ORIGINAL ARTICLE

Colon capsule versus CT colonography in patients with incomplete colonoscopy: a prospective, comparative trial

Cristiano Spada,[1] Cesare Hassan,[1] Brunella Barbaro,[2] Franco Iafrate,[3] Paola Cesaro,[1] Lucio Petruzziello,[1] Leonardo Minelli Grazioli,[1] Carlo Senore,[4] Gabriella Brizi,[2] Isabella Costamagna,[1] Giuseppe Alvaro,[2] Marcella Iannitti,[3] Marco Salsano,[2] Maria Ciolina,[3] Andrea Laghi,[3] Lorenzo Bonomo,[2] Guido Costamagna[1]

[1]Digestive Endoscopy Unit, Catholic University, Rome, Italy
[2]Department of Bioimaging and Radiological Sciences, Catholic University, Rome, Italy
[3]Department of Radiological Sciences, Oncology and Pathology, Sapienza University, Rome, Italy
[4]Epidemiologia dei Tumori II, AOU S Giovanni Battista—CPO Piemonte Torino, Torino, Italy

Correspondence to
Dr Cristiano Spada, Digestive Endoscopy Unit, Catholic University, Largo F. Vito 1, Rome 00168, Italy; cristianospada@gmail.com

Received 5 December 2013
Revised 4 June 2014
Accepted 5 June 2014
Published Online First 24 June 2014

ABSTRACT

Objective In case of incomplete colonoscopy, several radiologic methods have traditionally been used, but more recently, capsule endoscopy was also shown to be accurate. Aim of this study was to compare colon capsule endoscopy (CCE) and CT colonography (CTC) in a prospective cohort of patients with incomplete colonoscopy.

Design Consecutive patients with a previous incomplete colonoscopy underwent CCE and CTC followed by colonoscopy in case of positive findings on either test (polyps/mass lesions ≥6 mm). Clinical follow-up was performed in the other cases to rule out missed cancer. CTC was performed after colon capsule excretion or 10–12 h postingestion. Since the gold standard colonoscopy was performed only in positive cases, diagnostic yield and positive predictive values of CCE and CTC were used as study end-points.

Results 100 patients were enrolled. CCE and CTC were able to achieve complete colonic evaluation in 98% of cases. In a per-patient analysis for polyps ≥6 mm, CCE detected 24 patients (24.5%) and CTC 12 patients (12.2%). The relative sensitivity of CCE compared to CTC was 2.0 (95% CI 1.34 to 2.98), indicating a significant increase in sensitivity for lesions ≥6 mm. Of larger polyps (≥10 mm), these values were 5.1% for CCE and 3.1% for CTC (relative sensitivity: 1.67 (95% CI 0.69 to 4.00)). Positive predictive values for polyps ≥6 mm and ≥10 mm were 96% and 85.7%, and 83.3% and 100% for CCE and CTC, respectively. No missed cancer occurred at clinical follow-up of a mean of 20 months.

Conclusions CCE and CTC were of comparable efficacy in completing colon evaluation after incomplete colonoscopy; the overall diagnostic yield of colon capsule was superior to CTC.

Trial registration number NCT01525940.

Significance of this study

What is already known on this subject?

- Colonoscopy may be incomplete in 4–15% of patients.
- CT colonography (CTC) is the imaging modality of choice in case of incomplete colonoscopy.
- Preliminary data suggest that colon capsule endoscopy (CCE) is a feasible and safe tool for colon mucosa visualisation in patients with incomplete colonoscopy without stenosis.
- Studies comparing CCE with radiological imaging, and in particular with CTC, are lacking.

What are the new findings?

- CCE and CTC are very effective in completing incomplete colonoscopy.
- CCE diagnostic yield is superior to that of CTC, when using colonoscopy for positive cases as gold standard.
- The superiority of CCE appears mainly to be related with a higher accuracy for 6–9 mm and/or non-polypoid lesions.

How might it impact on clinical practice in the foreseeable future?

- Where CCE is available, it may be considered among the first-choice tests in case of incomplete colonoscopy.
- Incomplete colonoscopy might be considered an appropriate indication for CCE.

INTRODUCTION

Optical colonoscopy is the standard method for evaluating the colon.[1] This technique allows evaluation of the entire colon in most patients. Caecal intubation is associated with an increased detection rate of advanced neoplasia, as 33–50% of advanced neoplasia is located in the proximal colon.[2] Despite a recommendation of ≥90% and ≥95% caecal intubation rates in routine clinical practice and in screening colonoscopies, respectively,[3] the actual caecal intubation rate in daily clinical practice is often suboptimal.[4–11] After an incomplete optical colonoscopy, patients are required to undergo another test in order to exclude clinically relevant lesions to reduce the risk of proximal cancer which has been shown to increase by twofold when colonoscopy was incomplete.[12]

Endoscopic and radiological options to complete the colon assessment have been available in the last decades. Multiple alternative endoscopic techniques—such as colonoscopy with thinner colonoscopes, gastroscopes and device-assisted

To cite: Spada C, Hassan C, Barbaro B, *et al*. *Gut* 2015;**64**:272–281.

enteroscopes have been described.[13 14] However, none of them has been clearly standardised. Alternatively, double-contrast barium enema (DCBE) has been traditionally used to image the colon after failed or incomplete colonoscopy. However, data from the National Polyp Study Work Group already indicated a disappointing 48% sensitivity of DCBE for ≥10 mm polyps.[15]

CT colonography (CTC),[4 16–19] also known as virtual colonoscopy, is a relatively new imaging technique that was first described in 1994. In large randomised trials on symptomatic patients,[20 21] CTC has been shown to be substantially more effective than DCBE—as well as equally effective as colonoscopy—for the detection of large colorectal polyps and already-developed colorectal cancer. CTC has been also recommended by the American Gastroenterological Society (AGA) as the imaging modality of choice in case of incomplete colonoscopy.[22]

Colon capsule endoscopy (CCE) (Given Imaging, Yoqneam, Israel) is a new, minimally invasive, painless, endoscopic technique that is able to explore the colon without requiring sedation, gas insufflation and radiation exposure. Recently, a second-generation CCE has been released that provides a higher frame rate and a larger angle lens.[23 24] Preliminary data suggest that CCE is a feasible and safe tool for colon mucosa visualisation in patients with incomplete colonoscopy without stenosis, being able to guide further workup.[25–27] CCE has also been recently approved by the Food and Drug Administration (FDA, USA) specifically for a previously incomplete colonoscopy. However, studies comparing CCE with radiological imaging, and in particular with CTC, are lacking. Potential advantages of CCE over CTC are the lack of ionising radiation, the limited availability of CTC due to saturation of the time machine with other indications, and the possibility with CCE to directly visualise colorectal mucosa.

The aim of this study was to compare the performance of CCE and CTC in a prospective cohort of patients with a previously incomplete colonoscopy. Positive cases at any of the two tests were worked up with colonoscopy that acted as gold standard, while negative cases underwent a clinical follow-up.

PATIENTS AND METHODS

Study population and study overflow

This is a prospective, single-blinded study that evaluated the role of CCE and CTC in consecutive patients aged 18–75 years, who had an incomplete colonoscopy in our centre—as clinically indicated for any reason—or who were referred to our centre for an incomplete colonoscopy, unless an inadequate preparation and/or the presence of colonic stricture were the reasons for the prior incomplete examination. Exclusion criteria were those previously reported for small bowel capsule enteroscopy, CCE and CTC.[23 24 25 28 17] In detail, patients with dysphagia or any swallowing disorder, congestive heart failure, renal insufficiency, prior abdominal surgery of the gastrointestinal tract (other than uncomplicated procedures that would be unlikely to lead to bowel obstruction), cardiac pacemaker or other implanted electromedical device, allergy or other known contraindication to the medications used in the study; patients expected to undergo MRI examination within 7 days after ingestion of the capsule, with any condition believed to have an increased risk for capsule retention (such as Crohn's disease, intestinal tumours, radiation enteritis, or non-steroidal anti-inflammatory drugs enteropathy), women either pregnant or nursing at the time of screening, who intended to be pregnant during the study period, or were of childbearing potential and were not practicing medically acceptable methods of contraception. Patients with unremoved polyps at the incomplete colonoscopy were also excluded, in order to exclude interpretation bias of the study findings. In the enrolled patients, reasons for incomplete colonoscopy and sites reached by conventional colonoscopy were systematically collected. Each subject underwent CCE and CTC on the same day, using the same regimen of preparation. CCE was performed first, while CTC was performed after the natural excretion of colon capsule or 10–12 h postcapsule ingestion at the latest. In the case of ≥6 mm polyp/mass detection at either CCE or CTC, a second colonoscopy with segmental unblinding was performed within 1 month.

The study was approved by the local institutional ethics board and met all criteria put forth by the Declaration of Helsinki. The protocol was registered in ClinicalTrial.gov (NCT01525940). All participants signed written informed consent before participation in the study.

Patient preparation

Regimen of preparation for CCE and CTC is shown in table 1. Briefly, it consists of the standard regimen of preparation for CCE as previously described, with the inclusion of sodium-amidotrizoate and meglumine-amidotrizoate (75 mL) (Gastrografin, Bayer, Italy) which was added to the sodium-phosphate booster for faecal tagging.

Colon capsule endoscopy

The second-generation Given Diagnostic System (Given Imaging, Yoqneam, Israel) that was used in this trial is the same as previously described.[23 24] Colon cleanliness was graded by using a 4-point scale: excellent (ie, no more than small bits of adherent faeces in the colon), good (ie, small amount of faeces or turbid fluid not interfering with examination), fair (ie, enough faeces or turbid fluid to prevent a reliable examination) and poor (ie, large amount of faecal residue precludes a complete examination).[29] Patients with an excellent or good cleansing were considered having an adequate preparation, while patients with a fair or poor cleansing were considered having an inadequate preparation. Quality of preparation was evaluated for each of the following colonic segments: right colon (including caecum and ascending colon), transverse colon, left colon (including descending colon and sigmoid), and

Table 1 PillCam COLON 2 preparation regimen

Schedule	Intake
Day -2	
All day	At least 10 glasses of water
Bedtime	Four Senna tablets,12 mg each
Day -1	
All day	Clear liquid diet
Evening	2 L PEG
Exam day	
Morning	2 L PEG
~10:00	Capsule ingestion*
1st boost *Upon small bowel detection*	40 mL NaP& 1 L water with Gastrografin† (50 mL)
2nd boost‡ *3 h after 1st boost*	25 mL NaP& 0.5 L water with Gastrografin† (25 mL)
Suppository *2 h after 2nd boost*	10 mg Bisacodyl

*20 mg Domperidone tablet if capsule delayed in stomach >1 h.
‡Only if capsule not excreted yet.
†sodium-amidotrizoate and meglumine-amidotrizoate.

rectum.[29] An overall colon-cleansing grade also was evaluated by using the same grading system.[28]

When polyps were diagnosed, they were classified with respect to location, size and morphology (pedunculated, sessile, flat and depressed). Polyp size was estimated during capsule video reading by using the polyp size estimation tool included in the RAPID software (Given Imaging, Yoqneam, Israel, V.7.0). Other lesions, such as angiomas, diverticula, inflammation and haemorrhoids were also described but not considered for statistical analysis.

All generated CCE videos were reviewed by a physician (CS, CH) who was blinded to CTC results. CCE readers had prior experience with small bowel capsule and colon capsule.

CT-colonography

CTC examinations were performed with a 64-volume computed tomography (VCT) scanner (GE Medical Systems, Milwaukee, Wisconsin, USA). With the patient in the left lateral decubitus position, the colon was gently insufflated using a manual air insufflation device using a lubricated Foley catheter made of silicone, gently placed in the rectum. With the patient in the supine position, an antero-posterior CT scout image was obtained to assess the degree of colonic distension. If adequate colonic distension had not been achieved, air insufflation was repeated according to patient tolerance. All patients were examined by using 1.25 slice thickness, a 64×0.625 mm collimation, 0.5 tube rotation, and 1.0 mm reconstruction interval. Scans were obtained at 50 or fewer effective mA per second. Acquisition time was 6.1 s for each scan. A muscle relaxant was not routinely used. Intravenous contrast medium was not administered. CTC used CT to acquire images and advanced two-dimensional (2D) and 3D-image display techniques for interpretation. The CT datasets were postprocessed using commercially available software (Im3D, Torino, Italy).

Adequate procedure for CTC was defined as a proper visualisation of colonic segments which could not have been explored by conventional colonoscopy. The evaluation of the quality of CTC considered different parameters: colonic cleanliness, distension and faecal tagging. Each parameter was considered for the following colonic segments: caecum, ascending, transverse, descending, sigmoid and rectum. Cleansing level, distension and faecal tagging were graded as previously described.[4] An overall colon assessment (adequate vs inadequate) also was indicated. When polyps were diagnosed, they were classified with respect to location, size and morphology (pedunculated, sessile, flat and depressed). Polyp size was measured on zoomed axial slices, taking into account the largest diameter.

Other lesions, such as diverticula, inflammation and haemorrhoids were also described but not considered for statistical analysis.

Study CTC was performed by experienced CTC readers (BB, FI, AL, GB), who each had undertaken more than 500 CTC examinations with colonoscopy verification, and who were appropriately trained on use of computer-aided detection workstation. CTC readers were blinded to the results of the CCE.

Colonoscopy

After the CCE and CTC procedures, optical colonoscopy was performed only in those patients with a positive result (ie, least one ≥6 mm polyp) at CCE and/or CTC. Thus, colonoscopy acted as gold standard to differentiate between true-positive and false-positive results. Although the physician was aware that the patient had a significant finding, he was initially blinded to the type of result and location of finding detected by CCE and/or CTC. Colonoscopy under general anaesthesia or deep sedation was performed within 1 month after CCE and CTC procedures by two experienced endoscopists (LP and PC). Paediatric colonoscopes, gastroscopes and variable stiffness colonoscopes were used when indicated, according to the normal standard of the Centre. For each colonoscopy, completeness of the procedure was recorded, and colon cleansing level at the different segments was graded by using the 4-point scale similar to the one used for CCE. When polyps were diagnosed, they were classified with respect to morphology (pedunculated, sessile, flat, and depressed), location (colon segment and distance from anal verge), size (measured in vivo by using open biopsy forceps with an 8 mm length as reference), and histology. In case the finding by CCE and/or CTC was not detected by optical colonoscopy, a segmental unblinding was performed after the colonoscopist read the CCE and/or CTC report.

Clinical follow-up

Combination between CCE and CTC was expected to result into a very high cumulative sensitivity for significant findings (ie, large polyps and already-developed colorectal cancer (CRC)). Therefore, patients with negative results at the two previous tests did not receive a post-test colonoscopy. Since such colonoscopy acted as gold standard for positive cases, we decided to perform a 1-year clinical follow-up in those with negative results at CCE and CTC. Thus, all patients with negative results at both tests were contacted in order to exclude risks of missed cancer.

Statistical analysis

Continuous variables are reported as mean±SD and categorical variables as percentage. A two-sided Student t test was used to compare continuous variables, and the χ^2 test was applied to compare categorical variables. The exact method was used to calculate the CI for the proportions.[30] As only patients testing positive at one of the two tests under evaluation were examined with the gold standard (colonoscopy), we estimated the relative sensitivity and relative false-positive rate and their 95% CI, using the method proposed by Cheng and Macaluso.[31] These two parameters provide a measure of the increase in accuracy associated with preferring one test over the other; $p<0.05$ indicated statistical significance. The efficacy analysis (findings detected by CCE/CTC) is reported per patient. Statistical analyses were performed with SPSS for Windows software, V.12.0 (SPSS, Chicago, USA).

Study end-points

Primary end-point was the per-patient diagnostic yield (ie, ratio between the number of patients with significant findings and overall patients) of CCE and CTC for ≥6 mm polyps/mass undetected by previously incomplete colonoscopy by using post-CCE/CTC colonoscopy as reference standard. Secondary end-points were: (1) CCE/CTC completion rate; (2) rate of missed cancer at 1-year clinical follow up; (3) level of bowel preparation at CCE/CTC; (4) CCE/CTC safety.

Definition of diagnostic yield

CCE or CTC was reported as positive when at least one ≥6 mm polyp was detected, otherwise it was reported as negative. Diminutive polyps (ie, <6 mm) were not considered an indication for endoscopic polypectomy. At the second colonoscopy, that served as the reference standard,a given polyp was considered as identified by either or CCE and CTC, if it had been assessed within ±50% of the size of the reference standard

measure (ie, CCE/CTC vs second colonoscopy) and as appearing within the same colon segment or in adjacent segments. All findings were included in the analysis as follows: (1) findings detected by the CCE but not detected by CTC were marked as CCE new finding; (2) findings detected by the CTC but not detected by CCE were marked as CTC new finding; (3) findings detected by the CCE and CTC were marked as same findings. If CCE and/or CTC was positive, but the case was classified as negative at colonoscopy (confirmed by the unblinding process), it was considered a false positive.

Definition of secondary end-points

For the evaluation of completeness of colonic exploration with CCE and CTC, a complete procedure for CCE and CTC is defined as the visualisation of colonic segments which could not have been explored by conventional colonoscopy. Excretion rate of the colon capsule was also evaluated. Regarding the secondary end-point of CCE completion rate, in cases where the capsule was not excreted or did not reach the rectum during the recording time, in order to minimise the limitation of CCE to define the passage of the capsule beyond the most proximal point reached by colonoscopy, readings were performed by two observers (CS and PC) considering anatomic landmarks, appearance of the lumen and study findings. To further reduce the possibility of error, a third investigator (CH) made the decision in case of disagreement. Missed cancer at clinical follow-up was defined as pathological confirmation of any colorectal lesion diagnosed after the end of study participation.

Sample size

The sample size was calculated with the assumption of non-inferiority between CCE and CTC. Prevalence of patients with at least one polyp/mass equal to or larger than 6 mm after an incomplete colonoscopy was assumed to be 10%.[19] Non-inferiority was declared if the estimated difference between the diagnostic yield of CCE and CTC was ≤11%. In order to maintain that hypothesis as well as the type I error (α) of 5% and power (=1−β) of 80%, the required sample size was estimated to be 92 patients. Adding a dropout rate of 5% resulted in a total study size of 97 patients. Diagnostic yield with its 95% CI was calculated according to polyp size.

RESULTS

Study population

One hundred and twenty-eight consecutive patients (86 female, median age 60 years, range 33–75 years) with a previously incomplete colonoscopy performed in our as well as in other centres, and referred for completion of the colorectal examination were prospectively screened from November 2011 to January 2013. Twenty-eight patients were excluded because of inadequate colonic preparation at the incomplete colonoscopy (n=16), refusal to be included in the trial (n=6), Crohn's disease-related inflammatory stricture (n=2), neoplastic stricture (n=2) and presence of unremoved polyps at the incomplete colonoscopy (n=2). Finally, 100 patients (66 female, median age 59 years, range 33–75 years) were prospectively enrolled. A flow diagram with the inclusion and exclusion algorithm is shown in figure 1. Indication to colonoscopy, reasons for incomplete colonoscopy and the sites reached by conventional colonoscopy are showed in table 2. Two (2%) subjects refused to undergo CTC because of air insufflation and were excluded from the efficacy analysis. One patient was excluded since the presence of a non-excreted capsule in the sigmoid colon caused artefacts precluding an accurate CTC evaluation of the colon. Therefore, a total of 97 subjects who successfully undertook CCE and CTC were included in the efficacy analysis.

Cumulative findings at CCE/CTC

Overall, 26 (27%) patients were diagnosed with at least one ≥6 mm polyp by CCE, CTC or both the procedures. CCE/CTC diagnosis was eventually confirmed in 24/26 (92.3%) patients at second colonoscopy, while two patients with a ≥6 mm polyp detected by CCE (1 patient) or CTC (2 patients) resulted to be false positive. All the 26 CCE-/CTC-positive patients had at least one ≥6 mm polyp in the colorectal segments apparently unseen by the incomplete colonoscopy. Additionally, two of these patients also presented with a ≥6 mm polyp in the already seen segments, apparently being false negatives of the previously incomplete colonoscopy.

Diagnostic yield CCE/CTC

At a per-patient analysis, CCE was the only technique to detect at least one ≥6 mm polyp in 12 patients (all true positives) (figure 2), while CCE and CTC detected at least one ≥6 mm polyp in 13 cases (12 true positives, 1 false positive for both), and CTC was the only procedure to detect a positive finding in 1 patient (false positive) (figure 3). Overall, CCE detected 24 patients (24.5% (95% CI 16.6% to 34.4%)) with at least a ≥6 mm polyp, while CTC detected 12 patients (12.2% (95% CI 6.8% to 20.8%)) with at least a ≥6 mm polyp. The relative sensitivity of CCE compared to CTC was 2.0 (95% CI 1.34 to 2.98), indicating a significant increase in sensitivity for lesions ≥6 mm when using the CCE (tables 3 and 4).

When restricting the analysis to patients with polyps ≥10 mm, six patients were diagnosed to have at least one polyp ≥10 mm. At a per-patient analysis, CCE was the only technique to detect at least one ≥10 mm polyp in three patients (2 true positives, 1 false positive) (figures 3 and 4) (table 4), while CCE and CTC detected at least one ≥10 mm polyp in three cases (all true positives) (figures 5 and 6). In none of the cases, polyps ≥10 mm were detected only by CTC. Overall, CCE detected five patients (5.1% (95% CI 1.9% to 12.1%)) with at least a ≥10 mm polyp, while CTC detected three patients (3.1% (95% CI 0.8% to 9.3%)) with at least a ≥10 mm polyp. The relative sensitivity of CCE compared to CTC for polyps ≥10 mm was 1.67 (95% CI 0.69 to 4.00). The sensitivity increase with CCE did not reach the level of statistical significance. The diagnostic yield of CCE and CTC for polyps ≥6 mm and ≥10 mm is shown in table 3.

Both the procedures show a high positive predictive value (PPV). In the group of patients with polyps ≥6 mm, the CCE results were confirmed in 24 out of 25 patients (96% (95% CI 77.7% to 99.8%)), while the CTC results were confirmed in 12 out of 14 patients (85.7% (95% CI 56.2% to 97.5%)). The relative false-positive rate of CCE compared to CTC for polyps ≥6 mm was 2.0 (95% CI 0.50 to 8.00) and did not reach the level of statistical significance. In the group of patients with polyps ≥10 mm, the CCE results was confirmed in 5 out of 6 patients (83.3% (95% CI 36.5% to 99.1%)), while the CTC results were confirmed in 3 out of 3 patients (100% (95% CI 31.1% to 100%)). The difference in terms of PPV for polyps ≥10 mm between CCE and CTC did not reach the level of statistical significance.

When analysing the causes of the 12 false-negative cases at CTC after unblinding, in one case the radiologist was able to detect the initially missed >10 mm polyp (perceptual error), while lesions remained undetectable in the remaining 11 cases.

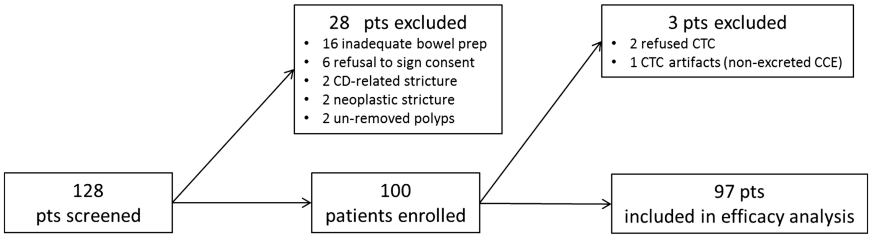


Figure 1 Patient's flow chart.

A poor quality of tagging was considered as a possible cause in two of the cases.

Clinical follow-up

All the 74 patients with negative results at CCE and CTC were successfully contacted after a mean of 20 months (range 10–24 months) from the study examinations. No missed cancer was reported.

Completion rate

CCE was complete in 98% of cases. In two out of 100 cases (2%) the CCE procedure was defined as incomplete. In one patient, the capsule delayed in the gut, and the recording stopped when the capsule reached the splenic flexure/descending colon. Due to long-lasting procedure, one patient refused to continue the CCE examination and was disconnected from the data recorder while the capsule was located in the descending colon. In 93 out of 100 patients (93%) the capsule was excreted within 10 h post-ingestion. CTC was complete in 98% of cases. In two out of 98 patients (2%) who underwent the CTC procedure, the evaluation of the colon was defined as incomplete due to a poor distension of the sigmoid colon.

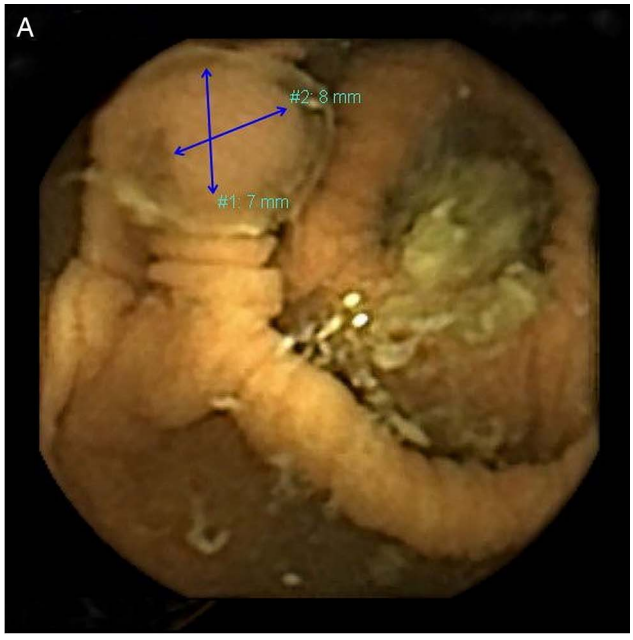
Bowel preparation

The CCE overall cleansing rate was adequate in 83% (CI 74% to 90%) of the cases. The overall CTC quality of the procedure was assessed considering the quality of tagging, distension and cleansing level. In 88 out of 98 patients (90% (CI 82% to 95%)) CTC procedure was considered adequate. No significant

Table 2 Indication, reason for incomplete colonoscopy, most proximal colonic segment reached at first incomplete colonoscopy

	n of pts	Per cent
Indication		
Abdominal pain	21	20
Rectal bleeding	19	18
Family history of CRC	17	16
Recent change of bowel habits	13	13
Positive FOBT	12	12
CRC screening	11	11
Post polypectomy surveillance	10	10
Anemia	1	1
Reason for incomplete		
Excessive pain	45	45
Difficult examination	38	38
Tortuosity of colon	17	17
Most proximal colonic segment reached		
Sigmoid	43	43
Descending	28	28
Transverse	25	25
Ascending	4	4

CRC, colo-rectal cancer.



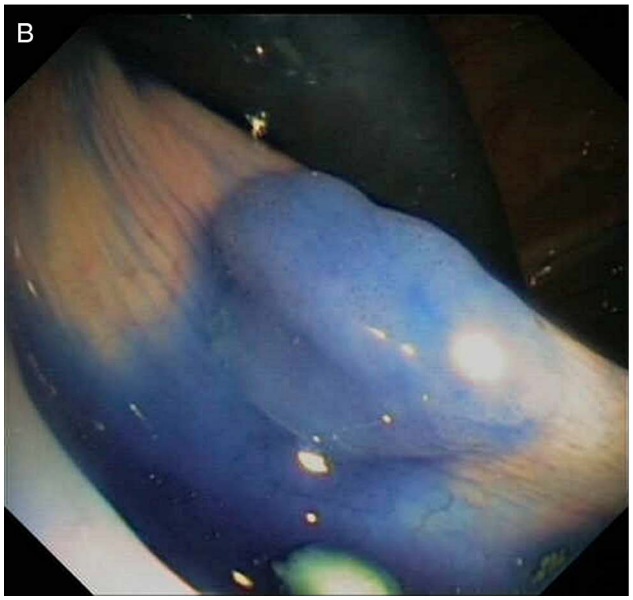


Figure 2 Colon capsule endoscopy (CCE) 'new finding': ≥6 mm polyp detected by the CCE but not detected by CT colonography (CTC). (A) An 8 mm caecal polyp with a mucous cap detected by CCE and missed by CTC. The polyp was confirmed by colonoscopy. (B) Histology showed a sessile serrated polyp.

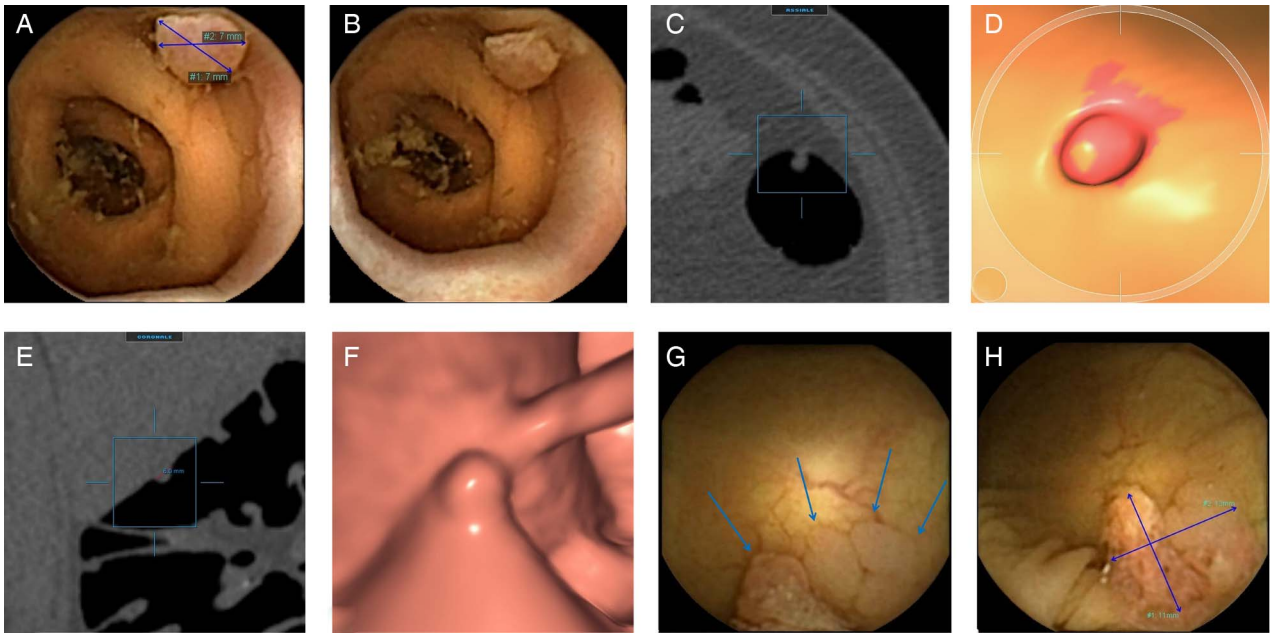


Figure 3 False positive cases. Case 1: a 7 mm polyp detected in the sigmoid by colon capsule endoscopy (CCE) (A and B) and CT colonography (CTC) ((C) axial two-dimensional (2D) CT image and (D), 3D endoluminal view after application of computer-aided detection (CAD)). This polyp was not confirmed by colonoscopy and it was considered a false positive case. Case 2: a 6 mm polyp detected by CTC ((E) coronal 2D CT image 3D endoluminal view and (F), 3D endoluminal view) at the hepatic flexure. This polyp was not visualised by CCE and colonoscopy (CTC false positive). Case 3: a 13 mm lesion detected in the proximal ascending by CCE ((G) and (H)). This lesion was not confirmed by colonoscopy and it was considered a CCE false positive case.

difference was observed when comparing the quality of the CCE and CTC procedures.

Adverse events

No CCE-related and/or CTC-related severe adverse events were observed. Once the protocol was completed, after CTC, probably because of air insufflation, one patient experienced very strong pain and lypothymia. The event resolved spontaneously and the patient was discharged. One CCE mild adverse event-related was reported. The patient experienced fatigue, he asked to have the data recorder disconnected and completed the procedure prematurely. The event resolved spontaneously within the same day.

Twenty-eight patients experienced adverse events that were reported as related to the colon preparation. They consisted of nausea (n=11), vomiting (n=7), headache (n=6), abdominal pain (n=3) and vertigo (n=1). All the events were classified as mild to moderate, and all spontaneously resolved within the same day.

Table 3 Diagnostic yield of CCE and CTC for polyps ≥6 mm and ≥10 mm

	Diagnostic yield % (95% CI)	Relative sensitivity
Polyps ≥ 6 mm		
CCE	24.5 16.6 to 34.4	2.0 1.34 to 2.98
CTC	12.2 6.8 to 20.8	
Polyps ≥10 mm		
CCE	5.1 1.9 to 12.1	1.67 0.69 to 4.00
CTC	3.1 0.8 to 9.3	

CCE, Colon capsule endoscopy; CTC, CT colonography.

DISCUSSION

According to our study, in patients with a previously incomplete colonoscopy, CCE can ensure a twofold increase in the diagnostic yield of clinically relevant colorectal neoplasia as compared with that of CTC, without an increase in the proportion of false-positive results. CTC has been extensively evaluated in patients with incomplete colonoscopy. Copel *et al*[19] published a large, retrospective series of 546 patients who underwent CTC after incomplete colonoscopy. CTC depicted endoscopically non-visualised lesions ≥6 mm in 13.2% of patients. In patients who repeated colonoscopy, per-patient and per-lesion PPVs of CTC for ≥20 mm masses, 10–19 mm polyps and 6–9 mm polyps were 90.9%, 91.7% and 64.7%, and 70%, 33.3% and 30.4%, respectively. Pullens *et al*,[31] retrospectively evaluated 136 CTCs performed after incomplete colonoscopy. CTC additionally revealed polyps in 11% of patients and a non-synchronous colorectal cancer in 2.9%. All these results support CTC as the imaging modality of choice in case of incomplete colonoscopy since it allows the evaluation of the non-visualised part of the colon and increases the diagnostic yield of masses and larger polypoid lesions.[19 32] Previous studies, all performed using the first generation of colon capsule, also evaluated the role of CCE or CTC in patients with an incomplete colonoscopy.[26 27 33] Pioche *et al*[33] for the first time, in a prospective multicenter series of 107 patients (ie, 77 with a colonoscopy failure and 30 with a colonoscopy contraindication), reported a 93% capsule completion rate and a 33.6% CCE diagnostic yield. Alarcon-Fernandez *et al*[26] evaluated the effects of CCE on medical decision making in patients with incomplete colonoscopy in 34 patients. The authors reported that CCE was able

Table 4 Cases of discrepancies between CCE and CTC for polyps ≥6 mm

Pt	CTC polyp detection	CCE polyp detection	Site	Size	Type	OC polyp detection	Site	Size	Type	Pathology
1	No	Yes	Ascending	7	sessile polyp	Yes	Ascending	8	LST	SSP
2	No	Yes	Rectum	6	sessile polyp	Yes	Rectum	6	sessile polyp	Hyperplastic
3	No	Yes	Ascending	10	flat polyp	Yes	Ascending	6	sessile polyp	LGD adenoma
4	No	Yes	Rectum	7	sessile polyp	Yes	Rectum	6	sessile polyp	Hyperplastic
5	No	Yes	Ceacum	7	sessile polyp	Yes	Ceacum	7	non-polypoid	SSP
6	No	Yes	Ceacum	6	sessile polyp	Yes	Ceacum	6	sessile polyp	SSP
7	No	Yes	Ascending	6	sessile polyp	Yes	Ascending	7	non-polypoid	SSP
8	No	Yes	Ascending	8	flat polyp	Yes	Ascending	20	LST	HGD TVA
9	No	Yes	Ascending	6	sessile polyp	Yes	Transverse	6	sessile polyp	LGD TA
10	No	Yes	Ascending	6	sessile polyp	Yes	Ascending	6	non-polypoid	SSP
11	No	Yes	Ascending	9	semipeduncolated polyp	Yes	Ascending	6	semi-peduncolated polyp	SSP
12	No	Yes	Ascending	7	sessile polyp	Yes	Ascending	10	sessile polyp	LGD adenoma

CCE, colon capsule endoscopy; CTC, CT colonography; HGD, high-grade dysplasia; LGD, low-grade dysplasia; OC, optical colonoscopy; SSP, sessile serrated polyp; TA, tubular adenoma; TVA, tubulovillous adenoma.

to exceed the most proximal point reached by conventional colonoscopy in 85% of patients, and to allow formulation of a specific medical plan in 59% of patients. Recently, Triantafyllou *et al*[27] studied 75 patients who underwent CCE either immediately after or were rescheduled after incomplete colonoscopy. CCE reached or went beyond the colon segment at which colonoscopy stopped in 91% of patients and detected additional findings in 44% of patients. Data available in literature, thus, homogenously suggest that CCE can be considered as a complementary procedure in case of incomplete colonoscopy, and can yield significant findings. However, the comparison between CCE (using the second generation of colon capsule) and CTC in this group of patients has never been evaluated before the present study.

The findings of our study are relevant for several reasons. First, despite the limited rate of incomplete colonoscopies, the

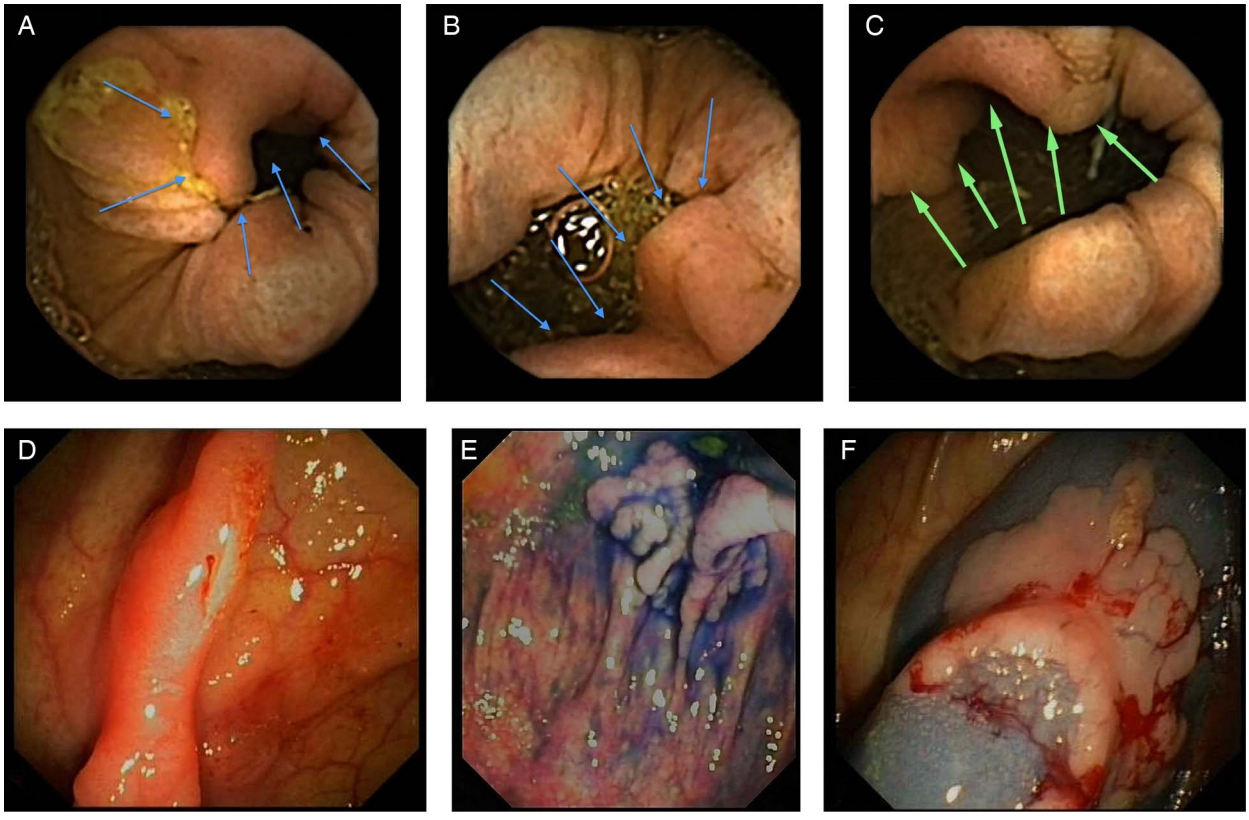


Figure 4 Colon capsule endoscopy (CCE) 'new finding': ≥10 mm polyp detected by the CCE but not detected by CT colonography (CTC). (A–C) A flat polyp detetcted by CCE in the area of the hepatic flexure missed by CTC. The polyp was confirmed by colonoscopy (D) that showed a 20 mm non-polypoid lesion (E) ((F) after injection) in the hepatic flexure. Histology showed a high-grade dysplasia tubular-villous adenoma.

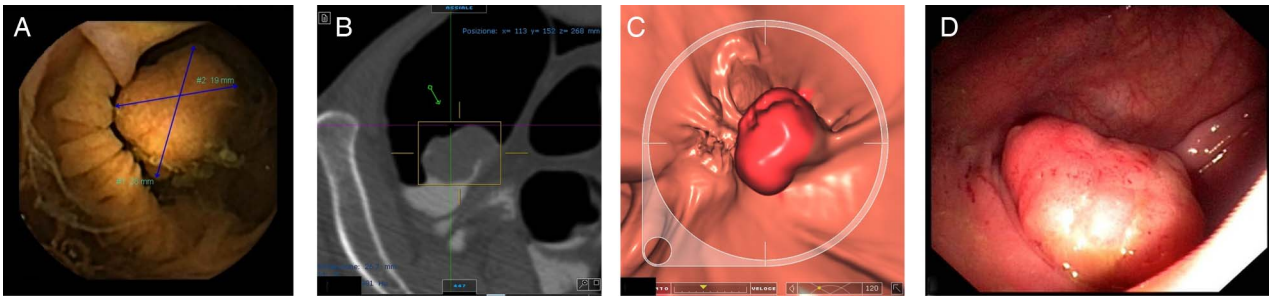


Figure 5 Colon capsule endoscopy (CCE) and CT colonography (CTC) 'same findings': findings detected by the CCE and CTC. A protruding lesion detected by CCE in the caecum (A). The same polyp was visualised by CTC and appeared as a sessile lesion at two-dimensional (2D) axial CT image (B) and 3D endoluminal view after the application of computer-aided detection (CAD) (C). The polyp was confirmed by colonoscopy (D). Histology showed a low-grade dysplasia tubular adenoma.

absolute number is substantial, because of the high volume of colonoscopies performed in Western countries.[14] Second, CTC has been generally considered as the first choice after an incomplete colonoscopy, because of its higher sensitivity for colorectal neoplasia as compared with barium enema, and because it may allow complete preoperative staging in case of obstructing colorectal cancer, when intravenous contrast is added. Third, the superiority of CCE over CTC challenges the clinical recommendation of CTC for patients with a previously incomplete colonoscopy, with the exception of those with a colonic stricture. In settings where CCE is already available, the choice between CCE and CTC will depend on local expertise, patient acceptance and economical resources. Fourth, the superiority of CCE appears mainly to be related with a higher accuracy for small and/or non-polypoid lesions (table 4). This is in line with the suboptimal sensitivity of CTC for such lesions already shown in previous head-to-head CTC colonoscopy series.[16 17 18 34–44] Of note, a more accelerated pathway towards cancer progression has been advocated for these lesions. Fifth, we used as gold standard, the repetition of colonoscopy in positive cases at any of the two initial tests. Thus, the discrimination between true-positive and false-positive cases was highly accurate. Moreover, negative cases at any of the two tests were clinically followed-up for one year, in order to exclude a simultaneous failure of the two tests in identifying a clinically relevant lesion. Sixth, despite CCE excretion rate of less than 95%, its ability to complete a full colonic study is overlapping with CTC performance, although at the expenses of a more demanding bowel preparation. This is due to the fact that the CCE-unexplored colon was in most cases visualised by the previous colonoscopy. Seventh, CTC has already been shown to be superior to barium enema, so that the higher diagnostic yield of CCE over CTC would marginalise the relevance of a comparison between CCE and barium enema. Eight, most of CTC-missed polyps was due

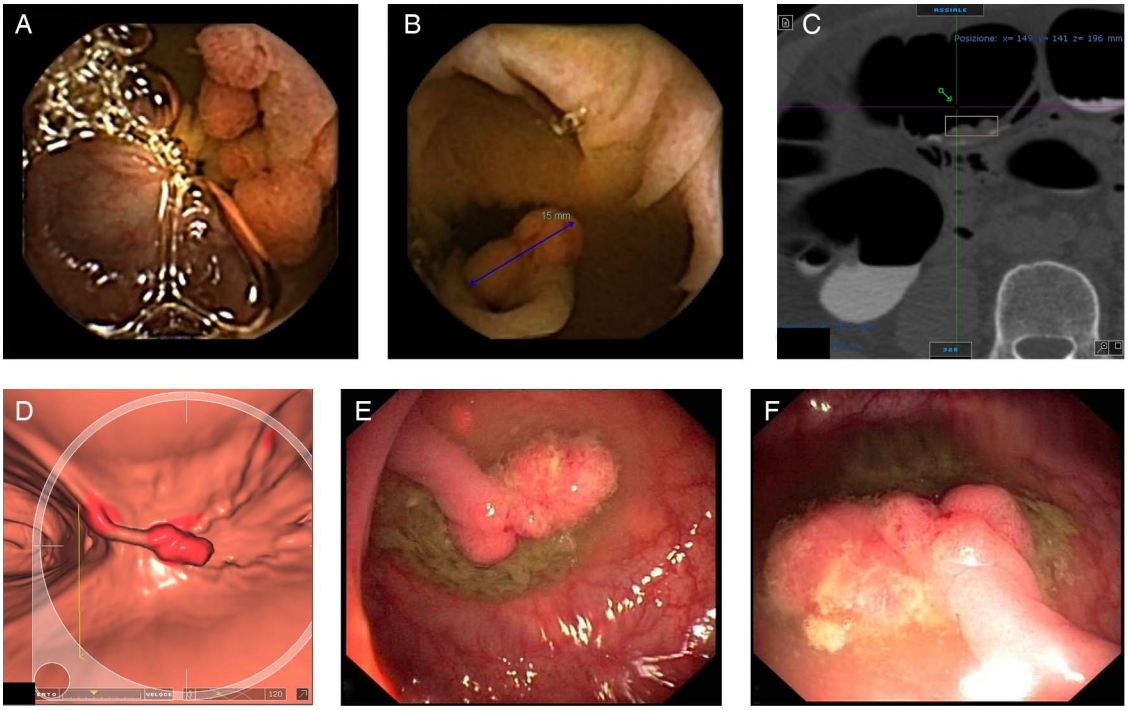


Figure 6 Colon capsule endoscopy (CCE) and CT colonography (CTC) 'same findings': findings detected by the CCE and CTC. A pedunculated polyp detected by CCE in the transverse colon (A and B). The same polyp was visualised by CTC at two-dimensional (2D) axial CT image (C) and 3D endoluminal view after the application of computer-aided detection (CAD) (D). The polyp was confirmed by colonoscopy (E and F). Histology showed a low-grade dysplasia tubular adenoma.

to technical rather than to perceptual errors, since only one out of 12 CTC-missed lesions was retrospectively identified in the review process.

The findings of our study confirms that both the procedures are very effective in completing incomplete colonoscopy, both being able to properly visualise the colonic segments proximal to the site where colonoscopy failed to reach in 98% of cases. Also when considering the capsule excretion rate, in 93 (93%) of the 100 cases, the capsule was naturally excreted within 10 h post-ingestion. The CCE completion and excretion rates observed in this trial are higher than those observed in previous trials.[23 24] In the present series, a regimen of preparation similar to those previously described[23 24] was adopted. The only difference consists in the inclusion of Gastrografin (Bayer, Italy) which was added to the sodium-phosphate booster for faecal tagging required for CTC. The volume effect caused by Gastrografin might enhance the propulsion of the capsule through the colon, and might have an effect on the quality of colonic preparation also. In this trial, a high rate of good quality examinations was observed, with CCE and CTC adequate overall quality rate of 83% (CI 74% to 90%) and 90% (CI 82% to 95%) of cases, respectively.

There are limitations to the present analysis. First, those without clinically relevant lesions at CCE and CTC did not undergo further colonoscopy, so that it cannot be excluded that these patients could be false negative at both the examinations. This is also the reason for which we preferred to provide our data results as diagnostic yield rather than as accuracy values. However, the double non-invasive approach is likely to have minimised the possibility of false negative results, when considering the relatively high accuracy shown by CCE and CTC in previous studies. Moreover, no missed CRC occurred at 1-year follow up. Second, we adopted as study end-point any ≥6 mm lesion, although there is uncertainty on the exact role of these lesions in CRC carcinogenesis. Third, we failed to show any difference between the two techniques with ≥10 mm lesions. This is likely to be due to the low prevalence of these lesions coupled with the relatively high sensitivity of CTC for these polyps. The low detection rate of large lesions and the very high PPV of the two methods also precluded the possibility to get informative results concerning the relative false-positive rates of the two tests. Fourth, since patients with an incomplete colonoscopy because of inadequate preparation and colonic stricture were excluded, the results of our study are not generalisable to this small subgroup of patients. Fifth, because we did not mark the segment at which colonoscopy stopped by tattooing, it might be difficult to determine whether CCE technically complemented incomplete colonoscopies in those few patients in whom the capsule had not reached the rectum. If CCE is to be used following an incomplete colonoscopy, it might be advisable to tattoo the site reached to objectively identify this point during capsule viewing. However, the high rate of excretion rate and the strict criteria adopted in this trial to define a 'complete' capsule colonoscopy would marginalise this limitation. Sixth, we did not evaluate patient preferences since the same bowel preparation was used for CCE and CTC. A dedicated trial comparing laxative-free CTC with CCE may be useful in order to assess patient experience with both methods. We cannot exclude that a difference in adherence to either examinations might change the final diagnostic yield. Moreover, CCE performance as far as inter-reader and intra-reader agreement was not evaluated. However, preliminary studies performed with the first generation of CCE showed a reasonable interobserver agreement that might be applicable also to the second generation of CCE.[45] Finally, this is a single-centre trial, and additional multicenter trials as well as studies taking into account also the interobserver and intraobserver variability are needed.

In conclusion, we showed that CCE is a highly technically feasible examination for patients with previously incomplete colonoscopy, with a diagnostic yield that is superior to that of CTC.

Correction notice One of the authors' names was wrong. The correct name is Maria Ciolina.

Contributors CS, CH, BB, GC, FI, AL and CS are responsible for the conception and design of the trial. CS, CH, BB, FI, AL, CS and GC made the analysis and interpretation of the data and were involved in the drafting of the article. All the authors made a critical revision of the article for important intellectual content and were involved in the final approval of the article.

Competing interests CS, CH and GC are paid consultant for Given Imaging.

Patient consent Obtained.

Ethics approval Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Winawer SJ, Zauber AG, Ho MN, *et al*. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993;329:1977–81.
2 Harrison M, Singh N, Rex DK. Impact of proximal colon retroflexion on adenoma miss rates. *Am J Gastroenterol* 2004;99:519–22.
3 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. *Gastroenterology* 2006;130:1872–85.
4 Gryspeerdt S, Lefere P, Herman M, *et al*. CT colonography with fecal tagging after incomplete colonoscopy. *Eur Radiol* 2005;15:1192–202.
5 Anderson ML, Heigh RI, McCoy GA, *et al*. Accuracy of assessment of the extent of examination by experienced colonoscopists. *Gastrointest Endosc* 1992;38:560–3.
6 Aslinia F, Uradomo L, Steele A, *et al*. Quality assessment of colonoscopic cecal intubation: an analysis of 6 years of continuous practice at a university hospital. *Am J Gastroenterol* 2006;101:721–31.
7 Bowles CJ, Leicester R, Romaya C, *et al*. A prospective study of colonoscopy practice in the UK today: are we adequately prepared for national colorectal cancer screening tomorrow? *Gut* 2004;53:277–83.
8 Imperiale TF, Wagner DR, Lin CY, *et al*. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. *N Engl J Med* 2000;343:169–74.
9 Lieberman DA, Weiss DG, Bond JH, *et al*. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med* 2000;343:162–8.
10 Mitchell RM, McCallion K, Gardiner KR, *et al*. Successful colonoscopy; completion rates and reasons for incompletion. *Ulster Med J* 2002;71:34–7.
11 Regula J, Rupinski M, Kraszewska E, *et al*. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. *N Engl J Med* 2006;355:1863–72.
12 Brenner H, Chang-Claude J, Jansen L, *et al*. Role of colonoscopy and polyp characteristics in colorectal cancer after colonoscopic polyp detection: a population-based case-control study. *Ann Intern Med* 2012;157:225–32.
13 Morini S, Zullo A, Hassan C, *et al*. Endoscopic management of failed colonoscopy in clinical practice: to change endoscopist, instrument, or both? *Int J Colorectal Dis* 2011;26:103–8.
14 Gawron AJ, Veerappan A, McCarthy ST, *et al*. Impact of an incomplete colonoscopy referral program on recommendations after incomplete colonoscopy. *Dig Dis Sci* 2013;58:1849–55.
15 Winawer SJ, Stewart ET, Zauber AG, *et al*. A comparison of colonoscopy and double-contrast barium enema for surveillance after polypectomy. National Polyp Study Work Group. *N Engl J Med* 2000;342:1766–72.
16 Arnesen RB, von BE, Adamsen S, *et al*. Diagnostic performance of computed tomography colonography and colonoscopy: a prospective and validated analysis of 231 paired examinations. *Acta Radiol* 2007;48:831–7.
17 Laghi A, Rengo M, Graser A, *et al*. Current status on performance of CT colonography and clinical indications. *Eur J Radiol* 2013;82:1192–200.
18 Van Gelder RE, Nio CY, Florie J, *et al*. Computed tomographic colonography compared with colonoscopy in patients at increased risk for colorectal cancer. *Gastroenterology* 2004;127:41–8.
19 Copel L, Sosna J, Kruskal JB, *et al*. CT colonography in 546 patients with incomplete colonoscopy. *Radiology* 2007;244:471–8.
20 Atkin W, Dadswell E, Wooldrage K, *et al*. Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomised trial. *Lancet* 2013;381:1194–202.

21 Halligan S, Atkin WS. CT colonography for diagnosis of symptomatic colorectal cancer: the SIGGAR trials and their implication for service delivery. *Clin Radiol* 2013;68:643–5.
22 AGA Clinical Practice and Economics Committee. Position of the American Gastroenterological Association (AGA) Institute on computed tomographic colonography. *Gastroenterology* 2006;131:1627–8.
23 Eliakim R, Yassin K, Niv Y, *et al*. Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. *Endoscopy* 2009;41:1026–31.
24 Spada C, Hassan C, Munoz-Navas M, *et al*. Second-generation colon capsule endoscopy compared with colonoscopy. *Gastrointest Endosc* 2011;74:581–9.
25 Spada C, Hassan C, Galmiche JP, *et al*. Colon capsule endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2012;44:527–36.
26 Alarcon-Fernandez O, Ramos L, Adrian-de-Ganzo Z, *et al*. Effects of colon capsule endoscopy on medical decision making in patients with incomplete colonoscopies. *Clin Gastroenterol Hepatol* 2013;11:534–40.
27 Triantafyllou K, Viazis N, Tsibouris P, *et al*. Colon capsule endoscopy is feasible to perform after incomplete colonoscopy and guides further workup in clinical practice. *Gastrointest Endosc* 2014;79:307–16.
28 Spada C, De VF, Cesaro P, *et al*. Accuracy and safety of second-generation PillCam COLON capsule for colorectal polyp detection. *Therap Adv Gastroenterol* 2012;5:173–8.
29 Leighton JA, Rex DK. A grading scale to evaluate colon cleansing for the PillCam COLON capsule: a reliability study. *Endoscopy* 2011;43:123–7.
30 Fleiss JI, Levin B, Cho Paik M. *Statistical methods for rates and proportions*. 3rd edn. Wiley & sons, 2003.
31 Cheng H, Macaluso M. Comparison of the accuracy of two tests with a confirmatory procedure limited to positive results. *Epidemiology* 1997;8:104–6.
32 Pullens HJ, van Leeuwen MS, Laheij RJ, *et al*. CT-colonography after incomplete colonoscopy: what is the diagnostic yield? *Dis Colon Rectum* 2013;56:593–9.
33 Pioche M, de LA, Filoche B, *et al*. Prospective multicenter evaluation of colon capsule examination indicated by colonoscopy failure or anesthesia contraindication. *Endoscopy* 2012;44:911–16.
34 Park SH, Ha HK, Kim MJ, *et al*. False-negative results at multi-detector row CT colonography: multivariate analysis of causes for missed lesions. *Radiology* 2005;235:495–502.
35 Park SH, Ha HK, Kim AY, *et al*. Flat polyps of the colon: detection with 16-MDCT colonography—preliminary results. *AJR Am J Roentgenol* 2006;186:1611–17.
36 Fidler J, Johnson C. Flat polyps of the colon: accuracy of detection by CT colonography and histologic significance. *Abdom Imaging* 2009;34:157–71.
37 Macari M, Bini EJ, Jacobs SL, *et al*. Significance of missed polyps at CT colonography. *AJR Am J Roentgenol* 2004;183:127–34.
38 Arnesen RB, Adamsen S, Svendsen LB, *et al*. Missed lesions and false-positive findings on computed-tomographic colonography: a controlled prospective analysis. *Endoscopy* 2005;37:937–44.
39 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* 2004;291:1713–19.
40 Pickhardt PJ, Levin B, Bond JH. Screening for nonpolypoid colorectal neoplasms. *JAMA* 2008;299:2743–4.
41 Pickhardt PJ, Nugent PA, Choi JR, *et al*. Flat colorectal lesions in asymptomatic adults: implications for screening with CT virtual colonoscopy. *AJR Am J Roentgenol* 2004;183:1343–7.
42 Pickhardt PJ, Kim DH. Colorectal cancer screening with CT colonography: key concepts regarding polyp prevalence, size, histology, morphology, and natural history. *AJR Am J Roentgenol* 2009;193:40–6.
43 Park SH, Lee SS, Choi EK, *et al*. Flat colorectal neoplasms: definition, importance, and visualization on CT colonography. *AJR Am J Roentgenol* 2007;188:953–9.
44 Halligan S, Park SH, Ha HK. Causes of false-negative findings at CT colonography. *Radiology* 2006;238:1075–6.
45 Eliakim R, Fireman Z, Gralnek IM, *et al*. Evaluation of the PillCam Colon capsule in the detection of colonic pathology: results of the first multicenter, prospective, comparative study. *Endoscopy* 2006;38:963–70.

Colon capsule versus CT colonography in patients with incomplete colonoscopy: a prospective, comparative trial

Cristiano Spada, Cesare Hassan, Brunella Barbaro, Franco Iafrate, Paola Cesaro, Lucio Petruzziello, Leonardo Minelli Grazioli, Carlo Senore, Gabriella Brizi, Isabella Costamagna, Giuseppe Alvaro, Marcella Iannitti, Marco Salsano, Maria Ciolina, Andrea Laghi, Lorenzo Bonomo and Guido Costamagna

Gut 2015 64: 272-281 originally published online June 24, 2014
doi: 10.1136/gutjnl-2013-306550

Notes