CT colonography in faecal occult blood test positives
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Summary of findings and implications
SUMMARY OF FINDINGS AND IMPLICATIONS

In this thesis several aspects of CT colonography have been discussed. All cohort studies reported in this thesis have included patients with a positive faecal occult blood test (FOBT). In these patients different minimal bowel preparations with iodine contrast agent were tested. We evaluated the accuracy of polyp detection and triage with CT colonography, assessed the learning curve of novice readers and different viewing methods, and evaluated radiation dose and matching of polyps by expert readers.

When the bowel preparation for a colonic examination is very burdensome, patient compliance for the ingestion of the preparation might be reduced. An advantage of CT colonography compared to colonoscopy is that cathartic agents are not necessary; a contrast agent that ‘tags’ the faeces is sufficient. One then needs to find a balance between patient burden and image quality, one that is adequate and leads to an optimal polyp detection. Cathartic agents will cause a liquid consistency of the faeces and/or will reduce the amount of faeces in the colon. A tagging agent mixes with the residual faeces, facilitating differentiation between the colon wall, polyps and faeces. An iodine contrast agent is often hyperosmotic and can result in diarrhoea just like the cathartic preparations. This makes it necessary to assess the patient burden for this preparation.

In the study reported in chapter 2 a one-day and a two-day preparation scheme with an iodine faecal tagging agent (meeglumine ioxithalamate, 300 mg I/ml) were compared in 100 patients. We found that when using a one-day preparation consisting of four times 50 ml of contrast agent and a low-fibre diet, the patient burden from diarrhoea was lower than when using the two-day preparation, while image quality remained excellent. The density of the tagged faecal residues was high and comparable in both preparation groups and also the homogeneity did not differ between both groups. When results of polyp detection in both preparation groups were compared we found no significant differences. The conclusion of this study was that a one-day preparation is preferred over a two-day preparation.

In studies that use tagging only bowel preparations often a low-fibre or low-residue diet is prescribed. The hypothesis is that fibres are not digested and cause an inhomogeneous mixing with the oral contrast agent which results in untagged stool particles. Yet no study had shown that a specific diet is necessary for an optimal tagging. In chapter 3 a study is described that compared 2 groups of 25 patients; one group used a tagging only preparation with a low-fibre diet, while the other group used the same tagging preparation but without a diet before the CT colonography. In the second group we found more untagged pieces of stool and a trend towards a decreased tagging quality. Because of these reasons, the number of false positive findings can increase, and it can possibly affect the sensitivity for polyp detection. No significant differences in sensitivity between groups were found, but this was probably due to the relatively low number of patients per group.
Our findings in this study suggest that a low-fibre diet is necessary to optimize image quality in a tagging-only iodine bowel preparation.

In chapter 2 we showed that a one-day preparation with four times a 50 ml dose of iodine contrast agent resulted in an excellent tagging quality. Subsequently we investigated if a lower amount of iodine contrast agent would also be sufficient for optimal tagging while further decreasing patient burden. In the study reported in chapter 4 we compared three groups of 15 patients who received different doses of iodine contrast; group 1 received three times a 50 ml dose of iodine, group 2 received four times a 25 ml dose and group 3 received three times a 25 ml dose. We found that group 1 had the best tagging quality; in group 2 and 3 more untagged stool pieces and more adherent faeces was found. The homogeneity and homogeneity ratio (=homogeneity/density) were higher in group 2 and 3, resulting in a decreased tagging quality. Three times a 50 ml iodine dose was thus considered the best preparation, despite the higher patient burden.

Overall, we showed in chapter 2 to 4 that an oral iodine contrast agent ingested the day before the examination can give an excellent image quality with a significant decrease in patient burden, compared to the cathartic preparation of the colonoscopy. When the dose of this iodine contrast agent is lowered from 350 ml to 150 ml the image quality decreases, but in most patients the colon can still be evaluated properly. A problem is that, when using only 75 ml, in some colonic segments the faeces is not homogenously tagged and untagged stool particles remain. The addition of barium may improve the image quality, as barium tags the solid components of the faeces. We did not test the combination of an iodine and barium preparation, as has been used in some other studies, because we wanted to keep the instructions to the patients as simple as possible. Another option to improve the image quality is to use a cleansing algorithm that subtracts the (inhomogenously) tagged stool. The problem is that insufficiently tagged faecal residues are not subtracted by the cleansing algorithms that are currently available and visibility on the colon wall is hampered, especially at 3D views. With the development of improved cleansing algorithms, even less extensive bowel preparations could be used, leading to a decrease in patient burden while maintaining image readability.

Screening for colorectal carcinoma can reduce the mortality from colorectal cancer. Several screening methods exist. The most simple and least expensive test shown to reduce the mortality of colorectal carcinoma is the faecal occult blood test (FOBT). A disadvantage of this test is that it has a relatively low sensitivity and a low positive predictive value resulting in a large number of false positives. These false positive patients will receive a colonoscopy without any benefit. One option to reduce the number of unnecessary colonoscopies is to use CT colonography as a triage test after a positive FOBT, in an effort to select only those patients that have relevant colonic lesions. This strategy has been evaluated in chapter 5. We found that CT colonography is unlikely to be an efficient triage technique in a first round of FOBT screening. Reasonably high positive predictive values but relatively low negative predictive values were obtained. The burden from the CT colonography was rated as less than that of the colonoscopy. Due to the high lesion prevalence in FOBT positive patients, a high number of patients would have...
to undergo two examinations – both CT colonography and colonoscopy – if CT colonography was to be used as a triage technique. We conclude that CT colonography cannot be used efficiently as a triage technique in this first round FOBT population screening.

An explanation for the low negative predictive value of CT colonography is that the effectiveness of triage has to be evaluated based on size. As the goal of screening has been defined as the detection of cancer and large adenomatous polyps, we used a lesion size cut-off at CT colonography to decide whether or not to refer patients for colonoscopy. Only patients with at least one lesion of a certain size - 10 mm, or 6 mm or larger - were considered as CT colonography positives. When the size of the lesion measured at CT colonography was below this cut-off, say 5 mm, the patient was considered a CT colonography negative. It is possible that in this case the same lesion, when found at colonoscopy, would measure 6 mm. If so, the patient would have been classified as a false negative for CT colonography. If the method of polyp matching had been used to determine the accuracy (thus allowing a certain difference in size between CT colonography and colonoscopy), this same patient would be considered a true positive for CT colonography.

Another important reason for the low negative predictive value was that the number of FOBT positive patients with relevant lesions was very high; half of the patients had at least one lesion of 10 mm and larger. Consequently a relatively small number of true negative patients remained which resulted in a lower negative predictive value than would have been in a population with a lower lesion prevalence. Because of these reasons CT colonography does not seem useful in a first round FOBT population screening. But in second or third rounds where the lesion prevalence is possibly lower, CT colonography might become more useful as a triage test. To investigate this, future research should be performed.

In the study described in chapter 6 the detection of advanced neoplasia with CT colonography in an FOBT positive population was evaluated. In this study we used the method of matching polyps between CT colonography and colonoscopy to estimate sensitivity and specificity. We found that CT colonography has a high diagnostic accuracy for the detection of colorectal neoplasia in an FOBT positive screening population. Even with the use of a limited bowel preparation, the sensitivity of CT colonography in the detection of large adenomas and carcinomas was similar to that of colonoscopy. Furthermore we found that double reading and additional 3D reading increased the sensitivity of CT colonography. Although CT colonography should not be used as a triage test in a first round FOBT positive population, it could be used in FOBT positive patients that cannot or are not willing to undergo colonoscopy. Our results on the sensitivity and specificity for detection of colorectal carcinomas and adenomas equal that of studies that evaluated CT colonography in screening and in symptomatic patients.

When CT colonography is used for screening purposes the risks of complications should be kept at a minimum. One of the risks associated with CT colonography is the development
of radiation induced cancer. A higher effective radiation dose will increase the mortality from radiation induced cancer. It is therefore important to minimize the radiation dose as much as possible, although it is still unclear what the exact risks of radiation are. Not only screening participants will benefit from a lower radiation dose, but also patients receiving CT colonography examinations in daily practice. Chapter 7 presents a dose evaluation study among all research institutions with publications on CT colonography between January 2004 and January 2007. We found that radiation doses of scan-protocols used for screening (median dose 5.7 mSv) were significantly lower than that of daily practice protocols (medium dose 9.1 mSv). Although the median effective doses were quite low, the range of different doses among institutions was very wide (range 2.8-22.0 mSv). Some institutions used an effective dose ten times higher then the dose in other institutions. This suggests that awareness of the possibility to decrease the effective dose should be extended among institutions that perform CT colonography. Even very low doses, e.g. 2 to 3 mSv, can be sufficient for an optimal visualisation of the colon and colonic polyps. It would be interesting to investigate in the next few years whether the effective doses of CT colonography have decreased further in these institutes.

In previous studies it has been shown that novice CT colonography readers have a lower sensitivity and specificity in polyp detection than experienced readers. Some CT colonography training studies have been performed but after 100 examinations readers were still not trained well enough to reach an accuracy identical to that of experienced readers. Up till now it remained unclear how many cases should be practiced to obtain a sufficient sensitivity and specificity. We performed a CT colonography learning curve study among radiographers and physicians using 200 CT colonography datasets with colonoscopic verification in chapter 8. We found that after an average number of 164 cases the novice readers were capable to read a CT colonography with a high sensitivity for detection of lesions of 6 mm and larger. Three of nine readers however did not reach a sufficient sensitivity after 200 cases. All novice readers, except one, had an average specificity higher than 80% for lesions 6 mm and larger, and no learning in specificity was observed during the training program. From these results we can conclude that most novice readers will reach an adequate level of polyp detection within 175 CT colonography training cases. When the desired level is not reached after this number of cases, additional training will be necessary. Because the number of cases in our study was limited to 200, we do not how many cases these readers will additionally need to practice to reach a level of sufficient polyp detection. It is also possible that these readers might even not be able to reach this level at all. Furthermore we evaluated only one training program with a certain prevalence of lesions. A training program with, for example, a higher lesion prevalence or a more extensive pitfalls training might result in different outcomes.

Specialized software for reading CT colonography exists that can visualize the colon in a three-dimensional view (3D view). Two reading strategies for reading a CT colonography are available: a primary 3D read with a 2D problem solving or a primary 2D read with 3D problem solving. An automatic subtraction of the tagged faeces can be done by specific ‘cleansing’ software so that at the 3D images faecal material cannot obscure polyps. We investigated which of the two reading paradigms, primary 2D or primary cleansed 3D,
resulted in the best outcomes for novice and experienced readers (Chapter 9). We found that for experienced readers there was no difference between 2D or 3D reading. In contrast, novice readers had a significantly better sensitivity with 3D reading compared to 2D reading. There were no significant differences in specificity.

A likely explanation for a better 3D detection of lesions is increased lesion conspicuity. This does not seem to affect experienced readers however. One advantage of 2D reading compared to 3D reading is that reading times are shorter both for inexperienced and experienced readers. Therefore, in large screening cohorts, the 2D reading paradigm can be more cost-effective. When a 2D read is combined with a secondary computer aided detection (CAD) read, sensitivity will probably increase, but so will reading times, to some extent. In our study the added value of a CAD system for 2D and 3D reading was not tested because the CAD algorithm generated too many false positives in the 3D cleansed images because of artefacts. When CAD systems are optimized for inhomogenous tagged stool or insufficiently cleansed examinations, their added value in a 2D and cleansed 3D paradigm should be tested. If so, differences with novice readers in reading 2D versus 3D may decrease. Further developments are mandatory before using CAD and cleansing algorithms in (very) low dose CT-colonography.

For calculating the sensitivity and specificity in CT colonography research, polyps found at CT colonography have to be compared with the polyps found at colonoscopy. This is often referred to as the ‘matching’ procedure. An experienced CT colonography reader judges if the polyp found at CT colonography is the same polyp as the polyp found at colonoscopy. Three aspects of the polyps are then taken into account: their size, the segmental location and the morphology of the polyps. When this matching procedure is performed differently by different readers, this will have influence on the outcomes of accuracy of studies. In chapter 10, we investigated how eight highly experienced readers performed the matching procedure in a set of 27 cases. We found that there were differences in the process of matching, especially for the smaller polyps. Furthermore we found that the matching criteria that readers used were not identical. This made us to develop uniform matching criteria. In cases that do not fit these standard criteria, a second expert reader has to be invited to perform a consensus read. Despite these small differences in matching, readers in our study agreed to a considerable extent when matching cases. The number of readers in this study was quite large, but the number of CT colonography cases was too low to draw statistically significant conclusions. To investigate if differences in matching result in significantly different estimates of sensitivity and specificity, a large unselected dataset should be presented to several readers. In that case the matching criteria, presented in our study, could be used by the readers and differences could be calculated.
CONCLUSIONS

1. Based on our studies on bowel preparation we conclude that CT colonography can be performed with a minimal bowel preparation using an iodine contrast agent only. The dose of the iodine contrast agent used (meeglumine ioxithalamate), can be reduced to three times 50 ml. This benefits the patient burden and eventually will also improve the patient compliance for ingesting the preparation. A low-fibre diet in combination with the iodine contrast agent is necessary to remain an optimal tagging quality.

2. CT colonography has a high accuracy, which equals that of colonoscopy in detecting relevant lesions in FOBT positive screening participants. However, when CT colonography is used as a triage method to select only those patients that need colonoscopy, it does not seem an efficient strategy in a first round of FOBT population screening. Because of the high lesion prevalence, too many patients would have to undergo two examinations: a CT colonography followed by a colonoscopy.

3. The median radiation dose used for CT colonography imaging among institutions all over the world is relatively low, especially when CT colonography is used for screening purposes. The range in the effective radiation dose used is however very wide in the same institutions. We should increase the awareness of radiation induced risks and of the possibilities to reduce the effective dose using the newest scanners available.

4. Training is necessary for reading CT colonography. After 175 cases most readers are able to reach a sensitivity that equals that of experienced readers.

5. When novice readers interpret CT colonography images, it is preferable that they use a 3D reading paradigm with cleansed images instead of a 2D reading paradigm. Experienced readers can either use 2D reading or 3D reading.

6. When matching CT colonography and colonoscopy polyps, standard matching criteria should be used. In cases that do not fit these standard criteria, a second expert reader has to be invited to perform a consensus read.