Clinical indications for computed tomographic colonography: European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) Guideline

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This is an official guideline of the European Society of Gastrointestinal Endoscopy (ESGE) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR). It addresses the clinical indications for the use of computed tomographic colonography (CTC). A targeted literature search was performed to evaluate the evidence supporting the use of CTC. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was adopted to define the strength of recommendations and the quality of evidence.

Main recommendations

1 ESGE/ESGAR recommend computed tomographic colonography (CTC) as the radiological examination of choice for the diagnosis of colorectal neoplasia. ESGE/ESGAR do not recommend barium enema in this setting (strong recommendation, high quality evidence).

2 ESGE/ESGAR recommend CTC, preferably the same or next day, if colonoscopy is incomplete. Delay of CTC should be considered following endoscopic resection. In the case of obstructing colorectal cancer, preoperative contrast-enhanced CTC may also allow location or staging of malignant lesions (strong recommendation, moderate quality evidence).

3 When endoscopy is contraindicated or not possible, ESGE/ESGAR recommend CTC as an acceptable and equally sensitive alternative for patients with symptoms suggestive of colorectal cancer (strong recommendation, high quality evidence).

4 ESGE/ESGAR recommend referral for endoscopic polypectomy in patients with at least one polyp ≥ 6 mm in diameter detected at CTC. CTC surveillance may be clinically considered if patients do not undergo polypectomy (strong recommendation, moderate quality evidence).

5 ESGE/ESGAR do not recommend CTC as a primary test for population screening or in individuals with a positive first-degree family history of colorectal cancer (CRC). However, it may be proposed as a CRC screening test on an individual basis providing the screenee is adequately informed about test characteristics, benefits, and risks (weak recommendation, moderate quality evidence).

Abbreviations

CI	confidence interval
C-RADS	CT Colonography Reporting and Data System
CRC	colorectal cancer
CT	computed tomography
CTC	computed tomographic colonography
ESGAR	European Society of Gastrointestinal and Abdominal Radiology
ESGE	European Society of Gastrointestinal Endoscopy
FIT	fecal immunochemical test
FOBT	fecal occult blood testing
GRADE	Grading of Recommendations Assessment, Development and Evaluation
NPV	negative predictive value
PEG	polyethylene glycol
PPV	positive predictive value
RCT	randomized controlled trial
SIGGAR	Special Interest Group in Gastrointestinal and Abdominal Radiology

This is an official guideline of the European Society of Gastrointestinal Endoscopy (ESGE) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR), **published in Endoscopy and European Radiology simultaneously.** It addresses the clinical indications for the use of computed tomographic colonography (CTC). A targeted literature search was performed to evaluate the evidence supporting the use of CTC. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was adopted to define the strength of recommendations and the quality of evidence.

Introduction

Colorectal cancer (CRC) is a major cause of morbidity and mortality [1,2]. CRC screening by fecal occult blood testing (FOBT) has been shown to reduce CRC mortality [3,4], and is currently used in several European countries. Colonoscopy is highly effective for detecting advanced neoplasia, and endoscopic polypectomy reduces subsequent CRC-specific incidence and mortality [5]. In Europe, colonoscopy is mainly used to investigate FOBT-positive or symptomatic patients, or as a preventive strategy in those with increased CRC risk [6].

Computed tomographic colonography (CTC) is a minimally invasive imaging technique that is highly accurate for detecting colorectal cancer (CRC) and adenomatous polyps. The technique is standardized [7], and CTC is more easily performed than barium enema. Evidence-based data suggest that CTC is the natural replacement for barium enema and a complementary rather than an alternative examination to colonoscopy. However, the clinical scenarios for which CTC is indicated remain unclear. To address this uncertainty – 20 years after the first presentation of CTC at a radiological meeting [8] – the European Society of Gastrointestinal Endoscopy (ESGE) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) decided to produce a common guideline regarding indications for CTC in clinical practice. Technical and quality issues of CTC have been deliberately excluded from this work as these have already been discussed separately [7].

Methods

The ESGE and ESGAR commissioned this Guideline (chairs C.S. and A.L.) and invited the listed authors to participate in the development of the Guideline. The key questions were prepared by the coordinating team (C.S. and A.L.) and then approved by the other members (see **Appendix e1**, available online). The coordinating team convened subgroup task forces, each with one radiologist and one endoscopist lead, and allocated the key questions to these task forces.

Each task force performed a systematic literature search to prepare evidence-based statements on their assigned key questions. Medline, EMBASE and other databases were searched including the following search terms as minimum: colon, cancer or malignancy or neoplasm, and CTC. All articles investigating CTC in symptomatic or screening contexts were selected by inspecting the title and abstract. Hereditary colorectal syndromes were excluded. After further exploration of the content, each task force summarized the included articles in a table of evidence (see **Appendix e2**, available online). All selected articles were graded on level of evidence and strength of recommendation according to the GRADE system [9, 10]. The literature searches were updated to September 2013.

Each task force prepared statements answering their assigned key questions. The statements were discussed subsequently and voted on during a face-to-face meeting of the whole group held on 1 October 2013. In May 2014, a draft prepared by the coordinating team was sent to all group members for comment. After agreement on a final version, the manuscript was reviewed by two experts selected by the ESGE and ESGAR Governing Boards and then submitted to the journals of ESGE and ESGAR.

This Guideline will be reviewed in 2019, or sooner if relevant new evidence becomes available. Any updates to the Guideline in the interim will be noted on the websites of ESGE (http://www.esge.com/esge-guidelines.html) and ESGAR (http://www.esgar.org).

Recommendations and statements

Evidence statements and recommendations are stated in italics, key evidence statements and recommendations are in bold.

CT colonography (CTC) and diagnosis of colorectal neoplasia

ESGE/ESGAR recommend computed tomographic colonography (CTC) as the radiological examination of choice for the diagnosis of colorectal neoplasia. ESGE/ESGAR do not recommend barium enema in this setting (strong recommendation, high quality evidence).

Computed tomographic colonography (CTC) can be considered to be the best radiological test for the diagnosis of colorectal cancer. Several randomized [11 – 13], multicenter [14,15], and single-center trials [16 – 18], and meta-analyses [19 – 26], have shown that regarding accuracy for both colorectal cancer (CRC) and large/advanced polyps, CTC is similar to colonoscopy in symptomatic and asymptomatic patients and is clearly superior to barium enema [11]. In a recent randomized trial (the SIGGAR trial) [11,13] comparing CTC with colonoscopy and barium enema, the detection rate for colorectal cancer or large polyps was significantly higher in patients assigned to CTC than in those assigned to barium enema (7.3 % vs 5.6 %, $P < 0.039$) but similar for colonoscopy and CTC (11 % for both procedures).

In a comparative study between colonoscopy and barium enema [27], the sensitivity and specificity of barium enema were respectively 38 % and 86 % for polyps of any size. In another publication [28], using a 5-mm threshold, per-patient sensitivity and specificity of barium enema were respectively 41 % and 82 %; at a threshold greater than 10 mm, these values were respectively 48 % and 90 %.

In a meta-analysis comparing the performance of barium enema with CTC [29] for detection of colorectal polyps ≥ 6 mm in average risk and high risk patients, CTC was more specific and more sensitive than barium enema for large polyps (≥ 10 mm) and small polyps (6 – 9 mm), in both per-patient and per-polyp analysis. In the per-patient analysis, CTC showed an incremental diagnostic yield in sensitivity of 12.0 % for polyps ≥ 10 mm and of 30.1 % for polyps of 6 – 9 mm, and in specificity of 10.3 % for polyps ≥ 10 mm. Apart from better diagnostic performance, CTC is more tolerable and acceptable to patients and delivers a lower effective radiation dose than barium enema [30].

CT colonography following incomplete colonoscopy

ESGE/ESGAR recommend CT colonography (CTC), preferably the same or next day, if colonoscopy is incomplete. Delay of CTC should be considered following endoscopic resection. In the case of obstructing colorectal cancer, preoperative contrast-enhanced CT colonography may also allow location or staging of malignant lesions. (strong recommendation, moderate quality evidence).

Incomplete colonoscopy has been reported to occur in 10%–15% of all colonoscopies [31,32], and it has been associated with a higher risk of interval cancers in epidemiological studies [33]. Incomplete colonoscopy may be addressed by repetition of colonoscopy or by radiological procedures. Repeat colonoscopy is likely to be considered when the reason for the previous failure was inadequate bowel preparation [34,35]. On the other hand, radiological referral appears most frequently indicated in the case of difficult anatomy or patient intolerance [35]. Several studies [36–46] have investigated CTC as a completion procedure following incomplete colonoscopy. These studies show high technical feasibility, a relatively high diagnostic yield, and an adequate positive predictive value (PPV), especially at a 10-mm threshold. However, none of the studies employed an independent reference standard for individuals with negative CTC findings, so that the accuracy of CTC in this setting is unknown. However, there is no apparent reason why the high accuracy shown by CTC in both asymptomatic and symptomatic settings, especially for large polyps or CRC, should not be extrapolated to those individuals with incomplete colonoscopy. For this reason, the superiority of CTC over barium enema recently shown in a large randomized study [11] should favor performance of CTC rather than barium enema following an incomplete colonoscopy.

Timing of CTC after incomplete colonoscopy

CTC after incomplete colonoscopy requires a different approach from primary CTC. When endoscopic biopsy has been done, CTC can be performed on the same day as the endoscopic procedure. An ultralow/low dose pre-CTC scan of the abdomen and pelvis before insertion of the rectal tube may rule out the presence of extraluminal gas that would indicate a colonoscopic perforation. In detail, in 262 patients undergoing CTC after incomplete colonoscopy, 2 perforations were detected (0.8%, 95% confidence interval [95%CI] 0.1–2.7) [47]. In the case of endoscopic resection (i.e. polypectomy/mucosectomy), it is prudent to consider an approximately 2-week delay before performing CTC. However, there is little scientific evidence concerning the interval between endoscopic resection and subsequent CTC, thus for each case there should be a clinical discussion between the endoscopist and the radiologist. However, in a recent study on 65 CRC patients with severe luminal narrowing after incomplete colonoscopy with either polypectomy or biopsy sampling, no extraluminal gas was detected at CTC within 24 hours [48]. Other evidence for the safety of radiologic imaging after endoscopic biopsy comes from barium enema studies, both experimental and clinical [49–52]. These studies concluded that in a nondiseased colon, barium enema could be performed immediately after endoscopic biopsy without any risk. In the case of endoscopic resection, barium enema could be performed without any risk after 6 days.

Incomplete colonoscopy due to obstructing CRC

Accurate preoperative assessment of the whole colon is required to exclude synchronous CRC. In a recent population-based study of 13 683 Dutch patients diagnosed with CRC, 3.9% were diagnosed with synchronous CRC, and in 34% of these cases the two tumors were located in different surgical segments [53]. These data were in line with those from a previous French study [54] and from other series [55]. Failure to detect synchronous cancer can increase morbidity, and one study has shown that intraoperative palpation can miss up to 69% of synchronous malignancies [56,57]. Thus, preoperative whole-colon assessment is needed.

CTC appears to be an effective and safe choice when obstructing CRC prevents a complete endoscopic assessment or when cecal intubation fails for other reasons. A recent study including 286 CRC cases after failed colonoscopy showed CTC negative predictive values (NPVs) of 100% and 97% for synchronous cancer and advanced neoplasia, respectively, in a preoperative setting [58]. This is in line with a previous systematic review, showing equivalent sensitivity of colonoscopy and CTC for established cancer [22], and in line with findings from similar cohort studies [44, 59–63].

Patients with abdominal symptoms suggestive of colorectal cancer

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When endoscopy is contraindicated or not possible, ESGE/ESGAR recommend CT colonography (CTC) as an acceptable and equally sensitive alternative for patients with symptoms suggestive of colorectal cancer (strong recommendation, high quality evidence).

Patients with abdominal symptoms suggestive of colorectal cancer (CRC) require detailed investigation, since neither clinical examination nor fecal testing reliably excludes CRC [64]. The ideal test would also diagnose non-neoplastic conditions responsible for the symptoms (both within the colon and beyond it). Patient acceptability and safety are also important.

Colorectal neoplasia

In the SIGGAR trial no significant difference in the detection rates for large polyps (≥10 mm) and for colorectal cancer was demonstrated between CTC and colonoscopy [13]. Furthermore, the crude pooled sensitivity of CTC for colorectal cancer in the studies of symptomatic patients was 96% (169 out of 176 colorectal cancers detected) [13]. This is compatible with the 96.1% sensitivity of CTC for colorectal cancer that was reported in a meta-analysis [22] that included both screening and symptomatic/high risk patients. When large polyps (≥10 mm) only were considered, per-patient sensitivity of CTC ranged from 82% to 92% in six meta-analyses that included screening, symptomatic, high risk, and FOBT-positive patients [19–21, 23,25,26]. In the studies specifically investigating symptomatic patients, pooled sensitivity for large≥10-mm lesions (excluding cancers) was 91.4% (53 of 58 patients).

These data suggest that CTC and colonoscopy have similar sensitivity for detecting CRC and large polyps in symptomatic patients. Small polyps (6–9 mm) and diminutive polyps (≤5 mm) are less relevant in symptomatic patients, since they cannot explain the patient's symptoms. Nonetheless, the ability to opportunistically detect and remove early precursor lesions and perform histopathologic analysis of diagnosed CRC remains a potential advantage of colonoscopy over CTC.

Colorectal non-neoplastic disease

Abdominal symptoms may be due to non-neoplastic colonic conditions, for which both CTC and colonoscopy may be useful. Diverticulosis is more commonly demonstrated at CTC than colonoscopy [13,65], although the relationship between diverticulosis and symptoms is less clear. Colonoscopy is more sensitive for the detection of colitis and anal pathology [13]; furthermore it offers the possibility of sampling tissue.

Extracolonic findings

CTC is an abdominal CT examination with the ability to detect extracolonic diseases. Although these extracolonic lesions may occasionally explain the symptoms, on the other hand, incidental findings that ultimately prove unimportant may prompt additional tests that are inconvenient, costly, and even harmful. Few studies of extracolonic findings focus specifically on symptomatic patients, in whom there is a higher prevalence of significant abnormality. The two largest series, of screening [66] and symptomatic [11,13] patients, respectively reported 0.35% and 1.9% rates of extracolonic malignancy. Importantly, in the paired SIGGAR trials, at 3-year follow-up there was no significant difference in rates of extracolonic malignancy between the two arms of each of the trials (CTC vs. barium enema, and CTC vs. colonoscopy), although all arms showed rates significantly above rates expected for the general population. The latter observation may be explained by subsequent use of CT to investigate persistent symptoms in patients randomized to colonoscopy or barium enema, although this remains unproven.

CT colonography and screening for colorectal cancer

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ESGE/ESGAR do not recommend CT colonography (CTC) as a primary test for population screening or in individuals with a positive first-degree family history of colorectal cancer (CRC). However, it may be proposed as a CRC screening test on an individual basis providing the screenee is adequately informed about test characteristics, benefits, and risks (weak recommendation, moderate quality evidence).

Accuracy of computed tomography colonoscopy (CTC)

To date, only guaiac FOBT (g-FOBT) and sigmoidoscopy have been shown to reduce CRC mortality, by 16% and 22%–31% respectively [67–69]. CTC has not been subjected to randomized trials with CRC incidence or mortality as end points. Therefore, the accuracy of CTC is used as a surrogate end point for CTC efficacy in a screening setting.

CTC accuracy in average risk screening populations has been investigated by a recent meta-analysis [24], which estimated per-patient sensitivity at 88% for advanced neoplasia ≥10 mm. One further primary study published after this review, showed similar results [16]. In six screening studies, none of the 12 CRCs present were missed by CTC in average risk individuals [14,16–18,70–72]. Individuals with a positive family history of CRC or adenomas should be considered to be at high risk [73]. One recent cohort study showed a 89% sensitivity of CTC for advanced neoplasia ≥10 mm in this setting [74].

CTC in screening: participation and yield

The efficacy of a screening program not only depends on the diagnostic accuracy of the screening test that is used, but also on participation. This is illustrated by the results of a large population-based randomized screening trial performed in the Netherlands: participation rates for colonoscopy and CTC of 22% and 34%, respectively, were reported, and detection rates for advanced neoplasia of 8.7 and 6.1 persons per 100 participants, respectively [12]. Despite the higher sensitivity of colonoscopy and the fact that CTC participants were only referred to colonoscopy if they had lesions ≥10 mm detected by CTC, the number of individuals per 100 invitees found to have advanced neoplasia was similar for both screening modalities, namely 1.9 (colonoscopy) versus 2.1 (CTC) per 100 invitees [12]. The poorer sensitivity of CTC compared with colonoscopy was countered by its approximately 1.5 times higher participation rate.

In the case of serrated adenomas the diagnostic yield of colonoscopy was 5 times higher than that of CTC. This is of particular importance, since approximately 10%–20% of CRC develops from the serrated pathway [75].

The diagnostic yield of CTC screening per 100 invitees would appear to be significantly higher than the yield of first-round g-FOBT, but similar to the yield of first-round flexible sigmoidoscopy screening (2.2 per 100 invitees) and fecal immunochemical testing (FIT) screening (2.0 per 100 invitees when using a cutoff of 50 ngHb/mL) [76]. One should however bear in mind that FOBT/FIT screening is repeated at 2-year intervals, whereas 5–10-year intervals are usually recommended for CTC and endoscopic screening.

Acceptability of CTC screening

A recent meta-analysis included articles on preferences and differences in burden for both average risk and high risk individuals who had undergone CTC as well as colonoscopy (tandem design) [77]. Amongst the included studies, 3573 patients reported a preference for CTC, 927 showed a preference for colonoscopy, and 1116 showed no difference in preference.

In a Dutch population-based screening trial, almost half of the nonparticipants made an informed decision on participation as they were provided with adequate knowledge of CRC and CRC screening, and showed a positive attitude towards screening, but nevertheless declined participation, which suggested that additional barriers to participation were present [78]. The reasons cited for declining screening by colonoscopy or by CTC were similar overall [79]. However, colonoscopy invitees who declined most often mentioned 'unpleasantness of the examination' as their prime reason, while for CTC invitees 'no time/too much effort' and 'lack of symptoms' were most often cited. The last finding is consistent with the findings of the study of Ho et al., in which 38% did not participate in CTC screening because of procrastination and 12% because they were too busy [80].

As indicated above, most previous screening studies, using a tandem design to compare perceived acceptability and burden of the two techniques, showed a significant preference for CTC, with 46% to 95% of participants preferring CTC for future investigation [17,81,82].

A recent Netherlands study performed within the population-based screening trial mentioned above showed that colonoscopy invitees expected the screening procedure and bowel preparation to be more burdensome than did CTC invitees [83]. CTC participants in the Dutch study however found their screening procedure slightly more burdensome than did colonoscopy participants. Colonoscopy participants gave higher burden scores to ingesting the bowel preparation, while CTC participants gave higher burden scores to related bowel movements (i.e. diarrhoea and bowel cramps). Although these differences were statistically significant, they were mostly small and thus the clinical relevance is limited for a clinical population, but more significant for a primary screening population. This is illustrated by the fact that intended participation in a subsequent screening round exceeded 90% for both colonoscopy and CTC.

Safety of CTC screening

Adverse events

The risk of major adverse events due to the CTC examination itself (including the bowel preparation) is low and presumed lower than for colonoscopy [13,84]. Adverse events of CTC screening, however, should include events related to the entire episode, also including those related to any colonoscopy required to investigate CTC findings (e.g. post-polypectomy bleeding).

In a randomized trial comparing CTC with colonoscopy screening, serious adverse events were comparable for both procedures, (0.2% for CTC; 0.3% for colonoscopy) [12]. These rates are similar to adverse events observed in randomized trials of FOBT and of flexible sigmoidoscopy screening [85]. In a recent meta-analysis [86] on 103 399 asymptomatic and symptomatic patients, the CTC perforation rate was estimated to be 0.04% overall; the rate was 19-fold higher in symptomatic compared with screening individuals. The CTC-induced surgery rate was 0.008% and no CTC-related deaths were reported.

Radiation risk in screening

Radiation exposure at CTC is associated with a risk of cancer induction. This risk is relevant for all individuals but especially so in screening where benefit should clearly outweigh potential harm. The risk associated with ionizing radiation at a single CTC is very small and has been estimated as an absolute lifetime cancer risk of 0.14% for a 50-year-old and 0.07% for a 70-year-old, and can be reduced substantially with protocol optimization [87]. Another study reported a less than 0.2% increase of the lifetime cancer risk in individuals undergoing CTC screening every 5 years between the ages of 50 and 80 years [88].

A study compared the anticipated cancer induced versus anticipated cancer prevented by CTC screening using the effective dose of a screening study (7 mSv for men and 8 mSv for women) [89]. In that study the radiation-related lifetime cancer risk for a single screening CTC was 0.06% for a 50-year-old person and decreased with age. The corresponding calculated benefit – risk ratio for a 50-year-old person ranged from 24:1 to 35:1 depending on the model used. A recent international survey reported that the effective dose of present day screening CTC was 4.4 mSv [90], which is lower than used in the aforementioned study. Further dose reduction is possible with technical developments such as iterative reconstruction algorithms and lower tube voltage, leading to doses of 1 mSv [91].

Extracolonic findings

Extracolonic findings are common at screening CTC and have been reported to occur in from one quarter to more than one half of screenees [92 – 97]. The incidence of extracolonic findings increases significantly with age; one study reported extracolonic findings in 55.4% of screenees younger than 65 years and in 74% of those 65 years or older [96]. The large majority of extracolonic findings are irrelevant and can be classified as such at CTC.

Work-up for (potentially) important extracolonic findings occurs in approximately 10% of cases [97 – 99]. The prevalence of extracolonic findings of moderate or high importance at CTC is commonly reported to be approximately 10% – 15% of screenees [94, 95,98,99], although higher prevalence is occasionally reported [92,100]. This difference is partly caused by variation in the definition of moderate and high importance findings. The proportion of findings of high importance is mostly in the order of 2% – 5% [95,97,99], and includes approximately 0.5% extracolonic cancers, of which renal cell cancer, lung cancer and lymphoma are most prevalent [66,97,99,100], and are usually localized at the time of diagnosis [66]. Further important extracolonic findings include abdominal aortic aneurysms, adrenal masses, and nonmalignant renal masses.

The costs reported for the additional work-up of extracolonic findings vary substantially and are influenced by the definition of a relevant finding needing work-up and by which costs are included. It appears that the average additional cost for extracolonic findings at CTC is of the order of 20 – 50 USD averaged over all attendees [94 – 96,100,101]. No studies report costs that might be saved by earlier detection of disease.

CTC as a primary screening modality for CRC: conclusions

Primary CTC and colonoscopy screening have similar yields for advanced neoplasia per invitee. However, the impact of extracolonic findings, both medically and economically, remains unknown. Although radiation exposure is a drawback, this disadvantage seems to be overemphasised especially given the current reduction in radiation exposure with CTC. Probably the most important factor is the question of whether CTC screening is cost-effective, and this is still unanswered. Based on these considerations, CTC cannot at this stage be recommended as the primary test for population CRC screening or in individuals with a positive first-degree family history. However, it may be suggested as a CRC screening test on an individual basis, providing the screenees are adequately informed about test characteristics, benefits, and risks.

CTC within a screening program, following positive fecal testing with incomplete/unfeasible colonoscopy

ESGE/ESGAR strongly recommend CT colonography (CTC) in the case of a positive fecal occult blood or fecal immunochemical test with incomplete or unfeasible colonoscopy, within organized population screening programs (strong recommendation, low quality evidence).

Repeated annual or biennial screening for colorectal cancer (CRC) by guaiac-based fecal occult blood testing (FOBT) reduces disease-specific mortality by approximately 15% – 18% [102]. Results of similar repeated screening by means of fecal immunochemical testing (FIT) are awaited. It is assumed that the impact on CRC-related mortality will be considerably higher than with FOBT, because of the higher uptake of FIT testing, and the higher sensitivity for advanced colorectal lesions [103]. This is confirmed by modelling studies [104]. This benefit is contingent on confirmation and treatment of underlying cancer or adenoma after a positive result. Colonoscopy combines sensitive diagnosis with therapy by endoscopic resection and is therefore regarded as the preferred test.

Since most screenees testing FOBT/FIT-positive will not have advanced neoplasia, CTC has been investigated as a possible triage test to select patients with lesions only of greater size for colonoscopy or surgery. The sensitivity of CTC for adenomas ≥ 6 mm was above 85% in six studies [15,25,105 – 108] and was over 90% for adenomas ≥ 10 mm, a finding confirmed by a meta-analysis published after our literature search [25]. A modelling study concluded that the use of CTC as an intermediate after positive FOBT/FIT can only be cost-effective if the costs of CTC were ≤ 43% of the costs of colonoscopy [109]. Furthermore, despite sensitivity exceeding 85%, lesion prevalence is so high that NPV is less than might be expected, ranging from 85% to 95% in the studies included. These factors mean that CTC should not be offered routi-

nely to those testing FOBT/FIT-positive, and colonoscopy is preferable.

Since CTC does have good diagnostic performance, it may be considered for those unwilling to undergo colonoscopy or in whom colonoscopy is unfeasible or incomplete, although screenees should be informed that sensitivity (particularly for smaller adenomas) is slightly inferior to that of colonoscopy. There is some evidence that offering CTC to those who decline colonoscopy increases uptake [110]. CTC is safe, and therefore may be preferable in those with contraindications to colonoscopy or judged particularly high risk, although observational data suggest absolute detection rates may be lower than in healthy screenees who are fit for colonoscopy [111]. Reasons for differences in detection rates are unknown and only speculative at this stage. If the difference is confirmed, and if it is due to suboptimal CTC practice (CTC technique and/or image interpretation), procedures for guaranteeing high quality of CTC exams within organized population screening programs will be necessary.

CT colonography and surveillance

Following curative-intent resection of colorectal cancer

ESGE/ESGAR suggest CT colonography (CTC) with intravenous contrast medium injection for surveillance after curative-intent resection of colorectal cancer only in patients in whom colonoscopy is unfeasible (weak recommendation, low quality evidence).

Patients with resected colorectal cancer are at a 30 % risk of recurrence [112, 113] which can be either colonic or extracolonic. Local recurrence is less common for colonic than rectal cancers [112, 114, 115]. Recurrence can occur either at the site of anastomosis or near the site of the primary resection. In contrast, metachronous lesions are colorectal adenomas and cancers that develop subsequently to the index cancer and do not originate from it. Extracolonic recurrent disease comprises distant metastases in the liver, lung, peritoneum, etc. CTC for postoperative surveillance following potentially curative resection of colorectal carcinoma has the potential to combine both colonic and extracolonic examination, and is therefore an alternative to combined optical colonoscopy and contrast-enhanced abdominal CT [116].

By means of a literature review, we identified eight cohort studies investigating contrast-enhanced CTC as a surveillance tool after resection of colorectal cancer [116 – 123]. All of these studies demonstrated a high technical feasibility.

Local recurrence and metachronous colorectal cancer

In these studies, all local recurrent (n = 65) and metachronous (n = 9) colonic cancers, were detected [116 – 123]. The largest study included 548 patients who had subsequent colonoscopy and pathologic confirmation of colonic lesions [116]. CTC sensitivity for anastomotic and metachronous recurrence was 100 %. Per-patient and per-lesion sensitivities for advanced neoplasia were 81.8 % and 80.8 %, respectively, and for all adenomatous lesions they were 80.0 % and 78.5 %, respectively [116]. NPVs for adenocarcinoma, advanced neoplasia, and all adenomatous lesions were 100 %, 99.1 %, and 97.0 %, respectively. CTC enabled detection of clinically unsuspected metastatic disease in 11 patients, none of them having a cancerous lesion in the colon [116].

CTC surveillance detection of adenoma/polyp

In a study on 548 consecutive patients, without clinical or laboratory evidence of recurrence following curative-intent CRC, who underwent contrast-enhanced CTC and subsequent colonoscopy and pathologic confirmation of colonic lesions, CTC sensitivity for all adenomas of 80.0 % (per-patient) and 78.5 % (per-lesion) were reported [116]. Unfortunately, accuracy data for these lesions cannot be extracted from the other studies, because of the low number of patients with polypoid lesions, inconsistent or insufficient reporting on the detection/presence of polyps/adenomas, and/or lack of histological polyp data that impeded any stratification and comparison of results [117 – 123].

CTC following polypectomy

ESGE/ESGAR suggest CT colonography (CTC) in patients with high risk polyps in surveillance after polypectomy only when colonoscopy is unfeasible (weak recommendation, low quality evidence).

The recent ESGE Guideline recommends endoscopic surveillance only for patients with high risk adenomatous lesions (adenomas with villous histology or high grade dysplasia or ≥ 10 mm in size, or ≥ 3 adenomas) or serrated lesions (≥ 10 mm in size, or any degree of cytological dysplasia) [124]. Colonoscopy is considered to be the method of choice for post-polypectomy surveillance, whose primary aim is to diagnose and remove polyps either missed at initial examination or newly developed during the time interval between the index and follow-up examination. However, compliance with colonoscopic surveillance is relatively low, ranging from 52 % to 85 %, with the highest levels obtained in research settings [125 – 128]. Despite weak evidence supporting CTC for surveillance [15], in patients who are unwilling or unable to undergo colonoscopy, CTC is the best alternative because of its high sensitivity and NPV, outperforming barium enema [11, 22, 29].

Safety of CT colonography

ESGE/ESGAR state that CT colonography (CTC) is contraindicated in patients with active colonic inflammation and in those who have recently undergone colorectal surgery (strong recommendation, low quality evidence).

Despite being generally regarded as safer than colonoscopy [129], CTC has been shown to be associated with potentially serious adverse events, in particular perforation of the large bowel [130, 131]. Acute abdominal conditions, for example diverticulitis or active inflammatory bowel disease (IBD), are absolute contraindications to CTC, because of the relatively high risk of complication [132], and CTC should be avoided [130]. Unfortunately, there are few studies supporting these strong recommendations. In a recent meta-analysis [86] including more than 100 000 individuals, 28 colonic perforations were reported. Moreover, eight case reports – not included in the meta-analysis – detail CTC perforation [133 – 140]. These reports allow identification of some risk factors for perforation. Among the 36 patients with perforation, four (11 %) were affected by inflammatory bowel diseases, four had a known inguinal hernia, and in one case the perforation occurred after erroneous inflation of a rectal stump. Moreover, mural frailty during active inflammation or in the postoperative setting suggests that any procedure involving colonic distension entails a risk.

Colonoscopy following CT colonography

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ESGE/ESGAR recommend referral for endoscopic polypectomy in patients with at least one polyp ≥ 6 mm in diameter detected at CT colonography (CTC). CTC surveillance may be clinically considered if patients do not undergo polypectomy (strong recommendation, moderate quality evidence).

Polyp size and risk of advanced neoplasia

Diminutive polyps (≤ 5 mm)

Most colorectal lesions encountered at endoscopy are polyps ≤ 5 mm (i.e. diminutive) [141]. However, only a small proportion of these lesions meet histological criteria for advanced neoplasia. In detail, a recent systematic review of 28 947 polyps found the frequency of advanced neoplasia to be 1.4 % (408 /28 947), while the risk of invasive cancer was 0.03 % (10/31 263) [142]. Little information is available regarding the natural history of untreated ≤ 5-mm polyps. In two prospective Northern European endoscopic studies, Hoff et al. [143] and Hofstad et al. [144] followed up 194 diminutive and 253 ≤ 9 mm polyps for 2 and 3 years, respectively. No diminutive polyp reached > 5 mm in size and only 0.5 % of polyps ≤ 10 mm exceeded the 10-mm threshold after 1 year; no cases of severe dysplasia or carcinoma were reported [143, 144]. Similar findings were reported by a Japanese study, in which only 2.9 % of 408 subcentimetric lesions followed up for 43.1 months reached ≥ 10 mm size, without any invasive cancer occurring [145].

Small polyps (6 – 9 mm)

Overall, polyps of 6 – 9 mm (i.e. small polyps) represent about 15 % of all the polyps detected during primary screening colonoscopy [141]. In a recent systematic review of 8605 polyps, the frequency of advanced neoplasia was 7.9 %, while the proportion with invasive cancer was 0.5 % (10 /8456) [142]. A retrospective analysis of 5124 individuals undergoing screening CTC confirmed a very low risk of advanced neoplasia and invasive cancer in 464 patients with polyps 6 – 9 mm in size as the largest lesion, corresponding to a 3.9 % and 0 % risk, respectively [146].

Recently, the natural history of 6 – 9-mm polyps detected at CTC was addressed by a longitudinal study. Specifically, 243 adults with 306 small polyps detected by CTC underwent a second CTC after a 2 – 3-year follow-up [147]. Overall, 22 % polyps had progressed, with 6 % exceeding 10 mm. The odds ratio was 16 for advanced adenoma among polyps that had shown growth during surveillance compared with advanced adenoma among 6 – 9-mm polyps detected and removed at initial CTC and colonoscopy in a reference cohort. An absolute polyp volume of more than 180 mm^3 at surveillance CTC was shown to predict advanced neoplasia (including one cancer) with a sensitivity of 92 % (22 of 24 polyps), specificity of 94 % (266 of 282 polyps), PPV of 58 % (22 of 38 polyps), and NPV of 99 % (266 of 268 polyps).

Recently, factors that may predict advanced neoplasia within a subcentimeter polyp have been investigated. Kolligs et al. [148] applied a logistic regression model to a large retrospectively obtained cohort of 1 077 956 colonoscopies, in which 106 270 small and 198 954 diminutive lesions were removed. The risk of advanced neoplasia within subcentimetric lesions was associated with increasing age, male sex, polyp morphology, polyp multiplicity, and occult or overt blood in the stools.

Large polyps (≥ 10 mm) and masses

Overall, ≥ 10-mm polyps (i.e. large polyps) represent about 10 % of all polyps detected during primary screening colonoscopy [141]. In a previous systematic review, 73.5 % (1363/1855) of these polyps appeared to be advanced adenomas, the remainder being nonadenomatous [141]. The prevalence of invasive cancer has been recently addressed in large colonoscopic and CTC screening series, with reported ranges between 2 % and 7 % [146, 148, 149].

Same-day polypectomy

ESGE/ESGAR suggest same-day polypectomy as a possible option after CT colonography (CTC) performed with full bowel preparation. The implementation of this policy should take into account technical and logistical factors, including patient consent (weak recommendation, low quality evidence).

Type of laxative used for CTC

Bowel preparation for CTC usually includes a low residue diet and clear liquids for 24 hours or more, and a laxative preparation that may be either a "wet prep" (e.g. polyethylene glycol [PEG]) or "dry prep" (e.g. phosphosoda, magnesium citrate, etc). In the studies identified in the literature search for CTC and same-day colonoscopy, a range of different preparations was used, with approximately half using PEG, and the remaining using phosphosoda or a similar laxative. The rationale for laxative choice was rarely stated, although some studies documented that choice was based on that routinely used for colonoscopy by the host institution. Furthermore, although data were sometimes presented on quality of CTC preparation, few studies formally graded bowel cleansing during same-day colonoscopy.

One large study of same-day CTC and colonoscopy in 734 patients [105], investigated the quality of CTC imaging according to the CT Colonography Reporting and Data System (C-RADS) and graded the quality of bowel preparation at colonoscopy. Patients were prepared before CTC, with clear liquid during the preceding 24 hours, 30 ml sodium phosphate and 20 mg bisacodyl as laxatives, and oral barium and iodine agents for tagging. Only 3.1 % of the procedures were classified as inadequate for CTC interpretation; in 20 of 23 cases this was due to insufficient insufflation. At colonoscopy, colonic preparation was classified by the endoscopist as excellent or good in 63 % of patients, fair in 28 %, poor in 8.5 %, and inadequate in 0.5 %.

A minority of studies commented regarding the quality of preparation during colonoscopy, but provided little detailed information.

The fact that the literature is so sparse regarding quality of preparation during same-day colonoscopy does suggest that it is not a major issue. However it cannot be determined from the available literature which bowel preparation is preferred for same-day colonoscopy after CTC. Although the frequency and extent of retention of fecal material and fluids at CTC has been extensively studied, the effects of the various CTC preparation protocols on the performance of same-day colonoscopy is less well known.

Laxative-free CTC

Reduced bowel preparations at CTC are gaining popularity but may prevent same-day endoscopy (although minor fecal residue may be suctioned during colonoscopy). Our literature search found no information regarding the quality of same-day colonoscopy after same-day laxative-free CTC. However several studies have reported using additional bowel cleansing subsequent to

laxative-free CTC when same-day colonoscopy is required. For example, in a study of 95 symptomatic patients undergoing reduced-laxative CTC, senna and 18 g magnesium citrate were used, with an additional 18 g of magnesium citrate after CTC but prior to colonoscopy [150]. Lefere et al. [151] compared standard bowel preparation, reduced bowel preparation, and oral barium for fecal tagging in 100 patients having CTC with same-day colonoscopy. In order to compensate for reduced bowel purgation, which may prohibit colonoscopy, PEG was administered after CTC, and colonoscopy performed 2 – 3 hours later.

Fecal tagging

Fecal tagging with oral barium or hyperosmolar/iso-osmolar iodine solutions or both is now considered mandatory for CTC [7]. Occasionally, concern has been raised that when barium is used, it may interfere with the diagnostic quality of same-day colonoscopy, potentially obscuring the endoscopic view by coating the colonic mucosa. Others have suggested that retained barium and iodine-based contrast agents are easily aspirated or flushed out of the way during endoscopy, and therefore are of no concern. Our literature search, including studies of same-day CTC and colonoscopy with or without fecal tagging, found little specific information on this issue. Frequency of incomplete colonoscopy was commonly cited, indicating causes such as tortuous bowel, pain, or strictures, but problems specifically related to fecal tagging were rarely mentioned.

Pickhardt et al. [18] analyzed 1233 asymptomatic patients undergoing CTC (with fecal and fluid tagging) and same-day colonoscopy with segmental unblinding. The quality of bowel preparation was not formally reported but only six of 1253 patients were excluded initially because of inadequate colonic preparation. Suboptimal colonoscopy quality was dismissed as a reason for missed adenomas since the colonoscopy completion rate was high at 99.4%.

A similar tagging regimen was used in another large study, mentioned above, of same-day CTC and colonoscopy in a population at average or high risk of colorectal cancer [105]. The quality of CTC imaging was assessed by the radiologist according to the C-RADS system and the quality of bowel preparation at colonoscopy was graded by the endoscopist on a 5-point scale, from excellent to inadequate. At colonoscopy, 63% of cases were classified as excellent or good, 28% as fair, 8.5% as poor and 0.5% as inadequate. At CTC, 23 (3.1% of the cases) cases were classified as C0, which includes preparation or insufflation that is inadequate for satisfactory interpretation; as noted above, 20 of the 23 cases were due to inadequate insufflation. These 23 cases were classified at colonoscopy as having excellent or good preparation in 65%, fair in 30%, and poor or inadequate in 5%. There was no mention that tagging agents were a complicating factor at colonoscopy.

It can therefore be inferred indirectly from the relatively large number of comparative same-day CTC and conventional colonoscopy studies aimed at diagnostic accuracy, that fecal tagging likely does not negatively affect colonoscopy results.

Logistics of same-day colonoscopy

To provide same-day endoscopy after CTC, the indications and logistics concerning patient selection, timing, patient transportation, availability of endoscopists and endoscopy suites etc. must be pre-planned jointly by radiology and endoscopy units. This modality also requires that CTC findings are reviewed by a radiologist immediately in order to identify patients in whom same-day colonoscopy is needed, and in order to identify the rare but well-recognised perforations that occur during CTC.

When a lesion detected at CT colonography (CTC) is not confirmed by a high quality colonoscopy, ESGE/ESGAR recommend careful review of the CTC findings. In cases when post-colonoscopy radiological confidence for the presence of a ≥ 10-mm lesion remains high, early repetition of colonoscopy should be considered (weak recommendation, low quality evidence).

It is possible that colorectal lesions reported at CTC may not be detected at colonoscopy, either because they are CTC false positives or colonoscopic false negatives. Clinical consequences include progression of colonoscopic false-negative polyps towards invasive CRC or anxiety due to CTC false-positive findings. In a recent prospective multicenter study of symptomatic patients, the PPV of CTC for large polyps was about 60%, indicating that colonoscopic inability to confirm CTC findings occurs frequently [11]. The sensitivity of colonoscopy for ≥ 10-mm polyps is higher [152], and may be presumed to be substantially increased when – as occurs in daily practice – the endoscopist is searching specifically for a CTC finding. Therefore, the possibility of missing large lesions at such colonoscopies may be considered too low to warrant a further endoscopic examination. However, it is well known that colonoscopy is not 100% sensitive even for large lesions that are present at CTC, a phenomenon that has been explained by the existence of colonoscopic "blind spots" [153]. Most post-colonoscopic interval cancers are related to missed rather than new lesions. In contrast to 6 – 9-mm polyps, the risk of established cancer in larger lesions is relevant [149]. Thus if, after negative colonoscopy findings, confidence in the CTC diagnosis remains high, an early repetition of colonoscopy should be considered, especially if the abnormality appears to be related to flexures or to be on the proximal side of colonic haustra.

ESGE guidelines represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply in all situations and should be interpreted in the light of specific clinical situations and resource availability. Further controlled clinical studies may be needed to clarify aspects of these statements, and revision may be necessary as new data appear. Clinical consideration may justify a course of action at variance to these recommendations. ESGE guidelines are intended to be an educational device to provide information that may assist endoscopists in providing care to patients. They are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment.

Competing interests: None

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Appendix e1 and e2

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