Magnetic resonance imaging in Crohn's disease
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Introduction

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BACKGROUND

Crohn's disease (CD) is a chronic, relapsing and remitting inflammatory bowel disease (IBD) that is characterized by transmural, patchy, granulomatous inflammation. CD can be localized in any part of the gastrointestinal tract, although location of predilection is the terminal ileum. Involvement of the terminal ileum is observed in 90% of the patients with CD limited to the small bowel, which in turn constitute 30-40% of all CD patients. In 40 to 55% of patients both ileum and colon are affected, while in a minority (15-25%) only a colonic localization is observed (1). During the last decades the incidence of CD has continued to rise worldwide, reaching incidence rates ranging from 3.1 to 14.6/100,000 in North America and from 0.7 to 9.8/100,000 in Europe (2).

In clinical practice it is important to establish a diagnosis and to assess exact location, extent and severity of CD at initial presentation. Meanwhile, in known CD imaging is needed for follow-up during treatment and to direct treatment strategies. Imaging especially plays a role in directing treatment when a choice needs to be made between continuation of medical treatment or surgical resection.

REFERENCE STANDARD FOR EVALUATION OF THE BOWEL

Currently, endoscopy is considered the reference standard for evaluation of the gastrointestinal tract and thus also for CD (3). The mucosa can be visualized in detail, allowing identification of the earliest superficial stages of disease (i.e. superficial ulcers) and the possibility of tissue sampling and therapeutic intervention (e.g. dilatation of strictures). However, the small bowel, which constitutes the larger part of the gastrointestinal tract, is only limitedly accessible with standard endoscopic techniques: inspection of the terminal ileum is reported to fail in up to 27.8% of examinations (4, 5) and more proximal small bowel loops are not accessible with conventional ileocolonoscopy. Other drawbacks are the extensive bowel preparation needed as well as the discomfort experienced during the procedure.

For assessment of the small bowel, barium enteroclysis has been the reference standard for years as with this technique the mucosa of the small bowel can be examined in detail. However, only indirect information is obtained about the bowel wall and the extraintestinal abdomen. Both superimposition of bowel loops and non-palpable thus non-compressible bowel loops deep in the pelvis can mask active disease or its complications. This technique requires a skilled radiologist, causes patient discomfort, involves ionizing radiation (between 1.5-13.9 mSv) (6, 7) and is time-consuming.

The advent of video capsule endoscopy (VCE) and double-balloon endoscopy (DBE) has increased the diagnostic possibilities. For VCE a video capsule is swallowed after a fasting period of up to 12 h and is propelled through the bowel by peristalsis. In this way, the mucosal surface of the small bowel can be depicted in detail. However, with VCE there
is no facility to increase visibility by insufflation of air or by tissue rinsing. Moreover, tissue sampling and therapeutic interventions are not possible, while the use of VCE is contraindicated in patients with (suspicion of) obstruction due to the risk of capsule retention. For DBE, a high-resolution video-endoscope with a flexible overtube is used. By alternately inflating and deflating two balloons attached to the overtube and endoscope the small bowel is threaded on the overtube. Both an oral and an anal approach are possible; for the oral approach no specific preparation is required, although patients are asked to fast for at least 6 h before the procedure. If the anal approach is used, bowel cleansing such as is employed for traditional colonoscopy is used. By using both the anal and oral approach, DBE allows visualization of the entire small bowel, with the possibility of obtaining tissue for analysis and the added advantage of the possibility of endoscopic therapy (e.g., dilatation of a stricture, cauterization of a bleeding site). DBE is a time-consuming examination, for which conscious sedation is a necessity. This technique is only limitedly available and is more expensive than a conventional endoscopy.

CROSS-SECTIONAL IMAGING TECHNIQUES

The trans- and extramural extent of CD cannot be visualized with any of the abovementioned techniques. Much research has been directed toward the potential of cross-sectional imaging modalities for the diagnosis and evaluation of CD as with these techniques the bowel lumen, the bowel wall and the extra-intestinal abdomen including the visceral fat, the lymph nodes and the vascular structures feeding and draining the bowel can be visualized. An added advantage of these techniques is the fact that they are limitedly to non-invasive.

Ultrasonography (US), Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are often used for the evaluation of the abdomen. While in the USA the technique of choice is CT, in Europe the focus is more on MRI and US. This inclination is reflected by the majority of CT studies on IBD patients originating from the USA, while the majority of published studies on MRI and US has been conducted in Europe.

Although CT is less sensitive than barium studies in detecting mucosal changes, it is valuable for depicting intramural and extraluminal disease. This technique is fast, readily available, and noninvasive. However, contrast resolution of CT is lower than of MRI. Thereby, the use of ionizing radiation precludes its frequent use in the often young patients, although the increased awareness for radiation exposure will most likely lead to imaging protocols with lower radiation exposure (e.g., dose modulation).

Due to the limited patient preparation necessary and the non-invasive nature of US, this technique can be considered relatively patient-friendly and straightforward. The thickening of the intestinal wall associated with Crohn’s disease can be reliably shown, especially in the terminal ileum. However, this technique is highly operator-dependent, while other disadvantages are the difficulty in quantifying sonographic findings, and the visualization of segmental involvement as well as rectal involvement. The use of Doppler-US might
provide helpful additional information on IBD, particularly on the degree of disease activity. Using Doppler-US the vascularity of the bowel wall can be assessed according to the intensity of color signals and/or by the analysis of Doppler curves (measurement of resistive index) obtained from vessels detected within the bowel wall. Measurement of flow parameters of the superior and inferior mesenteric arteries can also be performed. Several investigators have investigated the value of leukocyte scintigraphy in assessment of disease activity in CD. Several drawbacks can be contributed to this technique; stenoses, fistulas, and malignant tumors cannot be detected. Furthermore, this technique is expensive, time-consuming (due to the in vitro cell labeling procedure), and involves radiation exposure.

ABDOMINAL MRI IN LUMINAL CD
With MRI both inflammatory changes of the bowel wall and extramural complications of CD can be assessed. The non-invasiveness of this technique, as well as its lack of ionizing radiation, has prompted many groups to perform studies to evaluate the accuracy of MR imaging in CD.

Diagnostic accuracy
For CD patients MRI could possibly serve as an alternative to barium enteroclysis and ileocolonoscopy with sensitivity and specificity values ranging from 81.8% to 100% and specificity values varying from 57.1 to 100 (8-14).

Disease activity
Although many studies have been performed investigating the role of MRI in evaluation of CD patients, not much research has been directed towards the capability of MRI of assessing the degree of disease activity. The results of the studies evaluating disease activity vary; while in several studies false-negative MRI results were seen in patients with active, mostly mild, CD (15-18), in other studies disease activity was overestimated on MRI (19-21).

Bowel preparation
There is no consensus yet as to what bowel preparation should be used to perform MRI of the small bowel. While many authors emphasize that for adequate diagnosis the bowel loops should be distended by contrast medium, studies with good results have been performed without enteral contrast medium (8, 22), after oral administration of contrast medium (10, 23), and after enteral filling by a nasojejunal tube (MR enteroclysis) (9, 14, 16). For MR enteroclysis the nasojejunal tube is positioned under fluoroscopic guidance. MRI using oral contrast medium can be repeated frequently as it is a patient-friendly method.
using non-ionizing radiation. Surprisingly, no tendency can be observed towards improved accuracy in studies using luminal contrast medium as opposed to the studies abstaining from using luminal contrast. Data concerning a side-by-side comparison of MR of the small bowel without and with use of luminal contrast are lacking. However, it does seem from the scarce available data that accuracy values do not differ significantly between MR enteroclysis and MR enterography (24, 25).

Field Strength

With higher field strength Signal-to-Noise-Ratio (SNR) is improved, which can either be used for improved spatial resolution, or shorter acquisition times. The resulting better image quality might improve diagnostic accuracy. However, while on the one hand SNR is improved, on the other hand more artifacts are seen. Also, there are differences in image contrast due to changed relaxation rates.

T1-mapping

In CD actively inflamed bowel wall displays pathological enhancement on T1-weighted MR images after administration of intravenous Gadolinium-based contrast (10, 23, 26). This pathological enhancement is due to increased tissue perfusion and vascular permeability (27-29). However, with conventional MR imaging techniques, signal intensity is expressed on an arbitrary scale that differs from one imaging examination to another and therefore is unsuitable for direct signal quantification. A more objective and reproducible method to determine the degree of bowel wall enhancement would be valuable for follow-up purposes and for comparison between subjects.

The increase of the longitudinal relaxation rate (1/T1) is directly proportional to the tissue concentration of the contrast medium. Therefore, calculation of the absolute T1-values in tissue before and after intravenous injection of Gadolinium would provide objective measurements of the Gadolinium-uptake. As there is a correlation between mesenteric vascularisation and permeability and disease severity (28, 29), calculation of contrast agent concentration for every pixel in a parametric image (i.e. a T1-map) could possibly provide an objective, quantifiable, and reproducible means of determination of CD activity.

PERIANAL FISTULIZING CROHN’S DISEASE

In CD formation of perianal fistulas and/or abscesses can be seen in up to 38% of patients (30). Detailed information on the presence and extent of fistulas and abscesses is mandatory for proper treatment of patients with perianal fistulizing CD (31). Digital examination and probing under anesthesia (EUA) is considered the gold standard, but its accuracy is limited, especially when scarring and fibrosis are present (32, 33). Fistulography is the oldest imaging technique used for fistula assessment, yet this
technique is reported to be disappointing, one study providing a correct diagnosis in only 16% of cases (34). Occlusion of external openings and obliteration of tracks by active granulation tissue contribute to these poor results (32). Another drawback is the lack of sufficient anatomical information. Consequently, this imaging modality is seldom used anymore. CT is not the optimal technique for imaging of perianal fistulas due to its poor intrinsic contrast resolution. Another limitation is the ionizing radiation involved. Anal endosonography (AES) can easily be performed without special preparation and can be repeated frequently due to its lack of ionizing radiation. With this technique the anal sphincters can be clearly visualized. The diagnostic accuracy of AES is high, compared with surgical findings (35-37). No overall diagnostic benefit was demonstrated for the additional use of hydrogen peroxide (38). Not many studies have been performed specifically in patients with CD, but results of a prospective study in perianal CD showed that AES correctly classified fistulas in 91% (39). AES has also been reported to be helpful in guiding therapy in patients with perianal fistulizing CD (40).

MAGNETIC RESONANCE IMAGING OF PERIANAL CD

MRI has become one of the mainstays in the evaluation of patients with perianal CD, as it is a patient-friendly and non-invasive technique that is accurate in the depiction of fistulas and abscesses. The use of external coils is preferred over endoluminal MRI in patients with CD. This as disease may extend outside the effective volume of an endoluminal device and the advantage of using such a coil has not been demonstrated in this population. The discomfort associated with endoluminal coils is an additional disadvantage, more so since in patients with CD extensive rectal inflammation can be present. Both the American Gastroenterology Association (AGA) and the European Crohn’s and Colitis Organisation (ECCO) have stated the importance of MR imaging for perianal fistulas (30, 31).

Disease activity

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. Evaluation of perianal disease activity in CD has been performed by assessment of fistula drainage or by using the validated Perianal Disease Activity Index (PDAI), in which an important item is fistula drainage (41, 42). However, it has been demonstrated that cessation of drainage from cutaneous orifices does not necessarily mean that perianal disease diminishes or disappears (43-45). Therefore, an MRI-based score of disease severity might be more accurate in evaluation of disease activity. However, conventional post-contrast imaging provides a limited amount of information about tissue behavior as it is performed after most of the contrast distribution has been
accomplished and some of the contrast has already washed out. With dynamic contrast-enhanced MR imaging (DCE-MRI), images are acquired during the delivery of the contrast in the tissue of interest, highlighting the dynamic response of the tissue to the inflow of blood. Analysis of the time-dependent changes of signal intensity after gadolinium administration by DCE-MRI could add valuable information about disease activity in CD as the kinetic of the signal variation reflects the status of tissue microcirculation (46-48). Besides the degree of maximum enhancement, the initial slope of enhancement can be determined. Since local vascularization increases with the severity of disease, it could be hypothesized that in more severely inflamed bowel both maximum signal intensity is higher and a steeper slope could be observed.

**OUTLINE OF THESIS:**

This thesis focuses on the role of MRI in CD. In the first part of the thesis the role of MRI in luminal CD is investigated, while the second part focuses on the role of pelvic MRI for perianal fistulizing CD.

**PART 1 LUMINAL CROHN’S DISEASE**

Many studies have been performed to determine the diagnostic potential of radiological imaging techniques for IBD. Strongly divergent accuracy values have been reported, but comparative studies between imaging techniques were hardly ever performed. To determine the accuracy estimates for the clinically available radiological imaging techniques we have performed a meta-analysis of prospective studies investigating the accuracy of CT, US, MRI and scintigraphy for the diagnosis of IBD in **CHAPTER 2**. In known CD assessment of inflammatory activity is important to determine the therapeutic strategy and for follow-up purposes. In **CHAPTER 3** a meta-analysis was performed to determine how MRI performs in assessment of disease activity compared to a predefined reference standard.

We hypothesized that the use of enteral contrast medium installed via a nasojejunal tube would improve the reliability of MRI of the small bowel. The purpose of the study described in **CHAPTER 4** was to determine the reliability of MR imaging of the small bowel using an enteroclysis technique for bowel filling as opposed to abstaining from using luminal contrast medium.

In the study reported in **CHAPTER 5** we evaluated the value of MRI in determining disease severity in CD patients compared with endoscopic grading of disease and the Crohn’s Disease Endoscopic Index of Severity (CDEIS). We also looked at patient experience of endoscopy and MRI and patient preference for one of the two techniques.

Developments in MRI have led to the clinical application of high field scanning with field strength of 3.0 Tesla. In **CHAPTER 6** we have evaluated the value of 3.0 Tesla MRI for
evaluation of known CD in comparison with ileocolonoscopy. The study design was similar to the one used in **CHAPTER 5**.

Regarding the accuracy of MRI in differentiation between CD and ulcerative colitis (UC) conflicting results have been reported; while some authors report that based on the location of inflammatory changes, the degree of involvement, the continuity or discontinuity of disease and the presence of complications it is possible to differentiate between CD and UC, others report a limited value in differentiation of disease. In **CHAPTER 7** we describe results of our study in pediatric patients suspected of IBD, who underwent abdominal 3.0 Tesla MRI. We have compared the diagnostic potential of MRI for diagnosis of IBD in children as well as the potential of MRI to differentiate between its two main subtypes CD and UC. We have also looked at the accuracy of MRI in grading disease activity in CD and UC and have calculated interobserver agreement for important MRI parameters between three observers to determine the reproducibility of 3.0 Tesla MRI of the bowel in children. As reference standards ileocolonoscopy, barium enteroclysis and histopathological results were used.

Pathological enhancement of affected tissue is considered a very important criterion to indicate active CD. However, assessment of the degree of enhancement is subjective, rendering this a relatively unreliable parameter of disease activity. In **CHAPTER 8** we describe the results of a study we performed to determine whether an objective and reproducible approach of determining pathological enhancement and thus disease activity is feasible. We composed T1 maps and compared these with histopathological specimens, with endoscopic scores of disease activity and with clinical activity as measured by the CRP-value and the Harvey-Bradshaw Index.

**PART 2 PERIANAL FISTULIZING CROHN’S DISEASE**

In **CHAPTER 9** an imaging approach for pelvic MRI in perianal fistulizing CD is described. In **CHAPTER 10** we have validated an MRI-based score of disease severity that was developed for perianal fistulizing CD by determination of its clinical value and its reliability. MRI-scores before and after treatment with Infliximab, an anti-TNF alpha agonist, were compared as were clinical scores of activity.

The MRI-based score of disease severity used in **CHAPTER 10** uses anatomical and inflammatory MRI parameters for disease assessment, based on static MR images. In **CHAPTER 11** 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.

In **CHAPTER 12** we provide a summary, general discussion and conclusions.

**CHAPTER 13**
Samenvatting, algemene discussie en conclusies.
REFERENCES


