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CLINICAL REVIEW

CT colonography: role in FOBT-based screening programs for colorectal cancer

Lapo Sali[1] · **Grazia Grazzini**[2] · **Mario Mascalchi**[1]

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Abstract Computed tomographic colonography (CTC) is a minimally invasive imaging examination for the colon, and is safe, well tolerated and accurate for the detection of colorectal cancer (CRC) and advanced adenoma. While the role of CTC as a primary test for population screening of CRC is under investigation, the fecal occult blood test (FOBT) has been recommended for population screening of CRC in Europe. Subjects with positive FOBT are invited to undergo total colonoscopy, which has some critical issues, such as suboptimal compliance, contraindications and the possibility of an incomplete exploration of the colon. Based on available data, the integration of CTC in FOBT-based population screening programs for CRC may fall into three scenarios. First, CTC is recommended in FOBT-positive subjects when colonoscopy is refused, incomplete or contraindicated. For these indications CTC should replace double-contrast barium enema. Second, conversely, CTC is not currently recommended as a second-level examination prior to colonoscopy in all FOBT-positive subjects, as this strategy is most probably not cost-effective. Finally, CTC may be considered instead of colonoscopy for surveillance after adenoma removal, but specific studies are needed.

Keywords Colorectal cancer screening · Fecal occult blood test · Fecal immunochemical test · CT colonography

✉ Lapo Sali
lapo.sali@unifi.it

[1] Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", University of Florence, Viale Morgagni 50, 50134 Florence, Italy

[2] Cancer Prevention and Research Institute (ISPO), Via Cosimo il Vecchio 2, 50139 Florence, Italy

Introduction

Colorectal cancer (CRC) is the second most frequent malignant neoplasia and the second most common cause of death from cancer in Europe [1]. In 2012, the number of estimated new cases of CRC in both sexes was ~447,000, whereas the estimated deaths from CRC were nearly 215,000 [1].

When CRC is detected at an early stage, the disease can be successfully treated in the majority of cases. Data from the EUROCARE High Resolution study indicated that the 3-year relative survival rate was 93% for patients with Dukes' stage A cancers, whereas it dropped to 48–66% for patients with Dukes' stage C cancers [2]. More importantly, CRC can be prevented by removing its precursor lesion (adenoma). In the majority of cases, cancer development is the result of a multistep process called the adenoma–carcinoma sequence, which takes years and possibly decades and consists of the transformation of the normal colonic mucosa into an adenomatous polyp and finally into an invasive cancer [3]. Advanced adenoma, defined as any adenoma larger than 9 mm, and/or with a villous component greater than 20%, and/or with high-grade dysplasia, has an increased likelihood of malignant transformation and has to be considered the main target for CRC screening [3].

The Council of the European Union recommended the fecal occult blood test (FOBT) for mass screening of CRC [4], as it has been demonstrated to reduce mortality from CRC by 15–33% in randomized clinical trials (RCT) [5–7]. FOBT is a simple, cheap and safe laboratory test which relies on the assumption that asymptomatic CRC and large adenomas may bleed. There are two types of FOBT: guaiac-based (gFOBT) or immunochemical tests (FIT).

GFOBTs investigate the presence of any blood in stool specimens, whereas FITs are specific for human blood.

All randomized studies which demonstrated a reduction in CRC mortality were based on gFOBT [5–7]. Despite its efficacy in reducing CRC mortality, gFOBT has some drawbacks. It is not specific for human blood, and hence it can be affected by false-positive results caused by the presence in feces of non-human hemoglobin (i.e. red meat residues) or substances with peroxidase-like activity (i.e. some vegetables such as broccoli and cauliflower), and by false-negative results due to drug consumption (e.g. vitamin C). For this reason dietary restrictions are required prior to testing.

FIT uses specific antibodies to identify human blood components, such as hemoglobin. Unlike gFOBT, FIT does not require pre-test diet restrictions and test reading is automated. Another advantage of FIT over gFOBT is that it requires only one stool sample as opposed to three for FOBT. At the moment, there are no RCTs demonstrating a reduction in CRC incidence and mortality using FIT. However, some case–control studies, such as that by Saito et al. [8], demonstrated that screening with FIT reduces CRC mortality, and two retrospective studies suggested that FIT-based screening decreases the incidence of CRC [9, 10]. Most importantly, studies that compared the performance of FIT versus gFOBT showed that FIT is more accepted and efficient than the guaiac test in population screening [11, 12].

Notably, the RCTs that proved the efficacy of FOBT screening showed that a reduction in mortality from CRC is achieved by multiple rounds of fecal tests [5–7]. As a matter of fact, in FOBT-based screening programs, target subjects, usually aged between 50 and 70 years, are invited to undergo the test every one or two years. In population screening programs the positivity rate of FOBT at first round ranges between 1.6% for gFOBT and 5.6% for FIT, whereas the positivity rate at subsequent rounds is 1.8% for gFOBT and 4.2% for FIT [13, 14]. Subjects who test negative are invited to the subsequent FOBT round. Subjects with a positive FOBT are referred to colonoscopy, which is the definitive examination for ascertainment of colonic lesions, since it allows exploration of the entire colon, removal of polyps and histological diagnosis.

The use of colonoscopy as second-level examination in FOBT-positive subjects presents some critical issues, as colonoscopy can be incomplete, contraindicated or refused by screenees [4]. Colonoscopy is also the recommended examination for surveillance after removal of adenomas detected by screening. Surveillance colonoscopy consumes considerable endoscopic resources and may be refused by some patients [4]. In all these situations an alternative test to colonoscopy may be proposed to accomplish a complete colonic examination.

Computed tomographic colonography (CTC) is a minimally invasive pancolonic examination, which has proved to be safe, well tolerated and accurate for detection of cancer and advanced adenoma. The average sensitivity of CTC for CRC is 96%, similar to that of colonoscopy (95%) [15]. Moreover, CTC has a sensitivity of 83–93% for large (≥10 mm) polyps and of 60–86% for intermediate (6–9 mm) polyps [16–20]. CTC is also very specific for lesions greater than 9 mm (95–97%) [16, 18, 20]. Finally, a RCT showed that CTC performs better than double-contrast barium enema (DCBE), both for the detection of colonic lesions and for patient experience [21, 22].

CTC can be performed with a reduced bowel preparation [23], which is the most uncomfortable part of the imaging or endoscopic examinations of the colon [24]. CTC generally causes little discomfort to the patient [24] and it is a very safe examination, its complications, mainly colonic perforation, being exceedingly rare (0.02–0.04%) [25].

The role of CTC as a primary screening test for population screening of CRC has been evaluated by three RCTs carried out in Europe [26–28]. While the available results from these studies are promising for considering the potential implementation of CTC as a primary test for CRC, CTC can already be considered a valuable second-level test alternative to colonoscopy in the context of FOBT-based screening programs.

Herein we shall discuss available data on the role of CTC as a complementary examination in FOBT-based population screening programs for CRC. Although some uncertainties are still present and admittedly studies on some specific issues are few, from an operational point of view three scenarios can be already identified: (1) those in which CTC is recommended, (2) those in which CTC is not recommended and (3) those in which CTC is of uncertain recommendation and specific studies are needed.

CTC recommended

FOBT-positive subjects who refuse colonoscopy

The European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis recommended that in FOBT-positive subjects "high rates of compliance with follow-up colonoscopy should be achieved (85% is acceptable, >90% is desirable)" [4]. As a matter of fact, in all FOBT-based screening programs for CRC, attendance to work-up colonoscopy is incomplete, ranging between 73% and 92% [4, 29–32].

Factors affecting compliance to colonoscopy of FOBT-positive subjects are various and were investigated both in primary care and mass-screening settings. In the primary care setting it was found that general practitioners do not

always conform to expert recommendations for appropriate follow-up of FOBT-positive subjects, resulting in a reduced attendance to colonoscopy [33]. General practitioners' lack of adequate specific competence in screening with FOBT can partially account for this phenomenon [33].

In the setting of an organized screening program for CRC, reasons for non-compliance to colonoscopy were investigated by two studies [34, 35]. In one study exploring psychological characteristics of subjects who refused work-up colonoscopy, refusal of colonoscopy was higher in subjects with low attention to their personal health status, in subjects with "casual personality" and in those who had insufficient information about the test [34]. In the other study, a cohort of subjects screened by FOBT was interviewed about their intention to undergo colonoscopy in the case of a positive test [35]. Reasons for refusal of colonoscopy included fear of an embarrassing and painful procedure, and concerns about bowel preparation [35].

The incomplete compliance to work-up colonoscopy represents a critical issue of FOBT-based screening programs of CRC. In fact, considering that FIT has a positive predictive value (PPV) for CRC and advanced adenoma ranging from 32.5 to 51.8% [12, 13], and assuming that FOBT-positive subjects who refuse colonoscopy have the same frequency of advanced neoplasia as FOBT-positive subjects attending colonoscopy, at least one-third of FOBT-positive subjects refusing colonoscopy could be affected by a CRC or an advanced adenoma.

CTC is generally considered a reasonable alternative examination of the colon in patients unwilling to undergo colonoscopy. However, only one study by Sali et al. investigated attendance to CTC in FOBT-positive subjects who refused colonoscopy in the context of an organized screening program [36]. This study showed that in FOBT-positive subjects refusing first referral to colonoscopy, attendance to CTC (62.5%) was significantly higher than that to re-invitation to colonoscopy (25.6%) [36]. Thus CTC has the potential to recapture more than a half of subjects with positive FOBT who refuse first invitation to colonoscopy. The study was not intended to evaluate sensitivity and specificity of CTC in this setting because only patients with positive CTC underwent the reference test (i.e. colonoscopy).

FOBT-positive subjects with incomplete colonoscopy

Cecal intubation is one of the quality control measurements of colonoscopy. According to the European Guidelines for Quality Assurance in Colorectal Cancer Screening, the completion rate of work-up colonoscopy in FOBT-positive subjects should be greater than 90% (">95% is desirable") [4]. In Europe and in the US, the rates of cecal intubation in studies carried out in various clinical settings range between 76 and 98% [37, 38]. In FOBT-based population screening programs the colonoscopy completion rate varies between 72 and 95% [4]. Causes of an incomplete colonoscopy include colon redundancy/angulation, inadequate bowel preparation, presence of obstructive lesions, and subject's discomfort [38]. Incomplete colonoscopies are more frequent in elderly people, women and subjects with a history of previous abdominal surgery [39]. Advanced neoplasia can be missed in up to 4.3% of incomplete colonoscopies [40]. Thus, in these cases further colonic evaluation is required. This fact is even more significant in FOBT-positive subjects who have a high prevalence of advanced adenoma and CRC.

In order to complete the colon evaluation, DCBE has traditionally been used. Since DCBE has a low accuracy in detecting colonic neoplasms, as shown by a meta-analysis and a RCT [21, 41], it should not be used any longer for the evaluation of FOBT-positive subjects with an incomplete colonoscopy.

One study conducted in a small series of patients in the setting of a FOBT-based screening program showed that 65% of FOBT-positive subjects with incomplete colonoscopy accepted to undergo CTC and 50% of CTCs were positive for at least one polyp greater than 6 mm [42]. In that study, CTC proved to have a high PPV (87.5%) for colonic masses and polyps greater than 9 mm [42].

Given the high diagnostic accuracy of CTC for cancer [15], patients with colonic masses detected at CTC following an incomplete colonoscopy should be directly referred to the surgeon. If large polyps ($\geq$10 mm) are detected at CTC in a colonic segment not explored during the incomplete colonoscopy, a repeat colonoscopy under sedation could be attempted, whereas a follow-up with CTC could be considered in patients with small to medium polyps (6–9 mm) [26].

FOBT-positive subjects with contraindications to colonoscopy

Work-up colonoscopy is often performed under sedation. FOBT-positive subjects who have an increased anesthesia risk due to their medical conditions (e.g. cardiovascular, pulmonary or renal impairment) may be precluded from work-up colonoscopy. In these subjects CTC can be advantageously utilized for colonic assessment. In fact, CTC is a very safe examination [25], can be performed with a limited bowel preparation [23] and is well tolerated, even by patients with contraindications to colonoscopy [43]. Moreover, CTC does not require temporary warfarin cessation in subjects receiving anticoagulation therapy and may be considered as an alternative to colonoscopy in these subjects.

CTC not recommended

Triage test in FOBT-positive subjects

Subjects with a positive FOBT are usually examined by a total colonoscopy that represents the gold standard for the diagnosis of colonic lesions and allows biopsy and removal of polyps. This approach presents two critical issues. Besides the incomplete attendance to colonoscopy discussed in the previous paragraph [4, 29–32], a major drawback is that the PPV of FOBT for cancer and advanced adenoma is quite low, typically in the 32.5–51.8% range [12, 13]. Hence, up to half of the fecal tests can be false-positive, leading to unnecessary colonoscopies in asymptomatic subjects, with the risk of producing anxiety and complications from the invasive procedure (e.g. rectal bleeding, colonic perforation) [44].

In principle, the use of CTC as a triage test prior to colonoscopy in the work-up of FOBT-positive subjects could reduce the number of negative colonoscopy after a positive test. Attendance to primary CTC screening is higher than that to primary colonoscopy screening [26, 27] and the examination is perceived as less burdensome than endoscopy [45]. When considering CTC as a triage test for FOBT-positive subjects, both a high sensitivity/negative predictive value (NPV) and a high specificity/PPV for advanced neoplasia should be achieved. Four studies investigated diagnostic performance of CTC in FOBT-positive subjects using segmental unblinded colonoscopy as reference standard (Table 1) [46–49]. Two studies enrolled consecutive FOBT-positive subjects from organized screening programs [46, 48], whereas the other two enrolled FOBT-positive subjects as a subgroup of high-risk patients, not necessarily participating in a screening program [47, 49]. All studies reported a high prevalence of significant colonic lesions (i.e. cancer and polyps ≥6 mm) in this cohort of patients, ranging between 36 and 77%. Plumb et al. performed a meta-analysis of the sensitivity and specificity of CTC in FOBT-positive subjects based on these four studies [50]. CTC had a high average per-patient sensitivity (88.8%) for CRC and adenomas ≥6 mm, whereas average specificity was lower (75.4%) and heterogeneous between studies [50]. As a matter of fact, in two studies the PPV of CTC was quite low [47, 48]. Some authors observed that the expected high prevalence of colonic lesions in FOBT-positive subjects could predispose the radiologist towards false-positive reporting [47, 48]. Data from the English Bowel Cancer Screening Program showed that in 2731 FOBT-positive subjects who underwent CTC, the positivity rate of CTC was quite high (37.6%), whereas the PPV for CRC and polyps (including those ≤5 mm) was relatively low (72.1%) [51]. Thus, considering the high prevalence of CRC and polyps, with consequently a high referral rate to colonoscopy, and the relatively high number of false-positive results, the use of CTC as a triage examination in FOBT-positive subjects is most probably not cost-effective.

Other factors to consider in a screening context are exposure to ionizing radiation and discovery of extracolonic findings at CTC that could increment the cost of screening due to the additional examinations and treatments required to manage these findings [52].

Uncertain recommendation for CTC

Surveillance after adenoma removal

FOBT-positive subjects diagnosed with adenoma at work-up colonoscopy are at risk of harboring other colonic lesions. In fact, a large meta-analysis showed that individuals who underwent endoscopic removal of adenomas would be diagnosed with further advanced adenomas in

Table 1 Studies on CTC as a triage test in subjects with a positive FOBT

Author (year)	Total subjects	Subjects with cancer (%)	Subjects with polyps ≥6 mm (%)	NPV for lesions ≥6 mm	PPV for lesions ≥6 mm
Liedenbaum [46] (2009)	302	22 (7)	211 (70)	77% (95% CI: 69–85%)	87% (95% CI: 80–93%)
Regge [47] (2009)	221	32 (14)	90 (41)	85% (95% CI: 76–91%)[a]	79% (95% CI: 70–85%)[a]
Sali [48] (2010)	49	2 (4)	20 (41)	93% (95% CI: 68–100%)[b]	62% (95% CI: 44–78%)[b]
Heresbach [49] (2011)	50	2 (4)	16 (32)	94% (95% CI: 80–99%)	82% (95% CI: 57–96%)

NPV negative predictive value, *PPV* positive predictive value, *CI* confidence interval

[a] Calculated for advanced neoplasia (i.e. cancer and advanced adenoma)

[b] Calculated for adenoma and cancer

11.2% of the cases within an average follow-up period of 4 years from baseline colonoscopy and with a CRC in 0.6% of the cases within the same follow-up period [53]. The adenomas found at surveillance colonoscopy could be either new lesions or missed lesions at baseline colonoscopy [54]. The risk of developing new colonic lesions largely depends on the number and characteristics of adenomas detected at baseline colonoscopy. In the US National Polyp Study, 9% of patients with 3 or more adenomas and 5% of those with a large (≥10 mm) adenoma removed at baseline colonoscopy developed an advanced adenoma by their first follow-up examination, compared with only 1% of those with a single adenoma [55]. The risk of harboring an advanced adenoma is higher among patients with 5 or more adenomas at baseline colonoscopy (24.1%) and in those with an adenoma of 20 mm or greater (19.3%) [53].

One of the primary purposes of surveillance is to prevent development of CRC by removing new or missed adenomas before they have had the chance to progress to malignancy. In screening programs, surveillance after adenoma removal is currently performed by colonoscopy. Surveillance intervals are based on the number and size of adenomas found at baseline. The European Guidelines have defined three risk groups: low risk (1–2 adenomas <10 mm), intermediate risk (3–4 adenomas <10 mm or at least one ≥10 mm/<20 mm) and high risk (≥5 adenomas <10 mm or at least one ≥20 mm) [4]. Patients at low risk are returned to the FOBT screening program. Patients at intermediate risk are invited to surveillance colonoscopy

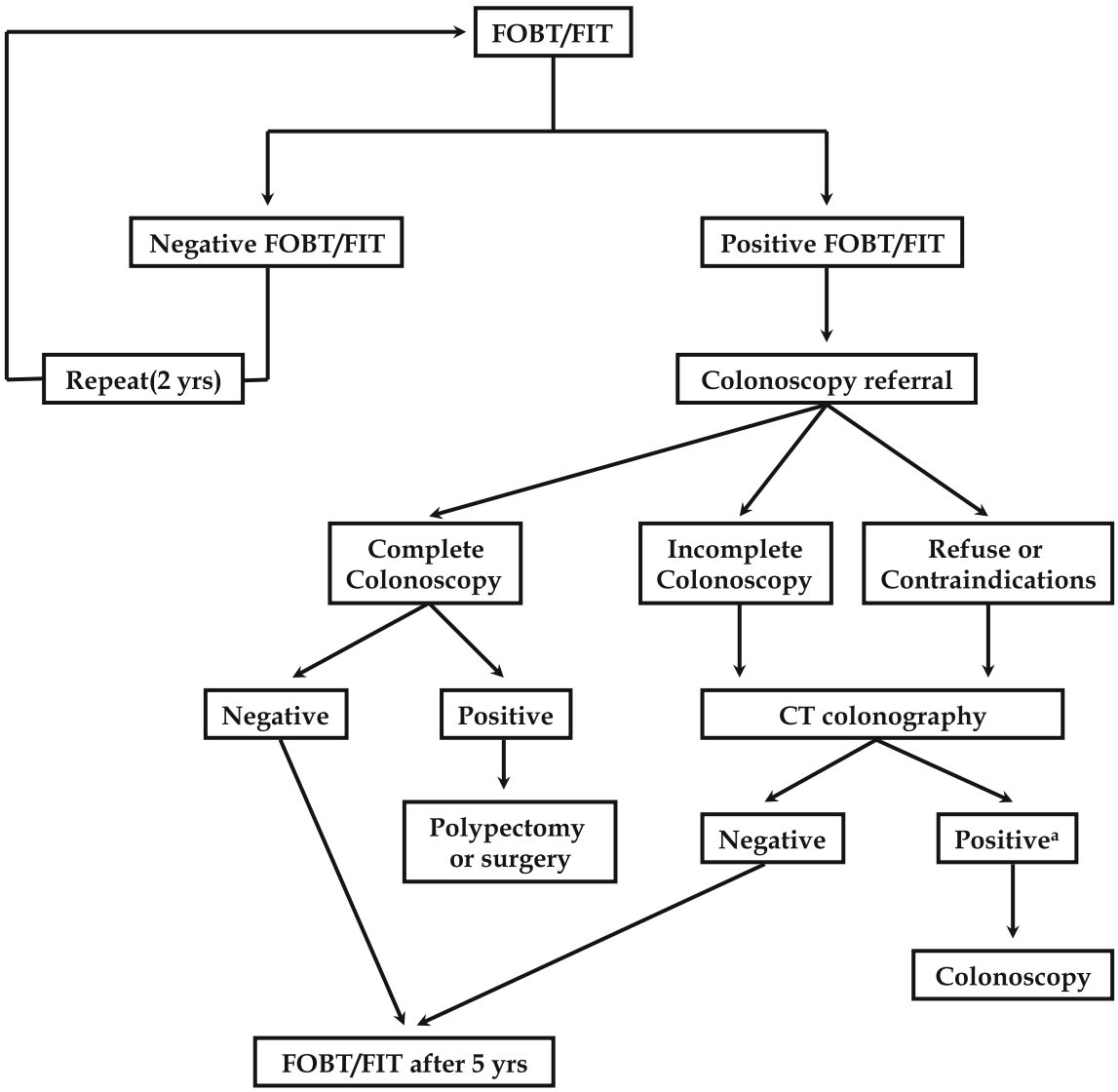

Fig. 1 Work-up for FOBT/FIT-positive subjects incorporating CT colonography. *FOBT* fecal occult blood test, *FIT* fecal immunochemical test. A re-screening interval of 5 years after a negative CTC is suggested by the US Preventive Service Task Force [61]. [a]Subjects with mass or at least one polyp ≥6 mm at CT colonography

after 3 years, whereas patients at high risk are invited to surveillance colonoscopy within 1 year [4].

Compliance to surveillance colonoscopy is not complete, ranging between 52 and 83% in different studies [55, 56]. Colonoscopy is an invasive procedure with a very low but not zero risk of severe complications [44]. Moreover, surveillance colonoscopy consumes considerable endoscopic resources [57] and may ultimately prolong waiting times for endoscopic services, with a negative effect especially for FOBT-positive subjects. For these reasons CTC could theoretically have a role in surveillance after adenoma removal. In fact CTC could both enhance attendance to surveillance, due to its less invasive approach and better subject's acceptance, shorten waiting times and especially reduce the number of colonoscopies in the intermediate risk group where the prevalence of adenomas at subsequent colonoscopy is low (5–9%) [55]. However, to date no study has investigated the use of CTC for surveillance in comparison to colonoscopy. Thus, at present CTC could be only proposed to subjects under surveillance refusing colonoscopy.

Medical and economic effects of CTC introduction in FOBT-based screening programs

The recommended use of CTC in subjects with positive FOBT who refuse or have contraindications to colonoscopy and in those with incomplete colonoscopy may allow the diagnosis of cancers and adenomas that would otherwise be missed. This may ultimately improve the detection rate of FOBT. Subjects who are diagnosed at CTC with a colonic mass can be directly referred to surgery, whereas subjects who are diagnosed with polyps can be referred to colonoscopy. If intermediate (6–9 mm) polyps are detected, a follow-up with CTC can be proposed as an alternative to colonoscopy [26, 58]. CTC follow-up for intermediate polyps could be especially advantageous in frail or elderly subjects, and in those in whom a complete colonoscopy may be unfeasible or harmful (e.g. patients with advanced diverticular disease).

Unlike colonoscopy, CTC allows the exploration of extracolonic abdominal organs. This could be beneficial for the screening subject as significant abdominal pathology (e.g. aortic aneurysms, renal solid nodules) can be discovered. However, this implies additional work-up examinations for extracolonic findings, also for those with low clinical significance, thus raising costs for the screening program.

From an economic perspective, screening CTC is estimated to be less expensive than screening colonoscopy in Europe (EUR 152 vs. 209) [59]. Costs for work-up of extracolonic findings of CTC was evaluated in a study in the USA and ranged between USD 31 and 68 [52].

Conclusions

CTC can advantageously be integrated as a complementary examination in FOBT-based population-screening programs for CRC. In this context CTC is recommended in FOBT-positive subjects who refuse or have contraindications to colonoscopy and in those with incomplete colonoscopy (Fig. 1). For these purposes CTC should replace DCBE. These recommendations have been included among the indications for CTC in a recent position paper by the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) and the European Society of Gastrointestinal Endoscopy (ESGE) [60]. CTC is currently not recommended as a triage examination prior to colonoscopy in all FOBT-positive subjects, as this strategy is most probably not cost-effective. Use of CTC for surveillance after adenoma removal is of uncertain recommendation, as it has not yet been investigated.

Compliance with ethical standards

Conflict of interest Lapo Sali, Grazia Grazzini and Mario Mascalchi declare that they have no conflict of interest.

Human rights This study does not include any data about human subjects.

Informed consent This study does not involve human subjects and giving informed consent does not apply.

References

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49:1374–403.
2. Ciccolallo L, Capocaccia R, Coleman MP, et al. Survival differences between European and US patients with colorectal cancer: role of stage at diagnosis and surgery. Gut. 2005;54:268–73.
3. Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology. 1997;112:594–642.
4. Segnan N, Patnik J, von Karsa L. European guidelines for quality assurance in colorectal cancer screening and diagnosis. 1st ed. Luxembourg: Publications Office of the European Union; 2010.
5. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota colon cancer control study. N Engl J Med. 1993;328:1365–71.
6. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet. 1996;348:1472–7.
7. Kronborg O, Fenger C, Olsen J, et al. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet. 1996;348:1467–71.

8. Saito H, Soma Y, Koeda J, et al. Reduction in risk of mortality by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. Int J Cancer. 1995;61:465–9.
9. Ventura L, Mantellini P, Grazzini G, et al. The impact of immunochemical faecal occult blood testing on colorectal cancer incidence. Dig Liver Dis. 2014;46:82–6.
10. Giorgi Rossi P, Vicentini M, Sacchettini C, et al. Impact of screening program on incidence of colorectal cancer: a cohort study in Italy. Am J Gastroenterol. 2015;110:1359–66.
11. Castiglione G, Zappa M, Grazzini G, et al. Immunochemical vs guaiac faecal occult blood tests in a population-based screening programme for colorectal cancer. Br J Cancer. 1996;74:141–4.
12. Van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology. 2008;135:82–90.
13. Zorzi M, Baracco S, Fedato C, et al. Screening for colorectal cancer in Italy, 2009 survey. Epidemiol Prev. 2011;35:55–77.
14. Weller D, Coleman D, Robertson R, et al. The UK colorectal cancer screening pilot: results of the second round of screening in England. Br J Cancer. 2007;97:1601–5.
15. Pickhardt PJ, Hassan C, Halligan S, et al. Colorectal cancer: CT colonography and colonoscopy for detection—systematic review and meta-analysis. Radiology. 2011;259:393–405.
16. Sosna J, Morrin MM, Kruskal JB, et al. CT colonography of colorectal polyps: a metaanalysis. AJR Am J Roentgenol. 2003;181:1593–8.
17. Mulhall BP, Veerappan GR, Jackson JL. Meta-analysis: computed tomographic colonography. Ann Intern Med. 2005;142:635–50.
18. Rosman AS, Korsten MA. Meta-analysis comparing CT colonography, air contrast barium enema, and colonoscopy. Am J Med. 2007;120:203–10.
19. Halligan S, Altman DG, Taylor SA, et al. CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting. Radiology. 2005;237:893–904.
20. Chaparro M, Gisbert JP, Del Campo L, et al. Accuracy of computed tomographic colonography for the detection of polyps and colorectal tumors: a systematic review and meta-analysis. Digestion. 2009;80:1–17.
21. 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;381:1185–92.
22. von Wagner C, Smith S, Halligan S, et al. Patient acceptability of CT colonography compared with double contrast barium enema: results from a multicentre randomised controlled trial of symptomatic patients. Eur Radiol. 2011;21:2046–55.
23. Liedenbaum MH, de Vries AH, Gouw CI, et al. CT colonography with minimal bowel preparation: evaluation of tagging quality, patient acceptance and diagnostic accuracy in two iodine-based preparation schemes. Eur Radiol. 2010;20:367–76.
24. Gluecker TM, Johnson CD, Harmsen WS, et al. Colorectal cancer screening with CT colonography, colonoscopy, and double-contrast barium enema examination: prospective assessment of patient perceptions and preferences. Radiology. 2003;227:378–84.
25. Bellini D, Rengo M, De Cecco CN, et al. Perforation rate in CT colonography: a systematic review of the literature and meta-analysis. Eur Radiol. 2014;24:1487–96.
26. 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 multicenter controlled trial. Lancet Oncol. 2012;13:55–64.
27. Sali L, Mascalchi M, Falchini M, et al. Reduced and full-preparation CT colonography, fecal immunochemical test, and colonoscopy for population screening of colorectal cancer: a randomized trial. J Natl Cancer Inst. 2016;108:djv319. doi:10.1093/jnci/djv319.
28. Regge D, Iussich G, Segnan N, et al. Comparing CT colonography and flexible sigmoidoscopy: a randomised trial within a population-based screening programme. Gut. 2016;. doi:10.1136/gutjnl-2015-311278.
29. van Roosbroeck S, Hoeck S, Van Hal G. Population-based screening for colorectal cancer using an immunochemical faecal occult blood test: a comparison of two invitation strategies. Cancer Epidemiol. 2012;36:e317–24.
30. van Roon AHC, Hol L, van Vuuren AJ, et al. Are fecal immunochemical test characteristics influenced by sample return time? A population-based colorectal cancer screening trial. Am J Gastroenterol. 2012;107:99–107.
31. Moss SM, Campbell C, Melia J, et al. Performance measures in three rounds of the English bowel cancer screening pilot. Gut. 2012;61:101–7.
32. Peris M, Espinàs JA, Muñoz L, et al. Lessons learnt from a population-based pilot programme for colorectal cancer screening in Catalonia (Spain). J Med Screen. 2007;14:81–6.
33. Baig N, Myers RE, Turner BR, et al. Physician-reported reasons for limited follow-up of patients with a positive fecal occult blood test screening results. Am J Gastroenterol. 2003;98:2078–81.
34. Li CM, Shiu MN, Chia SL, et al. Factors associated with referral compliance of abnormal immunochemical faecal occult blood test. J Med Screen. 2007;14:186–90.
35. Zheng YF, Saito T, Takahashi M, et al. Factors associated with intentions to adhere to colorectal cancer screening follow-up exams. BMC Public Health. 2006;6:272.
36. Sali L, Grazzini G, Ventura L, et al. Computed tomographic colonography in subjects with positive faecal occult blood test refusing optical colonoscopy. Dig Liver Dis. 2013;45:285–9.
37. Bowles CJ, Leicester R, Romaya C, et al. A prospective study of colonoscopy practice in the UK today: are we adequately prepared for national colorectal cancer screening tomorrow? Gut. 2004;53:277–83.
38. Rathgaber SW, Wick TM. Colonoscopy completion and complication rates in a community gastroenterology practice. Gastrointest Endosc. 2006;64:556–62.
39. Shah HA, Paszat LF, Saskin R, et al. Factors associated with incomplete colonoscopy: a population-based study. Gastroenterology. 2007;132:2297–303.
40. Neerincx M, sive Terhaar Droste JS, Mulder JJ, et al. Colonic work-up after incomplete colonoscopy: significant new findings during follow-up. Endoscopy. 2010;42:730–5.
41. Sosna J, Sella T, Sy O, et al. Critical analysis of the performance of double-contrast barium enema for detecting colorectal polyps ≥6 mm in the era of CT colonography. AJR Am J Roentgenol. 2008;190:374–85.
42. Sali L, Falchini M, Bonanomi AG, et al. CT colonography after incomplete colonoscopy in subjects with positive faecal occult blood test. World J Gastroenterol. 2008;14:4499–504.
43. Yucel C, Lev-Toaff AS, Moussa N, et al. CT colonography for incomplete or contraindicated optical colonoscopy in older patients. AJR Am J Roentgenol. 2008;190:145–50.
44. Anderson ML, Pasha TM, Leighton JA. Endoscopic perforation of the colon: lessons from a 10-year study. Am J Gastroenterol. 2000;95:3418–22.
45. Jensch S, Bipat S, Peringa J, et al. CT colonography with limited bowel preparation: prospective assessment of patient experience and preference in comparison to optical colonoscopy with cathartic bowel preparation. Eur Radiol. 2010;20:146–56.

46. Liedenbaum MH, van Rijn AF, de Vries AH, et al. Using CT colonography as a triage technique after a positive faecal occult blood test in colorectal cancer screening. Gut. 2009;58:1242–9.
47. Regge D, Laudi C, Galatola G, et al. Diagnostic accuracy of computed tomographic colonography for the detection of advanced neoplasia in individuals at increased risk of colorectal cancer. JAMA. 2009;301:2453–61.
48. Sali L, Falchini M, Della Monica P, et al. CT colonography before colonoscopy in subjects with positive faecal occult blood test. Preliminary experience. Radiol Med. 2010;115:1267–78.
49. Heresbach D, Djabbari M, Riou F, et al. Accuracy of computed tomographic colonography in nationwide multicenter trial, and its relation to radiologist expertise. Gut. 2011;60:658–65.
50. Plumb AA, Halligan S, Pendsé DA, et al. Sensitivity and specificity of CT colonography for the detection of colonic neoplasia after positive faecal occult blood testing: systematic review and meta-analysis. Eur Radiol. 2014;24:1049–58.
51. Plumb AA, Halligan S, Nickerson C, et al. Use of CT colonography in the English Bowel Cancer Screening Programme. Gut. 2014;63:964–73.
52. Pickhardt PJ, Hanson ME, Vanness DJ, et al. Unsuspected extracolonic findings at screening CT colonography: clinical and economic impact. Radiology. 2008;249:151–9.
53. Martínez ME, Baron JA, Lieberman DA, et al. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. Gastroenterology. 2009;136:832–41.
54. Rex DK, Cutler CS, Lemmel GT, et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterology. 1997;112:24–8.
55. Winawer SJ, Zauber AG, O'Brien MJ, et al. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Workgroup. N Engl J Med. 1993;328:901–6.
56. Yood MU, Oliveria S, Boyer JG, et al. Colon polyp recurrence in a managed care population. Arch Intern Med. 2003;163:422–6.
57. Lieberman DA, Holub J, Eisen G, et al. Utilization of colonoscopy in the United States: results from a national consortium. Gastrointest Endosc. 2005;62:875–83.
58. Tutein Nolthenius CJ, Boellaard TN, de Haan MC, et al. Evolution of screen detected small (6–9 mm) polyps after a 3-year surveillance interval: assessment of growth with CT colonography compared with histopathology. Am J Gastroenterol. 2015;110:1682–90.
59. Greuter MJ, Berkhof J, Fijneman RJ, et al. The potential of imaging techniques as a screening tool for colorectal cancer: a cost-effectiveness analysis. Br J Radiol. 2016;89:20150910. doi:10.1259/bjr.20150910.
60. Spada C, Stoker J, Alarcon O, et al. Clinical indications for computed tomographic colonography: European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) Guideline. Eur Radiol. 2015;25:331–45.
61. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of benefits, burden, and harms of colorectal cancer screening strategies: modeling study for the US Preventive Services Task Force. JAMA. 2016;315:2595–609.