Is whole-colon investigation by colonoscopy, computerised tomography colonography or barium enema necessary for all patients with colorectal cancer symptoms, and for which patients would flexible sigmoidoscopy suffice? A retrospective cohort study

Wendy Atkin,[1]* Kate Wooldrage,[1] Urvi Shah,[1] Kate Skinner,[1] Jeremy P Brown,[1] Willie Hamilton,[2] Ines Kralj-Hans,[1] Michael R Thompson,[3] Karen G Flashman,[3] Steve Halligan,[4] Siwan Thomas-Gibson,[1,5] Margaret Vance[5] and Amanda J Cross[1]

[1]Department of Surgery and Cancer, Imperial College London, London, UK
[2]Institute of Health Research, University of Exeter Medical School, Exeter, UK
[3]Department of Colorectal Surgery, Queen Alexandra Hospital, Portsmouth Hospitals NHS Trust, Portsmouth, UK
[4]University College London Centre for Medical Imaging, University College London, London, UK
[5]Wolfson Unit for Endoscopy, St Mark's Hospital, London, UK

*Corresponding author w.atkin@imperial.ac.uk

Declared competing interests of authors: Wendy Atkin reports grants from Cancer Research UK during the conduct of the study and from the National Institute for Health Research Health Technology Assessment programme for being a coprincipal investigator for study reference 02/02/01 [Halligan S, Dadswell E, Wooldrage K, Wardle J, von Wagner C, Lilford R, *et al.* Computed tomographic colonography compared with colonoscopy or barium enema for diagnosis of colorectal cancer in older symptomatic patients: two multicentre randomised trials with economic evaluation (the SIGGAR trials). *Health Technol Assess* 2015;**19**(54)], on which the current study is based. Steve Halligan also reports grants from the National Institute for Health Research Health Technology Assessment programme for being a coprincipal investigator for study reference 02/02/01, on which the current study is based.

Published November 2017
DOI: 10.3310/hta21660

Scientific summary

WCI, CT colonography or barium enema for CRC symptoms

Health Technology Assessment 2017; Vol. 21: No. 66
DOI: 10.3310/hta21660

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

With > 40,000 new diagnoses in the UK each year and an annual NHS expenditure of > £1B, to which diagnostic investigations are the single largest contributor, colorectal cancer (CRC) is a health priority area. The presenting features known to be associated with CRC are typically vague, and diagnostic yields for investigations are often low. It is current clinical practice to examine the whole large bowel when CRC is suspected in symptomatic patients because of the perceived risk of missing a cancer in the proximal colon when only the distal colorectum is examined by flexible sigmoidoscopy (FS). This is despite evidence of low predictive values of certain CRC symptoms for proximal cancer and the risks/disadvantages of whole-colon investigations (WCIs). In a single-centre study in Portsmouth, England, of 16,433 patients with suspected CRC, > 95% of cancers were detected by FS in patients found not to have iron deficiency anaemia (IDA) or an abdominal mass. This study, and others, suggested that an examination of the distal colorectum by FS is adequate for the majority of patients with distal features of this disease. Further assessment is required of CRC diagnostic yields in the proximal and distal colorectum by presenting features in the wider secondary care population, along with assessment of the diagnostic accuracy of FS for CRC in patients presenting with distal features. This information could be used to inform national guidelines and clinical practice to optimise diagnostic investigations for suspected CRC.

Objectives

The primary research objective is to:

- investigate the link between symptoms at presentation and proximal colon cancer risk, and provide evidence of whether or not FS is a clinically effective alternative to WCI in patients whose symptoms do not suggest proximal disease.

The secondary research objectives are to:

- determine the diagnostic miss rate of FS for cancers in the colon and rectum
- determine the prevalence of proximal and distal CRC in patients referred to hospital with symptoms suggestive of CRC.

Methods

The Symptoms of Colorectal Cancer Evaluation Research (SOCCER) study was proposed as an additional analysis of data collected for the Special Interest Group in Gastrointestinal and Abdominal Radiology (SIGGAR) randomised controlled trials [Halligan S, Dadswell E, Wooldrage K, Wardle J, von Wagner C, Lilford R, *et al.* Computed tomographic colonography compared with colonoscopy or barium enema for diagnosis of colorectal cancer in older symptomatic patients: two multicentre randomised trials with economic evaluation (the SIGGAR trials). *Health Technol Assess* 2015;**19**(54)]. These trials investigated the clinical effectiveness and cost-effectiveness of computerised tomography colonography compared with colonoscopy or barium enema in the diagnosis of CRC and significant polyps (≥ 10 mm). During the SIGGAR trials, all symptoms/clinical signs at referral were recorded at eligibility assessment. Potentially eligible patients were those experiencing symptoms suggestive of CRC, aged ≥ 55 years, clinically judged to need a WCI, judged as fit to undergo full bowel preparation and able to give informed consent. Patients were identified from outpatient clinics and endoscopy and radiology procedural lists, and included

suspected cancer 2-week-wait, urgent and routine referrals. Consenting eligible patients were randomised during the SIGGAR trials. To enhance the generalisability of the SOCCER study findings to the broader secondary care population, patients who had been assessed as potentially eligible for SIGGAR were included in the SOCCER study, whether or not they had been randomised.

Baseline symptoms, referral pathways and planned investigations for all patients were recorded during the SIGGAR eligibility assessment on bespoke pro formas, and this information was transferred to a SOCCER study database for analysis. Additional information to supplement that collected at baseline during the SIGGAR trials that pertained to symptoms and CRC diagnoses was collected from SIGGAR trial reports and hospital endoscopy, radiology, surgery and pathology records.

For patients for whom blood test data were available, anaemia/IDA was defined as laboratory-confirmed anaemia/IDA within 6 months before and 3 months after the date of referral. For patients with a diagnosis of CRC, blood tests dated on or after the date of diagnosis were excluded. Blood test parameters [haemoglobin (Hb) level (g/dl), mean corpuscular volume (MCV; fl) and serum ferritin (µg/l)] were collected from hospital haematology databases. When multiple results were available for a patient, the lowest recorded values were selected. We considered four different definitions of anaemia: broad anaemia, strict anaemia, broad IDA and strict IDA. Broad anaemia was defined solely by Hb level: < 13 g/dl in males and < 12 g/dl in females. Strict anaemia was defined as a Hb level of < 11 g/dl in males and < 10 g/dl in females, or as a Hb level of ≥ 11 g/dl but < 13 g/dl in males or ≥ 10 g/dl but < 12 g/dl in females accompanied by microcytosis (MCV < 80 fl) or low ferritin (< 20 µg/l). Broad IDA was defined as a Hb level of < 13 g/dl in males and < 12 g/dl in females accompanied by microcytosis (MCV < 80 fl) or low ferritin (< 20 µg/l). Strict IDA was defined as a Hb level of < 13 g/dl in males and < 12 g/dl in females accompanied by low ferritin (< 20 µg/l). For patients without blood test data, anaemia was defined by its inclusion on the SIGGAR trial pro forma.

The diagnostic accuracy of symptoms/clinical signs at presentation for site of cancer (proximal vs. distal) was estimated from CRC diagnoses up to 3 years post referral. Cancer diagnoses were obtained from registries via the Health and Social Care Information Centre (HSCIC) and hospital records. Cancers were classified as 'distal' if they were located in the anus, rectum, sigmoid colon or descending colon. Cancers located at colonic sites proximal to the descending colon were classed as 'proximal'. The sensitivities, diagnostic yields and numbers that needed to be examined to diagnose one cancer by presenting features were calculated for proximal and distal cancers. FS miss rates by clinical features for CRC were calculated in patients examined by FS at referral. The results were presented as percentages with 95% binomial exact confidence intervals.

Results

During the SIGGAR trials, 8484 patients with symptoms suggestive of CRC were registered as potentially eligible. For the purposes of the SOCCER study, 1104 patients were excluded prior to analysis: 936 who dissented to the use of their data in future research, 75 who were judged by a clinician as unable to provide informed consent for the use of their data in future research, 27 for whom no symptoms/clinical signs were recorded at presentation, 10 who had duplicate study records and 56 patients who could not be traced through the HSCIC. The final SOCCER cohort analysed comprised 7380 patients (4353 women; 59%). The median age of the cohort was 69 years (interquartile range 62–76 years). The majority of patients were referred via colorectal surgical outpatient clinics (84.5%) and under the suspected cancer 2-week wait pathway (53.9%). We obtained laboratory-confirmed anaemia status for 4741 (64.2%) patients. There were some differences between the patient cohorts with and without blood test data. The patients with blood test data were slightly older ($p < 0.001$), less likely to be referred via a colorectal outpatient clinic ($p < 0.001$) and more likely to be 2-week wait referrals ($p < 0.001$). Patients with blood test data were also more likely to present with weight loss ($p < 0.001$) and less likely to present with rectal bleeding ($p < 0.001$). In the cohort overall, 551 patients were diagnosed with CRC. Overall, the majority of these patients ($n = 429$, 77.9%) had distal cancer. Distal cancer was less common in the cohort with blood test data (5.1% vs. 7.2% in the cohort without blood test data; $p < 0.001$), whereas proximal cancer was

more common in the cohort with blood test data (2.0% vs. 1.2% in the cohort without blood test data; $p = 0.007$).

Clinical features at referral

In the cohort overall ($n = 7380$), a change in bowel habit (CIBH) and rectal bleeding were the most frequently presenting symptoms. Over 72% ($n = 5382$) of patients presented with a symptom profile including a CIBH and more than one-third of patients (37.6%) presented with rectal bleeding.

Rectal bleeding and rectal mass were more common in patients without blood test data (42.2% and 3.2%, respectively) than in those with blood test data (35.0% and 1.7%, respectively; both $p < 0.001$).

Among 4741 patients with blood test data, the proportions with laboratory-confirmed anaemia depended on the definition of anaemia. Using the broadest definition, 35.0% ($n = 1659$) of patients were anaemic, whereas 12.0% ($n = 567$) of patients presented with broad-definition IDA and 6.7% ($n = 318$) presented with strict-definition IDA. Some clinical features, such as abdominal pain, abdominal mass and a CIBH (except to harder stools and/or less frequent defecation), were more common in women ($p \leq 0.03$), whereas more men than women presented with rectal bleeding ($p < 0.001$) or anaemia ($p < 0.001$). The prevalence of rectal bleeding was lower in older than in younger men (27.8% vs. 44.5%) and higher in men than in women (22.8% vs. 37.8%). By contrast, anaemia was substantially more common in older than in younger men (73.3% vs. 23.8%) and more common in men than women (57.2% vs. 18.6%) for the broad definition of anaemia. Similar trends for anaemia by age were observed irrespective of the anaemia definition.

Sensitivity of clinical features for distal and proximal cancers

The sensitivity of any symptom for distal cancer was highest for a CIBH (72%), either in combination with other symptoms or as an isolated symptom. A CIBH was more sensitive for distal than for proximal cancer (71.7% vs. 54.2%; $p = 0.002$). The sensitivity of rectal bleeding for distal cancer was 64.2%, which was approximately three times higher than for proximal cancer (20.8%; $p < 0.001$). Anaemia was the most sensitive feature for proximal cancer and was more sensitive for proximal than for distal cancer ($p < 0.001$). More than 80% of patients with proximal cancer presented with a symptom profile including anaemia (by the broadest definition).

We examined the most common features (a CIBH, rectal bleeding and anaemia) in further detail in the full cohort of 7380 patients. Overall, 91% of 321 patients diagnosed with cancer who presented without anaemia or an abdominal mass had distal cancer. Of the patients without anaemia or an abdominal mass, 94% (221/234) of those diagnosed with cancer who presented with rectal bleeding had distal tumours. Of patients without anaemia, abdominal mass or rectal bleeding, who presented with a CIBH to looser and/or more frequent stools and were diagnosed with cancer, 100% (15/15) had distal cancer.

Diagnostic yields of clinical features for distal and proximal cancers

Anaemia and abdominal mass were highly predictive of both proximal and distal cancers. In the full cohort of 7380 patients, 2021 patients had either anaemia or an abdominal mass. These clinical features resulted in diagnostic yields of 4.8% for proximal cancer and 6.7% for distal cancer. No other feature exhibited proximal cancer diagnostic yields of more than approximately 1% and the number of patients that needed to be examined to diagnose one proximal cancer in patients without anaemia or an abdominal mass ranged from 75 to 293. Distal cancer diagnostic yields were generally higher than proximal cancer diagnostic yields, which was reflected in the lower numbers needed to be examined to diagnose one distal cancer (range 6–121). More than 1 in 14 patients with rectal bleeding alone (yield 7.5%) or rectal bleeding with a CIBH (yield 11.6%) were diagnosed with distal cancer. The findings were similar in the cohort who had blood test data available.

Flexible sigmoidoscopy examinations and cancer miss rates

Out of the 7380 patients, 20% ($n = 1483$) received a FS examination at referral. Patients examined by FS were more likely to present with rectal bleeding (41.3% vs. 36.6%; $p = 0.001$), abdominal pain (32.1% vs. 28.0%; $p = 0.002$) or rectal mass (3.2% vs. 2.0%; $p = 0.007$). Anaemia was more likely to be reported in the cohort without a FS examination ($p < 0.001$). Proportionately more cancers were diagnosed in patients examined by FS than in patients not examined by FS (9.6% vs. 6.9%; $p < 0.001$). Proportionately more patients examined by FS than not examined by FS were diagnosed with distal cancer (7.6% vs. 5.4%; $p = 0.0014$), but the rates of proximal cancer were not significantly different between these subgroups ($p = 0.22$). Over 78% ($n = 112$) of the 142 patients examined by FS and subsequently diagnosed with cancer had distal tumours; 101 (90.2%) of these patients had cancer identified at FS and only 11 patients were subsequently diagnosed with distal cancer when cancer had not been identified at FS. Of these 11 patients, only three had 'complete and normal FS'; the remainder had other findings at FS ($n = 2$) or incomplete FS ($n = 6$). In the FS group, 31 patients were subsequently diagnosed with proximal cancer and, of these, 22 (71.0%) were patients who had a 'complete and normal' FS.

In 493 patients who presented with rectal bleeding without anaemia or an abdominal mass, 94.5% ($n = 69$) of the 73 distal cancers were identified at FS. Of the three patients in this subset diagnosed with proximal cancer, two had findings at FS that might have warranted a WCI (in one patient cancer was identified at FS and in one patient three or more lesions were detected). A total of 578 patients presented with a CIBH without anaemia, an abdominal mass or rectal bleeding, 18 of whom were diagnosed with cancer. Only three patients examined by FS who presented with a CIBH were diagnosed with proximal cancer, none of whom had a CIBH to looser and/or more frequent stools. In patients presenting with anaemia or an abdominal mass ($n = 359$), 78% ($n = 18$) of distal cancers were identified at FS. Only one patient was subsequently diagnosed with distal cancer after a 'complete and normal' FS. However, 25 (52%) out of 48 patients with cancer in this group had a proximal tumour and 19 (76.0%) of these patients had a 'complete and normal' FS.

Conclusions

The diagnostic yield of proximal colon cancer was highest in patients presenting with anaemia or an abdominal mass. The rates of distal CRC were also comparatively high in these patients. By contrast, certain features that were present in a large proportion of patients were associated with relatively low risk of proximal cancer compared with anaemia/abdominal mass. Proximal cancer diagnoses were rare in patients presenting with rectal bleeding or a CIBH to looser and/or more frequent stools, a subgroup that constituted 40% of the total cohort. Our findings now add to the body of evidence supporting recommendations, which have yet to become standard practice, for tailoring diagnostic investigations for suspected CRC based on presenting features. As diagnostics is the single largest contributor to the £1.1B NHS cost associated with CRC, a cost-effectiveness analysis of symptom-based tailoring of diagnostic investigations for suspected CRC is recommended.

Trial registration

This trial is registered as ISRCTN95152621.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.236

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

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 11/136/120. The contractual start date was in June 2013. The draft report began editorial review in April 2016 and was accepted for publication in August 2016. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).