Received:
9 March 2013

Revised:
28 March 2013

Accepted:
30 March 2013

doi: [10.1259/bjr.20130137](https://doi.org/10.1259/bjr.20130137)

Cite this article as:

Halligan S. CT colonography for investigation of patients with symptoms potentially suggestive of colorectal cancer: a review of the UK SIGGAR trials. Br J Radiol 2013;86:20130137.

INVITED HOUNSFIELD REVIEW

CT colonography for investigation of patients with symptoms potentially suggestive of colorectal cancer: a review of the UK SIGGAR trials

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ABSTRACT

This paper argues for the use of CT colonography (CTC) to investigate patients with symptoms potentially suggestive of colorectal cancer. It describes the rationale for the UK Special Interest Group in Gastrointestinal and Abdominal Radiology (SIGGAR) randomised controlled trials that compared CTC with barium enema (BE) or colonoscopy for diagnosis of colorectal cancer or large polyps in symptomatic patients. Diagnostic outcomes from the trials are detailed for both intra- and extracolonic disease, along with psychological reactions of patients to the tests, and cost-effectiveness of the different diagnostic strategies. The author concludes that BE should be replaced by CTC immediately and that CTC is a sensitive, acceptable and equally cost-effective alternative to colonoscopy in patients in whom colonoscopy is contraindicated or undesirable.

CT colonography (CTC) was first described in 1994 [1]; Vining and colleagues detailed a method by which they could navigate “virtual reality” images of the endoluminal colon, reconstructed from thin-section helical CT obtained following

colonic purgation and gas insufflation. Subsequent early publications focused on technical aspects of the test such as scanning parameters [2] and dose [3]. The profile of CTC was raised considerably with the publication in the *New England Journal of*

Medicine of a study that described an intra-individual comparison with the subsequent same-day colonoscopy in 100 patients [4]. The researchers found that CTC had high sensitivity for colorectal adenomas, detecting 46 (90%) of 51 adenomas ≥ 6 mm in diameter. The authors concluded that “virtual and conventional colonoscopy have similar efficacy for the detection of polyps 6 mm or more in diameter” [4].

These papers set the standard for research publications over the subsequent few years: an intra-individual comparison with colonoscopy became the methodological design of choice for studies investigating the diagnostic accuracy of CTC. Accruals were simplified greatly by investigating symptomatic patients, or those above the population risk for colorectal cancer and polyps since they were scheduled for colonoscopy in any event. Despite being titled “CT colonography: the next colon screening examination?”, a 2000 commentary noted that “No investigators to date have reported on the performance of CTC in an asymptomatic screening population—the patient population most likely to benefit from the procedure” [5]. Emphasising this, a systematic review and meta-analysis, searching up to and including December 2003 [6], identified 24 primary studies that examined the diagnostic accuracy of CTC and fulfilled the pre-specified entry criteria for the review. Of these, only a solitary study recruited wholly asymptomatic patients at population risk for colorectal cancer or adenomas, yet the vast majority of researchers focused their interpretation on whether detection of polyps was acceptable enough for the test to be used for colorectal cancer screening.

Why use CT colonography to diagnose symptomatic colorectal cancer?

So, are asymptomatic screenees “the patient population most likely to benefit from the procedure” [5]? As noted in the section above, most studies have actually been performed in symptomatic patients in whom it is well established that the morphology of polyps and cancers differs substantially from those encountered in asymptomatic screenees. Symptoms arise because lesions, usually cancers, are large enough to cause them. Indeed, adenomatous polyps, the precursor of most colorectal cancers, rarely cause symptoms even when large. It is intuitive that it is easier for radiological imaging to detect larger lesions than smaller, so CTC would actually be expected to

be more sensitive for symptomatic cancers than asymptomatic polyps. Accordingly, the author would counter that *symptomatic* patients are the patient population most likely to benefit from the procedure (Figure 1).

An early, small UK case series [7] had suggested using CTC to detect symptomatic colorectal cancer but most published studies rarely documented the numbers of cancers present in their cohort despite accruing symptomatic patients. The researchers of the 2005 meta-analysis [6] needed to directly contact several authors of the primary studies in order to determine whether any cancers were present in the data and, if so, whether they had been detected by CTC. After doing so, they estimated that the average sensitivity of CTC for cancer was 96% (144 of 150 cancers detected overall) [6]. Since this was equivalent to the sensitivity oft-quoted for colonoscopy, the authors concluded that “This strongly suggests that CT colonography merits further investigation as a diagnostic tool for cancer” [6]. CTC would therefore seem to be an ideal test to examine patients with symptoms potentially suggestive of colorectal cancer, including change in bowel habit, rectal bleeding and abdominal pain.

Figure 1. Axial image from a CT colonogram showing a large colorectal cancer (arrow) in a symptomatic patient. On average, this type of lesion is easier to detect by CT than a non-malignant polyp.

However, do we need such a test? Colonoscopy is an excellent diagnostic test for colorectal cancer and can also obtain tissue, so why would an alternative be desirable? Older patients and those with comorbidities are more likely to have an incomplete or difficult colonoscopy, and are at greater risk of adverse events, some of which can be life threatening [8,9]. Also, the elderly constitute the largest proportion of patients with symptoms. Furthermore, there is no shortage of such patients—a 2007 UK report estimated that per annum 465 504 patients with symptoms potentially suggestive of colorectal cancer were referred for diagnostic tests [10]. Moreover, the large majority of these patients will ultimately prove to be normal since symptoms potentially suggestive of colorectal cancer are common in the general population. In the UK, government stipulations also require that such patients be examined rapidly. At the time of writing endoscopic capacity is stretched and will be stretched further owing to additional stresses caused by the introduction of national colorectal cancer screening by faecal occult blood testing and flexible sigmoidoscopy. Given all of these factors, a sufficiently accurate and safe alternative to colonoscopy would be most welcome.

Of course, barium enema (BE) is the traditional radiological alternative to colonoscopy. An audit has suggested that BE is less sensitive than colonoscopy for colorectal cancer [11] and there is evidence that patients find BE significantly more unpleasant than the alternatives, including CTC [12]. Nevertheless, BE is well established, relatively cheap and remains widely performed, a large proportion by radiographers. Although the numbers of BE is dwindling, the reality is that the procedure is still commonly performed worldwide, especially in smaller community hospitals. There were an estimated 4.1 million BE procedures worldwide in 2009 [Bracco UK, personal communication]. Supporting this, in 2011 more than 70 000 were performed in England alone [13]. However, few studies have directly compared BE and CTC, and none are randomised [14,15].

The Special Interest Group in Gastrointestinal and Abdominal Radiology (SIGGAR) trials *Design and rationale*

In 2002, the UK Department of Health identified CTC as a potentially viable alternative to both BE and colonoscopy for the diagnosis of colorectal cancer in symptomatic patients and, via the Health Technology

Assessment (HTA) arm of the National Institute for Health Research, asked for expressions of interest from researchers prepared to conduct a study [16]. The HTA stipulated that any study should be a randomised controlled trial (RCT), a design which, at that time, had not been used for CTC research. Within-subject comparisons of CTC and colonoscopy are undoubtedly convenient but introduce a number of unavoidable biases: most obviously, test ordering is fixed, with CTC almost always performed first. A single bowel preparation means that it cannot be optimised for both tests. Most importantly, in such designs, colonoscopy is used as an independent reference standard and therefore, by definition, cannot be “wrong” so it is impossible for the “new” test to perform better than the “reference”, even if this is the case. Perversely, if the new test is in reality more accurate than the reference standard, then its comparative performance in a research study actually diminishes.

Attempts to overcome this anomaly have been made by performing an initial colonoscopy of each colonic segment, recording the findings and then repeating the examination in the light of information disclosed from the prior CTC, so called “segmental unblinding” [17]. This procedure creates an “enhanced” reference standard against which CTC and the initial “unenanced” colonoscopy can both be compared. However, although it is superior to conventional designs, it is relevant to consider how effectively a colonoscopist will search for an abnormality that CTC suggests he or she has just missed [18]. There may also be factors intrinsic to colonoscopy that mean a lesion is simply very difficult to detect using this method (*e.g.* lying close behind a fold or in a tortuous segment). Because patients may have multiple abnormalities in multiple colonic segments, within-subject designs have also relied upon matching abnormalities detected by CTC with those detected at subsequent colonoscopy. In order to be reasonably sure that a lesion seen at colonoscopy is the same lesion seen previously at CTC, matching has generally depended upon lesions being in the same or adjacent colonic segment, and of a similar diameter to those seen at colonoscopy. However, it is well established that colonoscopy is frequently inaccurate when called upon to identify colonic location precisely [19], probably more so than CTC, and colonoscopy is also likely to be less accurate than CTC when estimating the maximal lesion diameter [20]. It is therefore likely that

CTC will be penalised by a relatively weak reference standard. To make matters worse, if, for example, a true-positive polyp detected by CTC is not found at subsequent colonoscopy owing to a size or location mismatch, then the result is not only a false-positive polyp by CTC but also an additional false-negative polyp because the lesion seen at colonoscopy was apparently not detected by CTC, a “double whammy” [21]!

Randomisation eliminates these biases because patients are allocated either one test or another purely by chance. Instead of comparing the results of both tests in each patient, detection rates and ultimate diagnostic outcomes for both groups overall are compared. Randomisation also has additional advantages: perhaps most importantly, it allows the clinical trajectory of a patient subsequent to the test result to be observed exactly as would happen in everyday clinical practice. In contrast to within-subject same-day comparisons, in daily practice it is not usual to request two tests simultaneously in each patient—further tests are only requested when there is an issue with the first, be it technical inadequacy or lack of clinical confidence in the result. If patients have two tests simultaneously, their subsequent trajectory is a conjecture based on predicting what would most probably have happened had the result of only one test been known. Such a conjecture confounds assessment of how a new test performs in “real life” and is especially problematic for economic assessments that rely on collecting information on all healthcare resource consumption downstream of the initial test.

Of course RCTs also have disadvantages. Because each patient is allocated only one test, large numbers of subjects are required to achieve adequate statistical power. Any study whose primary or secondary outcome is a comparison of detection rates by two tests will need sufficient patients with the target condition, colorectal cancer in this case. Surprisingly, colorectal cancer is relatively uncommon in patients with symptoms suggestive of the disease because such symptoms, for example abdominal pain or change in bowel habit, are very common in the general population; a study that recruited 1 million patients would have no power if none of the patients had cancer. One way to partially overcome this is to include lesions that are surrogates for cancer, such as polyps measuring ≥ 1 cm in diameter. It is also known that patients referred for BE

examination to exclude cancer are generally perceived by the referring clinician as being at lower risk than those referred for colonoscopy. Therefore, because BE and colonoscopy are not equivalent in daily practice, a three-way randomisation between CTC and BE and colonoscopy would be very unlikely to recruit sufficient subjects.

The author and colleagues therefore proposed two parallel RCTs: CTC vs BE and CTC vs colonoscopy, with a randomisation ratio of 2:1 in favour of the standard test so as not to overwhelm CT services [22]. The primary outcome for the CTC vs BE trial was detection rates of colorectal cancer and large polyps (≥ 1 cm). However, because a systematic review had suggested that colonoscopy and CTC were equivalent for diagnosis of colorectal cancer [6], a non-inferiority comparison of the two tests based on detection rates would require tens of thousands of patients. Assuming the tests are equivalent for detection, then utility will turn on other issues. A major issue for CTC is that subsequent colonoscopy and biopsy is usually required to further investigate any cancer detected. The benefits of avoiding an endoscopic examination are negated if CTC precipitates large numbers of unnecessary colonoscopy. At the same time, colonoscopy is likely to be more difficult (and incomplete) in older symptomatic patients than CTC, and this itself will precipitate further investigation of the colon. For these reasons, the authors proposed an RCT of CTC vs colonoscopy that was powered on the requirement for additional colonic tests following the randomised procedure [22]. In order to identify patients false-negative by any assigned test who were discharged from the trial, we proposed to obtain cancer diagnoses (both intra- and extracolonic) for the trial cohort via the National Health Service (NHS) Information Centre. The HTA funded the proposal [16] and the trials were registered (International Standard Randomized Controlled Trial Number 95152621).

Recruitment and procedures

The trials identified 8484 potential patients between March 2004 and December 2007 in 21 NHS hospitals [23,24]. After exclusions and dropouts, 3804 patients were analysed for the CTC vs BE trial (1277 having CTC and 2527 having BE) and 1580 for the CTC vs colonoscopy trial (533 having CTC and 1047 having colonoscopy) (Figure 2). There were 217 endoscopists/surgeons and 82 radiologists/reporting radiographers.

Figure 2. CONSORT diagram showing patient flow through the two randomised trials. BE, barium enema; csy, colonoscopy; CTC, CT colonography.

CTC was performed using multidetector row machines and in accordance with international guidelines on best practice [25]. Serious adverse events were rare for all procedures.

Detection rates

Via an intention-to-treat, per-person analysis, CTC detected significantly more cancers or large polyps than did BE, 93 (7.3%) in 1277 vs 141 (5.6%) in 2527; $p=0.0390$. Furthermore, CTC missed fewer cancers during the 3-year follow-up; 3 of 45 vs 12 of 85. In the colonoscopy trial, there was no significant difference in detection rates between procedures, 119 (11.4%) in 1047 vs 57 (10.7%) in 533; $p=0.69$. CTC missed 1 of 29 colorectal cancers and colonoscopy missed none (of 55).

Need for additional tests

As explained in the sections above, the primary outcome measure for the CTC vs colonoscopy trial was not detection rates, rather it was the rate of additional colonic investigation in the two arms: 160 (30.0%) patients in the CTC group had additional colonic investigation compared with 86 (8.2%, $p<0.0001$) in the colonoscopy

group. 118 (11.3%) patients had an incomplete colonoscopy, with 72 (6.9%) of these having an additional procedure for this reason. Most other additional procedures following colonoscopy were repeats owing to inadequate histology. By comparison, although 83 patients (15.6%) in the CTC group were referred to investigate a suspected cancer or large polyp, 49 (9.2%) were referred for smaller polyps and 28 (5.3%) because of clinical uncertainty. No cancers and just four polyps ≥ 1 cm were found in these 77 patients, *i.e.* the yield for clinically important lesions was low.

Interestingly, relative referral rates differed significantly between males and females, with males more than six times as likely to have an additional colonic examination after CTC than after colonoscopy, whereas females were just over twice as likely to do so.

Extracolonic findings

Both patients and their doctors often perceive the ability of CTC to identify extracolonic pathology as advantageous but it is uncertain whether this is ultimately beneficial. It is well established that patients

may undergo follow-up tests, with attendant inconvenience, distress and cost to clarify the nature of incidental extracolonic findings that may ultimately prove to be unimportant. In the two trials overall, at least one previously unknown extracolonic finding was diagnosed by CTC in 960 (58.6%) of 1639 patients who did not have colorectal cancer at the time of discharge. 135 (8.2%) were referred for additional investigations and 22 (1.6%) ultimately diagnosed with an extracolonic malignancy. Of the 135 referred for additional investigations, 48 (35.6%) received a diagnosis that explained their presenting symptoms. Compared with population rates, the rate of diagnosis for primary extracolonic cancers was twice as high as expected during the three years after randomisation. However, although this could be anticipated for patients having CTC, surprisingly it also applied to patients having BE or colonoscopy, *i.e.* there was no difference in rates between the arms of each individual trial. This finding is counter-intuitive and implies strongly that patients investigated using colonoscopy or BE initially are also having CT scanning subsequently within three years of their initial presentation.

Health psychology

To capture psychological reactions to the tests, patients completed a questionnaire the day after their procedure, which investigated acceptability using 29 individual items on a 7-point scale. Satisfaction, worry and discomfort during the test and over the subsequent 24 h were assessed. For the colonoscopy trial, a further questionnaire was administered at the third month to assess whether patients were ultimately satisfied with their diagnostic episode. This included satisfaction with the way results were conveyed and reactions to follow-up testing.

Patients undergoing BE were significantly less satisfied and experienced more physical discomfort than those undergoing CTC [26]. They were also significantly more likely to experience a range of post-procedural side effects. Patients undergoing colonoscopy were significantly less satisfied and more worried than those undergoing CTC [27] and also experienced more physical discomfort and adverse events. However, at 3 months, they were more satisfied with how their results were received. Surprisingly, patients did not seem to mind follow-up testing significantly.

Health economics

There are many existing models that attempt to estimate which test or combination of tests is cost-effective for diagnosis of colorectal cancer [28]. Models vary in their complexity and most researchers populate their model with estimates derived from the available medical literature. These estimates often vary widely, depending on the primary study chosen, or, sometimes, the information is simply unavailable. There is no doubt that the most accurate estimates are those observed in “real life”, and so a large RCT is the ideal platform from which to obtain estimates to populate a model that extrapolates data into the future, beyond the time horizon of the trial. Also, the vast majority of existing economic models focuses on screening rather than symptomatic patients.

For each individual patient randomised, we identified the allocated procedure and determined its unit cost using the NHS reference costs 2010–11. We also noted all consumables used (*e.g.* Buscopan, materials for biopsy). We then identified all subsequent clinical activity downstream of the initial test (*e.g.* outpatient visits, further tests, surgery, hospital stay) and aggregated these individual costs to derive a total cost per patient. We then calculated the cost per cancer or large polyp detected and compared costs for the tests used in the two trials.

Owing to downstream costs, total costs were approximately three times unit costs: total average costs for BE were £444 *vs* £512 for CTC. Total costs for colonoscopy were £651 *vs* £627 for CTC (patients in the colonoscopy trial had a greater prevalence of abnormality, accounting for increased procedural and downstream costs). Incremental cost-effectiveness per significant lesion detected by CTC compared with BE was £3952 and £21 333 per cancer. Because CTC detected significantly more clinically important colorectal lesions than BE, we assumed that CTC might save lives in the long term and evaluated this via a Markov modelling framework over the patients’ lifetimes [29]. This estimated an incremental cost per life year gained by CTC *vs* BE of £3486, a figure well within the National Institute for Health and Clinical Excellence threshold of £20 000–£30 000.

Interpretation and implications for practice

For their purposes, most medical practitioners will focus on how well CTC detects cancer and clinically important

polyps. We found that CTC detects significantly more cancers and large polyps than BE and misses fewer cancers. It is difficult to defend pursuing BE, especially at a time when enthusiasm to report BE is dwindling as is the ability to report the procedure competently [30]. This conclusion is underscored by the fact that we also found BE to be less cost-effective than CTC, both within and beyond the trial time horizon, and patients found it particularly unacceptable compared with other procedures. Indeed, upon learning of our result the NHS Bowel Cancer Screening Programme immediately suggested that centres discontinue BE in favour of CTC for those patients requiring a radiological examination [31]. Considering service delivery, health-care providers will need to manage a transition from BE to CTC or colonoscopy. Given the current pressures on endoscopic services owing to various cancer-awareness initiatives and the NHS Bowel Cancer Screening Programme, it seems most likely that CTC rather than colonoscopic capacity will need to increase, especially since hospitals will need to provide a non-invasive alternative for patients in whom colonoscopy is contraindicated.

The situation between CTC and colonoscopy is less clear-cut. Both tests appear to be similarly sensitive for cancer and clinically important polyps in symptomatic patients. Although patients prefer CTC in the short term, in the longer term they are more satisfied with the way results are conveyed following colonoscopy, *i.e.* quicker and face to face. Total costs appear finely balanced between colonoscopy and CTC despite the accrual of downstream costs after CTC owing to further testing. We believe that cost-effectiveness gains resulting from detection of extracolonic lesions will be the deciding factor: we estimated that CTC would be cost-effective compared with colonoscopy if detection of extracolonic cancer resulted in 1 life year gained for every 2000 CTC examinations, *i.e.* 1 life saved per 26 extracolonic tumours detected [29]. Benefits increase further if detection of significant aortic aneurysms is also considered. As noted in the sections above, we found indirect evidence that patients having BE or colonoscopy ultimately have abdominopelvic CT scanning within three years of their initial test, presumably because colorectal cancer has been excluded but symptoms persist. Clearly, this adds to the downstream costs of patients having colonoscopy considerably and may tip the balance in favour of CTC if true; more

research is needed to estimate the extent to which this happens.

At the same time, the costs of CTC could be reduced further. The pragmatic nature of the trials meant that patients' clinical trajectories closely mimicked real practice outside of a trial. A striking finding in the colonoscopy trial was the high rate of referral following CTC. 30% of patients had further testing but only 11% had a cancer or large polyp so the majority did not need subsequent endoscopy. Especially notable were referrals for either small polyps or clinical uncertainty, referrals that yielded few significant lesions. Limiting onward referral to those patients with suspected important pathology alone would have reduced the referral rate significantly and enhanced cost-effectiveness. It is clear that the radiological community needs to develop guidelines that stipulate who should and should not be referred for endoscopy following CTC. It is important to bear in mind at all times that these patients are symptomatic and that 6-mm polyps etc. do not cause symptoms nor are they likely to be important.

Ensuring that CTC is performed and interpreted to the very highest standards should also reduce unnecessary referrals. The standard of UK colonoscopy has soared as a consequence of quality assurance introduced to support the NHS Bowel Cancer Screening Programme—we observed a colonoscopic failure rate of 11%, half the figure we anticipated. Achieving similar improvements for CTC augers against allowing “general” radiologists to report CTC, just as “general physicians” do not perform colonoscopy. We used subspecialists in gastrointestinal radiology since they are the group best able to report CTC in everyday practice. Ongoing specific training, audits and perhaps accreditation will be necessary. There is also a current trend towards non- or reduced-purgation CTC, which has been shown to increase compliance with screening programmes [32]. However, compliance is not an issue for symptomatic patients. Rather, sensitivity for cancer is the prime aim. Qualitative research has shown that patients value sensitivity over all other factors and are quite prepared to accept some discomfort in order to maximise diagnostic accuracy [33]. Unnecessary referrals are likely to be reduced by adopting faecal tagging (to increase specificity) in association with full bowel purgation to increase diagnostic confidence. At the present time, it seems that either CTC or colonoscopy

could be offered to symptomatic patients where the local expertise to perform and interpret CTC exists.

Which patients should be offered CTC? CTC was associated with the fewest adverse events during the test and over the next 24 h so could be offered to patients who are particularly cautious of colonoscopy, although it should be noted that serious adverse events were rare for all three procedures. We found that males were significantly more likely than females to need further testing following CTC, both because they had more adenomas and because females were more likely to have an incomplete colonoscopy, a finding noted in other unrandomised studies [34]. Perhaps CTC is an appropriate first choice in symptomatic females?

SUMMARY

The paper has described the rationale for using CTC to detect colorectal cancer in symptomatic patients and has described findings from two large randomised trials, the only such trials performed in symptomatic patients at the time of writing. The author argues for the use of CTC to investigate patients with symptoms potentially suggestive of colorectal cancer, stating that CTC is now proven to be a sensitive, acceptable and equally cost-effective alternative to colonoscopy when the latter is contraindicated or undesirable. At the same time, BE should be abandoned as soon as local resources and expertise allow replacement by CTC. Evidence-based guidelines for the onward referral of patients following CTC are needed as are facilities to train gastrointestinal and abdominal radiologists in its interpretation. Further research is also needed to clarify the rate with which CT scanning is used in

symptomatic patients in whom endoscopy has been negative, since this could alter estimates of cost-effectiveness substantially.

Lastly, it should be noted that clinical trials such as SIGGAR are difficult but studies need to be large and methodologically sound in order to have scientific credibility and achieve funding in the current climate. The SIGGAR trials are an example of what is possible when research-interested NHS radiologists combine with researchers across a variety of disciplines. Such multicentre studies offer NHS radiologists the chance to participate in high-quality research at a time when it is very difficult for individual clinicians to access the considerable time, expertise and resources necessary for publication, and are to be encouraged.

ACKNOWLEDGMENTS

The author is grateful to all of the participating radiologists/radiographers, surgeons/endoscopists, local administrators, independent steering committees, his research collaborators, companies which donated equipment (Medicsight, Barco, Bracco, Viatronix), and ultimately the patients who agreed to participate in the SIGGAR trials. He is particularly indebted to Professor Wendy Atkin, who was his co-principal investigator, and her hardworking team. He is grateful to the National Institute for Health Research Health Technology Assessment programme for funding (NIHR HTA 02/02/01) and is also supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. The views and opinions expressed in this article are those of the author and do not necessarily reflect those of the Department of Health.

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