Magnetic resonance imaging in Crohn's disease
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Citation for published version (APA):

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Summary, general discussion and conclusions
SUMMARY

Patients with Crohn’s disease (CD) need frequent re-evaluation of disease status, as CD is a chronic relapsing and remitting disease. With ileocolonoscopy the mucosal surface of the colon and terminal ileum can be evaluated, while with the recently introduced double-balloon endoscopy the entire small bowel can be evaluated. The burden of the extensive bowel preparation, the necessity of conscious sedation and the pain and discomfort experienced during the procedure are disadvantages of this technique. Also, in CD the bowel can be inflamed to such an extent that endoscopic evaluation is not or only partly possible (e.g. when a stenosis is present).

Video Capsule Endoscopy (VCE) is another recently introduced technique with which the mucosal surface of the small bowel can be evaluated. Disadvantages of VCE are the fact that circumferential inspection is not always performed, biopsy and therapeutic interventions are not possible and there is a risk of capsule retention in patients with strictures, which are not uncommon in CD. Extensive bowel preparation is also often used for VCE.

With barium enteroclysis the mucosal surface of the small bowel can be depicted in detail, but disadvantages are the extensive bowel preparation needed and the ionizing radiation that is used during the examination. Endoscopy, VCE and barium enteroclysis focus on mucosal pathology and neither modality provides information on the transmural and extramural evaluation of CD.

Advances in Magnetic Resonance Imaging (MRI) have made it possible to evaluate the abdomen in CD patients in a non-invasive and patient-friendly manner and to evaluate both the transmural and extramural extent of disease. However, transition from the aforementioned techniques for evaluation of the gastrointestinal tract towards MRI can only take place if the accuracy remains unchanged.

The use of MRI for evaluation of CD of the colon and small bowel was the subject of the studies reported in the first part of this thesis.

The use of MRI for evaluation of perianal fistulizing CD was the subject of the second part of this thesis.

In recent years many studies have been performed investigating the diagnostic potential of ultrasonography (US), Magnetic Resonance Imaging (MRI), scintigraphy, and Computed Tomography scanning (CT). However, reported sensitivities and specificities vary widely between studies, from approaching the diagnostic capacity of ileocolonoscopy or small bowel barium examinations, to a considerable under- or overestimation of disease. Therefore, in chapter 2 results are reported of a meta-analysis we performed of prospective studies evaluating the accuracy of CT, US, MRI and scintigraphy for the diagnosis of Inflammatory Bowel Disease to determine accuracy estimates for the respective radiological imaging techniques. On a per-patient basis mean sensitivity and specificity estimates were high and the only significant difference was that scintigraphy had a significantly lower specificity.
than ultrasonography. Per bowel segment mean sensitivity estimates were lower, but specificity values remained high. CT proved to be slightly less sensitive and specific than scintigraphy and MRI, respectively.

While MRI is accurate in diagnosing active CD, the accuracy of MRI in staging disease activity is not clear yet. Therefore, we performed a meta-analysis of MRI studies to determine the accuracy of MRI in staging disease activity in CD of which results are described in chapter 3. Three disease stages were defined: remission, mild and frank disease. The accuracy rates of MRI per disease stage were calculated by means of a random-effects model. The accuracy of MRI for grading active disease was high; frank disease was correctly diagnosed in 86% of patients and mild disease in 65% of patients. Disease activity was overstaged on MRI in a large proportion of patients in remission, mostly as mild disease.

Although in literature the use of enteral contrast medium is mentioned as indispensable by most authors as collapsed bowel loops might hide or mimic disease, this is not an evidence-based observation as no studies have been performed to determine the value of enteral contrast medium. Chapter 4 focused on the value of enteral contrast medium installed via a nasojejunal tube. We determined the reliability of MRI of the small bowel using an enteroclysis technique for bowel filling as opposed to abstaining from using luminal contrast medium. To this end, baseline MRI scans acquired before infusion of contrast medium were compared with MRI images acquired when optimal bowel distension was achieved after contrast administration via a nasojejunal tube. The MR enteroclysis scans and the baseline MRI scans were independently evaluated by two observers who performed qualitative and morphological evaluation. Results of the two observers were compared and were also compared with scores of an expert reader. Interobserver agreement was higher on MR enteroclysis than on MRI for bowel wall thickness measurements as well as for the detection and grading of obstruction. For these items agreement with the expert reader was higher on MR enteroclysis than on MRI. The conclusion of our study was that the use of luminal contrast medium increases reliability for luminal findings in evaluation of the small bowel.

In chapter 5 we focused on the role of MR enterography as a patient-friendly and non-invasive technique to evaluate the abdomen in CD. Since literature regarding the value of MR in determining the degree of disease activity was limited, a study was performed in patients with known CD to determine the value of MRI for grading of disease activity. As the validity of a technique is dependent upon its accuracy and its precision, interobserver agreement was also determined for grading of disease activity. Two observers independently scored MR examinations. Ileocolonoscopy and the Crohn’s Disease Endoscopic Index of Disease Severity (CDEIS) were used as reference standard. This study demonstrates that radiological grading of disease severity showed moderate to good agreement with endoscopic grading and a moderate to strong correlation with
the CDEIS. Patients preferred MRI over ileocolonoscopy for their next examination since both the bowel preparation and the examination itself were considered less burdensome than ileocolonoscopy. An additional advantage of MRI was the fact that all bowel segments could be evaluated, including small bowel segments and bowel segments that were inaccessible at ileocolonoscopy. Also, with MRI extraintestinal pathology could be detected. Interobserver agreement for staging disease and for the rating of individual MR parameters was moderate to good.

Scanners with high field strength of 3.0 Tesla (as opposed to the clinically most common field strength of 1.5 Tesla) have become available for clinical practice only a few years ago. Theoretically, disease detection might be better at 3.0 Tesla than at 1.5 Tesla due to the higher Signal to Noise Ratio that can be used for better image quality or shortening of acquisition times. However, specific disadvantages of the higher field strength such as field inhomogeneity and increased sensitivity to artifacts could counterbalance these advantages. In chapter 6 we studied the accuracy of 3.0 Tesla MRI in grading disease activity in patients with known CD with a study design that was comparable to the study reported in chapter 5. We found agreement with endoscopic grading to be moderate to good, while no significant correlation was found between radiological grading and the CDEIS. Patients stated that they would prefer MRI over ileocolonoscopy for their next examination. Interobserver agreement with regard to grading disease activity was fair to moderate; for individual MR parameters (bowel wall thickness measurements and bowel wall enhancement) moderate to good correlations were seen.

Literature on the accuracy of MRI in diagnosing IBD in children is scarce. In chapter 7 results of our study in children suspected of IBD are reported. Results of MRI were compared with endoscopic, histopathological and small bowel radiological results, with regard to the diagnosis of IBD and the differentiation between Crohn’s disease and ulcerative colitis (UC). We also determined the agreement between MRE and endoscopic grading of disease severity and calculated interobserver reliability for individual MR parameters. In our study we have shown that the sensitivity of MRE for the diagnosis of IBD was moderate to good, ranging from 61 to 91%. Specificity was moderate to high, ranging from 60 to 100%. While CD was diagnosed correctly in a large proportion of patients, UC was not diagnosed accurately in most of the patients. MRE was more accurate than BE in diagnosing inflammation of the terminal ileum, compared with ileocolonoscopy. Disease activity was understaged in a large proportion of patients. Interobserver agreement for individual MRE parameters was fair to good.

Pathological enhancement of affected tissue is considered a very important criterion to indicate active CD. However, assessment of the degree of enhancement is done by visual evaluation of signal intensity, which renders this a relatively subjective parameter of disease activity. In chapter 8 we describe the results of a study we performed to determine whether
an objective and reproducible determination of pathological enhancement is feasible by calculating gadolinium-concentrations from T1 maps. Gadolinium-concentrations of affected bowel loops were compared with endoscopic and histopathological disease activity, the CDEIS, the Harvey-Bradshaw Index and C-reactive protein. The data from our feasibility study suggest that calculation of the Gadolinium-concentrations of affected bowel loops is possible. Mean Gadolinium-concentrations were higher in patients with frank disease than in patients with mild disease.

A large percentage of patients with Crohn’s disease will eventually develop perianal fistulizing disease. MRI has become the gold standard for anatomical evaluation of perianal fistulizing Crohn’s disease. In chapter 9 we describe an imaging approach for pelvic MRI in perianal fistulizing Crohn’s disease, illustrated by examples.

Besides anatomical evaluation determination of the degree of perianal disease activity is important, since the inflammatory aspect of perianal CD influences prognosis and therapeutic responses. No gold standard test exists yet for evaluation of perianal disease activity. In chapter 10 we have determined the clinical value and reliability of an MRI-based score of disease severity that was developed several years ago. MRI-scans were performed before and after treatment with infliximab remission induction therapy and MRI-scores were compared for responders and non-responders to therapy, as were results from the Perianal Disease Activity Index and the CRP. Interobserver agreement was determined for the individual items comprising the MRI score. Our results indicate that the MRI-based score is useful for the evaluation of response to treatment with infliximab remission induction therapy, resulting in improved identification of patients with persisting active inflammation after therapy than clinical disease indices. Interobserver agreement was fair or moderate for most items of the MRI-based score.

The MRI-based score of disease severity uses anatomical and inflammatory MRI parameters for disease assessment, based on static MR images. In chapter 11 the results of our study are described in which we have tried to determine disease severity by using a more physiological approach. We have used DCE-MRI to determine disease activity in perianal fistulizing CD and have compared DCE-MRI findings with clinical disease parameters to determine the usefulness of DCE-MRI. Our study demonstrates that DCE-MRI can be used to determine disease activity in perianal fistulizing CD as there is a significant correlation between the numbers of quickly enhancing pixels and clinical disease indices. In patients who needed medication changes or who developed new abscesses during follow-up significantly more quickly enhancing pixels were seen than in patients in whom no medication changes were necessary or who did not develop new abscesses.
CONCLUSIONS AND IMPLICATIONS

Results from this thesis show that MRI can be used to evaluate patients with CD as MRI (with oral administration of contrast medium) can be used to stage disease activity, both at 1.5 Tesla and at 3.0 Tesla. MRI also proved to be a patient-friendly technique compared with ileocolonoscopy. MRI could also be used to diagnose CD in patients suspected of IBD.

We have shown that the use of enteral contrast medium (by controlled infusion via a nasojejunal tube) improved precision of MRI, compared to MRI without contrast medium. While some authors prefer the controlled infusion of contrast medium by enteroclysis technique (MR enteroclysis) as the amount and speed of administration of contrast medium can be controlled, this technique is less patient friendly than oral administration of contrast medium due to the nasojejunal intubation. The use of a limited amount of ionizing radiation during intubation is another drawback. Oral administration of contrast medium is more patient-friendly and does not require the use of ionizing radiation. Oral administration is also more practical as the examination is only performed at the MRI suite. Thereby, the examination is faster as a standard imaging protocol is used, not influenced by the length of the filling phase as with enteroclysis. Studies comparing the two techniques are scarce, but the available data indicate that although the degree of bowel distension was greater with MR enteroclysis than with MR enterography, accuracy values did not show significant differences between techniques (1, 2).

Although bowel wall thickening and pathological bowel wall enhancement are important criteria for evaluation of active disease, it is still not clear how interpretation of these criteria should be done for staging of disease activity. This observation is supported by the moderate interobserver agreement values calculated for these MR parameters in our studies. It is very important to develop objective, standardized MR criteria for disease assessment to increase accuracy and reproducibility with regard to assessment of disease activity. A more objective parameter indicative of active disease might be the absolute Gadolinium-concentration of the affected bowel as shown in chapter 8. Future research should focus on the development and validation of objective, reproducible and quantifiable criteria for disease assessment.

Several other techniques are available for evaluation of the gastrointestinal tract. In recent years two techniques have become clinically available that can be used for evaluation of the entire small bowel, namely Video Capsule Endoscopy and Double Balloon Endoscopy. With these techniques the mucosal surface of the wall of the small bowel can be evaluated in detail. However, while the spatial resolution of MRI is not high enough to permit detailed information about the mucosal surface, with MRI transmural and extramural evaluation is possible. In this way, MRI certainly has an added value for the detection of abscesses or fistulas. The clinical implication of the fact that all bowel wall layers as well as the extraintestinal abdomen can be assessed with MRI is not clear yet as the information that MRI provides cannot be endoscopically verified. Comparison of MRI with macroscopic and
microscopic evaluation of all wall layers by surgery and histopathology might provide more insight in the possible merit of a comprehensive abdominal evaluation made possible with MRI.

Other techniques that have been shown to be able to detect active CD are ultrasonography, computed tomography and scintigraphy. However, their respective abilities to quantify disease severity have not been thoroughly investigated. Each technique also has its specific disadvantages. With scintigraphy it is difficult to detect extraintestinal complications, while it is a time-consuming and expensive technique, which is limitedly available and involves the use of ionizing radiation. Computed tomography (CT) is readily available and fast, but the considerable radiation dose associated with abdominal CT make this technique unsuitable for evaluation of the often young patients with CD, who will need frequent re-evaluation of disease (3). Ultrasonography is a relatively cheap, fast and patient-friendly procedure, but its use is limited by its operator dependency, its dependency on patient habitus (e.g. in adipose patients image quality can be poor, leading to an inconclusive examination) and the fact that not the entire gastrointestinal tract can be reliably visualized (e.g. bowel loops deep in the pelvis).

With the continuing improvements in soft-and hardware, the accuracy of MRI will probably increase so that MRI could possibly be used as a one-stop shop technique for the evaluation of the small bowel and colon as well as the extraintestinal abdomen in a non-invasive and patient-friendly manner.

MRI has already been recognized as the reference standard for perianal fistulizing CD. While anal endosonography (AES) could also be used for assessment of perianal disease with high accuracy, MRI is a more patient-friendly technique and the execution of the examination is not dependent upon operator experience as is AES. However, interobserver agreement for individual MRI parameters used for assessment of perianal fistulizing CD was only fair to moderate, even for experienced observers. This indicates the difficulty in evaluation of the perianal region with its complicated anatomical structures and also illustrates how complicated perianal fistulizing CD can be.

Pelvic MRI can be used for assessment of disease activity in perianal fistulizing CD; by using static MR images disease assessment can be performed using an MRI-based score. By using dynamic contrast-enhanced MRI extra information about disease activity is provided. Information from the dynamic scan might even be helpful in selecting a subpopulation of CD patients with perianal fistulas that should be monitored more closely for development of more extensive disease.

As pelvic MRI can be used for assessment of perianal disease activity as well as for anatomical evaluation, pelvic MRI could be used as a one-stop shop technique for comprehensive assessment of perianal fistulizing CD.

In conclusion, MRI provides the opportunity of evaluation of the abdomen in CD. For patients with known CD MRI can be used to stage disease activity and to diagnose trans- and extramural pathology. Development of objective criteria for assessment of
disease activity might further increase the accuracy of MRI. For diagnosis of IBD further improvements in accuracy and reproducibility of MRI should be awaited before considering implementation of MRI as the first-line technique for diagnosis. For patients with perianal fistulizing CD MRI can be used to evaluate the anatomical and inflammatory extent of perianal disease.

REFERENCES
