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Identification of Extra-colonic Pathologies by Computed Tomographic Colonography in Symptomatic Patients

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SH and WA were joint principal investigators. They designed the study and wrote the grant application, assisted by CvW, RE, CK, RJL, DM, and JW. RE generated the randomisation

codes and designed the study database. ED, IK-H, and WA were responsible for recruitment, data collection, and management, assisted by the SIGGAR investigators mentioned in the Acknowledgements. SH, KW, ED, US, IK-H, and WA had full access to the study data, and CvW, GY, RJL, JW had access to subsets of the data. KW, ED, IK-H, and WA analysed the data. SH, ED, and WA drafted the report and all named authors contributed to subsequent review and revision. All named authors have seen and approved the final version and all authors take responsibility for the decision to submit for publication. Both SH and WA will act as guarantors.

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ABSTRACT

Background & Aims: Symptoms suggestive of colorectal cancer may originate outside the colorectum. Computed tomographic colonography (CTC) is used to simultaneously examine the colorectum and abdomino-pelvic organs. We performed a prospective, randomized controlled trial to quantify the frequency, nature, and consequences of extra-colonic findings.

Methods: We studied 5384 patients from 21 UK National Health Service hospitals referred by their family doctor for investigation of symptoms of colorectal cancer from March 2004 through December 2007. The patients were randomly assigned to groups that received the requested test (barium enema or colonoscopy, n=3574) or CTC (n=1810). We determined the frequency and nature of extracolonic findings, subsequent investigations, ultimate diagnosis, and extracolonic cancer diagnoses 1y and 3 y after testing of patients without colorectal cancer.

Results: Extracolonic pathologies were detected in 959 patients by CTC (58.7%), in 42 patients by barium enema analysis, (1.9%), and in no patients by colonoscopy. Extracolonic findings were investigated in 142 of these patients (14.2%) and a diagnosis was made for 126 patients (88.1%). Symptoms were explained by extracolonic findings in 4 patients analyzed by barium enema (0.2%) and 33 patients analyzed by CTC (2.8%). CTC identified 72 extracolonic neoplasms, whereas barium enema analysis found only 3 (colonoscopy found none). Overall, CTC diagnosed extracolonic neoplasms in 72/1634 patients (4.4%); 26 of these were malignant (1.6%). There were significantly more extracolonic malignancies detected than expected 1 y after examination, but these did not differ between patients evaluated by CTC (22.2/1000 person-y), barium enema (26.5/1000 person-y; *P*=.43), or colonoscopy (32.0/1000 person-y; *P*=.88).

Conclusions: More than half of patients with symptoms of colorectal cancer are found to have extracolonic pathologies by CTC analysis. However, the proportion of patients found to have extracolonic malignancies after 1 year of CTC examination is not significantly greater than after barium enema or colonoscopy examinations.
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KEYWORDS: detection; diagnostic, digestive system, colon cancer

Introduction

Symptoms suggestive of colorectal cancer are common and non-specific, and may originate from pathology outside the large bowel.[1] Patients are often investigated with colonoscopy or barium enema (BE), which only image the colorectum. Computed tomographic colonography (CTC) is used increasingly to investigate symptomatic patients because it is sensitive for colorectal cancer while simultaneously examining other abdomino-pelvic organs. However, it is uncertain whether detection of extracolonic pathology is ultimately beneficial. While undoubtedly important in some patients, in others extracolonic findings can precipitate investigations that are costly, increase morbidity and anxiety, and are ultimately unnecessary. A systematic review of 3488 patients, most of whom were symptomatic, found that 14% underwent further investigation, yielding 2·7% extracolonic cancers overall.[2] An economic analysis by the same group found that average costs incurred to investigate extracolonic findings exceeded costs of the initial CTC.[3] Systematic review of 24 studies estimated false-positive diagnoses of extracolonic malignancy by CTC in 4·6% men and 6·8% women.[4]

The clinical impact of extracolonic findings at CTC has most often been assessed retrospectively,[5-7] and the largest studies have investigated asymptomatic individuals being screened for colorectal cancer.[8, 9] A systematic review by the authors found no prospective, randomized study examining the consequences of extracolonic detections in symptomatic patients in daily practice.[10] We performed parallel pragmatic randomized controlled trials of CTC versus colonoscopy or BE. Detection rates for intracolonic pathology are reported elsewhere.[11, 12] Here we describe the frequency and nature of extracolonic pathology detected by CTC, the rate and nature of subsequent investigations to investigate and/or treat extracolonic findings, adverse events related to investigation, and ultimate clinical outcome.

Methods

Study Design and participants

The protocol for these multicentre randomized trials has been published previously[13] and can be found online (http://www.hta.ac.uk/project/1366.asp). The trial is registered: International Standard Randomised Controlled Trials Number 95152621.

http://www.controlled-trials.com/ISRCTN95152621/95152621. Research nurses at 21 UK National Health Service (NHS) teaching and general hospitals recruited patients referred by their family doctor for investigation of symptoms suggestive of colorectal cancer. Patients were eligible if aged 55 years or older, fit to undergo full bowel purgation, had no known genetic predisposition to cancer, had no history of inflammatory bowel disease, had not had a whole-colon examination within 6 months, and were not being followed-up for previous colorectal cancer. We obtained demographic and baseline clinical data such as age, sex, and symptoms for all potentially eligible patients. The consulting clinician then decided in line with their usual clinical practice whether to investigate the patient using colonoscopy or BE (the default examinations). We created two parallel trials and, within each, patients were randomly assigned to the default examination or CTC.[13] There was no overlap of patients between trials. We obtained ethical approval from the Northern and Yorkshire Multicentre Research Ethics Committee and from all participating hospitals. The trials were supervised by independent data monitoring and trial steering committees. All patients gave informed written consent.

Randomization & masking

We used a randomization ratio of 2:1 to receive either the default examination (BE or colonoscopy) or CTC. A statistician (RE) generated the randomization codes at a remote site, and codes were concealed until interventions were assigned. Randomization was done centrally by computer random number generation, in blocks of six, stratified by centre and patient sex. Participants and those administering the procedures were not masked to the assigned study intervention.

Procedures

Methods for CTC reflected contemporary consensus on best practice,[14] including full bowel purgation and gas insufflation. Multidetector row CT scanners (minimum four rows) were used with maximum detector collimation of 2·5 mm and a pitch that allowed abdominal coverage (40 cm) within 20 seconds. Prone and supine scans were recommended. Readers used two-dimensional (2D) and/or three-dimensional (3D) visualization as preferred; the minimum requirement was primary 2D analysis with volume or surface rendering for problem solving. Reading platform depended on local preference, as did use of intravenous contrast and faecal tagging agents. Computer-assisted detection was available. 45

radiologists sub-specialising in gastrointestinal radiology interpreted the CTC studies. All radiologists were familiar with interpreting CTC, and those who had read fewer than 100 cases, or who desired additional training, attended a supplementary 2-day course. Double-contrast BE was undertaken after full bowel preparation and administration of an intravenous spasmolytic, with carbon dioxide or air for insufflation. Digital fluoroscopic images of the double-contrasted colorectum were obtained to the caecum, supplemented by overcouch decubitus films[15]. 217 gastroenterologists or colorectal surgeons undertook the colonoscopies[16].

For each procedure, the radiologist or endoscopist issued a report as usual that noted colonic lesions if present. As per normal practice, radiologists were free to describe/ignore any potential extracolonic lesion identified during their interpretation if they believed this relevant/irrelevant to the clinical situation. Referrals for additional investigation following the randomized procedure were made at the discretion of local clinicians in charge of the patient's care based on clinical judgment informed by symptoms, clinical examination, procedural findings, patient status, and local practice.

Research nurses collected reports from all subsequent diagnostic procedures related to the diagnostic episode, including surgical procedures intended to clarify and/or treat extracolonic findings. Referrals to investigate intracolonic pathology are described elsewhere.[11, 12] Referrals to investigate extracolonic findings are described here.

Outcomes

The primary outcome for the BE trial was the detection of colorectal cancer or large (≥10 mm) polyps, and for the colonoscopy trial was additional colonic investigation required to confirm or exclude such pathology.[11-13] The rate and nature of extracolonic findings at randomized procedures was a pre-specified secondary outcome[13] and such patients were followed up until either a diagnosis was given, the patient was placed into surveillance, or a decision was made not to investigate further during the diagnostic episode "on-trial".

A study researcher (ED) extracted references to extracolonic pathology from procedure reports into a database. Each extracolonic finding was then assigned an "E-RADS" score[17] by a radiologist (SH) blind to subtrial, reporting radiologist, centre, and ultimate diagnosis. E-RADS categorizes the perceived clinical importance of extracolonic findings as follows: E1 - Normal or anatomic variant, E2 - Clinically unimportant, E3 – Likely unimportant but

incompletely characterised, E4 – Potentially important.[17] A data manager coded the final diagnosis using the ICD-10 classification. An expert panel consisting of a radiologist (SH), gastroenterologist (JT), and colorectal surgeon (OF) reviewed extracolonic diagnoses independently to establish whether these could have explained patients' presenting symptoms. Specifically, the panel members were provided with a spreadsheet that detailed the presenting symptom(s) along with the final extracolonic diagnosis for each individual patient in whom such a diagnosis was made. Each panel member then made an independent decision as to whether, in their clinical opinion, the symptoms could have potentially been explained by the extracolonic finding. Panel members were blinded to the primary assigned randomized procedure in all cases to eliminate potential bias arising from their clinical specialty. If there was any disagreement, a consensus decision was reached between the panel members with the help of a data manager, who provided additional clinical details where necessary.

The total number and nature of surgical procedures, non-surgical but invasive procedures, and non-invasive procedures used to investigate and/or treat extracolonic findings were determined for each of the trial arms. Unit costs for these procedures were obtained from the National Schedule of National Health Service costs at 2014/14 estimates. Details of cancer diagnoses (colonic and extracolonic) and deaths in the trial cohort were obtained from the NHS Information Centre (NHSIC).

Statistical analysis

Sample size calculations for the primary outcome for each trial have been described previously.[11-13] We analysed extracolonic cancers by intention to treat, identifying those diagnosed within 36 months of randomisation. We included all reported primary malignant neoplasms, except colorectal cancers (ICD-10: C18–C20) and non-melanoma malignant neoplasms of the skin (C44). We calculated expected numbers of extracolonic cancers by applying age-sex-specific cancer incidence for the general population to our cohort, adjusting for reported mortality.[18] We compared incidence assuming a Poisson distribution. Categorical outcomes were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. We calculated relative risks (RRs) with 95% CIs. We analysed the data using Stata 10.1. The trial is an International Standard Randomised Controlled Trial, number 95152621. All authors had access to the study data and reviewed and approved the final manuscript.

Results

Recruitment began March 2004 and ceased December 2007. Our sample size was exceeded. Patient flow through the trial is shown in Figure 1. Of 8484 patients identified as potentially eligible, 3100 were excluded (2176 because of a doctor's decision, 898 because of a patient's decision, and 26 for unknown reasons) (Appendix Table 1), and 5384 were randomized (3804 within the BE trial and 1580 within the colonoscopy trial). After patients diagnosed with colorectal cancer during the study were excluded, a total of 4766 patients were analysed, 1634 of whom had CTC (1161 from the BE trial and 473 from the colonoscopy trial). In both trials, change in bowel habit was the commonest symptom (3623, 76% of all patients analysed), followed by abdominal pain (BE trial) and rectal bleeding (colonoscopy trial) (Appendix Table 2).

Reporting of extracolonic findings

Of the 1634 patients having CTC, 959 (58·7%) had at least one extracolonic finding described in the clinical report: 672 (57·9%) in the BE trial and 287 (60·7%) in the colonoscopy trial (Figure 1). 42 (1·9%) patients having BE and none having colonoscopy had an extracolonic finding reported. 1830 individual extracolonic findings were reported overall (Table 1): 1784 on CTC (1246 BE trial, 538 colonoscopy trial), 46 on BE, and none on colonoscopy; extracolonic findings seen at BE vs. CTC are available online (Appendix Table 1); The majority of BE findings were related to abnormal colonic location (e.g. 18 hernias) or displacement (e.g. 3 cases of extrinsic compression), calcifications (3 gallstones, 2 renal stones, 4 fibroids), or skeletal disease (e.g. degeneration, Paget's).

There was no association between sex and reporting of an extracolonic finding; however, patients were significantly more likely to have an extracolonic finding reported if they were older ($p<0.0001$). In both trials the proportion of patients with at least one extracolonic finding reported by CTC increased with age, rising in the BE trial from 48% for those aged 55-64 years, to 74% for those aged 85 years or over, and from 56% to 90% respectively in the colonoscopy trial (Table 2).

Of the 1830 individual extracolonic findings reported overall (Table 1): 1390 (75·9%) were categorised as E2 ("clinically unimportant"); 337 (18·4%) as E3 ("likely unimportant but

incompletely characterised"); 82 (4·5%) as E4 ("potentially important"). There were 21 E1 findings (normal anatomical variant or post-surgery appearance). E2 findings were reported most frequently and E4 least frequently, for both BE and CTC but the rate per 1000 patients was substantially higher for CTC. For example, in the BE trial E3 findings were reported for 3·1 patients per 1000 having BE vs. 209·3 for patients having CTC (Table 1). Rates for CTC were similar between trials (Table 1).

Subsequent investigation of extracolonic findings

Of 1001 individual patients with an extracolonic finding reported, 142 (14·2%) patients (136 having CTC, 6 having BE, none having colonoscopy) underwent subsequent procedures to investigate 144 extracolonic findings; Simple laboratory tests (e.g. blood and urine) are excluded from these data. Overall, 8·3% of patients having CTC eventually had an extracolonic finding investigated; 88 (7·6%) and 48 (10·1%) from the BE and colonoscopy trials respectively. Overall, 58 (76·3%) of 76 CTC findings classified as E4 were investigated compared to 57 (17·3%) of 330 classified as E3, and 23 (1·7%) of 1357 classified as E2 (Table 1).

The most invasive procedure used for investigation was surgical in 34 (23·6%) instances, invasive but non-surgical in 38 (26·4%), and non-invasive imaging in 69 (47·9%). The most common surgical procedures were nephrectomy (9 patients), oophorectomy (7 patients) and aortic aneurysm repair (5 patients). Some patients had multiple procedures (for example imaging followed by surgery) and surgery sometimes combined diagnosis and treatment (for example excision biopsy). As a result, the total number of individual procedures performed in the 142 patients referred was 208; surgical in 35 instances, invasive but non-surgical in 51, and non-invasive imaging in 122 (Appendix Table 4). 196 of these procedures (117 BE trial, 79 colonoscopy trial) occurred in patients randomized to CTC where 12 occurred in patients randomized to BE (Appendix Table 4). None occurred in patients randomized to colonoscopy.

The total unit costs generated to investigate and/or treat extracolonic findings in the BE trial were 10,289 Great British Pounds (GBP) for patients randomized to BE compared with 115, 059 GBP for patients randomized to CTC. These costs broke down as follows: For BE versus CTC respectively, unit costs for surgical procedures were 9,135 GBP vs. 100,740 GDP; for invasive non-surgical procedures, 532 GBP vs. 7,268 GBP; and for non-invasive procedures,

622 GBP vs. 7,051 GBP. Overall, the mean cost to investigate extracolonic findings per patient randomized to BE was 4.63 GBP versus 99.10 GBP for CTC.

The total unit costs generated to investigate and/or treat extracolonic findings in the colonoscopy trial was 72,358 (GBP) for patients randomized to CTC; there were no costs attributable to colonoscopy since no extracolonic findings were reported. These costs broke down as follows: Unit costs for surgical procedures were 63,361 GBP; for invasive non-surgical procedures, 4,243 GBP; and for non-invasive procedures, 4,754 GBP. Overall, the mean cost to investigate extracolonic findings per patient randomized to CTC was 152.98 GBP versus nil for colonoscopy.

Presenting symptoms and extracolonic diagnosis

An extracolonic diagnosis was reached in 126 (88·1%) of the 142 patients undergoing subsequent investigation for an extracolonic finding; this explained the presenting symptoms in 54 (38%) (Table 2). Overall, 4 (0·2%) patients undergoing BE received an extracolonic diagnosis that explained their presenting symptoms vs. 33 (2·8%) undergoing CTC, and none undergoing colonoscopy vs. 17 (3·6%) undergoing CTC. The association between presenting symptoms and a subsequent extracolonic finding that explained these was relatively weak, being highest for patients with abdominal pain in the colonoscopy trial (10%) and very low for most symptoms (Table 2).

There were 75 extracolonic neoplasms diagnosed, 72 of which were diagnosed by CTC (26 malignant), 3 by BE (all malignant) and none by colonoscopy (Table 3). Taking both trials together, extracolonic neoplasms were diagnosed in 71/1633 (4·3%) of patients having CTC in whom colorectal cancer had been excluded, with extracolonic malignancy diagnosed in 25 (1·5%) overall. The most frequent primary malignancies diagnosed by CTC were renal (7 cases), pancreatic (3 cases), and prostate (2 cases). The most frequent benign tumours were ovarian (16 cases). 23 of 26 patients with an extracolonic malignancy had presenting symptoms that were explained by this (Table 3).

Extracolonic cancers diagnosed within 1 and 3 years of randomisation

Primary extracolonic cancers diagnosed within 1 year of randomisation are shown in Table 4 and within 3 years of randomisation in Table 5. Kaplan-Meier plots displaying the cumulative incidence of extracolonic cancer in the two trials at both 1- and 3-years post-randomisation

are shown in Figure 2.

In the first year following randomisation, rates of primary extracolonic cancer diagnosis in the BE trial were nearly twice as high as expected from general population rates (incidence rate ratio [IRR] per 1000 person years 1·88, 95%CI 1·33–2·65; p=0·0002) and were more than twice as high as expected in the colonoscopy trial (IRR 2·33, 1·40–3·89; p=0·0007). However, incidence did not differ between trial arms: 22.2 for CTC vs. 26.5 BE (IRR 0·84, 0·54–1·30; p=0·43) and 30.6 for CTC vs. 32.0 colonoscopy (IRR 0·95, 0·53–1·73; p=0·88). At 3-years there was also no difference between trial arms: 21·3 for CTC vs. 18·0 for BE (IRR 1·18, 95% CI 0·89–1·57; p=0·24) and 17·6 for CTC vs. 18·7 for colonoscopy (IRR 0·94, 95% CI 0·59–1·49; p=0·79). Analysis of the Kaplan-Meier plots of the cumulative incidence of extracolonic cancer found no significant difference between trial arms for the BE trial and colonoscopy trials at both 1-year following randomization (p=0·35 and p= 0·18 respectively) and 3-years following randomization (p=0·97 and p=0·94 respectively) (Figure 2).

Six patients died within 60 days of follow-up for an extracolonic finding: 4 died from metastatic disease, one died following a Whipple procedure for pancreatic carcinoma and one died following open repair of an aortic aneurysm. There was no significant difference in the proportions of patients dying within 3 years of randomisation (including those with colorectal cancer): 188 (7·4%) of 2527 randomized to BE vs. 107 (8·4%) of 1277 patients randomized to CTC (p=0·306); 86 (8·2%) of 1047 patients randomized to colonoscopy vs. 36 (6·8%) of 533 randomized to CTC (p=0·304).

Discussion

Hara and co-workers[5] first highlighted extracolonic detections by CTC; their retrospective review found that 30 (11%) of 264 consecutive patients at high risk of colorectal cancer had potentially important extracolonic lesions. Retrospective review of 10,286 CTC screening examinations found extracolonic cancer exceeded colonic (0·35% vs 0·21%).[8] A retrospective study of 400 symptomatic patients found 23 extracolonic malignancies via CTC.[7] However, a 2009 commentary predicted a “deluge” of incidental extracolonic findings, triggering anxiety, expense, morbidity and mortality.[19] Our systematic review[10] found no randomized data regarding the rate of extracolonic findings nor their influence on subsequent investigation and ultimate diagnosis.

The pragmatic design of our two parallel, multi-centre, randomized controlled trials of CTC

for symptomatic patients[11, 12] allowed us to observe how reporting of extracolonic lesions influenced subsequent diagnostic trajectory and ultimate diagnosis. 58·7% CT reports described extracolonic findings, a figure similar to the 63% from a USA study of high and average risk patients.[20] We found extracolonic detections rose significantly with age; a USA study[21] found extracolonic abnormalities in 74% patients ≥65 years vs. 55·4% <65 and a UK series of older symptomatic patients found 67% had extracolonic abnormalities.[7]

The E-RADS classification[17] aims to clarify management by estimating the clinical significance of extracolonic findings. A study of 2,277 screenees found that while 46% had at least one extracolonic finding, only 11% were E3/E4,[9] approximately half the rate we observed and suggesting that CTC may have particular utility in symptomatic patients. While E3/E4 CTC findings may warrant further investigation, we found approximately 40% were not referred. Indeed, nearly one-quarter of E4 lesions were not pursued further, despite this category describing a lesion that is "potentially important". There may be several explanations for this observation. Firstly, there are no comprehensive classification tables that describe exactly what qualifies as an E4 lesion, or indeed any E category. Therefore, the precise E category ascribed depends not on the lesion itself but on its perceived importance according to the interpreting radiologist. Perceived importance may differ when the lesion is considered by the gastroenterologist or surgeon in charge of the patient's care. For example, in a symptomatic context, the clinician in charge may decide that the lesions does not warrant further investigation because it is unlikely to explain the patient's symptoms. It is also possible that the patient may be too ill, too frail and/or unwilling to have an incidental extracolonic finding investigated further.

Concerning additional procedures performed to diagnose and/or treat extracolonic findings that arose directly from the allocated procedure, in both trials we found that CTC generated many more procedures than either BE or colonoscopy; CTC generated approximately 20 times the number of individual procedures than generated by BE whereas colonoscopy generated none. Furthermore, investigation of incidental extracolonic lesions was not straightforward, with a third of the patients investigated needing two or more procedures. This also impacted on costs. Our simple analysis of unit costs found that patients allocated CTC generated on average approximately 20 times the additional costs needed to investigate extracolonic findings than BE (99.10 GBP per-patient vs. 4.63 GBP respectively). In the colonoscopy trial, on average the costs required to investigate extracolonic findings was 152.98 GBP per-patient as opposed to nil for colonoscopy. These figures are in

accordance with previous work that found the mean cost required to investigate unexpected extracolonic findings was approximately equal to the cost of the initial CTC[3]. Our study was performed in the National Health Service (NHS), which is funded by the Government via general taxation. Costs will differ in other healthcare systems.

We hypothesised that CTC would accelerate diagnosis of extracolonic cancer compared with BE or colonoscopy. Although we found extracolonic cancer was diagnosed at approximately double the expected rate 1-year post-randomisation, this applied to all procedures. This observation suggests that patients initially allocated BE or colonoscopy undergo further abdomino-pelvic investigation, presumably requested to investigate persistent abdominal symptoms that have not been clarified by the initial diagnostic procedure, and that this ultimately culminates in diagnosis of extracolonic cancer in some patients. Although we collected details of procedures arising directly from the randomized examination, we did not identify procedures carried out later once the diagnostic episode "on trial" had closed. We therefore do not know how often such procedures occur although our data suggest it is frequent. Furthermore, analysis of registry data will not identify the time of diagnosis precisely; it is possible that CTC may accelerate diagnosis by months, which may not have clinical impact ultimately but is likely to be highly desirable to both patients and policy-makers. We did not have ethical permission to obtain local data on tumour stage but it is likely that a significant proportion of the extracolonic cancers were incidental and their detection equivalent to "screening" rather than them being responsible for patients' presenting symptoms. Factoring in subsequent abdomino-pelvic investigation for patients initially allocated BE or colonoscopy will also increase the cost of follow-up in these patients relative to CTC. Because of this, it is highly likely that the mean costs attributed by us to investigation by BE and colonoscopy are grossly underestimated and we are seeking ethical permission currently to retrieve more comprehensive data regarding this.

We attempted to address whether extracolonic findings underpinned patients' symptoms: 3% patients having CTC in the BE trial and 4% in the colonoscopy trial had symptoms ultimately attributed to extracolonic pathology, a higher proportion than patients having BE (0·2%) or colonoscopy (0·1%). However association between specific reported symptoms and extra-colonic disease was generally low, limiting utility for individual patients. Although we believed we might identify symptoms associated with extracolonic disease, anaemia was the only symptom significantly associated with reporting of an extracolonic finding. While

particular constellations of extracolonic finding with symptoms, age, and sex may predict those in need of extra-colonic investigation, this requires complex multi-variate analysis.

Our study has limitations. As noted already, the E-RADS categories describe screening rather than symptomatic investigation[17] and a lack of comprehensive classification tables means the score attributed is dependent on the subjective opinion of the radiologist interpreting the study. 45 radiologists interpreted CTC and their personal thresholds for reporting extracolonic findings will differ, especially for those perceived as low-risk. We did not analyse centre-to-centre variation but the pragmatic design suggests our findings are generalisable. Patients with proven colorectal cancer were excluded because this diagnosis overwhelms others, influencing subsequent investigations. Although some patients may have both colorectal and extracolonic cancer, numbers will be small. There were several patients registered who were not ultimately randomized, the large majority being a result of clinician-declined consent rather than patient-declined consent (Appendix Table 1). The commonest single reason given was that the clinician held a strong a priori belief that colonoscopy should be performed (731 patients), followed by CT (303 patients), and flexible sigmoidoscopy (230 patients). Our publications detailing analysis of the primary outcome (detection of colorectal cancer and large polyps) compared included and excluded patients as is standard practice for randomized controlled trials. We found that patients included in both trials were significantly more likely to be younger than excluded patients. In the BE trial we found patients were also more likely to be female, to present with abdominal pain or change in bowel habit, and were less likely to present with rectal bleeding, anaemia, or weight loss.[22] In the colonoscopy trial we found patients were also more likely to be male, to present with a change in bowel habit, rectal bleeding, or abdominal pain and were less likely to present with anaemia.[16] A similar comparison was not possible in the present paper since we focus on extracolonic pathology detected in patients without colorectal cancer: The proportion of excluded patients without colorectal cancer is unknown, with the result that a similar comparison would not be statistically valid.

We intend to model the impact of extracolonic detections on lives saved versus morbidity/mortality due to unnecessary investigation. While the present focus is on extracolonic tumours, benign pathology is important; CTC is regarded as “highly cost-effective” for abdominal aortic aneurysm.[23]

In summary, extracolonic findings are identified commonly by radiologists reporting CTC in symptomatic patients. In this trial, approximately 8% of symptomatic patients having CTC were investigated for extracolonic findings, which explained symptoms in approximately 4%. Extracolonic malignancy was found in 1·6% but time to diagnosis was not reduced compared to BE or colonoscopy at 1- or 3- years.

References

1. Ng CS, Doyle TC, Courtney HM, et al. Extracolonic findings in patients undergoing abdomino-pelvic CT for suspected colorectal carcinoma in the frail and disabled patient. Clin Radiol 2004;59:421-30.
2. Xiong T, Richardson M, Woodroffe R, et al. Incidental lesions found on CT colonography: their nature and frequency. Br J Radiol 2005;78:22-9.
3. Xiong T, McEvoy K, Morton DG, et al. Resources and costs associated with incidental extracolonic findings from CT colonogaphy: a study in a symptomatic population. Br J Radiol 2006;79:948-61.
4. Wernli KJ, Rutter CM, Dachman AH, et al. Suspected Extracolonic Neoplasms Detected on CT Colonography: Literature Review and Possible Outcomes. Acad Radiol 2013.
5. Hara AK, Johnson CD, MacCarty RL, et al. Incidental extracolonic findings at CT colonography. Radiology 2000;215:353-7.
6. Hellstrom M, Svensson MH, Lasson A. Extracolonic and incidental findings on CT colonography (virtual colonoscopy). AJR Am J Roentgenol 2004;182:631-8.
7. Tolan DJ, Armstrong EM, Chapman AH. Replacing barium enema with CT colonography in patients older than 70 years: the importance of detecting extracolonic abnormalities. AJR Am J Roentgenol 2007;189:1104-11.
8. Pickhardt PJ, Kim DH, Meiners RJ, et al. Colorectal and extracolonic cancers detected at screening CT colonography in 10,286 asymptomatic adults. Radiology 2010;255:83-8.
9. Veerappan GR, Ally MR, Choi JH, et al. Extracolonic findings on CT colonography increases yield of colorectal cancer screening. AJR Am J Roentgenol 2010;195:677-86.
10. Halligan S, Altman DG, Taylor SA, et al. CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting. Radiology 2005;237:893-904.
11. 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.
12. Halligan S, Wooldrage K, Dadswell E, et al. Computed tomographic colonography versus barium enema for diagnosis of colorectal cancer or large polyps in symptomatic patients (SIGGAR): a multicentre randomised trial. Lancet 2013.
13. Halligan S, Lilford RJ, Wardle J, et al. Design of a multicentre randomized trial to evaluate CT colonography versus colonoscopy or barium enema for diagnosis of colonic cancer in older symptomatic patients: the SIGGAR study. Trials 2007;8:32.
14. Taylor SA, Laghi A, Lefere P, et al. European Society of Gastrointestinal and Abdominal Radiology (ESGAR): consensus statement on CT colonography. Eur Radiol 2007;17:575-9.
15. Halligan S, Dadswell, E., Wooldrage, K., Wardle, J., von Wagner, C., Lilford, R.J., Yao, G., L., Zhu, S., Atkin, W. Computed tomographic colonography versus colonoscopy or barium enema for diagnosis of colorectal cancer in older symptomatic patients: two multicentre randomised trials with economic evaluation (the SIGGAR trials). Health Technol Assess 2013.

16. 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.
17. Zalis ME, Barish MA, Choi JR, et al. CT colonography reporting and data system: a consensus proposal. Radiology 2005;236:3-9.
18. Statistics OfN. Cancer statistics registrations, England (series MB1), no. 40. Volume 2012. http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-222747, 2009.
19. Berland LL. Incidental extracolonic findings on CT colonography: the impending deluge and its implications. J Am Coll Radiol 2009;6:14-20.
20. Yee J, Kumar NN, Godara S, et al. Extracolonic abnormalities discovered incidentally at CT colonography in a male population. Radiology 2005;236:519-26.
21. Macari M, Nevsky G, Bonavita J, et al. CT colonography in senior versus nonsenior patients: extracolonic findings, recommendations for additional imaging, and polyp prevalence. Radiology 2011;259:767-74.
22. Halligan S, Wooldrage K, Dadswell E, et al. Computed tomographic colonography versus barium enema for diagnosis of colorectal cancer or large polyps in symptomatic patients (SIGGAR): a multicentre randomised trial. Lancet 2013;381:1185-93.
23. Pickhardt PJ, Hassan C, Laghi A, et al. CT colonography to screen for colorectal cancer and aortic aneurysm in the Medicare population: cost-effectiveness analysis. AJR Am J Roentgenol 2009;192:1332-40.

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Legends for Illustrations:

Figure 1: Patient flow through the trial.

Figure 2: Kaplan-Meier plots of the cumulative incidence of extracolonic cancer in the two trials: 1-year post-randomisation in the barium enema trial (A) and colonoscopy trial (B) and 3-years post-randomisation in the barium enema trial (C) and colonoscopy trial (D).

Tables.

Table 1: E-RADS category, referral for further procedures and most invasive procedure performed for all individual extracolonic findings by diagnostic pathway and randomized procedure*

	CT colonography (CTC) vs. barium enema (BE) trial				CT colonography (CTC) vs. colonoscopy trial§	
	BE performed (n=2223)		CTC performed (n=1161)		CTC performed (n=473)	
	Extracolonic findings reported	Extracolonic findings referred for further procedures†	Extracolonic findings reported	Extracolonic findings referred for further procedures †	Extracolonic findings reported	Extracolonic findings referred for further procedures †
	n rate (/1000)	n rate (/1000)	n rate (/1000)	n rate (/1000)	n rate (/1000)	n rate (/1000)
E-RADS category						
E4	6 2.7	4 1.8	53 45.6	38 32.7	23 48.6	20 42.3
E3	7 3.1	0 0	243 209.3	40 34.5	87 183.9	17 35.9
E2	33 14.8	2 0.9	932 802.8	11 9.5	425 898.5	12 25.4
E1	0 0	0 0	18 15.5	0 0	3 6.3	0 0
Most invasive procedure performed as a result of finding						
Surgical	-	3 1.3	-	19 16.4	-	12 25.4
Invasive, non-surgical	-	2 0.9	-	23 19.8	-	13 27.5
Non-invasive imaging	-	1 0.4	-	45 38.8	-	23 48.6
Other‡	-	0 0	-	2 1.7	-	1 2.1

*subjects could have multiple extracolonic findings reported.
†two patients had two unrelated findings investigated and included in the table.
‡includes two blood tests and one urine test.
§no patient having colonoscopy had an extracolonic finding reported.

Table 2: Proportion of patients* with at least one extracolonic finding at randomized procedure, the proportion referred for further investigation as a consequence of an extracolonic finding, the proportion in whom a diagnosis was made, and the proportion who had presenting symptoms attributable to the diagnosis.

	CT colonography (CTC) vs. barium enema (BE) trial																	CT colonography (CTC) vs. colonoscopy trial								
	BE									CTC																	
Characteristic	**BE performed**	**≥1 extracolonic finding**		**Referred for investigation**		**Received extracolonic diagnosis**		**≥1 symptom attributable to**		**CTC performed**	**≥1 extracolonic finding**		**Referred for investigation**		**Received extracolonic diagnosis**		**≥1 symptom attributable to**		**CTC performed**	**≥1 extracolonic finding**		**Referred for investigation**		**Received extracolonic diagnosis**		**≥1 symptom attributable to**	
		n	%	n	%	n	%	n	%		n	%	n	%	n	%	n	%		n	%	n	%	n	%	n	%
Total	2223	42	1.9	6	0.3	5	0.2	4	0.2	1161	672	57.9	88	8	79	7	33	3	473	287	60.7	48	1	42	9	17	4
Sex																											
Male	860	15	1.7	3	0.3	2	0.2	2	0.2	441	259	58.7	36	8	34	8	14	3	212	126	59.4	19	9	16	8	4	2
Female	1363	27	2.0	3	0.2	3	0.2	2	0.1	720	413	57.4	52	7	45	6	19	3	261	161	61.7	29	1	26	1	13	5
Age																											
55-64	760	7	0.9	2	0.3	2	0.3	1	0.1	385	185	48.1	25	6	22	6	7	2	201	112	55.7	20	1	18	9	10	5
65-74	871	13	1.5	1	0.1	1	0.1	1	0.1	451	258	57.2	30	7	28	6	14	3	164	94	57.3	17	1	13	8	4	2
75-84	542	22	4.1	3	0.6	2	0.4	2	0.4	290	203	70.0	29	10	25	9	9	3	98	72	73.5	10	1	10	1	2	2
85+	50	0	0	0	0	0	0	0	0	35	26	74.3	4	11	4	1	3	9	10	9	90.0	1	1	1	1	1	1
Symptoms/																											
Change in	1698	33	1.9	5	0.3	4	0.2	3	0.2	903	515	57.0	65	7	58	6	21	2	343	215	62.7	34	1	30	9	11	3
Rectal	664	11	1.7	0	0	0	0	0	0	345	198	57.4	21	6	18	5	4	1	210	126	60.0	24	1	22	1	9	4
Abdomina	728	12	1.7	3	0.4	3	0.4	3	0.4	376	213	56.7	28	7	27	7	20	5	108	64	59.3	14	1	13	1	11	1
Anaemia	250	9	3.6	1	0.4	1	0.4	1	0.4	129	93	72.1	15	12	14	1	8	6	48	33	68.7	7	1	6	1	1	2
Weight	283	5	1.8	2	0.7	2	0.7	2	0.7	168	105	62.5	18	11	16	1	5	3	69	45	65.2	9	1	9	1	3	4
Other	257	4	1.6	2	0.8	1	0.4	1	0.4	123	68	55.3	9	7	7	6	4	3	91	54	59.3	10	1	9	1	5	5

*Patients with CRC diagnosed were excluded.

Table 3: Final diagnosis of extracolonic neoplasms by ICD-10 category.

		CT colonography (CTC) vs. barium enema (BE) trial				CT colonography (CTC) vs. colonoscopy trial	
		BE		CTC		CTC	
		# patients diagnosed	# patients with ≥1 symptom related to diagnosis	#patients diagnosed	# patients with ≥1 symptom related to diagnosis	#patients diagnosed	# patients with ≥1 symptom related to diagnosis
Malignant neoplasms							
C64	Malignant neoplasm of kidney, except renal pelvis			4	3	3	2
C25	Malignant neoplasm of pancreas			2	2	1	1
C61	Malignant neoplasm of prostate	1	1	2	2		
C34	Malignant neoplasm of bronchus and lung			1	1	1	
C78	Secondary malignant neoplasm of respiratory and digestive organs			1	1	1	1
C82	Follicular [nodular] non-Hodgkin's lymphoma	1				1	1
C16	Malignant neoplasm of stomach					1	1
C17	Malignant neoplasm of small intestine			1	1		
C22	Malignant neoplasm of liver and intrahepatic bile ducts			1	1		
C48	Malignant neoplasm of retroperitoneum and peritoneum	1	1				
C56	Malignant neoplasm of ovary			1	1		
C65	Malignant neoplasm of renal pelvis					1	1
C77	Secondary and unspecified malignant neoplasm of lymph nodes					1	1
C80	Malignant neoplasm without specification of site			1	1		
C90	Multiple myeloma and malignant plasma cell neoplasms					1	1
C92	Myeloid leukaemia			1	1		
	Total:	**3**	**2**	**15**	**14**	**11**	**9**
Benign neoplasms							
D27.0	Benign neoplasm of ovary			10	5	6	2
D18.0	Haemangioma, any site			8		2	
D14.3	Benign neoplasm of bronchus and lung			3		3	
D25.9	Leiomyoma of uterus, unspecified			4	3	1	1
D30.0	Benign neoplasm of kidney			3		1	
D35.0	Benign neoplasm of adrenal gland			1		1	
D13.6	Benign neoplasm of pancreas					1	1
D36.1	Benign neoplasm of peripheral nerves and autonomic nervous system			1			
D44.1	Neoplasm of uncertain or unknown behaviour of adrenal gland					1	1
	Total:	**0**		**30**	**8**	**16**	**5**

Table 4: Extracolonic cancers diagnosed within one year of randomisation by ICD10 code for BE trial and colonoscopy trial.

	Barium enema trial				Colonoscopy trial			
	CT colonography (CTC) (n=1277)		Barium enema (BE) (n=2527)		CT colonography (CTC) (n=533)		Colonoscopy (csy) (n=1047)	
	Total	Found by CTC†	Total	Found by BE	Total	Found by CTC†	Total	Found by csy
All extracolonic cancers*	27	9	67‡	3	16	9	32	0
Person-years of follow-up§	1259		2489		523		1030	
Incidence (per 1000 person-years)	21.4		26.9		30.6		31.1	
Cancer type (ICD-10)								
Stomach (C16)	0		5		2	1	1	
Small Intestine (C17)	0		2		1		1	
Hepatobiliary system (C22, C24)	0		2		1		1	
Pancreas (C25)	3	2	7		1	1	6	
Digestive organs, other and ill defined (C26)	0		0					
Bronchus and lung (C34)	5	1	9		2	1	7	
Mesothelial and soft tissue (C45, C46, C48)	3	1	2	1				
Breast (C50)	3		6				4	
Cervix uteri (C53)			1					
Ovary (C56)	2	1	4					
Prostate (C61)	4	1	10	1			4	
Kidney (C64, C65)	2	2	3		5	4	3	
Bladder (C67)			1		1			
Lymphoid or haematopoietic tissue (C81, C82, C83, C85, C90, C91, C92)	2		6	1	2	2	1	
Primary site unknown (C80)	2	1	3					
Other¶	1		6		1		4	

Data are number, unless otherwise specified.

*All primary malignant neoplasms, excluding colorectal cancers (C18-C20) and non-melanoma malignant neoplasms of the skin (C44). Patients could have more than one cancer diagnosed.

†Comparison with the malignancies reported in Table 4: barium enema trial - eight malignancies were included in both tables, two malignancies from Table 4 were excluded from Table 5 as were diagnosed later than one year after randomisation, one secondary cancer from Table 4 was excluded from Table 5, four extracolonic cancers detected by CT colonography but not verified by the NHS Information Centre were included in Table 4 but excluded from Table 5 and one malignancy diagnosed in a subject also diagnosed with colorectal cancer in Table 5 was excluded from Table 4; colonoscopy trial – two secondary cancers from Table 4 were excluded from Table 5.

‡One patient assigned to barium enema had two extracolonic cancers diagnosed within 1 year: melanoma of skin and lymphoid leukaemia. No patients assigned to CT colonography in the barium enema trial had more than one extracolonic cancer diagnosed.

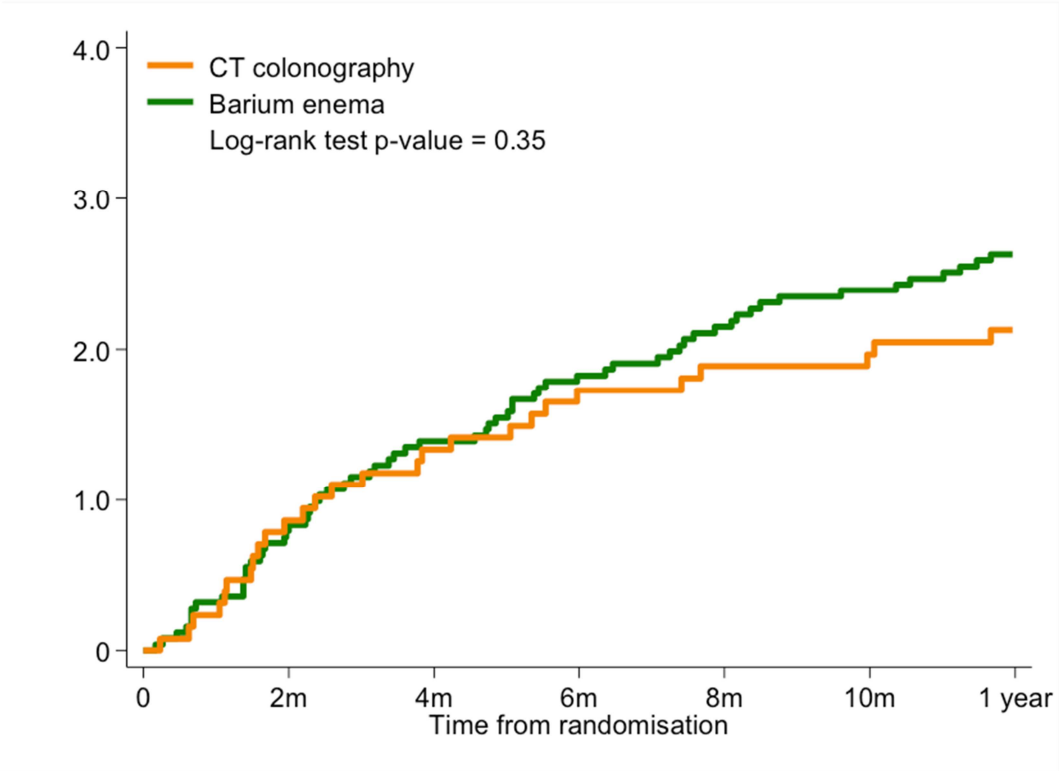
§Adjusted for reported mortality. ¶Comprises cancers of the oesophagus (C15); malignant melanoma of the skin (C43); vulva (C51); spinal cord, cranial nerves and other parts of central nervous system (C72); thyroid (C73); and other and ill-defined sites (C76).

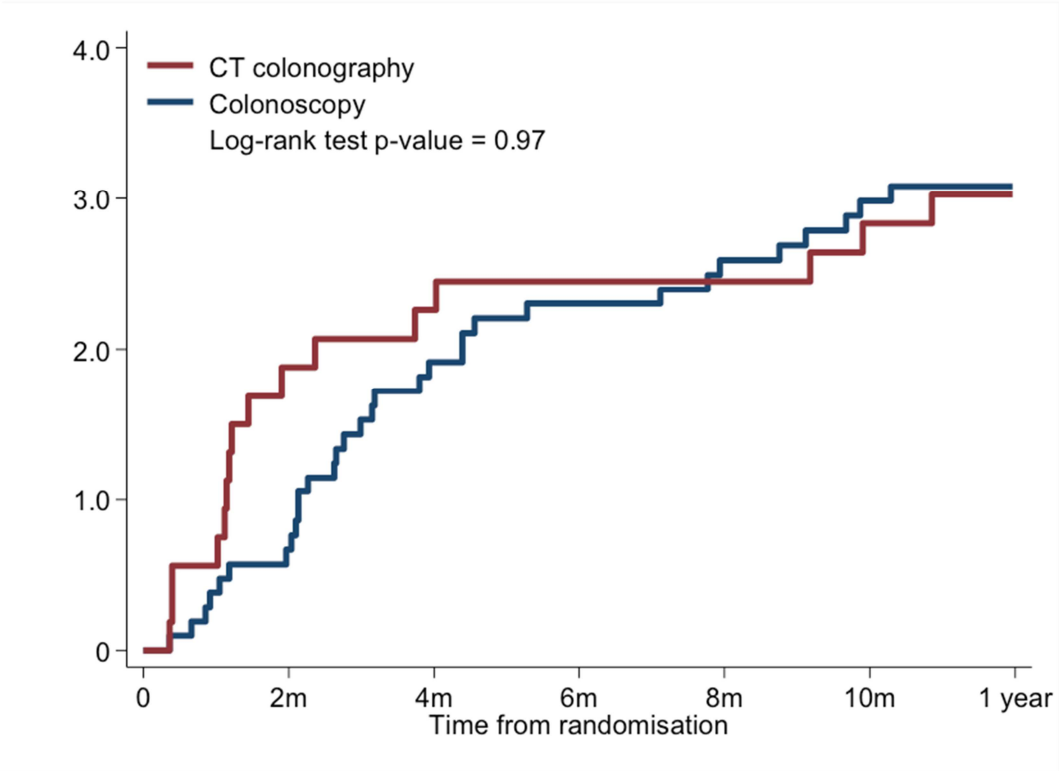
Table 5: Extracolonic cancers diagnosed within 3 years of randomisation by ICD10 code for BE trial and colonoscopy trial.

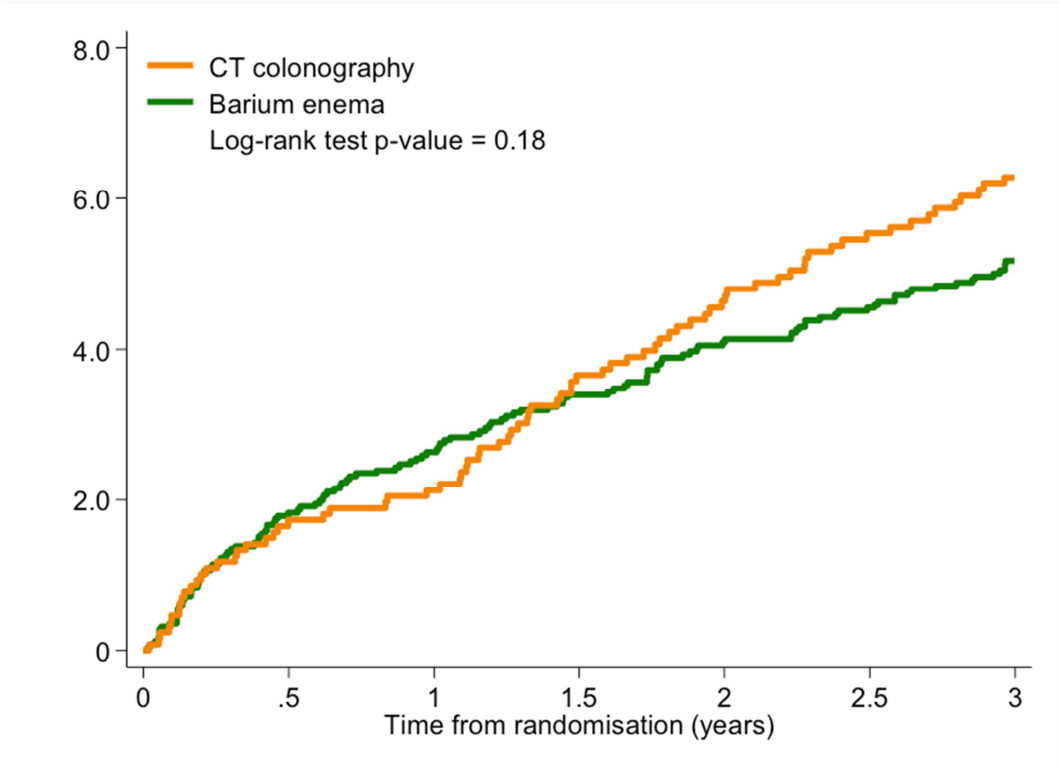
	Barium enema trial				Colonoscopy trial			
	CT colonography (CTC) (n=1277)		Barium enema (BE) (n=2527)		CT colonography (CTC) (n=533)		Colonoscopy (csy) (n=1047)	
	Total	Found by CTC†	Total	Found by BE	Total	Found by CTC†	Total	Found by csy
All extracolonic cancers*	78	11	132‡	3	27	9	55§	0
Person-years of follow-up¶	3663		7275		1536		2992	
Incidence (per 1000 person-years)	21.3		18.1		17.6		18.4	
Cancer type (ICD-10)								
Stomach (C16)	3		10		4	1	3	
Small Intestine (C17)	0		3		1		1	
Hepatobiliary system (C22, C24)	2	1	3		1		4	
Pancreas (C25)	5	2	9		2	1	7	
Digestive organs, other and ill defined (C26)	0		1					
Bronchus and lung (C34)	17	1	23		2	1	11	
Mesothelial and soft tissue (C45, C46, C48)	3	1	5	1			1	
Breast (C50)	14		14		2		7	
Cervix uteri (C53)			1					
Ovary (C56)	2	1	4		1			
Prostate (C61)	7	1	20	1	3		10	
Kidney (C64, C65)	4	3	6		5	4	4	
Bladder (C67)			4		2			
Lymphoid or haematopoietic tissue (C81, C82, C83, C85, C90, C91, C92)	7		12	1	2	2	3	
Primary site unknown (C80)	5	1	3					
Other‖	9		14		2		4	

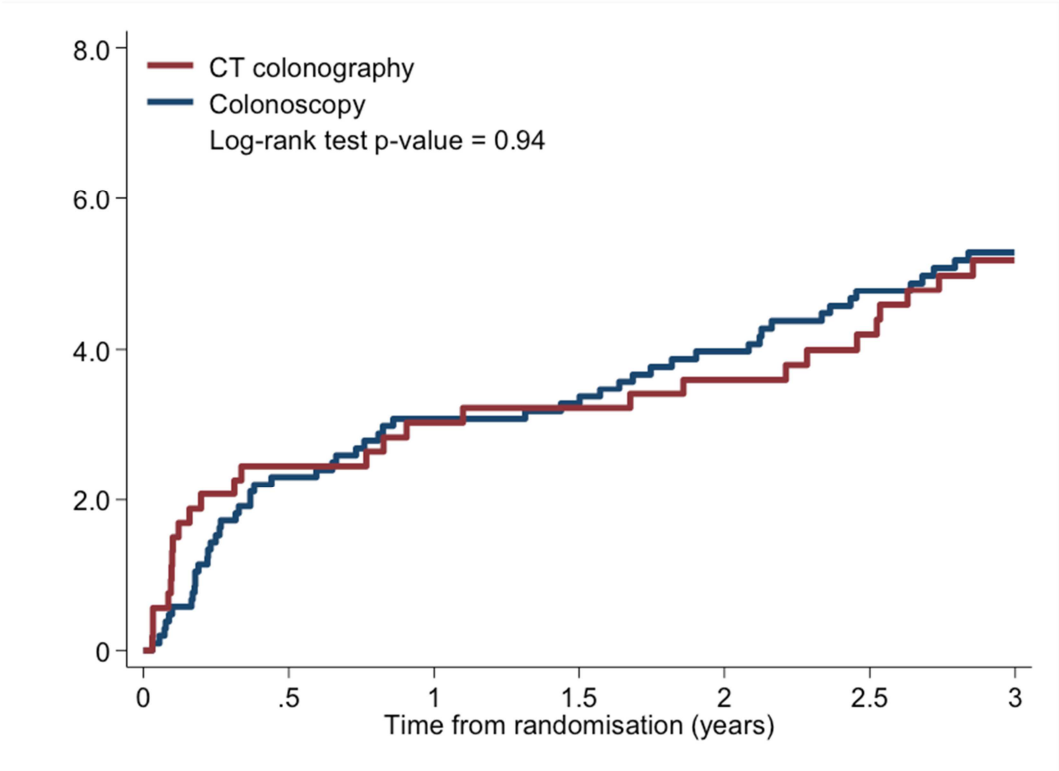
Data are number, unless otherwise specified. *All primary malignant neoplasms, excluding colorectal cancers (C18-C20) and non-melanoma malignant neoplasms of the skin (C44). Patients could have more than one cancer diagnosed. † Comparison with the malignancies reported in Table 4: barium enema trial - ten malignancies were included in both tables, one secondary cancer from Table 4 was excluded from Table 6, four extracolonic cancers detected by CT colonography but not verified by the NHS Information Centre were included in Table 4 but excluded from Table 6 and one malignancy diagnosed in a subject also diagnosed with colorectal cancer in Table 6 was excluded from Table 4; colonoscopy trial – two secondary cancers from Table 4 were excluded from Table 6.

‡Four patients assigned to barium enema had two extracolonic cancers diagnosed within 36 months: one stomach and prostate; one small intestine and biliary tract; one melanoma of skin and lymphoid leukaemia; one prostate and bladder. No patients assigned to CT colonography in the barium enema trial had more than one extracolonic cancer diagnosed. §One patient assigned to colonoscopy had two extracolonic cancers diagnosed within 36 months: lung and kidney cancer. No patients assigned to CT colonography in the colonoscopy trial had more than one extracolonic cancer diagnosed. ¶Adjusted for reported mortality. ||Comprises cancers of other and unspecified parts of the tongue (C02); oesophagus (C15); bone and articular cartilage of other and unspecified sites (C41); malignant melanoma of the skin (C43); vulva (C51); brain (C71); spinal cord, cranial nerves and other parts of central nervous system (C72); thyroid (C73); and other and ill-defined sites (C76).









SUPPORTING DOCUMENT: APPENDICES

Appendix table 1: Reasons for exclusions

REASON	n	(%)
Clinician reasons for declining consent		
Colorectal or other cancer already diagnosed		
Colorectal cancer diagnosed	56	1.8
Other cancer diagnosed	69	2.2
Specific procedure requested		
Colonoscopy	731	23.6
CT	303	9.8
Flexible sigmoidoscopy	230	7.4
Oesophagogastroduodenoscopy	218	7.0
Barium enema	19	0.6
Ultrasound	16	0.5
Magnetic resonance imaging	5	0.2
Unknown	39	1.3
Clinical situation too urgent or waiting list too long	52	1.7
Patient unfit for whole colon examination	215	6.9
Patient unable to give informed consent	75	2.4
No reason given	148	4.7
Total where clinician declined consent	**2,176**	**70.2**
Patient reasons for declining consent		
Patient wanted a specific procedure:		
Colonoscopy	15	0.5
CT	3	0.1
Barium enema	2	0.06
Unknown	128	4.1
Patient did not want a specific procedure:		
CT as claustrophobic	13	0.4
CT for other reasons	2	0.06
Colonoscopy	1	0.03
Barium enema	1	0.03
Patient had difficulty comprehending	84	2.7
Patient died before consent obtained	2	0.06
No reason given	583	18.8
Total where patient declined consent	**834**	**26.9**
Reason for exclusion unknown	**26**	**0.8**
Patient withdrew consent following randomisation	**64**	**2.1**
TOTAL EXCLUDED	**3,100**	**100.0**

Appendix table 2: Baseline demographic and clinical characteristics of patients with symptoms of colorectal cancer in whom CTC was performed. Patients ultimately found to have colorectal cancer are excluded.

Characteristic.	CT colonography (CTC) vs. barium enema (BE) trial				CT colonography (CTC) vs. colonoscopy trial			
	BE performed (n=2223)		CTC performed (n=1161)		CTC performed (n=473)		Colonoscopy performed (n=908)	
	n	%	n	%	n	%	n	%
Sex								
Male	860	39	441	38	212	45	402	44
Female	1363	61	720	62	261	55	506	56
Age								
55-64	760	34	385	33	201	42	350	39
65-74	871	39	451	39	164	35	330	36
75-84	542	24	290	25	98	21	206	23
85+	50	2	35	3	10	2	22	2
Symptoms†								
Change in bowel habit	1698	76	903	78	343	73	679	75
Harder, less frequent	278	13	143	12	60	13	105	12
Looser, more frequent	905	41	503	43	191	40	372	41
Variable frequency	210	9	106	9	47	10	109	12
Unspecified	305	14	151	13	45	10	93	10
Rectal bleeding	664	30	345	30	210	44	361	40
Abdominal pain	728	33	376	32	108	23	199	22
Anaemia	250	11	129	11	48	10	109	12
Weight loss	283	13	168	15	69	15	129	14
Other symptoms	257	12	123	11	91	19	151	17

† patients may have reported multiple symptoms/signs.

Appendix table 3: Non-neoplastic extracolonic findings on barium enema and comparative rates for CT colonography**.**

Finding*	CT colonography vs. barium enema trial				CT colonography vs. colonoscopy trial	
	Randomised BE performed (N=2223)		Randomised CTC performed (N=1161)		Randomised CTC performed (N=473)	
	n	%	n	%	n	%
Hernia (all types)	18	0.8	136	11.7	59	12.5
Gallstone(s)	3	0.1	88	8	39	8
Degenerative bone changes	5	0.2	75	6	30	6
Uterine fibroid(s)	4	0.2	28	2	16	3
Kidney stone(s)	2	0.09	23	2	5	1
Splenic cyst(s)	1	0.04	6	0.5	5	1
Bronchiectasis	1	0.04	8	0.7	2	0.4
Calcified lymph node(s)	4	0.2	0	0	0	0
Extrinsic compression	3	0.1	0	0	0	0
Paget's disease	1	0.04	1	0.09	1	0.2
Pericolic abscess	1	0.04	0	0	0	0
Rectocele	1	0.04	0	0	0	0
Possible mass in rectrorectal space	1	0.04	0	0	0	0
Possible prostate cancer with possible metastases	1	0.04	0	0	0	0

*Subjects may have multiple findings and have findings in more than one category.

Appendix table 4: Total number of procedures performed to investigate and/or treat extracolonic findings in the 142 individual patients referred.

	CT colonography vs. barium enema trial		CT colonography vs. colonoscopy trial†
	Barium enema*	**CT colonography†**	**CT colonography‡**
	n	n	n
Surgical procedures			
Radical nephrectomy	0	5	4
Oophorectomy +/- salpingectomy +/- hysterectomy	0	5	2
Aneurysm repair	0	5	0
Laparotomy	1	2	1
Inguinal hernia repair	2	1	0
Whipple procedure	0	0	1
Laproscopic cholecystectomy	0	0	1
Right Upper Lobectomy	0	0	1
Splenectomy	0	1	0
Adrenalectomy	0	0	1
Video-assisted thoracoscopy	0	0	1
Stent insertion	0	0	1
Total surgical procedures:	3	19	13
Non-surgical invasive procedures			
Ultrasound transvaginal	0	9	9
Oesophagogastroduodenoscopy	0	1	5
Hysteroscopy	0	4	0
Ultrasound-guided biopsy	0	4	0
Bronchoscopy	0	2	0
Lymph node biopsy	0	1	1
CT-guided biopsy	0	0	2
Prostate biopsy	1	1	0
Endoscopic retrograde cholangiopancreatography	0	2	0
Aspiration of fluid from abdomen	1	1	0
Extracorporeal shock wave lithotripsy	0	1	0
Flexible cystoscopy	0	1	0
Fluid aspiration and culture of uterus	0	1	0
Renal biopsy	0	0	1
Ultrasound-guided fine needle aspiration of pancreas	0	1	0
Bone marrow biopsy	0	1	0
Colonoscopy	0	0	1
Total non surgical, invasive procedures:	2	30	19
Non invasive imaging procedures			
Ultrasound	2	30	10
CT	1	23	17
X-ray	3	2	10
MRI	0	8	5
Bone scan	1	2	1
Barium meal	0	1	2
PET scan lung	0	1	1
Dimercaptosuccinic acid scan	0	0	1
Intravenous urogram	0	1	0
Total non invasive imaging procedures:	7	68	47

*Six findings in 6 patients having BE were referred for at least one of the procedures in the table: four patients had one procedure performed, one had three performed and one had five performed.
†87 findings were referred for at least one of the procedures in the table: 64 had one procedure performed, 17 had two performed, five had three performed and one had four procedures. Two other findings were referred but were not included in this table; one was only referred for a blood test and one only for a urine test.
‡48 findings were referred for at least one of the procedures in the table: 29 had one procedure performed, ten had two performed, six had three performed and three had four procedures. One other finding was only referred for a blood test and was not included in this table.