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THE ROLE OF IMAGING IN SCREENING SPECIAL FEATURE: REVIEW ARTICLE

Colon cancer screening with CT colonography: logistics, cost-effectiveness, efficiency and progress

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ABSTRACT

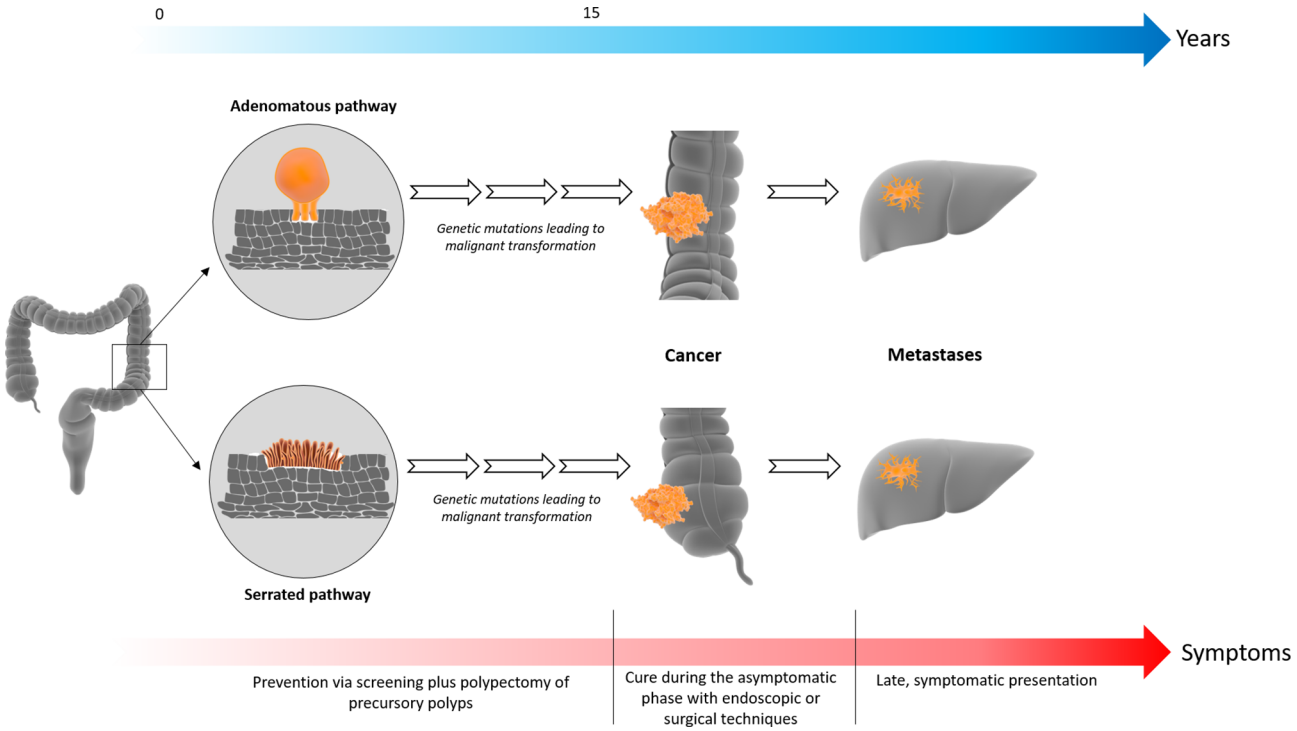
Colorectal cancer (CRC) incidence and mortality can be significantly reduced by population screening. Several different screening methods are currently in use, and this review focuses specifically on the imaging technique computed tomographic colonography (CTC). The challenges and logistics of CTC screening, as well as the importance of test accuracy, uptake, quality assurance and cost-effectiveness will be discussed. With comparable advanced adenoma detection rates to colonoscopy (the most commonly used whole-colon investigation), CTC is a less-invasive alternative, requiring less laxative, and with the potential benefit that it permits assessment of extra colonic structures. Three large-scale European trials have contributed valuable evidence supporting the use of CTC in population screening, and highlight the importance of selecting appropriate clinical management pathways based on initial CTC findings. Future research into CTC-screening will likely focus on radiologist training and CTC quality assurance, with identification of evidence-based key performance indicators that are associated with clinically-relevant outcomes such as the incidence of post-test interval cancers (CRC occurring after a presumed negative CTC). In comparison to other CRC screening techniques, CTC offers a safe and accurate option that is particularly useful when colonoscopy is contraindicated. Forthcoming cost-effectiveness analyses which evaluate referral thresholds, the impact of extra-colonic findings and real-world uptake will provide useful information regarding the feasibility of future CTC population screening.

INTRODUCTION

Colorectal cancer (CRC) is a significant public health burden, with over 200,000 deaths in Europe in 2012.[1] However, it can be prevented,[2] a fact that underpins the concept of CRC screening. Most colorectal cancers arise from benign precursors via one of two main pathways; the adenoma-carcinoma sequence or the serrated neoplasia pathway. In each case, benign polyps slowly transform into cancer as they accumulate genetic mutations, Figure 1.[3,4] Even after malignant transformation, most early CRC is curable, but 5-year survival decreases with higher tumour stage.[5] The long dwell-time of benign (pre-malignant) precursor lesions enables a large window of opportunity in which their removal can prevent cancer from ever occurring (*i.e.* reducing disease incidence).[6] Furthermore, detection of established cancers at an early stage facilitates their cure (*i.e.* reducing disease-specific mortality).[7,8]

The term "CRC screening" is generally reserved for population-based programmes (as recommended by the EU Commission)[9] with "opportunistic screening" or "asymptomatic assessment" used for individuals outside organised call-recall programmes, as performed in parts of the USA, Europe and the UK private sector.[9,10] In population-based CRC screening programmes, health authorities systematically target a specific age range of the population, usually between 50 and 74 years. Screening tests may directly visualise polyps or cancers [*e.g.* flexible sigmoidoscopy (FS), colonoscopy or computed tomographic colonography (CTC)]; or detect their sequelae [*e.g.* bleeding detected by faecal occult blood testing (FOBt)]. Internationally, most population-based CRC screening programmes use stool tests (FOBt or its immunochemical equivalent, FIT)[11] as they are cheap, readily available, safe and can be delivered via post on a population scale. Moreover, there is level 1 evidence that stool test-based screening reduces CRC mortality; by 16% in one meta-analysis, rising to 25% for those who actually participated in screening.[8] FS is also used for population screening, and has been shown to reduce both CRC incidence (by 18%) and mortality (by 26%).[12–15] Although colonoscopy is often advocated for CRC screening, the authors are not aware of any national-

Figure 1. Two main pathways contribute to the development of colorectal cancer (CRC), with most sporadic cancers occurring via the adenomatous pathway. Accumulation of genetic mutations leads to the development of cancer from benign, precancerous polyps; if removed, this can prevent CRC from occurring (*i.e.* reduce incidence). Detection and treatment of early cancer during its asymptomatic phase can improve survival rates (*i.e.* reduce mortality). Image constructed from elements available from www.somersault1824.com.



scale organised screening programme using colonoscopy on a call-recall basis as the primary test, although this is in setup in Poland.[16] More commonly, it is used after positive FOBt/FIT to confirm neoplasia and resect polyps,[17] or where FS has detected larger or multiple polyps in the distal colon.[12]

A more detailed discussion of the various CRC screening tests and their attributes, is beyond the scope of this review and can be found elsewhere,[18,19] instead, here we review the current imaging techniques in use for CRC screening with emphasis on CTC.

LOGISTICS OF IMAGING-BASED SCREENING

CT colonography

CTC was first described in 1994 as a diagnostic test for both colorectal cancer and polyps.[20] Its use has increased markedly, with approximately 100,000 performed each year in the UK.[21]CTC comprises reconstructed 2- and 3-dimensional (2D, 3D) X-ray images of the cleansed, gas-distended bowel, and requires no sedation or analgesia. CTC is less invasive than colonoscopy, and enables review of the appendix and extra colonic organs in addition to the colonic mucosa (Figure 2). Despite these advantages, use of CTC for CRC population screening in Europe has been hampered by several factors. Lack of long-term randomised control trial (RCT) evidence demonstrating an impact of CTC screening on CRC mortality (or incidence) is perhaps the most important. While similar evidence is also absent from the colonoscopy literature, use of colonoscopy as a screening investigation is extrapolated from robust evidence demonstrating the positive outcome of screening with FS.[12–14,22]

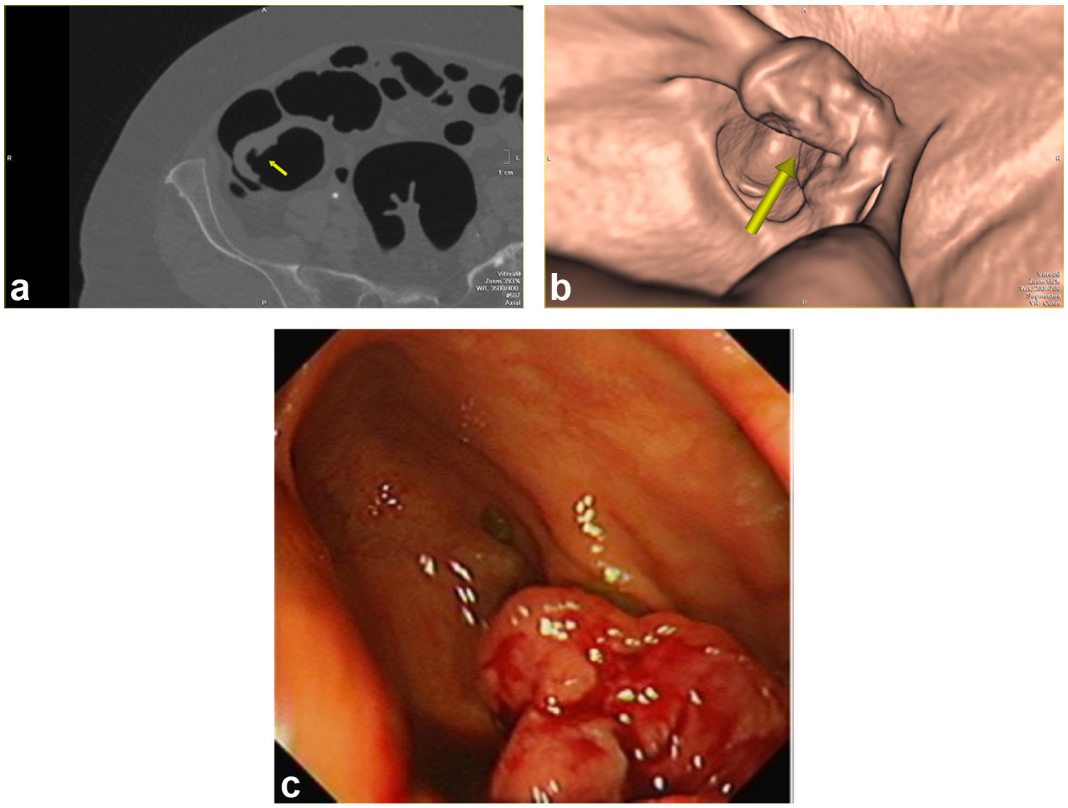
Are we testing early enough?

CRC is the prime cancer killer in many Western countries among people who do not smoke, affecting 1 in 14 males and 1 in 19 females.[23] Accordingly, most screening programmes target males and females equally. While current CRC screening recommendations advise targeting individuals between the ages of 50 and 74,[10,24] it is possible that lowering the starting age to 45 years may be beneficial.[25] In contrast to older populations, CRC incidence is increasing in patients aged <50 years.[26] A prospective single-centre study showed a significant increase in adenoma detection rate in people aged 45–49 years *vs* those 40–44 years (26 *vs* 13% respectively); a trend that persisted even after exclusion of personal and familial history of polyps or CRC.[27] Historically, adenoma (and advanced adenoma) detection rates were viewed as low in such age groups,[28] but these data were derived from a largely Caucasian, affluent population and using older endoscopic technology with limited quality assurance, suggesting true adenoma prevalence may have been underestimated. Ignoring cost concerns, CRC screening may therefore be beneficial at age 45. Further research is required to evaluate the potential role of CTC in this population.

Diagnostic accuracy and the screening target

Considerable evidence exists to suggest that CTC is as accurate as colonoscopy for detection of established CRC, including two

Figure 2. (a) Two-dimensional (2D) axial CTC image depicts a 4 cm saddle-shaped caecal lesion (arrow). (b) Three-dimensional (3D) endoluminal image shows the morphology of the tumour. (c) Corresponding colonoscopy image. The patient underwent right hemicolectomy, with final pathological diagnosis of a moderately differentiated adenocarcinoma, pT3 N0 V0 R0, Duke's B (TNM 5th edition).



separate meta-analyses.[29,30] CTC also has excellent sensitivity for large polyps, confirmed by meta-analyses of cohort studies[31,32] and a multicentre pragmatic randomised trial of symptomatic patients.[33] These results are achievable in a multicentre setting—for example, in the American College of Radiology Imaging Network (ACRIN) 6664 study of average-risk screenees, diagnostic sensitivity for adenomas measuring 10 mm or greater was 90%.[34] Although diagnostic sensitivity is lower for smaller lesions (estimated at 76% for 6–9 mm adenomas in one meta-analysis of studies recruiting asymptomatic screenees,[32] this must be balanced against their low biological risk.

Specific consideration must also be given to sessile serrated adenomas (SSAs), which account for approximately 15% of CRC, disproportionately contribute to interval CRCs and are located more frequently in the right colon.[4] In a Dutch randomised trial, CTC had significantly lower sensitivity than colonoscopy for flat high-risk dysplastic SSAs.[35] Previous research has also shown right-sided flat colonic polyps are more difficult to detect by both colonoscopy and CTC.[36,37] However, these studies are largely derived from an era in which techniques to identify SSAs at CTC were largely unknown; more recent data suggest that optimised CTC permits their detection.[38,39] Fortunately for radiologists and patients, these polyps are typically indolent, with a mean dwell time of up to 17 years before development of dysplasia which may then progress to carcinoma.[4] Furthermore, improved radiologist training with superior recognition of subtle, proximally located polyps will likely improve their detection.[40,41]

Test acceptability and uptake

Successful population screening requires good uptake (attendance and completion rates), since this affects the population-level diagnostic yield, and therefore the overall effectiveness of the programme. A test with 100% sensitivity that is declined by most patients will be substantially outperformed by a 50% sensitive test with universal uptake.

Participation in both population-based and opportunistic CRC screening programmes in Europe, falls well below the 65% recommended by the European Commission.[9,42] In fact, only 33% of the 50- to 74-year-old European population were invited for CRC screening in 2013/14, with only 14% ultimately being tested.[9] This contrasts with figures observed in the USA, where participation among the target population is estimated at 59%.[43] It is critical that we have wide access to well-tolerated, sensitive tests to improve these figures.

In randomised clinical trials involving CTC, highest uptake is for FIT (50%), followed by CTC (25 to 34%), FS (27%) and then colonoscopy (15 to 22%).[44–46] In general, screening with CTC is perceived as less onerous than colonoscopy, contributing to increased uptake.[46] For example, in a multicentre patient survey

of 1417 individuals, 68% chose CTC screening due to the less-invasive nature of the investigation and 47% because it avoided colonoscopy risks.[47] There are relatively little data regarding intentions to attend repeated screening rounds after initial CTC, but one Dutch study found 93% of patients stated they were likely to re-attend at their next screening round after initial CTC.[48]

Reasons for lack of participation in screening by CTC include perceptions and beliefs relating to both CRC screening in general and CTC in particular. For example, in one trial, CTC non-attenders cited lack of symptoms and unpleasantness of the procedure as the underlying reasons.[49] Laxative bowel preparation is frequently identified as the most unpleasant factor[48,50] and reducing discomfort from bowel preparation increases test acceptability.[50] In support, reduced laxative CTC (softener plus tagging agent) significantly increased uptake compared to standard laxative CTC (plus tagging)[45] in one randomised trial (28.1 *vs* 25.2%, $p = 0.047$), with no reduction in neoplasia detection.[45]

Diagnostic yield

The diagnostic yield of a screening test is essentially a function of its sensitivity and its uptake. Three recent RCTs provide diagnostic yield data of CTC when used for prevalent (first) round population screening, compared to either FIT or colonoscopy (SAVE trial, Italy),[45] FS (PROTEUS trial(s), Italy),[44] or colonoscopy (COCOS trial, Netherlands)[46] (Table 1). Taken together, the diagnostic yield for advanced neoplasia ranged from 5 to 6 neoplasms per 100 participants, with CTC superior to flexible sigmoidoscopy (diagnostic yield, 4.7%) and one round of FIT (1.7%); (Table 1). These results are encouraging since advanced neoplasia is the primary target of CRC screening and there is now RCT evidence to support its inclusion as a test option.

However, the possibility of lower detection of distal neoplasia by CTC warrants further consideration. In the PROTEUS study, the detection rate of advanced neoplasia in the distal colon was lower for CTC than FS (2.9 *vs* 3.9%).[44] One possible explanation is that this study employed a computer-assisted detection (CAD) program as the primary reader for the CTC scans. Increased reliance on CAD may have compromised detection of distal adenomas. However, detection of proximal advanced neoplasia by CTC (*vs* FS) is a significant benefit; in the PROTEUS study, approximately 80% of individuals with proximal advanced neoplasia had no distal lesion, and so would have been missed with FS screening.[44] While CTC substantially outperformed a single round of FIT screening, FIT is designed to be repeated frequently, thereby increasing advanced adenoma yield over time. The result of subsequent FIT rounds are awaited from the SAVE trial, which will inevitably increase yield above 1.7%.[45] Irrespective, current data strongly suggest that CTC is a viable alternative to both FS and FIT.

Data comparing CTC to colonoscopy are more nuanced. When considered on a per-attendee basis (*i.e.* patients attending their randomised procedure), the two most relevant trials showed neoplasia detection rates were lower for CTC than colonoscopy (6.1 *vs* 8.7% in the COCOS trial and 5.2 *vs* 7.2% in the SAVE trial).[45,46] However, participation was higher for those

Table 1. Results of three recent European multicentre trials evaluating CT colonography screening

Study acronym (first author and year)	Number of invitees	Population age range (years)	Participation rate (%)		Diagnostic yield; advanced neoplasms per 100 participants		Diagnostic yield; advanced neoplasms per 100 invitees	
			CTC	Comparator(s)	CTC	Comparator	CTC	Comparator
COCOS (Stoop et al 2012)[46] (Tutein et al 2015)[51]	8,844 82[b]	Never screened 50–75	34	OC - 22	6.1[a] 8.6[b]	OC - 8.7	2.1 2.9[b]	OC - 1.9
SAVE (Sali et al 2016)[45]	16,087	Never screened 54–65	28[c] 25[d]	FIT - 50[d] OC - 15	5.5[c] 4.9[d]	FIT - 1.7[e] OC - 7.2	1.5[c] 1.2[d]	FIT - 0.9[e] OC - 1.1
PROTEUS1 & 2 (Regge et al 2017)[44]	42,929	Never screened 58–60	30[f]	FS - 27[f]	5.1a	FS - 4.7a	–	–

CTC, computed tomographic colonography; OC, optical colonoscopy.
[a]Using a threshold of 10 mm or greater to precipitate referral for colonoscopy. Patients with 6–9 mm polyps were initially enrolled in CTC follow-up.
[b]After inclusion of the follow-up cohort of patients with 6–9 mm polyps detected at initial CTC.
[c]Reduced preparation CTC group.
[d]Full-preparation CTC group.
[e]Data from PROTEUS1.

randomised to CTC, offsetting the lower detection rate. This results in slightly superior per-invitee detection rates for CTC, albeit not statistically significant (2.1% for CTC *vs* 1.9% for colonoscopy in the COCOS trial, and 1.4% for CTC *vs* 1.1% for colonoscopy in the SAVE trial).[45,46] In the COCOS study (radiologist as first-reader and secondary read with CAD) patients with polyps measuring 6–9 mm detected by CTC were not referred for polypectomy but instead enrolled in a CTC follow-up programme.[46,51] When polyps were subsequently resected from these individuals, the advanced neoplasia detection rate of CTC mirrored that of colonoscopy per-attendee (8.6% *vs* 8.7%), and was superior per-invitee (2.9% *vs* 1.9%).[51] This radiologist reader approach is how a CTC-based screening programme is likely be deployed in clinical practice. These data replicate existing non-randomised cohorts, in which advanced neoplasia detection rates were equivalent between CTC and colonoscopy.[52] Overall, the current data strongly suggest CTC is a viable alternative screening strategy to colonoscopy, with potentially superior uptake and similar sensitivity for advanced neoplasia.

Referral thresholds and diminutive polyps

It is currently unclear what number or diameter of polyps found at CTC should trigger referral for assessment by colonoscopy for consideration of biopsy or excision. Many radiologists recommend referral of all polyps with maximal diameter 10 mm or greater to colonoscopy, with CTC follow-up or colonoscopy for polyps 6–9 mm, and return to normal screening for patients with diminutive polyps (≤5 mm).[53] In contrast, endoscopists typically perform routine polypectomy, removing all polyps they see. However, diminutive polyps have very low risk of high grade dysplasia or malignancy, each less than 0.5%,[54] supporting Japanese national guidance which permits endoscopists to ignore diminutive polyps unless flat or depressed.[55] Consequently, referral for colonoscopy without any size threshold appears counterintuitive, since it necessitates considerable use of precious resource for no gain.[56,57] A decision analysis model suggested that the 10-year CRC risk for unresected diminutive polyps was 0.08%, equating to over 2000 polypectomies to prevent a single CRC, which in any case would be prevented by detection of a progressing polyp at scheduled 5-year repeat screening CTC.[56]

Small polyps (6–9 mm maximal diameter) can be reassessed by interval CTC or referred for consideration of polypectomy.[24,58,59] CTC follow-up for 6–9 mm diameter polyps appears safe; two studies[60,61] showed no patients (of 259 enrolled) developed invasive cancer during 24–36 months of follow-up. Indeed, small polyps can regress over time; in one series 50% of polyps were unchanged, 28% regressed (decrease in diameter) and only 22% increased in size over a three period.[60] However, such follow-up requires excellent recall systems; in one series,[60] a patient with an enlarging polyp was lost to follow-up, and re-presented over 5 years later with established cancer. This has clear implications for service design and patient care; risk management systems must be incorporated.

Ultimately, the most important quality indicator of CTC management is the rate of interval cancer after negative CTC. A recent systematic review has shown this rate to be 4.4% in the published literature,[62] which compares favourably with colonoscopy (published rates 3–9%).[63] These data translate to a low interval cancer incidence of 0.6 per 1000 person-years of follow-up, particularly encouraging given that only 7% of the interval cancers retrospectively reviewed in this study were truly occult.[62] These data support current CTC management strategies of not reporting diminutive polyps and the option of CTC follow-up for small polyps. Since most missed cancers at CTC were visible in retrospect, formal training and accreditation is warranted to ensure consistent high-quality practice (inter)nationally.

Safety and radiation dose

CTC is minimally invasive and extremely safe, with no reported deaths and very few severe complications since its inception.[64] Luminal perforation is very uncommon at CTC (approximately 1 in 3,500 patients overall, and under 1 in 5,000 at screening)[65] and most perforations are asymptomatic, as CT is exquisitely accurate for detection of extra luminal gas.[66] Furthermore, most patients with CTC-associated perforation require no surgical intervention (fewer than 1 in 12,500 require it overall).[65] It is impossible to know the true number of perforations after colonoscopy, as patients do not undergo imaging routinely, even when there is abdominal discomfort. Therefore, known colonoscopy-associated perforation rates of approximately 1 in 1000 procedures significantly underestimates the total, but is still 20 times more frequent than the 'symptomatic perforation rate' for CTC.[67] CTC is also associated with fewer serious complications than colonoscopy such as cardiovascular events.[68,69]

The other commonly-cited concern regarding CTC screening is radiation dose. Many radiation scientists acknowledge there is no conclusive evidence that radiation from medical imaging causes harm to adults.[70] However, given the lack of certainty, radiologists adhere to the principle of minimising radiation dose as much as possible under the linear no threshold (LNT) model of dose-response used to determine risk. This assumes potential harm from all radiation, with a linear relationship between magnitude of dose and risk of inducing cancer (starting at zero for both).[71] However, these theoretical harms must be balanced against the known benefits of cancer prevention. Under LNT assumptions, one risk projection model estimated that for every radiation-induced cancer, 24 to 35 CRCs are prevented by 5 yearly CTC-screening between the ages of 50 and 80 years.[72] This estimate was based on mean effective doses of 8 mSv for females and 7 mSv for males, far higher than current estimates of 4 mSv,[73] implying the benefit-risk ratio is even more favourable. Use of low dose scanning protocols and iterative reconstruction techniques are likely to reduce the effective dose of CTC even further, without compromising image quality.[74,75]

Extra-colonic findings

People who choose CTC for primary screening anecdotally describe extra colonic organ review (including appendix) as an important factor influencing this choice over competing tests. Indeed, many will recall a close relative or friend who suffered with cancer of an extra colonic organ and so they seek reassurance from a normal CTC. One study of patient preference supports this anecdote and found 43% of people would prefer

CTC to colonoscopy for screening because of its ability to detect abnormalities outside the colon.[47] Importantly, in a screening setting, CTC detects extracolonic cancer as frequently as it finds CRC.[76] The majority of these extracolonic cancers (54%) were detected at an early stage, implying better prognosis for many.[76] CTC also detects important non-malignant conditions such as aortic aneurysm and osteoporosis. The potential negative impact from additional tests and related patient anxiety following detection of extra colonic findings should be balanced against the reassurance patients feel after a normal CTC with no significant abnormality; indeed, most patients would trade many false-positive extra colonic diagnoses at CTC for the benefit of finding a single cancer.[77] It is very important that patients are given the opportunity to be counselled about the accuracy, limitations and potential risks of CTC for visualising extra colonic organs. It is also very important that radiologists reporting screening CTC are experienced in detection and management of extra colonic abnormalities with specific strategies tailored to the asymptomatic context in which they have been found.

Quality assurance

CTC quality assurance (QA) is critical to achieving high standards of examination quality and reporting accuracy. Radiologists reporting CTC in both primary and secondary screening settings must be highly experienced and consciously competent to detect and characterise subtle advanced colonic neoplasia and avoid unnecessary referral of healthy asymptomatic people for additional investigation which will in turn increase anxiety, potential for harm and financial cost for no benefit. To help achieve this, screening CTC radiologists must follow their screening colonoscopy colleagues; for example, regularly reporting both symptomatic and screening CTC in routine practice; demonstrate a subspecialty interest in colorectal cancer imaging; attend multidisciplinary colorectal cancer and/or polyp meetings; and audit their practice including management recommendations.

However, quality of screening CTC has not been subject to the same degree of scrutiny as colonoscopy and pathology. A national survey of CTC in the English Bowel Cancer Screening Programme (BCSP), found 10% of radiographers performing CTC examinations had received no formal training and one-third of radiologists interpreting the images were inexperienced.[78] Perhaps unsurprisingly, when investigating CTC performance in the BCSP, CTC was found to have a 50% lower detection rate for CRC and high-risk polyps compared to colonoscopy, although whether due to lower sensitivity or selection bias is uncertain.[79] Perhaps analogous, a pre-BCSP review of UK colonoscopy practice revealed poor performance and wide variation in practice, with adjusted caecal intubation rates (CIR) of only 57% (and inadequate training).[80] This finding led to a multi-million pound training programme for colonoscopy and subsequent formal QA programmes. Developing and monitoring key performance indicators (KPIs) for colonoscopy, supported by a robust training and accreditation process, has transformed the quality of colonoscopy. Consequently, colonoscopists in both screening and symptomatic practice are now monitored via numerous evidence-based metrics including adenoma detection rate (ADR), CIR, withdrawal time and adverse event rate. Poor performance in these markers (ADR and CIR) is associated with higher post-colonoscopy cancer rates.[81–83] There is no analogous training or accreditation programme for CTC, either in the UK or internationally, and no universally-agreed KPIs. This lack of evidence-based performance indicators hampers the development of the robust QA required for implementation of CTC screening programmes (Table 2).

Improved recording of CTC data, use of standardised reports (C-RADS or the adapted version employed by the UK BCSP) and follow up of objective endpoints such as post-test CRC rates are imperative to successful implementation of screening CTC. This process will help identify which metrics best permit monitoring and improvement of services and practitioners. The National Co-ordinating Group for Radiology in the BCSP introduced and have since updated guidelines for practice and standards for reporting CTC findings.[84] Radiologists have accompanied BCSP peer review visits, but the evidence base and impact of these initiatives has not been formally evaluated. To address this gap, the authors and collaborators have initiated PERFECTS, a national study to evaluate a training and testing programme for CTC; this cluster-randomised trial will determine the impact

Table 2. Logistical factors that would be necessary to implement CT colonography population screening

Test characteristics	Patient management considerations
Access and availability • Local and national CTC screening infrastructures • Appropriate local colonoscopy services	Information systems to (a) send out invitations for initial screening with integrated reminders to ensure participation and (b) recall individuals for repeat screening
High diagnostic accuracy and sensitivity	Consensus population age for CTC-screening
Acceptability • Perceived—optimised to boost initial uptake • Absolute—to ensure re-attendance at subsequent screening rounds	Management and treatment pathways for colonic findings • Consensus polyp size referral threshold • Follow-up pathway for unresected polyps
Consensus quality assurance and training for reporting radiologists, including evidence-based KPIs	Integration with other screening programmes • *E.g.* abdominal aortic aneurysm screening / follow-up; thoracic CT for lung cancer
Safety monitoring system to identify and manage adverse events	Management pathways for extracolonic findings
Cost-effective in comparison to alternative screening modalities	

CTC, computed tomographic colonography; KPI, key performance indicators.

of a potential accreditation and QA process on CTC diagnostic accuracy.[85]

Cost-effectiveness

Cost-effectiveness analyses of CTC as a screening test typically use models incorporating assumptions about the natural history of polyps, CTC sensitivity, test uptake, frequency of screening rounds, and use of follow-up colonoscopy (and CTC, where appropriate). These models attempt to estimate the impact on CRC-related mortality using these assumptions, and balance the benefits against the economic costs of the (theoretical) programme. While results have been variable,[86] CTC screening is typically more cost-effective than no screening.[87,88]

In comparison to other screening tests, the comparison is more complex. CTC appears less cost-effective than FIT,[89] but comparable to FOBt and FS in an earlier systematic review.[86] When compared to colonoscopy, results are variable.[86] The reason for such heterogeneous results is multifactorial, but largely related to the sensitivity of economic models to their original inputs and assumptions. For example, applying a larger polyp diameter threshold for colonoscopy after CTC improves cost-effectiveness, whereas a threshold of ≥6 mm is often used for modelling. Moreover, few studies have incorporated a strategy of CTC follow-up for 6–9 mm polyps (*vs* referral for polypectomy). Complicating matters further is the highly variable unit cost of each test internationally, and different uptake rates for tests by both gender and geographical region; for example, Italian males were more likely to accept CTC than FS, whereas there was no difference for Italian females.[44] Fundamentally, all such modelling depends on assumptions regarding the natural history of colorectal polyps (*i.e.* how many will transition to cancer, and at what rate). Since our knowledge of this biology continues to evolve, existing cost-effectiveness models may be incorrect. For example, most studies ignore the serrated pathway entirely, assuming all cancers arise from adenomas; and predate current knowledge that a significant proportion of adenomas regress over time.[60] Moreover, we are now aware that both adenomas and serrated polyps have longer pre-malignant phases than previously assumed,[4,90] meaning existing models may over estimate the significance of both missed and unresected lesions. Finally, extracolonic findings are rarely incorporated, despite these having the potential to both increase costs (via additional testing) or reduce them (via prevention of cancer or aneurysm-related morbidity and healthcare costs).

MRI colonography

MR colonography (MRC) is occasionally offered for CRC screening and a recent systematic review showed MRC can accurately detect CRC and polyps larger than 10 mm diameter.[91] However, the number and size of studies is relatively small, and the data too heterogenous to perform reasonable meta-analysis of the detection of smaller polyps.[91] Notably, MRC was found to have a sensitivity of 75% for advanced neoplasia compared to 97% for CTC published by the same authors in a similar size of screening population.[92,93] The main potential advantage of MRC over CTC is lack of radiation, but its relative importance is diminishing as CTC dose falls. Furthermore, patient experience of retaining a colon filled with liquid or gas within the confines of an MRI scanner for a longer examination time than CTC will require thorough evaluation prior to recommendations for its routine use. Such evaluation, as well as further assessment of the diagnostic accuracy of small polyps, will be necessary before radiological societies can produce consensus recommendations on the use of MRC.

Future

Now CTC technique has evolved and reporting excellence is achievable, future CTC-screening research should focus on establishing more robust training and quality assurance programmes with the identification of measurable KPIs that predict clinically relevant outcomes. Further research on the natural history and pathogenesis of CRC will help inform decisions regarding appropriate polyp size thresholds for referral to colonoscopy and length of CTC-screening intervals. Existing cost-effectiveness analyses should be updated based on real-world participation data, contemporary management pathways, detailed simulation of colorectal polyp biology, and incorporation of extracolonic findings.

SUMMARY

Most cases of CRC are potentially preventable by screening. CTC is accurate for detection of important polyps in both primary and secondary screening settings, with advantages in patient safety and experience, while being highly cost-effective. However, there is considerable variation in quality of practice, and so renewed focus on training and accreditation will help assure the quality of CTC screening. Refinements in imaging technology, resulting in lower radiation dose and more detailed cost analyses, particularly addressing the impact of extra colonic findings, will help inform whether CTC screening should be implemented more widely.

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