Crohn's disease, advances in MRI
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Citation for published version (APA):

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Chapter I

General introduction

Parts of this chapter are adapted from:

Ziech MLW, Stoker J. MRI of the Small Bowel Enterography.

**Crohn’s disease**

Crohn’s disease is an inflammatory bowel disease that is most often located in the terminal ileum and is often diagnosed in young patients. The disease is chronic and frequently patients relapse and remit. Because clinical symptoms do not accurately represent luminal disease activity, other methods have been researched. Traditionally, imaging of the small bowel was done by barium enteroclysis, the first technique to visualize the entire small bowel. The limitation of barium enteroclysis is that only abnormalities of the luminal wall could be visualised. The development of cross-sectional imaging techniques cleared this void. Computed tomography (CT) can be used for this purpose, however, the use of ionising radiation is an evident drawback. Ultrasound is not associated with ionising radiation exposure and can visualise diseases of the bowel. However, the field of view is limited by bowel gas and some deeper pelvic areas of the gastrointestinal tract are not accessible by abdominal ultrasound. Also, comparison between consecutive studies is hampered as only limited views are captured and assessment is operator dependent. Magnetic resonance imaging (MRI) is capable of diagnosing Crohn’s disease, evaluating severity and monitoring treatment response. Several findings seen on MRI reflect active disease such as T1 enhancement after intravenous contrast injection, increased T2 signal intensity, thickening of the bowel wall, the presence of skip lesions (pathological bowel segments are separated by normal bowel) and a layered appearance of bowel wall.

**Reference standards**

Currently, there is no gold standard for assessment of disease activity in Crohn’s disease. Usually, a combination of clinical findings, laboratory tests, (ileo-)colonoscopy, and MRI is used. For clinical studies, the Crohn’s disease endoscopic index of severity (CDEIS) is most often used. This endoscopic scoring system assesses the presence of ulcerations (superficial and deep) and other non-ulcerative lesions (such as edema and erythema) per bowel segment and also includes the presence or absence of a (ulcerative) stricture. This score is calculated per patient, though it is also possible to calculate a per segment score.

Some of the other reference standards in the literature are histopathology-based. The acute inflammatory score (AIS) measures several parameters in histological sections of resected bowel specimens, such as amount and depth of neutrophils, presence of ulcerations and severity of edema in the bowel wall. A separate score exists for histopathological assessment of biopsies.

The Crohn’s disease activity index (CDAI) or laboratory parameters such as C-reactive protein (CRP), can also be used to evaluate disease activity but these are not reliable for assessing disease severity.

**MRI**

MRI is currently recommended in international guidelines to evaluate small bowel involvement in Crohn’s disease. The sensitivity of MR enterography is 80% on a per patient basis, the specificity is 82% when using ileo-colonoscopy as reference standard. Per segment the sensitivity is 70% and the specificity 89%. In a meta-analysis by Horsthuis et al, the accuracy of grading Crohn’s disease activity was assessed. Eighty-seven percent of patients with frank disease were correctly depicted by MRI, in contrast to only 65% of patients with mild disease activity. Mild disease activity consists of superficial ulcerations and aphtoid lesions. Emphasis in recent studies has been on MR scoring systems based on already known parameters. New techniques aimed at evaluating mild and severe disease activity are being developed to clear this void, such as dynamic contrast-enhanced MRI (DCE-MRI).

**DCE-MRI**

DCE-MRI consists of a series of fast MRI scans that are acquired while a contrast agent is injected intravenously. The time-dependent signal intensity of the tissue can be depicted in a time intensity curve (TIC). In actively diseased bowel, a marked increase in signal intensity (enhancement) can be seen due to increased perfusion and vascular permeability in inflammatory tissue, possibly with a positive correlation between mesenteric hypervascularity/vascular permeability and disease activity. Until now, in many studies either enhancement ratios of pathological bowel wall versus normal bowel wall have been determined, while in others degree of enhancement was subjectively determined (e.g. mild, moderate or marked enhancement). However, with these methods no objective, reproducible, quantifiable measurement of activity is possible. This may be an important factor explaining the limited value of MRI to accurately identify remission or mild disease activity. DCE-MRI could indeed be used to determine activity of disease in an objective, quantifiable, reproducible manner and could be a valuable contribution to the currently imperfect disease scores.
High field strength
In several studies the added value of 3T MRI has been investigated for abdominal purposes\textsuperscript{25–27}. With higher field strength an increase in signal to noise ratio (SNR) is expected. This increased SNR can be used to increase spatial and/or temporal resolution in 3T sequences. Previous DCE-studies on 1.5T were limited by the use of breathholds because of low temporal resolution of the sequence. With a 3T scanner it is possible to perform the sequence in free-breathing with high temporal resolution (<1 s). To analyze the DCE-sequence registration of the data set is needed.

Perianal fistulizing Crohn’s disease
Perianal fistulas have a prevalence in the general population of 1 per 10.000, most frequently in males in their forties\textsuperscript{28}. The most common type is the cryptoglandular fistula, representing up to 90\%\textsuperscript{28}. Around 40\% of patients with Crohn’s disease will develop a perianal fistula\textsuperscript{29–31} and up to 36\% of patients with Crohn’s disease present with a perianal fistula as their initial complaint\textsuperscript{31}.

Treatment in Crohn’s disease is primarily medical while patients with cryptoglandular fistulas will have surgery when conservative measures have failed. In Crohn’s disease detection of abscesses prior to start of medical treatment is important. With the exception of small abscesses, all other abscesses will first be drained surgically. During medical treatment objective monitoring of treatment response is necessary.

Major problem with current treatment of perianal fistulas is recurrence, both after medical treatment and surgery. Reason for recurrence after surgery is that fistula extensions are not detected accurately during surgery. Hence, preoperative imaging is very important. Further problem is that surgical treatment is hampered by the potential detrimental effect of surgery on continence, that limits the extent of possible surgery. In medical treatment timely identification of treatment response is important. Perianal fistulas are often remain active even if there is clinically external closure of the fistula and will not heal if medical treatment is discontinued.

Current imaging techniques for assessing disease activity are endoanal ultrasound and MRI\textsuperscript{12}. Endoanal ultrasound is a simple and fast technique that gives a detailed visualization of the anal sphincter complex, though it has the disadvantage its operator-dependency\textsuperscript{22}. MRI examinations are in general time-consuming, but offer a high contrast resolution for depiction of pelvic anatomy and fistulas. Assessment of disease activity is currently performed in a subjective way. Ideally, an objective grading system would be better especially when evaluating therapy response in patients. DCE-MRI could be such an objective way to assess disease activity.

Outline of this thesis
This thesis focuses on MRI of the small bowel for luminal and perianal Crohn’s disease, especially the role of DCE-MRI.

In chapter 2 we provide current and optimal protocols for performing MRI of the small and large bowel at 3 Tesla.

The problem that not all MR enterography/enteroclysis exams for luminal Crohn’s disease are evaluated in the same way, is assessed in chapter 3. We conducted a survey on which MR features are used for grading by experienced radiologists to assess which features are used most often and which features are considered important.

In chapter 4 MRI features for Crohn’s disease are compared with a histopathology-based reference standard, and interobserver variability is assessed between three radiologists.

Current conventional MRI exams have low sensitivity (63\%) for detection of mild ulcerative disease. The value of DCE-MRI for detecting disease activity, with an emphasis on mild ulcerative disease is assessed in chapter 5.

In children with suspected IBD the diagnosis of Crohn’s disease or ulcerative colitis based on clinical symptoms is often not apparent. The standard protocol is to perform gastroscopy and ileocolonoscopy under general anesthesia. In chapter 6 we tested the diagnostic accuracy of ultrasound and MRI in combination with DCE-sequences for inflammatory bowel diseases (IBD) in a paediatric population to investigate if imaging can replace endoscopy as a primary diagnostic modality.

Perianal fistulas can be evaluated with either MRI or with endoanal ultrasound. In chapter 7 we present an imaging approach for perianal fistulas. We determine the value of DCE-MRI for grading of disease activity in patients with a perianal fistula and Crohn’s disease in chapter 8. We also assess if DCE-MRI is an indicator of early therapy response in those patients who started with anti tumor necrosis factor (TNF)\textsuperscript{9}.

In chapter 9 we provide a summary, general discussion and conclusions and recommendations for further research.
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