based on the antigen-antibody agglutination between human haemoglobin in the sample and polyclonal anti-human Hb antibodies absorbed on polystyrene particles. Agglutination is measured as an increase in absorbance at 570 nm compared to a standard calibration curve and is proportional to the concentration of human Hb in the sample. Between-run confidence values were 5.6 % at a Hb mean concentration of 80.3 ng/mL and 4.6 % at a Hb mean concentration of 304 ng/mL, respectively. The FIT was performed in each of the 2 samples per patient, and the higher value among these 2 entered the calculation. The lowest detection limit was 14 ng/mL, which corresponds to the cut off value for the calculations for specificity and sensitivity.

Statistical Analysis

Prior to commencement of the trial, we performed statistical analyses to determine the required population size. These were based on the expected prevalence of colonic adenomas in an asymptomatic European population. Our statistician determined the number of individuals to be screened by precision of the 95% confidence interval using normal approximations of binomial distributions. The study was powered to detect a 10% difference in OC and CTC sensitivity for detection of polyps larger than 5 mm, and the number of patients to be screened was determined to be 300. All data was entered into a database and calculations were done using SAS Statistical Software Version 9.1 (SAS Institute Inc., Cary, NC, USA). Sensitivities and specificities were calculated for OC and CTC on a per-polyp basis for advanced adenomas and for any polyp histology at cutoff sizes of 5 mm and 9 mm. Per-patient sensitivities and specificities were calculated for all tests at size thresholds of 5 and 9 mm. Specificities, positive and negative predictive values were calculated for all tests.

Results

311 consecutively enrolled asymptomatic adults underwent same-day CTC and OC (171 men and 140 women, 50-81 years of age, mean 60.5 ± 7.0 years). 4 persons had to be excluded because of withdrawal from the trial after CTC (n=2) or incomplete colonoscopy (n=2). Stool samples for FIT testing were available in 285 persons, and FOBT slides were available in 276. Based on an interview prior to inclusion, all patients were considered to be at average risk. There were no clinically relevant complications due to OC or CTC. 168 persons (54.7%) chose sedation for colonoscopy. Mean radiation dose for CTC was 4.5±0.6 mSv (range, 3.5-6.1 mSv). The supine scan at 70 reference mAs contributed a mean of 3.2 mSv, and the prone scan, a mean of 1.3 mSv.

Table 1 summarizes the distribution of polyps according to size and location. A total of 1,842 colonic segments were analyzed in 307 patients. Based on the gold standard (segmentally unblinded OC), 511 lesions were detected, 221 (43.2%) were adenomatous and 290 (56.8%) non-adenomatous. At least one adenoma of any size was detected in 113 participants (36.8%). The maximum number of polyps detected in one participant was 9. 418 (81.8%) polyps were 5 mm or smaller, 56 (11.0%) polyps measured 6-9 mm, and 37 (7.2%) polyps were larger than 9 mm. 248 polyps (48.6%; 78 adenomatous and 170 nonadenomatous polyps) were located within the reach of flexible sigmoidoscopy. A total of 46 advanced lesions was detected: 7 lesions measuring ≤5 mm, 6 lesions measuring 6-9 mm, and 33 lesions measuring at least 10 mm, including one stage T3 carcinoma of the transverse colon. The characteristics of patients with advanced adenoma are shown in table 2.

Table 3 summarizes the performance characteristics of the different methods for detection of adenomas according to the patient. OC reached the highest sensitivities for patients with adenomas of all size categories and identified 97.3% of patients with adenoma of all sizes, 97.8% of patients with adenomas ≥6 mm, and all patients with adenomas ≥10 mm. With sensitivities for identifying patients with adenomas ≥6 mm and ≥10 mm of 91.3% and 92%, respectively, CTC reflected the excellent performance data reported recently (8, 13). In contrast, sigmoidoscopy, FIT, and FOBT only identified 68%, 33.3%, and 23.8% of patients with adenomas ≥10 mm. All tests except sigmoidoscopy identified a stage T3 colorectal cancer in the transverse colon of a 72 year old man. Combination of sigmoidoscopy with FOBT or FIT resulted in increased detection rates for large adenomas of 76.2% and 71.4%, respectively, compared to FS alone (68%). 269 patients had both stool tests, while only one of the tests was available in 38 patients; analysis of the group of 269 patients who had all tests did not differ significantly from the analysis including all 307 patients.

We detected 147 adenomas ≤5 mm and 41 adenomas 6-9 mm in size. 13 of these small adenomas were of advanced histology. The other 33 (72%) advanced adenomas were ≥10 mm in size. OC identified 100% and CTC 96.7% of patients with advanced colonic neoplasia. Specificities of both methods equalled each other and resulted in similar positive and negative predictive values (table 3).Sensitivity according to the patient of sigmoidoscopy was higher for advanced lesions (25/30 patients, 83.3%) than for adenoma ≥10 mm (17/25 patients, 68.0%), reflecting the higher likelihood of advanced lesions in the rectosigmoid (27 of 46) compared to the rest of the colon (19 of 46). Sensitivities of FOBT and FIT for advanced lesions and adenoma ≥10 mm were not significantly different. Therefore, combination of sigmoidoscopy with stool tests did not increase sensitivity for advanced colonic neoplasia.

An analysis according to the polyp was performed for colonoscopy and CTC (Table 4). The sensitivities for adenomas of all sizes was much higher for colonoscopy with

212 of 221 (95.9%) lesions detected compared to 155 adenomas (70.1%) detected by CTC. This is mainly due to the comparably low performance of CTC in the diminutive size group. CTC only detected 59.2% of diminutive but 90.2% of 6-9 mm adenomas compared to colonoscopy which detected 94.6% and 92.7%. In contrast, CTC detected 31 of 33 (93.9%) lesions in the large adenoma group and 43 of 46 (93.5%) lesions in the advanced colonic neoplasia group. This was comparable to the detection rates of colonoscopy with sensitivities of 100% and 97.8%, respectively, in the two categories. CTC had a higher sensitivity for small adenomas with advanced histology. While sensitivity of CTC for adenomas <10 mm was only 66%, CTC missed only one adenoma of those with advanced histology in this size group, resulting in a sensitivity of 93.5% for advanced colonic neoplasia of all sizes which equals the sensitivity of colonoscopy.
Next to identifying all patients with advanced colonic neoplasia an ideal colorectal cancer screening test would also be negative in all unaffected individuals. CT colonography had a per-patient specificity for polyps ≥6 mm of 93.1% and a specificity for patients without a polyp ≥10 mm of 97.9%. Specificity of FOBT and FIT was 89.8% and 88.2%, respectively.
256 patients (83.4%) returned questionnaires for analysis, and 114 of these had sedation for OC. Regarding patient comfort, there was no difference between CTC and OC: 214 (83.6%) patients rated discomfort at CTC as “absent”, “very mild” or “mild”, and 210 (82.0)% chose these categories for OC. 37% preferred OC for future screening, 46% CTC ($p<0.001$), and 17% had no preference.

Discussion

Colorectal cancer is believed to be largely preventable through effective screening (2). However, compliance with current screening recommendations is low and several predictors of non-adherence to screening colonoscopy have been identified (31-33). A major deterrent from screening is non-compliance with colonoscopy. Therefore, alternative strategies, including self-propelling and self-navigating colonoscopes, capsule colonoscopy, virtual colonography based on CT or MRI, and new generation stool tests based on immunological detection of blood or detection of DNA mutations, have been proposed and are at different stages of development (8, 34). Prior to introduction, these methods need to be prospectively evaluated and compared to established tests.

There is good evidence that screening of asymptomatic persons with the use of FOBT or sigmoidoscopy can reduce mortality from colorectal cancer (23, 35, 36). Several studies have analyzed the combination of sigmoidoscopy with FOBT and found that combining the tests resulted in increased sensitivity for advanced neoplasia (2, 4, 37). In our study, we deducted FS results from colonoscopy by determining the rectum and sigmoid colon as being accessible for this test. Population sensitivity of sigmoidoscopy for advanced adenoma was 83.3% which is in accordance with above mentioned studies. Our results for FS might have been improved by the rigorous bowel preparation, which normally would not be employed for sigmoidoscopy. FOBT only detected 20% of advanced adenomas and combination of FS with FOBT only resulted in an increase of the detection rate of large adenomas but not advanced adenomas. Immunochemical based FIT tests detect human haemoglobin in stool and have higher sensitivities for advanced colonic neoplasia than guaiac-based FOBT (14, 38). We found that FIT identified 32% of patients with advanced and 33.3% of patients with large adenomas and the combination of FIT with FS resulted in a slight increase in detection rates only.

CTC is currently the most promising new screening method and several studies have reported high sensitivities for adenomas (8, 13). Additionally, CTC has now for the first time been recommended for colorectal cancer screening by the American Cancer Society (39). We used a 64-MDCT scanner that provides 0.4 mm isotropic resolution and employed 3D endoluminal CT colonography interpretation using a dedicated workstation. Reconstructing 0.75 mm slices leads to higher spatial resolution than in other trials published to date. This may have contributed to the high sensitivities for adenomas in our study. Interestingly, our CTC approach detected the majority of advanced adenomas smaller than 10 mm in diameter. This may have been caused by the small number of advanced lesions in this size group; however, it has been postulated that adenomas in general are less deformable than non-neoplastic lesions which leads to increased conspicuity at CTC (40, 41).

The relevance of diminutive and small polyps 1 – 9 mm in size has recently become a controversial topic (42). At least 20 – 30% of the average-risk asymptomatic population above age 50 carry adenomatous polyps (43). The majority of these are smaller than 10 mm. However, controversy exists as to the likelihood that small adenomas harbour significant advanced histology or progress to colorectal cancer. This has important implications on reporting and follow-up. A recent consensus proposal for CTC reporting suggested that diminutive polyps do not need to be reported and patients with 2 or less polyps <10 mm are recommended to undergo follow up CTC after 3 years rather than immediate colonoscopy for polypectomy, which is recommended for large polyps or if 3 or more small polyps are present (26). As small and medium size lesions may contain advanced histology (42), following this recommendation might lead to an increase in colorectal cancer incidence and mortality (25).

Another important issue is radiation exposure during CT colonography. Standard CTC techniques apply up to 12 mSv (12, 15, 44). It has been estimated that any amount of ionizing radiation may lead to an increase in radiation related cancer and death, and that up to 2% of cancers in the U. S. may be induced by diagnostic CT examinations (12, 19). Therefore, medical imaging-associated radiation needs to be kept to a minimum especially in screening procedures. Using low dose protocols and new dose modulation techniques, we were able to decrease the mean radiation dose to 4.5 mSv for the entire examination. This value is significantly lower than the dose values reported in or calculated from other major trials that used spatial resolutions inferior to our protocol, and is lower than measured values for a 64-detector system without dose modulation techniques (45). Remarkably, image quality remained high even in the pelvis, an anatomical region that is prone to image noise-induced artifacts in CT colonography (22, 45).

Although more patients preferred CTC than OC for future screening (46 vs. 37%), this preference was not as clear as in other comparative trials. Preferences were dependent on use of sedation for OC.

In conclusion, our results show that CT colonography performs equally well as colonoscopy in detecting advanced adenomas. Therefore, future screening guidelines might include CTC as a primary screening test as alternative to colonoscopy. Prerequisites for colorectal cancer screening by CTC are adequate training of radiologists, employment of high resolution low dose CT technique, and opportunity of same day colonoscopy in case of relevant findings in order to avoid repeat bowel preparation. Flexible sigmoidoscopy should be preferred to stool tests in patients who refuse to undergo full bowel preparation or total colonoscopy. FIT has a higher sensitivity for adenomas than FOBT, but both stool tests are inferior to tests that allow visualization of the colonic mucosa.

Acknowledgements
We appreciate the continuing support provided by the staff of the endoscopy and CT units during the duration of the study. We thank Roche Diagnostics for providing the FOBT tests, and E-Z-EM for providing the CO_2 insufflator unit.
Competing interest statement All authors hereby state that there are no competing interests that could have affected their work in this research project or in the writing and editing of the manuscript.
Figure 1.

a) High resolution 3D CT colonography endoluminal view shows 2.2 cm sessile polyp (marker “22a”) in the ascending colon in a 72 year old asymptomatic female.
b) Corresponding coronally reformatted CT image showing the same lesion. Isotropic datasets allow for reformation of images in any desired plane.
c) At colonoscopy, the lesion is confirmed. Histopathology revealed villous adenoma.

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Table 1: Distribution of adenomas and nonadenomatous polyps in 307 asymptomatic adults.

		Polyp Size			
		<6 mm	**6-9 mm**	**>9 mm**	**all**
Rectum					
	adenomatous	5	4	5	14
	nonadenomatous	84	6	1	91
Sigmoid colon					
	adenomatous	33	16	15	64
	nonadenomatous	78	1	0	79
Descending colon					
	adenomatous	24	6	4	34
	nonadenomatous	26	2	0	28
Transverse colon					
	adenomatous	22	4	4	30
	nonadenomatous	36	3	1	40
Ascending colon					
	adenomatous	41	9	2	52
	nonadenomatous	23	2	1	26
Cecum					
	adenomatous	22	2	3	27
	nonadenomatous	24	1	1	26
All segments					
	adenomatous	147	41	33	221
	nonadenomatous	271	15	4	290

Table 2. Characteristics of patients with advanced colonic neoplasia.

Pt No	lesion no	sex	age	site	Size [mm]	histology	dysplasia	OC	CTC	FS	FIT	FOBT
1		M	61	Sigmoid colon	14	villous	low	+	+	+	28	+
2		F	73	Ascending colon	22	villous	low	+	+	−	<14	−
3		M	66	Sigmoid colon	13	villous	low	+	+	+	<14	−
				Transverse colon	5	Villous	low	+	+	−		
				Cecum	4	villous	low	+	+	−		
4		M	68	Cecum	16	tubular	low	+	+	−	<14	−
5		M	73	Sigmoid colon	10	villous	low	+	+	+	61	+
				Rectum	7	villous	low	+	+	+		
6		M	67	Rectum	12	villous	low	+	+	+	<14	−
7		M	68	Descending colon	11	tubular	high	+	+	−	<14	−
8	1	F	74	Cecum	13	villous	low	+	+	−		
	2			Transverse colon	38	villous	low	+	+	−		
	3			Transverse colon	12	tubular	low	+	+	−		
	4			Transverse colon	8	villous	low	+	+	-		
	5			Sigmoid colon	17	villous	low	+	+	+		
9	1	M	68	Sigmoid colon	10	tubular	low	+	+	+	<14	−
	2			Sigmoid colon	11	villous	low	+	+	+		
10	1	F	63	Ascending colon	4	villous	low	+	−	−	50	−
	2			Descending colon	11	tubular	low	+	+	−		
	3			Sigmoid colon	14	tubular	low	+	+	+		
11		M	73	Sigmoid colon	11	tubular	low	+	+	+	<14	−
12	1	M	66	Ascending colon	11	tubular	low	+	+	−	<14	−
	2			Rectum	15	tubular	low	+	+	+		
	3			Rectum	12	villous	low	+	+	+		
13		M	64	Sigmoid colon	16	villous	low	+	−	+		
14		M	57	Sigmoid colon	22	villous	high	+	+	+	96	+
15	1	F	56	Sigmoid colon	13	tubular	low	+	+	+	132	−
	2			Sigmoid colon	7	tubular	high	+	+	+		
16		M	56	Rectum	15	villous	low	+	+	+	<14	−
17		M	70	Transverse colon	57	carcinoma	low	+	+	−	>765	+
18		M	61	Transverse colon	18	tubular	low	+	+	−		
19		F	58	Sigmoid colon	13	tubular	low	+	+	+	<14	−
20	1	M	53	Sigmoid colon	11	villous	low	+	+	+		
	2			Sigmoid colon	14	villous	low	+	+	+		
21		M	55	Cecum	12	tubular	low	+	+	−	<14	−
22		M	69	Rectum	13	tubular	low	+	+	+	>765	−
23		F	69	Sigmoid colon	12	tubular	low	+	+	+	<14	−
24		M	51	Descending colon	13	tubular	low	+	+	−	<14	+
25		F	63	Descending colon	10	serrated	low	+	−	−	<14	−
26		M	67	Descending colon	8	villous	low	+	+	−		−
27	1	F	64	Descending colon	5	tubular	high	+	+	−	248	−
	2			Rectum	8	villous	low	+	+	+		
	3			Sigmoid colon	4	villous	low	+	+	+		
28		F	69	Sigmoid colon	5	villous	low	+	+	+	<14	−
29		F	70	Sigmoid colon	5	serrated	low	+	+	+	<14	−
30		M	55	Sigmoid colon	8	villous	low	+	+	+	<14	-

Table 3. Performance characteristics of OC, CTC, FS, FOBT and FIT in the detection of colonic adenomas in asymptomatic adults. Analysis according to the patient.

		All sizes	>5mm	>9mm	advanced colonic neoplasia
		no./total no. (% [95%CI])	no./total no. (% [95%CI])	no./total no. (% [95%CI])	no./total no. (% [95%CI])
OC	Sens	110 / 113 (97.3 [92.4-99.4])	45 / 46 (97.8 [88.5-99.9])	25 / 25 (100.0 [86.3-100.0])	30 / 30 (100 [88.4-100])
	Spec	116 / 194 (59.8 [52.5-66.8])	250 / 261 (95.8 [92.6-97.9])	278 / 282 (98.6 [96.4-99.6])	119 / 277 (43.0 [37.1-49])
	PPV	110 / 188 (58.5 [51.1-65.6])	45 / 56 (80.4 [67.6-89.8])	25 / 29 (86.2 [68.3-96.1])	30 / 188 (16.0 [11.0-22.0])
	NPV	116 / 119 (97.5 [92.8-99.5])	250 / 251 (99.6 [97.8-100])	278 / 278 (100.0 [98.7-100.0])	119 / 119 (100 [96.9-100])
FS	Sens	81 / 113 (71.7 [62.4-79.8])	31 / 46 (67.4 [52.0-80.5])	17 / 25 (68.0 [46.5-85.1])	25 / 30 (83.3 [65.3-94.4])
	Spec	138 / 194 (71.1 [64.2-77.4])	258 / 261 (98.9 [96.7-99.8])	281 / 282 (99.6 [98.0-100.0])	165 / 277 (59.6[53.5-65.4])
	PPV	81 / 137 (59.1 [50.4-67.4])	31 / 34 (91.2 [76.3-98.1])	17 / 18 (94.4 [72.7-99.9])	25 / 137 (18.2[12.2-25.7])
	NPV	138 / 170 (81.2 [74.5-86.8])	258 / 273 (94.5 [91.1-96.9])	281 / 289 (97.2 [94.6-98.8])	165 / 170 (97.1[93.3-99])
CTC	Sens	95 / 113 (84.1 [76.0-90.3])	42 / 46 (91.3 [79.2-97.6])	23 / 25 (92.0 [74.0-99.0])	29 / 30 (96.7[82.8-99.9])
	Spec	92 / 194 (47.4 [40.2-54.7])	243 / 261 (93.1 [89.3-95.9])	276 / 282 (97.9 [95.4-99.2])	109 / 277 (39.4 [33.6-45.4])
	PPV	95 / 197 (48.2 [41.1-55.4])	42 / 60 (70.0 [56.8-81.2])	23 / 29 (79.3 [60.3-92.0])	29 / 197 (14.7[10.1-20.5])
	NPV	92 / 110 (83.6 [75.4-90.0])	243 / 247 (98.4 [95.9-99.6])	276 / 278 (99.3 [97.4-99.0])	109 / 110 (99.1[95.0-100])
FOBT	Sens	20 / 99 (20.2 [12.8-29.5])	7 / 40 (17.5 [7.3-32.8])	5 / 21 (23.8 [8.2-47.2])	5 / 25 (20.0 [6.8-40.7])
	Spec	166 / 177 (93.8 [89.2-96.9])	212 / 236 (89.8 [85.2-93.4])	229 / 255 (89.8 [85.4-93.2])	225 / 251 (89.6 [85.2-93.1])
	PPV	20 / 31 (64.5 [45.4-80.8])	7 / 31 (22.6 [9.6-41.1])	5 / 31 (16.1 [5.5-33.7])	5 / 31 (16.1 [5.5-33.7])
	NPV	166 / 245 (67.8 [61.5-73.6])	212 / 245 (86.5 [81.6-90.5])	229 / 245 (93.5 [89.6-96.2])	225 / 245 (91.8 [87.7-94.9])
FIT	Sens	25 / 102 (24.5 [16.5-34.0])	16 / 40 (40.0 [24.9-56.7])	7 / 21 (33.3 [14.6-57.0])	8 / 25 (32.0 [14.9-53.5])
	Spec	163 / 183 (89.1 [83.6-93.2])	216 / 245 (88.2 [83.4-91.9])	226 / 264 (85.6 [80.8-89.6])	223 / 260 (85.8 [80.9-89.8])
	PPV	25 / 45 (55.6 [40.0-70.4])	16 / 45 (35.6 [21.9-51.2])	7 / 45 (15.6 [6.5-29.5])	8 / 45 (17.8 [8.0-32.1])
	NPV	163 / 240 (67.9 [61.6-73.8])	216 / 240 (90.0 [85.5-93.5])	226 / 240 (94.2 [90.4-96.8])	223 / 240 (92.9 [88.9-95.8])
FS + FOBT	Sens	71 / 99 (71.7 [61.8-80.3])	28 / 40 (70.0 [53.5-83.4])	16 / 21 (76.2 [52.8-91.8])	20 / 25 (80.0 [59.3-93.2])
	Spec	120 / 177 (67.8 [60.4-74.6])	211 / 236 (89.4 [84.8-93.0])	228 / 255 (89.4 [85.0-92.9])	143 / 251 (57.0 [50.6-63.2])
	PPV	71 / 128 (55.5 [46.4-64.3])	28 / 53 (52.8 [38.6-66.7])	16 / 43 (37.2 [23.0-53.3])	20 / 128 (15.6 [9.8-23.1])
	NPV	120 / 148 (81.1 [73.8-87.0])	211 / 223 (94.6 [90.8-97.2])	228 / 233 (97.9 [95.1-99.3])	143 / 148 (96.6 [92.3-98.9])
FS + FIT	Sens	79 / 102 (77.5 [68.1-85.1])	32 / 40 (80.0 [64.4-90.9])	15 / 21 (71.4 [47.8-88.7])	21 / 25 (84.0[63.9-95.5])
	Spec	119 / 183 (65.0 [57.6-71.9])	215 / 245 (87.8 [83.0-91.6])	225 / 264 (85.2 [80.4-89.3])	138 / 260 (53.1 [46.8-59.3])
	PPV	79 / 143 (55.2 [46.7-63.6])	32 / 62 (51.6 [38.6-64.5])	15 / 54 (27.8[16.5-41.6])	21 / 143 (14.7 [9.3-21.6])
	NPV	119 / 142 (83.8 [76.7-89.4])	215 / 223 (96.4 [93.1-98.4])	225 / 231 (97.4[94.4-99.0])	138 / 142 (97.2 [92.9-99.2])

Table 4. Performance characteristics of OC and CTC in the detection of colonic adenomas. Analysis according to polyp.

	All sizes	<6 mm	6-9 mm	>9 mm	advanced colonic neoplasia
	no./total no. (%[95%CI])	no./total no. (%[95%CI])	no./total no. (%[95%CI])	no./total no. (%[95%CI])	no./total no. (%[95%CI])
Senitivity OC	212/221 (95.9[92.4-98.1])	139/147 (94.6[89.6-97.6])	38/41 (92.7[80.1-98.5])	33/33 (100[89.4-100])	45/46 (97.8[88.5-99.9])
Sensitivity CTC	155/221 (70.1[63.6-76.1])	87/147 (59.2[50.8-67.2])	37/41 (90.2[76.9-97.3])	31/33 (93.9[79.8-99.3])	43/46 (93.5[82.1-98.6])