

# Computed tomographic colonography compared with colonoscopy or barium enema for diagnosis of colorectal cancer in older symptomatic patients: two multicentre randomised trials with economic evaluation (the SIGGAR trials)

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**Declared competing interests of authors:** Steve Halligan reports non-financial research and development evaluation work provided for iCAD Inc., which develops CAD for computed tomographic colonography. This author also provides expert witness testimony on matters relating to radiological diagnosis of colorectal cancer and holds patents/patent applications for computed tomography imaging technology (2010; International PCT no. PCT/GB2011/050448 'Apparatus and Method for Registering Medical Images Containing a Tubular Organ'). Wendy Atkin reports funds to support this work were also obtained from Imperial College London, London, UK.

Published July 2015

DOI: 10.3310/hta19540

## Scientific summary

### CTC compared with colonoscopy or BE for diagnosis of colorectal cancer

Health Technology Assessment 2015; Vol. 19: No. 54

DOI: 10.3310/hta19540

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# Scientific summary

## Background

Colorectal cancer (CRC) is a UK health-care priority: 1 in 20 people will develop the disease and approximately half will die as a result. An ageing population also means that these proportions are increasing. Diagnosis is usually by colonoscopy or barium enema (BE) when a whole-colon examination is deemed necessary. However, symptoms of CRC (e.g. abdominal pain and change in bowel habit) are common and non-specific, with the result that most investigated patients will ultimately prove to be normal. Diagnosis must therefore be accurate, acceptable, safe and cost-effective. Colonoscopy is the most accurate test, as it examines the endoluminal surface directly, via an endoscope. However, it requires considerable operator experience, is relatively expensive, is uncomfortable for patients (requiring intravenous sedation) and is associated with potentially serious adverse events. BE requires no sedation, is safer and is performed by technicians (making it less expensive), but has a lower sensitivity for cancer than colonoscopy.

Computed tomographic colonography (CTC) is a relatively new technology that uses a computed tomography scanner to examine the colon. After bowel preparation (as for BE and colonoscopy), the colon is distended with gas and the patient undergoes two scans of approximately 5 seconds each. The CTC data are interpreted subsequently by a radiologist using modern medical image displays that mimic the endoluminal view obtained at colonoscopy, hence the alternative term 'virtual colonoscopy'. CTC is promoted as a safe, rapid and accurate test for CRC screening, particularly in the USA, but meta-analysis suggests it is also sensitive in symptomatic patients. CTC potentially combines the sensitivity of colonoscopy with the safety of BE and may be more acceptable to patients than either of the other tests. Furthermore, because CTC can image organs outside the bowel, it could potentially combine intra- and extracolonic diagnosis at a single examination and so be more cost-effective in patients with non-specific abdominopelvic symptoms. However, there have been no randomised controlled trials (RCTs) of CTC in symptomatic patients; therefore, high-quality evidence to guide implementation is unavailable.

## Objective

Our objective was to examine the diagnostic efficacy, acceptability, safety and cost-effectiveness of CTC compared with BE or colonoscopy.

## Methods

We performed two RCTs: CTC compared with colonoscopy and CTC compared with BE. Ethics approval was granted in 2004 and an independent Trial Steering Committee and Data Monitoring Committee monitored the research. We recruited from 21 NHS hospitals, including both teaching and general hospitals to increase the generalisability of the results. Consenting patients aged  $\geq 55$  years with symptoms suggestive of CRC were referred for either colonoscopy or BE (the 'default' examinations), depending on whether the clinician preferred radiological or endoscopic investigation for the patient in question in their normal clinical practice. Patients were then randomised in a 2 : 1 ratio between the default examination or CTC, respectively. Demographic and baseline clinical information was collected on all potentially eligible patients.

All procedures were performed following full bowel preparation. BE was interpreted by 82 experienced practitioners. Colonoscopy was performed and interpreted by 217 experienced practitioners. CTC was interpreted by 46 subspecialty radiologists, representative of those likely to report CTC in the NHS. We collected details of suspected cancers and polyps, lesion diameter, location, diagnostic confidence, technical quality and adverse events.

After the randomised procedure, we collected details of confirmed cancers or polyps and additional referrals for bowel tests (usually performed either to confirm lesions suspected at BE or CTC, or to continue investigation in cases which diagnosis remained uncertain because of technical failure or continuing unexplained symptoms). Procedure costs and downstream costs were collected. Acceptability was assessed via psychological questionnaires completed the day after and 3 months after the randomised procedure. National databases were used to identify missed colonic and extracolonic cancers.

The primary outcome in the BE trial was the detection rate of CRC or large polyps ( $\geq 10$  mm), with an estimated sample size of 3402 giving 80% power to detect a significant difference. The primary outcome in the colonoscopy trial was the proportion of patients undergoing additional colonic investigation after the randomised procedure, with a sample size of 1430 giving 80% power to detect a significant difference.

Secondary outcomes for the BE trial were referral rates for additional colonic investigation and positive predictive values. A secondary outcome for the colonoscopy trial was the detection rate of CRC or large polyps. Secondary outcomes for both trials were patient acceptability, cost-effectiveness, time to diagnosis, serious adverse events and diagnoses of cancer within 3 years. Extracolonic findings at CTC were also analysed.

Analyses were performed on a per-patient basis, using the most advanced colonic lesion. Lesions were matched between procedures based on size and location. Lesions detected at flexible sigmoidoscopy prior to the randomised procedure were excluded. All tests were two-tailed, with significance assigned at the 5% level. For the economic analysis, unit costs of procedures and all associated downstream costs were obtained to calculate total costs per patient. Cost per additional cancer or large polyp detected by CTC was compared with BE and colonoscopy.

## Results

Recruitment ran from March 2004 to December 2007. A total of 8484 patients were registered, and 3036 were ultimately not randomised, usually because the clinician demanded a specific test (72%). A total of 5384 patients were randomised and ultimately analysed: 3804 in the BE trial (2527 BE and 1277 CTC) and 1580 in the colonoscopy trial (1047 colonoscopy and 533 CTC).

### Barium enema trial

A significantly lower proportion of patients randomised to BE had the procedure (91.0% vs. 94.4%;  $p = 0.0002$ ). Prior flexible sigmoidoscopy was performed in 199 patients (7.9%) in the BE arm and 89 (7.0%) in the CTC arm ( $p = 0.32$ ). Significantly more BE examinations were judged difficult to perform (24.1% vs. 9.0%;  $p < 0.0001$ ). In a significantly higher proportion of BE examinations visualisation was rated as 'poor' in at least one segment (22.3% vs. 16.1%;  $p < 0.0001$ ).

A total of 141 patients randomised to BE had a CRC or large polyp diagnosed, compared with 93 randomised to CTC. In an intention-to-treat analysis, the overall detection rate was 7.3% (93/1277) in the CTC arm compared with 5.6% (141/2527) in the BE arm ( $p = 0.0390$ ). The difference was mainly because of the higher detection rates of large polyps by CTC (3.6% vs. 2.2%;  $p = 0.0098$ ). There was no

significant difference for CRC (3.7% vs. 3.4%;  $p = 0.66$ ). Analysing per protocol, a cancer or large polyp was diagnosed in 7.0% (85/1206) of patients undergoing CTC and 5.2% (119/2300) undergoing BE ( $p = 0.0243$ ).

A significantly higher proportion of patients who received CTC underwent a second colonic investigation (23.5% vs. 18.3%;  $p = 0.0003$ ) because of the higher detection rates. Conversely, a significantly lower proportion required further investigation because of technical inadequacy or clinical uncertainty (5.2% vs. 8.5%;  $p = 0.0005$ ). The positive predictive value for suspected cancers or large polyps was similar for CTC and BE (56% vs. 62%). Of those referred because of suspected smaller lesions, a cancer or large polyp was diagnosed in 10% following CTC and 7% following BE. Of the 195 patients who had a second procedure because of clinical uncertainty after BE, four had cancers and four had large polyps. No cancers or large polyps were detected in the 63 patients referred because of clinical uncertainty after CTC. Five serious adverse events occurred that were possibly attributable to the randomised procedure: four for BE and one for CTC.

In the 3 years following randomisation, the miss rate for patients undergoing the randomised procedure was 6.7% for CTC (45 cancers diagnosed, of which three were missed) and 14.1% for BE (85 cancers diagnosed, of which 12 were missed).

## Colonoscopy trial

There was no significant difference in the proportion of patients undergoing their randomised procedure (92.4% for colonoscopy vs. 94.4% for CTC;  $p = 0.14$ ) but significantly more patients randomised to colonoscopy refused their procedure or did not attend (6.0% vs. 3.0%;  $p = 0.0093$ ). Flexible sigmoidoscopy was performed in eight patients randomised to CTC and none randomised to colonoscopy. A significantly higher proportion of colonoscopy examinations were rated as 'difficult' (27.4% vs. 8.3%;  $p < 0.0001$ ). Colonoscopy was incomplete in 12.2% and, of those undergoing CTC, at least one segment was poorly visualised in 16.1%.

A total of 30% of patients (160/533) randomised to CTC underwent further colonic investigation, compared with 8.2% (86/1047) patients randomised to colonoscopy [relative risk (RR) 3.65, 95% confidence interval (CI) 2.87 to 4.65;  $p < 0.0001$ ]. In the 1% randomised to colonoscopy, referral was because of a suspected cancer or large polyp for which biopsy was inadequate or absent. In the 16% randomised to CTC, referral was to confirm a suspected cancer or large polyp and in 9% to investigate smaller lesions. There was no significant difference in referrals precipitated by clinical uncertainty (7% for colonoscopy vs. 5% for CTC;  $p = 0.19$ ).

All cancers confirmed following CTC occurred in patients in whom a cancer or large polyp was suspected; three large polyps were found in patients in whom smaller polyps were suspected. Of 28 patients having a second procedure because of clinical uncertainty after CTC, one had a large polyp. Of the 73 patients having a second procedure because of clinical uncertainty after colonoscopy, three had cancers and one had a large polyp.

A total of 10.7% of patients (57/533) randomised to CTC had a CRC or large polyp diagnosed, compared with 11.4% (119/1047) randomised to colonoscopy. There was no significant difference in detection rates (RR 0.94, 95% CI 0.70 to 1.27;  $p = 0.69$ ), nor was there any difference when cancers ( $p = 0.94$ ) and large polyps ( $p = 0.53$ ) were analysed separately. Similar results were obtained when analysing per protocol, that is 10.7% for CTC compared with 12% for colonoscopy (RR 0.89, 95% CI 0.66 to 1.21;  $p = 0.47$ ), with no difference when cancers ( $p = 0.92$ ) and large polyps ( $p = 0.38$ ) were analysed separately. Three serious adverse events possibly attributable to colonoscopy occurred; there were none for CTC. In the 3 years following randomisation, there was no new CRC diagnosis after discharge in patients who had colonoscopy. One patient was diagnosed with CRC 15 months after an apparently normal CTC.

## Extracolonic findings

A total of 1748 CTC examinations were analysed; 1042 (59.6%) had at least one extracolonic finding reported (1945 individual findings) and the number of findings per patient rose with age ( $p < 0.0001$ ). A total of 149 patients (8.5%) underwent subsequent investigation, 52 (34%) of whom underwent multiple procedures and 32 (21.5%) had surgery. Seventy-nine extracolonic neoplasms were ultimately diagnosed, 29 of which were malignant. Overall, extracolonic neoplasia was diagnosed in 79 patients (4.5%) having CTC and malignancy in 29 (1.7%). However, the positive predictive value of presenting symptoms for extracolonic disease was low. When registry data were examined, the proportion of patients diagnosed with extracolonic malignancy did not differ significantly between the three diagnostic procedures within 3 years of randomisation. Fourteen patients (0.8%) had extracolonic abdominopelvic cancer diagnosed within 3 years of an apparently normal CTC.

## Patient acceptability

In the BE trial, 921 patients (606 BE, 315 CTC) returned the post-test questionnaire completed on the day following the procedure. Patients having a BE were significantly less satisfied ( $p = 0.003$ ) and experienced more discomfort ( $p < 0.001$ ) than those having CTC. After the test, patients having a BE were significantly more likely to experience unpleasant side effects (e.g. abdominal pain, soreness, nausea/vomiting).

In the colonoscopy trial, 547 patients (362 colonoscopy and 185 CTC) returned the post-test questionnaire. Patients having colonoscopy were significantly less satisfied ( $p = 0.008$ ) and significantly more worried ( $p = 0.007$ ) than those having CTC; they also experienced more physical discomfort and more adverse events. However, at 3 months, patients having colonoscopy were more satisfied with how their results had been given ( $p < 0.0005$ ). No differences were observed in longer-term psychological consequences at 3 months.

## Health economic assessment

The total costs associated with each procedure were considerably higher than the unit cost of each procedure itself. This is because total costs included those of follow-up procedures (especially colonoscopy). Total costs for BE were £460, compared with £532 for CTC, in the BE trial. Total costs for colonoscopy were £739, compared with £674 for CTC, in the colonoscopy trial. Patients originally referred for colonoscopy were likely to be at higher risk than those referred for BE. The cost of follow-up investigations made the overall cost of CTC higher in the colonoscopy trial than in the BE trial.

In the BE trial, the incremental cost-effectiveness ratio (ICER) per neoplasm detected by CTC was £4235 (95% CI £395 to £9656). The corresponding ratio for detection of an additional three cases of colon cancer per 1000 patients was £24,000 per cancer.

The ICER per significant lesion detected by colonoscopy compared with CTC was £9543, and £650,000 per cancer, but these estimates are subject to considerable statistical uncertainty. The health gains and costs, contingent on bringing forward the time of diagnosis of serious treatable extracolonic lesions by means of CTC, are hard to compute.

## Conclusions

### *Implications for patient care*

- Computed tomographic colonography detects more cancers and large polyps than BE, misses fewer cancers and improves patient experience, but also precipitates more follow-up investigations.
- Computed tomographic colonography is a safe alternative to colonoscopy in symptomatic patients, with similar sensitivity and improved patient experience short term. The way in which the results are conveyed (i.e. quicker and face to face) favours colonoscopy. CTC precipitates significantly more follow-up examinations – which, in a limited sample, did not adversely impact on patient experience – but criteria for subsequent referral are needed.
- Most patients have extracolonic findings reported at CTC and 8.5% undergo further investigation for these. Approximately 2% overall have an extracolonic malignancy detected. Offering CTC as the primary procedure did not significantly alter the proportion of patients diagnosed with extracolonic malignancy at 3 years, compared with colonoscopy or BE.
- When compared with BE, CTC detected one extra serious colonic neoplasm for approximately £4000. However, the detection rates were similar for CTC and colonoscopy and costs were also similar, such that there was little evidence on which a firm recommendation could be based.

### *Recommendations for research*

1. The benefits of CTC observed in both trials will improve if referrals for clinically unnecessary subsequent investigations are diminished: there is a need to develop evidence-based guidelines for referral after CTC. This applies especially to patients for whom the normal default examination would be colonoscopy. A multivariate analysis should be performed on the data set generated by these trials in order to identify combinations of both symptoms and imaging findings on CTC that best predict a need for subsequent colonoscopy.
2. No difference was found between tests regarding the proportion of extracolonic cancers detected within 3 years. The reasons for this are unclear, but it appears that many patients undergoing BE or colonoscopy also have subsequent extracolonic investigation if no colonic abnormality was found. How and why this happens merits further research to clarify the clinical effectiveness and cost-effectiveness of CTC.
3. Detection of extracolonic pathology by CTC should be modelled beyond the trial data set over an extended time horizon and combined with detection of intracolonic pathology to estimate if CTC is cost-effective overall compared with colonoscopy. This is not a trivial undertaking.
4. Research is needed to guide implementation of CTC, especially the training needed for competent interpretation.
5. The acceptability to patients of increased referrals following CTC needs further investigation.
6. In the context of the NHS Bowel Cancer Screening Programme, research on what determines the acceptability of further investigations following positive faecal occult blood test and the potential role of CTC and other less invasive diagnostic technologies are warranted.

## Trial registration

This trial is registered as ISRCTN95152621.

## Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research and the UK Department of Health, which stipulated a randomised controlled design but had no involvement in the collection, analysis or interpretation of data, in writing the report, or in the decision to submit for publication. This was also the case for manufacturers who donated equipment for the study (Bracco UK Ltd, High Wycombe, UK; Viatronix Inc., Stony Brook, NY, USA; Medicsight plc, London, UK; Barco Ltd, Bracknell, UK).



ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

*Health Technology Assessment* is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

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## This report

The research reported in this issue of the journal was funded by the HTA programme as project number 02/02/01. The contractual start date was in October 2003. The draft report began editorial review in March 2012 and was accepted for publication in May 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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