IMAGING ALTERNATIVE TO COLONOSCOPY: CT COLONOGRAPHY AND COLON CAPSULE - ESGE/ESGAR guideline – update 2019

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This is an update of 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 alternative imaging to standard colonoscopy. A targeted literature search was performed to evaluate the evidence supporting the use of computed tomographic colonography (CTC) or colon capsule endoscopy (CCE). 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 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. The timing depends on an interdisciplinary decision including endoscopic and radiological factors (strong recommendation, low quality evidence). In centres with expertise and availability of CCE, CCE preferably the same or the next day may be considered if colonoscopy is incomplete (weak recommendation, low quality evidence).*
3. *When colonoscopy is contraindicated or not possible, ESGE/ESGAR recommend CTC as an acceptable and equally sensitive alternative for patients with alarm symptoms (strong recommendation, high quality evidence). Due to lack of direct evidence, ESGE/ESGAR do not recommend CCE (very low quality evidence). ESGE/ESGAR recommend CTC as an acceptable alternative to colonoscopy for patients with non-alarm symptoms (strong recommendation, high quality evidence). In centres with availability CCE may be considered (weak recommendation, low quality evidence).*
4. *Where there is no organised FIT based population colorectal screening programme, ESGE/ESGAR recommend CT colonography as an option for colorectal cancer screening providing the screenee is adequately informed about test characteristics, benefits, and risks, and depending on local service and patient related factors (strong recommendation, high quality evidence). WE do not recommend CCE as first line screening test for colorectal cancer (weak recommendation, low quality of evidence).*
5. *ESGE/ESGAR recommend CTC in the case of a positive fecal occult blood test (FOBT) or FIT with incomplete or unfeasible colonoscopy, within organized population screening programs. (strong recommendation, moderate quality evidence). ESGE/ESGAR also suggest the use of CCE in this setting based on availability (weak recommendation, moderate evidence).*
6. *ESGE/ESGAR suggest CTC with intravenous contrast medium injection for surveillance after curative-intent resection of CRC only in patients in whom colonoscopy is contra-indicated or unfeasible (weak recommendation, low quality evidence). There in insufficient evidence to recommend CCE in this setting (very low quality of evidence).*
7. *ESGE/ESGAR suggest CTC in patients* with high risk polyps in surveillance after polypectomy only when colonoscopy is unfeasible *(weak recommendation, low quality evidence). There is insufficient evidence to recommend CCE in the post-polypectomy surveillance* (very low quality evidence).
8. *ESGE/ESGAR recommend against CTC in patients with acute colonic inflammation and in those who have recently undergone colorectal surgery pending a multidisciplinary evaluation (strong recommendation, low quality evidence).*
9. *ESGE/ESGAR recommend referral for endoscopic polypectomy in patients with at least one polyp ≥ 6mm detected at CTC or CCE. Follow-up CTC may be clinically considered for 6-9 mm CTC-detected lesions if patients who do not undergo polypectomy because of patient choice, comorbidity and/or low risk profile for advanced neoplasia (Strong recommendation, moderate quality evidence).*

Abbreviations			
AN	Advanced Neoplasia	**FIT**	Fecal Immunochemical Test
ANDR	Advanced Neoplasia Detection Rate	**FOBT**	Fecal Occult Blood Testing
CCE	Colon Capsule Endoscopy	**GRADE**	Grading of Recommendations Assessment, Development and Evaluation
CRC	ColoRectal Cancer	**IBD**	Inflammatory Bowel Disease
CT	Computed Tomography	**OC**	Optical Colonoscopy
CTC	Computed Tomographic Colonography	**NPV**	Negative Predictive Value
DCBE	Double Contrast Barium Enema	**PEG**	Polyethylene Glycol
ECCO	European CanCer Organitation	**PPV**	Positive Predictive Value
ECF	Extracolonic Findings	**RCT**	Randomized Controlled Trial
ESGAR	European Society of Gastrointestinal and Abdominal Radiology	**SIGGAR**	Special Interest Group in Gastrointestinal and Abdominal Radiology
ESGE	European Society of Gastrointestinal Endoscopy	**TFs**	Task Force subgroups

Introduction

Colorectal cancer (CRC) represents a major cause of cancer-related morbidity and mortality in European countries (1). Colonoscopy has a pivotal role in early diagnosis and CRC prevention due to its high accuracy for detection of precancerous lesions as well as to the possibility to remove them (2–6). Despite incremental technical improvement, colonoscopy is still incomplete in a proportion of patients due to patient and/or endoscopist-related factors. Furthermore, patients may be reluctant to undergo a procedure i.e. colonoscopy that is still perceived as invasive, despite the availability of sedation (7).

Computed Tomographic Colonography (CTC) and Colon Capsule Endoscopy (CCE) have been proposed as alternative imaging modalities to explore the colonic mucosa. CTC is a non-invasive imaging method that uses computed tomography for data acquisition combined with specialized imaging software to examine the colon (8,9). CCE, introduced several years later, (10) is a painless and radiation-free alternative for the study of the entire colon. It is an ingestible, wireless, disposable capsule which can explore the colon without sedation or gas insufflation.

In this document, the European Society of Gastrointestinal Endoscopy (ESGE) and the European Society if Gastrointestinal and Abdominal Radiology (ESGAR) updated and merged the previously published guideline on CTC (11) and CCE (add reference) with new evidence.

Methods

ESGE and ESGAR commissioned the update of this guideline and appointed two guideline leaders (C.S., D.R.), who invited the listed authors to participate in the project development. The key questions were prepared by the coordinating teams using PICO methodology (12) and were then approved by the other members. The coordinating team formed task force subgroups (TFs), based on the statements of the previous guideline, each with its own leader, and divided the key topics among these task forces (**Appendix 1s**) with a specific focus on the update of literature and revision of the statements. The work included telephone conferences, a face-to-face meeting and online discussions.

TFs conducted a literature search using Medline (via Pubmed) and the Cochrane Central Register of Controlled Trials up to November 2019. New evidence on each key question was summarized in tables using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (13). Grading depends on the balance between the benefits and risk or burden of any health intervention (14), **(Appendix 2s).** Further details on guideline development have been reported elsewhere (15). This guideline applies only to patients under screening or suspicion of colorectal neoplasia, whilst the role of these techniques in inflammatory bowel disease (IBD) is out from the purpose of this guideline.

The results of the search and guideline statements were presented to all members of the guideline committee during a face-to-face meeting in Wien on November 4th, 2019 and were voted on. Consensus was defined as an agreement of at least 80%. If consensus was not reached during the first voting session, agreement was sought after further discussion and the modified statement voted again, until consensus was reached. After this meeting drafts were made by the chairs of each TF and distributed between the TF members for revision.

In February 2020, a draft prepared by C.S. and D.R. and the chairs of all TFs was sent to all group members. After agreement of all members, the manuscript was reviewed by two external reviewers and was sent for further comments to the ESGE and ESGAR national societies and individual members. After this, the manuscript was submitted to the journal Endoscopy for publication. The final revised manuscript was agreed upon by all the authors. This Guideline was issued in 2020 and will be considered for update in 2025. Any interim updates will be noted on the ESGE website: http://www.esge.com/esge-guidelines.html.

Statement I
Radiological imaging for the diagnosis of colorectal neoplasia

RECOMMENDATION
ESGE/ESGAR recommend 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).

CTC has been considered the best radiological examination for the diagnosis of colorectal neoplasia. The accuracy for both, CRC and large/advanced polyps has shown to be similar to colonoscopy in symptomatic and asymptomatic patients and clearly superior to barium enema (11). The review of literature provides further evidence to support this statement. Two new European randomized trials (16,17) and a follow-up evaluation (18) have shown detection rates for advanced neoplasia (AN) being similar to optical colonoscopy (OC) in asymptomatic individuals invited for screening. A systematic review has shown the rate of interval cancers after a negative CTC (4.5%) compares favourably with the one of OC (3-9%) (19). In a Japanese multicentre trial, including 1177 patients, sensitivities and specificities over 90 % were achieved for detection of colorectal neoplasia > 9mm (20). CTC is superior to double contrast barium enema (DCBE) for detection of CRC and large polyps (21). A review of the recent literature, did neither contain new patient studies, evaluating specifically the performance of DCBE for the detection of colorectal neoplasia, nor did it provide new evidence supporting the primary use of DCBE for this indication. Continuous decrease in using DCBE (20) may furthermore negatively affect its performance. Barium studies have been also mainly replaced by either endoscopic or cross-sectional imaging techniques for the evaluation of non-neoplastic conditions as inflammatory bowel diseases. European Cancer Organization (ECCO)-ESGAR discourage barium studies for the evaluation of IBD unless local facilities preclude alternatives (22). Water-soluble contrast enemas are, however, still used in clinical practice for a relatively narrow spectrum of indications. These indications include mainly imaging of postsurgical situs and detection of anastomotic leaking. They vary, depending on local experience and clinical practice. Some of these indications, however, are discussed controversially.

Statement II
Completion of a previously incomplete colonoscopy

RECOMMENDATION
ESGE/ESGAR recommend CTC, preferably the same or next day, if colonoscopy is incomplete (strong recommendation, low quality evidence). CCE, preferably the same or the next day, may also be considered (weak recommendation, low quality evidence).

Incomplete colonoscopy for neoplastic lesions - CTC

Almost all cases of incomplete colonoscopy due to occlusive cancer can be examined successfully with CTC (23,24) and one study showed that pre-operative CTC contributes to a change in the surgical plan in 14 of 65 patients (21.5%). Up to 35.1% (range 22.3-45.4%) of synchronous neoplasms occur in a different segment(s) to the distal tumour so their detection will change management in a significant number of patients (25). CTC is useful as a one-stop examination for proximal colonic evaluation in cases of obstructing malignant colonic lesions in addition to overall pre-treatment cancer staging of the abdomen and pelvis when performed with intravenous contrast enhancement. Suboptimal bowel preparation occurs in 3.6% of patients with non-emergent obstructing colon cancer versus 1.1% (screening), however the CTC completion rate across all studies greater than 95%.

Incomplete colonoscopy for non-neoplastic lesions - CTC

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 (26) although the relationship between diverticulosis and symptoms is less clear. Colonoscopy is more sensitive for the detection of colitis and anal pathology (26); furthermore it offers the possibility of tissue sampling. In non-obstructing lesions, colonoscopy should be the preferred modality (27). Colonoscopy allows biopsies and removal of most benign lesions during the same procedure. If active colitis identified at incomplete colonoscopy, it is reasonable to repeat colonoscopy to facilitate serial colonic biopsies. Moreover, areas of colitis-related dysplasia will be missed at CTC. If there is an obstructing lesion, it is reasonable to refer for CTC. In the setting of incomplete colonoscopy due to factors such pelvic post-operative adhesions, strictures due to diverticular disease/inflammatory processes, and/or refractory looping colonoscopy is less likely to be successful. If pain/spasm is the main reason for incomplete colonoscopy, then either repeating the procedure with more sedation or CTC are both reasonable options.

Timing of CTC after incomplete colonoscopy

The timing of CTC after incomplete colonoscopy depends on an interdisciplinary decision including endoscopic and radiological factors. O'Shea et al. (28) recently assessed 245 same-day, post-incomplete colonoscopy CTC studies post routine bowel preparation and 30 mls diatrizoate tagging agent. Mean time from ingestion of tagging agent to CTC was 4 hours 26 minutes. Contrast reached the left hemi-colon in 84% of patients; and 99% of studies were considered diagnostically adequate. The effectiveness of reduced 2-hour iodinated contrast preparation was evaluated by Chang et al. (29) who found that a reduced 2-hour iodinated preparation failed to reach the left hemi-colon in 26% of patients. Although Theis et al. (30) suggest that separate CTC is superior for this reason, the vast majority of patients can have a diagnostic study when same-day CTC is performed with a minor increase in the time interval between OC and CTC. In situations where the left hemi-colon has been well visualized by OC, some consideration could be given to reduced preparation time; a thought echoed by other authors (31). Clinically-suspected perforation, possibly moderate/severe diverticulitis, or moderate/ severe colitis are contraindications to same day CTC (28,32). Same day CTC may be ill-advised post hot snare (snare cautery) or EMR. Lara et al. (33) looked at patients who had same day CTC (3%). They found that 72 polypectomies were performed in 34 (or 17%) of patients. There were no reported complications or perforations associated with same-day CTCs, suggesting that CTC is safe when performed same day as procedure.

Incomplete colonoscopy – CCE

In case of non-neoplastic obstruction, CCE can be considered as an alternative to CTC to explore proximal colonic segments. 7 studies using CCE II have been reported in literature. Overall, visualization of colonic segments not reached by previous colonoscopy was obtained between 75% and 100% with CCE II and between 85% and 93% (34–40) with CCE I (41–43), with significant findings between 24% and 100% in CCE II studies, and between 34% and 59% in CCE I studies. Spada et al. (38) in a prospective, single-blinded, head-to-head study compared CTC with CCE in patients with incomplete colonoscopy. In this study, CCE identified a ≥ 6 mm polyp in 24.5% of patients (95% CI 16.6% to 34.4%), while CTC in 12.2% (95% CI 6.8% to 20.8%), with a relative sensitivity of 2.0 (95% CI 1.34 to 2.98) which indicated a significant increase in sensitivity for lesions ≥ 6 mm when using CCE. Stratifying the analysis for larger polyps, CCE detected a ≥ 10 mm polyp in 5.1% of patients (95% CI 1.9% to 12.1%), while CTC in 3.1% (95% CI 0.8% to 9.3%), with a relative sensitivity of 1.67 (95% CI 0.69 to 4.00). Both procedures i.e. CTC and CCE showed similar high positive predictive values (PPV).

Timing of CCE after incomplete colonoscopy

Optimal timing of CCE after incomplete colonoscopy is still unclear. Two studies analyzed the possibility to perform CCE the same day after the incomplete colonoscopy. Hussey et al. (35) used NaP booster plus 1 liter of gastrografin to perform CCE II the same day after the incomplete colonoscopy, with an overall completion rate of 76%, a full colonic visualization of 84% and a mean colon passage time of 233 minutes. Image quality was considered suboptimal in 9% of patients.

In the other study, Triantafyllou et al. (41) used 1 liter Polyethylene glycol (PEG) plus 2 tablets of domperidone as bowel preparation and NaP as booster to perform CCE I the same day after the incomplete colonoscopy, with an overall completion rate of 90.7%, while a complete colonic visualization was obtained in 76% of patients. Quality of preparation was considered adequate in 60.3% and 63.4% in the right and left colonic segments, respectively.

Statement III

Patients with alarm symptoms

When colonoscopy is contraindicated or not possible, ESGE/ESGAR recommend CTC as an acceptable and equally sensitive alternative for patients with alarm symptoms (strong recommendation, high quality evidence). Due to lack of direct evidence, ESGE/ESGAR do not recommend CCE (very low quality evidence).

Patients with non-alarm symptoms

ESGE/ESGAR recommend CTC as an acceptable alternative to colonoscopy for patients with non-alarm symptoms (strong recommendation, high quality evidence). CCE may be considered as an alternative in this setting (weak recommendation, low quality evidence).

Patients with abdominal symptoms suggestive of CRC require detailed investigation, since neither clinical examination nor fecal testing reliably excludes CRC (44). The ideal test would also diagnose non-neoplastic conditions responsible for the symptoms (both within the colon and/or extracolonic).

Colorectal neoplasia detection - CTC

In a recent meta-analysis including 34 studies for a total of 41,680 subjects, sensitivity for detection of CRC cancer was 93% among senior aged patient (>65 years old) and 92% among younger patients (45). These data and results of SIGGAR trial (26) 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.

Extracolonic findings (ECF)
ECF are common in symptomatic patients. A recent meta-analysis (45) reported an incidence of potentially significant ECF of 5.2% in a cohort with symptoms and of 2.8% in a cohort of patients without symptoms. In patients with ECF rates of recommended work-up was 8.2%. In the SIGGAR trial 59.6% of patients had at least one extracolonic finding at CTC and the proportion increased with age; a total of 149 patients (8.5%) underwent further work-up. In the same trial (21), significantly more patients randomized to CTC underwent additional investigation than colonoscopy (30% vs. 8.2%; $p < 0.0001$) raising concerns of additional costs for CTC. However, of the 1634 patients that underwent CTC, 72 (4.4%) were diagnosed with extracolonic malignancy. Overall in SIGGAR, total costs of CTC and colonoscopy were similar (46).

Colorectal neoplasia detection – CCE
Few studies evaluated the role of CCE in patients at high risk for CRC, with abdominal or alarm symptoms (rectal bleeding, anemia, weight loss, intestinal subocclusion). One prospective, single center study (40) including 67 patients at risk of CRC, who were unable or unwilling to undergo colonoscopy underwent CCE. CCE detected colonic and ECF in 23 (34%, 95%CI: 21.6%-44.1%) patients. Six patients were diagnosed with cancer: 4 colon cancers, 1 gastric cancer and 1 small bowel cancer. The CCE findings were confirmed after surgery in all patients. CCE might be considered as an alternative diagnostic tool in this setting. However, evidence was considered insufficient to recommend CCE in subjects with alarm symptoms. In patients with non-alarm symptoms and for fragile patients (state of decreased physiologic capacity) (47) CCE can be considered (weak recommendation).

Statement IV

CT colonography and screening for colorectal cancer

ESGE/ESGAR do not recommend CTC or CCE as primary test for population screening or in individuals with a positive first-degree family history of CRC (strong recommendation, high-quality of evidence). However, where organised FIT based population colorectal screening programme are lacking, CTC may be considered as an option providing the screenee is adequately informed about test characteristics, benefits, and risks (strong recommendation, high quality evidence). CCE may also be considered as an option in this setting (weak recommendation, low quality of evidence).

CTC in screening: participation
Between 2009 and 2014 three European randomized population screening trials have been performed. These trials respectively compared primary CTC screening test to colonoscopy [COCOS (48) and SAVE (16)], sigmoidoscopy [PROTEUS (17)] and FIT [SAVE (16)]. Participation rates were: 34% and 22% for CTC and colonoscopy respectively in the COCOS trial; 30% and 27% for CTC and sigmoidoscopy respectively in the PROTEUS trial; 28% and 50% respectively for CTC and FIT in the SAVE trial. In the PROTEUS trials participation was higher in males than females (35% vs 27%). Modalities of invitation and preparation, which differed between trials, may have affected participation rate (49). In COCOS 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 (48). In the PROTEUS trial the two main factors affecting participation were screening related anxiety and consideration that screening is ineffective (50).

CTC in screening: detection rate and yield

In COCOS, advanced neoplasia detection rate (ANDR) per 100 participants was lower for CTC than colonoscopy, (6.1 persons versus 8.7). However, CTC detected 6-9mm polyps underwent surveillance and when subsequently resected, CTC ANDR (8.6%) was similar to colonoscopy (51). In the SAVE trial, CTC ANDR was 4.9 to 5.5 (depending on bowel preparation) versus 7.2 for colonoscopy, 1.7 for one round of FIT. In PROTEUS, CTC ANDR was similar to that of sigmoidoscopy (5.1 versus 4.7 per 100 participants).

However due to higher CTC participation, in the COCOS trial, ANDR per 100 invitees for CTC (2.1) was similar to colonoscopy (1.9), and higher (2.9%) once 6-9mm polyps were included. A slightly higher per invitee ANDR was also observed for CTC than colonoscopy in the SAVE trial (1.4 versus 1.1 per 100 invitees) and compared to sigmoidoscopy in the PROTEUS trial (1.6 versus 1.3 invitees). In the case of serrated adenomas, the diagnostic yield of colonoscopy was 5 times higher than that of CTC. This is relevant, since approximately 10%–20%of CRC develops from the serrated pathway (52). The PROTEUS trial also reported a lower CTC ANDR in the distal colon than sigmoidoscopy (2.9 vs 3.9%).

Acceptability of CTC screening

As noted above, randomized controlled trial (RCT) data suggests that in general participation rates for CTC are higher than colonoscopy or sigmoidoscopy. In the PROTEUS trial, only a small percentage of attendees would not recommend CTC to friends or relatives (6.7%) and would not repeat the test in the future if invited (7.2%)(25). However, these rates were significantly higher than in the flexible sigmoidoscopy arm. Bowel preparation was considered the most negative aspect of preparation, 17.9% having moderate or severe discomfort and pain being perceived by 16.8%. Sali et al. (53) reported no preparation-related symptoms in 88% of interviewed screenees undergoing reduced bowel preparation compared to 70% of subjects undergoing full bowel preparation and improved participation rate in the former.

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 likely lower than for colonoscopy (26,54–56). In a meta-analysis (57) on 103,399 asymptomatic and symptomatic patients, the CTC overall perforation rate was estimated to be 0.04%; the rate was 19-fold higher in symptomatic compared with screening individuals. 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) (48). Adverse events of CTC screening should also consider those related colonoscopy following a positive result; it would be expected that these would be similar to those observed in randomized trials of fecal occult blood testing (FOBT) and of flexible sigmoidoscopy screening (58).

Radiation risk in screening

The topic has been covered in the previous guidelines. Dose reducing CTC protocols using iterative reconstruction algorithms and lower tube voltage are increasingly implemented, leading to doses of less than 1 mSv (59).

Extracolonic findings

ECF may be identified in up to half of asymptomatic screenees (60–62) with additional work-up requiring and rising costs for the screening programs. However, considering only indeterminate but likely unimportant findings (E3) and potentially important ECF (E4) the rate is significantly lower. In the European COCOS trial and in a large opportunistic CTC screening series in the USA the prevalence of E3+E4 ECF was around 11%, considering only of E4 ECF between 1.2% and 5% (2,3,49,50). Potentially important ECF included aortic aneurysms, solid or complex cystic renal lesions, pancreatic masses, adnexal masses and non-calcified lung nodules > 10 mm. In the PROTEUS to identify ECF that needed additional examinations findings were reviewed by two experienced radiologists. By this approach prevalence of ECF requiring further work-up was 1.2%.

Cost and cost-effectiveness

Costs of a population based screening program with CTC, including the invitation process, was 169 Euro in the Netherlands (63) and 197 in Italy (64); average cost per-subject with AN was respectively 2773 Euros (63) and 3777 Euros (64). Other than average cost-per subject, cost-effectiveness of a screening test is dependent on participation rate and on the number of screening rounds. According to Meulen et al. (65), which based their analysis on unit costs and participation rates in the COCOS trial, CTC was the most cost-effective strategy in subjects who underwent more than 2 lifetime screens and was the preferred test for willingness to pay thresholds of 3200 Euro per QALY (Quality-Adjusted Life-Year) gained. However, with equal participation, colonoscopy was the preferred test independent of willingness to pay thresholds. Meulen et al. (65) did not include ECF in their cost-effectiveness analysis, stating long-term follow-up data are lacking. A sensitivity analysis was performed, treating extra-colonic findings as pure costs, or potentially cost saving via detection of aortic aneurysms. In either scenario, CTC remained dominant over colonoscopy assuming more than 2 lifetime screens. In a recent systematic review, CTC every 5 to 10 years was shown to be more cost-effective than no screening (66). Robust cost effectiveness data comparing CTC with stool-based tests, notably FIT, is not yet available.

CTC as a primary screening modality for CRC: conclusions

In average risk individuals, screening CTC achieves an ANDR at least matching colonoscopy and flexible sigmoidoscopy, in part secondary to increased screenee participation. The full impact of ECF, both medically and economically, remains unknown, although the prevalence of ECF potentially requiring further work up is 11% or less in European screening populations. Sensitivity analysis based on one European screening trial suggests that even when incorporating ECF, CTC remains more cost effective than colonoscopy with more than 2 lifetime screens. Full cost effectiveness data from trials comparing CTC with flexible sigmoidoscopy and FIT are however awaited. Although radiation exposure is a drawback, this disadvantage seems to be overemphasised especially given the current reduction in radiation exposure with CTC. Based on these considerations, CTC is not recommended as the primary test for population CRC screening, pending data showing superior efficacy and cost effectiveness compared to established alternate strategies, notably stool based techniques such as FIT. It is recommended as a CRC screening test on an individual basis, providing the screenees are adequately informed about test characteristics, benefits, and risks.

CCE and screening for colorectal cancer

Participation

Four studies investigated the participation rate of CCE in a CRC screening population. Participation rates varied from 4.2–17.4%, depending on the design of the study and how CCE was used as screening modality, e.g. primary screening modality or as filter test (67). The lowest participation

rate of 4.2% was reported in a German opportunistic screening study where CCE was offered as an alternative to primary OC screening. In another study (68) CCE was offered to patients who were unwilling to undergo OC after a positive FIT, a participation rate of 5% was found. Although contradictory data on patient preference is available, recent data from the large Denmark series of screening patients suggests CCE was associated with less discomfort than OC and may be preferable to some patients (69).

Detection rate and yield

Only few studies evaluated the role of CCE as primary screening test. Rex et al. (70) performed a prospective multicenter study including 695 patients to assess CCE accuracy as primary screening test in an average-risk screening population. CCE sensitivity and specificity for adenomas 6 mm or larger were 88% and 82% respectively, that seem adequate for patients who cannot undergo colonoscopy or who had incomplete colonoscopies. Based on these results, recently a multicenter, prospective, randomized study (71) evaluated the diagnostic yield of CCE versus CTC for the identification of colonic polyps in a screening population. Results showed a higher detection rate of CCE (polyps > 6mm: 32% and polyps > 10mm: 14%) compared to CTC (polyps > 6mm: 9% and polyps > 10mm: 6%). Sensitivity of CCE for polyps >6 mm (84%) and polyps >10 mm (84%) was higher compared to CTC (32% for polyps >6mm; and 53% for polyps >10mm). Specificity was higher for CTC vs CCE (99% vs 93% respectively) for polyps >6 mm and comparable for polyps >10mm (99% vs 97% respectively). These observations add additional evidence to previous comparisons demonstrating CCE to have, at least, non-inferior test performance compared to CTC. Based on available evidence, CCE should be considered an acceptable CRC screening option in appropriately selected patients.

Few studies evaluated the diagnostic yield (detection of polyps and cancer) of CCE in patients with a positive family history of CRC. Two studies evaluated the role of CCE in screening first-degree relatives . Parodi et al. (72) showed that CCE sensitivity and specificity for polyps >6 mm are 91% and 88%, respectively, with a positive and negative predictive values of 78% and 95%. respectively. Moreover, restricting the results to polyps ≥10 mm, CCE showed 89% of sensitivity and 95% of specificity. Also Adrián-de-Ganzo et al. (73) in a prospective study of 329 asymptomatic first-degree relatives randomly assigned to CCE (n = 165) or colonoscopy (n = 164) assessed screening uptake of CCE vs. colonoscopy in first-degree relatives. Unexpectedly, 57.4% of subjects crossed over from the CCE group, and 30.2% crossed over from the colonoscopy group meaning that most preferred to undergo colonoscopy. Although the crossover rate between groups was significantly higher in the CCE group (57.4%) than in the colonoscopy group (30.2%), among patients who were invited to undergo colonoscopy 16.8% who declined colonoscopy were offered CCE, and 15.0% actually did so. The study confirmed that CCE can be as effective as colonoscopy in detecting significant lesions that were detected in 14 subjects (11.7%) in the CCE group and 13 subjects (11.5%) in the colonoscopy group (OR, 1.02; 95% CI, 0.45−2.26; P = 0.96). However, the higher crossover rate from the CCE group to the colonoscopy group, mainly due to unwillingness to repeat bowel preparation in the case of a positive result, suggested better acceptance of screening colonoscopy in these group of patients.

Statement V

Indications and contraindications of CTC/CCE: positive FOBT/FIT

RECOMMENDATION
ESGE/ESGAR recommend CTC in the case of a positive FOBT or FIT with incomplete or unfeasible colonoscopy, within organized population screening programs (strong recommendation, moderate quality evidence).

ESGE/ESGAR also suggests the use of CCE in this setting (weak recommendation, moderate evidence).

Indications and contraindications of CTC: positive FOBT/FIT

Fecal blood testing, whether by guaiac-based or immunochemical methods, is predominantly deployed as a population screening test, as it is safe, cheap, well-tolerated and has been proven to reduce CRC-specific mortality by approximately 15 % – 18 % (for guaiac testing). Although long-term mortality data for FIT screening are awaited, it will likely have even better results due to higher uptake and superior sensitivity for advanced colorectal lesions. More recently, highly-sensitive FIT at a low threshold (e.g. 10) has been advocated as a possible tool to identify patients with colorectal symptoms who are at very low risk of CRC, and so might avoid the need for further colonic investigation.

Whether derived from a population screening program or via a symptomatic service, patients with positive FOBT or FIT results require further testing to confirm or refute the presence of an underlying cancer or adenoma, permitting subsequent treatment. Colonoscopy combines sensitive diagnosis with therapy by endoscopic resection and is therefore regarded as the preferred test.

However, most patients testing FOBT/FIT-positive will not have AN, meaning that CTC can be considered as a possible triage test to select patients with lesions only of greater size for colonoscopy or surgery. A meta-analysis published in 2014 found 5 studies, together including 622 patients, in whom the average sensitivity of CTC for 6mm+ adenomas or colorectal cancer was 88.8%, at a specificity of 75.4% (74). A more recent study of 50 patients (75) found almost identical results (sensitivity = 88.2%, specificity 84.8%). However, since the prevalence of 6mm+ polyps is relatively high in this cohort, negative predictive value (NPV) is less than might be expected, ranging from 85% to 95% in the studies included. Moreover, many patients still require colonoscopy after CTC since so many polyps are found; 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 (76). These factors mean that CTC should not be offered routinely to those testing FOBT/FIT-positive, and colonoscopy is preferable. One possible exception is where the absolute quantity of fecal blood is low (e.g. quantitative FIT result of <40), where the prevalence of AN may be sufficiently low to render CTC triage cost-effective. However, to date we are not aware of any studies directly assessing this patient population.

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 (77). CTC is safe and well-tolerated in this cohort (55) and therefore may be preferable in those with contraindications to colonoscopy or judged particularly high risk. Some observational data suggest absolute detection rates may be lower than in healthy screenees who are fit for colonoscopy (78), and post-test cancer rates may be higher (79), although this is probably due to patient factors rather than differences in test sensitivity (i.e. patients who are unfit for colonoscopy are difficult to investigate with any technique, including CTC).

Indications and contraindications of CCE: positive FOBT/FIT

Three studies were performed comparing the accuracy of CCE and colonoscopy in FIT-positive patients in a CRC screening setting. In two studies, patients with a positive FIT underwent both CCE and colonoscopy. The primary outcome was to assess the polyp detection rate and accuracy of CCE compared to colonoscopy. The polyp detection rate ranged between 69%-74% for CCE vs 58%-64% for colonoscopy (67,75,80). The study by Holleran et al. (80) showed that the detection rate of

significant lesions was comparable between CCE and colonoscopy. However, in the study of Kobaek-Larsen et al. (67), repeat colonoscopies were performed to explain the high miss rate of colonoscopy. Repeat colonoscopies resulted in the detection of additional polyps, suggesting that the discrepancy in detection rate between CCE and colonoscopy is most likely explained by the false negative findings of colonoscopy. In a third study, patients with a positive FIT underwent both CCE, CTC and colonoscopy, using colonoscopy as the reference standard (75). Both CCE and CTC detected polyps of 6mm and larger with high levels of accuracy. Based on these studies, the sensitivity of CCE for polyps > 9 mm ranges between 87% and 92.8% and the specificity is around 92% (67,75). One study investigated the use of CCE in patients unwilling to undergo a colonoscopy after a positive FIT within the CRC screening program (68). The aim of this study was to compare CCE and CTC in terms of detection rate as well as participation outcomes. A total of 756 patients were invited to participate of whom only 5% underwent CCE and 7.4% underwent CTC, showing that participation for both CCE and CTC after a positive FIT in patients unwilling to undergo colonoscopy is very low. However, the detection rate was higher when using CCE compared to CTC, with 60% detection of neoplastic lesions in the CCE group compared to 28.6% in the CTC group.
Finally, only one multicenter prospective study aimed to assess the diagnostic accuracy of CCE-2 for AN in subjects with a positive FIT within an organized screening program (81). Overall, CCE-2 sensitivity and specificity for AN were 90% and 66.1%, with a PPV and NPV of 57.4% and 92.9% respectively when using a 6 mm cut-off (colonoscopy referral rate: 52.8%), while sensitivity and specificity were 76.7% and 90.7%, with PPV and NPV of 80.7% and 88.4% when using 10 mm cut-off (colonoscopy referral rate: 32%)
In conclusion, these data would support the use of CCE as an alternative to CTC in FIT positive subjects unwilling or unfeasible to undergo colonoscopy.

Statement VI
Following curative-intent resection of CRC

RECOMMENDATION
ESGE/ESGAR suggest CTC with intravenous contrast medium injection for surveillance after curative-intent resection of CRC only in patients in whom colonoscopy is unfeasible (weak recommendation, low quality evidence).
There is insufficient evidence to recommend CCE in this setting (very low quality evidence).

Patients with previous CRC are at increased risk of future colorectal neoplasia, and therefore require surveillance of the remnant colon. Additionally, contrast-enhanced computed tomography (CT) is the mainstay of surveillance for extraluminal local recurrence and remote metastases. Since CTC combines intraluminal assessment with evaluation of the extracolonic structures for locoregional recurrence and remote metastases, it has the potential to simplify follow-up pathways and reduce costs.
Porté et al. (82) conducted a systematic review and meta-analysis of cohort studies which showed that CTC was highly sensitive (95%, 18/19 cases detected) and 100% specific for anastomotic recurrence following CRC resection. Moreover, CTC detected all 10 metachronous cancers in these patients. However, no data were provided regarding diagnostic accuracy for polyps or adenomas; only CRC was considered.
Three single center prospective cohort studies (83–85) reported the diagnostic accuracy of CTC for polyps or adenomas after prior CRC resection. The largest study (84), of 550 patients, found CTC was 81.8% sensitive for AN (specificity of 93.1%). However, these studies were of variable quality, with incomplete (85) or delayed (84) comparison to reference standard tests such as colonoscopy for the presence/absence of polyps.

More recently, a prospective, multicenter, cross-sectional study (86) recruited 231 patients scheduled for colonic surveillance 1 year after curative-intent resection of CRC. Patients underwent CTC and same-day colonoscopy with segmental unblinding (i.e. sequential revelation of the CTC result to the colonoscopist on a segment-by-segment basis, thereby providing an enhanced reference standard for the presence or absence of neoplasia). The sensitivity of CTC was only 44.0% for ≥ 6mm polyps (76.9% for > 10 mm polyps). This is surprisingly low when compared to meta-analyses of the accuracy of CTC in other situations. One possible explanation is the absence of an ileocaecal valve in patients with prior right hemicolectomy, thereby permitting gas reflux into the small bowel and reducing the likelihood of optimal colonic distension.
The same cohort of patients (87) was asked which of the two tests they preferred; of the 223 patients who completed their questionnaires, 95 (42.6%) preferred colonoscopy, 79 (35.4%) had no preference, and only 49 (22.0%) preferred CTC.
Limited cost-effectiveness analysis of this cohort, using cost data from a single centre, suggests that a CTC-based surveillance strategy is cost-saving relative to colonoscopy; however, as noted above, this comes with the trade-off that fewer adenomas will be detected. Beck et al. (88) estimated that the additional cost ≥ 6mm polyp detected by using colonoscopy rather than CTC would be $5,700; or $28,000 per additional > 10 mm polyp detected. Whether these cost data would be replicated in other healthcare systems is uncertain.

Statement VII
Post-polypectomy surveillance

RECOMMENDATION
ESGE/ESGAR suggest CTC in patients with high risk polyps in surveillance after polypectomy only when colonoscopy is unfeasible (weak recommendation, low quality evidence).
There is insufficient evidence to recommend CCE in the post polypectomy surveillance (very low quality evidence).

CTC in post-polypectomy surveillance

The previous ESGE Guideline recommends endoscopic surveillance only for patients with high risk adenomatous lesions (adenomas with high grade dysplasia or ≥ 10mm in size, or ≥5 adenomas) or serrated lesions (≥ 10mm in size, or any degree of cytological dysplasia) (89). 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 (90–93). Moreover, according to a recently published paper (94), the adherence to surveillance ESGE guidelines (89), is dramatically low, only 13.8% of patients.
The impact of FIT on surveillance was recently investigated. Atkin et al. (95) reported annual low-threshold FIT (10 μg/g) with colonoscopy in positive cases had high sensitivity for CRC and advanced adenomas (sensitivity and specificity were 84.6% and 70.8%, respectively) and would be cost saving compared with 3-yearly colonoscopy.
Despite weak evidence supporting CTC for surveillance (96), 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 (96,97).

CCE in post-polypectomy surveillance

The accuracy of CCE in post-polypectomy surveillance has not been carefully investigated. Only one study investigated CCE as a possible filter test in colonic surveillance in patients scheduled for follow-up colonoscopy (98). In this study 102 of 180 patients (57%) who underwent CCE also underwent a supplemental colonoscopy, as significant pathology was detected on CCE or because the CCE examination was incomplete. The completion rate of CCE was 66.7% and the polyp detection rate was 69%. CCE detected 120 polyps, of which 60 were found at colonoscopy, meaning that half of the detected polyps could not be removed by supplemental colonoscopy. Colonoscopy detected 16 additional polyps that were not found at CCE. More studies are needed to determine the applicability of CCE as a filter test for surveillance colonoscopy after polypectomy. To date, there is no sufficient data to support the use of CCE in post-polypectomy surveillance.

Statement VIII
Indications and contraindications of CTC: other (diverticular disease, IBD, fragile patient)

RECOMMENDATION
ESGE/ESGAR recommend against CTC in patients with acute colonic inflammation and in those who have recently undergone colorectal surgery pending a multidisciplinary evaluation (strong recommendation, low quality evidence).
ESGE/ESGAR also recommends against CCE in those with symptoms or sign of occlusion, unless a patency capsule excluded it.

In 2006, large surveys from the UK and America showed CTC was very safe with symptomatic luminal perforation occurring in approximately 1 in 3,000 to 1 in 20,000 examinations and an even lower risk for people undergoing CTC for CRC screening (99,100). To date there has been no reported death directly attributable to CTC despite its use in routine practice across the World for over a decade.
In 2015, a Japanese national survey of 147,439 CTC examinations (56) revealed lower luminal perforation rates of 0.014% overall albeit with a higher rate when CTC was used for preoperative staging (0.028%); and a much lower rate for screening (0.003%; approximately 1 in 30,000 patients). Most of patients (81%) with perforation did not require surgical intervention. Vasovagal reaction was reported in 0.081%

There is limited evidence about the safety of same day or next day CTC in patients following incomplete colonoscopy, particularly when polypectomy was performed. A single centre retrospective review (33) of 198 patients undergoing same day CTC after incomplete colonoscopy showed no patient had colonic perforation or other recorded complication. This patient population included screening, diagnostic and surveillance examinations and 34 (17%) had one or more polypectomies.
In general, CTC is avoided in patients with IBD, particularly where there is acute or subacute colonic mucosal inflammation due to increased risk of colonic perforation, difficulty detecting mucosal dysplasia without biopsies and inaccurate differentiation of inflammatory polyps or strictures from neoplasia. However, when patients with IBD are in clinical remission, then CTC can be considered if colonoscopy is contraindicated or incomplete. In support, a single centre study (101) of 20 patients with ulcerative colitis in clinical remission who underwent both colonoscopy and CTC showed good correlation between colonoscopy and CTC findings, with patients preferring CTC over colonoscopy. However, in the same year, a case report (102) of colonic perforation in an 89 years old patient with ulcerative colitis who declined colonoscopy in favour of CTC for surveillance reminds radiologists of the increased potential risk.

A retrospective study (103) of elderly patients from 2014, compared 6114 outpatients undergoing initial CTC with 149,202 outpatients undergoing initial OC and found the odds ratio of complications was higher for colonoscopy compared to CTC as follows; lower gastrointestinal bleeding (OR 1.9); other gastrointestinal events (OR 1.35); and cardiovascular events (R 1.38). Risk of colonic perforation was 0.07% for CTC and 0.12% for colonoscopy but comparisons of perforation risk frequently take no account of asymptomatic perforation in the colonoscopy group (and the large majority of patients with CTC related perforation are asymptomatic).

Finally, a 2018 UK survey (104) of patients undergoing CTC, colonoscopy and CCE and incorporating an additional survey of people who did not have prior colonic investigation, concluded that patient tolerance and experience favour CTC and CCE over colonoscopy and people would more commonly choose CTC or CCE over colonoscopy for colonic investigation.

Practical advice for radiologists
1. CTC is very safe but is absolutely contraindicated in patients with generalized peritonitis, acute bowel perforation, mechanical bowel obstruction and when a competent patient does not provide consent.
2. Relative contraindications include; healing of localized diverticular perforation; acute inflammatory bowel disease; or children and young adults.
3. When CTC is requested soon after colonoscopy, particularly after polypectomy, we recommend the CTC radiologist communicates directly with the endoscopist to assess an individual's risk of perforation. Risk factors include large, deep colonic wall defects, mucosal inflammation and patient comorbidity.
4. If a radiologist thinks bowel perforation may have occurred prior to undertaking CTC, then a standard CT of the abdomen and pelvis should be performed prior to colonic insufflation to help exclude extra-luminal gas.

Statement IX

Work-up after CTC

RECOMMENDATION
ESGE/ESGAR recommend referral for endoscopic polypectomy in patients with at least one polyp ≥ 6mm in diameter detected at CTC or CCE. *Follow-up CTC may be clinically considered for 6-9 mm CTC-detected lesions if patients do not undergo polypectomy because of patient choice, comorbidity and/or low risk profile for AN (Strong recommendation, moderate quality evidence.).*

The need for additional endoscopy depends on several clinical characteristics. As it is known that with increasing size, an increasing number of polyps appears to be advanced (i.e. advanced adenoma or carcinoma), polyp size is one of the most important factors (105–107). In two systematic reviews including large numbers of polyps, only 1.4% of lesions < 5mm were advanced adenomas and 0.3% malignant, while approximately 7.9% of 6-9 mm lesions and approximately 80% of lesions ≥ 10mm were AN (remaining polyps being i.e. hyperplastic or inflammatory) (106,107).
Increasing age and male gender are also associated with a higher risk of AN regardless of polyp size (108). In case of sub-centimetre lesions, number of lesions (> 4), occult blood or overt blood in stool, and pedunculated lesions are associated with a higher risk of AN (109).

The natural history of small polyps detected at CTC has been studied in two prospective observational CTC studies. In the first study, 22% of 306 polyps increased in size 2-3 years after the initial CTC, 6% became > 10mm (110). However, approximately 28% of polyps regressed. This was also found in another study, in which 35% of 95 polyps progressed, and 26% of polyps regressed (including 15% apparent resolution)(18). None of the regressing polyps were advanced adenomas. Longer follow-up of the lesions is not available.

Follow-up of CTC findings

In general, it is suggested to consult a gastroenterologist in case of colorectal findings, to decide whether colonoscopy and/or follow-up CTC is needed. The gastroenterologist can assess the (future) risk for CRC based on background risk factors, the actual risk profile and the possibility to perform colonoscopy in patients with comorbidity. Nevertheless, some general rules can be used based on the size of the polyps.

In case of large polyps (≥ 10mm) and suspected masses, colonoscopy should be performed to remove the polyp or take biopsies for a histological diagnosis. In case of a highly suspicious mass and incomplete colonoscopy without a biopsy (despite optimal bowel preparation and an experienced endoscopist), one could consider treatment without histopathology verification but this should be discussed at a multi-disciplinary team.

As stated above, the risk of intermediate polyps (6-9 mm) to be AN is low (105,106) and these might remain stable in size or might (completely) regress (18,110). Therefore, in case of intermediate polyps (6-9 mm) either a subsequent colonoscopy or a follow-up CTC can be considered, depending on the clinical setting number of polyps, higher age, male gender and comorbidity. Colonoscopy is strongly favoured in patients with genetic predisposition (e.g. Lynch syndrome) and patients with multiple polyps (> 3), while substantial comorbidity favours follow-up CTC.

Lesions < 6mm can be mentioned in the CTC report, but the specificity for diminutive lesions is low and the risk of malignancy is low, therefore it is justifiable to ignore them. Radiologists and gastroenterologists should define the local strategy about reporting polyps < 6mm in their hospital.

In case of a negative colonoscopy for CTC findings a repeat examination should be considered, as in a retrospective study (111) false negative colonoscopy findings have been reported in up to 21.5% (false negative findings were more common in the right colon). This repeat examination could be a second colonoscopy or a follow-up CTC; an immediate repeat CTC can be considered. To prevent the need for a repeat examination, it is strongly advised to perform a high-quality colonoscopy procedure with adequate information of the location of the lesion found on CTC, to be able to perform a “second look” during the initial colonoscopy.

Follow-up of CCE findings

Regarding findings, most colonic polyps discovered at screening are diminutive, with negligible risk of harbouring advanced features (high grade dysplasia, villous component, or malignancy) (106,107,112,113). Moreover, 40% of diminutive colonic polyps are hyperplastic rather than adenomatous (114). Diminutive lesions identified by a non-invasive test may also be missed by the colonoscopy, because of the sensitivity of the latter for diminutive lesions (115,116). By extrapolating data from CTC studies that modelled the impact of colonoscopy or continued surveillance for diminutive polyps discovered at CTC, it can be concluded that referral for removal of diminutive lesions found at CCE might carry an unjustified burden of costs and complications relative to a minimal gain in clinical efficacy (117). Moreover, studies on second-generation CCE provided accuracy data in relation to lesions ≥ 6mm in size, specificity for diminutive lesions is

largely unknown (117). The only exception regarding post-CCE referral for diminutive polyps is the presence of at least 3 diminutive polyps. Polyp multiplicity has appeared to be a strong predictive factor of subsequent AN development in post-polypectomy follow-up studies (118). Most AN has been shown to be restricted to the relatively small proportion of patients with polyps ≥ 6 mm in size (106). Consequently, post-CCE colonoscopy referral of these patients may be expected to lead to a substantial reduction of the prevalence of AN in patients initially evaluated with CCE. Using a cut-off of significant findings defined as no more than 2 polyps of 10 mm, 43% of patients could avoid colonoscopy, however in only 10.7% of patients who underwent a colonoscopy, high risk findings were detected. (98) This approach implies that small polyps will leave untreated until the subsequent follow-up. Polyps of 6-9 mm in size may be safely followed up for a relatively short period of time (117). There is still no evidence that repetition of CCE after 2-3 years may lead to re-identification of the previously unremoved polyp.

APPENDIX (Statement X e XI)

Technical issues CTC

Perforation

In a recent meta-analysis (57) 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.

In the systematic review (119) for the U.S. Preventive Services Task Force (2016), it was concluded that based upon findings in 15 studies, there is little to no risk of serious adverse events for screening CTC (e.g. symptomatic perforation). There were no reports of perforation in 11 prospective screening studies (n=10722). In Japan, a retrospective national, multi-institutional review of 141,739 patients showed an overall perforation rate of 0.014%. Perforation rate in screening patients, symptomatic patients and preoperative staging was 0.003%, 0.014% and 0.028%, respectively. Surgery was required in 19% of perforations (n=4), resulting in an overall surgery rate of 0.00003% (56).

Radiation risk in screening

A recent international survey reported that the effective dose of present day screening CTC was 4.4 mSv (120), which is lower than used in the aforementioned study. In a randomized trial, performed within a population-based screening program, radiation dose was ≤ 4 mSv (17,121). Further dose reduction is possible with technical developments such as iterative reconstruction algorithms and lower tube voltage, leading to doses of 1 mSv (122).

Preparation

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. PEG) or “dry prep” (e.g. sodium picosulphate, phosphosoda etc). Dry preparations can be obtained with sodium picosulphate or sodium phosphosoda. In a 2013 European consensus sodium phosphate was considered not appropriate for bowel cleansing because of potential adverse effects (123). In a recent meta-analysis including 13 RCT’s in optical colonoscopy, sodium picosulphate was equally effective as sodium phosphate and may be considered as a first-choice cathartic in colonoscopy, because of its safety (124). There are currently no studies comparing sodium phosphate and sodium picosulphate in CTC.

Technical issues CCE

RECOMMENDATION
ESGE suggests a clear liquid diet the day before the procedure and a split- regimen of PEG solution with intake the day before and on the day of examination to increase the tolerability and efficacy of the preparation. Both 2 and 4 L of PEG seems similar in terms of colon cleansing and excretion rate (Strong recommendation, moderate quality evidence).

ESGE recommends sulfate-based solutions as booster to improve capsule egestion rates and to complete visualization of the colonic mucosa. Due to possible severe adverse events (i.e. electrolyte disturbance, acute nephropathy and kidney failure), ESGE recommends against sodium phosphate (Strong recommendation, moderate quality evidence).

The initial experiences with CCE adopted preparation regimens including high volumes (4 liters) of PEG split in two doses (on the evening before the examination and on the morning of procedure). With such high volume regimens, Eliakim et al. (125), Spada et al. (126) and Rex et al. (70) showed an adequate overall cleansing level of 78% (95 %CI 68–86), 81% (95% CI, 73%-88%) and 80% (95% CI, 76%–83%), respectively.
Low-volumes PEG-based regimens were also evaluated in order to improve compliance and acceptability. An overall adequate cleansing level ranged between 60% and 90% (75,127–129).
Two studies compared high versus low volumes confirming a comparable efficacy between high- and low-volumes. Kakugawa et al. (130) compared a 2 liters, same day PEG regimen to 3 liters PEG regimen, splitted on the night before (2L) and the day of procedure (1L). The authors showed an adequate colon cleanliness in 94% and 86%, respectively. Finally, in a prospective randomized trial, Argüelles-Arias et al. (131) compared 2 liters PEG + ascorbic acid versus 4 liters PEG showing an adequate cleansing in 78.34 % and 64.56 % of cases, respectively ($p = 0.252$).

To improve capsule egestion rates and obtain a complete visualization of the colonic mucosa, boosters are recommended. In the initial experiences, sodium-phosphate based boosters were adopted showing an excretion rate less than 8 hours ranging from 73% to 85% (80,125,126). However, due to possible severe adverse events (i.e. electrolyte disturbance, acute nephropathy and kidney failure), the use of sodium phosphate should be limited (132–134). Alternative to NaP have been proposed.

In a large prospective study Rex et al. (70) adopted an oral sulfate solution as a booster and showed that 92% (95% CI, 90%–94%) of capsule excreted the capsule within 12 hours. Kroijer et al. (135) in a multicenter RCT showed compared PEG versus sulfate solution and versus gastrografin as booster and showed that sulfate solution had the highest excretion rate (73% vs 70% vs 68%), even if not statistically significant, and no adverse events. Kashyap et al. (136) in a prospective, single-center, single-arm study evaluating the safety of PEG bowel preparation plus an oral sulfate solution as booster confirmed the feasibility of sulfate-based solution, showing no serious adverse events and no clinically significant changes in serum chemistry from baseline to 1 and 7 days after the procedure.
In order to improve capsule excretion (i.e. complete colonoscopy) other boosters were also used as alternative or in addition to sodium phosphate or oral sulfate boosters. Spada et al. (38) in a prospective single-center study with 97 patients firstly reported the use of gastrografin as booster with no severe adverse events. Also Togashi et al. (137) in a multicenter case series, showed promising results of gastrografin as booster, since capsule excretion rate was 97%, median colon transit time was 165 minutes and gastrografin was well tolerated by all patients with no adverse events. Finally, Kastenberg et al. (138) in a multicenter RCT comparing sulfate-based solution plus

gastrografin as boosters versus sulfate-based solution alone showed that CCE completion and colonic transit were faster (90.9% vs 76.9%, p = 0.048 and 21.8% < 40 min vs 4%, p = 0.007, respectively) using sulfate-based solution plus gastrografin. Adverse events (no serious) were experienced more frequently in the group that used gastrografin (P = 0.0061), although this difference did not appear related to it. Although the results are promising, the role of gastrografin as a booster is still under evaluation and its use cannot be recommended in routine use.
Finally, Ohmiya et al. (139), in a retrospective multicenter study, showed that capsule excretion rate was higher with castor oil (97% vs 81%, P < 0.0001) and use of castor oil (adjusted OR, 6.29; p = 0.0003) were predictors of capsule excretion within its battery life.

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Appendix 1s: task forces

Topic	**Task force (Chair in bold)**
1: Radiological imaging for the diagnosis of colorectal neoplasia	***D. Regge*** *T. Mang*
2: Completion of a previously incomplete colonoscopy	***C. Spada, S.*** **Halligan** *M. Morrin; E. Dekker, A. Koulaouzidis, D. McNamara, C. Carretero*
3: Patients with and without alarm symptoms highly suggestive of colorectal cancer	***C. Hassan, S.*** **Halligan** *I. Fernandez Urien, A. Koulaouzidis,*
4: Screening for colorectal cancer	***E. Dekker, S.*** **Halligan** *D. Regge, M. F. Kaminski, C. Hassan*
5: Positive FOBT/FIT	***D. Regge, D. McNamara*** *A. Plumb; M. C. W. Spaander*
6: Following curative-intent resection of colorectal cancer	***E. Neri, M. Pioche*** *A. Plumb, C. Carretero*
7: Post-polypectomy surveillance	***J, Stoker; M. C. W. Spaander*** *A. Laghi, C. Hassan*
8: Diverticular disease, IBD, fragile patient	***A. Laghi, R. Eliakim*** *D. Burling, A. Koulaouzidis*
9: Work-up after CTC/CCE	***A. Laghi, M. F. Kaminski*** *J. Stoker, C. Hassan, E. Dekker*
10: Technical issues CTC/CCE	***C. Spada, P. Lefere*** *C. Carretero, R. Eliakim, M. Pioche*
11: Reporting CTC/CCE	***E. Neri, I. Fernandez Urien,*** *C. Carretero, M. Pioche*

Appendix 2s: Levels of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (14)

Evidence Level	
High quality	One or more well-designed and well-executed randomized controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality	RCTs with important limitations (i.e. biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, well-designed cohort or case–control analytic studies, and multiple time series with or without intervention are in this category. It also means that further research will probably have an important effect on our confidence in the estimate of effect and may change the estimate.
Low quality	Observational studies would typically be rated as low quality because of the risk for bias [1]. It also means that further research is very likely to have an important effect on our confidence in the estimate of effect and will probably change the estimate.
Very low quality [2]	Evidence is conflicting, of poor quality, or lacking, and hence the balance of benefits and harms cannot be determined. Any estimate of effect that is very uncertain as evidence is either unavailable or does not permit a conclusion.

[1] Quality of evidence based on observational studies may be rated as moderate or even high, depending on circumstances under which evidence is obtained from observational studies. Factors that may contribute to upgrading the quality of evidence include a large magnitude of the observed effect, a dose–response association, or the presence of an observed effect when all plausible confounders would decrease the observed effect.

[2] Insufficient evidence to determine for or against routinely providing a service.