Gastroenterology 2015;149:89–101

Identification of Extracolonic Pathologies by Computed Tomographic Colonography in Colorectal Cancer Symptomatic Patients

Steve Halligan,[1] Katherine Wooldrage,[2] Edward Dadswell,[2] Urvi Shah,[2] Ines Kralj-Hans,[2] Christian von Wagner,[1] Omar Faiz,[2] Julian Teare,[2] Rob Edwards,[3] Clive Kay,[4] Guiqing Yao,[5] Richard J. Lilford,[6] Dion Morton,[7] Jane Wardle,[1] and Wendy Atkin,[2] for the SIGGAR Investigators

[1]*University College London, London, United Kingdom;* [2]*Imperial College London, London, United Kingdom;* [3]*Queen Mary University of London, London, United Kingdom;* [4]*Bradford Teaching Hospitals National Health Service Foundation Trust, Bradford, United Kingdom;* [5]*University of Southampton, Southampton, United Kingdom;* [6]*University of Warwick, Warwick, United Kingdom;* [7]*University of Birmingham, Birmingham, United Kingdom*

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This article has an accompanying continuing medical education activity on page e15. Learning Objective: Upon completion of this test, successful learners will be able to discuss the frequency and location of extra-colonic findings after CT colonography, identify extra-colonic findings seen most commonly in presence of colon cancer, and review different categories of E-RADS classification for extra-colonic findings on CT colonography.

BACKGROUND & AIMS: Symptoms suggestive of colorectal cancer may originate outside the colorectum. Computed tomographic colonography (CTC) is used to examine the colorectum and abdominopelvic organs simultaneously. We performed a prospective randomized controlled trial to quantify the frequency, nature, and consequences of extracolonic findings. **METHODS:** We studied 5384 patients from 21 UK National Health Service hospitals referred by their family doctor for the investigation of colorectal cancer symptoms from March 2004 through December 2007. The patients were assigned randomly 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 1 and 3 years after testing 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 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 in 33 patients analyzed by CTC (2.8%). CTC identified 72 extracolonic neoplasms, however, barium enema analysis found only 3 (colonoscopy found none). Overall, CTC diagnosed extracolonic neoplasms in 72 of 1634 patients (4.4%); 26 of these were malignant (1.6%). There were significantly more extracolonic malignancies detected than expected 1 year after examination, but these did not differ between patients evaluated by CTC (22.2/1000 person-years), barium enema (26.5/1000 person-years; $P = .43$), or colonoscopy (32.0/1000 person-years; $P = .88$). **CONCLUSIONS:** More than half of the 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. International Standard Randomised Controlled Trials no: 95152621.isrctn.com.

Keywords: Detection; Diagnostic; Digestive System; Colon Cancer.

Symptoms suggestive of colorectal cancer are common and nonspecific, and may originate from pathology outside the large bowel.[1] Patients often are 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 abdominopelvic organs. However, it is uncertain whether detection of extracolonic pathology ultimately is beneficial. Although undoubtedly important in some patients, in other patients extracolonic findings can precipitate investigations that are costly, increase morbidity and anxiety, and ultimately are 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] A systematic review of 24 studies estimated false-positive diagnoses of extracolonic malignancy by CTC in 4.6% of men and in 6.8% of women.[4]

The clinical impact of extracolonic findings at CTC has been assessed most often retrospectively,[5–7] and the

Abbreviations used in this paper: **BE, barium enema; CI, confidence interval; CTC, computed tomographic colonography; GBP, Great British Pounds; IRR, incidence rate ratio; NHS, National Health Service.**

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2015.03.011

largest studies have investigated asymptomatic individuals being screened for colorectal cancer.[8,9] In a systematic review we 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 vs colonoscopy or BE. The detection rates for intracolonic pathology have been 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 investigations, and the ultimate clinical outcome.

Methods

Study Design and Participants

The protocol for these multicenter randomized trials has been published previously[13] and can be found online (http://www.hta.ac.uk/project/1366.asp). The trial is registered as follows: International Standard Randomised Controlled Trials Number 95152621 (available: 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 the 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 undergone 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 by colonoscopy or BE (the default examinations). We created 2 parallel trials and, within each trial, patients were assigned randomly 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 provided informed written consent.

Randomization and Masking

We used a randomization ratio of 2:1 to undergo either the default examination (BE or colonoscopy) or CTC. A statistician (R.E.) generated the randomization codes at a remote site, and codes were concealed until interventions were assigned. Randomization was performed centrally by computer random number generation, in blocks of 6, stratified by center 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, 4 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 2-dimensional and/or 3-dimensional visualization as preferred; the minimum requirement was primary 2-dimensional analysis with volume or surface rendering for problem solving. The reading platform depended on local preference, as did use of intravenous contrast and fecal tagging agents. Computer-assisted detection was available. Forty-five radiologists subspecializing 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 performed 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 cecum, supplemented by overcouch decubitus films.[15] A total of 217 gastroenterologists or colorectal surgeons performed the colonoscopies.[11]

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 it was relevant/irrelevant to the clinical situation. Referrals for additional investigation after 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 polyps ($\geq$10 mm), and the primary outcome 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 prespecified 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 (E.D.) extracted references to extracolonic pathology from procedure reports into a database. Each extracolonic finding then was assigned an E-RADS score[16] by a radiologist (S.H.) who had been blinded to the subtrial, reporting radiologist, center, 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 characterized; and E4, potentially important.[16] A data manager coded the final diagnosis using the International Classification of Diseases, 10th revision, classification. An expert panel consisting of a radiologist (S.H.), gastroenterologist (J.T.), and colorectal surgeon (O.F.) reviewed extracolonic diagnoses independently to establish whether these could have explained