CT-colonography in population-based colorectal cancer screening

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Chapter 12

Summary of findings and implications
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This thesis discusses several aspects of computed tomography colonography (CT-colonography) when used as primary screening technique within an invitational, population-based, colorectal cancer (CRC) screening program.

Chapter 2 reports on the diagnostic accuracy for the detection of advanced neoplasia of CT-colonography, when used as a screening technique in an average risk population. Several meta-analyses had been performed previously on the diagnostic value of CT-colonography, reporting on the accuracy for all polyps including both non-advanced lesions (hyperplastic lesions and serrated adenomas) and advanced lesions (advanced adenomas and/or CRC), while it is known that advanced adenomas are important precursors for CRC. Importantly, these studies included subjects at average risk for the development of CRC as well as subjects that were at high risk for CRC for example because they had a positive family history for CRC. By including both average and high risk participants, the accuracy per participant of CT-colonography in screening might be overestimated, as the radiologist might be more focused on the detection of polyps when he knows that it concerns a scan of a person at high risk for the development of CRC. Therefore, we performed a meta-analysis to estimate the diagnostic value of CT-colonography for the detection of advanced neoplasia in an average risk population aged 50 to 75 years. Our literature search resulted in five relevant studies, including 4,086 participants of which less than 1% was at high risk. We found that CT-colonography detected 82.9% of participants with adenomas of 6 mm and larger and 87.9% of participants with adenomas of 10 mm and larger. Corresponding specificities were 91.4% and 97.6%, respectively. These results showed that CT-colonography has a high sensitivity for the detection of adenomas of 10 mm and larger, but that the per patient sensitivity for the detection of smaller adenomas is somewhat lower.

The remaining articles included in this thesis are related to (the results of) the Cocos trial - COlonoscopy or CT-COlonography for Screening –, in which 8,844 subjects aged 50 to 75 years, derived from the Dutch population in the regions of Amsterdam and Rotterdam, were randomly invited in a 2:1 ratio for colonoscopy (n=5,924) or CT-colonography (n=2,920) screening. A detailed description of the materials and methods of the Cocos trial, as well as an overview of the primary and secondary endpoints, is provided in Chapter 3.

Both colonoscopy and CT-colonography can be valuable alternatives for CRC screening, as both techniques are highly accurate in the detection of
(advanced) adenomas and CRC. However, the diagnostic yield of a screening program does not only depend on the accuracy of the screening technique but also on the participation rate. Prior to the COCOS trial, no previous randomised controlled trials had been performed comparing participation and diagnostic yield of colonoscopy and CT-colonography screening using an intention-to-treat analysis. The COCOS trial was primarily designed to investigate the participation rate and diagnostic yield of an invitational, population-based CRC screening program, using either colonoscopy or CT-colonography for primary screening.

In our trial, significantly more CT-colonography invitees completed the screening procedure than colonoscopy participants (34% vs. 22%) (Chapter 4). Due to the decision of the Dutch Health Council, which approves population-based screening trials, CT-colonography participants were only referred for colonoscopy in case of lesions of 10 mm and larger. Concerning the diagnostic yield, colonoscopy detected significantly more advanced lesions per 100 participants: colonoscopy detected advanced neoplasia in 8.7 per 100 participants whereas CT-colonography detected advanced neoplasia in 6.1 per 100 participants. The differences in participation rate and diagnostic yield per participant more or less cancelled out in the diagnostic yield per invitee: advanced neoplasia was detected in 1.9 per 100 colonoscopy invitees and in 2.1 per 100 CT-colonography invitees. The last difference was not significant, indicating that both screening techniques resulted in a comparable diagnostic yield per invitee.

We also compared the expected burden between colonoscopy and CT-colonography invitees, the perceived burden between colonoscopy and CT-colonography participants, and the willingness of participants to participate in future screening rounds. The results are reported in Chapter 5. The intended participation in a first screening round can be influenced by the expected burden of the screening technique, while the participation in future screening rounds will probably be influenced by the perceived burden in previous rounds.

To our knowledge, no previous randomised controlled studies had been performed comparing the expected burden of colonoscopy and CT-colonography. To evaluate the expected burden, we sent a baseline questionnaire by mail to all invitees. This questionnaire collected information on the expected burden of the bowel preparation and the screening procedure itself, scored on a 5-point Likert scale. In this study more colonoscopy invitees expected the bowel preparation to be rather or
extremely burdensome: 34% of colonoscopy vs. 10% of CT-colonography participants. In addition, a relative larger proportion of colonoscopy invitees expected the procedure itself to be rather or extremely burdensome (36% vs. 9%, respectively).

Previous studies that compared the perceived burden of both techniques used a tandem design, meaning that all subjects received a CT-colonography prior to colonoscopy. In most of these studies, participants indicated that they would prefer a CT-colonography the next time as they found it less burdensome than colonoscopy. We therefore expected that when comparing the perceived burden of either colonoscopy and of CT-colonography screening, CT-colonography would be experienced as a less burdensome screening technique. Especially, because we performed the CT-colonography with non-cathartic bowel preparation consisting of three bottles of 50 millilitres of iodinated contrast agent, while colonoscopy participants were prepared with a more extensive bowel preparation of 2 litres of laxatives and 2 litres of clear fluids. To this aim, all participants received a burden questionnaire by mail two weeks after the procedure. Both questionnaires were based on questionnaires that were used and validated in previous screening trials. The burden questionnaire collected information on perceived burden of the bowel preparation and the entire screening procedure (from intake until receiving the results). In addition, participants were asked to indicate the most burdensome part of the examination and whether they were willing to participate in future screening rounds.

Relatively more CT-colonography participants scored drinking of the bowel preparation as not or only slightly burdensome. We were surprised to learn that relatively more colonoscopy participants experienced the related bowel movements (i.e. related diarrhoea) as not burdensome. In addition, the entire screening procedure was more often scored as not burdensome by colonoscopy participants than by CT-colonography participants (48% vs. 34%). However, the differences in mean burden scores of the overall procedure were small (1.8 in colonoscopy vs. 2.0 in CT-colonography; p<0.001). The majority of colonoscopy participants experienced the bowel preparation as the most burdensome aspect of the entire screening procedure, while the large majority of CT-colonography participants scored the examination itself or the bowel preparation as most burdensome aspect. The finding that CT-colonography participants assigned higher burden scores to the overall procedure might be explained by the fact that they did not expect the procedure to be very burdensome or underestimated the impact
of these complaints. Perhaps CT-colonography participants did not expect the watery diarrhoea caused by the tagging agent, which lasts for one to two days after the examination, or did not expect the bowel cramps occurring during the procedure (related to the insufflation of CO\textsubscript{2}). This is supported by the observation that 21% of CT-colonography participants indicated that the examination turned out worse than expected, compared to 12% of colonoscopy participants. As the intended participation in future screening rounds was comparable between colonoscopy and CT-colonography participants, it remains to be seen whether these differences in perceived burden will be reflected in different participation rates in the future.

Nevertheless, based on the results of our study, we should search for a less burdensome bowel preparation scheme for CT-colonography with similar accuracy. A possibility would be to use a combination of iodine and barium, which could be a good compromise between homogeneous tagging and related side effects. A disadvantage of such a preparation scheme is that it may be more complicated for screening participants. Secondly, use of additional analgesia during CT-colonography should be considered, in order to minimize the burden related to the insufflation of CO\textsubscript{2}. We should also consider the possibility that the information provided to invitees in the information leaflets was not sufficient enough to inform them adequately on all potential burdensome aspects of the screening procedure. Further efforts should also target the improvement of CT-colonography information leaflets.

Within screening programs, invitees should have enough decision-relevant knowledge on the disease and the screening technique. This can be achieved by providing all relevant information in leaflets, for example. COCOS trial invitees received an invitation letter that was accompanied by an information leaflet. The information leaflets that were sent to all colonoscopy and CT-colonography invitees provided identical information on CRC and its precursors, as well as some information on the screening procedure the invitee was invited for, including advantages and possible disadvantages. To evaluate whether the invitees made an informed decision on participation, all invitees received a baseline questionnaire by mail that contained knowledge questions on CRC and on the screening method to which the invitee was randomised. In addition, this questionnaire addressed some items covering the invitees’ attitude towards CRC screening and participation. We defined an informed decision as a decision that was based on adequate decision-relevant knowledge, leading to a behaviour that is consistent with the personal attitude towards participation in screening. The results are described in
Chapter 7. More than 80% of colonoscopy and CT-colonography participants completed the questionnaire, but only 15% of colonoscopy non-participants and 10% of CT-colonography non-participants, representing a selected group of non-participants. For both modalities, more than 90% of participants were found to have adequate knowledge and a positive attitude towards CRC screening, making an informed decision. However, within responding non-participants, almost half had adequate knowledge and a positive attitude towards screening, but still decided to decline the invitation. This finding suggests the presence of additional barriers to participation.

To gain more insight in the reasons for participation and non-participation, which might help in the design of future information leaflets and development of information campaigns, we asked all invitees to indicate their reasons for accepting or declining the invitation in the baseline questionnaire described above. They could do so by ticking one or more of the predefined reasons for (non-)participation. In addition, they were asked to indicate the most important reason. The results are summarised in Chapter 8. The two most reported decisive reasons to accept colonoscopy or CT-colonography screening were ‘early detection of CRC’ and ‘early detection of precursors’. In colonoscopy screening, the most indicated decisive reason for non-participation was ‘examination unpleasant’, while the most reported decisive reason to decline CT-colonography screenings was ‘no time/too much effort’, followed by ‘no symptoms, examination not necessary’. Our results indicate that future information leaflets should emphasize more on the fact that, although a subject is asymptomatic, this does not imply that there is no chance on having CRC or precursors.

Apart from the comparison between CT-colonography and colonoscopy, the COCOS trial also provided the possibility to assess CT-colonography related issues. We compared distension of the colon, perceived burden, and occurrence of side effects in CT-colonography participants that received either Buscopan or GlucaGen as bowel relaxant. Buscopan is known to have a positive effect on bowel distension during CT-colonography. An adequately distended colon improves the diagnostic accuracy of this technique. Whether GlucaGen also has a positive effect on distension remains questionable, as it has never been shown to be significant better than placebo or no medication. However, it has also never been shown that it leads to a significant worse distension than Buscopan. The use of GlucaGen as bowel relaxant is therefore controversial. Both Buscopan and GlucaGen also have side effects. We compared the number of adequately distended colons,
the difference in perceived burden (collected by the burden questionnaire described in Chapter 5) and the difference in frequency and nature of side effects between CT-colonography screening participants receiving Buscopan or GlucaGen. The study is reported in detail in Chapter 6.

The study demonstrated that Buscopan resulted in significant more adequately distended colons, mainly caused by better distension of the sigmoid. In addition it showed that participants that received Buscopan assigned lower burden scores to the insufflation of CO₂, and to ‘changing from position during the procedure’, as well as the overall procedure. There were no significant differences in experienced pain between both groups. The number of side effects was not significantly different; however the nature of the most often reported symptoms differed between groups. Participants that received Buscopan as bowel relaxant, most often reported a dry mouth (15%), while the most often reported side effect among participants that received GlucaGen was nausea (13%). As there was no significant difference in pain related to the procedure, the difference in nature of side effects could be the most important explanation for the difference in related burden. Based on our results we can conclude that Buscopan resulted in significant better distension than GlucaGen, and in a less burdensome screening procedure. We therefore concluded that when Buscopan can be used, it is the preferred bowel relaxant. In addition we suggested that the effect of GlucaGen needs to be evaluated in a large placebo-controlled study, with primary focus on possible differences in number of adequately distended colons, experienced burden and occurrence of side effects.

Chapter 9 reports a study in which we evaluated whether trained technicians are able to detect a similar number of CT-colonography screening participants with relevant intracolonic lesions (advanced neoplasia) per 100 participants, compared to a radiologist. A reading strategy of one or two technicians (serving as primary readers for intracolonic lesions) instead of a reading strategy of one radiologist may lower evaluation costs per participant, decreasing the total costs of CT-colonography screening. This was the first study comparing the diagnostic yield for advanced neoplasia of technicians and a radiologist within a population-based screening trial. All scans of the 982 CT-colonography participants were read by one of three physicians (two radiologists and one resident, each with an experience of more than 800 CT-colonographies), using primary 2D read with 3D problem solving, followed by CAD read (Computer Aided Detection). In addition, all scans were read by two of four trained technicians (all technicians had finished a structured
training program including 175 training cases and 25 test cases (with colonoscopy verification)), using primary 2D read, followed by secondary 3D read and CAD read. In case of discordant recommendations from the two technicians, they were instructed to reach consensus by the research fellow (not involved in reading of the cases). If at least one of the readers scored a CT-colonography lesion of 10 mm or larger, the participant was referred for colonoscopy. We compared several alternative reading strategies with a reading strategy of one radiologist. The strategy of one technician resulted in a significant lower diagnostic yield, compared to a reading strategy of one radiologist. However, a strategy of two technicians with or without consensus resulted in a comparable diagnostic yield when compared to one radiologist, with less false positive referrals for colonoscopy. In addition, this strategy would lead to lower evaluation costs (based on the Dutch (screening) rates for radiologists and technicians and the mean interpretation time) of €10.40 per scan instead of €15.45 per scan. However, one of the main problems for this reading strategy would be the fact that the radiologist will keep the final responsibility for the participant and will be needed for the evaluation of extracolonic findings. Another possibility would be to use a reading strategy consisting of one radiologist and one or two technicians as second readers. These strategies resulted in a significant higher diagnostic yield in comparison to a reading strategy of one radiologist, but would lead to higher costs associated with the evaluation of intracolonic findings.

Chapter 10, describes a study in which we aimed to estimate the actual unit costs associated with CT-colonography when used for population-based CRC screening. Previous cost-effectiveness studies on colonoscopy and CT-colonography based their unit costs for CT-colonography on the average reimbursement costs for abdominal and pelvic computed tomography, for example, which might have over- or underestimated the actual costs associated with CT-colonography screening. The unit costs for CT-colonography as used in these studies ranged from €346 to €594 per screening procedure. We collected data within the COCOS trial. We calculated the costs associated with of all the individual parts of the screening procedure, namely: invitation letter, reminder, intake, confirmation of CT-colonography appointment, performance of the CT-colonography procedure, evaluation, and communication of the results. In addition we collected information on the number of invitees that were reminded, were scheduled for intake, were scheduled for CT-colonography, underwent CT-colonography and number of invitees that needed a re-examination because of inadequate quality of the
CT-colonography, as well as number of invitees with lesions of 10 mm and larger. This gave us the opportunity to estimate the costs associated with the invitation process and intake (€15.44), costs associated with the screening procedure itself (€155.70), and costs associated with the communication of negative or positive results (€1.16 and €10.16, respectively). In addition we were able to estimate the average costs of CT-colonography screening per invitee and per participant: €64.86 and €192.86, respectively. The average costs of less than €200 per participant that we found were substantially lower than the unit costs for CT-colonography screening that were used in previous cost-effectiveness analyses. We therefore concluded that our finding necessitates an update of previous cost-effectiveness analyses.

**Does CT-colonography have a role for population-based colorectal cancer screening?**

The last chapter of this thesis (Chapter 11) describes several issues that are related to the question ‘Does CT-colonography have a role for population-based colorectal cancer screening?’, with special focus on CRC screening in Europe. The primary goal of CRC screening is to decrease CRC-related mortality by detecting CRC in an early phase and by prevention of CRC by detecting precursors (i.e. advanced adenomas).

Only gFOBT and sigmoidoscopy screening have been shown to lead to a decrease in CRC related mortality with 14% and 31%, respectively\(^3,4\). Whether CRC screening with FIT, colonoscopy, and CT-colonography also results in a decrease in CRC related mortality has not been demonstrated yet, but is highly likely. Nevertheless, large long-term follow-up studies are needed to confirm that CT-colonography screening leads to a decrease in mortality and to which extent.

The diagnostic yield of a screening programme depends on the accuracy of the screening test as well as the attendance. The COCOS trial demonstrated that colonoscopy screening leads to a lower participation rate, a higher diagnostic yield per 100 participants and a slightly lower burdensome examination, when compared to CT-colonography screening. On the other hand, colonoscopy and CT-colonography screening resulted in a comparable diagnostic yield per 100 invitees. Colonoscopy and CT-colonography are not the only examinations that can be used for population-based CRC screening (see also Table 1).

The last few years several invitation-based CRC screening trials have been performed in the Netherlands, enabling a comparison of first-round
participation rates and diagnostic yield between the several CRC screening techniques. When looking at the participation rate only, gFOBT and FIT screening would be superior to screening with sigmoidoscopy, colonoscopy and CT-colonography, with participation rates of 47% and 59-60%, respectively\(^1\). Although participation rates of faecal testing were relatively high, first round detection rates for advanced neoplasia were only 0.6 and 1.4 to 1.5 per 100 invitees\(^1\), respectively, compared to a detection rate of 1.9 in colonoscopy screening and 2.1 per 100 invitees in CT-colonography screening. Sigmoidoscopy screening results in a participation rate of 30%, which is comparable to CT-colonography screening, and in a diagnostic yield of 2.2 per 100 invitees, comparable to colonoscopy and CT-colonography screening\(^1\).

**Table 1** Overview of Dutch participation rates and yield of different CRC screening techniques

<table>
<thead>
<tr>
<th></th>
<th>gFOBT(^1,2)</th>
<th>FIT(^1,2)</th>
<th>sigmoidoscopy(^3)</th>
<th>colonoscopy</th>
<th>CTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participation rates (%)(^a)</td>
<td>47%</td>
<td>59%-60%</td>
<td>30%</td>
<td>22%</td>
<td>34%</td>
</tr>
<tr>
<td>Yield advanced neoplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- per 100 examinations</td>
<td>1.2</td>
<td>2.4-2.5</td>
<td>7.3</td>
<td>8.7</td>
<td>6.1</td>
</tr>
<tr>
<td>- per 100 invitees</td>
<td>0.6</td>
<td>1.4-1.5</td>
<td>2.2</td>
<td>1.9</td>
<td>2.1</td>
</tr>
</tbody>
</table>

\(^a\) Participation rate defined as number of invitees that completed the screening procedure CT, CT-colonography.

At this point it remains unknown whether the differences in participation rate and yield between the different screening techniques can be extrapolated to future screening rounds. In a second or third screening round, participation rates can both increase as well as decrease, e.g. due to more public awareness or positive/negative experiences of previous participants. In addition, the diagnostic yield can also increase, because of higher participation rates, or decrease, due to the fact that the prevalence of relevant lesions decreases as most have been removed in previous screening rounds. To answer these questions, large, long-term follow-up studies are needed.

The decision whether CT-colonography should be used in CRC screening also depends on other factors that are not fully elaborated yet, like the impact of the detection of extracolonic findings (e.g. does it result in a decrease in mortality of extracolonic illnesses or does it only lead to an increase in medical costs and unnecessary complications related to the
follow-up?), the risks of exposure to ionizing radiation, cost-effectiveness and available screening capacity (for example the available number of adequately trained endoscopists and/or CT-colonography readers).

Therefore we concluded that, although CT-colonography can be considered as a viable option for CRC screening based on the results on diagnostic yield of a first screening round, there is at this point not yet enough crucial evidence to fully evaluate its role as primary population-based CRC screening technique.

References


