POST-IMAGING COLORECTAL CANCER OR INTERVAL CANCER RATES AFTER COMPUTED TOMOGRAPHIC COLONOGRAPHY: A SYSTEMATIC REVIEW AND META-ANALYSIS

AUTHORS AND INSTITUTIONS:

Anu E Obaro FRCR*[1,2]

Andrew A Plumb FRCR*[1]

Thomas R Fanshawe PhD[3]

Ulysses S Torres PhD[4]

Rachel Baldwin-Cleland MSc[2]

Professor Stuart A Taylor FRCR[1]

Professor Steve Halligan F Med Sci[1]

David N Burling FRCR[2]

[1]Centre for Medical Imaging, University College London, London, UK

[2]St Mark's Academic Institute, St Mark's Hospital, Harrow, UK

[3]Nuffield Department of Primary Care Health Sciences, Oxford University, Oxford, UK

[4]Grupo Fleury, São Paulo, Brazil

*These authors contributed equally to this work.

CORRESPONDENCE TO:

Dr Andrew Plumb, Centre for Medical Imaging, Podium Level 2, University College London Hospital, 235 Euston Rd, London, NW1 2BU.

SUMMARY

Background: CT colonography (CTC) is highly sensitive for colorectal cancer, but “interval” or post-imaging colorectal cancer (PICRC) rates (diagnosis of cancer after initial negative CTC) are unknown, as are their underlying causes.

Methods: We conducted a systematic review and meta-analysis of post-CTC PICRC rates and causes by searching MEDLINE, EMBASE and the Cochrane Register. We included randomised, cohort, cross-sectional or case-control studies published Jan 1994-Feb 2017, using CTC performed according to international consensus standards with aim of detecting cancer or polyps, and reporting PICRC rates or sufficient data to allow their calculation. Two independent reviewers extracted data from the study reports. We used random-effects meta-analysis to estimate pooled PICRC rates, expressed using (a) total number of cancers and (b) total number of CTC scans as denominators, and (c) per 1000 person-years. Primary study authors provided details of retrospective CTC image review and causes for each PICRC. The study is registered (PROSPERO:CRD42016046838).

Findings: 2977 articles were screened and 12 analysed. These reported 19,867 patients (18-96 years; of 11,590 with sex data available, 6532 (56·4%) female) from March 2002-May 2015. At mean 34 months’ follow-up (range: 3 to 128·4 months), CTC detected 643 cancers and 29 PICRCs were diagnosed. The pooled PICRC rate was 4·42 PICRCs/100 cancers detected; 95%CI 3·03-6·42, corresponding to 1·61 PICRCs/1000 CTCs (95%CI 1·11-2·33) or 0·64 PICRCs/1000 person-years (95%CI 0·44-0·92). Heterogeneity was low (I^2=0%). Over half (17/28, 61%) of PICRCs were due to perceptual error and visible in retrospect.

Interpretation: The 3-year PICRC rate post-CTC is 4·4%, or 0·64 per 1000 person-years, towards the lower end of range reported for colonoscopy. Most arise from perceptual errors. Radiologist training and quality assurance may help reduce PICRC rates.

Funding: St Mark's Hospital Foundation and the UCL/UCLH Biomedical Research Centre.

RESEARCH IN CONTEXT

Evidence before this study:

Prior meta-analysis has shown that CT colonography (CTC) has similar diagnostic sensitivity to colonoscopy for established colorectal cancer (CRC) and approximately 90% sensitivity for large (≥10mm) polyps, since confirmed by a multicentre randomised trial (SIGGAR). However, meta-analyses have also shown that CTC is less sensitive than colonoscopy for small (6-9mm) and diminutive (≤5mm) polyps, and a Dutch randomised trial (COCOS) of CRC screening showed that CTC had significantly poorer detection of high-risk serrated adenomas, which can progress rapidly to CRC. Previous studies of colonoscopy have shown that lower adenoma detection rates are strongly associated with higher rates of subsequent colorectal cancer. This raises the possibility that "interval cancer" or "post-imaging CRC" (PICRC) rates may be correspondingly higher after CTC than colonoscopy, due to these missed lesions. We searched Pubmed for systematic reviews (article type) CT colonography (MeSH term) and found none which dealt with this topic specifically for CTC.

Since CTC is often compared to colonoscopy, to establish a benchmark post-colonoscopy CRC (PCCRC) rate, we also searched Pubmed for "(interval cancer) or (post colonoscopy cancer)" and "colonoscop*), considering articles published in English. We found several large series and a meta-analysis, which reported PCCRC rates ranging from to 2·9 to 8·6% at 36 months of follow-up.

Added value of this study:

We identified 12 studies that reported relevant data, and estimated the pooled PICRC rate 3 years after negative CTC to be 4·4%, comparable to those published for colonoscopy (2·9 to 8·6%). Heterogeneity was low, implying that the literature is consistent. The quality of study reporting was variable, with many studies failing to provide age and sex distribution of the included participants, or details of CTC technique, radiologist expertise and interpretation strategy. PICRC rates were similar at both 3 and 5 years after initial CTC (albeit with limited data for the longer time-point), and they were significantly more likely to be located in the right colon. On review of the underlying causes for

PICRCs, the most common aetiology was perceptual error, with most PICRCs visible in retrospect as either a polyp or mass on the index CTC examination.

Implications of all the available evidence:

Although most radiologists routinely do not report diminutive (≤5mm) polyps at CTC, and it has a lower detection rates of 6-9mm polyps, this does not lead to an excess of post-test cancers relative to colonoscopy within 3-5 years. The low 5-year PICRC rate by meta-analysis confirms that the currently recommended CTC screening interval of 5 years is safe. Since most PICRCs are due to perceptual errors in CTC interpretation, improved radiologist training and quality assurance may help reduce PICRC rates. There is a need for large-scale epidemiological series linking national imaging databases to colorectal cancer registries. Due to the excess in proximal colonic PICRCs, this should particularly focus on detection of right-sided lesions.

INTRODUCTION

Worldwide, over 1·4 million colorectal cancers (CRC) are diagnosed annually[1]. Survival is strongly influenced by disease stage at diagnosis; patients with tumours confined to the bowel wall have over 90% 5-year survival[2]. Most cases of CRC arise from precursor adenomatous polyps[3] or serrated lesions[4], the removal of which reduces future CRC incidence[5]. Therefore, whether precipitated by colorectal symptoms or in a screening programme, colonic investigations can both detect and prevent CRC.

Colonoscopy and computed tomographic colonography (CTC) are commonly-employed whole-colon investigations. CTC comprises high-resolution CT imaging of the gas-distended colon, following cathartics and oral contrast medium to label (“tag”) any residual stool[6]. The test has disseminated rapidly, with approximately 100,000 examinations per annum in England alone[7]. Although both colonoscopy and CTC are highly sensitive for CRC and polyps, neither provides absolute protection against subsequent CRC. These post-test CRCs are termed “interval cancer” in the context of call-recall screening programmes[8], or “post-colonoscopy colorectal cancer (PCCRC)” where no routine interval exists, for example in symptomatic practice[9-13]. The analogous term “post-imaging colorectal cancer” (PICRC) can be applied to CTC.

Missed neoplasia at initial testing likely accounts for over 50% of post-test CRCs[14]; colonoscopists with low adenoma detection rates (ADR), a proxy for examination quality, have correspondingly higher PCCRC rates[15,16]. Although meta-analysis shows CTC and colonoscopy are equally sensitive for detection of established CRC[17], CTC has lower sensitivity for small (6-9mm) and diminutive (≤5mm) polyps; 74% for 6-9mm polyps in one meta-analysis[18]. Furthermore, a recent randomised trial showed that CTC had a significantly lower detection rate than colonoscopy for high-risk serrated lesions[19]; although many serrated lesions are indolent, a subset can progress rapidly to CRC[20]. The impact of such CTC false-negatives on longer-term PICRC incidence is largely unknown presently. Moreover, little is known regarding the time to development of PICRCs, nor their stage, anatomical location, or predisposing factors when they occur. Consequently, clinicians and policy-makers are unable to provide evidence-based recommendations regarding future testing following apparently negative CTC. These data are important, since CTC accounts for over 15% of all whole-colon testing in the UK[7], a figure predicted to rise to nearly 20% by 2020[21].

To address this, we performed a systematic review and meta-analysis to establish the prevalence of PICRC in patients following CTC, in screening and symptomatic settings. We examined the clinical characteristics of PICRCs, and explored factors associated with their occurrence.

METHODS

This report adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[22]. The review is registered (PROSPERO:CRD42016042437) and the protocol publicly-available[23] (https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-017-0432-8).

Search strategy and selection criteria:

We defined CTC as CT scanning of the prepared, gas-distended colon[6]. We defined CTC-detected cancers in component primary studies as those in which authors had inspected radiology reports or used trial case report forms (CRFs) and confirmed that such cancers had been prospectively identified by the original reporting radiologist. We defined PICRCs as diagnoses of CRC occurring after a CTC that did not detect cancer, either on radiology reports or study CRFs. Our review protocol[23] also allowed for the situation in which CTC reports were not available; in which case CTC-detected cancers were defined as those diagnosed within 6 months of the date of CTC, and PICRCs defined as cancers diagnosed more than 6 months after initial CTC, by analogy with colonoscopy literature[9-13]. However, no articles included in this review required these criteria; all primary component study authors accessed CTC reports or study CRFs. We required that included studies had identified PICRCs via cancer registries, regional databases or cancer intelligence networks[23]; or where the true disease status of each patient at follow-up was determined by a dedicated whole-colon test.

Inclusion criteria were: (i) randomised controlled trials, cohort studies, cross-sectional or case-control studies reporting original research data from adult humans; (ii) published between January 1994 (the year CTC was conceived[24]) and February 2017; (iii) reported a PICRC rate or data sufficient for this to be calculated; (iv) minimum average per-patient follow-up of 12 months; (v) written in English, French, German or Spanish. We excluded studies with any of the following biases: (i) all CTCs performed due to incomplete colonoscopy (e.g. in the presence of stenosing cancer); (ii) CTC performed in knowledge of colonoscopy findings; (iii) CTC technique deviating from international consensus guidelines[6,25].

The study co-ordinator and an information scientist searched the MEDLINE and EMBASE databases and the Cochrane Register of Controlled Trials. We used medical subject headings (MeSH) and free-text terms relating to CTC and colorectal cancer in combination (Appendix, page 1), and examined reference lists of relevant articles and reviews for additional studies.

Search results were retrieved to an Endnote X7 (Thomson Reuters, Toronto, Canada) database, and duplicates removed. Two review authors screened abstracts independently using the predetermined eligibility criteria, excluding articles deemed ineligible by both authors. Full text versions of remaining articles were reviewed independently by the same two authors, who excluded ineligible studies and recorded the reason. Discrepancies regarding eligibility were resolved by consensus, arbitrated by a third investigator.

Data analysis

For each primary study, two investigators independently extracted data into a specifically-designed spreadsheet (Excel 2016, Microsoft, Redmond, USA). We recorded agreement between extractors and resolved discrepancies in consensus with a third author. We extracted: (a) study characteristics: author, publication year, recruitment period, number of centres, study design and follow-up duration; (b) patient characteristics: sex, age, numbers included and lost to follow-up, and reason for CTC; (c) CTC test characteristics: number of CTC examinations conducted, cathartic vs. non-cathartic bowel preparation, use of faecal tagging, intravenous contrast and spasmolytics, and CT scan reconstruction interval; (d) radiologist characteristics: number of study radiologists and experience, mode of interpretation (two-dimensional, three-dimensional or mixed) and use of computer-assisted detection; (e) tumour characteristics: the number of patients with CRC detected by CTC, the number of patients with PICRC, and, for each PICRC, the time delay before PICRC diagnosis, their colonic location, morphology and histology, their mode of ultimate identification, and the reason for initial non-detection. This final category was divided into (i) perceptual error (polyp or mass visible at initial CTC in retrospect), (ii) technical error in CTC acquisition, (iii) management error (e.g. incomplete or non-removal of CTC-detected lesion), and (iv) occult lesion (adequate quality CTC judged normal, even in retrospect)[23]. We contacted authors of component studies for additional data where necessary.

The quality of each study was rated by each extractor using an adapted Newcastle Ottawa Scale for non-randomised studies[26]; studies scoring zero for individual components (selection, comparability, or outcome assessment) were excluded from the quantitative analysis.

Our *a priori* pre-specified primary outcome was the prevalence of PICRC 36 months after CTC, expressed as the proportion of PICRC to the total number of cancers detected (i.e. number of CRCs as the denominator). 36 months was emphasised to align with colonoscopic literature[9-13]. However, since no individual component study reported data for this time-point, we chose to present a pooled PICRC rate using the maximum follow-up reported by each component study (mean = 34 months). We also expressed the PICRC rate relative to the total number of CTC examinations conducted (i.e. number of CTC examinations as the denominator). The latter approach is influenced by CRC prevalence (if no CTC examinations harbour a cancer, it is impossible to have a PICRC), but provides a rate indicative of clinical practice[12].

Secondary outcomes included the 60-month PICRC rate, corresponding to the typical CTC screening interval[27], and PICRC rates per 1000 person-years of follow-up, as recommended by others[8]. Since individual patient data were not available, the number of person-years of follow-up per study was estimated as the average follow-up per person, multiplied by the number of individuals in the study, discounting those lost to follow-up. The average follow-up per person was taken from component study reports by using (in decreasing order of priority) the mean, median, 0.5*(maximum – minimum) or maximum/2. These were used on five, one, five and one occasions respectively. Additional secondary outcomes were the colonic segmental location of detected CRC and PICRC; aetiological factors contributing to PICRCs; and literature quality.

Meta-analysis was conducted using a random-effects model, using the “meta” package for version 3·2·4 of R (R Foundation for statistical computing, Vienna, Austria)[28] to pool the PICRC rate across studies with corresponding 95% confidence intervals (CI). Between-study heterogeneity was assessed using the I^2 statistic and we investigated sources of heterogeneity using meta-regression according to use of faecal tagging, study population (symptomatic, screening or mixed), patient sex, and number of radiologists in the study. The anatomical distribution of both CTC-detected cancers and PICRCs were also combined to provide a pooled estimate, presented as the proportion located in the proximal colon (caecum to transverse colon inclusive). We assessed for publication bias and small study effects using funnel plots[29]. The strength of the overall weight of evidence was rated using GRADE methodology[30].

Role of the funding source:

The funders had no role in study design, data collection, analysis, interpretation, or writing of the report. The corresponding author had full access to all study data, and had final responsibility for the decision to submit for publication.

RESULTS

Initial searching identified 2977 studies. After removal of 967 duplicates, 2010 studies underwent abstract screening, of which 1947 were excluded, leaving 63 articles for full-text review. Ultimately, 12 studies were eligible for inclusion (figure 1). Two of these studies[31,32] were parallel randomised trials, for which some additional data were extracted from a combined, more detailed study monograph published separately[33]. Two further studies[34,35] that derived from the same research group included partly overlapping patient cohorts; we received additional data from this group, permitting separate analysis of the two patient cohorts to avoid patient duplication.

Characteristics of included studies[31,32,34-43] are shown in table 1. Most were retrospective (nine studies[34,36-43]) and conducted at a single centre (nine studies[34,36-41,43]). Overall, 19,867 patients underwent 19,570 CTCs between March 2002 and May 2015 inclusive, with a mean overall follow-up of 34 months (range 13.5 to 68·3 months). The number of patients exceeds the number of CTCs because in one study[39], all patients with post-test CRC were included, rather than just those having CTC. The sex and age range of included patients was only reported in seven[31,32,36,37,39-41] of 12 studies (58·3%); 6532 of 11,590 patients with data available (56·4%) were female, ranging from 18 to 99 years of age. Studies frequently included a mixed screening and symptomatic population (five[36-39,41] of 12 studies, 41·7%), accounting for 10,276 of 19,867 patients (51·7%). Studies including patients with colorectal symptoms alone (five[31,32,40,42,43] of 12 studies, 41·7%) contributed 7,519/19,867 (37·8%) of all patients reviewed, and in two[34,35] of 12 component studies (16·7%), all patients included were asymptomatic screenees (2,111/19,867; 10·6%).

CTC technique was reported incompletely (Table 1). A single study[39] did not report whether or not cathartic bowel preparation was used; all others used cathartics. Faecal tagging was used routinely in five of the 12 studies[34,35,37,38,41] (41·7%), used variably (either over time or by recruitment site) in four of 12 studies[31,32,36,42] (33·3%), not used at all in two of 12 studies[40,43] (16·7%) and its use was not reported by one study[39]. Seven of 12 studies, (58·3%) did not report radiologist experience, four of 12 studies (33·3%) used radiologists with varying levels of experience, and in one study[38] of 12, the radiologists had prior experience of <100 cases. Interpretation method was via two-dimensional display with three-dimensional images as necessary in eight of 12 (66·7%) studies[31,32,34-36,38,40,41], two-dimensional review alone in one of 12 studies[43], and was unreported in three of 12 (25·0%) studies[37,39,42]. Use of computer aided detection (CAD) was not stated in seven of 12 studies (58·3%)[34,35,37,39,40,42,43]; two of 12 (16·7%) studies[38,41] employed it routinely, and in three of 12 (25·0%) studies[31,32,36] it was optional. Five of 12 (41·7%) studies[34,35,37,38,41] used the C-RADS reporting scheme (6mm polyp reporting threshold), one study[36] used a modified C-RADS scheme (also with a 6mm threshold), two of 12 (16·7%) studies used a 10mm threshold[40,42], two of 12 (16·7%) studies[31,32] allowed radiologists to follow their routine clinical practice and two of 12 (16·7%) studies[39,43] did not detail which reporting threshold was used.

All studies met the quality threshold for inclusion in the quantitative synthesis (quality scores in Appendix, page 2). Two of 12 (16·7%) studies[34,35], reporting a total of three PICRCs, used negative initial CTC as an inclusion criterion, and were therefore excluded from the analysis of PICRC rate per 100 cancers detected, as, by definition, these studies had a zero denominator. A further article[39] reported only the number of detected cancers and PICRCs, and not the number of negative CTC examinations, and was therefore excluded from calculations of PICRC rates per 1000 CTCs.

Across all 12 studies, 643 cancers were detected by CTC, with 29 PICRCs diagnosed subsequently. After exclusion of the two studies with negative CTC as an inclusion criterion, the pooled PICRC rate per 100 cancers detected was 4·42% (95%CI 3·03 to 6·42; figure 2a). When considering PICRCs as a proportion of the total number of CTC examinations, the pooled estimate was 1·61 PICRCs per 1000 CTCs (95%CI 1·11 to 2·33; figure 2b). This was unaffected by exclusion of the two studies using negative initial CTC as an inclusion criterion (1·64 PICRCs per 1000 CTCs, 95% CI 1·11 to 2·42). When presented as incidence per 1000 person-years of follow-up, there were 0·64 PICRCs per 1000 person-years (95%CI 0·44 to 0·92; figure 2c). In all analyses, heterogeneity was low (I^2=0).

Meta-regression found no statistically-significant variation in the primary outcome according to use of faecal tagging (p=0·88, Appendix, page 3), screening vs. symptomatic patient population (p=0·65), proportion of females (p=0·74) or the number of radiologists used (p=0·48). Only two of 12 studies (16·7%) had follow-up sufficient to permit estimation of 5-year PICRC rates[34,35]. These two studies reported 2072 patients (1094 female, 52·8%), all with complete follow-up (pooled estimate: 61 months' average follow-up). A total of three PICRCs were diagnosed during this period, corresponding to a pooled PICRC rate of 1·45 PICRCs per 1000 CTCs (95%CI 0·47 to 4·48, Figure 3), similar to that of the unrestricted analysis.

The colonic segmental location of detected CRC was only reported in five of 12 (41·7%) studies[31,32,36,40,41]; 160 of 353 (45%) detected CRCs were proximal, corresponding to a pooled estimate of 0·43 (95%CI 0·32 to 0·55; figure 4a) being proximal. In contrast, 20 of 29 (69%) PICRCs were located proximally, with the pooled estimate of this proportion being 0·66 (95%CI 0·47 to 0·81, I^2=0; figure 4b). Therefore, PICRCs were significantly more likely than detected CRCs to be located proximally (odds ratio 2·68, 95%CI 1·19 to 6·05, p=0·018).

Clinical and imaging characteristics of PICRCs were reported incompletely (table 2), particularly regarding the tumour stage of PICRCs at diagnosis. However, after additional data were provided by component study authors[32,36,41,42], information regarding aetiology was available for 28 of 29 PICRCs. In 5 cases, more than one aetiological factor was deemed contributory. The majority of PICRCs were missed because of perceptual errors (17 of 28, 60·7%). Technical error accounted for 8 of 28 PICRCs (28·6%) and management errors were associated with 6 PICRCs (6 of 28, 21·4%). Two of the 28 PICRCs were not visible even in retrospect (7·1%).

Funnel plots showed no clear indication of small study effects, including publication bias, whether presented as a percentage of CRC detected, or as a proportion of CTC examinations conducted (Appendix, page 4). According to the GRADE working group methodology[30], the confidence in the result of the quantitative synthesis is summarised as high.

DISCUSSION

CRC is highly preventable because most cancers arise from precursors that can be detected and removed. Both colonoscopy and CTC are highly sensitive for large (≥10mm) polyps and CRC, but colonoscopy better detects small (6-9mm) and diminutive (≤5mm) adenomas; and serrated lesions, which are most commonly indolent[4], but a subset is associated with rapid carcinogenesis[20]. This might lead to the *a priori* expectation that PICRC rates will be higher for CTC than colonoscopy. This systematic review of 19,867 patients demonstrates this is unlikely, at least within a 3-year time horizon: We calculated a PICRC rate of 4·4%, at the lower end of the range estimated for colonoscopy (2·9 to 8·6%)[13] at similar follow-up (34 vs. 36 months). The incidence of 0·64 PICRCs per 1000 person-years of follow-up is also at the lower end of the range reported for colonoscopy (0·78 to 2·9 cases per 1000 person-years in one review)[8]. Importantly, although data were derived from various settings and study designs, heterogeneity was low (I^2=0%), meaning that our estimates are consistent across the published literature. The low PICRC rate we found here is consistent with prior observational series showing similar detection rates of advanced neoplasia between CTC and colonoscopy[44,45]. CTC also detected as many advanced neoplasms as colonoscopy in a Dutch randomised screening trial[46] once all 6-9mm polyps scheduled for CTC follow-up had been resected and undergone histological analysis[47]. This high diagnostic performance clearly translates to excellent longer-term patient outcomes.

The optimum interval between CTC screening examinations is unknown currently, but 60 months is recommended in the USA[48]. Although fewer data were available for this time threshold (only two studies, both derived from the same research group), we found PICRC rates remained low, similar to the rate at 3 years, meaning that the current approach is likely safe. Given the fact that we found PICRC rates after CTC to be similar to those for colonoscopy, the 60 month interval may even be over-conservative. Therefore, the original C-RADS recommendation of a 5-10 year interval[27] remains a viable strategy. Nonetheless, despite potentially improving patient acceptance and reducing healthcare costs with a longer screening interval, the impact of non-detection of small polyps may be greater during this time window, since it takes many years for most adenomas to transition to CRC[49]. We found a paucity of published data at even a 60 month follow-up period, implying a clear need for additional research examining PICRC rates both at 60 month and at 60-120 month intervals before definitive recommendations for routine CTC screening intervals can be made.

The aetiology of PICRCs is multifactorial, but in most cases (61%) the culprit lesion was visible in retrospect and potentially detectable. This is similar to colonoscopy; for example, Robertson et al[14] identified 30 of 58 (52%) post-colonoscopy CRCs as potentially avoidable, similar to our data for CTC. We found that errors of CTC technique or patient management were less common, and genuinely CTC-occult lesions were rare; just two of 28 cases. These findings highlight the need for radiologist training, robust patient management pathways and quality assurance processes to avoid these preventable cancers from accumulating. Although, in many countries, colonoscopists are subjected to routine accreditation and performance monitoring using metrics such as caecal intubation rate (CIR) and adenoma detection rate (ADR)[50,51] this is not the case for radiologists interpreting CTC. Colonoscopists with higher ADRs have lower PCCRC rates[15,16], implying that, by extension, monitoring and improvement of radiologists' polyp detection rates (PDR) may be valuable, particularly as relevant benchmarking data emerge[52,53]. Computer-aided detection (CAD) improves radiologist performance for detecting polyps[54-56] and so may be of benefit. With optimised CTC, our data suggest that a 36-month PICRC rate of 1% is an achievable target. Such a low residual rate would likely make repeat CTC a poor use of healthcare resources under most circumstances; specific economic evaluation would be needed to answer this question with greater certainty.

PICRCs were considerably more likely to be proximal than initially-detected cancers. We believe the reason for this right-sided preponderance (which has also been reported for colonoscopy[12]) is multifactorial. In several instances, CTC did not employ faecal tagging, now universally recognised as a pre-requisite for good practice. We were unable to confirm that failure to use faecal tagging was associated with a higher PICRC rate, but this may be due to underpowering for this subgroup comparison. Furthermore, right-sided tumours are more commonly associated with microsatellite instability and the serrated carcinogenesis pathway. Although sessile serrated lesions can be diagnosed by optimised CTC[57], historically they are considered harder to detect. In one randomised trial, CTC detected significantly fewer high-risk (large or dysplastic) serrated neoplasms than colonoscopy[19], the specific subset that can progress rapidly to carcinoma[58]. As radiologists learn how best to detect these lesions at CTC (e.g. surface coating by oral contrast tagging[59]), it is plausible that this excess of right-sided PICRCs will reduce.

Strengths of our study include adherence to methodological and reporting recommendations, robust data extraction and quality assessment, and comprehensive review of PICRC aetiology, including obtaining unpublished data from component study authors. The work also has limitations. Component studies rarely reported PICRC morphology, location and time to diagnosis. Follow-up duration varied between different studies, and few included data beyond 36 months. Studies rarely reported more than one of mean, median or maximum and minimum follow-up, meaning we were unable to conduct a sensitivity analysis to explore whether such inconsistent reporting has affected our summary estimates of PICRC incidence. Individual patient data were not available, meaning it was not possible to link patient-level or radiologist-level factors (such as radiologist experience, or use of CAD) to PICRC rates. Although we aimed to explore the influence of patient, CTC technique, radiologist and institutional factors associated with higher PICRC rates, this was frequently impossible due to incomplete reporting and relative underpowering for such comparisons, meaning it is possible that important drivers of PICRCs have been undetected. Such missing data may also bias these comparisons, although since none of our factors chosen for meta-regression were statistically significant, this will have limited clinical impact. Finally, this meta-analysis represents a synthesis of data from clinical trials and observational studies, which are likely generated by CTC enthusiasts; whether similarly low rates would be replicated in large-scale epidemiological series is unknown. It is surprising that, to date, there are no published data linking national imaging databases to cancer registries; this is an important avenue for future research.

In summary, the estimated rate of post-imaging colorectal cancer (PICRC) 34 months after negative CT colonography is approximately 4·4%, or 0·64 per 1000 person-years of follow-up, at the lower end of the range reported for colonoscopy. PICRCs following CTC are more common in the right colon and most are due to perceptual errors. Improved radiologist training and quality assurance of imaging will likely reduce PICRC rates, as most are potentially avoidable.

CONTRIBUTORS

AAP conceived the study and wrote the protocol with AEO, UST, TRF, SH and DB. AEO and AAP performed the literature search. AEO and UST performed data extraction and collection. TRF designed the statistical analysis plan and performed the analysis. AEO and AAP drafted the manuscript. All co-authors edited, revised and contributed to the intellectual content of the manuscript.

DECLARATION OF INTERESTS

Dr. Plumb reports grants from St Mark's Hospital Foundation, non-financial support from UCL/UCLH Biomedical Research Centre, during the conduct of the study; and has received honoraria for educational lectures delivered at events arranged by Acelity, Actavis, Dr Falk, Janssen-Cilag and Takeda on the subject of inflammatory bowel disease. Dr. Obaro reports grants from St Mark's Hospital Foundation, during the conduct of the study. Dr. Fanshawe has nothing to disclose. Dr. Torres has nothing to disclose. Mrs. Baldwin-Cleland has nothing to disclose. Dr. Taylor reports grants and non-financial support from UCL/UCLH Biomedical Research Centre, during the conduct of the study; personal fees from Robarts, outside the submitted work. Dr. Halligan reports grants and non-financial support from UCL/UCLH Biomedical Research Centre, grants from St Mark's Hospital Foundation, during the conduct of the study; non-financial support from iCAD, outside the submitted work. Dr. Burling reports grants from St Mark's Hospital Foundation, during the conduct of the study; grants from Bracco UK, outside the submitted work.

ACKNOWLEDGEMENTS

The authors would like to thank component study authors for providing additional data. This study was funded by St Mark’s Hospital Foundation and the National Institute for Healthcare Research (NIHR) via the UCL/UCLH Biomedical Research Centre scheme (AAP, SAT and SH). The views expressed in this publication are those of the authors and not necessarily those of the National Health Service (NHS), the NIHR or the Department of Health. The funding source had no role in the study design,

data collection, data analysis, or writing of the report. The corresponding author had full access to all study data, and had final responsibility for the decision to submit for publication.

Institutional review board approval was not required for this systematic review.

Table 1.

Study	Year	Period (mm / yy)	Region	No. of sites	Design	Popul-ation	No. of patients	Age range	Fem-ales (%)	No. of radio-logists	Positivity threshold	No. of CTCs	Recon-struction interval	Follow-up in months	Means of PICRC identification	Purg-ation	Faecal tagging	IV contrast	Anti-spasmodic
Atkin et al	2013	03/04 - 12/07	UK	21	prosp	sympto	538	55 to 85	293 (54.5)	41	Variable	503	Variable	**36 (0)**	National registry	Yes	Variable	Variable	Variable
Badiani et al	2011	03/02 - 12/07	UK	1	retro	sympto	1177	27 to 96	714 (60.7)	8	10mm	1177	NR	*34.5 (18 to 84)*	Regional registry	Yes	No	Yes	Buscopan or glucagon if CI
Halligan et al	2013	03/04 - 12/07	UK	21	prosp	sympto	1285	55 to 85	787 (61.2)	39	Variable	1206	Variable	**36 (0)**	National registry	Yes	Variable	Variable	Variable
Hock et al	2015	06/03 – 08/10	Belgium	1	retro	mixed	1890	18 to 96	NR	NR	6mm	1890	0.625mm	6 to 60	Regional registry	Yes	Yes	NR	Buscopan
Kim et al	2012	04/04 - 05/05	USA	1	retro	screen	643	NR	358 (55.7)	NR	6mm	643	1mm	**54.2 (NR)**	Regional registry	Yes	Yes	NR	NR
Lung et al	2014	01/07 - 12/11	UK	1	retro	mixed	4355	23 to 99	2503 (57.5)	4	6mm	4349	NR	**26.4 (NR)**	Regional registry	Yes	Variable	Variable	Buscopan
Moore et al	2013	01/04 - 07/09	New Zealand	1	retro	mixed	2026	19 to 87	1066 (52.6)	6	6mm	2026	NR	3 to 24	National registry	Yes	Yes	NR	NR
Pickhardt et al	2017	01/04 - 05/15	USA	1	prosp	screen	1429	NR	736 (51.5)	12	6mm	1429	1mm	**68.4 (10.8)**	Repeat whole-colon test	Yes	Yes	NR	NR
Sabanli et al	2010	01/04 - 09/08	New Zealand	3	retro	sympto	3888	NR	NR	NR	10mm	3888	Variable	3 to 59	National registry	Yes	Variable	NR	NR
Simons et al	2013	01/07 - 01/11	Nether-lands	1	retro	mixed	1855	NR	NR	4	6mm	1855	NR	6 to 24	National registry	Yes	Yes	No	Buscopan or glucagon if CI
Than et al	2015	08/10 - 07/11	UK	1	retro	mixed	150	32 to 90	75 (50.0)	NR	NR	NR	NR	NR to 36*	New CRC cases*	NR	NR	NR	NR
Thomas et al	2009	01/03 - 12/05	UK	1	retro	sympto	631	NR	NR	3	NR	604	1.5mm	24 to 60	Regional registry	Yes	No	Yes	Buscopan or glucagon if CI

Table 2.

Study	No. of PICRCs	Details of PICRC occurrence	Aetiological factors contributing to PICRC	Histology/Characteristics of PICRC at detection	Timepoint of detection (months)
Atkin et al 2013	1	1. Initial CTC negative (poor distension, no follow-up imaging)	1. Technical error + management error	1. Rectosigmoid tumour	1. 15m
Badiani et al 2011	3	1. Initial CTC negative (lesion visible in retrospect) 2. Initial CTC negative (lesion visible in retrospect) 3. Initial CTC negative (lesion visible in retrospect)	1. Perceptual error 2. Perceptual error 3. Perceptual error	1. Polypoid sigmoid lesion 2. Sessile ascending colon lesion 3. Flat caecal lesion	1. 5m 2. 11m 3. 10m
Halligan et al 2013	3	1. 6mm caecal polyp not removed 2. Initial CTC negative 3. CTC interpreted as diverticulitis	1. Management error 2. Perceptual error 3. Perceptual error	1. 12mm caecal adenocarcinoma 2. Ascending colon cancer, Dukes D 3. T4 N0 M0, Dukes B	1. 28m 2. 7m 3. 10m
Hock et al 2015	3	1. Initial CTC negative (flat lesion visible in retrospect) 2. Non-diagnostic initial CTC (patient declined second view) 3. Initial CTC negative (lesion visible in retrospect)	1. Perceptual error 2. Technical error 3. Perceptual error	1. Adenocarcinoma 2. Adenocarcinoma 3. Adenocarcinoma	1. NR 2. NR 3. NR
Kim et al 2012	1	1. Initial CTC negative (lesion just visible in retrospect)	1. Perceptual error	1. T3 N0 M0	1. 35m
Lung et al 2014	2	1. Only one of two lesions present identified 2. Initial CTC negative (lesion visible in retrospect)	1. Perceptual error 2. Perceptual error	1. T3 N0 M0, Dukes B 2. T3 N1 M0, Dukes C1	1. 4m 2. 42m
Moore et al 2013	2	1. Local recurrence at ileocolic anastomosis (poor distension, very minor smooth wall thickening) 2. Only one of two lesions present identified	1. Technical error + Perceptual error 2. Perceptual error	1. 35mm 'plaque-like' anatomic recurrence 2. 10mm caecal polyp cancer	1. 4m
Pickhardt et al 2017	2	1. Initial CTC negative (flat lesion visible in retrospect) 2. Initial CTC negative (lesion not visible in retrospect - occult lesion)	1. Perceptual error 2. Occult lesion	1. T3 N1b M0 2. T2 N0 M0	1. 60m 2. 120m
Sabanli et al 2010	7	1. Non-diagnostic initial CTC (poor faecal tagging, no follow-up imaging) 2. Non-diagnostic initial CTC (poor distension, no follow-up imaging) 3. Non-diagnostic initial CTC (poor quality scan on single detector CT) 4. Non-diagnostic CTC (motion artefact, poor distension, no follow-up imaging) 5. Initial CTC negative (lesion not visible in retrospect - occult lesion) 6. Lesion misinterpreted as thickened fold (lesion visible in retrospect) 7. Initial CTC negative (lesion visible in retrospect)	1. Technical error + Management error 2. Technical error + Management error 3. Technical error 4. Technical error + Management error 5. Occult lesion 6. Perceptual error 7. Perceptual error	1. Caecal carcinoma 2. Caecal carcinoma 3. Caecal carcinoma 4. Rectosigmoid carcinoma 5. NR 6. Caecal carcinoma 7. NR	1. NR 2. NR 3. NR 4. NR 5. NR 6. NR 7. NR
Simons et al 2013	3	1. Non-diagnostic initial CTC (poor distension) 2. Initial CTC negative (flat lesion visible in retrospect) 3. Initial CTC negative (lesion visible in retrospect, obscured by rectal balloon)	1. Technical error 2. Perceptual error 3. Perceptual error	1. Caecal carcinoma 2. Flat advanced adenoma in ascending colon 3. Distal rectal malignancy	1. 9m 2. 14m 3. 5m
Than et al 2015	1	1. NR	1. NR	1. TNM stage II Dukes B	1. 4m
Thomas et al 2009	1	1. 9mm sigmoid colon polyp not removed	1. Management error	1. Invasive adenocarcinoma	1. 31m

Figure 1. Study flowchart. Of the 63 full texts reviewed for eligibility, 16 were identified by both abstract screeners and 47 were identified by one screener alone. Of the 51 articles excluded at the full text review stage, 42 were identified by both independent reviewers as clearly ineligible and the other 9 were excluded after consensus discussion with arbitration by a third author.

Figure 2. Pooled estimate of PICRC rate. (a) presented as the number of PICRCs per 100 cancers detected. Two studies[34,35] that used negative initial CTCs as inclusion criteria were excluded from this analysis, as the number of detected cancers in these cases was zero. (b) presented as the number of PICRCs per 1000 CTCs. One study[39] that reported only the number of cancers and not the number of negative CTCs was excluded. (c) Presented as incidence of PICRC per 1000 person-years follow-up. The study[39] reporting only the number of cancers detected, rather than the number of negative CTCs, was excluded.

Figure 3. Pooled estimate of PICRC rate, restricted to the studies with an average of 5 years follow-up, presented as the pooled PICRC estimate per 1000 CTCs.

Figure 4. Anatomical distribution (distal vs. proximal) of CRC. (a) for detected cancers. (b) for PICRCs.

Table 1. Characteristics of studies reporting post-CTC PICRC rates and meeting inclusion criteria. The number of included patients may differ from published reports, because we have extracted data solely for the patients in whom we have data regarding their PICRC rate. Follow-up was reported variably, and is presented, in order of preference, as **mean (standard deviation),** *median (range)*, or range alone. For studies with standard deviation of zero, all patients were followed up for the same length of time. "Positivity threshold" refers to the size of polyp at which a CTC examination was regarded as positive for disease. NR – not recorded, CI – contra-indicated, prosp = prospective study, retro = retrospective study, mm = millimetre. *Than et al[39] included patients with a new CRC diagnosis and identified those with CTC in the 3 years prior.

Table 2. Characteristics of PICRCs reported in component primary studies. Some PICRCs were associated with more than one type of aetiological factor. NR – not recorded

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**(5): E359-86.
2. National Cancer Intelligence Network. Colorectal cancer survival by stage - NCIN data briefing. National Cancer Intelligence Network; 2009.
3. Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. *Cancer* 1975; **36**(6): 2251-70.
4. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. *Gastroenterology* 2010; **138**(6): 2088-100.
5. Brenner H, Stock C., Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. *British Medical Journal (Clinical Research Ed)* 2014; **348**.
6. Neri E, Halligan S, Hellstrom M, et al. The second ESGAR consensus statement on CT colonography. *Eur Radiol* 2013; **23**(3): 720-9.
7. Health and Social Care Information Centre. Diagnostic Imaging Dataset. Health and Social Care Information Centre. 2017. https://did.hscic.gov.uk/ (accessed 8 Aug 2017).
8. Sanduleanu S, le Clercq CM, Dekker E, et al. Definition and taxonomy of interval colorectal cancers: a proposal for standardising nomenclature. *Gut* 2015; **64**(8): 1257-67.
9. Bressler B, Paszat LF, Chen Z, Rothwell DM, Vinden C, Rabeneck L. Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. *Gastroenterology* 2007; **132**(1): 96-102.
10. Cooper GS, Xu F, Barnholtz Sloan JS, Schluchter MD, Koroukian SM. Prevalence and predictors of interval colorectal cancers in medicare beneficiaries. *Cancer* 2012; **118**(12): 3044-52.
11. le Clercq CM, Bouwens MW, Rondagh EJ, et al. Postcolonoscopy colorectal cancers are preventable: a population-based study. *Gut* 2014; **63**(6): 957-63.
12. Morris EJ, Rutter MD, Finan PJ, Thomas JD, Valori R. Post-colonoscopy colorectal cancer (PCCRC) rates vary considerably depending on the method used to calculate them: a retrospective observational population-based study of PCCRC in the English National Health Service. *Gut* 2015; **64**(8): 1248-56.
13. Singh S, Singh PP, Murad MH, Singh H, Samadder NJ. Prevalence, risk factors, and outcomes of interval colorectal cancers: a systematic review and meta-analysis. *Am J Gastroenterol* 2014; **109**(9): 1375-89.
14. Robertson DJ, Lieberman DA, Winawer SJ, et al. Colorectal cancers soon after colonoscopy: a pooled multicohort analysis. *Gut* 2014; **63**(6): 949-56.
15. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med* 2014; **370**(14): 1298-306.
16. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. *N Engl J Med* 2010; **362**(19): 1795-803.
17. Pickhardt PJ, Hassan C, Halligan S, Marmo R. Colorectal cancer: CT colonography and colonoscopy for detection-systematic review and meta-analysis. *Radiology* 2011; **259**(2): 393-405.
18. De Haan MC, Van Gelder RE, Graser A, Bipat S, Stoker J. Diagnostic value of CT-colonography as compared to colonoscopy in an asymptomatic screening population: A meta-analysis. *European Radiology* 2011; **21**(8): 1747-63.
19. Ijspeert JEG, Tutein Nolthenius CJ, Kuipers EJ, et al. CT-Colonography vs. Colonoscopy for Detection of High-Risk Sessile Serrated Polyps. *American Journal of Gastroenterology* 2016; **111**(4): 516-22.
20. Bettington M, Walker N, Rosty C, et al. Clinicopathological and molecular features of sessile serrated adenomas with dysplasia or carcinoma. *Gut* 2017; **66**(1): 97-106.
21. Cancer Research UK. Scoping the future. An evaluation of endoscopy capacity across the NHS in England. 2015. https://www.cancerresearchuk.org/sites/default/files/scoping_the_future_-_final.pdf (accessed 8 Aug 2017).
22. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; **151**(4): 264-9, W64.
23. Plumb AA, Obaro A, Fanshawe T, et al. Prevalence and risk factors for post-investigation colorectal cancer ("interval cancer") after computed tomographic colonography: protocol for a systematic review. *Syst Rev* 2017; **6**(1): 36.

24. Vining DJ, Gelfland DW. Non-invasive colonoscopy using helical CT scanning, 3D reconstruction and virtual reality. 23rd Meeting and Postgraduate Course of the Society of Gastrointestinal Radiologists. Maui, Hawaii; 1994.
25. McFarland EG, Fletcher JG, Pickhardt P, et al. ACR Colon Cancer Committee White Paper: Status of CT Colonography 2009. *Journal of the American College of Radiology* 2009; **6**(11): 756-72.e4.
26. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2016. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed June 2016 2016).
27. Zalis ME, Barish MA, Choi JR, et al. CT colonography reporting and data system: a consensus proposal. *Radiology* 2005; **236**(1): 3-9.
28. R, Core, Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2015.
29. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991; **337**(8746): 867-72.
30. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336**(7650): 924-6.
31. 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**(9873): 1194-202.
32. 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**(9873): 1185-93.
33. Halligan S, Dadswell E, Wooldrage K, 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): 1-134.
34. Kim DH, Pooler BD, Weiss JM, Pickhardt PJ. Five year colorectal cancer outcomes in a large negative CT colonography screening cohort. *European Radiology* 2012; **22**(7): 1488-94.
35. Pickhardt PJ, Pooler BD, Mbah I, Weiss JM, Kim DH. Colorectal Findings at Repeat CT Colonography Screening after Initial CT Colonography Screening Negative for Polyps Larger than 5 mm. *Radiology* 2017; **282**: 139-48.
36. Lung PF, Burling D, Kallarackel L, et al. Implementation of a new CT colonography service: 5 year experience. *Clin Radiol* 2014; **69**(6): 597-605.
37. Moore H, Dodd N. Computed tomographic colonography (CTC); Colorectal cancer diagnosis with CTC in an Auckland population. *Journal of Medical Imaging and Radiation Oncology* 2013; **57**(5): 572-5.
38. Simons PC, Van Steenbergen LN, De Witte MT, Janssen-Heijnen ML. Miss rate of colorectal cancer at CT colonography in average-risk symptomatic patients. *European Radiology* 2013; **23**(4): 908-13.
39. Than M, Witherspoon J, Shami J, Patil P, Saklani A. Diagnostic miss rate for colorectal cancer: An audit. *Annals of Gastroenterology* 2015; **28**(1): 94-8.
40. Badiani S, Hernandez ST, Karandikar S, Roy-Choudhury S. CT Colonography to exclude colorectal cancer in symptomatic patients. *European Radiology* 2011; **21**(10): 2029-38.
41. Hock D, Materne R, Ouhadi R, Mancini I, Aouachria SA, Nchimi A. Test-positive rate at CT colonography is increased by rectal bleeding and/or unexplained weight loss, unlike other common gastrointestinal symptoms. *European Journal of Radiology Open* 2015; **2**: 32-8.
42. Sabanli M, Balasingam A, Bailey W, Eglinton T, Hider P, Frizelle FA. Computed tomographic colonography in the diagnosis of colorectal cancer. *British Journal of Surgery* 2010; **97**(8): 1291-4.
43. Thomas S, Atchley J, Higginson A. Audit of the introduction of CT colonography for detection of colorectal carcinoma in a non-academic environment and its implications for the national bowel cancer screening programme.[Erratum appears in Clin Radiol. 2009 Jun;64(6):654]. *Clin Radiol* 2009; **64**(2): 142-7.
44. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *New England Journal of Medicine* 2003; **349**(23): 2191-200.
45. Kim DH, Pickhardt PJ, Taylor AJ, et al. CT colonography versus colonoscopy for the detection of advanced neoplasia. *New England Journal of Medicine* 2007; **357**(14): 1403-12.
46. Stoop EM, de Haan MC, de Wijkerslooth TR, et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: A randomised controlled trial. *Lancet Oncol* 2012; **13**(1): 55-64.

47. Tutein Nolthenius CJ, Boellaard TN, de Haan MC, et al. Computer tomography colonography participation and yield in patients under surveillance for 6-9 mm polyps in a population-based screening trial. *European Radiology* 2016; **26**(8): 2762-70.
48. Force USPST, Bibbins-Domingo K, Grossman DC, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA* 2016; **315**(23): 2564-75.
49. Rutter CM, Knudsen AB, Marsh TL, et al. Validation of Models Used to Inform Colorectal Cancer Screening Guidelines: Accuracy and Implications. *Med Decis Making* 2016; **36**(5): 604-14.
50. Rees CJ, Thomas Gibson S, Rutter MD, et al. UK key performance indicators and quality assurance standards for colonoscopy. *Gut* 2016; **65**(12): 1923-9.
51. Rembacken B, Hassan C, Riemann JF, et al. Quality in screening colonoscopy: position statement of the European Society of Gastrointestinal Endoscopy (ESGE). *Endoscopy* 2012; **44**(10): 957-68.
52. Pooler BD, Kim DH, Hassan C, Rinaldi A, Burnside ES, Pickhardt PJ. Variation in diagnostic performance among radiologists at screening CT colonography. *Radiology* 2013; **268**(1): 127-34.
53. Pooler BD, Kim DH, Lam VP, Burnside ES, Pickhardt PJ. CT Colonography Reporting and Data System (C-RADS): Benchmark values from a clinical screening program. *American Journal of Roentgenology* 2014; **202**(6): 1232-7.
54. Halligan S, Mallett S, Altman DG, et al. Incremental benefit of computer-aided detection when used as a second and concurrent reader of CT colonographic data: multiobserver study. *Radiology* 2011; **258**(2): 469-76.
55. Dachman AH, Obuchowski NA, Hoffmeister JW, et al. Effect of Computer-aided Detection for CT Colonography in a Multireader, Multicase Trial. *Radiology* 2010; **256**(3): 827-35.
56. Regge D, Della Monica P, Galatola G, et al. Efficacy of computer-aided detection as a second reader for 6-9-mm lesions at CT colonography: multicenter prospective trial. *Radiology* 2013; **266**(1): 168-76.
57. Kim DH, Matkowskyj KA, Lubner MG, et al. Serrated Polyps at CT Colonography: Prevalence and Characteristics of the Serrated Polyp Spectrum. *Radiology* 2016; **280**(2): 455-63.
58. Bettington M, Walker N, Clouston A, Brown I, Leggett B, Whitehall V. The serrated pathway to colorectal carcinoma: current concepts and challenges. *Histopathology* 2013; **62**(3): 367-86.
59. Kim DH, Hinshaw JL, Lubner MG, Munoz del Rio A, Pooler BD, Pickhardt PJ. Contrast coating for the surface of flat polyps at CT colonography: a marker for detection. *Eur Radiol* 2014; **24**(4): 940-6.

Figure 1

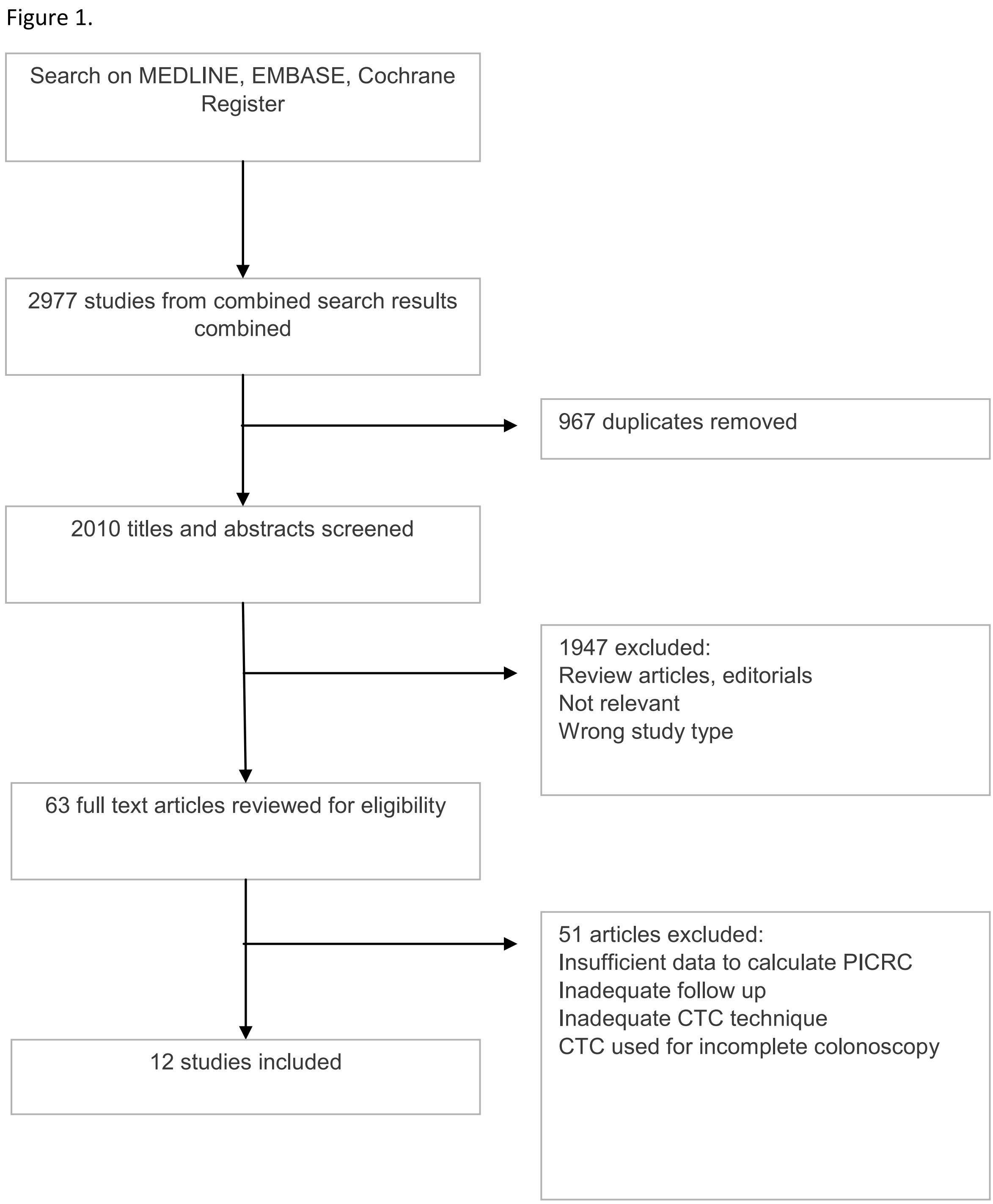


Figure 1.
Search on MEDLINE, EMBASE, Cochrane Register
2977 studies from combined search results combined
967 duplicates removed
2010 titles and abstracts screened
1947 excluded:
Review articles, editorials
Not relevant
Wrong study type
63 full text articles reviewed for eligibility
51 articles excluded:
Insufficient data to calculate PICRC
Inadequate follow up
Inadequate CTC technique
CTC used for incomplete colonoscopy
12 studies included

Figure 2
Click here to download high resolution image

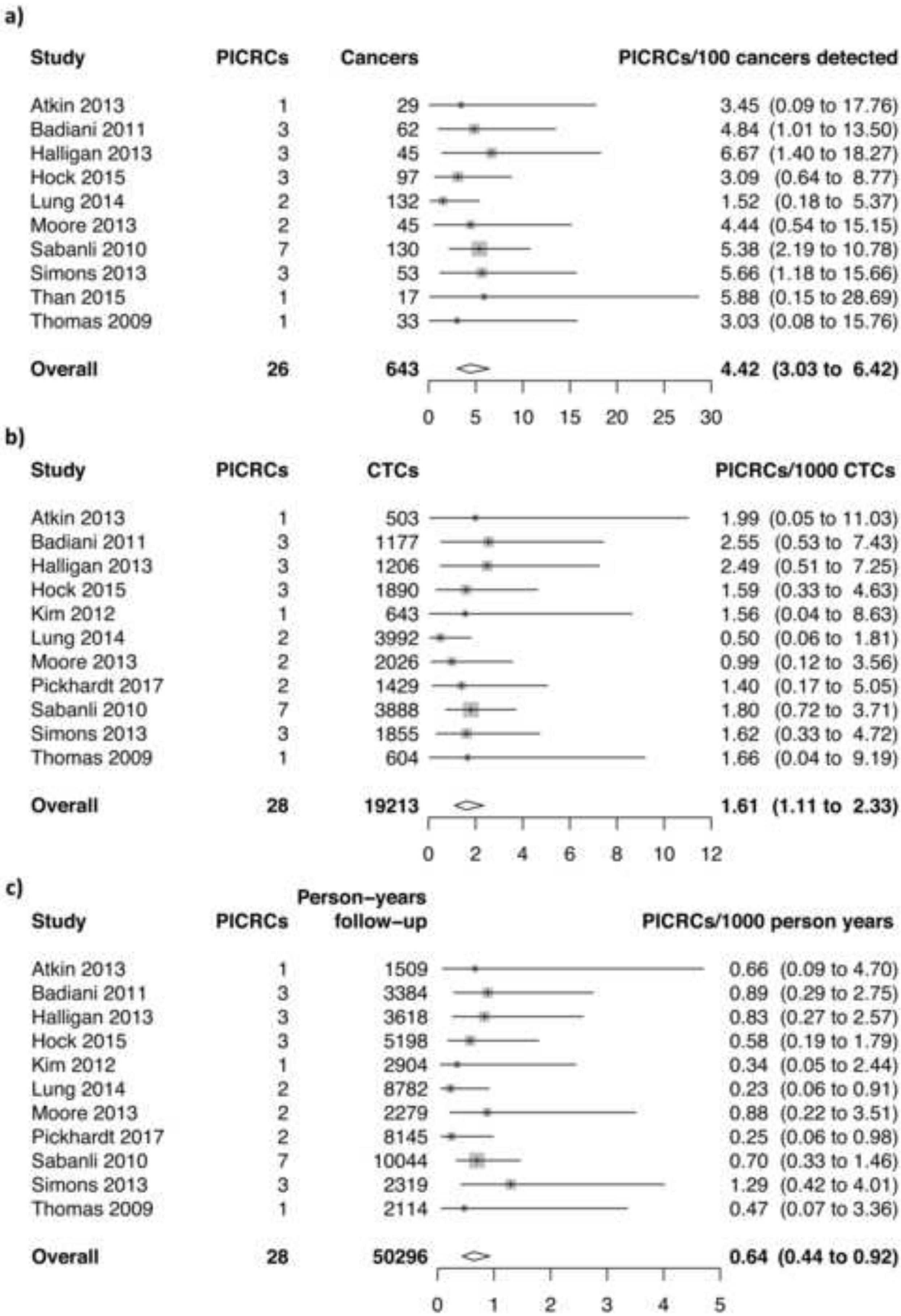
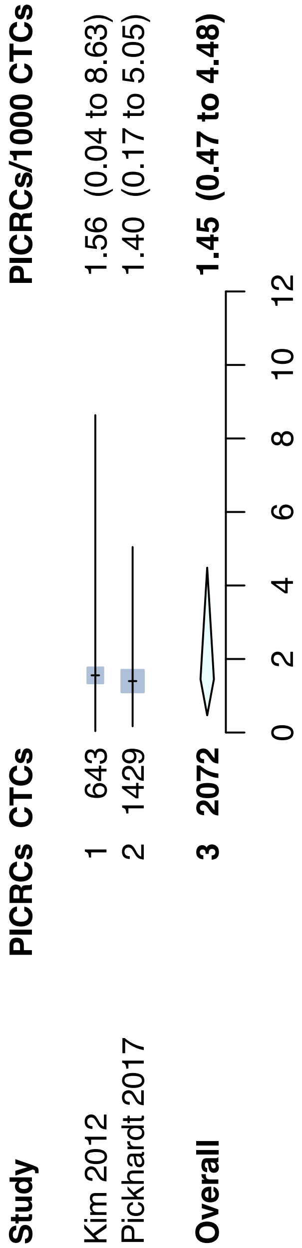


Figure 3



Study
PICRCs
CTCs
PICRCs/1000 CTCs
Kim 2012
1
643
1.56 (0.04 to 8.63)
Pickhardt 2017
2
1429
1.40 (0.17 to 5.05)
Overall
3
2072
1.45 (0.47 to 4.48)
0
2
4
6
8
10
12

Figure 4a

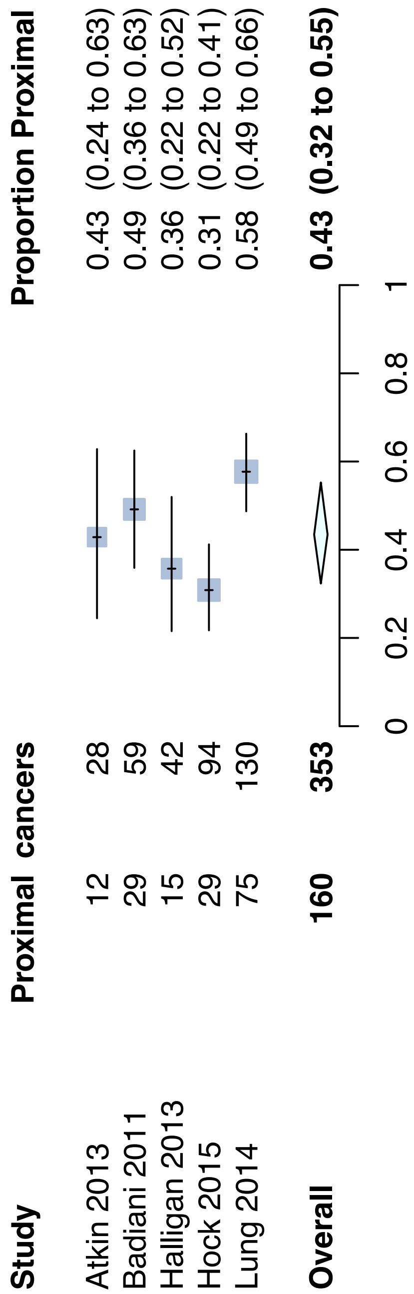
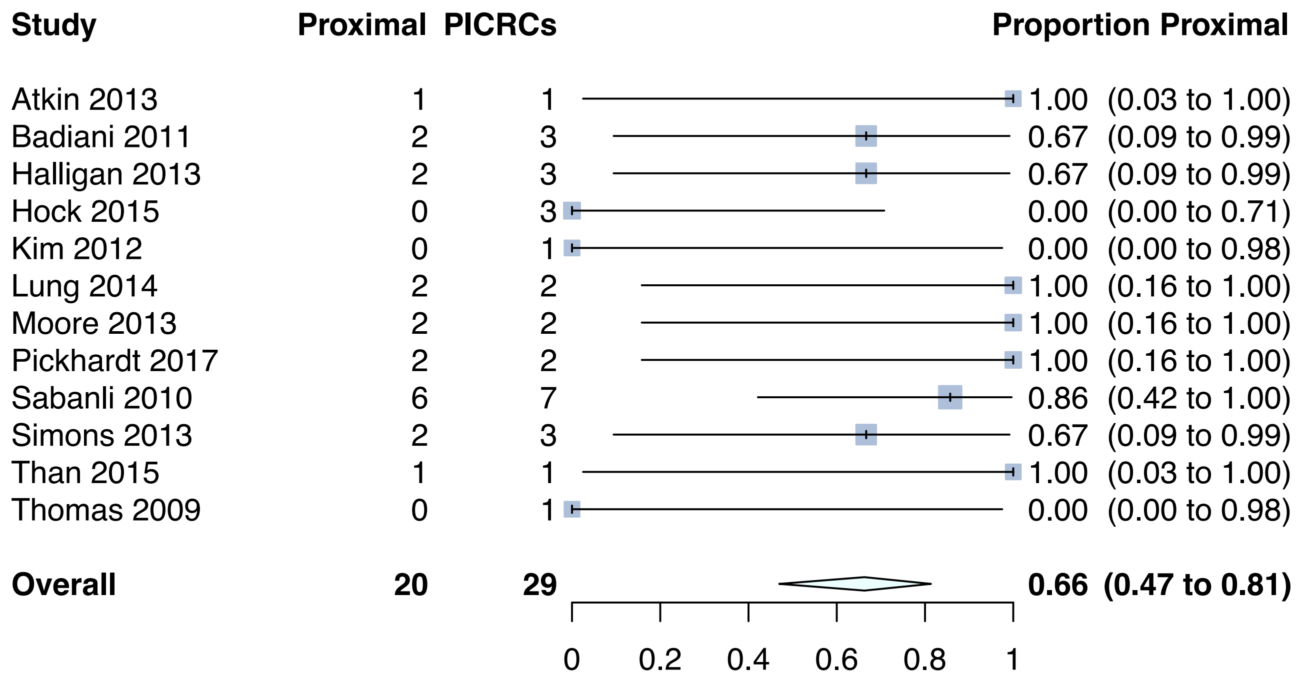

Study
Proximal
Total cancers
Proportion Proximal
Atkin 2013
12
28
0.43 (0.24 to 0.63)
Badiani 2011
29
59
0.49 (0.36 to 0.63)
Halligan 2013
15
42
0.36 (0.22 to 0.52)
Hock 2015
29
94
0.31 (0.22 to 0.41)
Lung 2014
75
130
0.58 (0.49 to 0.66)
Overall
160
353
0.43 (0.32 to 0.55)
0
0.2
0.4
0.6
0.8
1

Figure 4b


Study
Proximal
PICRCs
Proportion Proximal
Atkin 2013 1 1 1.00 (0.03 to 1.00)
Badiani 2011 2 3 0.67 (0.09 to 0.99)
Halligan 2013 2 3 0.67 (0.09 to 0.99)
Hock 2015 0 3 0.00 (0.00 to 0.71)
Kim 2012 0 1 0.00 (0.00 to 0.98)
Lung 2014 2 2 1.00 (0.16 to 1.00)
Moore 2013 2 2 1.00 (0.16 to 1.00)
Pickhardt 2017 2 2 1.00 (0.16 to 1.00)
Sabanli 2010 6 7 0.86 (0.42 to 1.00)
Simons 2013 2 3 0.67 (0.09 to 0.99)
Than 2015 1 1 1.00 (0.03 to 1.00)
Thomas 2009 0 1 0.00 (0.00 to 0.98)
Overall 20 29 0.66 (0.47 to 0.81)
0
0.2
0.4
0.6
0.8
1

Appendix

Database search terms

1. ((CT or (comput* and tomogra*)) and colonogra*).af
2. (virtua* and colono*).af
3. 1 or 2
4. colonography, computed tomographic.sh
5. 3 or 4
6. 5 and Journal Article.pt
7. ((colon or colorect*) and (cancer or carcinoma)).af
8. colorectal neoplasms.sh
9. 7 or 8
10. 9 and Journal Article.pt
11. 6 and 10

Individual study quality assessment

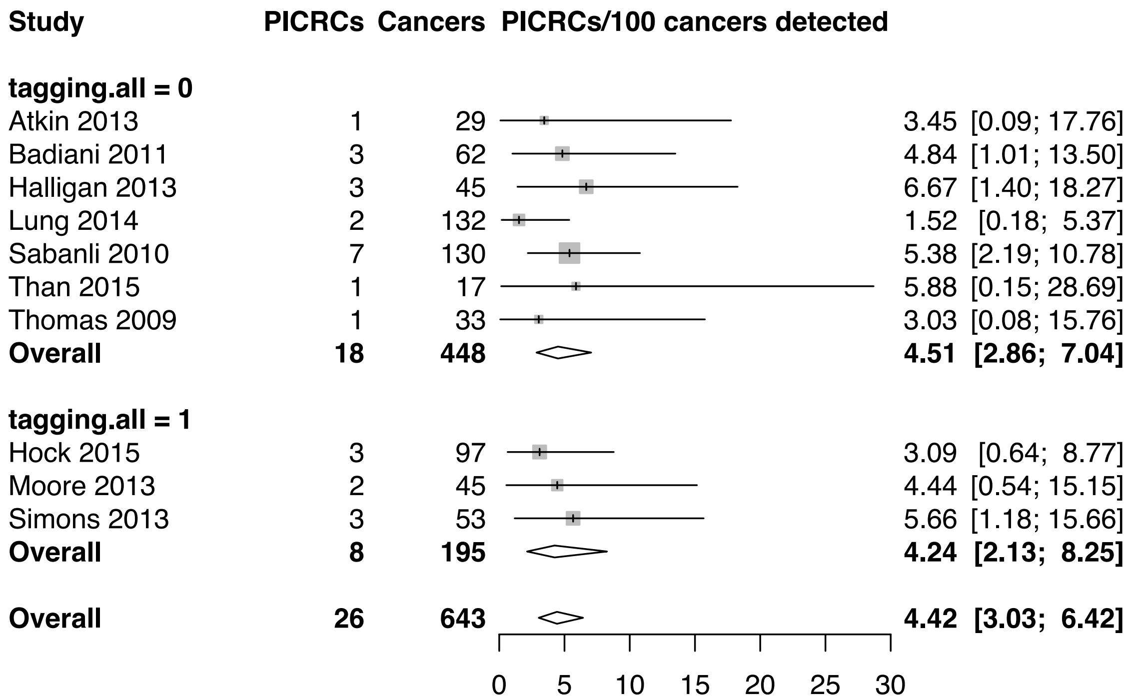
	Selection (max 3 stars)			Comparability (max 2 stars)			Outcome (max 3 stars)		
	Rater 1	**Rater 2**	**Consensus**	**Rater 1**	**Rater 2**	**Consensus**	**Rater 1**	**Rater 2**	**Consensus**
Atkin 2013	★★★	★★★	★★★	★★	-	★★	★★★	★★★	★★★
Badiani 2011	★★★	★★★	★★★	★★	★	★★	★★★	★★★	★★★
Halligan 2013	★★★	★★★	★★★	★★	-	★★	★★★	★★★	★★★
Hock et al 2015	★★★	★★★	★★★	★★	★	★★	★	-	★
Kim et al 2012	★★★	★★★	★★★	★★	★★	★★	★★	★★	★★
Lung et al	★★★	★★★	★★★	★★	-	★★	★★	★★	★★
Moore et al	★★★	★★★	★★★	★	★	★	★★	★★	★★
Pickhardt et al 2017	★★★	★★★	★★★	★★	★	★★	★★	★	★★
Sabanli et al 2010	★★★	★★★	★★★	★★	★	★★	★★	★★	★★
Simons et al 2013	★★★	★★★	★★★	★★	★	★★	★★	★★	★★
Than et al 2015	★★★	★★★	★★★	★	-	★	★★	★★	★★
Thomas et al 2009	★★★	★★★	★★★	★★	★	★★	★★★	★★	★★★

Studies were evaluated using a modified Newcastle-Ottowa Scale (scoring sheet available with protocol supplementary data at https://static-content.springer.com/esm/art%3A10.1186%2Fs13643-017-0432-8/MediaObjects/13643_2017_432_MOESM3_ESM.xlsx). The separate components (selection, comparability and outcome) were assigned stars by considering separate sub-questions within each component. Selection consisted of sub-questions relating to population representativeness (1 star), ascertainment of CTC result (1 star) and knowledge of disease status prior to study entry (1 star). Comparability consisted of CTC blinding (1 star) and standardisation of CTC technique (1 star). Outcome consisted of method to identify PICRCs (1 star), length of follow-up (1 star) and rate of loss to follow-up (1 star).

Raters agreed initially on 63·9% of scores (23 of 36), with the greatest variability evident within the comparability category, in which rater 2 consistently provided lower scores than rater 1. Following discussion, consensus agreement was reached in the remaining 36·1% (13 of 36) of scores.

Effect of faecal tagging

Forest plot for the primary outcome, presented as the number of PICRCs detected divided by the total number of cancers detected, split by use of faecal tagging. Studies in which all patients received faecal tagging are labelled tagging.all=1; studies in which tagging was used variably, not used at all, or its use was not reported, are labelled tagging.all=0. We also found no significant difference when comparing the number of PICRCs divided by the number of CTCs conducted; or when considering use of faecal tagging as three categories (i.e. used for all patients, used variably, not used at all; data not shown).



Small study effects and publication bias

Funnel plots for the primary outcomes of (a) Number of PICRCs / Total cancers detected; and (b) Number of PICRCs / Number of CTCs