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REVIEW ARTICLE

CT colonography for population screening of colorectal cancer: hints from European trials

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ABSTRACT

CT colonography (CTC) is a minimally invasive radiological investigation of the colon. Robust evidence indicates that CTC is safe, well tolerated and highly accurate for the detection of colorectal cancer (CRC) and large polyps, which are the targets of screening. Randomized controlled trials were carried out in Europe to evaluate CTC as the primary test for population screening of CRC in comparison with faecal immunochemical test (FIT), sigmoidoscopy and colonoscopy. Main outcomes were participation rate and detection rate. Participation rate for screening CTC was in the range of 25–34%, whereas the detection rate of CTC for CRC and advanced adenoma was in the range of 5.1–6.1%. Participation for CTC screening was lower than that for FIT, similar to that for sigmoidoscopy and higher than that for colonoscopy. The detection rate of CTC was higher than that of one FIT round, similar to that of sigmoidoscopy and lower than that of colonoscopy. However, owing to the higher participation rate in CTC screening with respect to colonoscopy screening, the detection rates per invitee of CTC and colonoscopy would be comparable. These results justify consideration of CTC in organized screening programmes for CRC. However, assessment of other factors such as polyp size threshold for colonoscopy referral, management of extracolonic findings and, most importantly, the forthcoming results of cost-effectiveness analyses are crucial to define the role of CTC in primary screening.

INTRODUCTION

Colorectal cancer (CRC) is a significant social health issue, with 1.4 million new cases every year worldwide.[1] In Europe, CRC is the most frequent tumour in both sexes, accounting for >400,000 cases per year, and the second cancer-related cause of death, determining >200,000 casualties per year.[2] Incidence of CRC is higher in males than in females.[1]

Over the past decades, mortality from CRC substantially decreased in Western countries; in the USA, a 45% reduction was observed between 1975 and 2010.[3,4] This is most likely due to adoption of screening interventions and to the availability of more effective treatment options.[4] Costs for treatment of CRC are escalating, in particular for advanced cases, while screening for CRC is most probably cost-effective, regardless of the test employed.[5,6]

CRC fulfils many criteria as a suitable disease for screening. Specifically, most CRCs develop from a detectable, treatable precancerous lesion (adenoma) over a long time interval, through the accumulation of multiple subsequent gene mutations, in the so-called adenoma–carcinoma sequence.[7] Malignant transformation may take about 10 years, leaving an adequate time window to detect cancer at an early stage, which can be cured, or to identify adenomatous polyps, which can be removed by colonoscopy.[8,9] Several tests, such as faecal occult blood test (FOBT), faecal immunochemical test (FIT), sigmoidoscopy and colonoscopy, have been shown to have a role in detecting malignancy and its precursors.

Since 2003, CT colonography (CTC) has been proposed as a less invasive, viable alternative to colonoscopy.[10] CTC has been validated in two large multicentre trials, one in Europe on a high-risk population and the other in the USA on an asymptomatic population.[11,12] The sensitivity and specificity of CTC for CRC or advanced adenomas ≥6 mm were 78 and 88%, respectively, in the former, and 85 and 88%, respectively, in the latter.[11,12] In a randomized UK trial, the overall accuracy of CTC in detecting cancer and large polyps (≥10 mm) in patients who were symptomatic was found to be comparable with that of colonoscopy.[13] In a meta-analysis, the estimated sensitivity of CTC for large polyps in asymptomatic subjects was 83–88%.[14]

In order to evaluate the performance and costs of CTC as a primary screening test for CRC, three randomized trials were conducted in Europe between 2009 and 2014.[15–17]

We reviewed established screening tests for CRC and performance of CTC as a primary and second-level screening test with a special focus on the results of the three above-mentioned European randomized trials.

ESTABLISHED SCREENING TESTS FOR COLORECTAL CANCER

Screening tests for CRC can be divided into indirect (*i.e.* FOBT or FIT) and direct or endoscopic tests (*i.e.* sigmoidoscopy and colonoscopy). Direct tests may reduce both the incidence and mortality of CRC, as they can identify CRC precursors at an early stage, while indirect tests predominantly detect cancer rather than adenomas. With respect to this classification, CTC can be considered a direct test.

FOBT is aimed to identify microscopic blood traces in faeces, relying on the assumption that cancer and large polyps may bleed. Subjects tested positive are invited to undergo total colonoscopy. As bleeding from colorectal lesions can be intermittent, FOBT has to be repeated every 1 or 2 years to be an effective screening tool.

There are two types of FOBT, guaiac-based FOBT and FIT.

Guaiac faecal occult blood test

- Guaiac FOBT is based on a natural phenolic compound that reacts with haemoglobin. It requires diet restrictions, as certain foods can determine false-positive (*e.g.* meat) or false-negative results (*e.g.* C vitamin), and three stool samples.
- Randomized trials demonstrated that screening with Guaiac FOBT reduces mortality from CRC.[18]

Faecal immunochemical test

- FIT quantitatively detects human haemoglobin through an immunochemical method. It usually requires a single stool sample and its cut-off level can be adjusted, optimizing the sensitivity and specificity of the test.[19]
- No randomized trials have been performed to demonstrate a reduction in mortality by FIT screening.
- Comparative studies showed that FIT has higher uptake and sensitivity for CRC and adenomas than guaiac test in population screening.[20,21] Thus, FIT is the test recommended by the European Commission for population screening in Europe.[22]

Sigmoidoscopy

- Sigmoidoscopy consists in an endoscopic examination of the distal colon performed after a cleansing enema.
- If polyps are found at sigmoidoscopy, the subject is referred to total colonoscopy.
- Randomized trials demonstrated that screening with sigmoidoscopy reduces incidence of CRC.[23,24]
- In general, sigmoidoscopy has lower participation but higher detection rate than guaiac FOBT and FIT.[25]

Colonoscopy

- Colonoscopy is considered the gold standard examination for the diagnosis of colorectal lesions and it has the ability to prevent cancer by directly removing adenomatous polyps.[9]
- To date, there is no evidence from randomized trials demonstrating its capacity to reduce incidence and mortality for CRC.
- The use of colonoscopy for population screening is limited by its invasiveness and costs and, especially, by the low attendance observed in screening studies.[26,27]

Two different approaches are possible for CRC screening: (1) organized or population-based screening and (2) opportunistic screening. Organized screening is offered by health authorities at a national or regional level in the form of a screening programme targeted at subjects at average risk for CRC, usually in the age range of 50–70 years. In this approach, individuals are invited to perform a screening test and are followed up in case of a positive finding. Organized screening programmes are implemented in many European countries, Canada and Australia, and they are based on FOBT, FIT, sigmoidoscopy or colonoscopy.[28,29]

In opportunistic screening, eligible subjects undergo a screening test after referral by their general practitioner or as a self-prompted request. This screening modality is in use in the USA, Germany and some Eastern European countries.[29]

EUROPEAN TRIALS EVALUATING CT COLONOGRAPHY SCREENING

In Europe, three randomized screening trials were performed or are still ongoing to evaluate population screening with CTC, one in the Netherlands comparing CTC *vs* colonoscopy (COCOS study)[26] and two in Italy: the SAVE study (Tuscany region) comparing reduced preparation and full-preparation CTC, FIT and colonoscopy[27] and the PROTEUS study (Piedmont region) comparing CTC *vs* sigmoidoscopy.[30] Study designs and populations are shown in Table 1, whereas the main results are summarized in Table 2.

PARTICIPATION IN CT COLONOGRAPHY SCREENING

Participation is crucial for the effectiveness of a population-based screening programme. Ideally, a screening programme should guarantee full coverage of the target population. However, participation in CRC screening programmes is influenced by organizational (*e.g.* modality of invitation and test delivery, involvement of general practitioners) or individual factors (*e.g.* gender, socioeconomic status, subject attitude towards screening), which may limit uptake.[31–34] Participation in FIT, which is the most employed test in organized screening programmes, is in the range of 48–62%.[35–37]

In the European randomized trials, participation rates in CTC screening were quite similar to each other, in the range of 25–34%.[26,27,30] Participation was higher in the COCOS trial (34%) with respect to Italian trials (25–30%). This difference in participation between the two countries was typically observed for FIT screening also.[35,36]

Table 1. European randomized trials evaluating screening CT colonography (CTC): study design and population

Authors (years)	Study acronym	Study type	Sample size	Population Age range (years)	Comparator	Main outcomes	Polyp size for OC referral (mm)
Stoop et al (2012)[26]	COCOS	MC	8844	Never screened 50–75	OC	Participation rate Detection rate	≥10
Sali et al (2015)[27]	SAVE	SC	16,087	Never screened 54–65	FIT (3 rounds)[a] OC[a]	Participation rate Detection rate	≥6
Regge et al (2016)[30]	PROTEUS1	MC	1984	Never screened 58–60	FS	Participation rate	≥6
	PROTEUS2	MC	40,945	Volunteers, never screened 58–60	FS	Detection rate	≥6

FIT, faecal immunochemical test; FS, flexible sigmoidoscopy; MC, multicentre; OC, optical colonoscopy; SC, single centre.
[a]In the SAVE trial, subjects were randomized into four groups: (1) FIT, (2) reduced preparation CTC, (3) full-preparation CTC and (4) OC.

Modalities of invitation to screening CTC in the three trials are reported in Table 3. In the PROTEUS trial, subjects were offered a pre-fixed appointment for the examination, a strategy that is known to improve participation in CRC screening.[38] This invitation modality could represent a more feasible option for a CTC screening programme, as it requires less resources than a strategy based on a face-to-face consultation. Moreover, the involvement of general practitioners, who signed the invitation letter in PROTEUS trial, could help further enhance participation.[39,40]

Bowel preparation is perceived as one of the most burdensome aspects of screening CTC.[41] As a matter of fact, in the European trials, screening CTC was offered with a reduced or laxative-free bowel preparation, with the exception of the SAVE trial, in which subjects were randomized to be invited to full cathartic preparation CTC or reduced cathartic preparation CTC (Table 3). In the SAVE study, participation was higher for reduced preparation CTC (28%) with respect to full-preparation CTC (25%), demonstrating that a reduced preparation improves participation in CTC screening, as was previously speculated.[42,43]

In comparison with other screening tests, participation rate for CTC (25–34%) was higher than that for colonoscopy (15–22%),[26,27] similar to that for sigmoidoscopy (27%)[30] and lower than that for one FIT round (50%).[27] These data confirm that screening CTC is perceived as less burdensome than screening colonoscopy.[44] However, participation rate for CTC is still much below than that for FIT, which remains the most attended screening test. A feasible strategy to increase the overall participation in CRC screening by CTC is the offer of FIT to non-attendees for CTC.[45]

Interestingly, in the Italian trials, participation in CTC screening was higher in males than in females, 31 *vs* 26%, respectively, for reduced preparation CTC in the SAVE study and 34 *vs* 27% in the PROTEUS study.[27,30] This gender-based difference in participation was observed for other screening tests.[46,36] Typically, endoscopic tests are favoured by males,[46] whereas FIT screening is usually preferred by females.[36,47] This feature of CTC may be of importance for the efficacy of a screening programme, as the incidence of CRC and adenomas is higher in males.

POSITIVITY RATE AND COLONOSCOPY REFERRAL OF SCREENING CT COLONOGRAPHY

CTC screening subjects with positive findings are invited to undergo colonoscopy. The best size threshold of colorectal lesions that are referred to colonoscopy is still under debate. The European Society of Gastrointestinal and Abdominal Radiology (ESGAR) and the American College of Radiologists guidelines suggest referral to colonoscopy of subjects with at least one polyp ≥6 mm.[48,49] In fact, the likelihood of malignancy or advanced histology in smaller polyps (<6 mm) is very low, namely 1.4% according to a recent systematic review,[50] and given the low specificity of CTC for these lesions, their reporting should be avoided, at least in a screening setting.

The Italian trials adopted a size threshold of 6 mm for colonoscopy referral, whereas the COCOS trial used a cut-off of 10 mm and followed up subjects with 6–9-mm polyps with CTC. The positivity rate of CTC was similar in the three studies (range 9–10%)[26,27,30] and significantly lower than previously speculated in asymptomatic subjects.[51] This may be important in CTC screening, where availability and costs of subsequent tests might be prohibitive.

In the COCOS trial, the positivity rate of CTC would have been 17% if polyps of 6–9 mm had been referred to colonoscopy.[26] However, findings from the follow-up study indicated that the majority of 6–9-mm polyps (65%) did not progress within 3 years.[52] Similar results were observed in a longitudinal study performed in the USA, where only 22% of 6–9-mm polyps progressed after a 2–3-year follow-up.[53] These data suggest that further investigations are needed to establish the optimal polyp size threshold for colonoscopy referral for CTC screening, especially in the 6–9-mm range.

Colonoscopy compliance in subjects with a positive CTC study was 98–100% compared with sigmoidoscopy (87%) or FIT (84%).[26,27,30] This is a convincing point in favour of CTC screening.

In the three trials, CTC was non-diagnostic in 1.6–4% of the cases,[26,27,30] owing to inadequate distension, insufficient faecal

Table 2. European randomized trials evaluating screening CT colonography (CTC): main results

Authors (years)	Participation rate (*n*)		Non-diagnostic CTC (*n*)	Positivity rate CTC (*n*)	Compliance to OC work-up (*n*)	Detection rate (*n*)		ECF
	CTC	Comparator				CTC	Comparator	
Stoop et al (2012)[26]	34% (982/2920)	OC 22% (1276/5924)	4% (44/982)	9%[a] (84/982)	100% (84/84)	6.1% (60/982)	OC 8.7% (111/1276)	11% (107/982)
Sali et al (2015)[27]	28%[b] (674/2395)[b] 25%[c] (612/2430)[c]	FIT 50%[d] (4677/9288)[d] OC 15% (153/1036)	2.5%[b] (17/674)[b] 0.5%[c] (3/612)[c]	10.2%[b] (69/674)[b] 9.8%[c] (60/612)[c]	97.7% (126/129)	5.5%[b] (37/674)[b] 4.9%[c] (30/612)[c]	FIT 1.7%[d] (79/4677)[d] OC 7.2% (11/153)	5% (65/1286)
Regge et al (2016)[30]	30%[e] (298/980)[e]	FS 27%[e] (264/976)[e]	3%[f] (79/2674)[f]	10.2%[f] (264/2595)[f]	99%[f] (260/264)[f]	5.1%[f] (133/2595)[f]	FS 4.7%[f] (127/2673)[f]	1.2%[e,f] (35/2972)[e,f]

ECF, extracolonic findings; FIT, faecal immunochemical test; FS, flexible sigmoidoscopy; OC, optical colonoscopy.
[a]It would have been 17% if polyps of 6–9 mm had been referred to OC.
[b]Reduced preparation CTC group.
[c]Full-preparation CTC group.
[d]Data refer to first FIT round.
[e]Data from PROTEUS1 study.
[f]Data from PROTEUS2 study.

tagging or both. These figures were comparable with those of colonoscopy (3%) and sigmoidoscopy screening (2.4%).[26,30]

SCREENING CT COLONOGRAPHY DETECTION RATE

The aim of a screening test for CRC is to identify advanced neoplasia, *i.e.* cancer or advanced adenoma. In the three European trials, the detection rates of CTC for advanced neoplasia were similar, ranging from 5.1 to 6.1%.[26,27,30]

The detection rate of CTC was lower than that of colonoscopy, both in the COCOS trial (6.1 *vs* 8.7%) and in the SAVE trial (5.2 *vs* 7.2%).[26,27] However, considering the detection rate per subject invited to screening, no differences between CTC and colonoscopy were observed in the COCOS (2.1 *vs* 1.9%) and SAVE (1.4 *vs* 1.1%) trials, because the higher participation rate for CTC counterbalanced its lower detection rate.[26,27] Previously, a large non-randomized US trial found no significant difference in detection rate between CTC and colonoscopy in an asymptomatic population.[54] A potential disadvantage of CTC over colonoscopy could be its lower detection rate for high-risk sessile serrated polyps, as suggested by data of the COCOS trial.[55]

In the PROTEUS trial, the detection rates of CTC and sigmoidoscopy were similar (5.1 *vs* 4.8%), but CTC had lower detection rate than sigmoidoscopy in the distal colon (2.9 *vs* 3.9%).[30] This apparent lower capability of CTC to detect polyps in the distal colon was also observed in the SAVE trial and deserves further investigation.[27]

In the SAVE trial, the detection rate of CTC (5.2%) was threefold that of one FIT round (1.7%). However, FIT has a cumulative sensitivity for CRC and advanced adenoma and has to be repeated in multiple annual or biennial rounds to be effective. Thus, for the overall assessment of the performance CTC *vs* FIT, we have to await the results of the two subsequent rounds of FIT of the SAVE trial that are accruing.

Interestingly, in the SAVE trial, the detection rate for advanced neoplasia was not significantly different between reduced preparation (5.5%) and full-preparation CTC (4.9%). This is in line with previous studies on the performance of CTC with limited bowel preparations.[56–58] Data indicate that reduced bowel preparation should be adopted for screening CTC as it enhances participation without detriment in the diagnostic yield.

CT COLONOGRAPHY READER EXPERIENCE AND COMPUTER-AIDED DETECTION

Sensitivity of CTC is proportional to reader experience.[59,60] The number of CTC examinations that should be read to obtain an adequate competence is still under debate. A study by Liedenbaum et al[61] showed that even training with 175 CTC cases might not suffice to reach proficiency in polyp detection. An analysis on the use of CTC in the English Bowel Screening Programme showed that the detection rate and positive-predictive value of CTC were significantly higher for radiologists who had read >1000 CTC overall and >175 cases per year.[62] Selection criteria for CTC readers in the three studies are shown in Table 4.

Table 3. Modalities of invitation and bowel preparation for screening CT colonography (CTC) in the European randomized trials

Authors (years)	Invitation	Pre-examination face-to-face consultation	Appointment for CTC	Diet restrictions	Bowel preparation	Faecal tagging
Stoop et al (2012)[26]	Mail	Yes	Fixed at consultation	Yes	No cathartics	IOCM (100 + 50 ml)
Sali et al (2015)[27]	Mail	Yes	Fixed at consultation	Yes	Low-dose PEG[a] PEG[b]	IOCM (70 ml)
Regge et al (2016)[30]	Mail	No	Pre-fixed	Yes	Low-dose PEG	IOCM (70 ml)

IOCM, iodinated oral contrast media; PEG, polyetilenglycole.
[a]Reduced preparation CTC group.
[b]Full-preparation CTC group.

Computer-aided detection (CAD) can be particularly useful in a screening setting where the workload for the radiologist is often huge and fatiguing. CAD as "second reader" can be helpful as it improves the sensitivity for 6–9-mm polyps.[63] Studies demonstrated that CAD as "first reader" reduces reading time and its performance in terms of sensitivity and specificity is not significantly different with respect to a "second reader" CAD.[64,65] CAD was used in all the European trials (Table 4). In particular, in the Italian trials, a "first reader" CAD was adopted for the first time in screening CTC. In these studies, the radiologist first examined CAD polyp candidates and then performed a two-dimensional evaluation of the colon in order to find lesions that could have been missed by CAD.

SAFETY OF CT COLONOGRAPHY SCREENING

Patient safety is an essential requisite for a population-based screening programme. CTC has two potential safety issues: (1) the risk of colonic perforation due to pneumocolon and (2) the exposure to ionizing radiations.

Colonic perforation after CTC is an extremely rare event.[66] A recent meta-analysis showed that the estimated rate of perforation due to colonic insufflation is very low (0.04%), especially in asymptomatic subjects (0.02%—about 1 in 5000), which can be representative of a screening population.[67] In the meta-analysis, 44% of perforations were asymptomatic and only 32% required surgery, with no deaths.[67]

Perforation rates observed for FOBT and sigmoidoscopy population-based screening programmes are comparable or higher than that estimated for CTC screening. Data from the English Bowel Cancer Screening Programme showed that the perforation rate of colonoscopy in the context of organized screening with FOBT was 0.06%,[68] whereas perforation rate after flexible sigmoidoscopy was reported to be 0.09%.[69] Opposite to CTC, colonoscopic perforations have been reported as requiring surgery in 78% of cases in one large analysis.[70]

Noteworthy, in the European trials, no perforations were observed after CTC or the subsequent colonoscopy in the CTC-positive subjects.[26,27,30] Only minor complications such as vasovagal reactions, cutaneous rashes after iodinated oral contrast media administration and post-polypectomy bleeding were reported.[26,27,30] Taking into account the complications that occurred after follow-up colonoscopy in CTC-positive subjects, the complication rates of CTC and colonoscopy screening in the COCOS trial were comparable.[26]

CTC exposes subjects to ionizing radiation. An international survey showed that the average effective dose for a screening CTC is 4.4 mSv using low-dose scanning protocols.[71] Even lower doses can be obtained using iterative reconstructions.[72] Although controversies still exist on the carcinogenic risk of such small doses of ionizing radiation, models suggest that the number of radiation-induced cancers will be significantly outnumbered by the number of CRC prevented by screening.[73]

EXTRACOLONIC FINDINGS IN CT COLONOGRAPHY SCREENING

Unlike colonoscopy, CTC can detect extracolonic abnormalities, although with limitations when low-dose protocols are employed. The identification of significant extracolonic findings (ECF) could be beneficial for the screening subjects but may require additional

Table 4. Selection criteria for CT colonography (CTC) readers and use of computer-aided detection (CAD) in the European randomized trials

Authors (years)	Reader experience	Preliminary training	Proficiency examination	Reading approach	CAD use
Stoop et al (2012)[26]	≥800 CTCs	No	No	Primary 2D	Second reader
Sali et al (2015)[27]	≥300 CTCs	Yes	Yes	Primary 2D	First reader
Regge et al (2016)[30]	≥300 CTCs	Yes	Yes	Primary 2D	First reader

2D, two dimensional.

diagnostic work-up, with rising costs for the screening programme and potential harms and anxiety for the patient.

ECF can be identified in up to half of the asymptomatic subjects undergoing CTC.[74–76] However, the proportion of clinically relevant ECF is substantially lower, namely 2–3%, as shown in two large opportunistic CTC screening series in the USA.[77,78]

In the European trials, only potentially important ECF according to the CT Colonography Reporting and Data System (C-RADS) classification (E3–E4) were reported in CTC screening;[79] for example, aortic aneurysms, solid or complex cystic renal lesions, pancreatic masses, adnexal masses and non-calcified lung nodules >10 mm. In the three trials, the prevalence of ECF ranged from 1 to 11%.[26,27,30] In the Italian trials, the radiologist did not perform a specific search for extracolonic pathology, but annotated only the ECF seen during colonic evaluation. This could partially justify the lower prevalence of ECF in the Italian trials with respect to the COCOS trial.

In the PROTEUS trial, ECF were reviewed by two radiologists who separated those that needed additional examinations from those that were unlikely to be clinically relevant. With this approach, the prevalence of ECF deserving further work-up was only 1.2%.[30] This can be a rational approach to the management of ECF within a CTC screening programme that could limit the number of second-level examinations and interventions to the strictly necessary and also reduce overall costs of the programme.[30] Notably, the issue of ECF could be especially important in the first CTC screening round, as in the next screening rounds, most of them would be already known.

COST-EFFECTIVENESS OF CT COLONOGRAPHY SCREENING

Whether CTC is cost-effective for population screening of CRC with respect to other screening modalities is still under debate, as most existing studies are based on theoretical models.[80]

A systematic review on cost-effectiveness analyses of CTC screening including 16 studies showed heterogeneous results, owing to differences in assumptions and reported unit costs.[80] Screening CTC is cost-effective in comparison with no screening.[81] CTC is cost-effective compared with faecal tests and sigmoidoscopy in some studies.[80] Cost-effectiveness of CTC in comparison with colonoscopy depends on various factors, such as screening uptake, polyp size threshold for referral and CTC costs.[80] In this regard, data from unit costs of CTC screening from the COCOS trial are encouraging, as the average cost per participant was about 170 euros, significantly less than previously reported.[82]

An analysis based on data of the COCOS trial indicated that CTC screening could be cost-effective in comparison with colonoscopy screening but not with FIT screening.[83] Cost-effectiveness analyses from the SAVE and PROTEUS trials are not yet available.

Reporting and following up ECF is probably a crucial factor for the cost-effectiveness of CTC screening.[84,85] Although the published average costs related to the follow-up of ECF are relatively low (31–68 USD), it is still debated whether the report of ECF could be ultimately cost saving or cost generating.[78]

CT COLONOGRAPHY SCREENING: POSITION OF SCIENTIFIC SOCIETIES

At present, available guidelines do not recommend CTC for population screening of CRC. CTC is not recommended as primary test for population screening by the ESGAR and the European Society of Gastrointestinal Endoscopy (ESGE), mainly because of the lack of robust evidence about its cost-effectiveness.[48] The European Guidelines for Quality Assurance in Colorectal Cancer Screening, which recommend FIT for organized screening of CRC, consider CTC as a new screening technology under evaluation.[22]

Positions about the role of CTC for opportunistic screening of CRC are heterogeneous. Since 2008, CTC has been recommended by the American Cancer Society for screening of CRC in asymptomatic subjects older than 50 years.[86] The same recommendation has been made by the American College of Radiologists.[49] ESGAR and ESGE guidelines suggest that CTC "may be proposed as a CRC screening test on an individual basis providing the screenee is adequately informed about test characteristics, benefits, and risks".[48] A recent position statement of the US Preventive Service Task Force includes CTC among recommended tests for CRC screening, owing to its high diagnostic accuracy for CRC and large polyps and its safety profile, although concerns still remain about the management of ECF.[87]

ROLE OF CT COLONOGRAPHY IN FAECAL OCCULT BLOOD TEST-BASED SCREENING PROGRAMMES

FOBT and FIT are the most adopted tests in European organized programmes for CRC screening. CTC may have a complementary role in FOBT-based screening. According to the ESGAR and ESGE guidelines, CTC is recommended in FOBT-positive subjects who refuse or have contraindications to colonoscopy work-up (1) and in those with incomplete colonoscopy (2), whereas CTC is not recommended as a triage test in all FOBT-positive subjects before colonoscopy (3).[48]

(1) FOBT-positive subjects who refuse or have contraindications to colonoscopy
- In Italian screening programmes, average compliance to colonoscopy work-up among FOBT-positive subjects was 81%.[36] This implies that about one-fifth of subjects at risk of harbouring significant colonic lesions are precluded from endoscopic assessment and treatment.
- An Italian study showed that in FOBT-positive subjects refusing first referral to colonoscopy, attendance to CTC (63%) was significantly higher than that to reinvitation to colonoscopy (26%).[88] Thus, CTC has the potential to recapture more than a half of subjects with positive FOBT who refuse first invitation to colonoscopy.

(2) FOBT-positive subjects with incomplete colonoscopy
- In FOBT-based population screening programmes, the colonoscopy completion rate varies between 72 and 95%.[22]

- A study showed that advanced neoplasia could be missed in up to 4.3% of patients with incomplete colonoscopy, suggesting that further colonic evaluation is mandatory in these cases.[89]
- A large proportion of FOBT-positive subjects with incomplete colonoscopy accept to undergo CTC, which proved to have a high positive-predictive value (88%) for colonic masses and large polyps (≥10 mm) in these subjects.[90]

(3) CTC as a triage test in FOBT-positive subjects

- The positive-predictive value of FOBT or FIT for advanced neoplasia is relatively low and typically in the 33–52% range.[36,21] Hence, up to half of the faecal tests can be false positive, leading to unnecessary colonoscopies in asymptomatic subjects.
- CTC has been advocated as a triage test in these subjects. However, a meta-analysis by Plumb et al[91] on four studies showed that in FOBT-positive subjects, CTC has a high average per-patient sensitivity (89%) for CRC and adenomas ≥6 mm, but a fairly low average specificity (75%).
- Considering the high prevalence of CRC and polyps in FOBT-positive subjects, with consequently a high referral rate to colonoscopy, and the relatively high number of false-positive results in this specific population, the use of CTC as a triage examination prior to colonoscopy is most probably not cost-effective.[92,93]

CONCLUSION

After two decades since its introduction, robust evidence has been accumulated to endorse CTC as an accurate, safe and well-tolerated investigation of the colon. Recently, the results of three European trials evaluating CTC within population-based screening of CRC have been published. The results in terms of participation rate, positivity rate and detection rate of CTC were quite homogeneous among the three studies. Participation rate for screening CTC was higher than that for primary screening colonoscopy, with slightly lower detection rate, but with comparable yield per invitee. Participation rate for screening CTC was much lower than that for FIT, but its detection rate was threefold that of one FIT round. CTC and sigmoidoscopy showed similar participation and detection rate. These results are encouraging to consider a potential implementation of CTC in organized screening programmes for CRC. However, assessment of other factors such as polyp size threshold for colonoscopy referral, management of ECF and, most importantly, the forthcoming results of cost-effectiveness analyses are crucial to define the role of CTC in primary screening.

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