TITLE: CT Colonography versus Colonoscopy and/or Sigmoidoscopy for the Diagnosis and Treatment Planning of Colorectal Cancer: A Review of the Comparative Clinical and Cost Effectiveness and Guidelines for Use

DATE: 19 December 2012

CONTEXT AND POLICY ISSUES

Colorectal cancer is the third-ranked neoplasm in order of incidence and mortality worldwide, and it is the second cause of cancer death in industrialized countries. Risk factors that increase the likelihood of developing colorectal cancer include diet, genetic mutations, alcohol abuse, smoking, and being over 50 years of age. In Canada, over 20,000 cases of colorectal cancer are diagnosed annually, highlighting the importance of early detection, diagnosis and treatment of the disease. Colorectal cancer can be screened using fecal occult blood testing (FOBT), double contrast barium enema (DCBE), sigmoidoscopy and colonoscopy.

More than 90% of colorectal cancers arise from adenomatous polyps, which are abnormal growths of tissue projecting from the lining of the colon or rectum. Colonoscopy and flexible sigmoidoscopy are two procedures that are currently used to detect and locate colon polyps and carcinomas. Both colonoscopy and flexible sigmoidoscopy involve the insertion of an endoscope through the anus into the colon, with exploration of the entire colorectum in colonoscopy and exploration of the sigmoid colon in sigmoidoscopy. Colonoscopy is considered the gold standard test for colon cancer as it can detect lesions with high sensitivity and specificity, but it is invasive, and requires sedation and extensive bowel preparation.

Computed tomographic colonography (CTC), or virtual colonoscopy, is an imaging technique of the colon involving helical computed tomography and computer software to generate high-resolution two- and three-dimensional images of the inner surface of the colon. CTC is less invasive, requires less bowel preparation, does not require sedation or analgesia, takes less time, and can be performed in patients who have had incomplete colonoscopy or are contraindicated for colonoscopy. Disadvantages of CTC include high cost, high radiation dose, and less sensitivity and specificity than colonoscopy.

A previous CADTH report published in 2008 compared the clinical- and cost-effectiveness of colonoscopy to sigmoidoscopy and CTC in the context of colorectal cancer screening. This report found that CTC did not perform as well as colonoscopy in the detection of colorectal
lesions, particular for smaller polyp sizes (<10 mm). The report also found colonoscopy to be more cost effective than CTC and flexible sigmoidoscopy for the screening of middle-aged people at high or average risk of colorectal cancer. Similar results were found in a CADTH systematic review comparing the clinical and cost-effectiveness of CTC and colonoscopy for colorectal cancer screening. Although there have been reports published on the comparative effectiveness of these techniques for colorectal cancer screening, there has been less information on the use of these techniques for the diagnosis and treatment of colorectal cancer with regards to clinical and cost effectiveness, and patient appropriateness.

The purpose of this review is to assess the clinical effectiveness and cost effectiveness of CTC compared to colonoscopy and sigmoidoscopy for the diagnosis and treatment of colorectal cancer, as well as guidelines for the use of CTC.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of CT colonography (virtual colonoscopy) compared to colonoscopy and/or sigmoidoscopy for the diagnosis and treatment of colorectal cancer?

2. What is the cost effectiveness of CT colonography (virtual colonoscopy) compared to colonoscopy and/or sigmoidoscopy for the diagnosis and treatment of colorectal cancer?

3. What are the guidelines regarding the use of CT colonography for the diagnosis and treatment of colorectal cancer?

KEY FINDINGS

In observational trials, CT colonography was found to be as effective as colonoscopy for the diagnosis of colorectal cancer. CT colonography performed better than colonoscopy for the pre-operative evaluation of colorectal tumours due to incomplete colonoscopies in patients with obstructive masses. Clinical practice guidelines recommended that CT colonography may be beneficial in specific sub-groups of patients. No evidence was identified regarding the cost-effectiveness of CT colonography or how it compares to sigmoidoscopy.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2012, Issue 10), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type for research questions 1 and 2. A guideline filter was used for research question 3. The search was also limited to English language documents published between Jan 1, 2007 and Nov 23, 2012.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications ad evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.
Table 1: Selection Criteria

| Population                  | Adult patients who are diagnosed with colorectal cancer  
|                            | Adult patients undergoing treatment for colorectal cancer (not a screening question) |
| Intervention               | Computed tomographic colonography (Virtual Colonoscopy) |
| Comparators                | Colonoscopy, Sigmoidoscopy (flexible/ rigid) |
| Outcomes                   | Clinical Effectiveness (diagnosis and treatment), Safety and Harms, Cost Effectiveness, Guidelines and Recommendations |
| Study Designs              | Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies, evidence-based guidelines and economic evaluations |

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications or included in a selected systematic review, or were published prior to 2007.

Critical Appraisal of Individual Studies

The quality of included systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool. Diagnostic accuracy studies were assessed using the revised version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2). Guidelines were assessed for quality using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument. A numeric score was not calculated for each study. Instead, strengths and limitations of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 500 citations. Upon screening titles and abstracts, 469 citations were excluded and 31 potentially relevant articles were retrieved for full-text review. An additional six potentially relevant reports were identified through grey literature searching. Of the 37 potentially relevant reports, 25 did not meet the inclusion criteria. Twelve reports were included in this review. The study selection process is outlined in a PRISMA flowchart (Appendix 1). Two systematic reviews, six non-randomized studies, and four evidence-based guidelines met the inclusion criteria. No economic evaluations were identified.

Summary of Study Characteristics

Details on study characteristics can be found in Appendix 2.

Study design and country of origin

Two systematic reviews and meta-analyses, four prospective studies, two retrospective studies, and four guidelines were included. In the systematic reviews, both RCTs and non-randomized studies were considered in the inclusion criteria.
Non-randomized studies were retrieved in one systematic review\textsuperscript{10} and the other did not specify the type of studies retrieved.\textsuperscript{11}

Two systematic reviews,\textsuperscript{10,11} one prospective study,\textsuperscript{12} and one retrospective study\textsuperscript{16} considered the use of CTC for the diagnosis of colorectal cancer. Three prospective studies\textsuperscript{13-15} and one retrospective study\textsuperscript{17} considered the use of CTC to guide treatment for colorectal cancer.

One systematic review\textsuperscript{10} and one guideline\textsuperscript{21} were from The Netherlands. One systematic review\textsuperscript{11} and two guidelines\textsuperscript{18,20} were from the USA. One prospective study\textsuperscript{14} and one retrospective study\textsuperscript{16} were from Italy. One prospective study each was from Bosnia and Herzegovina,\textsuperscript{12} Poland,\textsuperscript{13} and Turkey.\textsuperscript{15} One retrospective study was from South Korea.\textsuperscript{17} One guideline was from the UK.\textsuperscript{19}

**Patient characteristics**

One systematic review\textsuperscript{10} included asymptomatic subjects at average risk for colorectal cancer, while the other systematic review\textsuperscript{11} included both asymptomatic and symptomatic subjects. Both systematic reviews examined the use of CTC for the diagnosis of colorectal cancer in subjects.\textsuperscript{10,11}

Of the non-randomized studies that examined CTC for the diagnosis of colorectal cancer, a prospective study\textsuperscript{12} included patients with suspected symptoms of colorectal cancer, while a retrospective study\textsuperscript{16} included patients that had a $\geq 6$ mm colorectal lesion as determined by CTC.

Of the studies that examined CTC for the guidance of surgical treatment of colorectal cancer, two prospective studies\textsuperscript{13,14} included patients with colorectal tumours identified at colonoscopy, while one prospective study\textsuperscript{15} and one retrospective study\textsuperscript{17} included patients who were scheduled to undergo laparoscopy-assisted colectomy for colorectal cancer.

**Intervention and comparators**

All studies included a comparison between CTC and colonoscopy for diagnosis\textsuperscript{10-12,16} or treatment\textsuperscript{13-15,17} of colorectal cancer. In the studies that used CTC for the diagnosis of colorectal cancer, complete colonoscopy was used as a reference standard and conducted after CTC.\textsuperscript{10-12,16} In one systematic review\textsuperscript{11} and one prospective study,\textsuperscript{12} histology of samples taken during colonoscopy was used to confirm cancer diagnosis. In the studies that used CTC to guide treatment of colorectal cancer, CTC was performed after complete or incomplete colonoscopy.\textsuperscript{13-15,17} Standard cathartic bowel preparations involving the ingestion of an electrolyte solution were used in all but one retrospective study\textsuperscript{17} where the method of bowel preparation was not described. One retrospective study\textsuperscript{16} also used fecal tagging with an iodinated contrast agent in the CTC protocol.

**Outcomes measured**

CTC images were interpreted by two radiologists in two studies,\textsuperscript{14,16} by one radiologist in one study,\textsuperscript{13} and was not specified in the remaining studies.

One systematic review and meta-analysis evaluated the ability of CTC to detect adenomas, advanced adenomas and colorectal cancer by calculating per-patient and per-polyp sensitivities.
and specificities using colonoscopy as a reference standard. The other systematic review and meta-analysis reported the sensitivity of CTC and colonoscopy for detecting colorectal lesions, using histological analysis of biopsied samples as a reference standard.

One prospective study reported the ability of CTC and colonoscopy to detect colorectal cancers by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) using biopsies taken during colonoscopy to confirm histology. One retrospective study reported the PPV of CTC for the detection of colorectal neoplasia, using colonoscopy as a reference standard.

All of the studies evaluating the use of CTC in guiding treatment for colorectal cancer reported on the ability of CTC and colonoscopy to localize colorectal lesions for the pre-operative evaluation of patients with colorectal cancers. One prospective study also reported the ability of CTC and colonoscopy to evaluate tumour size and volume.

**Summary of Critical Appraisal**

Details on critical appraisal can be found in Appendix 3.

Both systematic reviews were based on clearly pre-defined criteria and included a detailed summary of study characteristics of included studies with appropriate assessment of the scientific quality. One systematic review only searched one electronic source in detail. Although the review stated that this was due to a failure to detect additional references using other electronic sources based on a preliminary search, this may have resulted in missed studies. In both systematic reviews, it was unclear whether grey literature was included in the search strategy.

In the diagnostic accuracy studies, included patients were generally appropriate for the objectives of the studies, though the studies may have been biased due to patient selection. In a retrospective study, only patients that had a ≥6 mm lesion identified by CTC was referred for colonoscopy. In the studies that used CTC for pre-surgical evaluation of colorectal cancer, many of the patients underwent CTC after incomplete colonoscopy. CTC scans were read, and consensus reached, by two radiologists in two studies, which would decrease the risk of error due to reader interpretation.

Colonoscopy was used as a reference standard in one retrospective study. In the remaining diagnostic accuracy studies, histology or surgical verification was used as a reference standard. In one retrospective study where colonoscopy was performed after CTC, the endoscopist was blinded to the CTC results. In a prospective study, it was unclear whether the endoscopist was blinded to the CTC results. In one prospective study evaluating the use of CTC for pre-surgical evaluation of colorectal cancer, the radiologist who interpreted the CTC images were blinded to the colonoscopy results. In the remaining studies that used CTC for pre-surgical evaluation of colorectal cancer, it was unclear whether radiologists were blinded to the results of the colonoscopy. The lack of blinding may introduce bias during the assessment of CTC images or colonoscopy analysis.

All of the included guidelines had a clear objective, scope, and target population and were developed by appropriate professional groups. All recommendations were derived from supporting evidence, and this evidence was directly referenced in one guideline. The same guideline provided a grade for the included recommendations. Potential barriers of applying
the recommendations were considered in one guideline. Cost implications of applying the recommendations were not considered or reported in all guidelines.

Summary of Findings

Details on findings can be found in Appendices 4 and 5.

What is the clinical effectiveness of CT colonography (virtual colonoscopy) compared to colonoscopy and/or sigmoidoscopy for the diagnosis and treatment of colorectal cancer?

**Diagnosis of colorectal cancer**

Two systematic reviews and meta-analyses examined the use of CTC and colonoscopy for the diagnosis of colorectal cancer. In one meta-analysis, CTC was found to have good sensitivity for advanced adenomas ≥10 mm in size, but lower sensitivity for advanced adenomas ≥6 mm in size when using colonoscopy as a reference standard. In this study, sensitivity and specificity values were not calculated for the detection of advanced neoplasia and colorectal cancer due to the small number of cancers detected in the included studies. However, no colorectal cancers were missed in all included studies. In the other meta-analysis, the pooled per-patient sensitivity for the detection of colorectal cancer was found to be equivalent with CTC and colonoscopy despite a wide range of CTC techniques used in the included studies. In total, 16 cancers were missed using CTC, but no cancers were missed when both cathartic bowel preparation and fecal tagging were used.

One prospective study examined the ability of CTC to detect colorectal cancer compared with colonoscopy. This study found that CTC and colonoscopy were equally sensitive in the detection of colorectal tumours, having identical sensitivity, specificity and positive predictive values. One retrospective study calculated the positive predictive value of CTC for detecting colorectal neoplasia using colonoscopy as a reference standard in patients with a ≥6 mm lesion detected by CTC. This study found that CTC was characterized by a very low rate of false-positive results for lesions ≥6 mm and that all cases of advanced neoplasia were found in patients with a ≥10 mm lesion.

**Treatment of colorectal cancer**

All studies that used CTC for pre-operative staging of colorectal cancer found that CTC was able to accurately localize colorectal tumours and was superior to colonoscopy due to the ability to visualize the entire colon in patients who were unable to complete colonoscopy. In one prospective study, 51.1% of included patients were unable to complete colonoscopy due to obstructive or occlusive masses, compared to 10.2% who were unable to complete CTC. One prospective study found that CTC had better performance in the defining the segmental location of the colon cancer than colonoscopy. Another prospective study found that the accuracy rate of colorectal tumour localization was statistically significantly higher using CTC than with colonoscopy. One retrospective study found that the sensitivity of CTC for detecting colorectal tumours and the accuracy for tumour localization was high.

What is the cost effectiveness of CT colonography (virtual colonoscopy) compared to colonoscopy and/or sigmoidoscopy for the diagnosis and treatment of colorectal cancer?
No evidence on the cost effectiveness of CT colonography (virtual colonoscopy) compared to colonoscopy and/or sigmoidoscopy for the diagnosis and treatment of colorectal cancer was identified.

What are the guidelines regarding the use of CT colonography for the diagnosis and treatment of colorectal cancer?

Four evidence-based guidelines provided recommendations on the use of CT colonography for the diagnosis of colorectal cancer, particularly with regards to when this technology is appropriate and when it is contraindicated.\textsuperscript{18-21}

Both the American Gastroenterological Association (AGA, 2011) and the American College of Radiology (ACR, 2009) provided recommendations on the indications and contraindication of patients undergoing CTC.\textsuperscript{18,20}

According to both guidelines, CTC is indicated for:

- Patients who failed to complete colonoscopy in whom evaluation of the colon is deemed necessary including, but not limited to, those with abdominal pain, diarrhea, constipation, gastrointestinal bleeding, anemia, intestinal obstruction, weight loss
- Patients at increased risk for complications during optical colonoscopy (advanced age, anticoagulant therapy, sedation risk, prior incomplete colonoscopy)
- The evaluation of the colon proximal to an obstructing lesion
- Patients with colorectal lesions indeterminate on optical colonoscopy\textsuperscript{18,20}

According to both guidelines, CTC is contraindicated for:

- Patients with symptomatic acute colitis, acute diarrhea, recent acute diverticulitis, recent colorectal surgery, symptomatic colon-containing abdominal wall hernia, recent deep endoscopic biopsy or polypectomy/mucosectomy, known or suspected colonic perforation, symptomatic or high-grade small bowel obstruction
- Routine follow-up of inflammatory bowel disease, hereditary polyposis or nonpolyposis cancer syndromes, evaluation of anal canal disease, the pregnant or potentially pregnant patient\textsuperscript{18,20}

The Scottish Intercollegiate Guidelines Network (SIGN, 2011) recommends that CTC can be used as a sensitive and safe alternative to colonoscopy.\textsuperscript{19} For frail elderly patients, CT colonography with minimal bowel preparation can be used.\textsuperscript{19}

The National Working Group on Gastrointestinal Cancers (2008) states that CTC can be indicated as a diagnostic or adjuvant diagnostic test for patients with incomplete colonoscopy without diagnosis, when colonoscopy is not possible, or when precise tumour localization is needed and not sufficiently determined by colonoscopy.\textsuperscript{21} CTC can be used as a second-line diagnostic test to detect or rule out colorectal carcinoma, and is preferred over barium enema.\textsuperscript{21}

Limitations

Different models of CTC scanners were used in all of the studies, which may limit the comparability of results between studies. Earlier studies that were included may have used CT scanners that perform differently than current models, limiting the generalizability of results to
current settings. Included prospective and retrospective studies were observational and enrolled a specific subset of patients, which may not be representative of the general population and which may have biased the results. For example, one retrospective study only performed colonoscopy analysis on patients that had a ≥6 mm lesions determined by CTC. Also, the studies that used CTC as pre-surgical evaluation of colorectal tumours performed CTC after incomplete colonoscopy, which may have biased the results in favour of CTC.

Colonoscopy was used as a reference standard in the systematic reviews and one retrospective study, which is not ideal as colonoscopy is not 100% accurate. The length of time between when CTC, colonoscopy, and reference tests were performed was not reported in four studies. In the studies where the length of time between techniques was reported, it ranged from same day analysis to within 3 months. Longer time intervals between CTC and colonoscopy may have affected the results due to changing pathology of the disease condition.

None of the included guidelines were published by a Canadian society, which may limit generalizability to the Canadian setting. In addition, only one guideline assigned grades of recommendations based on the evidence supporting it. No economic evaluations on CTC compared to colonoscopy and/or sigmoidoscopy for the diagnosis and treatment of colorectal cancer were identified. No studies were identified that compared CTC to flexible or rigid sigmoidoscopy.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

According to the included studies, CTC was generally found to perform equally as well or almost as well as colonoscopy for the diagnosis of colorectal tumours. For the pre-operative evaluation of colorectal tumours, CTC was found to have better performance than colonoscopy, mainly due to incomplete colonoscopies in patients with obstructive masses. In pre-operative staging, CTC was found to accurately detect and localize colorectal tumours, which is important for planning resection of the appropriate colon segment. Colonoscopy is still considered the gold standard for diagnosis and tumour staging due to its high sensitivity and specificity, but it fails to show the entire colon in cases where the patient cannot tolerate the procedure or there are obstructive masses within the colon.

The CADTH report published in 2008 found that CTC did not perform as well as colonoscopy in the detection of smaller colorectal lesions in the context of colorectal cancer screening. This current report aimed to determine the performance of CTC compared with colonoscopy in the context of diagnosis and treatment of colorectal cancer. From the included studies, it appears that CTC performs well in the detection of colorectal cancer and advanced adenomas, which are characterized by larger lesions. It should be noted, however, that detection of late-stage cancers does not necessarily improve survival rate, emphasizing the importance of early screening for non-cancerous colon polyps and adenomas.

Guidelines suggest that CTC can be used as an alternative to colonoscopy in patients that are contraindicated for colonoscopy, who are at risk for complications during colonoscopy, who failed to complete colonoscopy, or when precise tumour localization is needed and not sufficiently determined by colonoscopy. In addition, CTC should not be performed in patients with severe colon issues or who have recently undergone a deep endoscopic biopsy.
No evidence was identified regarding the cost effectiveness of CTC compared to colonoscopy for the diagnosis and treatment of colorectal cancer. No studies were identified that compared CTC to flexible or rigid sigmoidoscopy.

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REFERENCES


20. ACR practice guideline for the performance of computed tomography (CT) colonography in adults. Reston (VA): American College of Radiology (ACR); 2009.

APPENDIX 1: Selection of Included Studies

500 citations identified from electronic literature search and screened

468 citations excluded

31 potentially relevant articles retrieved for scrutiny (full text, if available)

6 potentially relevant reports retrieved from other sources (grey literature, hand search)

37 potentially relevant reports

25 reports excluded:
- irrelevant comparator (3)
- no comparator (1)
- irrelevant outcomes (6)
- irrelevant guidance (3)
- already included in at least one of the selected systematic reviews (7)
- published in language other than English (1)
- other (review articles, editorials) (4)

12 reports included in review
APPENDIX 2: Summary of Study Characteristics

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design and Length</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Clinical Outcomes Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Haan* 2011 The Netherlands</td>
<td>Systematic review and meta-analysis</td>
<td>5 studies (non-RCTs) including 4086 asymptomatic subjects aged 50-75 years at average risk for CRC</td>
<td>CTC</td>
<td>Colonoscopy (performed within 3 months after CTC)</td>
<td>Ability to detect advanced adenomas and CRC, sensitivity, specificity</td>
</tr>
<tr>
<td>Pickhardt* 2011 USA</td>
<td>Systematic review and meta-analysis</td>
<td>49 studies including 11 151 subjects (4883 asymptomatic subjects, 6668 symptomatic subjects)</td>
<td>CTC - after standard bowel preparation in 44 studies - cancers were histologically proven</td>
<td>Optical colonoscopy (after cathartic preparation)</td>
<td>Sensitivity for detecting CRC</td>
</tr>
<tr>
<td>Sofic* 2010 Bosnia and Herzegovina</td>
<td>Prospective study</td>
<td>231 patients with suspected symptoms of CRC (mean age 57.9±11.3 years; 53% female)</td>
<td>CTC (4-slice multi-detector CT scanner, Volume zoom Siemens) - standard bowel preparation (Ducolax® and Coloclens®)</td>
<td>Colonoscopy (biopsies taken to confirm CRC using histology) - performed after CTC</td>
<td>Ability to detect CRC, sensitivity, specificity, PPV, NPV</td>
</tr>
<tr>
<td>Iafrate* 2011 Italy</td>
<td>Retrospective study May 2009-May 2010</td>
<td>516 patients with a ≥6 mm lesion determined by CTC that were subsequently referred for colonoscopy (n=76)</td>
<td>CTC (64-channel multi-detector CT scanner, GE Healthcare) - fecal tagging with iodinated contrast agent</td>
<td>Colonoscopy (performed within 8 weeks after CTC, used as reference standard)</td>
<td>PPV for detecting neoplasia</td>
</tr>
<tr>
<td>Leksowski* 2011 Poland</td>
<td>Prospective study</td>
<td>49 consecutive patients with colorectal tumours identified with colonoscopy (median age 70 years, range 24-88 years; 63% male)</td>
<td>CTC (64-slice row CT scanner, Siemens Sensation Cardiac 64) - standard bowel preparation (polyethylene glycol electrolyte solution) - performed after colonoscopy on the same day</td>
<td>Colonoscopy</td>
<td>Tumour presence/location/size/morphologic features</td>
</tr>
<tr>
<td>Neri* 2009 Italy</td>
<td>Prospective study</td>
<td>65 symptomatic patients with CRC diagnosed at colonoscopy (mean age 64 years; 70% female)</td>
<td>CTC (multi-row CT scanner, LightSpeed Plus, GE Medical Systems) - standard bowel</td>
<td>Colonoscopy</td>
<td>Segmental localization of colorectal masses</td>
</tr>
<tr>
<td>First Author, Publication Year, Country</td>
<td>Study Design and Length</td>
<td>Patient Characteristics</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Clinical Outcomes Measured</td>
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<tr>
<td>Baca 2007 Turkey</td>
<td>Prospective study</td>
<td>40 consecutive patients who were scheduled to undergo laparoscopic resection for colorectal neoplasm (median age 63.7 years, range 32.9; 60% male)</td>
<td>CTC (multiphase contrast-enhanced, multidetector CT scanner) - standard bowel preparation (Na-phospho soda)</td>
<td>Optical colonoscopy</td>
<td>Localization of colonic lesions</td>
</tr>
<tr>
<td>Cho 2007 South Korea</td>
<td>Retrospective study</td>
<td>310 patients who underwent laparoscopy-assisted colectomy</td>
<td>CTC (n=94)</td>
<td>Colonoscopy (n=310)</td>
<td>Accuracy of localizing colorectal lesions</td>
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</tbody>
</table>

CRC=colorectal cancer; CTC=computed tomographic colonography; NPV=negative predictive value; PPV=positive predictive value
APPENDIX 3: Summary of Critical Appraisal

<table>
<thead>
<tr>
<th>First Author, Publication Year, Study Design</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
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</tr>
</tbody>
</table>
| de Haan10 2011 Systematic review and meta-analysis | • Comprehensive literature search based on pre-defined criteria  
• Summary of study characteristics and list of included studies provided  
• Scientific quality of included studies assessed  
• Risk of publication bias assessed | • Unclear whether grey literature was included in search strategy  
• Pooled data of studies was highly heterogeneous  
• Data was too limited to calculate sensitivities per patient for the detection of CRC |
| Pickhardt11 2011 Systematic review and meta-analysis | • Literature search based on pre-defined criteria  
• Summary of study characteristics and list of included studies provided  
• Scientific quality of included studies assessed | • Only one electronic source (Pubmed) was searched in detail  
• Unclear whether grey literature was included in search strategy  
• Risk of publication bias not assessed |
| Sofic12 2010 Prospective study | • A reference standard (histology) was used | • Unclear how study sample was selected  
• Time period between index (CTC) and reference test (histology from colonoscopy biopsy) not specified  
• Unclear whether readers were blinded to the results of other tests |
| Iafrate16 2011 Retrospective study | • The index test was described in sufficient detail to permit replication  
• CTC scans were read by two radiologists  
• Study was reflective of clinical practice in a dedicated centre | • Colonoscopy was used as a reference standard  
• Endoscopist was not blinded to the CTC results  
• Only a subset of patients (≥6 mm lesions on CTC) underwent colonoscopy, not a randomized sample |
| **Treatment**                               |           |             |
| Leksowski13 2011 Prospective study | • A consecutive sample of patients was enrolled  
• A reference standard (histology) was used  
• Both CTC and colonoscopy (where histological samples were taken) were performed on the same day  
• Radiologist who interpreted CTC images were blinded to colonoscopy results | • CTC images were interpreted by only one radiologist  
• Standard deviations of values were not reported |
| Neri14 2009 Prospective study | • A reference standard (surgery) was used  
• Two radiologists interpreted CTC images | • Specificity, PPV, and NPV values were not reported for colonoscopy  
• Standard deviations of values were not reported  
• Time period between CTC and colonoscopy not specified  
• Unclear whether radiologists were blinded to colonoscopy results |
| Baca15 2007 Prospective study | • A reference standard (histology) was used | • Time period between CTC and colonoscopy not specified  
• Unclear whether radiologists were blinded to colonoscopy results  
• Machine used to perform CTC not specified  
• Standard deviations of values were not reported |
<table>
<thead>
<tr>
<th>First Author, Publication Year, Study Design</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Cho, 2007 Retrospective study               | - A reference standard (operative location) was used | - Time period between CTC and colonoscopy not specified  
- Unclear whether radiologists were blinded to colonoscopy results  
- Machine used to perform CTC not specified  
- Standard deviations of values were not reported |

<table>
<thead>
<tr>
<th>Guidelines</th>
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<tr>
<td>American Gastroenterological Association (AGA), USA, 2011</td>
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</table>
| Clearly defined objectives, scope and target populations  
- Guideline development group included individuals from relevant professional groups  
- Recommendations are based on evidence | Grading of recommendations not reported  
- Evidence supporting recommendations not directly referenced  
- Guideline development methodology not described in detail  
- No standardized grading of recommendations  
- Cost implications of applying the recommendations not considered or reported |

| Scottish Intercollegiate Guidelines Network (SIGN) 2011 |
| Clearly defined objectives, scope and target populations  
- Guideline development group included individuals from relevant professional groups  
- Guideline development methodology described  
- Recommendations are directly linked to evidence | Cost implications of applying the recommendations not considered or reported  
- Potential barriers of implementing guideline not considered or reported  
- Unclear whether patients' preferences were taken into consideration  
- Cost implications of applying the recommendations not considered or reported |

| American College of Radiology (ACR) 2009 |
| Clearly defined objectives, scope and target populations  
- Guideline development group included individuals from relevant professional groups  
- Guideline development methodology described  
- Recommendations are directly linked to evidence | Grading of recommendations not reported  
- Cost implications of applying the recommendations not considered or reported  
- Potential barriers of implementing guideline not considered or reported  
- Unclear whether patients' preferences were taken into consideration |

| National Working Group on Gastrointestinal Cancers 2008 |
| Clearly defined objectives, scope and target populations  
- Guideline development group included individuals from relevant professional groups  
- Guideline development methodology described  
- Potential barriers of implementing guideline considered | Grading of recommendations not reported  
- Evidence used to support recommendations not referenced  
- Cost implications of applying the recommendations not considered or reported |

CTC=computed tomographic colonography
### APPENDIX 4: Summary of Findings

<table>
<thead>
<tr>
<th>First Author, Publication Year, Study Design</th>
<th>Main Study Findings</th>
<th>Authors’ Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
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</table>
| de Haan**10** 2011 Systematic review and meta-analysis | Pooled per-patient sensitivity and specificity of CTC (colonoscopy reference standard)  
*Detection of adenomas ≥6 mm*  
Sensitivity: 75.9% (95% CI 62.3-85.8)  
Specificity: 94.6 (95% CI 90.4-97.0)  
*Detection of adenomas ≥10 mm*  
Sensitivity: 87.9% (95% CI 82.1-92.0)  
Specificity: 97.6% (95% CI 95.0-98.9)  
Pooled per-polyp sensitivity and specificity of CTC (colonoscopy reference standard)  
*Detection of adenomas ≥6 mm*  
Sensitivity: 80.0% (95% CI 66.9-88.7)  
*Detection of adenomas ≥10 mm*  
Sensitivity: 85.9% (95% CI 80.4-90.0)  
*Detection of advanced adenomas ≥6 mm*  
Sensitivity: 83.9% (95% CI 77.6-88.7)  
*Detection of advanced adenomas ≥10 mm*  
Sensitivity: 83.3% (95% CI 77.1-88.8)  
Detection of advanced neoplasia and CRC  
Sensitivity and specificity not calculated due to small number of CRCs (n=6) detected in the included studies. No CRCs were missed in all studies. | “In summary, this meta-analysis of prospective studies studying the diagnostic value of CT-colonography compared to colonoscopy in an average risk population, shows that CT-colonography has a good sensitivity for (advanced) adenomas ≥10 mm. For (advanced) adenomas ≥6 mm, sensitivity is somewhat lower.” (p. 1757) |
| Pickhardt**11** 2011 Systematic review and meta-analysis | Pooled per-patient sensitivity for the detection of CRC  
*CTC*  
398/414 cancers, 96.1% (95% CI 93.8-97.7)  
- 16 cancers missed (10 in rectosigmoid colon, 6 in rectum, 6 proximal to splenic flexure)  
- No cancers missed when both cathartic bowel preparation and fecal tagging were used  
*Colonoscopy (compared to OC enhanced by knowledge of prior CTC results)*  
178/188 cancers, 94.7% (95% CI 90.4-97.2) | “Our meta-analysis shows that the pooled sensitivities of CT colonography and OC for colorectal cancer were about 96% and 95%, respectively. When one considers the large number of cancer cases included, the wide range in CT colonography techniques used, and the lack of heterogeneity in the CT colonography sensitivity estimate, our study results support the clinical equivalence between CT colonography and OC for the detection of invasive cancer.” (p. 400-401) |
| Sofic**12** 2010 Prospective study | Histological examination was conclusive in 227/231 patients.  
*CTC for the detection of colorectal polyps*  
Sensitivity: 89.7%  
Specificity: 100%  
PPV: 100% | “In our research CTC was equally sensitive (100%) in detection of CRC lesions as colonoscopy and much better than barium enema (94.6%). The CTC is very efficient in pain-intolerant patients and in cases of tumours causing obstruction, dolichocolons, spasms, and other reasons preventing the colonoscopy to
<table>
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<tr>
<th>First Author, Publication Year, Study Design</th>
<th>Main Study Findings</th>
<th>Authors’ Conclusions</th>
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| **Colonoscopy for the detection of colorectal polyps**  
Sensitivity: 94.9%  
Specificity: 100%  
PPV: 100%  
**CTC for the detection of colorectal tumours**  
Sensitivity: 100%  
Specificity: 100%  
PPV: 100%  
**Colonoscopy for the detection of colorectal tumours**  
Sensitivity: 100%  
Specificity: 100%  
PPV: 100%  | reach the caecum. The CTC is suitable for screening and staging of tumours, as well as for obtaining unexpected findings on other abdominal or pelvic organs. In the detection of lesions smaller than 5 mm, colonoscopy showed to be better in regard to the other two methods." (p. 22) |
| **Iafrate** 2011  
Retrospective study  
CTC images were read by two abdominal radiologists experienced in CTC interpretation (>5000 cases).  
76/516 (14.7%) patients were identified to have at least one lesion ≥6 mm on CTC and underwent colonoscopy.  
Positive predictive value of CTC (colonoscopy reference standard)  
Detection of neoplasia: 68.4% (95% CI 58-79)  
Detection of advanced neoplasia: 30% (95% CI 20-41)  
All cases of advanced neoplasia were found in patients with a ≥10 mm lesion.  
4% false positive rate among 76 patients identified to have at least one ≥6 mm lesion.  | “In conclusion, our study showed that, in a dedicated centre, CTC appears to be a highly accurate procedure characterized by a very low rate of false-positive results for ≥6 mm lesions. This supports the use of CTC in clinical practice, although radiologists’ training may be more extensive than previously suggested.” (p. e292) |
| **Treatment**  
**Leksowski** 2011  
Prospective study  
CTC images were interpreted by radiologist blinded to other colorectal findings from colonoscopy.  
25 patients (51.1%) were unable to complete colonoscopy due to obstructive or occlusive masses.  
5 patients (10.2%) had incomplete CTC due to inadequate bowel distension or occlusive tumour, 44 patients (89.8%) completed CTC.  
Percentage of patients with proper evaluation of tumour size and volume by CTC  
Size: 100  
Volume: 100  | “Our study findings show that CTC is a useful method for the diagnosis of advanced colorectal tumors. It allows diagnosis of tumor, determination of local tumor progression, and detection of synchronous lesions in the large bowel, even in endoscopically inaccessible regions. On the basis of our patients, we cannot evaluate whether CTC is a useful method for low disease stages as well.” (p. 2348) |
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<tr>
<td>Neri 2009 Prospective study</td>
<td>Percentage of patients with proper evaluation of tumour size and volume by colonoscopy. Size: 59.2 Volume: 30.6. Histology results revealed 42 adenocarcinomas, 3 adenomas, 1 adenoma with focal cancer, and 3 nonspecific cells.</td>
<td>“Our study confirms the superiority of CTC over CC in the study of patients with colorectal masses. CT colonography has better performance in the identification of colonic masses and in the completion of colonic evaluation, but its main goal is the precise definition of the segmental location of the colon cancer, which increases the efficacy of the surgical resection.” (p. 594)</td>
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<td>Baca 2007 Prospective study</td>
<td>Histopathologic investigation was used as a reference standard. 9 patients were unable to complete optical colonoscopy due to a partially obstructing tumour. Accuracy rate of colorectal tumour localization CTC: 97.5% Optical colonoscopy: 55% P&lt;0.05. Polypectomy sites were localized with CTC in 5 patients. Histopathologic analysis revealed 34 adenocarcinomas, 3 adenoma demonstrating low-grade dysplasias, 2 high-grade dysplasias, and 1 neuroendocrine carcinoma.</td>
<td>“According to our results, we concluded that [virtual colonoscopy] may improve colorectal cancer localization by providing an accurate, safe, and painless examination. It provides a prior knowledge of tumor size, morphologic characteristics and specific location, vascular anatomy, extracolon findings such as larger lymph nodes, adjacent organ invasion.” (p. 1980)</td>
</tr>
<tr>
<td>Cho 2007 Retrospective study</td>
<td>Accuracy was verified against actual operative location. Complete colonoscopy records was available for 203 patients. Colonoscopy was inaccurate for tumour localization in 23</td>
<td>“Computed tomography colonography is useful for detecting not only the primary tumor but also synchronous colon lesions, and it provides additional information regarding regional and distant metastatic disease, the depth of wall invasion, and the</td>
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<td>patients (11.3%)</td>
<td>precise location of the lesion in the colon prior to surgery. The sensitivity of CT colonography for detecting tumors and the accuracy for localization was 96.8% and 94.7%, respectively.” (p. 1494)</td>
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<td>CTC identified 91/94 lesions (96.8%)</td>
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<td>Accuracy of tumour localization</td>
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<td>CTC: 89/94 (94.7%)</td>
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<td>Colonoscopy: 180/203 (88.7%)</td>
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CI = confidence interval; CRC = colorectal cancer; CTC = computed tomographic colonography; OC = optical colonoscopy.
### APPENDIX 5: Guidelines and Recommendation for the Use of CTC

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<tr>
<th>Guideline Society, Country, Year, Intervention, Indication</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>American Gastroenterological Association (AGA), USA, 2011</td>
<td><strong>Indications</strong></td>
</tr>
<tr>
<td>Performing CT colonography</td>
<td>1. “CT colonography is indicated for adults with failed colonoscopy in whom evaluation of the colon is deemed necessary.” (p. 2248)</td>
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<td>2. “CT colonography is indicated for evaluation of the colon proximal to an obstructing lesion.” (p. 2248)</td>
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<td>3. “CT colonography should be considered in patients unwilling to undergo colonoscopy as a primary screening modality.” (p. 2248)</td>
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<tr>
<td></td>
<td><strong>Contraindications</strong></td>
</tr>
<tr>
<td></td>
<td>1. “CT colonography should not be performed immediately after failed colonoscopy in patients who had polyps removed or large biopsy specimens taken.” (p. 2248)</td>
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<td>2. “Additional data regarding the benefits of CT colonography relative to other modes of diagnostic testing as well as a better understanding of the long-term effects of ionizing radiation in children are needed before CT colonography can be recommended in pediatric populations.” (p. 2248)</td>
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<td>3. “Relative contraindications or conditions that require caution in performing a CT colonography examination include, but are not limited, to the following: symptomatic acute colitis, acute diarrhea, recent acute diverticulitis, recent colorectal surgery, symptomatic colon-containing abdominal wall hernia, recent deep endoscopic biopsy or polypectomy/mucosectomy, known or suspected colonic perforation, symptomatic or high-grade small bowel obstruction.” (p. 2247)</td>
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<td>4. “Absolute contraindications include the following: routine follow-up of inflammatory bowel disease, hereditary polyposis or nonpolyposis cancer syndromes, evaluation of anal canal disease, the pregnant or potentially pregnant patient.” (p. 2247)</td>
</tr>
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| Scottish Intercollegiate Guidelines Network (SIGN), Scotland, 2011 | **Diagnosis of CRC** |
| Diagnosis and management of CRC | 1. “CT colonography can be used as a sensitive and safe alternative to colonoscopy.” [Grade C, based on well-conducted case control or cohort studies] (p. 18) |
|                                                         | 2. “Minimal preparation CT is an alternative to CT colonography in frail elderly patients.” [Grade D, based on non-analytic studies and expert opinions or extrapolated from well conducted case control or cohort studies] (p. 18) |

| American College of Radiology (ACR), USA, 2009 | **Indications** |
| Performing CT colonography in adults | 1. “Diagnostic examination in symptomatic patients, particularly in the setting of incomplete colonoscopy, including, but not limited to, those with: abdominal pain, diarrhea, constipation, gastrointestinal bleeding, anemia, intestinal obstruction, weight loss.” (p. 2) |
|                                                         | 2. “Following incomplete screening, surveillance, or diagnostic colonoscopy and for characterization of colorectal lesions indeterminate on optical colonoscopy.” (p. 2) |
|                                                         | 3. “Patients who may be at increased risk for complications during optical colonoscopy (e.g., advanced age, anticoagulant therapy, sedation risk, prior incomplete colonoscopy).” (p. 2) |

<p>|                                                         | <strong>Contraindications</strong> |
|                                                         | 1. “The relative contraindications or conditions that require caution in performing a CTC examination include, but are not limited to: symptomatic acute colitis, acute diarrhea, recent acute diverticulitis, recent colorectal surgery, symptomatic colon-containing abdominal wall hernia, recent deep endoscopic biopsy or polypectomy/mucosectomy, known or suspected colonic perforation, symptomatic or high-grade small bowel obstruction.” (p. 2) |</p>
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<th>Recommendations</th>
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| National Working Group on Gastrointestinal Cancers, The Netherlands, 2008 | Diagonsis of CRC  
1. “CT colonography (virtual colonoscopy) or barium enema is indicated as a diagnostic or adjuvant diagnostic test for patients with incomplete colonoscopy without diagnosis, when colonoscopy is not possible, or when precise tumour localization is needed and not sufficiently determined by colonoscopy.”  
2. “As a second-line diagnostic test to detect or rule out colorectal carcinoma, CT colonography (virtual colonoscopy) is preferred over barium enema.” |

CRC=colorectal cancer; CTC=computed tomographic colonography