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ARTICLE

Clinical indications of CT Colonography: European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) guidelines

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Abstract

Background and aim: This paper 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 CT Colonography (CTC).

Methods: 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 recommendation and the

quality of evidence.

Main recommendations:

- 1) ESGE/ESGAR recommend CT colonography 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 CT colonography, preferably the same or next day, if colonoscopy is incomplete. Consideration should be made to delaying CTC following endoscopic resections. In the case of obstructing colorectal cancer, pre-operative contrast-enhanced CT colonography may also allow locating/staging malignant lesions. (strong recommendation, moderate quality evidence)
- 3) ESGE/ESGAR recommend CT colonography as an alternative to colonoscopy for patients with symptoms suggestive of colorectal cancer (Recommendation: Strong; Evidence Level: High)
- 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 (Recommendation: Strong; Evidence Level: Moderate).
- 5) ESGE/ESGAR do not recommend CT colonography (CTC) as a primary test for population screening or in subjects with a first-degree positive family history of 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. (Recommendation: Weak; Evidence Level: Moderate).

INTRODUCTION

Colorectal cancer (CRC) is a major cause of morbidity and mortality (1, 2). CRC screening by faecal 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 preventive strategy in subjects with increased CRC risk (6).

Computed Tomographic Colonography (CTC) is a minimally invasive imaging technique, highly accurate for detecting colorectal cancer (CRC) and adenomatous polyps. Technique is standardized (7), and CTC is easier to be 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 – twenty years after the first presentation of CTC in 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.

METHODS

The ESGE and ESGAR commissioned this guideline (chairs C.S. and A.L.) and invited the listed authors to participate to 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**, available online). The coordinating team formed subgroups, each with its

own leader, and divided the key topics among 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 key words 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 summarised the included articles in a table of evidence (see **Appendix**, 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 individual task force prepared statements answering their assigned key questions, which were discussed subsequently and voted on during a face-to-face meeting of the whole group held October 1st, 2013. In May 2014, a draft prepared by the coordinating team was sent to all group members for comment. After agreeing 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 respective organizations. This guideline will be reviewed in 2019 or sooner if new and relevant evidence becomes available. Any updates to the guideline in the interim will be noted on the ESGE (<http://www.esge.com/esge-guidelines.html>) and ESGAR (<http://www.esgar.org>) websites.

RECOMMENDATIONS AND STATEMENTS

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

1. ESGE/ESGAR recommend CT colonography 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 can be considered the best radiological test for the diagnosis of colorectal cancer. Several randomised (11-13), multi-(14, 15) and single-centre trials (16-18), and meta-analysis(19-26), showed that CTC accuracy for both CRC and large/advanced polyps is similar to colonoscopy in symptomatic and asymptomatic patients and clearly superior to barium enema (11). In a recent randomised trial (SIGGAR)(11, 13) comparing CTC with CS and BE, the detection rate of colorectal cancer or large polyps was significantly higher in patients assigned to CTC than in those assigned to BE (7.3% vs 5.6%, $p < 0.039$) and similar between CS and CTC (11% for both procedures). In a comparative study between CS and BE (27), 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 were respectively 41% and 82%; at a threshold greater than 10 mm, 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- and high-risk patients, CTC was more specific and more sensitive than barium enema for large (≥ 10 mm) and small (6-9 mm) polyps in both per-patient and per-polyp analysis. In this study, CTC showed an incremental diagnostic yield in sensitivity of 12.0% for polyps ≥ 10 mm and 30.1% for polyps between 6 and 9 mm and in specificity of 10.3% for polyps ≥ 10 mm in per-patient analysis. Apart from better diagnostic performance, CTC is more tolerated and acceptable to patients and delivers a lower effective radiation dose than barium enema (30).

2. ESGE/ESGAR recommend CT colonography, preferably the same or next day, if colonoscopy is incomplete. Consideration should be made to delaying CTC following endoscopic resections. In the case of obstructing colorectal cancer, pre-operative contrast-enhanced CT colonography may also allow locating/staging malignant lesions. (strong recommendation, moderate quality evidence)

Incomplete colonoscopy

Incomplete CC 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 worked up by repetition of colonoscopy or by radiological procedures. Repeating colonoscopy is likely to be considered when the reason of 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 PPV, especially at 10 mm threshold. However, no study exploited an independent reference standard for subjects with a negative CTC, so that the specificity 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 subjects with incomplete colonoscopy. For this reason, the superiority of CTC over barium enema recently shown in a large randomized study should favour CTC over barium enema when colonoscopy was incomplete (11).

CTC timing

CTC after incomplete colonoscopy requires a different approach than primary CTC. In case of endoscopic biopsy, same-day CTC can be performed. An (ultra-) low dose pre-CTC scan of the abdomen and pelvis before insertion of the rectal tube may rule out extraluminal gas indicating a colonoscopic perforation. In detail, 2 (0.8% 95% CI 0.1-2.7) perforations were detected in 262 patients undergoing CTC after incomplete colonoscopy (47). In case of endoscopic resection (i.e. polypectomy/mucosectomy), it is prudent to consider an approximately 2 week-delay before performing CTC. There is little scientific evidence concerning the interval between endoscopic resection and subsequent CTC, thus each case should undergo 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) (50-52). These studies concluded that in a non-diseased colon, barium enema could be performed immediately after endoscopic biopsy without any risk. In 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 tumours were located in different surgical segments (53). These data were in line with those from a

previous French study (54), as well as from other series (55). Failure to detect synchronous cancer can increase morbidity, and one study has shown that intra-operative palpation can miss up to 69% synchronous malignancies (56, 57). Thus, pre-operative whole-colon assessment is needed. CTC appears to be an effective and safe choice when obstructing CRC prevents a complete endoscopic assessment or when caecal intubation fails for other reasons. A recent study including 286 CRC cases after failed colonoscopy showed CTC-negative predictive values of 100% and 97% for synchronous cancer and advanced neoplasia in a pre-operative setting (58). This is in line with a previous systematic review, showing an equivalent sensitivity for established cancer between colonoscopy and CTC(22), as well as similar cohort studies (44, 59-63).

3. ESGE/ESGAR recommend CT colonography as an alternative to colonoscopy for patients with symptoms suggestive of colorectal cancer (Recommendation: Strong; Evidence Level: High)

Patients with abdominal symptoms suggestive of CRC require detailed investigation, since neither clinical examination nor faecal 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 of large polyp ($\geq 10\text{mm}$) and CRC between CTC and CS was demonstrated(13). Furthermore, crude pooled sensitivity for CRC in the studies of symptomatic patients was 96% (169 CRC detected from 176 (13). This is compatible with the 96.1% sensitivity for CRC reported in a meta-analysis(22) that included both screening and symptomatic/high risk patients. When considering large ($\geq 10\text{mm}$) polyps alone, per-patient sensitivity ranged from 82% to 92% (19-21, 23, 25, 26) in five meta-analyses including screening, symptomatic, high-risk and FOBT positive patients. In the studies specifically investigating symptomatic patients, pooled sensitivity for large ($\geq 10\text{mm}$) 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 (6-9mm) and diminutive ($\leq 5\text{mm}$) polyps 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 patho-histologic analysis of diagnosed CRC remains as a potential advantage of colonoscopy over CTC.

Colorectal non-neoplastic pathology

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 it 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. Despite these lesions may occasionally explain the symptoms, incidental findings that ultimately prove unimportant may nonetheless provoke 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 reported a 0.35% and 1.9% rate of extracolonic malignancy respectively. Importantly, in the paired SIGGAR trials, at three-year follow-up there was no significant difference in rates of extracolonic malignancy between the two arms of each individual trial, although all arms were 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 randomised to colonoscopy or barium enema, although this remains unproven.

4. ESGE/ESGAR do not recommend CT colonography (CTC) as a primary test for population screening or in subjects with a first-degree positive family history of 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.
(Recommendation: Weak; Evidence Level: Moderate).

CTC Accuracy

To date, only guaiac FOBT (gFOBT) and sigmoidoscopy have shown to reduce CRC mortality by 16% and 22-31% respectively (67-69). CTC has not been subject to randomized trials with CRC incidence or mortality as endpoints. Therefore, CTC accuracy 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 subjects (14, 16-18, 70-72). Subjects with a positive family history CRC or adenomas should be considered at high risk (73). One recent cohort study showed a 89% CTC sensitivity for advanced neoplasia ≥ 10 mm in this setting(74).

Attendance and yield of CTC in screening

The efficacy of a screening program does not only depend on the diagnostic accuracy of the screening test that is used, but also depends on participation. This is illustrated by the results of a large population-based randomised screening trial performed in the Netherlands reporting participation rates for colonoscopy and CTC of 22 % and 34% 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 invitees per 100 invitees found to have advanced neoplasia was similar between both screening modalities, namely 1.9 versus 2.1 per 100 invitees (12). The poorer sensitivity of CTC compared to colonoscopy was countered by its approximately 1.5 times higher participation rate. In case of serrated adenomas the diagnostic yield of colonoscopy was 5-time higher than CTC. This is of particular importance, since approximately 10-20% of CRC develops from serrated pathway(75). The diagnostic yield of CTC screening per 100 invitees would appear significantly higher than the yield of first round gFOBT, but similar to the yield of first round flexible sigmoidoscopy screening (2.2 per 100 invitees) and FIT screening (2.0 per

100 invitees when using a cut-off of 50 ngHb/ml)(76). One should however bear in mind that FOBT/FIT screening is repeated at 2-year intervals, whereas CTC and endoscopic screening are usually recommended at 5-10 year intervals.

Acceptability of CTC screening

A recent meta-analysis included articles on preferences and differences in burden for both average and high risk subjects who had undergone CTC as well as colonoscopy(77) (tandem design). Amongst the included studies, 3573 patients reported a preference for CTC, 927 subjects showed a preference for colonoscopy and 1116 showed no difference in preference. Almost half of the non-participants in a Dutch population-based screening trial made an informed decision on participation, as they were provided with adequate knowledge of CRC and CRC screening, and a positive attitude towards screening but nevertheless declined participation, suggesting that additional barriers to participation were present(78). Most declined screening by colonoscopy and CTC for similar reasons(79). However, colonoscopy invitees who declined most often mentioned 'unpleasantness of the examination' as their prime reason, while for CTC 'no time/too much effort' and 'lack of symptoms' were most 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 comparing perceived acceptability and burden of both techniques using a tandem design, 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 a population-based screening trial showed that colonoscopy invitees expected the screening procedure and bowel preparation to be more burdensome than CTC invitees(83). CTC participants in the Dutch study however found their screening procedure slightly more burdensome than colonoscopy participants. Colonoscopy participants gave higher burden scores to drinking 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 flexible sigmoidoscopy screening, respectively(85). In a recent meta-analysis(86) on 103,399 asymptomatic and symptomatic patients, CTC perforation rate was estimated to be 0.04 %, 19-fold higher in symptomatic than in screening subjects. The surgical 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 ionising 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 optimisation(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 4.4mSv(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 one quarter to more than 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 74% in 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 moderately 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 usually localised at the time of diagnosis (66). Further important extracolonic findings include abdominal aortic aneurysms, adrenal masses and non-malignant 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 on-costs are included. It appears that the average additional costs for extracolonic findings at CTC is of the order of 25-50 USD averaged over all attendees (101) (94-96, 100). No studies report costs that might be saved by earlier detection of disease.

Conclusion

Primary CTC and colonoscopy screening have similar yields of 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 over-emphasised especially given current reduction in radiation exposure of CTC. Probably the most important factor is the question whether CTC screening is cost-effective, which is still unanswered. Based on these considerations, CTC cannot be at this stage recommended as primary test for population CRC screening or in subjects with a first-degree positive 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.

5. ESGE/ESGAR strongly recommend CTC in the case of positive FOBT/FIT with incomplete or unfeasible colonoscopy within organized population screening programs. (Recommendation: Strong; Evidence Level: Low).

Repeated annual or biennial screening for colorectal cancer (CRC) by faecal occult blood testing (FOBT) reduces disease-specific mortality by approximately 15-18% (102). Results of similar repeated screening by means of faecal immunochemical testing 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 of greater size only for colonoscopy or surgery. The sensitivity of CTC for ≥ 6 mm adenomas was above 85% in all the studies included below (15, 25, 105-108) and over 90% for ≥ 10 mm adenomas, a finding confirmed by 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 $\leq 43\%$ of the costs of colonoscopy (109). Furthermore, despite sensitivity exceeding 85%, lesion prevalence is so high that negative predictive value is less than might be expected, ranging from 85 to 95% in the studies included. These factors mean that CTC should not be offered routinely 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 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 healthy screenees who are fit for colonoscopy(111). Reasons for differences in detection rates are unknown and only speculative at this stage. If confirmed, and if due to suboptimal CTC practice (CTC technique and/or image interpretation), programs for guaranteeing high quality of CTC exams within organized population screening programs will be necessary.

6. ESGE/ESGAR recommend CT colonography with intravenous contrast medium injection for surveillance after resection of colorectal cancer with curative intent only in patients in whom colonoscopy is unfeasible (Recommendation: Weak; Evidence Level: Low).

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 subsequent 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 showed a high technical feasibility.

Local recurrence and metachronous CRC:

In these studies all local recurrent (n=65) and metachroneous (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 metachroneous recurrence was 100%. Per-patient and per-lesion sensitivity for advanced neoplasia was 81.8% and 80.8%, and for all adenomatous lesions 80.0% and 78.5%, respectively (116). NPV 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).

Adenomas / polyps:

In a study on 548 consecutive patients without clinical or laboratory evidence of recurrence following curative-intent CRC who underwent contrast-enhanced CT colonography and subsequent colonoscopy and pathologic confirmation of colonic lesions, CTC sensitivity for all adenomas of 80.0% (per-patient) and 78.5% (per-lesion) have been reported in per-patient and per-polyp analysis, respectively (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 impairing any stratification and comparison of results (117-123).

7. *ESGE/ESGAR recommend CT colonography in patients with high-risk polyps in surveillance after polypectomy when colonoscopy is unfeasible (Recommendation: weak; Evidence Level: Low).*

The recent ESGE guidelines recommend endoscopic surveillance only for patients with high-risk adenomatous (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 the method of choice for post-polypectomy surveillance, whose primary aim is to diagnose and remove either polyps missed at initial examination or newly developed during the time interval between the index and follow-up exam. However, compliance with colonoscopic surveillance is relatively low, ranging from 52% to 85%, with the highest levels obtained in research setting (125-128). Despite weak evidence supporting CTC for surveillance(15), CTC is desirable in the following scenarios: for patients who are unwilling or unable to undergo colonoscopy, CTC is the best alternative due to high sensitivity and negative predictive value, outperforming (11, 22, 29).

8. *ESGE/ESGAR state that CT colonography is contraindicated in patients with active colonic inflammation and in those who recently underwent colorectal surgery (Recommendation: Strong; Evidence Level: Low).*

Despite being generally regarded as safer than colonoscopy (129), CTC was shown to be associated with potentially serious adverse events, in particular large bowel perforation (130, 131). Acute abdominal conditions, for example diverticulitis or active inflammatory bowel diseases (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. According to a recent metanalysis(86) including more than 100,000 subjects, twenty-eight colonic perforations were reported. Moreover, eight case reports – not included in the meta-analysis – detail CTC perforation (133-140). These reports allow to identify some risk factors for perforation. Four (11%) out of 36 perforated patients were affected by inflammatory bowel diseases, four patients 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 any procedure involving colonic distention entails a risk.

9. *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 (Recommendation: Strong; Evidence Level: Moderate).*

Diminutive (≤ 5 mm) polyps

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 of advanced neoplasia. In detail, a recent systematic review of 408/28,947 polyps found the frequency of advanced neoplasia 1.4%, 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 ≤ 10 mm polyps for 3 and 2 years, respectively. No diminutive polyp reached >5 mm in size and only 0.5% of ≤ 10 mm polyps eclipsed 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 (6-9 mm) polyps

Overall, 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 8,605 polyps, the frequency of advanced neoplasia was 7.9%, while the proportion of invasive cancer was 0.5% (41/8,456) (142). A retrospective analysis of 5,124 individuals undergoing screening CTC confirmed a very low risk of advanced neoplasia and invasive cancer in 464 patients with 6–9 mm polyps 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 progressed, with 6% exceeding 10 mm. The odds ratio for a growing polyp to become an advanced adenoma

during surveillance was 16 compared with 6–9 mm polyps detected and removed at initial CTC (i.e. without surveillance). An absolute polyp volume of more than 180 mm³ 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), positive-predictive value of 58% (22 of 38 polyps), and negative-predictive value of 99% (266 of 268 polyps). Recently, factors that may predict advanced neoplasia within a subcentimeter polyp has 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 (>10 mm) polyps and masses

Overall, ≥ 10 mm (i.e. large) polyps represent about 10% of all polyps detected during primary screening colonoscopy(141). In a previous systematic review, 73.5% (1,363/1,855) of these polyps appeared to be advanced adenomas, the remaining being non-adenomatous (141). The prevalence of invasive cancer has been recently addressed in large colonoscopic and CTC screening series, and ranges between 2% and 7% (146, 148, 149).

10. ESGE/ESGAR suggest same-day polypectomy as a possible option after CTC performed with full bowel preparation. The implementation of this policy should take into account technical and logistical factors, including patient consent. (Recommendation: Weak; Evidence Level: Low).

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 literature search identifying studies employing CTC and same day colonoscopy, a range of different preparations were 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 was 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 C-RADS system and graded the quality of bowel preparation at colonoscopy, after preparing the patient 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 due to insufficient insufflation. At colonoscopy, colonic preparation was classified by the endoscopist as excellent or good in 63%, fair in 28%, poor in 8.5% and inadequate in 0.5% of patients. A minority of studies commented regarding the quality of preparation during colonoscopy, but providing 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 whether one or the other bowel preparation is preferred for same-day colonoscopy after CTC. Although the frequency of and extent of retained fecal material and fluids at CTC has been extensively studied, the

effects on the performance of same-day colonoscopy of the various CTC preparation schemes 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 OC). Our literature search found no information regarding the quality of same day OC after same day laxative-free CTC. However several studies have reported using additional bowel cleansing subsequent to laxative-free CTC when same day OC is required. For example, a study of 95 symptomatic patients undergoing reduced laxative CTC used senna and 18g magnesium citrate, with an additional 18g of magnesium citrate after CTC but prior to OC (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 OC. In order to compensate for reduced bowel purgation, which may prohibit OC, PEG was administered after CTC, and OC 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 OC, 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 OC with or without fecal tagging, found little specific information on this issue. Frequency of incomplete OC are 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 OC with segmental unblinding. The quality of bowel preparation was not formally reported but only six of 1253 patients were excluded initially due to inadequate colonic preparation. Suboptimal colonoscopy quality was dismissed as a reason for missed adenomas since the OC completion rate was high at 99.4%. A similar tagging regime was used in another large study 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 five 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 inadequate preparation or insufflation for satisfactory interpretation. Twenty 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 OC.

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

Logistics

In order for 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 paradigm also requires that CTC be reviewed by a radiologist immediately in order to identify patients in whom same day OC is needed, and in order to identify rare but well-recognised perforations that occur during CTC.

11. ESGE/ESGAR do not recommend repetition of colonoscopy when a CTC lesion is not confirmed by a high-quality colonoscopy unless confidence for the presence of a ≥ 10 mm lesion remains high following CTC re-evaluation (Recommendation: Weak; Evidence Level: Low).

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-positives. In a recent prospective multicentre study of symptomatic patients, positive predictive value 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 it 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-colonoscopy 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 confidence in the CTC diagnosis remains high, an early repetition of colonoscopy should be considered, especially if the abnormality appears related to flexures or on the proximal side of colonic haustra.

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