Chapter 10

Summary, conclusions and implications
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CT colonography is a structural radiological method to evaluate the colorectum for polyps and cancer. The technique is being used in clinical practice when colonoscopy is incomplete and as an alternative for colonoscopy. Additionally its role as possible screening tool for colorectal cancer is under continuous investigation. Naturally, all techniques have their limitations or for certain aspects there is a lack of data. For CT colonography this includes: insufficient insight into different reading approaches for screening, use of ionising radiation, a painful colonic distension and a burdensome oral bowel preparation. In this thesis we explored opportunities to work on these limitations and thereby refine CT colonography methods.

For the possible future role of CT colonography as a screening tool, the cost-effectiveness is of great importance and therefore we have to scrutinise opportunities to save costs. Since radiographers are able to report CT colonography for intracolonic lesions as accurate as a radiologist [1–3], reporting of intracolonic findings by radiographers may be a cost-reducing strategy for screening. With this radiographer reading strategy it is impractical that a radiologist has to read all CT colonographies for extracolonic findings. In chapter 2 we therefore studied whether radiographers can be trained to triage extracolonic findings in CT colonography into four triage categories: normal, unimportant, likely unimportant and potentially important findings [4]. Likely unimportant and potentially important findings require further work-up, while normal and unimportant findings do not. If radiographers are able to perform an effective triage, a radiologist only has to evaluate a small proportion of the CT colonographies for extracolonic findings. In this study we offered an initial structured extensive training to eight radiographers. Subsequently radiographers triaged 280 CT colonography examinations for extracolonic findings. The first and last 40 CT examinations were identical test cases without feedback from the radiologist report. The other 200 CT examinations were part of the second training phase where feedback from the radiologist report was provided after reading a case. We found that radiographers had a sensitivity and specificity of 70% for triaging findings that require further work-up. For the likely unimportant findings there was a significant improvement between the first and final test (52% vs. 70%). However, for the potentially important findings no improvement was observed between the two tests (in both tests 69%).
Although we observed a learning effect, the triage after training was insufficiently effective to consider our triage strategy for CT colonography screening practice. Even with a good performance, the medicolegal issues may have been a hurdle for this approach in many countries. Our study implicates that the complex anatomy and large differential diagnosis of abdominal CT is likely not appropriate for evaluation by radiographers. Therefore studies on CT colonography evaluation by radiographers should focus on intracolonic findings only.

The exposure to ionising radiation is a risk in CT colonography and the risk-benefit ratio is especially important in screening. The benefit of CT colonography is clear in terms of the sensitivity and specificity for colorectal cancer and polyps. However, the risk of cancer induction with radiation exposure may change over time as a result of stricter guidelines and more efficient radiation use by newer CT systems. It is therefore important to know the current radiation burden. For this purpose we performed an international radiation dose inventory among CT colonography research institutions, which we report in chapter 3. We aimed to determine the radiation burden in 2011 and whether it has reduced since 2007, in which the last radiation dose inventory was performed. We emailed 109 institutions and asked to provide all available CT colonography protocols (screening, daily practice with and daily practice without intravenous contrast medium). Protocols were provided for by 58 institutions. We found that the median effective dose in 2011 was 7.6 mSv for daily practice and 4.4 mSv for screening protocols. Radiation dose had not reduced since 2007 for both daily practice protocols and screening protocols. Berrington de González calculated the benefit-risk ratio for a screening CT colonography in 2011 and used 7 mSv for men and 8 mSv for women for this calculation [5].

Our results indicate that the radiation dose used for screening CT colonography is close to half this dose. Therefore the benefit-risk ratio is in fact twice as high as in the aforementioned study. Radiation dose reduction to 2 mSv and even lower seems feasible and would further improve the benefit-risk ratio. Implementation of stricter guidelines and use of dose reducing tools, such as iterative reconstruction algorithms may help to achieve this.

Chapter 4 is a narrative review in which we summarise the literature on two important CT colonography aspects: colonic insufflation and radiation dose. Based on the literature we come to the following recommendations and conclusions: To obtain sufficient colonic distension we recommend using automatic carbon dioxide
insufflation via a thin flexible catheter. Hyoscine butylbromide is the preferred spasmolytic for CT colonography because of its positive effect on pain, burden and insufflation and its lower costs (than the alternative: glucagon hydrochloride). Scans should be performed in both prone and supine position, although lateral decubitus position may be used as an alternative for prone. Low-dose protocols without intravenous contrast medium should be used when extracolonic findings are deemed unimportant. Dose reduction can be realised by lowering tube voltage or tube current and dose modulation should be used when available. Iterative reconstruction algorithms allow for the use of lower radiation dose without reduced image quality.

The next issue we addressed in this thesis is the burden caused by the colonic insufflation. For adequate interpretation of the whole bowel lumen, colonic insufflation is a prerequisite. Unfortunately, insufflation leads to stretching of the bowel wall that causes discomfort and cramping pain. In several studies, both in screening and in patients, the pain and burden of CT colonography even compares unfavourably to conventional colonoscopy under conscious sedation [6–9]. Apart from the burden and anxiety, this may influence the adherence to CT colonography. We therefore studied the effectiveness of analgesia in reducing pain during bowel insufflation and thereby improve CT colonography acceptance. In chapter 5, the design of a prospective randomised double-blind, placebo-controlled trial is described. In that trial was evaluated whether a single bolus of intravenous alfentanil can provide a clinically relevant reduction of maximum pain during colonic insufflation. This was the first study on analgesia in CT colonography. The results were described in chapter 6 and show that a single intravenous alfentanil bolus resulted in a clinically relevant decrease in pain during colonic insufflation. The total pain and burden of the total CT colonography procedure were also reduced with alfentanil. In the alfentanil group more dizziness and desaturations (< 90% SpO2) were observed, however all desaturations were clinically irrelevant because they were short and resolved spontaneously. Recovery times were different directly after the procedure, but similar at 30 minutes after injection of study medication. Procedure time was comparable for both groups. Our study showed that a single bolus intravenous alfentanil reduces CT colonography pain and burden and may therefore improve the acceptance of CT colonography among physicians, patients and screening participants. Especially for persons with a low pain threshold, the use
of an analgesic such as alfentanil may be a viable option. However, more information about the safety profile of a low-dose alfentanil bolus is warranted.

If a centre would consider using alfentanil during CT colonography insufflation, this will have implications for their practice. A physician trained in the use of opioids should perform the procedure while at many institutions a radiographer now performs the examination. Emergency medication and equipment should be available on site. Because the pain of the patient will be less reliable for assessing the amount of insufflated gas, it is important to use automatic insufflation because the safety valves will prevent too high pressures. Another implication is that patients have to arrange transportation, as they are not allowed to drive the day they received alfentanil. Patients who receive hyoscine butylscopalamine bromide are already not allowed to drive within half an hour after the procedure, but for glucagon hydrochloride there are no driving restrictions at all. To avoid the abovementioned changes in practice, it may be an option for future studies to assess the use of oral pain medication to reduce insufflation pain in CT colonography. However, current literature generally shows insufficient analgesic effect of oral (non-opioid) pain medication for the prevention of procedural pain [10–12].

Another factor that may influence the pain and burden is the type of spasmolytic used. For CT colonography a spasmolytic is injected to improve colonic distension and to reduce cramping pains and motion artefacts. Two spasmolytics are commonly used for this purpose, hyoscine butylbromide and glucagon hydrochloride. Very little is known about the possible differences in distension and burden between these spasmolytics. Only two studies performed a direct comparison between hyoscine butylbromide and glucagon hydrochloride in CT colonography and in these studies no differences were detected. In chapter 7 we describe a comparison of the distension, pain and burden within a large population-based screening trial in the area of Amsterdam and Rotterdam, comparing the participation, yield and burden of colonoscopy and CT colonography screening. Hyoscine butylbromide resulted in significantly more adequately distended colon, mainly caused by better distension of the sigmoid. Furthermore we observed that in the group receiving hyoscine butylbromide, lower burden scores were given for colonic insufflation, changing table positions and the entire procedure. No significant differences were found in the pain experienced or side effects. However, the type of side effects was different in both groups. For hyoscine butylbromide the most common side effect was a dry mouth (15%) and for glucagon hydrochloride the most common side effect was...
nausea (13%). The difference in type of side effects may explain the difference in burden between the groups. The pain was similar in both groups and is therefore no explanation for this difference. Because of superior bowel distension and burden scores, hyoscine butylbromide is the preferred spasmolytic. A randomised placebo-controlled trial could answer the question whether glucagon hydrochloride is beneficial for distension and burden compared to the use of no spasmolytic.

Finally we strived to reduce discomfort of the bowel preparation that is required for CT colonography. Together with the colonic insufflation, the bowel preparation is the most burdensome aspect of this technique. Although preparations used nowadays are often moderately purgative, we would prefer to obviate the need for a preparation. With CT colonography, colorectal polyps and cancers are visible within the stool by using stool/fluid tagging, creating enough contrast between bowel content and polyps. Intravenous contrast medium is administered to detect (liver-) metastases and – as it does not improve intracolonic visualisation – not for intracolonic lesion detection. However, dual-energy is a technique which allows better detection of iodine and post-processing allows construction of ‘iodine-only’ images, the so called ‘iodine maps’ [13, 14]. Possibly with dual-energy CT intracolonic lesions may be detected because of improved conspicuity of lesion enhancement by intravenous contrast medium. This might open the way to perform CT without bowel preparation or insufflation for colorectal cancer detection, which is the primary target in frail and elderly patients. Further, visibility of cancers without bowel preparation or insufflation may indicate that contrast-enhanced dual-energy CT colonography may be feasible for detection of both colorectal polyps as well.

In chapter 8 we assessed the feasibility of colorectal cancer detection using contrast-enhanced dual-energy CT with iodine mapping and without further preparation. We included 21 patients with proven or highly suspected for colorectal cancer and scheduled for a pre-operative abdominal CT scan. Patients were scanned with intravenous contrast medium on a dual-energy CT system without use of oral bowel preparation or colonic insufflation. For post-processing, we first estimated the parameters needed to distinguish stool from the colonic lumen. Images were subsequently scored for image quality, lesion detection without and with knowledge of the reference standard. All cancers were visible on the iodine maps. Sensitivity during the blinded read was 90% without and 96.7% with iodine maps. Median carcinoma enhancement was 29.9 Hounsfield units. Two large benign lesions were
visible on the iodine map, lesions of 15 mm and smaller were not visible. In our high prevalence population the sensitivity for colorectal cancer was high with the dual-energy technique with intravenous contrast medium but without bowel preparation or insufflation regardless of using iodine maps or not.

Our patient-friendly strategy should be further studied in a low-prevalence population. Because our study was too small to stratify for different size categories, it is important for future studies to evaluate the detection of cancers with different sizes. Future studies should also consider a larger training set for the use of iodine maps as there may well be a learning curve for interpretation of these maps. Iodine maps have the potential to help for the detection of colorectal cancers, although in our study we did not detect a significant advantage of reading the iodine map in addition to weighted average images only. An appropriately powered study should be performed to test whether reading the iodine maps in addition to weighted average images can improve diagnostic accuracy. In our study the largest visible polyp measured 25 mm. An opportunity to allow for detection of smaller polyps and further improve carcinoma detection may be the use of colonic insufflation with dual-energy CT colonography, although for frail and elderly patients the burden caused by colonic insufflation is undesirable. Finally, we observed artefacts created by dense stool even after an optimisation step to differentiate dense stool from bowel wall. These artefacts could simulate enhancing lesion and also could hinder identification of true enhancing lesion. Possibly mild stool softening may prevent these artefacts and this need to be studied.

Apart from attempts to obviate the CT colonography bowel preparation, attempts have been made to reduce the catharsis of the preparation. Evaluating the two-dimensional images is possible with just a small amount of ionic iodine, such as meglumine ioxithalamate [15]. For optimal evaluation, however, use of both two-dimensional and three-dimensional images is advisable [16, 17]. Three-dimensional visualisation of lesions covered by tagged bowel content is possible using electronic cleansing (i.e. electronic removal of the colonic residue). However, reduced bowel preparations cause more heterogeneous tagging, leading to cleansing artefacts that preclude three-dimensional evaluation of CT colonography. We therefore attempted to develop a cleansing algorithm able to handle this minimally prepared examination, and thereby allow three-dimensional visualisation. First we developed and tested a new cleansing algorithm, which we describe in chapter 9. For this algorithm a principal curvature flow algorithm was adapted to remove poorly tagged
faecal matter. Additionally, a pattern recognition based approach was taken to reconstruct eventual errors, such as erroneous removal of protrusions on the bowel wall. We tested the performance in two parts: First two observers evaluated 40 CT colonographies with a 24-hour minimal bowel preparation in three-dimensional and two-dimensional manner. The observers also rated their confidence and noted the reporting time. Secondly all polyps in the dataset were evaluated for their conspicuity. In this part, polyps surrounded by air were left uncleansed and cleansing was used for polyps surrounded by stool. The sensitivity for lesions measuring 6 mm or larger was better during the three-dimensional evaluation, but no difference between two-dimensional and three-dimensional evaluation was found for lesions measuring 10 mm or larger. Three-dimensional reading was associated with longer times and lower reader confidence. Polyp conspicuity was not different between polyps surrounded by air without cleansing, compared with polyp surrounded by tagged material after cleansing.

This study shows that high polyp sensitivity is achievable with three-dimensional evaluation in the 24-hour minimally prepared CT colonographies using our newly developed cleansing algorithm. Previously, three-dimensional evaluation was not possible on minimally prepared scans because of severe cleansing artefacts. There may still be opportunity for some improvement, for example in finding the optimal balance in the number of iterations of the algorithm or the cut-off values to distinguish contrast medium from polyps. However very low-density stool adjacent to the bowel wall cannot be removed even after optimisation. Further research is required to test our algorithm with larger number of patients and efforts should be made to improve reader confidence and shorten three-dimensional evaluation times. Finally, this algorithm should be tested on datasets not used for optimising the algorithm, which will be even more challenging than the dataset used in our study.
Summary, conclusions and implications

Conclusions

After training radiographers to triage CT colonography for extracolonic findings, accuracy is insufficient to consider their involvement in screening CT colonography.

Radiation dose in 2011 was 7.6 mSv for daily practice and 4.4 mSv for screening protocols and radiation dose had not reduced since 2007. Further dose reduction is desired to improve the benefit-risk ratio, especially for screening.

A single low-dose intravenous alfentanil bolus provides a clinically relevant reduction of maximum insufflation pain during colonic insufflation for CT colonography and also reduces the pain and burden of the total CT colonography procedure. Alfentanil may therefore improve the acceptance of CT colonography, especially in patients with a low pain threshold.

Hyoscine butylbromide is the preferred spasmolytic over glucagon hydrochloride because it results in a significantly better distension, lower burden scores and lower costs and its milder side effects.

Dual-energy CT with intravenous contrast medium en without bowel preparation or insufflation is feasible for colorectal cancer detection, although iodine maps did not improve the detection significantly and results need to be confirmed in a low-prevalence population.

With our newly developed cleansing algorithm, a three-dimensional primary read seems possible in 24-hour minimally bowel prepped CT colonography with good sensitivity for polyps of 6 mm and larger. However, reading time and confidence are in favour of two-dimensional primary read in these data.
References