Crohn's disease, advances in MRI
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**Summary of findings/discussion**

The work described in this thesis focuses on new imaging techniques in the assessment of Crohn’s disease. The first part presents innovations in the imaging of luminal Crohn’s disease; the second part is about perianal fistulising Crohn’s disease.

Since several years sequences for scanning the abdomen at 3T have become available. In chapter 2 we presented an overview of MR imaging of the small and large bowel at 3T, including the several common artefacts, namely susceptibility artefacts, B1 artefacts and banding artefacts. We discussed the use of oral contrast agents and faecal tagging. The sequences that can be readily used on 3T scanners are single-shot fast spin echo sequences and 3D T1 weighted gradient echo sequences. Balanced steady state free precession sequences are less applicable at 3T, because of the banding artefact induced by the extreme sensitivity of this sequence to B0 inhomogeneity. Imaging indications include inflammatory bowel diseases and the detection of (precursors of) colorectal cancer. Finally we discussed the use of 3T versus 1.5T. Although theoretically it would be expected that the signal-to-noise ratio is twice as high at 3T, sequence restrictions related to the SAR and artefacts result in a lower gain in signal-to-noise ratio.

The problem that many different imaging features for MRI small bowel are currently in use for grading disease activity is addressed in chapter 3. We conducted an international questionnaire among expert radiologists to assess which features they considered important for grading disease activity. The features that were mentioned as most important for grading were the presence of an abscess, T1 enhancement, T1 stratification and bowel wall thickness. The assessment if a certain MRI feature was mandatory for grading was very diverse (from 4% of respondents for T2 stratification of bowel wall to 79% for bowel wall thickness). Also, in cases where the features were used for grading no consensus existed between radiologists on the implication of the feature (mild, moderate, severe, chronic or acute disease activity).

In chapter 4 we assessed the value of several MRI features of luminal disease activity against a pathology based reference standard, the acute inflammation score (AIS). MRI features were scored by three experienced abdominal radiologists. Bowel wall thickness correlated with AIS for all observers (observer 1: correlation 0.452, \( p = 0.004 \); observer 2: \( r = 0.409 \), \( p = 0.010 \);
Around 40 percent of patients with Crohn’s disease will develop perianal fistulising disease. For the monitoring of therapy or the guidance of surgery, imaging with either MRI or endoanal ultrasound is the current standard. In chapter 7 we describe an imaging approach for perianal fistulising Crohn’s disease with MRI or endoanal ultrasound. We focus on the anatomy and etiology and explain the classification systems of perianal fistulas (Parks classification and St. James University hospital MRI classification) and assess the clinical value of CT, fistulography, MRI and endoanal ultrasound in the assessment of perianal fistulas.

Grading of severity of disease activity is important in patients with Crohn’s disease to optimally determine the treatment strategy and response to treatment. Mild disease activity can be detected at colonoscopy as superficial ulcerations of the bowel wall. In chapter 5 we evaluated dynamic contrast enhanced (DCE)-MRI in patients with luminal Crohn’s disease with the emphasis on the mild ulcerative disease. We found correlations (with continuous parameters) or associations (with ordinal parameters) between segmental CDEIS and wall thickness ($r=0.418, p<0.001$), T2 signal intensity ($p<0.001$), subjective T1 enhancement ($p<0.001$) and maximum enhancement ($r=0.485, p<0.001$). In addition, maximum enhancement was significantly higher in segments with mild or severe ulcerative disease compared to normal mucosa (both $p<0.001$). At conventional sequences these ulcerations were not detected. Maximum enhancement also correlated with disease duration in diseased segments ($r=0.492, p=0.002$).

In chapter 6 we studied the use of (DCE-)MRI and abdominal ultrasound for the diagnosis of IBD in paediatric patients. To assess both the small and the large bowel, patients ingested 2x 400ml contrast medium. Because of burden, no rectal contrast medium was administered. Sensitivity and specificity were 55% and 100% for ultrasound, and 57% and 75-100% for MR entero- and colonography, respectively. Combined MRI and ultrasound had a sensitivity of 70-74% and a specificity of 80-100%. Cases of IBD that were false negative were either mild disease cases or rectal disease. The latter is difficult to assess with imaging because of its deep pelvic position or relative low disease activity that does not demonstrate any bowel wall changes. With the addition of a DCE-sequence sensitivity increased to 83-87% and specificity to 80-100%, though this was not significant. Ultrasound and MRI could only distinguish between Crohn’s disease and ulcerative colitis when terminal ileum lesions were found. Because of the low sensitivity ultrasound and MRI are not recommended as first line imaging technique for differentiating between Crohn’s disease and ulcerative colitis.
Conclusions and implications

Current use of MRI features for the assessment of Crohn’s disease.

Multiple features are currently used in clinical practice for the evaluation of Crohn’s disease activity such as: wall thickness, T1 wall enhancement and stratification and the presence of an abscess. Other features, for instance, T2 signal intensity/stratification, presence/enhancement of lymphnodes, comb sign are used by some radiologists while others do not assess that particular feature at all, which creates variations in evaluation of the same MR exam. Moreover, the features that are used by the majority of radiologists are prone to a high interobserver variability. The development of an international guideline on the evaluation of MR enterography or enteroclysis exams will partly solve this problem. Several scoring systems, such as the Magnetic Resonance Index of Activity (MaRIA) and Crohn’s Disease Activity (CDA) score1–3, have recently been developed and are being validated several institutions. The remainder of this dilemma may be resolved by the development of more objective assessment features, such as DCE-MRI.

Clinical applicability of DCE-MRI in Crohn’s disease

DCE-MRI in its current form can be used as an addition to conventional sequences with the specific purpose to detect mild disease activity. As sensitivity of conventional MRI sequences is already high for detecting severe disease activity, DCE-MRI is not of additional value in these specific patients. A benefit of DCE-parameters is that they offer objective parameters derived from automated analyses, compared to the traditionally used parameters that are subjective.

There are some remaining limitations that lower the clinical applicability of DCE-MRI in Crohn’s disease. For instance, the sequence takes more time to perform than currently used MRI sequences (up to 10 minutes versus several breath holds). The DCE-MRI data needs offline post processing (registration of the data and calculation of the maximum enhancement and other DCE-MRI parameters), which takes approximately 15 minutes per patient. Automatic post-processing and subsequent transfer to the radiology PACS system of the DCE data would increase its clinical applicability. Ideally the radiologist should analyse the DCE data in concurrence with assessments of the conventional MRI sequences. This would also enable comparisons of DCE data between studies.

Relations between disease duration and maximum enhancement have been recognised, suggesting that prolonged inflammation may alter perfusion dynamics of the bowel wall4.

Further research should therefore be aimed at therapy response and changes in DCE-MRI data over time. Further investigations also need to establish what processes are the causes of T1 enhancement; does T1 enhancement increase when an exacerbation of disease activity occurs, is it a continuous process where the perfusion dynamics of the bowel wall are also altered by the disease when the patient is in clinical remission? This knowledge can then be used for the grading of disease activity: when a bowel segment displays enhancement, one can base treatment choices upon the extent of the measured inflammation.

Pharmacokinetic modelling can be performed in luminal Crohn’s disease patients yielding physiological parameters for the grading of Crohn’s disease activity. Recent papers discuss the ability of Ktrans to detect disease activity in Crohn’s disease patients4,5. Next step would be to evaluate if Ktrans is a marker for the sensitivity of the treatment efficacy of anti-TNFα inhibitors that are currently applied in clinical trials. These parameters should be determined. However, the results of the pharmacokinetic model depend on several parameters that are imputed in the model such as arterial input function, T1 of blood and hematocrit of the capillary vessels, which are unknown values and therefore must be estimated. The estimated values of these parameters are not uniform between different published studies. To perform pharmacokinetic modelling in luminal Crohn’s disease, consensus should be reached which models are used to make results more comparable between studies. A semi-quantitative model, as is used in this thesis, does not incorporate any unknown values and is thus more comparable between studies.

Ultrasound and MRI in paediatric patients

Current imaging techniques - either ultrasound or MRI - are not recommended to be used as a first diagnostic step to diagnose IBD because sensitivity is still too low to detect IBD especially in patients with mild disease or rectal disease. A separate oral preparation for the large bowel combined with the normal small bowel preparation can be considered in these patients to increase sensitivity. Ileocolonoscopy combined with upper gastrointestinal endoscopy, which combine visual inspection of the ileum and colon with histologic examination, remain the reference standard.

Perianal Crohn’s disease

MRI is now used to assess deep healing of perianal fistulas because clinical fistula closure does not necessarily imply that the track is healed. In clinically closed tracks activity may...
still be seen at MRI indicating a track that most likely will open again after therapy is discontinued. DCE-MRI can aid in the disease evaluation of perianal disease activity as it shows moderate correlations with PDAI and CRP. Main limitation is the fact that there is no perfect reference standard available for perianal fistula disease activity. The PDAI includes subjective clinical parameters and is subjective to interobserver variability. CRP is a highly sensitive marker for inflammation, but not specific for perianal disease activity and is less sensitive in patients with prolonged disease activity. The MRI score by Van Assche et al. is now often used as a reference standard in clinical trials. This score is partially anatomy based and does not include T1 enhancement. As in luminal Crohn’s disease future research should focus on the development of DCE-parameters over time. In this thesis, only six patients were scanned for a second time after commencement of therapy. All these patients demonstrated some decrease in $K_{trans}$ values after these six weeks. This decrease should be compared with clinical response to the anti-TNFα therapy.

In conclusion, this thesis demonstrates that:
1. The DCE-MRI parameter maximum enhancement is dependent on both active inflammation and disease duration.
2. Measured bowel wall thickness on MRI is a reliable marker of disease activity in Crohn’s disease patients.
3. Endoscopy remains the method of primary assessment of IBD in paediatric patients.
4. DCE-MRI can be used to evaluate disease activity in perineal Crohn’s disease patients and is a possible marker of therapy response.

References