CT colonography as surveillance technique for patients at increased risk for colorectal cancer
Jensch, S.

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Summary

This thesis addresses different aspects of CT colonography that are important for the potential implementation of this technique for surveillance of patients at increased-risk for colorectal cancer. In the first part of the thesis (chapter 2 through 4) image quality, diagnostic value and patient acceptance of CT colonography with a limited bowel preparation was investigated. In the next chapters, the diagnostic performance of radiographers (chapter 5) and of a computer aided detection algorithm was evaluated (chapter 6). Finally, the last study (chapter 7) presents an overview of the radiation doses used for CT colonography.

In chapter 2 our objective was to determine the optimal dosage of laxatives for CT colonography with limited bowel preparation with regard to both image quality and patient acceptance. Therefore, we compared four regimens with increasing levels of mild catharsis, using bisacodyl and magnesium citrate as laxative agents in forty patients. Our results showed good to excellent image readability of CT colonography examinations (37/40) regardless of the preparation used. Increasing the amount of laxatives did not lead to a higher attenuation of tagging or to more homogeneous tagging, and subjective image quality did not show significant improvement. A higher dosage of laxatives was however associated with a higher burden of diarrhoea and a higher overall burden of the bowel preparation. Our results are important because a mild bowel preparation with low catharsis will probably increase patient willingness to participate in a surveillance or screening program.

Chapter 3 addressed the diagnostic accuracy of CT colonography with limited bowel preparation. For this purpose, sensitivity and specificity for the depiction of colonic polyps was prospectively evaluated in 168 consecutive increased-risk patients, using colonoscopy as the reference standard. Two readers (a radiologist and a research fellow) evaluated all cases. Consensus, e.g. a double-read strategy, was performed if the reviewers were not in agreement on a lesion. Segmental unblinding was applied during colonoscopy. This allowed a second-look when CT colonography and colonoscopy results were discrepant for a given segment. In this way, the reference standard was enhanced. We found a sensitivity for CT colonography with limited bowel preparation of 76% and 82% for the identification of patients with polyps ≥6 mm and those with polyps ≥10 mm, respectively. Specificity was respectively 79% and 97% for these size-thresholds. Double reading improved reader performance.
slightly, but not significantly. Detection rates were higher for colonoscopy (91% for ≥6mm and 88% for ≥10 mm), than those at CT colonography, but this difference was not statistically significant. Our results concur with other studies that flat lesions are relatively frequent in a surveillance population, in our study 24%. This explains the somewhat lower sensitivity for CT colonography because the observers missed 50% of the lesions with a flat morphology.

In chapter 4 patient experience and preference was assessed for CT colonography with limited bowel preparation in comparison to full-preparation colonoscopy. A five week follow-up study was conducted as adverse reactions to tests tend to temper in time and the attitude at that time point will better reflect the attitude towards future screening. Participants were asked to fill out questionnaires with regard to experience of the preparation and procedure. Furthermore, participants preference for CT colonography or optical colonoscopy as future examination of choice was assessed. Preference was based on the presumption that 20% of CT colonography examinations would result in an optical colonoscopy referral for polyp removal. Possible associations between preference outcome and experience parameters were determined with logistic regression. With regard to the results, 94% of participants experienced diarrhoea during the CT colonography preparation. This side-effect was perceived as severely or extremely burdensome by 29% of participants. To optimize patient acceptance, further efforts should be made to reduce this side-effect. Nonetheless, the overall burden was significantly lower for the CT colonography preparation than for the colonoscopy preparation. Furthermore, participants experienced significantly more pain and discomfort during the colonoscopy procedure. After 5 weeks, the majority (69%) of participants preferred CT colonography as future examination. Determinants of preference were a burdensome preparation and pain during the procedure. The fact that CT colonography with a limited bowel preparation was significantly better tolerated suggests that this technique could be of value to increase participation rates in surveillance or screening programs for colorectal cancer.

A double-read strategy might improve sensitivity of CT colonography. This approach however is time-consuming and expensive, and may therefore not be feasible in every radiology department. The deployment of trained paramedical personnel as second readers might be an attractive alternative. Preliminary reports have showed promising results with regard to polyp detection for non-radiologists. Therefore in
**Summary**

**Chapter 5**, the performance characteristics of radiographers were studied in comparison to those of radiologists in 150 cathartic prepared patients. Furthermore, we hypothesized that combining detection rates would lead to a substantial increase in sensitivity. Our data showed that the detection rates for lesions 10 mm and larger were identical for radiographers and radiologists (sensitivity was 78% for both). Specificity was respectively 91% and 94% for this size-threshold. Combining detection rates for this size-threshold did not lead to an increased sensitivity because all observers detected and missed the presence of polyps in the same patients. Therefore, we conclude that radiographers can be considered as adequate reviewers in CT colonography. However, in this thesis no added value with regard to sensitivity for significant lesions could be determined if the detection rates of radiographers were combined with those of radiologists.

Another possible double-reading strategy is the use of a computer aided detection (CAD) algorithm. Promising results in reducing false-negative findings for less experienced observers have been published. However, the potential increase in accuracy for experienced observers is still controversial. Furthermore, to date performance of CAD was investigated in selected and polyp-enriched populations but not in a daily-practice clinical situation. Therefore, in **Chapter 6** we determined whether CAD in a second read paradigm could improve the performance characteristics of experienced readers. Sensitivity of CT colonography without CAD for patients with lesions ≥6 mm and ≥10 mm was respectively 80% and 64%. With CAD one additional patient with a lesion ≥6 mm and two with a lesion ≥10 mm were detected, resulting in a sensitivity of 82% and 72%, respectively. This small increase was not significant. Specificity with and without CAD remained (nearly) unchanged. Thus, although CT colonography with CAD detected a few more patients than CTC without CAD, it had no statistically significant positive influence on the performance of experienced readers in a population at increased-risk for colorectal cancer.

A drawback of CT colonography is the fact that patients are exposed to ionizing radiation. Because no stringent data on the effective doses associated with CT colonography was available, the potential radiation risks could not be estimated. In **Chapter 7** an inventory of scan protocols for CT colonography among research institutions (survey) was performed and effective doses were estimated. In addition, we investigated trends over time for the effective dose and various scan parameters. Twenty-eight of 36 contacted institutions provided their scan protocol. We estimated
a median effective dose for CT colonography of 10.2 mSv in 2004. If this dose is applied to a population aged 50, this may result in one fatal cancer in 4,000 individuals. A considerable variance in technique and radiation dose between institutions was observed. The use of multislice scanners increased between 1996 and 2004 but the median effective dose remained approximately constant in this time-period. This was mainly caused by the use of lower tube current (mAs) settings. Further studies on reducing the effective dose for CT colonography are warranted because a reduction of dose will result in a proportional reduction of risk.

**Conclusions**

Chapter 2. CT colonography with barium and an iodinated contrast medium as tagging agents, requires minimal amounts of laxatives.

Chapter 3. CT colonography with limited bowel preparation has comparable accuracy to optical colonoscopy but detection of flat lesions remains a concern.

Chapter 4. CT colonography with a limited bowel preparation is significantly better tolerated than optical colonoscopy with regard to preparation and procedure.

Chapter 5. Radiographers perform equally to radiologists in the detection of polyps but combining radiologists with radiographers does not improve CT colonography performance.

Chapter 6. CT colonography with CAD does not significantly increase sensitivity of experienced observers.

Chapter 7. In 2004, the effective dose for a complete (supine and prone) CT colonography was approximately 10.2 mSv.

**Implications and future research**

This thesis demonstrates that CT colonography with limited bowel preparation has the potential to be implemented in surveillance programs because it is an accurate, non-invasive and patient-friendly technique. This is important because a patient-friendly alternative to colonoscopy might increase compliance with surveillance
guidelines. However, several important limitations regarding accuracy, patient acceptance and radiation should first be resolved.

With regard to accuracy; a relatively high number of CT colonographic occult (not-visible in retrospect) or difficult-to-detect lesions are present in a surveillance population. These concern flat lesions that may be inherently more frequent in increased-risk patients or might have developed from flat polyp remnants after prior (incomplete) polypectomy. Prior colonoscopy might also result in the detection and removal of conspicuous polyps (regardless of morphology) while more difficult-to-detect lesions are not detected and remain in situ. Some investigators have therefore proposed that the use of CT colonography in surveillance populations has to be considered with caution, especially in patients who underwent polypectomy. Further research should concern the nature of these occult and difficult-to-detect lesions and focus on how to improve detection rates. Strategies on how to increase accuracy are twofold; enhance reader performance and improve technical aspects. Individual reader performance can be enhanced by training and experience. It is well known that CT colonography is a difficult exam to master with a relatively long learning curve. Extensive training and feedback should therefore be provided to radiologists that perform CT colonography. As was hypothesized in this thesis, reader performance might be improved if two observers read the examination instead of one. Our data demonstrated a slight increase in the detection of polyps (combining radiologists with radiologists, radiographers or a CAD algorithm), but this was not significant. Further research in a larger cohort is needed to establish the efficacy of a double-reading strategy. Focus should probably be on CAD as a second reader because CAD is in potential the most time-efficient and cost-effective approach. With regard to the technical aspects, newer CT scanners are able to scan with thinner (sub-millimeter) slices. This is expected to result in better conspicuity for difficult-to-detect lesions, in particular flat lesions. The use of intravenous contrast agents might improve detection rates because flat lesions may enhance and become visible. Furthermore, the development of electronic cleansing software (e.g. electronically removing tagged faecal material from the colon lumen) might help improving accuracy. With electronic cleansing, the complete colon surface is visible for evaluation as feces is removed, observers will not be distracted by tagged feces, a 3-dimensional fly-through review method can be applied and a CAD algorithm might be more efficient.
With regard to patient acceptance; the extent of diarrhea associated with the limited bowel preparation should be further reduced. In our study, almost all participants (95%) experienced diarrhea as a result of the preparation and the occurrence of this side-effect was considered very burdensome by patients. Reducing the extent of diarrhea can be accomplished by decreasing the dose of laxatives or by altering the use of contrast agents. As was demonstrated in this thesis, decreasing the dose of laxatives leads to a significantly better patient tolerance. Another approach that might work is to change the amount or type of contrast agents for fecal tagging. Three types are available: ionic and non-ionic iodinated contrast and barium. Ionic iodinated contrast has a strong laxative side-effect and the need to add laxatives to the bowel preparation is probably not necessary. In fact, we no longer add any form of laxatives to the preparation with ionic contrast, and we believe this has not impaired the image quality of the examination. We have also decreased the dosage of the ionic contrast with promising results. Finally, to reduce diarrhea contrast media can be used that have none or only a small laxative side-effect. In that case, barium or non-ionic contrast agents are available. Barium is traditionally used for solid stool tagging and often administered in combination with iodinated contrast for adequate fluid tagging. When Barium or non-ionic contrast media are used, the need to add some form of laxatives is probably still required for homogeneous tagging. Focus should be on what combination and dosage of laxatives and contrast agents are optimal for a limited bowel preparation.

With regard to radiation; further efforts should be made to lower the dose for CT colonography. In 2004 we reported a median effective dose of 10.2 mSv. As was discussed previously, it is estimated that this amount of radiation will induce 1 fatal cancer in 4000 patients. If patients are scanned more than once (as with surveillance guidelines), the risk will increase proportionally. At present (2009), the use of dose reduction (dose modulation or automated current selection) and multi-detector CT scanners enable a more efficient use of dose. Therefore, updated scan protocols are needed to determine current effective doses for CT colonography. Furthermore in recent years low-dose techniques for CT colonography have been widely investigated. Several studies have reported that scanning with low tube currents (up to 10 mAs) for CT colonography is feasible. This means that effective doses for CT colonography can be in the order of 1 to 2 mSv. Such low amount of dose is widely considered acceptable for surveillance or screening.
We conclude that CT colonography is an accurate, non-invasive and patient friendly technique for patients at increased-risk for colorectal cancer. An important advantage is that patients can be prepared with a mild bowel preparation. However the high prevalence of flat and “difficult-to-detect” pathology in a surveillance population is of much concern and most likely not easily resolved. Therefore, at present we believe it is best to limit the use of CT colonography for surveillance only to patients who can or will not undergo optical colonoscopy.