Refining CT colonography methods
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Citation for published version (APA):
Boellaard, T. N. (2013). Refining CT colonography methods

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Chapter 8

The feasibility of colorectal cancer detection using dual-energy computed tomography with iodine mapping

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Clinical Radiology (in press)
Abstract

Aim: To assess the feasibility of colorectal cancer detection using dual-energy computed tomography with iodine mapping and without bowel preparation or bowel distension.

Materials and Methods: Consecutive patients scheduled for preoperative staging computed tomography (CT) because of diagnosed or high suspicion for colorectal cancer were prospectively included in the study. A single contrast-enhanced abdominal CT acquisition using dual-source mode (100 kV/140 kV) was performed without bowel preparation. Weighted average 120 kV images and iodine maps were created with post-processing. Two observers performed a blinded read for colorectal lesions after being trained on three colorectal cancer patients. One observer performed an unblinded read for lesion detectability and placed a region of interest (ROI) within each lesion.

Results: In total 21 patients were included and 18 had a colorectal cancer at the time of the CT acquisition. Median cancer size was 43 mm [interquartile range (IQR) 27–60 mm] and all 18 colorectal cancers were visible on the 120 kV images and iodine map during the unblinded read. During the blinded read, observers found 90% (27/30) of the cancers with 120 kV images only and 96.7% (29/30) after viewing the iodine map in addition (P = 0.5). Median enhancement of colorectal cancers was 29.9 HU (IQR 23.1–34.6). The largest benign lesions (70 and 25 mm) were visible on the 120 kV images and iodine map, whereas four smaller benign lesions (7–15 mm) were not.

Conclusion: Colorectal cancers are visible on the contrast-enhanced dual-energy CT without bowel preparation or insufflation. Because of the patient-friendly nature of this approach, further studies should explore its use for colorectal cancer detection in frail and elderly patients.
Introduction

Colorectal cancer is one of the leading causes of cancer-related mortality worldwide and the incidence increases with age [1]. Frequently used tests for colorectal cancer detection such as colonoscopy and computed tomography (CT) colonography are considered to be burdensome procedures [2, 3], require bowel preparation [4, 5], and have complication risks (colonoscopy more than CT colonography) [6, 7]. Alternative less burdensome tests are being considered in frail and elderly patients [8–13]. These patients have more difficulties with diarrhoea because of incontinence [14] and cognitive impairment, are at risk of dehydration and electrolyte disturbance [15], and have a higher risk of having a suboptimal bowel preparation [5, 16]. Therefore, a test without bowel preparation, colonic insufflation, sedation, or position changes on the examination table would be favourable in these patients, and might be feasible as colorectal cancers are the main target lesions in this patient group.

Previous studies using routine abdominal CT with oral iodine bowel preparation have shown reasonable sensitivity for colorectal cancers [8–13]. Intravenous contrast medium in the portal phase is routinely administered for the detection of (liver) metastases, but is not used for detection of colonic lesions [4]. However, recently dual-energy CT has become available for clinical practice. Dual-energy CT is a technique that uses two energies (e.g., 100 kV and 140 kV) and is designed to detect of iodine compared with conventional (single-energy) CT and construct iodine only images (iodine maps) [17, 18]. The study of Karcaaltincaba and colleagues showed that one colorectal cancer was visible on the iodine map using dual-energy CT colonography with intravenous iodine contrast medium [19]. The fact that cancers show enhancement of approximately 40 HU on single-energy CT during the portal phase, strengthens the idea that enhancement of colorectal cancers may be used for their detection, especially when conspicuity can be increased [20, 21]. Therefore, it was hypothesized that dual-energy CT with intravenous contrast medium and iodine mapping may be sufficiently sensitive for colorectal cancer detection and does not require any bowel preparation or insufflation.

The present study assessed the feasibility of colorectal cancer detection of dual-energy CT with intravenous contrast medium and iodine mapping, without bowel preparation or bowel distension.
Material and methods

Population
Consecutive adult patients in a small general hospital (Bronovo, The Hague, the Netherlands) with either a recent diagnosis of colorectal cancer or with a very high suspicion of colorectal cancer, who were scheduled for a preoperative abdominal staging CT examination with intravenous contrast medium were included. Exclusion criteria were a body mass index (BMI), above 30 kg/m² [22] pregnancy, and insufficient renal function defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m². The local Medical Ethics Committee had approved this study and all participants gave their written informed consent.

CT acquisition protocol
Patients did not receive bowel preparation (including no oral contrast agent), anti-spasmodic drugs, or colonic insufflation as commonly used for CT colonography [4]. CT examinations were acquired using a 128-section dual-energy CT system (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany). The smaller of the two detectors has a field of view (FOV) of 33 cm, which allows coverage of a large area of the abdomen. CT acquisitions were performed in dual-energy mode and using dose modulation. A single acquisition in the supine position was performed 70 seconds after the administration of 120 ml intravenous iodinated contrast medium (iodixanol, 320 mg iodine/ml; Visipaque 320, GE Healthcare, Carrigtohill, Cork, Ireland) at an infusion rate of 4 ml/s. One hundred and twenty millilitres of intravenous contrast medium was administered irrespective of the patients’ weight. Furthermore, patients with a high body weight were excluded by excluding patients with a BMI 30 kg/m². CT imaging parameters were as follows: 140 kV and 178 reference mAs (tube A), 100 kV and 230 reference mAs (tube B), 0.5 seconds gantry rotation time, 0.6 pitch, and 32 x 0.6 mm collimation.

Post-processing
Post-processing was performed at a workstation (Syngo mmWP VE36A, Siemens Medical Solutions, Forchheim, Germany). Weighted average reconstructions were made (i.e., 50:50 ratio mixed contrast-enhanced 100 kV and 140 kV images) with a section thickness of 3 mm (hereafter called “120 kV images”). The “virtual non-contrast” application of the dual-energy software was used to create virtual non-contrast images and iodine maps. The iodine maps were superimposed onto
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virtual non-contrast images to combine the iodine distribution with anatomical information. A radiologist (O.D.F.H., with 11 years of experience as a radiologist) adjusted the window levels of grey and colour of the iodine maps until satisfied with the visualization of the colonic wall.

**Settings for iodine map reconstruction**

In the standard “virtual non-contrast” application, virtual non-contrast images and iodine maps are reconstructed with a standard three-material decomposition model containing fat, soft tissue, and iodine [18]. When using the preset parameters of this application, stool is often visible in the iodine maps as well, while not containing an iodinated contrast medium, making a differentiation with colonic wall very difficult. In the present study, optimal differentiation between the gastrointestinal wall, faeces, and iodine was achieved by adjusting the three-material decomposition model for iodine map construction, based on CT values (in HU) of the colonic stool and gastrointestinal wall. In the three-material decomposition model, graphically the stool should be on a straight line with gastrointestinal wall.

To estimate the required settings for the application, 25 measurements were performed in dense stools and 25 in the stomach wall for six anonymised dual-energy CT images without intravenous contrast medium (the stomach wall was chosen because it is easier to measure than the thin colonic wall). Region of interest (ROI) measurements were placed in the 100 kV and the 140 kV acquisitions with automatic correlation between the two acquisitions to ensure that the ROI location was exactly the same in both scans. The scan protocol for these true non-enhanced acquisitions was as follows: 140 kV and 162 reference mAs (tube A), 100 kV and 210 reference mAs (tube B), 0.5 seconds gantry rotation time, 0.7 pitch, and 32 x 0.6 mm collimation.

**Reference standard**

The reference standard comprised information from the available sigmoidoscopy, colonoscopy, surgery, pathology (operation specimen and biopsy), and MRI reports. Lesion size was determined by the surgical specimen or when unavailable by endoscopic measurements. For rectal tumours, MRI was used when surgical specimen and endoscopy size measurements were unavailable.

**Unblinded reading**

An unblinded reading was performed to acquire data regarding the visibility, conspicuity, and the CT values of all lesions present in the reference standard. For
the unblinded reading, one observer (O.D.F.H.) scrutinised the 120 kV images and iodine maps for the lesions with knowledge of the results of the reference standard. For each lesion, the size (mm), morphology (tumour or sessile, flat or pedunculate polyp), conspicuity (five-point scale: 1 = not good, 5 = very good), and segment (six-segment model) were rated [23]. Additionally, the observer indicated how well the lesion could be discriminated from collapsed colon, stool, and hypertrophic haustral folds (all on the same five-point scale as used for conspicuity). Finally, a ROI measurement was performed in each lesion to obtain CT values. One ROI measurement provided information about both overlay (i.e., enhancement) and virtual non-contrast CT values, and one ROI measurement was performed with automatic location correlation between the contrast-enhanced 100, 120, and 140 kV images.

**Blinded reading**
Two observers (C.Y.N., abdominal radiologist with 17 years of experience including > 1500 CT colonography examinations, and M.C.D., general radiologist with 10 years of experience but without CT colonography experience) were trained in interpreting iodine maps using three dual-energy CT examinations, which were not part of the examinations used for evaluation. The number of cancers left in the dataset for the blinded evaluation was 15 (18 minus the three cancers in the training cases).
For the blinded evaluation, the observers began by reading the 120 kV images and then continued with the iodine map reading. They indicated for each lesion on which series it was detected, and for both 120 kV and iodine maps, they annotated characteristics similar to the unblinded reading and indicated their level of confidence regarding each lesion (0, 25, 50, 75, or 100%). Findings during the blinded and unblinded reading were only compared for segments of which the reference standard was available. Annotations were matched with the reference standard by an experienced CT colonography observer (T.N.B., evaluated > 300 CT colonographies). Size and morphology as used for CT colonography matching are less reliable without distension; therefore, a stricter criterion for the location was used [24]. For a match, the lesion at CT had to be in the same segment or in the first third of the adjacent segment indicated by the reference standard.

**Image quality**
For image quality evaluation, one observer (O.D.F.H.) scored image noise and image quality on a five-point scale for the 120 kV and iodine map images (for quality:
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1 = very good image quality to 5 = unacceptable image quality and for noise: 1 = no significant noise to 5 = detrimental image noise) [25]. Furthermore, whether any part was missing in the field of view (FOV) was assessed for all six colonic segments.

Statistical analysis
SPSS version 19 (SPSS, Chicago, IL, USA) was used for all statistical analysis and a P value of less than 0.05 was considered to indicate a statistically significant difference. Median and interquartile ranges (IQR) were calculated for size, radiodensity, and five-point scales. Sensitivity for cancer detection was calculated for both observers combined for 120 kV images only and after adding the iodine map and subsequently compared with a McNemar test with continuity correction.

Results

Population
Twenty-four patients were assessed for eligibility between March and September 2011, and 21 patients were included in this study. Two patients were excluded because of a BMI above 30 kg/m² and one was lost to follow-up. The average age was 70 years (range 50–90 years), the percentage of males was 52.4 (11/21), and the average BMI was 24.5 kg/m² (range 19.5–28.7). All patients had a colonoscopy (n = 19), sigmoidoscopy (n = 1), or both (n = 1). Fifteen of 20 colonoscopies reached the caecum. Fourteen patients underwent surgery, and therefore, histopathology of the surgical specimen was available.

Lesions according to the reference standard
Nineteen patients had an adenocarcinoma of the colon, but one was endoscopically removed before the dual-energy CT. Therefore, 18 adenocarcinomas were present at the time of the dual-energy CT. These carcinomas were located in the caecum (n = 4), ascending colon (n = 5), sigmoid (n = 5), and rectum (n = 4). The median size according to the reference standard was 43 mm (IQR 27–60 mm). In two patients, the final diagnosis was unexpectedly not a malignant tumour (i.e., a 25mm pedunculate adenoma and a diverticular segment). There were three benign lesions of 6–9 mm in size (7, 7, and 8 mm, respectively) and three large benign lesions (i.e., ≥ 10 mm): a 15 mm pedunculate villous adenoma, a 25 mm pedunculate adenoma, and a 70 mm villous adenoma.
Table 1 Computed tomography (CT) value measurements.

<table>
<thead>
<tr>
<th>Radiodensity at CT (HU)</th>
<th>100kV</th>
<th>140kV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dense stool</td>
<td>46.6 (4.9)</td>
<td>42.3 (3.9)</td>
</tr>
<tr>
<td>Stomach wall</td>
<td>51.8 (4.1)</td>
<td>55.0 (3.4)</td>
</tr>
</tbody>
</table>

Settings of the three-material decomposition application

The CT value measurements of dense stool and stomach wall are presented in Table 1. These values were used to estimate the optimal settings of the three-material decomposition application. The straight line calculated using the CT value measurement is shown in Figure 1.

Unblinded reading

All 18 adenocarcinomas were visible both in the 120 kV images and in the iodine maps (examples are shown in Figures 2 and 3). The 25 mm pedunculated adenoma (Figure 4) and the 70 mm villous adenoma were also visible on the 120 kV images and the iodine map. All other benign lesions (7, 7, 8, and 15 mm, respectively) were invisible on both the 120 kV images and iodine maps. Median cancer conspicuity was 4 (IQR 3–4) for 120 kV images and 4 (IQR 4–4.25) for the iodine maps.

Figure 1 The straight line to be determined for the appropriate settings of the three-material decomposition model with the CT values of stool and gastrointestinal wall (stomach wall). The calculated virtual non-contrast application settings were -12 HU for fat and 52 HU for soft tissue for 100 kV and -100 HU for fat and 55 HU for soft tissue for 140 kV.
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**Figure 2** A sigmoid adenocarcinoma in one of the training scans (arrows) is seen on the 120 kV image (left) and iodine map (right). Notice the large difference in wall thickness compared with other parts of the colon. The thickening is well appreciated on the iodine map.

**Figure 3** A caecal adenocarcinoma (arrows) in one of the training scans is seen on the 120 kV image (left) and iodine map (right). In the 120 kV image, the thickened wall has to be differentiated from grey stool, whereas on the iodine map this is more easily performed, as the coloured wall has to be differentiated from non-coloured stool.

**Figure 4** A large 25 mm pedunculated adenoma in the sigmoid (arrows) was detected on the iodine map by both observers, but by only one observer on the contrast-enhanced 120 kV images.
The median CT radiodensity of the carcinomas was 44.6 HU (IQR 42.8–45.9) on the virtual non-contrast images and median enhancement was 29.9 HU (IQR 23.1–34.6). Median CT radiodensity values on the contrast-enhanced images were 85.7 HU (IQR 72.3–94.1) for 100 kV, 73.8 HU (IQR 66.5–80.1) for 120 kV, and 60.6 HU (IQR 54.1–65.6) for 140 kV. For both 120 kV images and iodine maps, the ability to discriminate colorectal cancer from collapsed lumen was 4 (IQR 3–4) from stool 4 (IQR 4–4) and hypertrophic folds 4 (IQR 3–4). Figure 5 shows a hypertrophic diverticular segment and Figure 6 shows stool that may be difficult to distinguish from tumour.

**Blinded reading**

The average sensitivity for colorectal cancers was 90% (27/30) for the 120 kV images only and 96.7% (29/30) after reading the iodine maps in addition (P = 0.50). For observer 1, the sensitivity was similar for 120 kV images only and after reading the

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**Figure 5** A diverticular colon (arrows) shows vivid enhancement and wall thickness very similar to the enhancement and thickness of a carcinoma, although the length of the involved segment is more indicative of an inflammatory or vascular cause. Although in this patient no carcinoma was present, detecting a tumour in such a segment would be very difficult. Both observers did not annotate a lesion in this segment.

**Figure 6** Stool in the rectum (arrows) causing artefacts on the iodine map (right), which can make distinction of a tumour difficult. Both observers did not annotate this particular piece of stool.
additional iodine maps, both 93.3% (14/15). Observer 2 detected two carcinomas on the iodine map that were initially missed on the 120 kV images, and therefore, the sensitivity increased from 86.7% (13/15) to 100% (15/15). The cancer that was missed by observer 1 after reading both 120 kV images and the iodine map was 20 mm in size. No cancers were dismissed after reading the iodine maps. The 70 mm tubulovillous adenoma was scored as tumour by both observers; however, one observer dismissed it after reading the iodine map. The 25 mm pedunculated adenoma was scored as tumour by both observers. One of them only detected the lesion after evaluating the iodine map. The four smallest benign lesions varying from 7–15 mm were not detected by either reader on 120 kV images or iodine maps. The 70 mm tubulovillous adenoma was scored as tumour by both observers; however, one observer dismissed it after reading the iodine map. The 25 mm pedunculated adenoma was scored as tumour by both observers. One of them only detected the lesion after evaluating the iodine map. The four smallest benign lesions varying from 7–15 mm were not detected by either reader on 120 kV images or iodine maps. The average specificity of both readers (of two scans without a large lesion) was 75% (3/4) for 120 kV images only and 75% (3/4) after reading the iodine maps. Observer 1 scored three false-positive tumours and a false-positive polyp, but dismissed one tumour and the polyp after looking at the iodine map. Observer 2 scored two false-positive tumours and one false-positive flat polyp on both 120 kV images and iodine map. The median confidence for colorectal cancers was 100% (IQR 75–100) for both 120 kV images and iodine maps. The conspicuity of colorectal cancers was 4 (IQR 4–5) for 120 kV and 4 (IQR 4–5) for iodine maps. For both 120 kV images and iodine maps, the ability to discriminate colorectal cancer from collapsed lumen was 4 (IQR 3–5) from stool 4 (IQR 4–5) and hypertrophic folds 4 (IQR 4–5).

**Image quality**

There were no missing parts of a segment in the FOV in the caecum, ascending colon, sigmoid, and rectum. In 14.3% (3/21) of the patients, there was a part of the descending colon missing in the FOV, and in 4.8% (1/21) of the patients, there was a part of the transverse colon missing in the FOV. For all segments combined, 3.2% (4/126) were partly missing in the FOV. The median image quality of the 120 kV images was 2 (IQR 2–2), and for the iodine maps also 2 (IQR 2–3). The median noise score for the 120 kV images was 2 (IQR 2–2.5) and for iodine maps 2 (IQR 2–3).

**Discussion**

The present feasibility study shows that the large majority of colorectal cancers are visible on contrast-enhanced dual-energy CT without bowel preparation or distension. There was no significant difference in detection rate of the 120 kV
images or iodine maps (90% versus 96.7%; \( P = 0.50 \)). A 70 mm and a 25 mm benign lesion showed enhancement on the iodine map, but four other lesions > 6 mm were unidentifiable even with knowledge from the reference standard. Karcaaltincaba et al. performed CT colonography with colonic distension and intravenous contrast medium but without bowel preparation, and showed one colorectal cancer that was visible on an iodine map [19]. The present study has elaborated their finding with 18 colorectal cancers, which were all visible on the iodine map to the unblinded reader and almost all (29/30 of two readers combined) to the blinded readers. Importantly, CT was performed without insufflation, which further reduces the burden of the examination [2, 26, 27]. The fact that the colorectal cancers were all visible on the iodine maps indicates that iodine maps may be helpful for detection of colorectal cancers.

The sensitivity for colorectal cancer was similar to studies using single-energy CT with oral iodine contrast medium and without insufflation [8–12, 28]; however, the reference standard was limited in these studies (e.g., short clinical follow-up or barium enema). The sensitivity of the present study was higher compared with another colonoscopy-verified study using intravenous contrast medium in the portal phase and no insufflation (72.4% versus 96.7% sensitivity) [13]. However, in that retrospective study, oral contrast medium was given to most patients. Importantly, the prevalence of colorectal cancer in that series was much lower than in the present study and more closely resembled clinical practice.

One colorectal cancer was missed after reading both 120 kV and iodine map images by one of the two blinded observers. This cancer measured 20 mm and was together with another cancer of the same size, the smallest in the present study. This may indicate that cancers of 20 mm are more difficult to detect with the present technique. However, the number of cancers in the present dataset is too small to draw conclusions. Further studies on dual-energy CT with intravenous contrast medium and iodine mapping are warranted to obtain more extensive data on the detection of colorectal cancers and on the detection of colorectal cancers in different size categories (especially small cancers). Moreover, future studies to study characteristics that may be able to differentiate benign from malignant lesions are recommended.

The assessment of benign colonic polyps was not the primary goal of this study and the dataset was too small for any firm statement. Two of three large lesions were visible (70 mm villous adenoma and 25 mm pedunculated adenoma were visible), whereas a 15 mm pedunculated villous adenoma was not visible. However, the latter was directly adjacent to a tumour, making distinction between polyp and tumour
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very difficult without insufflation. One might speculate that using our dual-energy protocol with intravenous contrast medium and insufflation might be sufficient for detecting both colorectal cancers and large benign lesions. The enhancement value of 30 HU for cancers is somewhat lower when compared with studies of CT colonography with intravenous contrast medium [20, 21]. This might be caused by more accurate placements of the ROIs in tumours in a distended colon. Some segments were partly missing in the FOV (smallest detector). It is likely that future dual-source CT systems will have a larger FOV and, therefore, partly missing segments will no longer be an issue. The radiation dose of the dual-energy protocol used in this study is approximately 1.5 times higher compared with the single-energy protocol. However, virtual non-contrast can be generated with post-processing. Depending on whether an institution’s protocol contains a non-enhanced acquisition, this may reduce the radiation dose. Importantly, the benefits of the radiation dose outweigh the risks by far in a symptomatic frail and elderly population for which the present technique may be useful. Furthermore, promising tools, such as iterative reconstructions, are expected to reduce the radiation dose. A limitation of the dual-energy technique is that it is not advised in patients with a BMI above 30, and obesity is relatively common among elderly patients in Western countries.

The present study has several limitations. The aim of the present feasibility study was to evaluate the potential of dual-energy CT for cancer detection in a highly selected and limited number of colorectal cancer cases. This design was chosen as a first step to evaluate the potential applicability of such a technique, which, when feasible and further studied, could be considered in elderly and frail patients. This design with a high prevalence of cancer limits conclusions with respect to accuracy of the technique in daily practice, although readers were not aware of the prevalence in the cohort. On the other hand, the readers were trained using only three cases and they might have performed better had they had a larger training series. Further, the study does not give adequate information with respect to adenoma detection. However, given the inherent limitations of the technique, a reasonable detection rate for polyps smaller than 10 mm was not anticipated, and the authors did not put much weight on the evaluation of these lesions in this feasibility study. Colonoscopy and surgery reports were available, but correlation with CT is still less precise as compared with, for example, matching CT colonography with videotaped colonoscopy. Although optimal parameters were calculated for iodine map reconstruction, some stool artefacts were still present. Efforts should be made to reduce these artefacts to improve the strategy presented in this paper. Moreover, there was not comparison...
with other minimally invasive CT techniques, such as contrast-enhanced single-energy abdominal CT with or without oral bowel preparation. The 70 seconds delay was chosen because previous CT colonography studies have shown enhancement using this timing; however, the optimal timing for colonic lesion enhancement is to the authors’ knowledge unknown. Optimal timing of intravenous contrast medium may improve the present strategy.

The present study shows that detection of colorectal cancer is feasible at dual-energy CT without bowel preparation or insufflation. To the authors’ knowledge, this is the first study to show the feasibility of this technique. Such a strategy might be a sensible option for colorectal cancer detection, especially in frail and elderly patients. However, further studies should evaluate this technique in an appropriately powered lower prevalence population.
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References


