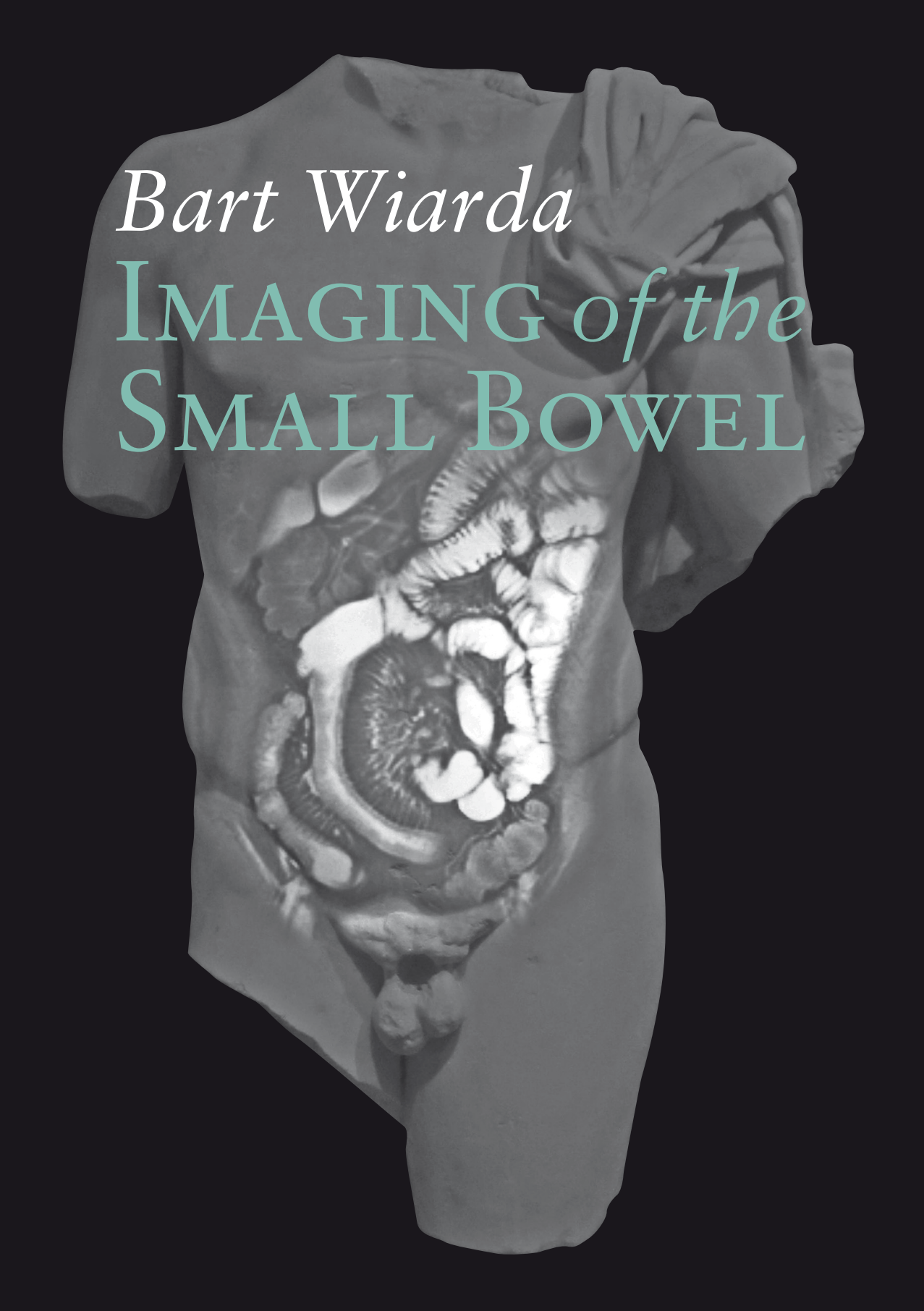

Bart Wiarda

Imaging of the Small Bowel

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Chapter 1
Introduction

Introduction

Visualization of the small bowel is a clinical challenge due to its length, motility, shape, and central location distal to the stomach and proximal to the coecum. During the last decade, several new techniques have been introduced for visualizing the small bowel. Radiologists and clinicians are now faced with a dilemma in deciding which technique to use in two common groups of adult patients: those with known or suspected Crohn's disease, and those with obscure gastrointestinal bleeding. This decision is primarily based on the accuracy, burden, and patient preference of each technique.

In patients with suspected Crohn's disease, diagnosing the disease and establishing the location, extent, and severity of the disease is essential. Symptoms of Crohn's disease can sometimes overlap those of other common gastrointestinal problems, such as irritable bowel syndrome (IBS), celiac disease, and other gastrointestinal abnormalities. Crohn's disease is characterized as a chronic, relapsing, and remitting inflammatory bowel disease (IBD), which can start at an early age and may require lifelong surveillance. In the last few decades the incidence of Crohn's disease has continued to increase worldwide, and the prevalence and incidence are the same in Europe and the United States. A north-south gradient and lower incidence of Crohn's disease is present in Asian and African people (1). Crohn's disease has a predilection for the terminal ileum; the disease localizes to the small bowel in 70% of patients, but it can also occur in any other part of the gastrointestinal tract (2). The inflammation is characterized by patchy, transmural, granulomatous lesions, which can cause a range of complications, such as small bowel stenosis, fistulas, and abscesses. In addition, colon involvement increases the risk of developing colorectal cancer.

Obscure gastrointestinal bleeding (OGIB), which is another important affliction of the small bowel, requires a diagnosis of the cause of the bleeding. OGIB is defined as persistent or recurrent gastrointestinal bleeding following a negative initial endoscopic evaluation (3). OGIB may be categorized into obscure overt bleeding and obscure silent bleeding on the basis of the presence or absence of clinically evident bleeding (3,4). Silent OGIB may manifest as blood in the stool detectable only by chemical tests or as iron deficiency anaemia. Overt OGIB is high-volume bleeding manifesting as haematemesis, melena, or haematochezia from an unidentified source after an initial

upper endoscopy and colonoscopy. In middle-aged or younger adults (<40-50 years of age), overt OGIB can be caused by small bowel erosions related to the use of non-steroid anti-inflammatory drugs (NSAIDs), which are often due to small bowel tumours. In middle-aged adults and older individuals, the cause is often angiodysplasia, a superficial crowding of vascular structures with an increased risk of bleeding. The treatment of angiodysplasia is either primary endoscopic sclerosing therapy or clipping. If the endoscopic treatment is unsuccessful, surgical resection can be performed.

The uncertainty of clinical symptoms for determining disease activity in patients with known or suspected Crohn's disease, and the burden, complications, and costs associated with the use of immunosuppression or biologicals, requires a test that can determine disease activity. Such a test is the Crohn's disease activity index (CDAI), which is used as a clinical parameter to determine disease activity in patients with Crohn's disease. However, this test has limitations: it does not predict the outcome of the disease, the extent of the disease, or unexpected symptoms (5). Biomarkers of active inflammatory Crohn's disease also perform poorly. Elevated C-reactive protein is found in only 50% of patients with endoscopic inflammation (6). Calprotectin is a protein that is elevated in the faeces of patients with active Crohn's disease, but it is also elevated in patients with ulcerative colitis and neoplasms in the gastrointestinal tract. Because this protein is not elevated in patients with IBS, it is used to differentiate between IBD and IBS. Although it is a relatively new test, faecal calprotectin is regularly used as an indicator of IBD during treatment and as a diagnostic marker (7).
Endoscopy is currently considered to be the best option for differentiating active Crohn's disease from IBS and other co-existent conditions because the inflamed mucosa can be viewed directly and biopsied. Thus far, the standard work-up of a patient suspected of Crohn's disease is ileocolonoscopy. However, a diagnostic dilemma of this modality is that only a short part of the terminal ileum is visualized. Moreover, intubation of the terminal ileum is not successful in some patients, especially if stenosis is present at the ileocaecal junction. Therefore, the disease cannot be ruled out and the extent of the disease cannot be established in a large part of the small bowel. A modality is needed that visualizes the complete small bowel with high accuracy, low patient burden, and no or low ionizing radiation.

Similar difficulties arise in diagnosing patients with OGIB. Until recently, the standard modalities for detecting abnormalities of the small bowel in patients with OGIB were push enteroscopy and intra-operative enteroscopy. However, the area of the small intestine that push enteroscopy can reach is limited because of the short length of the scope, and intra-operative enteroscopy is an invasive method (8). Moreover, push enteroscopy and other conventional imaging modalities, including computed tomography (CT) and small bowel barium series, fail to detect small bowel neoplasms in up to 50% of cases (9, 10). Therefore, new modalities were developed to diagnose and locate the cause of OGIB (6).

Imaging techniques for the small bowel

Radiology

For almost all radiological imaging techniques (conventional radiography, CT, and magnetic resonance imaging (MRI)), small bowel distension is mandatory in order to evaluate the small bowel wall (11,12). Only ultrasound can be applied to diagnose small bowel abnormalities without special bowel preparation, though some also favour luminal distension with this technique (13). Two techniques, enterography and enteroclysis, are used for small bowel distension. The enterography technique achieves small bowel distension by having the patient drink a solution that is not absorbed by the small bowel. The enteroclysis technique requires the placement of a nasoduodenal tube, which provides control over small bowel distension and achieves a better distension of the small bowel, particularly of the jejunum, than enterography (14,15). Which level of distension is optimal for diagnosing small bowel disease is not clear.

Conventional contrast studies

For decades the small bowel was imaged by radiography and fluoroscopy, either after oral ingestion of barium solution (enterography) or after enteroclysis with barium (and methylcellulose). Conventional barium studies provide a detailed image of the mucosal surface and, indirectly, information on disease extension inside and outside of the small bowel wall. Multiple views are available during the examination. Compression films are required to visualize overlapping small bowel loops, to diagnose fixated loops, and to establish mucosal abnormalities. Limitations of this modality are operator dependency,

use of ionizing radiation, and the visualization of mucosal abnormalities, whereas the detection of wall abnormalities primarily concerns stenoses. Due to these limitations and the availability of cross sectional modalities, conventional contrast studies are increasingly being replaced by cross sectional techniques (16). Conventional contrast studies have little use in the evaluation of OGIB (17).

Ultrasound

Ultrasound can be used to diagnose small bowel disease. Ultrasound is a modality without radiation exposure, at a low cost, and with high accessibility. In the case of Crohn's disease, the technique can diagnose small bowel wall thickening, infiltration, free fluid, and abscesses. Unfortunately, ultrasound has important limitations: the field of view is limited, comparing examinations is often cumbersome, and the technique is operator-dependent. In daily practice, these factors make it a less suitable technique for the follow-up of small bowel disease in adult patients (13). Ultrasound does not currently play a role in the diagnostic work-up of OGIB.

CT

Multi-detector CT provides a complete and multi-planar view of the abdomen. In combination with an intravenous contrast agent, the technique can identify Crohn's disease and some causes of OGIB. However, differentiating bowel wall thickening and collapsed bowel loops can be difficult with CT because the abdomen is only scanned once due to the use of ionizing radiation (18,19).

MRI

MRI combines multi-planar capabilities with high contrast resolution of soft tissue without using ionizing radiation. Due to the development of shorter scanning techniques, e.g. single shot techniques, the small bowel can be visualized without artefacts caused by small bowel peristalsis and respiration movements. MR enteroclysis provides dynamic information and excellent distension of small bowel loops, especially the jejunum and proximal ileum. MR enterography entails shorter in-room time and lower patient burden, but it results in less small bowel distension of the jejunum than MR enteroclysis. With both techniques, Crohn's disease grading can be established by evaluating the wall thickness, wall enhancement, bowel wall oedema, ulceration, perimural infiltration, and lymph node contrast enhancement, all of which are associated with active disease

(20,21). In daily practice, mainly MR enterography is used because it has a lower patient burden and shorter in-room MRI time than MR enteroclysis, whereas bowel distension in the ileum is sufficient for diagnosing small bowel diseases in most cases. An international questionnaire among experienced radiologists in regards to grading Crohn's disease concluded that considerable variation exists in choosing which features (and their respective weight) contribute to the grading of disease activity (22). In patients with OGIB, the role of MRI is not yet fully understood (23).

Leucocyte scintigraphy

Scintigraphy with labelled leucocytes is an imaging technique used to detect IBD. The small bowel and colon are assessed simultaneously, allowing Crohn's disease and ulcerative colitis to be distinguished accurately. In a meta-analysis, no significant difference in diagnostic accuracy was observed between scintigraphy, ultrasound, MRI, or CT (24). The drawbacks of leucocyte scintigraphy are the lower detection rate of extramural disease and the use of ionizing radiation (25). No data are available to suggest that leucocyte scintigraphy is indicated in patients with OGIB.

PET

PET using fluorine-18-labelled fluoro-2-deoxy-D-glucose (FDG) is a functional imaging method that detects abnormalities in glucose metabolism. PET imaging is widely used in oncology to diagnose and monitor malignancies. However, FDG can also accumulate in areas of active inflammation, and PET has been found to be beneficial in inflammatory diseases. PET currently is not used in Crohn's disease because not all active segments have increased FDG-uptake (26). The role of PET/CT in patients with OGIB has been evaluated only in patients with small bowel neoplasms (27).

Endoscopy

Apart from the widely used ileocolonoscopy, which only allows for visualization of the terminal ileum, two other endoscopic techniques are available that result in the visualization of a large part of the small bowel, or even the complete small bowel. The first option is an endoscope with one or several balloons attached. Using this technique, by inflating and deflating the soft balloon around the scope, almost the

complete small bowel can be visualized. Balloon-assisted endoscopy allows tissue sampling for histological examination and the treatment of fibrotic strictures (28,29). The visualization achieved with this technique is comparable to standard enteroscopy; therefore, the technique can be considered the reference standard for imaging the small bowel. The second modality is capsule endoscopy, which was introduced in 2001. This technique consists of a large capsule with a camera inside that takes two images of the bowel lumen every second for 8 hours (30). Several studies have reported promising results for capsule endoscopy in patients with Crohn's disease and OGIB (31). In a meta-analysis, capsule endoscopy was superior to other techniques.

Only one study (32) compared capsule endoscopy with MR enterography in a small patient group with Crohn's disease and OGIB without using a reference standard. This study revealed that capsule endoscopy diagnosed significantly more inflammatory lesions in the proximal and middle portion of the small bowel than MR enterography in patients with Crohn's disease, and that capsule endoscopy was also superior to MR enterography in patients with OGIB.

So far, no head-to-head comparison studies have been performed concerning MR enteroclysis, which has important advantages over other imaging techniques than MRI, such as an unlimited multi-planar field of view, reproducibility, and no ionizing radiation. The role of this technique needs to be better defined, especially when compared with the newer endoscopic techniques for small bowel visualization, including balloon-assisted enteroscopy, which can visualize the small bowel with an endoscope, and capsule endoscopy, which uses a patient-friendly camera capsule that can visualize the entire small bowel.

Outline of thesis

This thesis focuses on the performance of MR enteroclysis in small bowel pathology in adult patients. Various aspects of MR enteroclysis are presented: the MRI protocol, the variety of abnormalities diagnosed by MR enteroclysis, the level of small bowel distension, the accuracy of MR enteroclysis compared to capsule endoscopy in Crohn's disease and occult gastrointestinal bleeding, and patient preference and burden.

Chapter 2 describes an MRI protocol for MR enteroclysis and establishes the influence MR enteroclysis-based diagnosis has on clinical strategy.
In **chapter 3**, various aspects of small bowel abnormalities diagnosed by MR enteroclysis are described in a pictorial essay indicating the features used to diagnose Crohn's disease, which features are important to grade disease activity, and the complications of Crohn's disease.
Chapter 4 presents a review of abnormalities in the jejunum diagnosed by MR enteroclysis.
In **chapter 5**, the level of distension achieved by MR enteroclysis is compared to MRI of the small bowel without bowel preparation.
In **chapter 6**, MR enteroclysis is compared to capsule endoscopy in patients with known or suspected Crohn's disease using balloon-assisted enteroscopy as part of the reference standard.
In **chapter 7**, MR enteroclysis is compared to capsule endoscopy in patients with OGIB. The reference standard consisted of an expert panel with knowledge of the results of balloon–assisted enteroscopy.
Chapter 8 presents a comparison of MR enteroclysis, capsule endoscopy, and balloon-assisted enteroscopy in terms of patient burden and patient preference as indicated by the patients who are also presented in chapters 6 and 7.
Chapters 9 and 10 provide a summary of the previous chapters in English and Dutch, respectively, and a discussion of future aspects.

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MR enteroclysis: Imaging technique of choice in diagnosis of small bowel diseases

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Abstract

MR enteroclysis is becoming a very important imaging modality in the workup and follow-up of small bowel diseases. The technique has many advantages, including the lack of ionizing radiation, ability to control luminal distension, superior tissue characterization, multiplanar capabilities, and mural and extramural visualization. These abilities can be obtained with a simple protocol showing excellent agreement with conventional enteroclysis. In 29 (18 with new or known Crohn's disease) of the 50 patients pathology was detected, with a very good clinical correlation. In 14 patients MR enteroclysis data altered therapeutic strategy. This contributes to the acceptation of this modality as a primary tool in small bowel diseases.

Introduction

Disorders of the small bowel are not uncommon. This significant part of the gastrointestinal tract is often involved or even the main affected site in a variety of disorders including inflammatory bowel diseases, hereditary gastrointestinal cancer syndromes, motility disorders, gastrointestinal bleeding, and malabsorption syndromes. Unfortunately, however, the diagnosis and follow-up of patients with these disorders is largely hampered by the strong limitations of current small bowel imaging techniques. Ideally, such techniques should allow visualization of the whole small bowel with adequate sensitivity and specificity and limited patient burden. The current standard endoscopical techniques include gastroduodenoscopy and colonoscopy; both, however, visualize only the surface of a very small part of the small bowel. Push enteroscopy allows further visualization of the proximal small bowel beyond Treitz ligament, but this technique is still limited in its reach. The most widely accepted method is conventional enteroclysis (CE). With its maximal luminal distension and high spatial resolution, it can depict small mucosal pathologies (1). As such, capsule endoscopy is the current standard, but this technique is limited by patient burden and radiation exposure. Several new visualization techniques are video capsule, double-balloon enteroscopy, and CT and MR enteroclysis (MRE). These techniques are of significant clinical interest because of the limitations of the current standard. The double-balloon endoscopic technique is a recent development which is currently under investigation in a number of clinical

centres. The noninvasive techniques, in particular the video capsule, have already gained somewhat more application. The capsule technique appears to be sensitive for the detection of small lesions, but costs, time consumption, specificity, and anatomic localization may be its limitations. CT enteroclysis uses radiation and does not yield functional information, as there is only a single chance for maximal luminal dilatation during the investigation (2). Because of its excellent soft tissue contrast and multiplanner imaging capabilities, MR imaging could be the optimal imaging method for evaluation of the small bowel. Our aim was to analyze the efficacy of MR enteroclysis as the standard imaging technique in the workup and follow-up of small bowel diseases and to develop an adequate preparation and scanning technique.

Materials and Methods

Population

From November 2003 till August 2004, 52 consecutive patients with an indication for small bowel visualization in the presence of suspected or known small bowel disease or low-grade small bowel obstruction were included in the study. Fifty patients were studied (24/26 male/female). Their mean age was 48 years (range, 16 to 85 years). Patients were excluded in case of suspicion of an intra-abdominal abscess or postoperative suture leakage. In 2 of the 52 patients placement of a nasoduodenal catheter was not possible, due to patient refusal (*n*=1) and previous gastric surgery (*n*=1). The indications for MR enteroclysis were suspicion of small bowel Crohn's disease (*n*=12), suspicion of disease recurrence in previously diagnosed small bowel Crohn's disease (*n*=16), small bowel obstruction of unknown etiology (*n*=8), abdominal pain/ diarrhoea/ motility disorder (*n*=11), follow-up after resection of a small bowel adenocarcinoma (*n*=1), and other tumor (ovarian cancer and cervical cancer) (*n*=2).

Technique

The cleansing preparation of the small and large bowel included a low-residue diet, ample fluids (minimal 2 litres; no milk products), a laxative (twice a day: 15 g of magnesium sulphate and 2 tablets of bisacodyl) on the day prior to the exam, and nil per mouth on the day of the examination. These preparations were intended for clearance of the cecum and ascending colon to improve contrast passage and reduce

contrast volume. Under fluoroscopy a 10-F nasoduodenal catheter (Flocare; Nutricia, Switzerland) was placed in the distal part of the duodenum. The mean placement time of the nasoduodenal catheter was 8 min. The mean area dose product was 39 µGy/m². After transferring the patient to the MR unit (1.5-T Magnetom Symphony; Siemens, Erlangen, Germany) the catheter was connected to an electric infusion pump located outside the unit. The patient was placed in supine position in the MR imager. The small bowel was distended with 1000-3000 mL methylcellulose (0.5%)-water solution using an electric infusion pump at an infusion rate of 80-200 mL/min. This solution is an inexpensive biphasic contrast agent. The contrast medium was administered in two phases. In the first phase the infusion rate was started at 80 mL/min. In patients with adequate contrast passage through the small bowel without retrograde filling of the stomach, the infusion rate was increased to a maximum of 160 mL/min till the terminal ileum was reached. During the second phase the infusion rate was then maintained at 120-200 mL/min to create reflex atony of the small bowel. In case of retrograde filling of the stomach, the infusion rate was decreased to prevent vomiting. The examination time of each patient during the MR study was calculated.

MR technique

A three-stage MR scanning was applied (Table 1) using a phased array body coil. The first stage/modality consisted of MR fluoroscopy using a thick-slab, 50-mm coronal half-Fourier single-shot turbo spin echo (HASTE) with fat sat (fs) every 8 sec during breathing to study contrast passage speed, luminal distension, peristalsis, and retrograde filling of the stomach. This sequence is heavily T2-weighted and provides high-contrast resolution images in less than 1 sec per slice. The second modality consisted of morphological series every 5 min using coronal and transversal true fast imaging with steady-state precession with fs (true FISP fs) sequences with a slice thickness of 5 mm without a slice distance (breath hold). A multislice HASTE fs (coronal and transversal) was added during maximal distension (breath hold). This is a more T2-weighted sequence, therefore better visualizing bowel wall oedema than the true FISP fs sequence. Finally, with maximal distension, pre- and postcontrast (0.1 mmol/kg gadolinium; Magnevist, Schering, Germany) fast low-angle shot (FLASH) 2d with fs coronal and transversal 60 sec after contrast injection was used to evaluate activity of the disease (breath hold).

Table 1. MR enteroclysis technique

	HASTE fatsat	True FISP fatsat	HASTE fatsat	FLASH 2 d fatsat
Plane	coronal	coronal and transversal	coronal and transversal	coronal and transversal
Breathold	no	yes	yes	yes (multi-)
Timing	every 8 sec	every 4 minutes	in last part of study	in last part of study (pre and post (60 sec after) contrast)
Nr. of slices	1	23 (trans 2 packages)	20 (trans 2 packages)	20 (trans 2 packages)
Slice thickness	50 mm	5 mm	5 mm	5 mm
Slice distance	-	0	0	0
Field of view (mm2)	400	400	400	400
Matrix	256	256	256	256
Repetition time (msec)	849	5.04	849	212
Echo time (msec)	58	2.52	58	308
Flip angle	150	80	150	70
Imaging time per section (sec)	0.8	1.1	0.8	1.2
Imaging time per volume (sec)	0.8	26	23	23 (x 2)

Evaluation

The studies were reviewed by two radiologists, both with more than 5 years of abdominal MR experience. A small bowel wall, up to 3 mm thick, was considered normal, and a thickness of 4 mm or more as evidence of pathology (3). Skipped lesions were scored as thickened loops with a segment of normal bowel wall thickness in between. With the enteroclysis technique, bowel stenosis was scored as absent, mild, moderate or severe. Mild stenosis was defined as a one-third decrease in luminal distension, moderate as a two-thirds decrease, and severe as (sub-)total occlusion of the small bowel lumen. Extramural effects of Crohn's disease were fibrofatty proliferation, enlarged lymph nodes, and ascites. Complications as fistulas and abscesses were also scored. Increased contrast enhancement of pathologically thickened bowel wall and lymph

nodes were considered as evidence of disease activity, even as bowel wall edema and mucosal ulcerations (4). The presence of different artifacts (motion, respiratory and susceptibility) was noted, which led to problems in interpretation.

Results

The average examination time was 55.5 minutes (range 28 to 98 min). Two patients vomited at the end of the investigation as a result of retrograde gastric filling. In two patients the MR enteroclysis was not conclusive. In both the contrast material did not reach the terminal ileum in the presence of coprostasis as a result of incomplete bowel preparation.

Artifacts as a cause of intraluminal air on the true FISP fs sequence decreased during the study and did not cause problems in the interpretation. There were no artifacts caused by motion. In 20 (40%) patients, FLASH 2d T1 fs showed artifacts due to peristalsis of the small bowel, but this did not give problems in interpretation of the enhancement of the small bowel wall and lymph nodes. Two patients showed a susceptibility artifact of an operation clip.

In 21 (42%) patients no significant radiological findings were found. In the remaining 29 patients, the following pathology was detected. Eighteen patients had small bowel wall abnormalities compatible with Crohn's disease; in 5 this disease was newly diagnosed. One patient had colitis, one had a diverticula of the ileum, one peritoneal carcinomatosis, one had signs of radiation enteritis, one had an aneurysm of the abdominal aortae, leading to duodenal compression, and one patient had an entero-colonal fistula as a cause of colon carcinoma.

Fifteen patients had evidence of small bowel obstruction, being mild (*n*=7), moderate (*n*=4), or severe (*n*=4). In 10 patients, the obstruction was due to Crohn's disease. In the other five patients, obstruction either resulted from a tumor (*n*=3; being loco regional recurrence of a cervical carcinoma in one patient, small bowel carcinoid in two patients) (Fig. 1), postoperative adhesions (*n*=1), or transmural endometriosis (*n*=1; Fig. 2).

In the 18 patients with Crohn's disease, the length of thickened small bowel varied between 3 and 67 cm. In two patients more than one segment was involved. Eight of these patients had active disease (Fig. 3a and b). Ten of the 18 patients with Crohn's disease had low to intermediate small bowel obstruction (Fig. 4), and 3 patients had

fistulas; entero-enteral, entero-vesical and entero-cutaneous.
The enteroclysis outcome correlated well in 49 of the 50 patients with colonoscopy, surgery and/or clinical course. One patient, scored as having no abnormality, was operated 3 weeks after enteroclysis because of small bowel perforation due to vasculitis. In 14 patients MR enteroclysis data altered therapeutic strategy: Six patients underwent surgical treatment and eight patients had a change of treatment. In two patients, the MR enteroclysis raised the suspicion of a small bowel neoplasma which was the indication for surgery in both patients. One patient had an infiltrating carcinoid with lymph node metastasis and one had transmural endometriosis.

Discussion

Our study shows that MR enteroclysis is an optimal first-line technique for small bowel visualization. The advantages of MR enteroclysis are the superior tissue characterisation, control over maximal luminal distension, ability to detect trans- and extramural lesions, and evaluation of disease activity, all without the use of ionizing radiation. Since introduction of fast imaging techniques, which provide high-resolution images of the small bowel, the problems of artifacts due to motion, bowel peristalsis and respiration have been solved. Therefore, MR enteroclysis is now the method of choice at our hospital when evaluating inflammatory bowel disease and/or small bowel. The technique is still only used in a small proportion of clinics worldwide, but this could change rapidly because of the simple protocols and the rapid increase in the availability of 1.5-T scanners with further technical refinements. This enteroclysis technique gives not only morphological but also dynamic information and allows control over the maximal small bowel distension, which is a requirement for an imaging modality of the small bowel. The protocol here presented is simple, reproducible and reliable, and can be performed by trained technicians. In the literature (5) the prone position of the patient is recommended because of associated abdominal autocompression, which means that fewer coronal images have to be obtained. Because of better patient comfort and condition, however, we prefer the supine position, which does not impair imaging quality. The importance of adequate cleansing preparation of the small and large bowel was illustrated by the two patients who did not follow the protocol and therefore had faecal stasis within the terminal ileum and cecum, which lead to a noninterpretable study. Oral

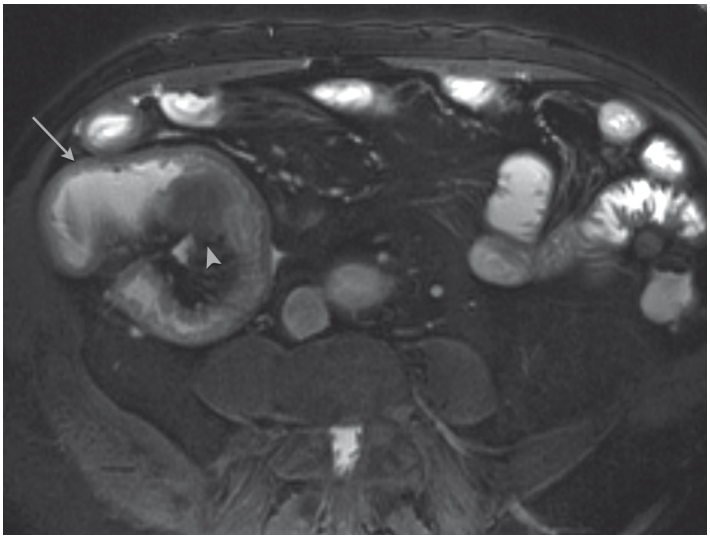

Figure 1.
Infiltrative carcinoid with lymph node metastasis. Transversal True FISP fs shows diffuse bowel wall thickening of the ileum (arrow) with enlarged lymph node (arrowhead), which causes intermediate small bowel obstruction. In the mesenterium near the lymph node, there is a desmoplastic reaction.

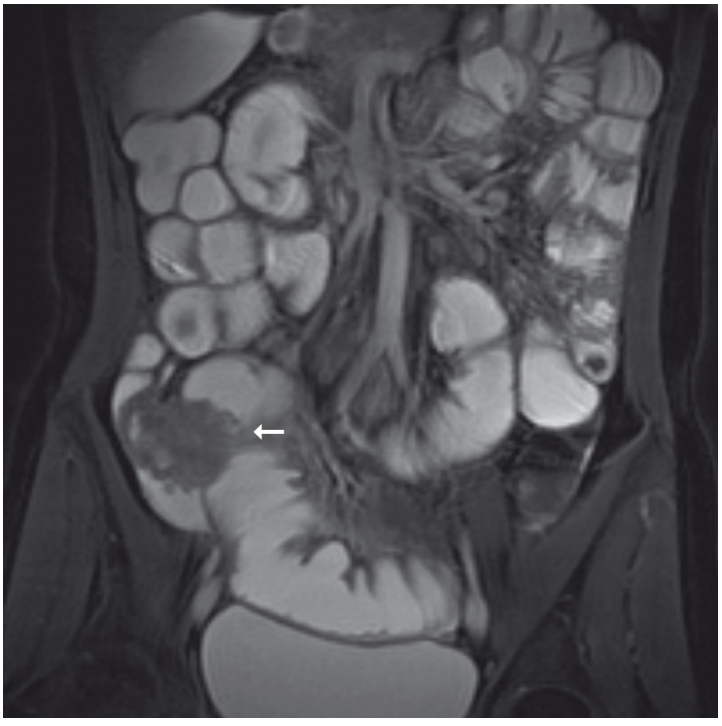

Figure 2.
Transmural endometriosis. Coronal True FISP fs shows solid mucosal tumor (arrow) in terminal ileum which caused complaints of intussusception.

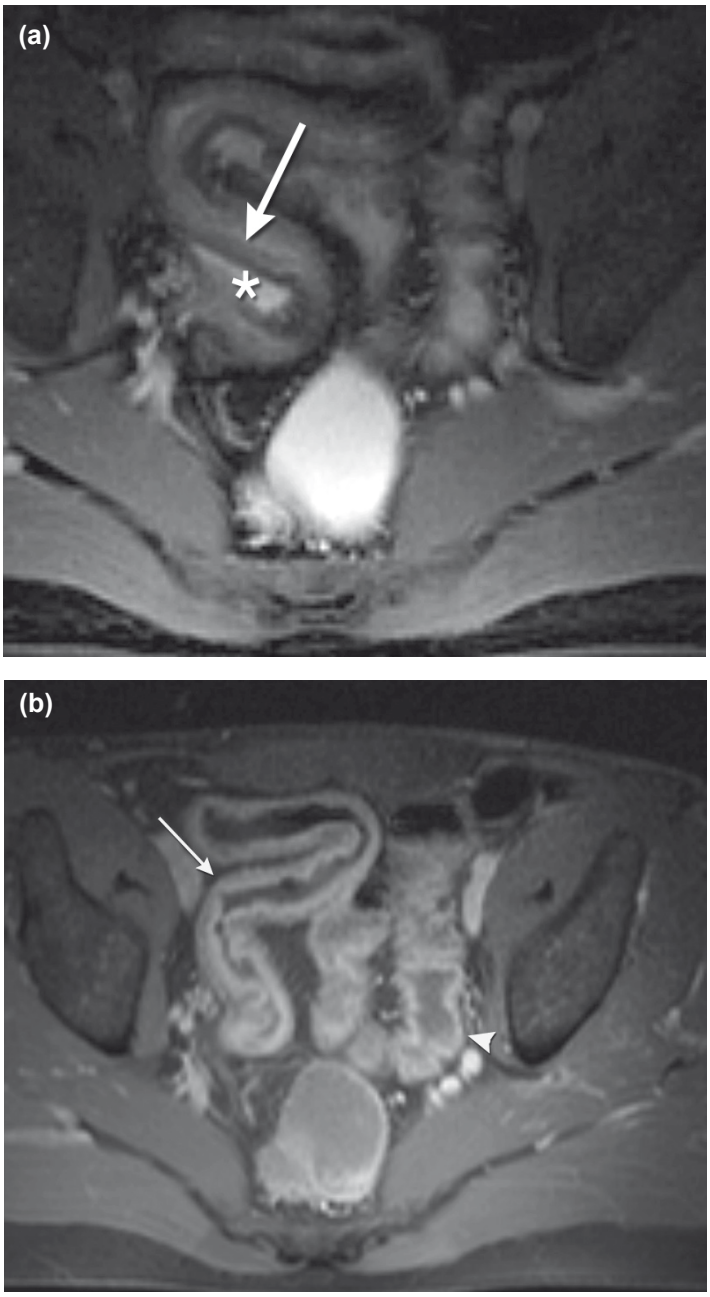

Figure 3.
Active Crohn's disease. Transversal true FISP fs (a) and post-contrast FLASH 2d fs (b) show diffuse thickening, oedema, irregular mucosa (a, arrow), and intense contrast enhancement of the bowel wall of the ileum (b, arrow). A small amount of ascitis (asterisk) was found in this region. Also, active disease is localized in the sigmoid (arrowhead).

Figure 4.
Crohn's disease with intermediate small bowel obstruction. Coronal true FISP fs shows two segments of bowel tickening and mucosal ulcerations (arrowhead) of the ileum, with persistent narrowing of the lumen and compensatory prestenotic dilatation (arrow). The image also shows fibrofatty proliferation (creeping fat, asterisk).

contrast agents are described in literature, but a good distension is only described in a voluntary population (6). Comparison of MRI after enteroclysis with oral contrast agent in patients with Crohn's disease showed no important significance (7). In our population MR enteroclysis is needed for maximal distension to exclude small bowel disease.

True FISP fs has an advantage over the same sequence without fs, because of the elimination of black boundary artifacts using the fs technique. The detection of subtle bowel wall thickness is therefore improved (8). Multislice HASTE fs was recently added, because of the more T2-weighted sequence and, therefore, better visualizing of bowel wall edema than with the true FISP fs sequence. The disadvantages of this technique are the sensitivity of motion artifacts and identification of the mesentery, including vessels and lymph nodes (9). Artifacts due to intraluminal air in the bowel lumen decreases during the study and did not gave problems in our population. The FLASH 2d fs sequence has motion artifacts of bowel wall peristalsis, but interpretation of the level of enhancement of the bowel wall and lymph nodes were not hindered. The literature (10) has propagated the use glucagon intravenously; in our experience, however, this is not necessary for optimal bowel distension and may increase the risk for vomiting as occurred in two of the five patients who received this medication. It is important to start scanning 60 sec after contrast injection to have the optimal enhancement of the bowel wall (11).

MR enteroclysis shows excellent agreement with conventional enteroclysis, with better lesion detection. In addition, conventional enteroclysis provides only luminography information, whereas MR enteroclysis provides transmural visualization. MR enteroclysis is now correlated with disease activity instead of conventional enteroclysis in the past and can definite disease activity (4).

For patients with suspected or known Crohn's disease, MR enteroclysis is of major benefit. This often young population with a chronic disease must be evaluated frequently to investigate disease activity. MR enteroclysis can also be used as a primary tool to evaluate presence and extent of a disease. In cases where colonoscopy did not reach the terminal ileum, MR enteroclysis may help to determine the optimal therapeutic strategy. Nowadays disease activity can be predicted by MR enteroclysis by looking at bowel edema and contrast enhancement of bowel wall and lymph nodes (4). The range of other indications in particular include small bowel obstruction, motility disorders, persistent diarrhea and abdominal pain, and relapse of intessusception and a problem-solving tool when other imaging modalities cannot diagnose an small bowel abnormality.

In conclusion, MR enteroclysis is an excellent technique that allows optimal transmural visualization of the small bowel and thus provides answers to clinical questions regarding etiology, location, distribution, activity, and complications of small bowel disease. Thus, MR enteroclysis may soon become the method of choice for the noninvasive evaluation of small bowel disorders.

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MR Enteroclysis of inflammatory small bowel diseases

Pictorial Essay

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Objective

MR enteroclysis has been introduced in the work up of smallbowel diseases. The major advantage of this technique over others is the combined visualization of luminal, mural and extramural abnormalities. In this article we propose an MR enteroclysis protocol, present a stepwise approach for evaluation of these examinations, and discuss the different inflammatory conditions that can be detected.

Conclusion

MR enteroclysis can be considered as the current first-line imaging technique for inflammatory small bowel disorders.

Table 1

	HASTE fatsat	**True FISP fatsat**	**HASTE fatsat**	**FLASH 2 d fatsat**
Plane	coronal	coronal and axial	coronal and axial	coronal and axial
Breathold	no	yes	yes	yes (multi-)
Timing	every 8 sec	every 4 minutes	in last part of study	in last part of study (pre and post (60 sec after) contrast)
Nr. of slices	1	23 (trans 2 packages)	20 (trans 2 packages)	20 (trans 2 packages)
Slice thickness	50 mm	5 mm	5 mm	5 mm
Slice distance	-	0	0	0
Field of view (mm2)	250 x 250	coronal: 400 x 400 axial: 350 x 240	coronal: 400 x 400 axial: 350 x 350	coronal: 400 x 350 axial: 350 x 262
Matrix	218 x 256	151 x 256	205 x 256	157 x 256
Repetition time (msec)	849	5.04	849	212
Echo time (msec)	58	2.52	58	308
Flip angle	150	80	150	70
Imaging time per section (sec)	0.8	1.1	0.8	1.2
Imaging time per volume (sec)	0.8	26	23	23 (x 2)

Note—FISP = fast imaging with steady-state precession; FLASH = fast low-angle shot.

Introduction

MRI with enteroclysis can be used as the initial imaging method for small bowel diseases. The enteroclysis technique enables optimal distension of the small bowel, which results in accurate visualization of stenoses and obstructions (1). The high-volume-induced reflex atony leads to well-defined visualization of the bowel wall almost without peristalsis-induced artifacts. MR enteroclysis has shown excellent correlation with conventional enteroclysis in grading small bowel obstruction and functional information while also providing transmural and extramural visualization (2).

MRI Technique

After placement of a nasoduodenal catheter under fluoroscopy, the small-bowel is distended with 1,000-3,000 mL methylcellulose (0.5%)-water solution using an electric infusion pump (Roentgen Contrast Mittel Pumpe, Nicholas), located outside the scanner room, at an infusion rate of 80-200 mL/min. The MR protocol (Table 1) consists of MR fluoroscopy using a thick-slab 50-mm coronal HASTE sequence with fat saturation, starting at the beginning of infusion and repeated every 8 seconds during normal breathing. This allows the study contrast passage speed, luminal distension, peristalsis and retrograde filling of the stomach. Subsequently, every 5 minutes, depending on the degree of distention observed from the HASTE images, coronal and axial true fast imaging with steady-state precession (FISP) with fat saturation are performed with a slice thickness of 5 mm to study morphological changes. Finally, with maximal distension, multi-slice HASTE images wit fat saturation and unehanced and enhanced (0.1 mmol/kg gadolinium) coronal and axial fast low-angle shot (FLASH) 2D images with fat saturation are obtained 60 seconds after contrast injections are made.

Normal appearance

The coronal thick-slab HASTE images give valuable information, both for identifying fixed bowel loops and luminal stenosis and for timing of morphological sequences with optimal distended bowel loops (Fig. 1). The higher spatial and contrast resolution

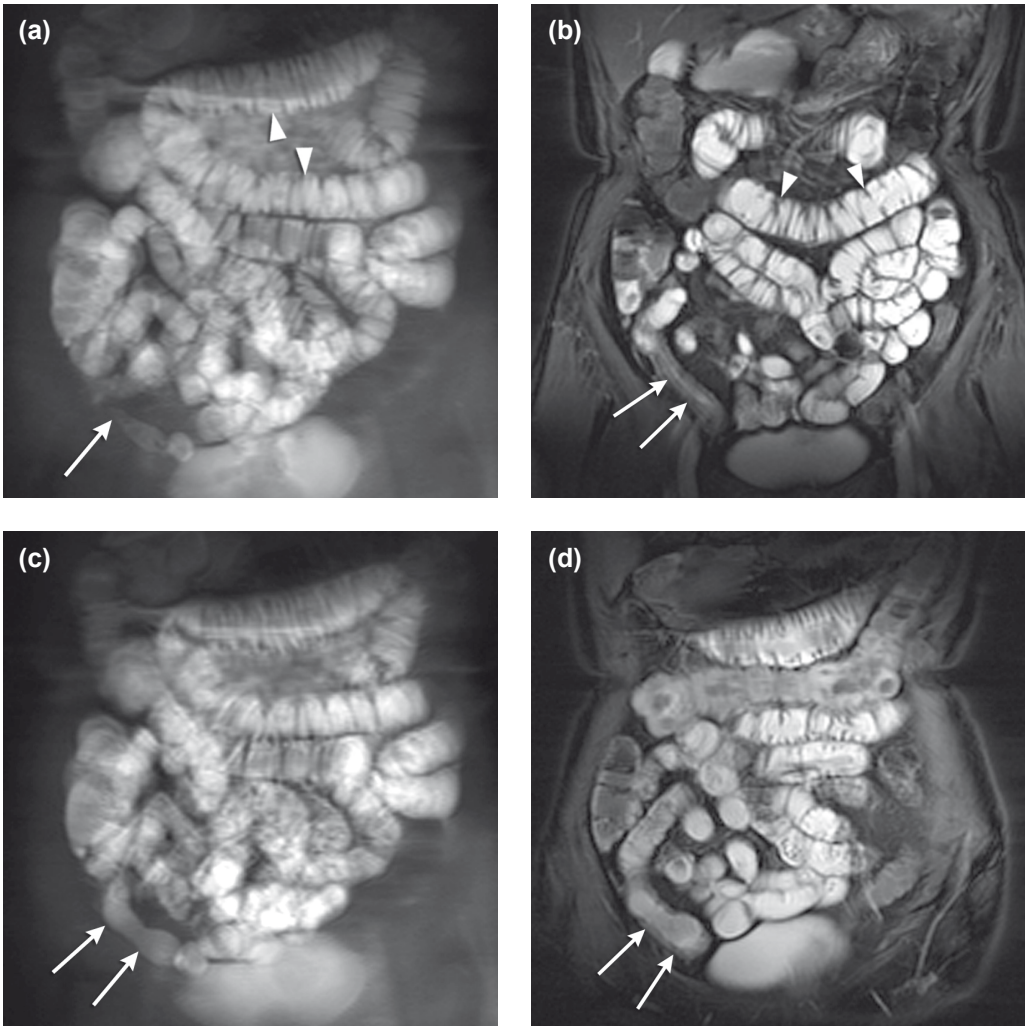


Figure 1.
63-year-old female with suspected Crohn's disease.
a, Coronal thick slab HASTE fat-saturation image shows adequate distention of jejunal loops (arrowheads) but collapsed or stenotic terminal ileum (arrow).
b, Coronal true fast imaging with steady-state precession (FISP) fat-saturation image obtained at the same time as A shows wall thickening of the terminal ileum (arrows) with collapsed or stenotic lumen. Note normal folds without wall thickening of jejunal loops (arrowheads).
c, Coronal thick-slab HASTE fat-saturation image obtained a few minutes later than A shows distention of the terminal ileum (arrows).
d, Coronal true FISP fat-saturation image otbained at the same time as C shows distended terminal ileum with wall thickening without stenosis (arrows). Thick-slab HASTE imaging facilitates optimal timing of true FISP fat-saturation sequences with maximal distention. This increases certainty of grading small-bowel stenosis.

Figure 2.
35-year-old woman with healthy-appearing small-bowel. During optimal distention, coronal true fast imaging with steady-state precession fat-saturation image shows normal folds in jejunum (arrowheads) and no stenosis or bowel wall thickening in terminal ileum (arrows).

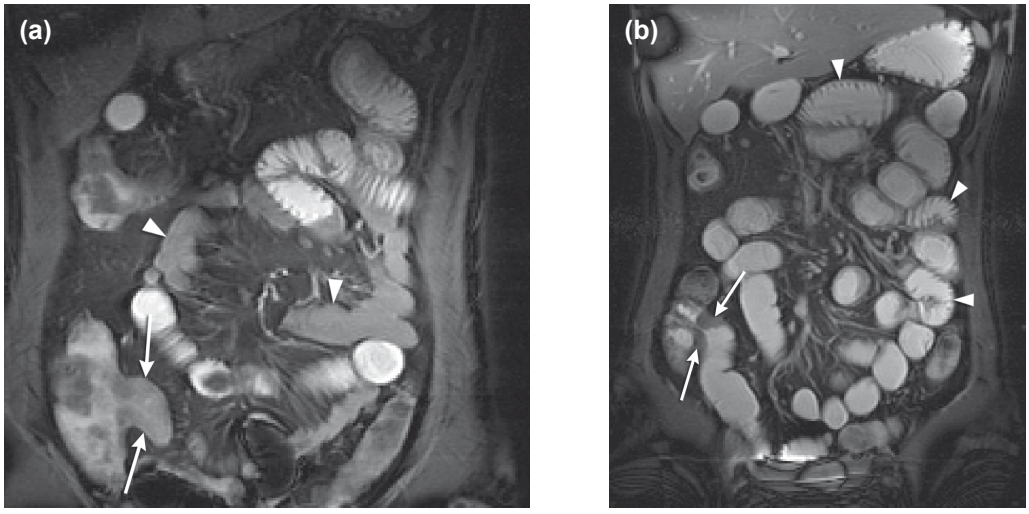


Figure 3.
31-year-old male with known Crohn's disease.
a, Coronal true fast imaging with steady-state precession (FISP) and fat saturation shows no distention of jejunum (arrowheads) and suggesting a wide-open terminal ileum (arrows).
b, Coronal true FISP image obtained with fat saturation during optimal distention shows normal jejunal loops (arrowheads) and short segment of bowel wall thickening of terminal ileum with high-grade stenosis (arrows). Optimal distention contributes to differentiation between stenosis or collapsed bowel loops.

of morphological series facilitates evaluation of surface structures (e.g., folds, ulcerations), bowel wall morphology, and thickness and extramural abnormalities (e.g., lymphadenopathy, increased mesenteric vascularization, and abscess) (Fig. 2). Bowel wall thickness larger than 3 mm must be considered as abnormal (3). We used morphological sequences to identify and localize abnormalities. Enhanced T1-weighted fat-saturation series are used to establish enhancement of the abnormalitiesand evaluate disease activity, especially in Crohn's disease.

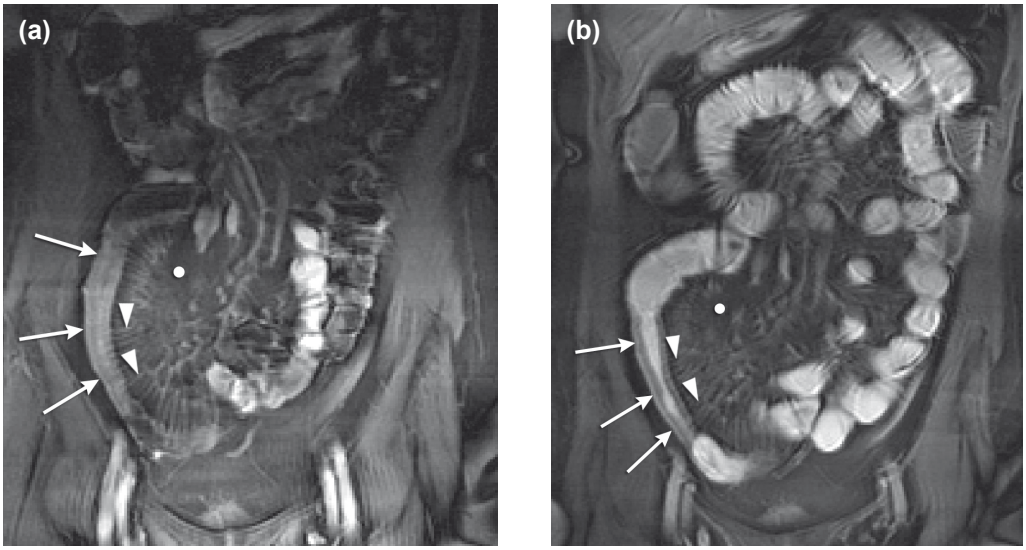


Figure 4.
38-year-old female with suspected Crohn's disease.
a, Coronal true fast imaging with steday-state precession (FISP) and fat saturation without optimal distention of small-bowel loops shows wall thickening of the ileum (arrows), with increased mesenteric vascularization (comb sign, arrowheads) and creeping fat (dot).
b, Coronal true FISP fat-saturation image obtained during optimal distention shows that the thickened ileum loop has an intermediate- to high-grade stenosis (arrows). In accordance with A, comb sign (arrowheads) and creeping fat (dot) are visualized.

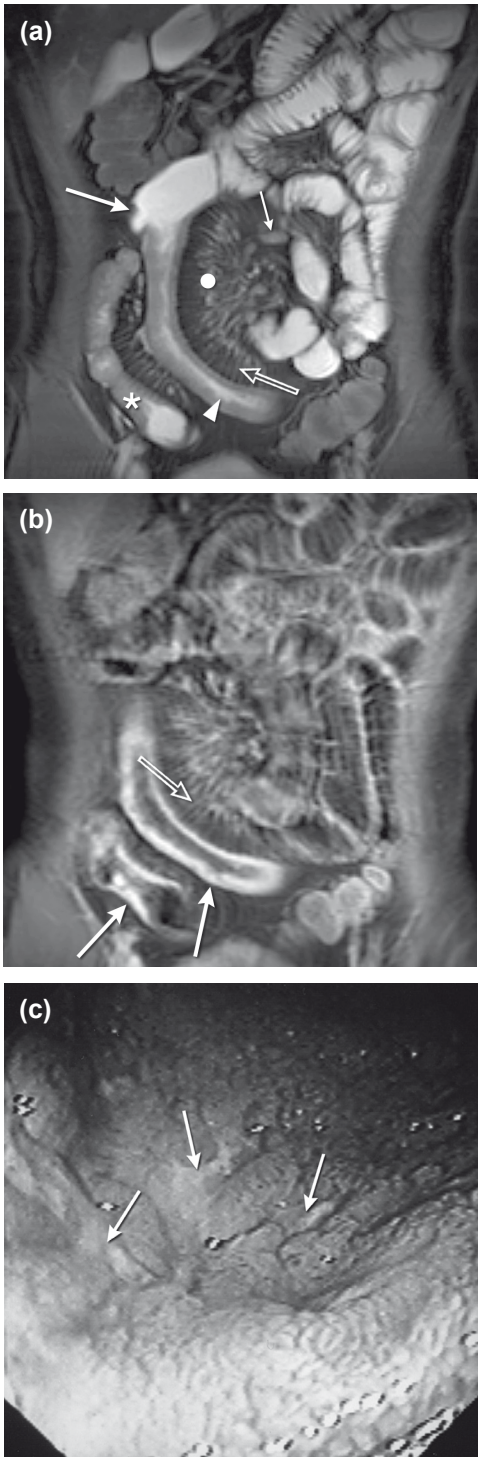


Figure 5.
21-year-old male with proven Crohn's disease.
a, Coronal true fast imaging with steady-state (FISP) and fat saturation shows two segments of bowel wall thickening, mucosal ulcerations (arrowhead), and stenosis with prestenotic dilatation (thick solid arrow) of the ileum. This figure also shows fibrofatty proliferation (creeping fat, dot), mesenteric lymph nodes (thinarrow), and increased mesenteric vascularity (comb sign, open arrow). Distal from diseased proximal segment is a second segment of thickened ileum loop (asterix): skip lesion.
b, Coronal fast low-angle shot (FLASH) 2D fat-saturation image obtained after contrast injection shows increased contrast enhancement of the two thickened segments of the small-bowel loops (skip lesion, arrows) and increased mesenteric vascularity (comb sign, open arrow).
c, Endoscopy shows ulcerations (arrows) and loss of ileal folds.

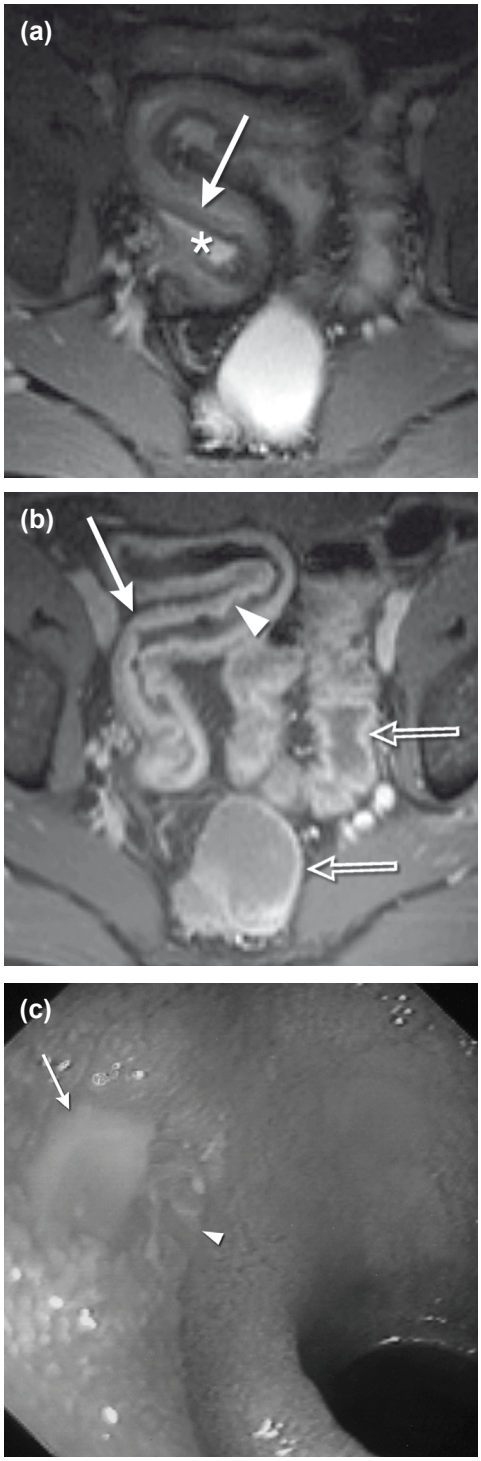


Figure 6.
42-year-old male with known Crohn's disease.
a, Axial true fast imaging with steady-state precession (FISP) and fat saturation shows diffuse thickening, edema (arrow), irregular mucosa of mainly mucosa of bowel wall of ileum. Small amount of ascitis (asterisk) was found in this region.
b, Axial enhanced fast low-angle shot (FLASH) 2D fat-saturation image shows diffuse thickening, irregular mucosa (arrowhead) and intense contrast enhancement of mainly the mucosa of bowel wall of ileum (arrow). This implies active disease. Active disease is also visible in sigmoid and rectum (open arrows).
c, Endoscopy of terminal ileum shows ulcu (arrow) with wall of edema (arrowhead).

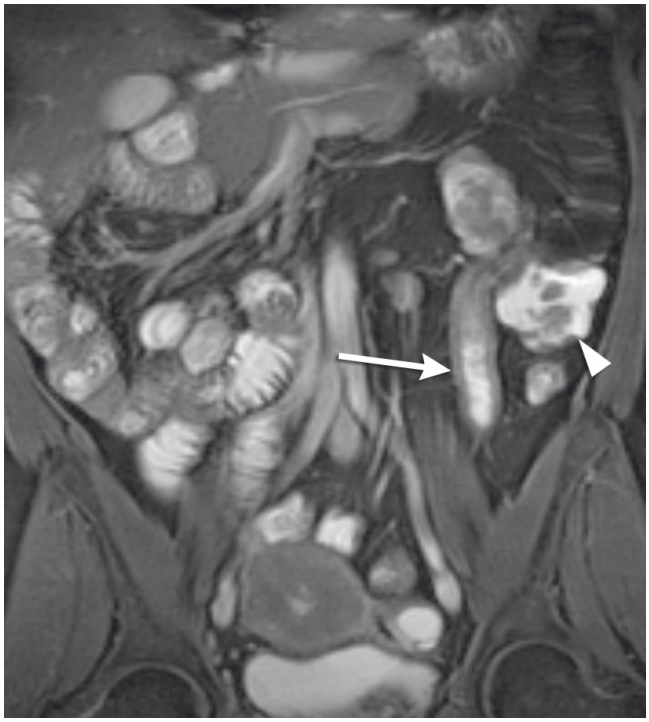


Figure 7.
46-year-old woman with midgut malrotation type 1 and suspected Crohn's disease. Coronal true fast imaging with steady-state precession (FISP) and fat saturation shows thickening of the terminal ileum (arrow), without increased contrast enhancement (not shown). Wall thickness of cecum (arrowhead). Absence of ulcerations, bowel wall edema, and increased contrast enhancement are features of inactive Crohn's disease.

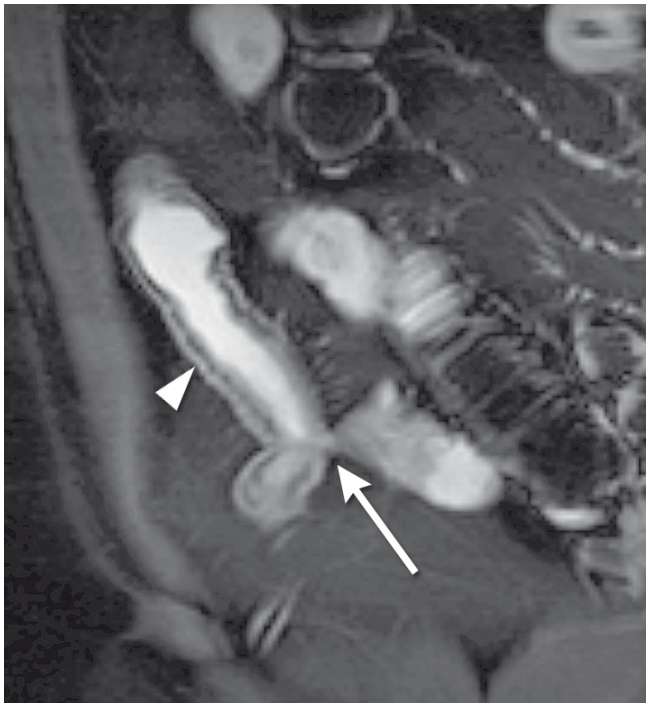


Figure 8.
60-year-old man with proven Crohn's disease. Coronal true fast imaging with steady-state precession (FISP) and fat saturation shows fat accumulation in submucosa (arrowhead), which implies subacute or chronic disease stage. Fistula between two ileum loops (arrow) is also visualized.

Crohn's disease

Crohn's disease can be localized in every segment of the small bowel, with a predilection for the terminal ileum. The major advantage of MR enteroclysis over other techniques for detection of small-bowel abnormalities is visualization of the complete small bowel and of extramural disease manifestations without the use of ionizing radiation. The imaging protocol enables identification of both the diagnosis and the extent of the disease. Functional information can be used to differentiate between collapsed normal bowel wall, active disease, inactive disease, and bowel wall stenosis (Fig. 3). Within the morphologic series, the most important characteristics for disease activity (i.e., bowel wall edema, ulcerations, and increased mesenterial vascularization (comb sign) are contained (Fig. 4). The contrast-enhanced series contributes to the differentiation between active and chronic disease. Specific characteristics for Crohn's disease– that is, creeping fat (increased mesenteric fat), skip lesions, and fistulas- can be identified on both the morphologic and contrast-enhanced series. Characteristics of active inflammation of the small bowel are bowel wall edema, ulcerations, increased mesenteric vascularization, increased enhancement of bowel wall and mesenteric lymph nodes (Fig. 5) (4). In acute inflammation, the bowel wall can have a layered pattern. A double-halo sign is related to submucosal edema (Fig. 6). Inactive disease is characterized by no abnormalities (i.e., optimal distension of bowel loops, healthy peristalsis, and no stenosis) or bowel wall thickening with relative low signal intensity representing fibrosis with limited, homogenous contrast enhancement (Fig. 7). Fat accumulation in the submucosa can be found in the subacute or chronic stage (Fig. 8). MRI can show infiltration of mesenteric fat that may evolve into a fistula (Fig. 9). Intraluminal fluid and the use of IV contrast medium can improve detection of fistulas. Abscesses are more readily identified on the sequences after the injection of IV contrast medium (Fig. 10). MRI also allows evaluation of complications associated with Crohn's disease, including intussusception, stricture formation and carcinoma.

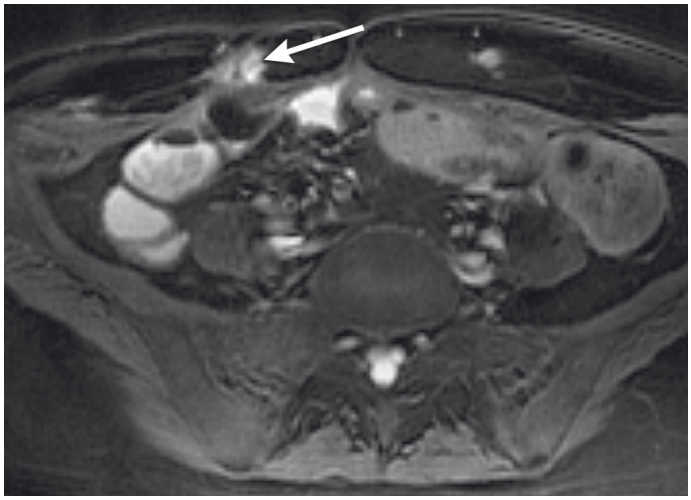


Figure 9.
45-year-old woman with proven Crohn's disease. Axial true fast imaging with steady-state precession (FISP) and fat saturation shows fistula between small bowel and soft-tissue layers of abdominal wall (arrow).

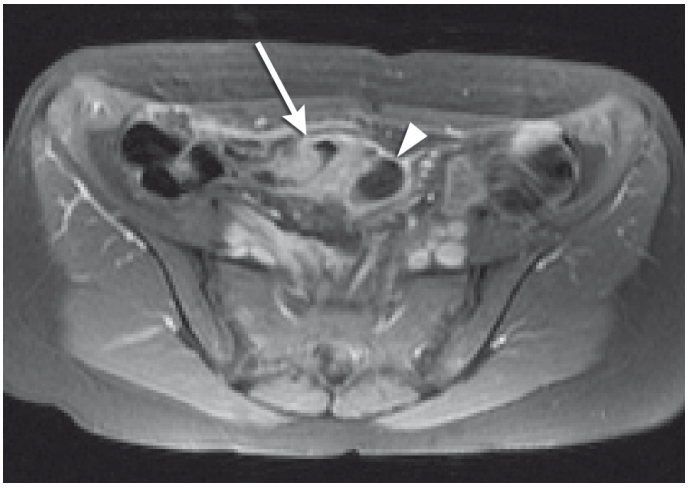
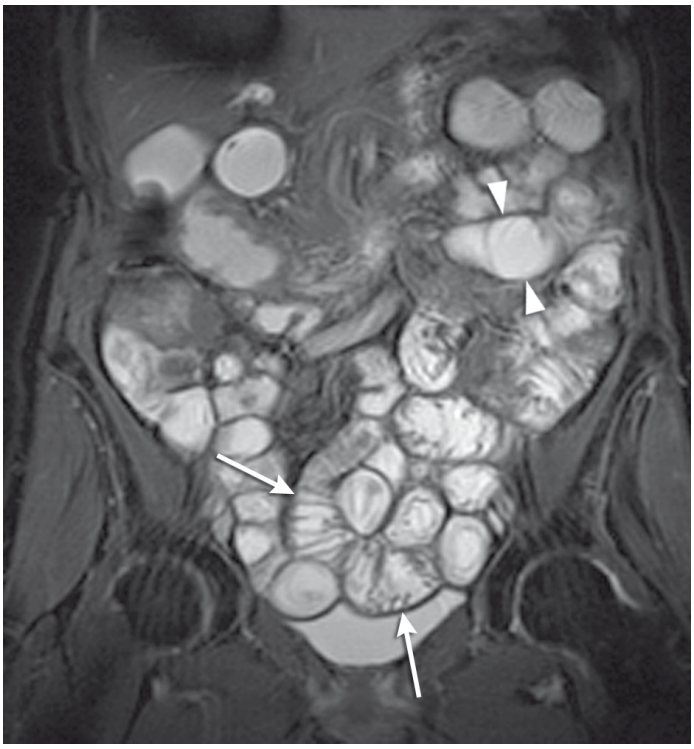


Figure 10.
37-year-old woman with known Crohn's disease. Axial fast low-angle shot (FLASH) 2D fat-saturation image obtained after contrast injection shows thickened ileum loop with intense contrast enhancement (arrow). On left side of this loop is small abscess (arrowhead).



Figuur 11.
75-year-old woman with recently proven celiac disease. Coronal true fast imaging with steady-state precession (FISP) and fat saturation shows decrease in jejunal folds (arrowheads) and increase in ileal folds ("ileal jejunization", arrows), which are characteristic features of celiac disease.

Other inflammatory small-bowel diseases

Other inflammatory small-bowel diseases can have features that resemble Crohn's disease, such as wall thickening, loss of folds, ulcerations, stenosis and increased mesenteric vascularization (comb sign). Identification of disease-specific features is therefore important in the diagnosis of Crohn's disease and include creeping fat, skip lesions and fistulas.

Celiac disease is a gluten-sensitive malabsorption syndrome, characterized by villous atrophy and crypt hyperplasia of the small intestinal mucosa, occurring at any age. Imaging features of celiac disease are small-bowel atonia, mucosal fold thickening, increased fold separation and increased ileal folds ("ileal jejunization") (Fig. 11) (5).

In a quarter of the patients with proven celiac disease, no macroscopic abnormalities can be found.

Jejunitis can be described as a most likely inflammatory entity of only the jejunum without a proven cause. It is characterized by a thickening of all jejunal wall layers

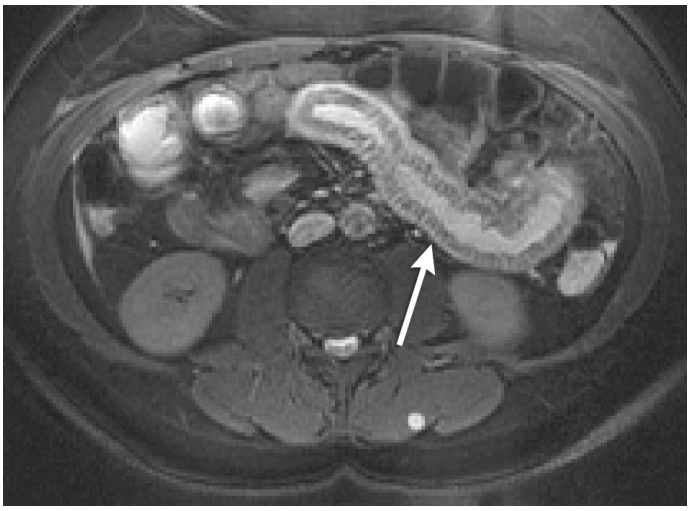


Figure 12.
31-year-old woman with abdominal pain and diarrhea. Axial true fast imaging with steady-state (FISP) and fat saturation shows diffuse thickened jejunum loop (arrow), with edema of all wall layers, especially serosa. Without proven cause, her complaints resolved spontaneously. In follow-up, no relapse of complaints is established. This is example of jejunitis without proven cause.

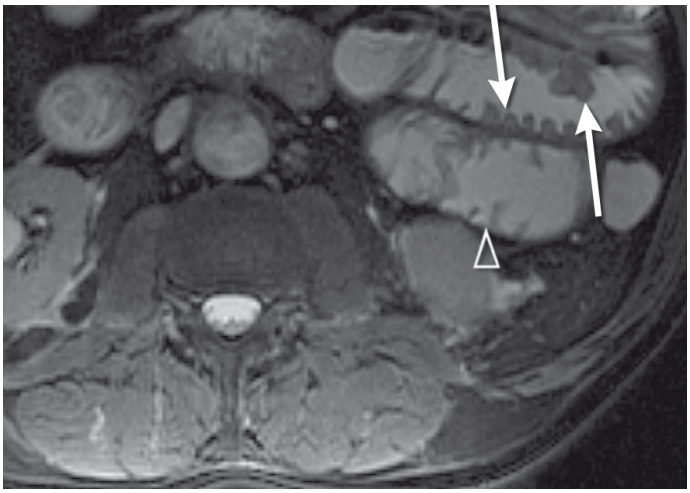
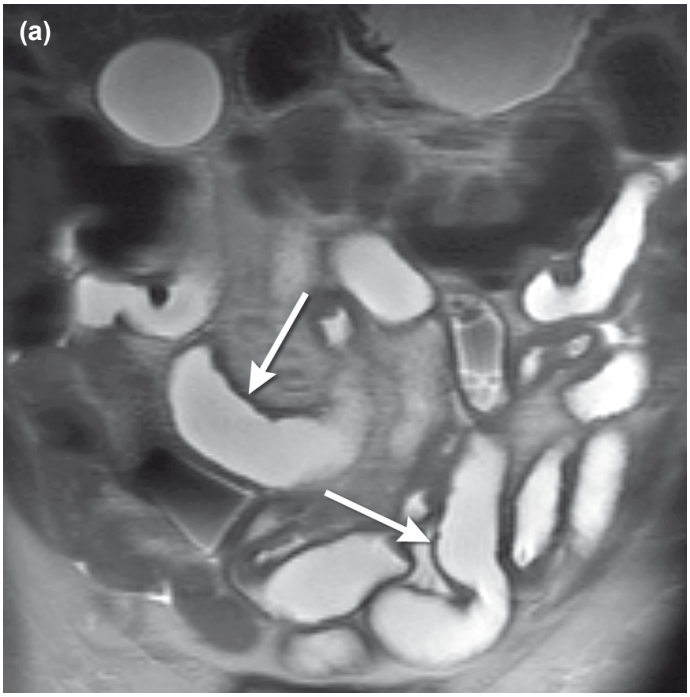


Figure 13.
65-year-old man with left flank pain and infectious jejunitis. Axial true fast imaging with steady-state precession (FISP) and fat saturation shows thickened jejunal folds (arrows). Normal folds in distal jejunum (arrowhead) are shown. Parapelvic cyst in right kidney. Sstool of this patient was giardiasis-positive.

with serosal edema (Fig. 12). The findings can resolve completely and should be differentiated from jejunitis in Crohn's disease using specific Crohn's disease features. Inflammation related to bacteria or parasites causes diffuse wall and fold thickening and resolves completely after therapy (Fig. 13). Intestinal tuberculosis is a rare manifestation in which the ileocecal region is commonly involved. In the acute stage, ulcerations can be seen; in the sub acute stage,scarring effects on the bowel wall can be identified.
Eosinophilic gastroenteropathy is a rare disorder characterized by peripheral and tissue eosinophilia infiltrating all three layers of the bowel wall that can involve any segment of the gastrointestinal tract, especially the stomach and small bowel. It is



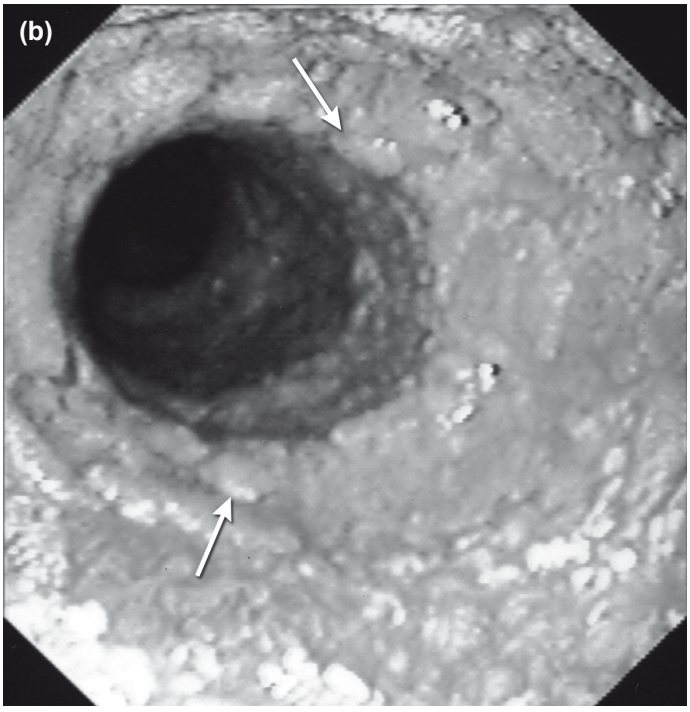


Figure 14.
66-year-old woman with proven eosinophilic gastroenteropathy.
a, Coronal true fast imaging with steady-state precession (FISP) shows diffuse loss of mucosal folds and diffuse thickened wall of all small-bowel loops (arrows). Lack of motility on the thick-slab HASTE sequence with fat saturation (not shown) is also a characteric of this disease.
b, Endoscopy shows loss of ileum folds with nodularity (arrows) of mucosa.

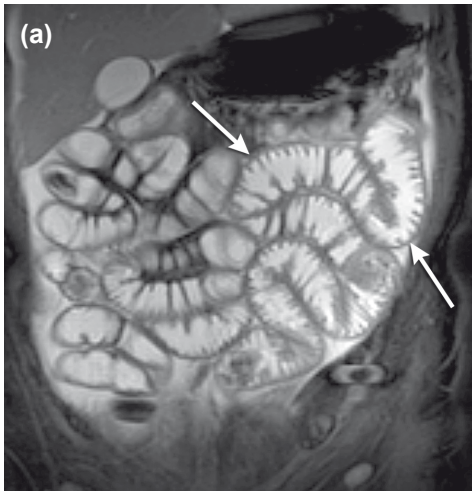
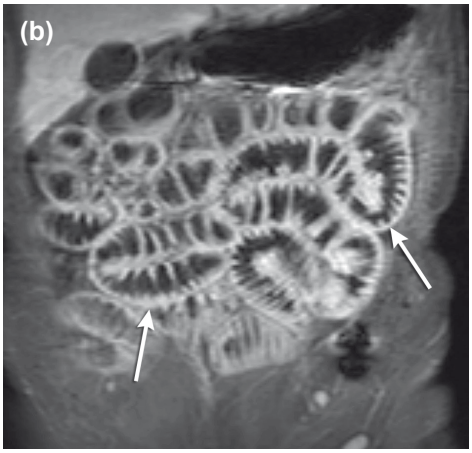
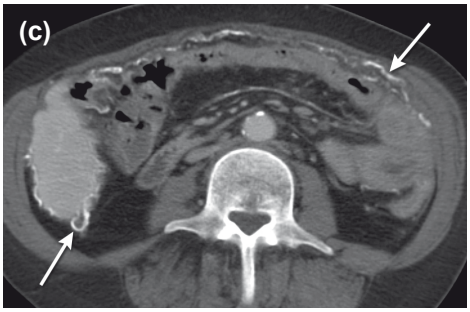


Figure 15.
44-year-old woman with peritoneal dialysis and sclerosing encapsulating peritonitis.
a, Coronal true fast imaging with steady-state precession (FISP)and fat saturation shows diffuse pronounced small-bowel wall thickening (arrows) and central localization. Thick-slab HASTE fat-saturation images reveal lack of motility (not shown).
b, Coronal fast low-angle shot (FLASH) 2D fat-saturation image obtained after contrast injection shows increased diffuse enhancement of small-bowel wall (arrows).
c, Axial CT after contrast injection shows diffuse peritoneal calcifications (arrows).

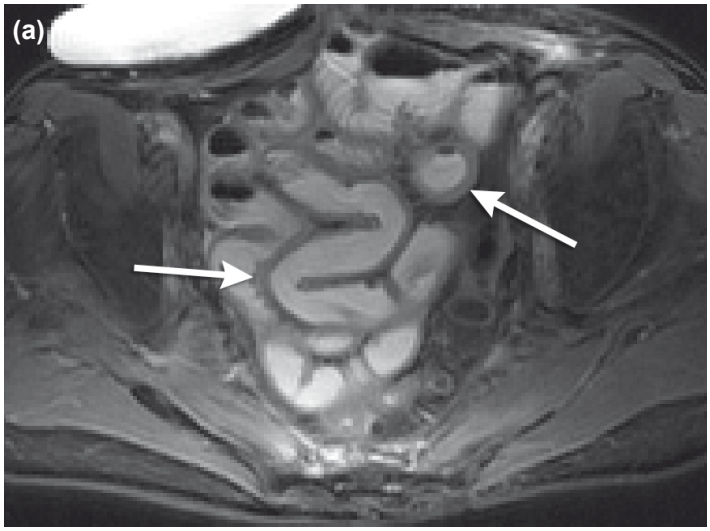




characterized by loss of all mucosal folds in the small bowel, bowel wall thickening, and atonia (Fig. 14) (6).

Sclerosing encapsulating peritonitis is a rare disorder, occurring in patients undergoing peritoneal dialysis. Lack of peristalsis at MR fluoroscopy and diffuse bowel wall thickening in the appropriate clinical setting provide ethe diagnosis. Peritoneal calcifications are conspicuous at CT (Fig. 15) (7).

Radiation enteritis is a complication after radiation therapythat occurs often within 2 years, sometimes as long as 10-20 years, after radiotherapy. The disease is characterized by diffuse mild thickening, intense contrast enhancement, loss of folds, and lack of peristalsis of the small-bowel loops in the area of previous radiotherapy (Fig. 16) (8).



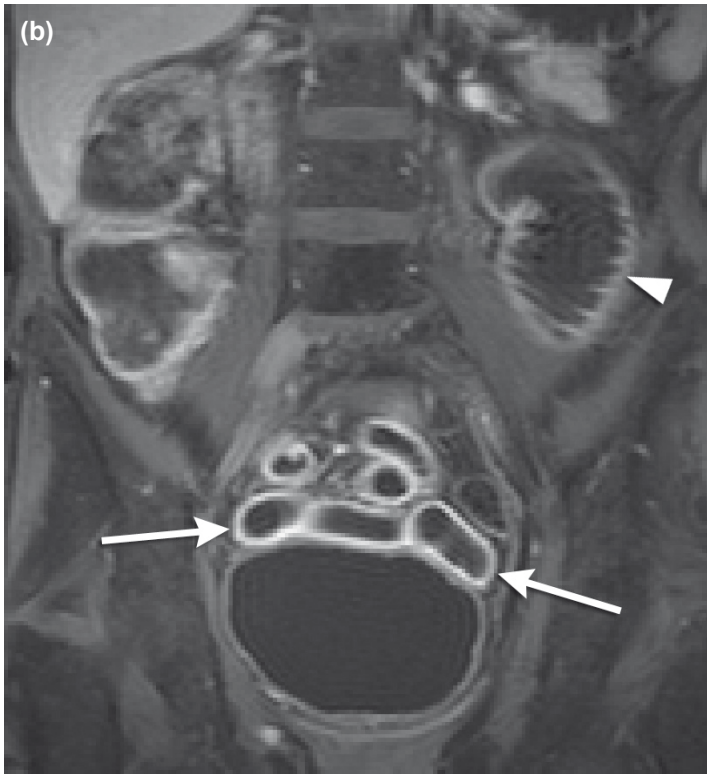


Figure 16.
75-year-old woman with radiation enteritis, 20 years after abdominal hysterectomy and radiation therapy for endometrial carcinoma.
a, Axial true fast imaging with steady-state precession (FISP) and fat saturation shows diffuse mild thickened distented ileum loops (arrows), without peristalsis (not shown). Note colostomy bag ventral of right abdominal wall after resection of colon carcinoma 2 years ago.
b, Coronal fast low-angle shot (FLASH) 2D image shows increased contrast enhancement of thickened ileum loops (arrows) in contrast with normal enhancement of colon (arrowhead).

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Jejunum abnormalities at MR enteroclysis

Review

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Abstract

Objective

MR enteroclysis has become an important tool to visualize the complete small bowel wall and extramural structures. In many centers, this technique is rapidly becoming the first-line technique for small bowel visualization. MR enteroclysis yields a diagnosis of thickened jejunal loops in some patients. In this paper, we describe an MR enteroclysis protocol and review the literature on jejunum abnormalities with several sample cases.

Conclusion

Jejunum abnormalities are not uncommon. These abnormalities can be self-limiting, but some patients suffer from infectious and other pathologic conditions of the small bowel necessitating intervention.

Introduction

MR enteroclysis is rapidly becoming the first-line technique for visualization of the complete small bowel wall and extramural structures. The technique combines excellent soft tissue contrast and multi planar imaging capabilities without the use of ionizing radiation (1). It allows control of maximal bowel distension and identification of wall abnormalities. Optimal distension under direct visualization enables evaluation of small bowel wall thickness. In some cases, this leads to a diagnosis of thickening of the jejunal wall. Until now, disorders of the jejunum have been described at conventional enteroclysis in a few case reports (2,3). In the endoscopic literature, jejunum abnormalities are more frequently described. Introduction of new techniques, in particular videocapsule endoscopy and double balloon enteroscopy, enable the evaluation of almost the complete small bowel. In this paper, we discuss the MRI technique of MR enteroclysis, review the literature of jejunum abnormalities, and demonstrate examples of jejunitis from our large teaching hospital.

MR Technique

Patient preparation

The cleansing preparation of the small and large bowel consists of a low-residue diet, ample fluids, a laxative (15 grams of magnesium sulphate (hospital pharmacy) and 2 tablets of bisacodyl (hospital pharmacy) twice a day) on the day prior to the exam, and nil per mouth on the day of the examination. Under fluoroscopic guidance (the mean area dose product is 39 μGy/m²) (4), an 8 or 10 F nasoduodenal catheter (Flocare, Nutricia, Chatel-ST-Denis, Switzerland) is placed in the distal part of the duodenum. After intubation, patients are transferred to the MR unit (1.5 T Magnetom Avanto and Symphony, Siemens, Erlangen, Germany) where the catheter is connected to an electric infusion pump (KMP 2000 Guerbet, Sulzbach, Germany). The small bowel is distended with 1,000-3,000 mL of a solution containing 0.5% methylcellulose (hospital pharmacist, Alkmaar) at an infusion rate of 60-150 mL/min. The amount administered and the infusion rate depends on the degree of bowel distension, the occurrence of gastric reflux, and the grade of bowel obstruction present.

MRI technique

MR enteroclysis is performed as previously described (1). MR imaging is performed using a torso phased-array surface coil. The MR protocol (Table 1) consists of MR fluoroscopy using a thick slab 50 mm coronal half-Fourier single-shot turbo spin echo (HASTE) with fat saturation (fs), starting at the beginning of infusion and repeated every 10 seconds during normal breathing. This allows the evaluation of small bowel transit time, luminal distension, peristalsis, and retrograde filling of the stomach. Subsequently, every 4 minutes, depending on the degree of distension observed from the HASTE images, coronal and axial true fast imaging with steady-state precession with fat saturation (True FISP fs) sequences are performed with a slice thickness of 5 mm to study morphological changes. Finally, with maximal distension, coronal and axial T2-weighted HASTE sequences and T1-weighted Volume Interpolated Breath-hold Exam (VIBE) sequences are performed. The T1-weighted VIBE-sequence is repeated 60 seconds after intravenous administration of 0.1 mmol/kg of bodyweight of Gadolinium (Magnevist, Bayer Schering, Berlin, Germany). Twenty mg butylscopolaminebromide, (Buscopan, Boehringer, Ingelheim, Germany) used as a spasmolytic, is injected before the injection of Gadolinium.

	HASTE	True FISP	HASTE	VIBE 3d
Plane	coronal	coronal and axial	coronal and axial	coronal and axial
Fatsat	yes	yes	no	yes
Breathold	no	yes	yes	yes
Timing	every 10 sec	every 4 minutes	in last part of study	in last part of study (pre and post (60 sec after) contrast)
Nr. of slices	1	coronal: 23 axial: 72	coronal: 23 axial: 75 (multi)	coronal: 80 axial: 120
Slice thickness	50 mm	5 mm	5 mm	coronal: 2 mm axial: 3 mm
Slice distance	-	coronal: 0 axial: 0,3 mm	0	coronal: 0,4 mm axial: 0,6 mm
Field of view (mm2)	400 x 400	coronal: 400 x 400 axial: 350 x 240	coronal: 350 x 350 axial: 350 x 350	coronal: 400 x 400 axial: 400 x 250
Matrix	218 x 256	coronal: 230 x 384 axial: 148 x 256	coronal: 218 x 256 axial: 154 x 256	coronal: 205 x 256 axial: 128 x 256
Repetition time (msec)	849	coronal: 3,97 axial: 3,69	coronal: 938 axial: 800	coronal: 3,23 axial: 3,23
Echo time (msec)	59	coronal: 1,99 axial: 1,85	coronal: 85 axial: 118	coronal: 1,18 axial: 1,31
Flip angle	150	70	150	12
PAT factor	No	2	no	2
Imaging time per section (sec)	0.8	coronal: 0,6 axial: 0,4	coronal: 0,9 axial: 0,8	coronal: 0,3 axial: 0,2
Imaging time per volume (sec)	0.8	coronal: 14 axial: 30	coronal: 22 axial: 60 (multi)	coronal: 26 axial: 18
Voxel size (mm)	2,0 x 1,6 x 50	coronal: 1,7 x 1,0 x 5,0 axial: 1,6 x 1,4 x 5,0	coronal: 1,6 x 1,4 x 1,5 axial: 1,7 x 1,4 x 5,0	coronal: 2,0 x 1,6 x 2,0 axial: 2,0 x 1,6 x 3,0

Table 1.
MRI enteroclysis scan parameters

Normal appearance

The normal jejunum has more and thicker folds as compared to the ileum. Optimal distension of this part of the jejunum is important to rule out intraluminal and mural abnormalities (e.g. polyps, ulcerations, neoplasms). The coronal thick slab HASTE images therefore facilitate acquisition of valuable information, not only for timing of morphological sequences with optimal distended bowel loops, but for identifying fixed bowel loops and luminal stenosis as well. The higher spatial and contrast resolution

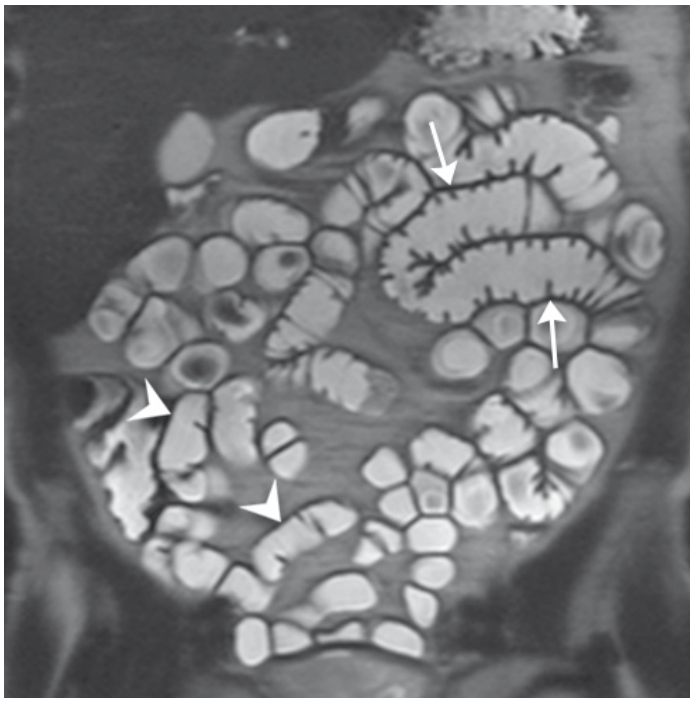

Figure 1.
Normal appearance of small bowel. Coronal HASTE shows normal folds and wall thickness of jejunum (arrows) and ileum (arrowheads) with optimal small bowel distension.

of the morphological series facilitates evaluation of mucosal structures (e.g. folds, ulcerations), bowel wall morphology (Fig. 1), thickness, and extramural pathology (e.g. lymphadenopathy, increased mesenterial vascularization, or abscess). Bowel wall thickness greater than 3 mm must be considered as abnormal (5). We used morphological sequences to identify and localize pathology. Post-contrast T1 fat saturation series are used to identify normal and pathologic enhancement and evaluate disease activity, especially in Crohn's disease. In the absence of pathology, the jejunum shows increased contrast enhancement after contrast injection, in contrast to the ileum as a cause of the fold and wall anatomy difference (Fig. 2).

Abnormalities

Only a few papers have reported on jejunum abnormalities detected by either MR imaging, CT, or conventional enteroclysis. These papers (6,7,8) often focused on diseases which generally affect the small bowel without jejunum predilection (e.g. Crohn's disease, familial adenomatous polyposis, Peutz-Jeghers syndrome). Some patients have localised jejunal disorders due to conditions such as a jejunal neoplasm,

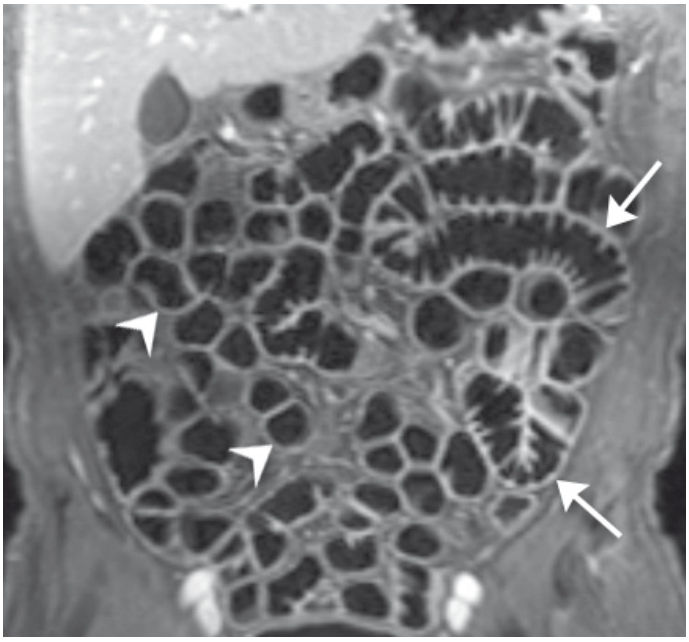

Figure 2.
Normal contrast enhancement of small bowel. Coronal VIBE with fat saturation shows normal enhancement of jejunum (arrows) and ileum (arrowheads). Jejunum has a higher contrast enhancement in contrast to ileum as a cause of folds and wall thickness morphology.

malignant histiocytosis, angiosarcomatosis of the jejunum, or jejunitis after chemotherapy (9,10,11). The clinical information (e.g. chemotherapy) and morphology (e.g. neoplasm typically shows abrupt transition with adjacent normal bowel and lobulated, irregular contours, with wall thickness of more than 1 cm) are important for a correct diagnosis. Jejunum abnormalities without involvement of other bowel segments are rare, even in selected cases referred for enteroclysis.

Jejunal wall thickness greater than 3 mm must be considered as abnormal (5). There are different types of bowel wall thickening. Uniform thickening is wall thickening with isointense signal intensity as compared to normal bowel wall. In contrast, submucosal and subserosal edema is based, respectively, on a submucosal and subserosal linear band of high signal intensity on the true FISP sequences. Jejunal wall thickening can be mild (<1.5 cm) or marked (>1.5 cm), and can symmetric or asymmetric. The length of bowel wall thickening can be focal (<10 cm), segmental (10-30 cm), or diffuse (12). Mesenterial infiltration is presented as a sign of linear or diffuse high signal intensity in the mesentery on the True FISP sequences.

Jejunal wall abnormalities can be divided into infectious- and non-infectious inflammatory abnormalities, and neoplasms (Table 2). Inflammatory small bowel diseases can have features as in Crohn's disease, such as wall thickening, loss of

Table 2. Differential diagnosis of jejunum wall thickening

- Infectious inflammatory
  - Infectious jejunitis of (un)known origin
  - Gastrointestinal tuberculosis
  - Diverticulitis
- Non-infectious inflammatory
  - Crohn's disease
  - Celiac disease
  - Eosinophilic jejunitis
  - Eosinophilic gastro-enteropathy
  - Ulcerative jejunitis
  - Ischemia: primary vascular or extrinsic causes (e.g. strangulation, volvulus)
  - Submucosal hemorrhage
  - Edema as a cause of low protein and cirrhosis
  - Radiation enteropathy
  - Graft-versus-host disease
- Neoplasms
  - Malignant
    - Carcinoid
    - Adenocarcinoma
    - Lymphoma (malignant histiocytosis)
    - Malignant Gastrointestinal stromal tumor (GIST)
    - Metastases (melanoma, breast, bronchial carcinoma)
    - Leiomyosarcoma
    - Angiosarcomatosis
  - Benign
    - Leiomyoma
    - Adenoma
    - Lipoma
    - Hemangioma
    - Lyphangioma
    - Endometriosis
    - Intramural hemorrhage
    - Angioedema
    - Benign Gastrointestinal stromal tumor (GIST)
    - Hyperplastic polyp
    - Familial adenomatous polyposis
    - Hamartomatous polyps in Peutz-Jeghers syndrome

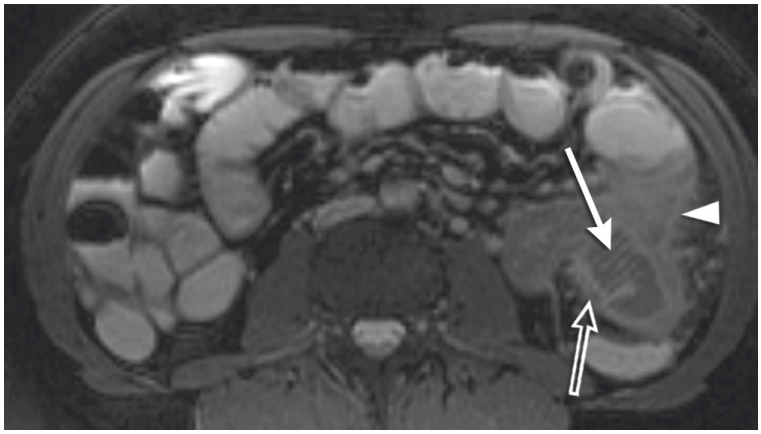

Figure 3.
Infectious jejunitis. Axial True FISP with fat saturation shows diffuse thickened jejunum folds (arrow) with subserosal edema (open arrow), mesenterial infiltration (arrowhead), lymph nodes and ascites (not shown).

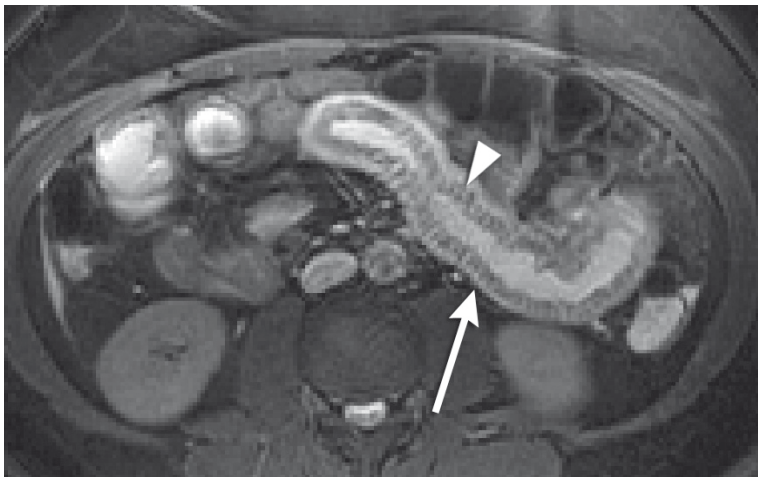

Figure 4.
Jejunitis without proven cause. Axial True FISP with fat saturation shows diffuse thickened jejunum loop, with subserosal edema (arrow) and thickening of folds (arrowhead). Note: the bright spot on left longissimus dorsi muscle is an infolding artefact of the enteroclysis tube. Reprinted with permission from the American Journal of Roentgenology.

folds, ulcerations, stenosis, and increased mesenterial vascularisation (comb sign). Therefore, identification of disease specific features is important. In Crohn's disease, these include creeping fat, skip lesions, and fistulas.

Infectious inflammatory jejunitis

Jejunitis is more often described in endoscopic literature than in radiological literature. This led to the description of different types of jejunitis, such as infectious jejunitis, with or without a definite etiology (13,14). Jejunitis can be described as a most likely inflammatory entity of only the jejunum without a proven cause (Fig. 3). Infectious jejunitis mostly presents as a mild, symmetric, segmental thickening of all jejunal wall layers with

serosal edema (Fig. 4). Inflammation due to bacteria or parasites causes diffuse wall and fold thickening, and resolves completely after therapy (Fig. 5). Intestinal tuberculosis is a rare manifestation, especially in the jejunum, where in the acute stage, ulcerations can be seen; in the sub acute stage, scarring effects on the bowel wall can be identified.

Non-infectious inflammatory jejunitis

Crohn's disease can selectively affect the jejunum, but this is rare. The disease has a high recurrence rate in this segment, and the radiological features differ in frequency

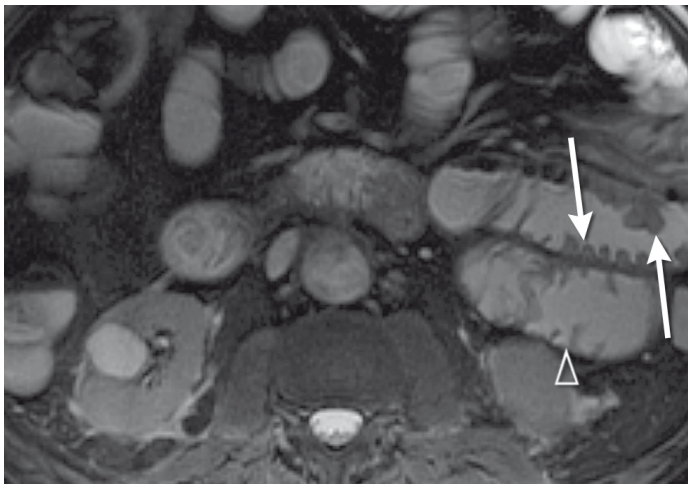

Figure 5.
Infectious jejunitis as a cause of giardiasis. Axial True FISP with fat saturation shows focal thickened jejunal folds (arrows). Normal folds in distal jejunum (arrowhead). Parapelvine cyst in right kidney.

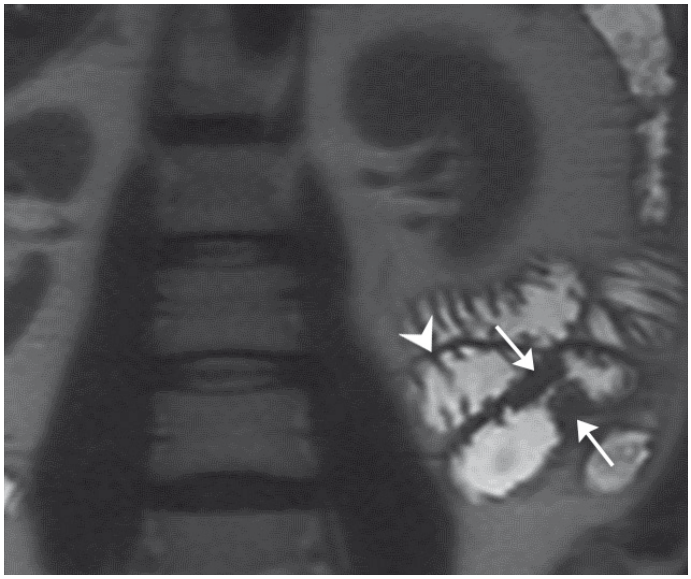

Figure 6.
Inactive Crohn's disease. Coronal HASTE shows short segment of bowel wall thickness (arrows) and stenosis, without edema and without increased contrast enhancement (not shown) in contrast to normal jejunal wall (arrowhead).

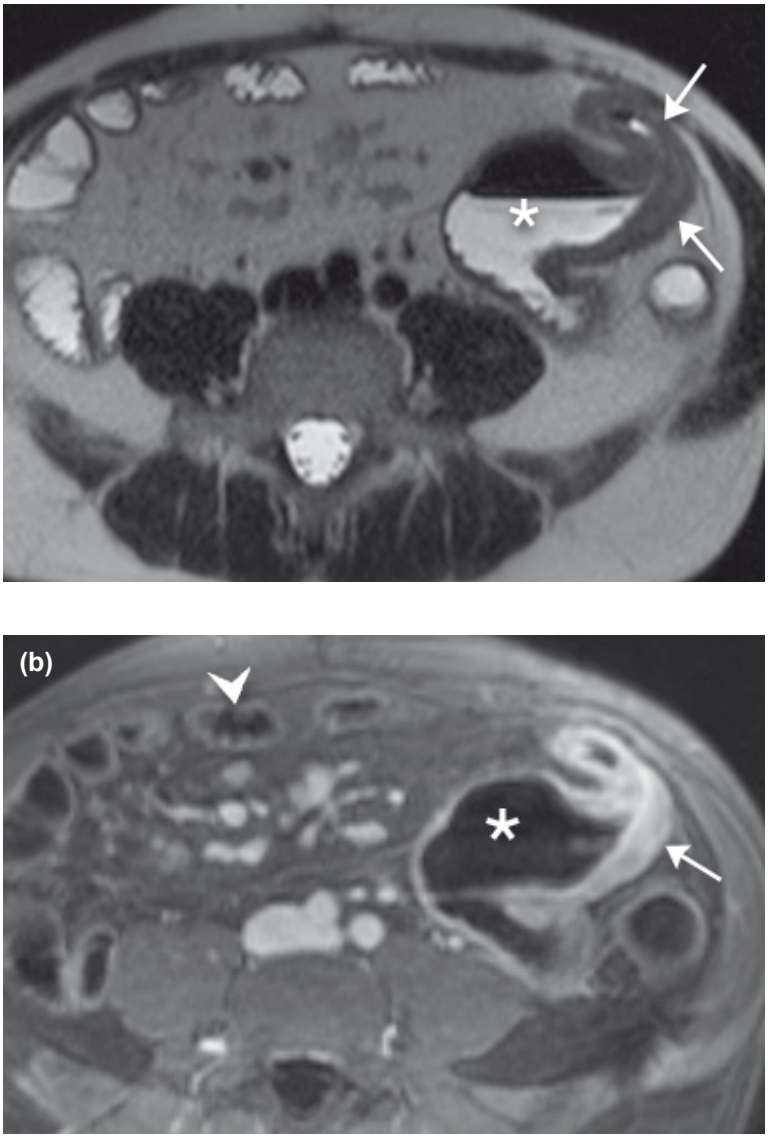

Figure 7.
Active Crohn's disease. Axial HASTE (a) and axial VIBE with fat saturation (b) shows segmental mild thickening of jejunum loop (arrows) with prestenotic dilatation (asterisk), with increased enhancement (arrows). Enhancement of normal jejunum loops (arrowhead).

from those in the ileum (Fig. 6) (15). Major advantages of MR enteroclysis over other techniques for detection of small bowel pathology are visualization of the complete small bowel and demonstration of extramural disease manifestations, without the use of ionizing radiation. The imaging protocol enables identification of both the diagnosis and the extent of the disease. Within the morphological series, the most important characteristics for disease activity [i.e. bowel wall edema, ulcerations, and increased mesenterial vascularization (comb sign)] are contained. Jejunal wall thickening is mostly mild, symmetric, and segmental. With controlled small bowel distension, small mucosal lesion can also be identified. The post-contrast series contributes to the differentiation between active (Fig. 7) and chronic disease. This is important for therapy in high grade stenosis. Active lesions will require medical therapy, in contrast to inactive stenosis in which surgery is an option. Specific characteristics for Crohn's disease, i.e. creeping fat (increased mesenterial fat) (Fig. 8), skip lesions, and fistulas, can be identified on both the morphological and post-contrast series. MR also allows evaluation of Crohn's disease complications, including fistulas, abscesses, intussusception, stricture formation and carcinoma.

The specific imaging features of celiac disease in the jejunum are small bowel atonia and increased fold separation (Fig. 9) (16). Jejunal wall thickening is not a common sign in celiac disease. MR enteroclysis can also diagnose celiac complications such as small bowel lymphoma.

Rare non-infectious disorders leading to inflammation of the jejunum include eosinophilic jejunitis (17), eosinophilic gastro-enteropathy, Henoch-Schönlein purpura (sometimes without skin abnormalities) (18), Sjögren disease (19), and jejunitis after chemotherapy or radiotherapy. Eosinophilic gastro-enteropathy is a rare disorder, characterized by peripheral and tissue eosinophilia, infiltrating all three layers of the bowel wall that can involve any segment of the gastrointestinal tract, especially stomach and small bowel. It is characterized by loss of all mucosal folds in the small bowel, bowel wall thickening, and atonia (Fig. 10) (20).

The most common causes of (chronic) intestinal ischemia is of arterial origin, such as atherosclerotic lesions, embolism, or a low cardiac output (21). Chronic intestinal ischemia presents as mild symmetric bowel wall thickening of a large segment (Fig. 11). In some cases, the jejunum wall is very thin as caused by necrosis.

Submucosal hemorrhage, as caused by undergoing anticoagulation therapy or

Figure 8.
Crohn's disease. Coronal True FISP with fat saturation shows focal symmetric thickening of distal jejunum wall (arrow) with prestenotic dilatation and hypertrophic mesenterial fat (asterisk).

Figure 9.
Celiac disease. Coronal True FISP fs shows decrease in jejunal folds (arrowheads) and increase in ileal folds ("ileal jejunization", arrows), which are characteristic features of celiac disease.

Figure 10.
Eosinofilic gastro-enteropathy. Coronal True FISP with fat saturation shows diffuse loss of mucosal folds and diffuse thickened wall of all small bowel loops, especially jejunum loops (arrows).

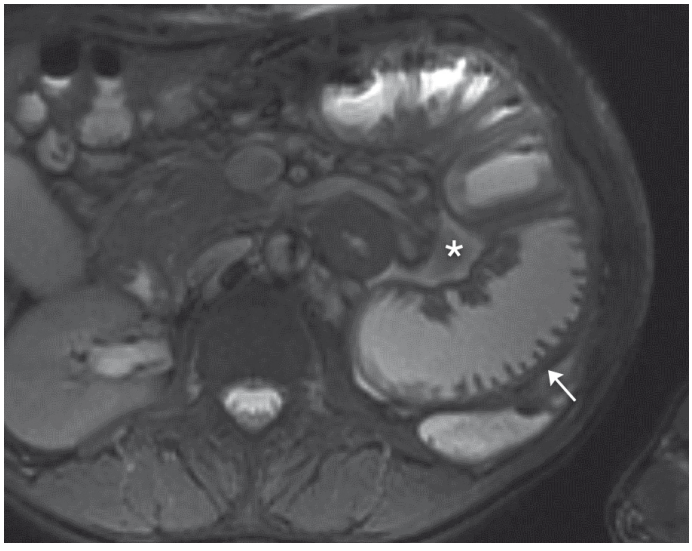

Figure 11.
Chronic jejunal ischaemia. Axial True FISP with fat saturation shows mild jejunal wall thickening of a large segment (arrows) with small amount of ascites (asterisk). CT-angiography (not shown) revealed mesenteric arterial stenosis, and 24 h jejunal tonometry (not shown) revealed ischemia.

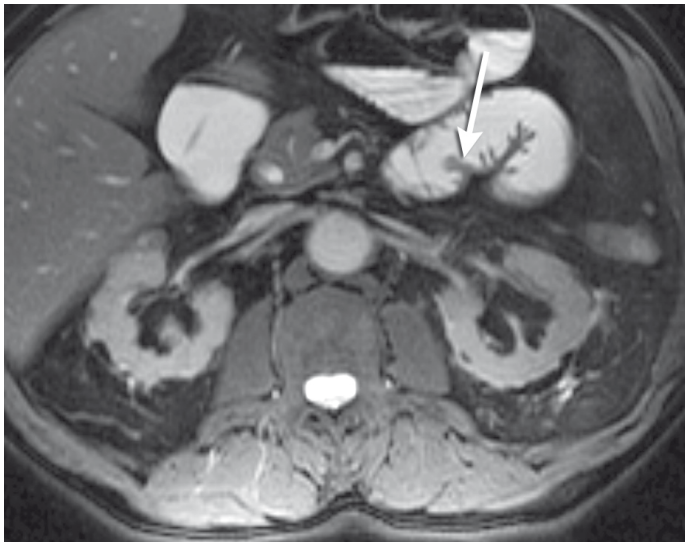

Figure 12.
Adenoma. Axial True FISP with fat saturation shows a polyp (arrow) in proximal jejunum.

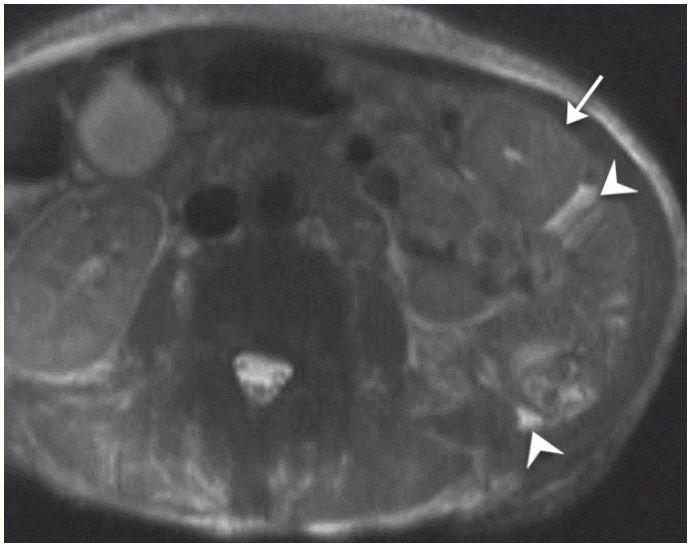

Figure 13.
Lymphoma. Axial True FISP with fat saturation shows focal marked symmetric thickening of jejunum (arrow). Small amount of ascites (arrowhead).

underlying diathesis, presents as a mild, symmetric, segmental jejunal wall thickening and has a characteristic clinical presentation.
Edema, as caused by low protein and cirrhosis, presents as mild, symmetric diffuse bowel wall thickening.
Diverticula can occur either solitarily or multiply in the jejunum. They can be inflamed which leads to a focal mild jejunal wall thickening.

Neoplasms

Leiomyomatous tumors are the most common benign small bowel neoplasms and can be either intraluminal or extraluminal. Adenoma can be solitary or multiple. Detection of polypoid lesions requires adequate small bowel distension which is facilitated by MR enteroclysis (Fig. 12). Multiple adenomas are seen in Peutz-Jeghers syndrome and familial adenomatous polyposis (7). These tumors mostly enhance with Gadolinium, becoming isointense in contrast to the small bowel wall.
Adenocarcinoma is the most common malignant neoplasm of the small intestine, most common in the duodenum and jejunum. On MR enteroclysis, it appears as a focal mild asymmetric wall thickening, narrowing of the lumen, possibly with polypoid or ulcerations. It enhances homogeneously after contrast injection. In 50% of cases, associated lymphadenopathy is found.
Lymphoma can be primary or secondary, based on whether it is preceded by other disorders, such as adult celiac disease, immunoproliferative disease, or immunodeficiency syndromes. On MR enteroclysis (Fig.13), lymphoma can present as a marked symmetric segmental jejunal wall thickening with mesenteric involvement (22). After contrast injection, lymphomas tend to enhance homogeneously.
Gastrointestinal stromal tumors (GIST) present as marked asymmetric focal jejunal wall thickening (Fig. 14). In contrast with adenocarcinoma, GIST is an assymetric, mostly large tumor with intense Gadolinium enhancement.
Metastases of tumors can be located in the jejunal wall. Melanoma has a predilection for spreading to the small bowel (Fig. 15), with solitary or diffuse wall thickening. It can have a high signal intensity on the pre-contrast images and can enhance homogeneously after contrast injection.
Rare malignant neoplasms located in the jejunum are carcinoid, malignant histiocytosis (6), leiomyosarcomas, and angiosarcomatosis (9). Neoplasms can develop into fistulas between small bowel loops and surrounding structures (Fig. 16).

Figure 14.
Gastrointestinal stromal tumor. Coronal True FISP with fat saturation shows asymmetric marked thickening of proximal jejunum wall (arrows). Normal jejunal wall distal to this abnormality (solid arrowhead). Normal ductus choledochus (open arrowhead), aorta (asterisk), and stomach wall (open arrow).

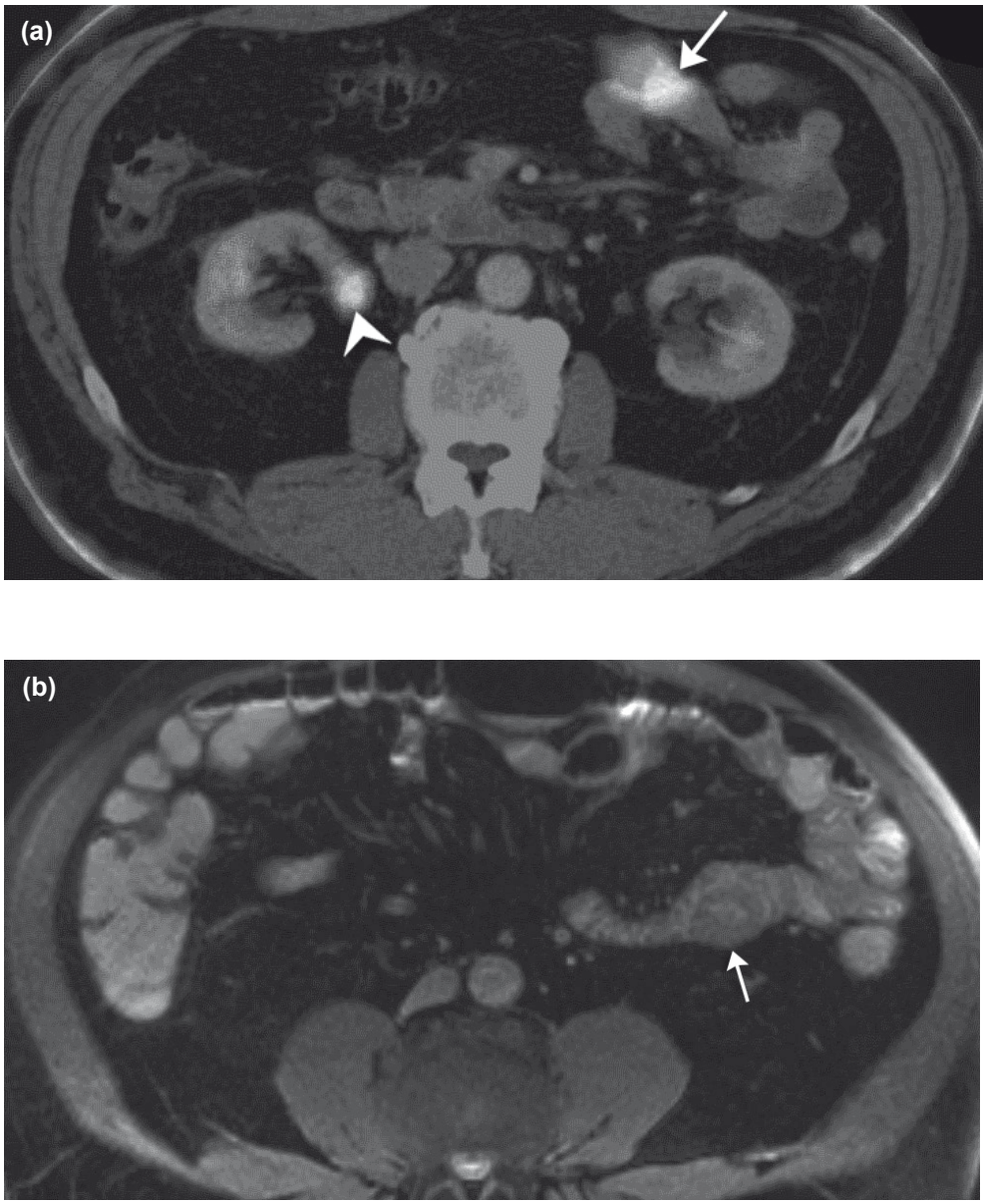

Figure 15.
Melanoma metastasis. PET/CT (a) shows focal increased FDG-uptake in jejunal loop. FDG excretion in right renal pelvis (arrowhead). (b) Axial True FISP with fat saturation shows focal mild asymmetric thickening of jejunum (arrow).

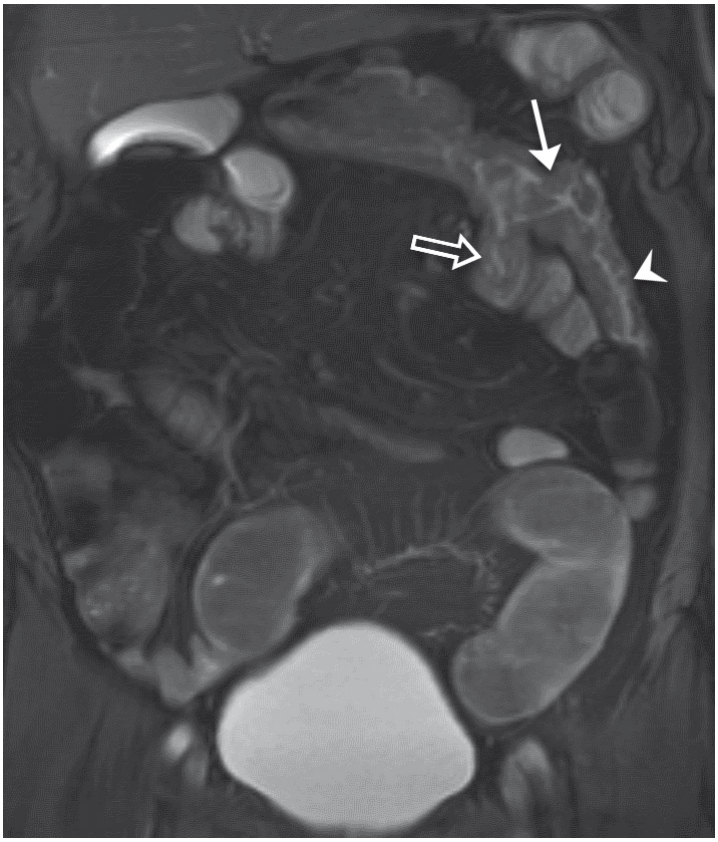

Figure 16.
Jejuno-colonal fistula as a cause of coloncarcinoma. Coronal True FISP with fat saturation shows fistula (solid arrow) between proximal jejunum (open arrow) and colon (arrowhead).

In conclusion, MR enteroclysis occasionally identifies patients with thickened jejunum wall abnormalities. This finding has not attracted much attention until now. It could be of inflammatory origin and may be self limiting; however, some patients require intense treatment and follow-up.

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Magnetic Resonance Imaging of the Small Bowel with the True FISP Sequence: Intra- and Inter-observer Agreement of Enteroclysis and Imaging without Contrast Material

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Abstract

Purpose:
This study aimed to determine the reliability of magnetic resonance imaging (MRI) without luminal contrast medium versus MR enteroclysis for evaluating small bowel pathology, to compare MRI and MRE findings per observer, and to compare these findings with those of an expert reader in order to determine the influence of luminal contrast medium on morphological evaluations.
Conclusion: The use of luminal contrast medium bowel improves reliability for measuring bowel wall thickness and for the diagnosis and grading of obstruction when evaluating the small bowel.

Introduction

Magnetic resonance imaging (MRI) is widely used modality for imaging the small bowel; however, optimal bowel preparation for MR examination has yet to be determined (1-4). Luminal contrast medium is used in most studies, either by enteroclysis (5-8) or by oral administration (9-12), although imaging can be performed without the use of luminal contrast medium (13-16).
There are little data that directly compare MR findings of the small bowel with and without use of luminal contrast, and the relative accuracies and reliabilities are not known. However, information about the contribution of luminal contrast medium is important. If administration of luminal contrast medium was not a prerequisite for MRI of the small bowel, then patient planning, the duration of scanning, and patient acceptance might all be affected.
The purpose of our study was to compare image quality, the degree of bowel distension, and interobserver variability of MRI using enteroclysis (MR enteroclysis) and MRI of the small bowel without luminal contrast medium (MRI). A secondary aim was to compare MRI and MR enteroclysis findings between blinded observers and compare their findings with scores made by an expert reader in order to determine the influence of luminal contrast medium on morphological evaluation.

Materials and Methods

Study population

Consecutive patients referred to the radiology department of a teaching hospital for evaluation of the small bowel by MR enteroclysis from November 2003 through August 2004 were included in this prospective cohort study. Patients had been referred by a gastroenterologist or a surgeon on suspicion of small bowel pathology. The general exclusion criteria for MR procedures (e.g. claustrophobia, pregnancy) were applicable. Also, patients were excluded on the basis of suspicion of small bowel obstruction, an intra-abdominal abscess or post-operative suture leakage. Informed consent was waived by the Institutional Review Board.

MR imaging

Patient preparation

Preparative cleansing of the small and large bowels consisted of a low-residue diet, ample fluids, and laxatives (15 g of magnesium sulphate [hospital pharmacy] and two tablets of bisacodyl [hospital pharmacy; twice per day]) on the day prior to the examination, and nil per mouth on the day of the examination. Under fluoroscopic guidance, a 10 F nasoduodenal catheter (Flocare, Nutricia, Châtel-St-Denis, Switzerland) was inserted into the distal part of the duodenum. After intubation, patients were transferred to the MR unit (1.5 T Magnetom Symphony, Siemens, Erlangen, Germany) where the catheter was connected to an electric infusion pump (Roentgen Contrast Mittel Pumpe, Nicholas, Sulzbach/Taunus, Germany). The patients were positioned in supine position and the small bowel was distended with 900-3500 ml of 0.5% methylcellulose at 40-200 ml/min at body temperature. The amount administered and the infusion rate depended on the degree of bowel distension, the occurrence of gastric reflux, and the grade of bowel obstruction present.

MRI technique

MRI was performed using a torso phased-array surface coil. At baseline (i.e., before starting contrast infusion) a fat suppressed (fs) true fast imaging with steady-state precession (FISP) sequence (TR=5.04 ms, TE=2.52 ms, matrix=151 × 256,

FOV=400 × 400, slice thickness=5 mm) was performed in the coronal and axial planes. These sequences were repeated approximately every 5 min during the filling process. To monitor the filling process, a coronal fs half-Fourier single-shot turbo spin echo (HASTE) sequence (TR=849 ms, TE=58 ms, matrix=218 × 256, FOV=250 × 250; one 50-mm slice) was performed repeatedly after infusion of luminal contrast medium. When maximum bowel distension was obtained, as judged on the coronal HASTE images, the FISP sequence was again performed in the coronal and axial planes. Additionally, coronal and axial fs T1-weighted fast low angle shot (FLASH) sequences (TR=212 ms, TE=308 ms, matrix=157 × 256, FOV=400 × 350, slice thickness=5 mm) were performed. The T1-weighted FLASH fs sequence was repeated 60 seconds after intravenous administration of 0.1 mmol/kg of bodyweight of gadolinium (Magnevist, Schering, Germany). No spasmolytic medication was administered.

Image evaluation

In order to determine the contribution of luminal contrast medium to small bowel assessment, the true FISP fs images made at baseline were compared with the true FISP fs images made at maximum bowel distension. Comparison of the T1-weighted FLASH sequences was not performed because intravenous contrast medium was administered only once per examination. Two data sets were prepared for each patient in order to allow independent assessment of the baseline images and the images with maximal distension. One set of images consisted of the coronal and axial true FISP fs images made before contrast administration (MRI) and one set consisted of the images acquired after contrast administration by enteroclysis (MR enteroclysis).

In order to evaluate the images, the small bowel was divided into four segments: duodenum, jejunum, proximal ileum, and distal (last 30 cm) ileum. If patients had previously undergone ileocecal resection, the neoterminal ileum was scored as distal ileum. Small bowel loops left of an imaginary line from the liver dome to the roof of the left acetabulum were considered jejunum; all bowel loops located right of this imaginary line were considered ileum.

The MR images were evaluated both qualitatively and morphologically. For qualitative assessment, both image quality and degree of bowel distension were scored. Image quality was graded per examination on a three–level scale: nondiagnostic images (with disturbing artifacts), images with numerous artifacts (without disturbing artifacts), or images of good diagnostic quality (without artifacts); bowel distension was graded

per bowel segment as either insufficient (i.e., collapsed bowel loops) or sufficient for diagnosis (small bowel lumen measuring >0.5 cm). For morphological evaluation, bowel wall thickness was measured in each bowel segment using digital calipers. Measurements were made at the site of the most bowel wall thickening as visualized on the MR images. The observers could use both the axial and coronal images for this purpose. Abnormal bowel wall thickness was defined as greater than 3 mm. Bowel obstruction was scored on a three-level scale as absent, low grade (luminal reduction without prestenotic dilatation), or high grade (luminal reduction with prestenotic dilatation). Bowel obstruction was considered present if it could be observed in both image planes. Normal contraction was discriminated from low-grade obstruction by evaluating the different planes as they were made consecutively.

Absence or presence of mucosal ulcerations, polyps, and increased mesenteric vascularisation (comb sign) was scored per bowel segment. Ulcerations were defined as mucosal irregularities. A polyp was defined as an intraluminal mass larger than the surrounding folds, and the comb sign was deemed present if pronounced linear structures were noted on the mesenteric site of the bowel. Absence or presence of fibrofatty proliferation and presence of mesenteric lymph nodes, ascites, fistula, and abscess were scored per examination. Fibrofatty proliferation was defined as a focal increase in mesenteric fat. Mesenteric lymph nodes were defined as round or oval structures in the mesentery. The short-axis diameter of the largest lymph node was measured. Ascites was defined as free intraperitoneal fluid. A fistula was defined as a fluid-filled connection between two organs or structures. An abscess was defined as a localized encapsulated fluid collection, with or without contained air.

Observers

The MRI and MR enteroclysis data sets were presented to two blinded observers at two different times, with a minimum interval between presentations of 6 weeks. MRI and MR enteroclysis datasets were presented in random order and were evaluated independently.

No perfect reference standard is available for the small bowel. Therefore, for this study, to determine the degree of consensus, the scores of the two blinded observers were compared to the scores of an expert reader (unblinded) who had performed over 200 MR enteroclysis assessments and 50 MRI studies of the small bowel with oral contrast medium. The reproducibility of the expert's readings was evaluated by an intraobserver

agreement procedure. A 6-month interval occurred between the first and second scorings by the expert reader in order to prevent recall bias. The findings from the first read were used to determine the degree of consensus between the observers and the expert reader.

The expert reader had access to all patient and clinical data (including follow-up) and used these data in combination with all available MR images (including the T1-weighted images) to reach a conclusion regarding disease status. The two observers had no access to patient or clinical data. The first observer was a radiologist with 5 years of abdominal MR experience (more than 100 MRI studies of the bowel), while the second observer was a radiology research fellow who had read approximately 50 abdominal MRI examinations for Crohn's disease with ileocolonoscopic verification prior to this study.

Statistical analysis

Intra- and interobserver agreement

Descriptive analysis was used to characterize bowel distension and image quality. For all morphological variables, with the exception of bowel wall measurements, agreement was quantified using Cohen's κstatistics. κ values ranged from 0 – 1, where 0 – 0.2 was considered 'poor', 0.2 – 0.4 was considered 'fair', 0.4 - 0.6 was considered 'moderate',

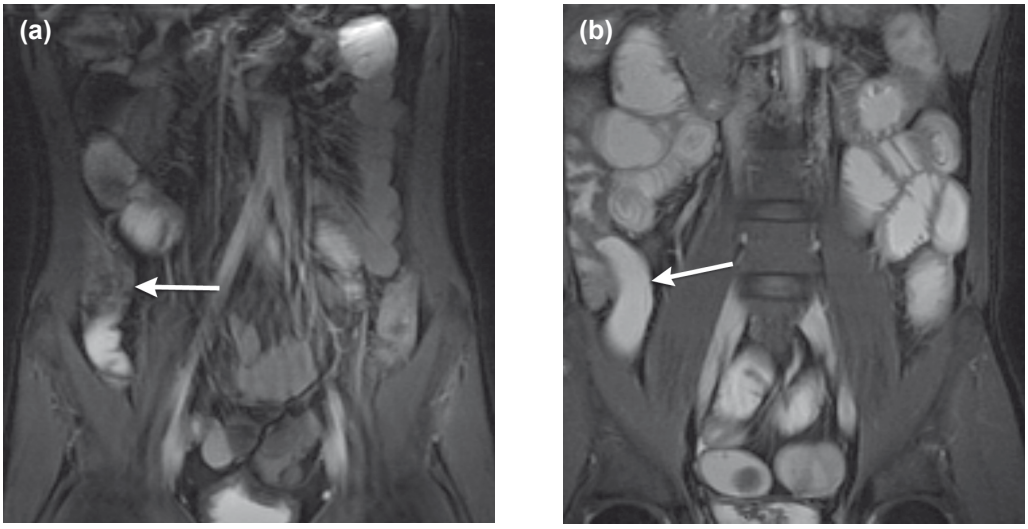

Figure 1.
Twenty-eight-year-old male for whom MRI was performed to differentiate between Crohn's disease and ulcerative colitis. (a) Coronal true FISP fs shows collapsed terminal ileum (arrow). Small bowel wall thickening cannot be excluded. (b) Coronal true FISP fs shows optimal distended terminal ileum (arrow), without bowel wall thickening. No small bowel pathology was detected elsewhere. This patient was diagnosed with ulcerative colitis in follow-up.

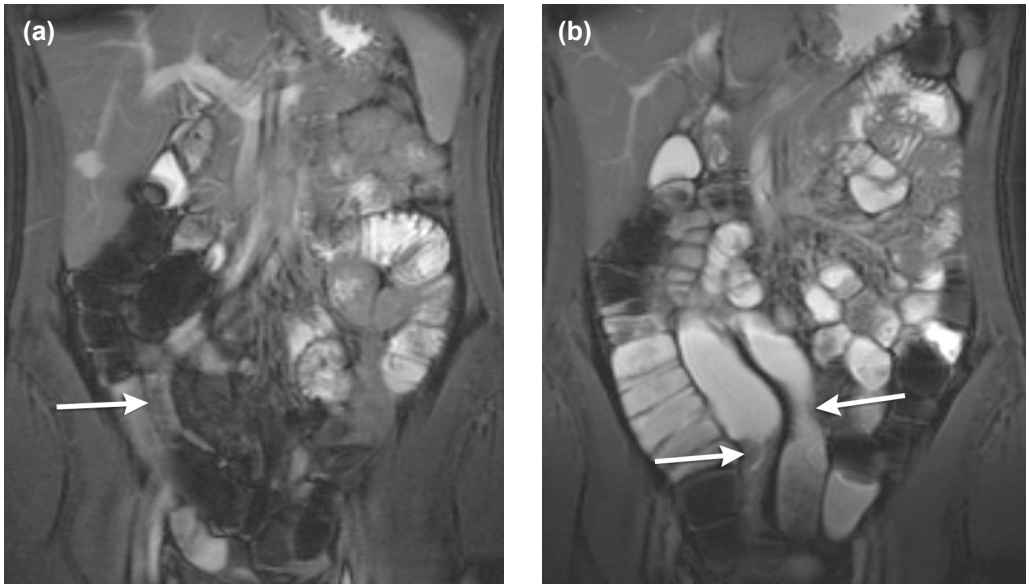

Figure 2.
Forty-one-year-old female with abdominal complaints and suspicion of Crohn's disease. No pathology was seen on colonoscopy. (a)Coronal true FISP fs shows collapsed small bowel of ileum (arrow). Bowel wall thickening and stenosis are not detected on this and other images. (b) Coronal true FISP fs shows bowel wall thickening of the optimally distended ileum with two stenotic segments (arrows).

0.6 - 0.8 was considered 'good,' and > 0.8 was considered 'very good' agreement (17). The intraclass correlation coefficient was used to calculate agreement for measured wall thickness.

Comparisons with the expert reader

Agreement between the morphological scores of the expert reader and the two observers was calculated using κstatistics.

Comparing MRI and MR enteroclysis

The McNemar test was used to evaluate whether there were any significant differences between the scores made by two blinded observers using MRI or MR enteroclysis (except for wall thickness). The Wilcoxon signed ranks test was used to calculate whether there were statistically significant differences in measured wall thicknesses. SPSS (version 14.0; SPSS, Chicago, Ill)) and StatXact (StatXact 3.0 for Windows; Cytel Software Corporation, Cambridge, MA) were used for statistical analysis. P-values < 0.05 indicated statistical significance.

Results

Fifty-five patients underwent MR enteroclysis. Seven patients were excluded because of incomplete MR scans; therefore, 48 patients were included for analysis (Figs. 1-3), of whom 25 were male (mean age = 44.3 yrs, range = 20.2-82.6). Indications for MR enteroclysis were suspected increase in disease activity in patients with known Crohn's disease (*n* = 12), suspected Crohn's disease (*n* = 20), suspected low-grade small bowel stenosis (*n* =13), and suspected small bowel neoplasm (*n* = 3). One patient with known Crohn's disease had undergone an ileocecal resection five years earlier. The mean amount of methylcellulose solution administered was 2600 ml (range = 900-3500 ml) at a mean infusion rate of 95 ml/min (range = 40-180 ml/min). The clinical diagnoses (based on MR findings, clinical history, laboratory findings, endoscopy, surgery, and/or follow-up) are presented in Table 1.

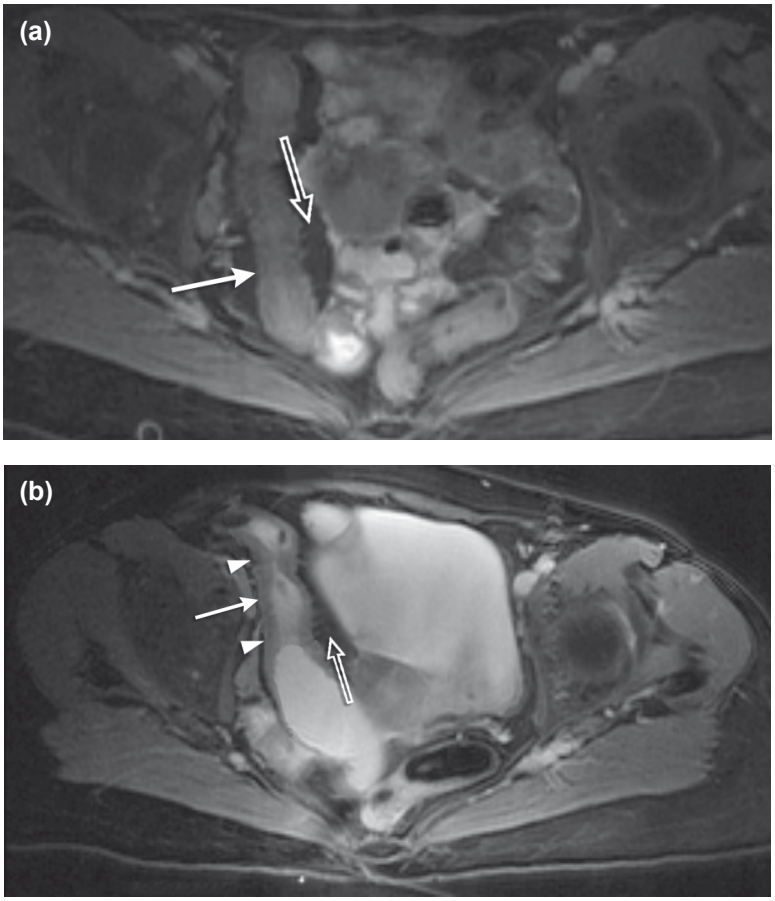

Figure 3.
Sixty-three-year-old female with abdominal pain in the right lower quadrant for 10 months. Bowel wall thickening of the terminal ileum was observed on ultrasound.

(a) Axial true FISP fs shows thickened terminal ileum loops without distension (solid arrow). Increased mesenteric vascularization (comb sign, open arrow) and creeping fat are visible. Grading of stenosis is not possible on these images.

(b) Axial true FISP fs shows optimal distension of the terminal ileum with wall thickening (solid arrow) and two segments with stenosis (arrow heads). This image shows the same extramural pathology as the baseline images: increased mesenteric vascularization.

Qualitative analysis

Both observers found that the image quality from MR enteroclysis examinations was superior to that from MRI. Whereas both observers scored all MR enteroclysis studies as having good image quality [100%; 95% confidence interval (CI)=93-100%], Observer 1 scored 33/48 MRI studies (69%; 95% CI=54-81%) to be of good quality while Observer 2 scored 38/48 MRI studies (79%; 95% CI=65-90%) as being of good diagnostic quality. Both observers judged significantly more bowel segments as adequately distended on MR enteroclysis than on MRI ($P < 0.001$).

For MRI, agreement on image quality was 85% (41/48): in 9 cases the observers agreed that image quality was poor; in 32 cases, they agreed that image quality was good. For MR enteroclysis, agreement on bowel distension was 83% (160/192): inadequate, 18 versus adequate, 142. The proportion of examinations in which the observers agreed on bowel distension on MRI was 84% (162/192), but on MRI, most bowel segments were scored as inadequately distended (n =142).

Table 1. Clinical Diagnoses

Diagnosis	N
Crohn's disease	18
Jejunitis	3
Carcinoid	1
Duplication cyst duodenum	1
Radiation enteritis ileum	1
Sclerosing encapsulating peritonitis	1
Colitis	4
Transmural endometriosis	1
No abnormality	18
Total	48

Comparison of MRI and MR enteroclysis

Both observers diagnosed more segments as having a thickened bowel wall on MR enteroclysis than on MRI; however, this difference was not statistically significant for either observer (Observer 1: $P = .86$; Observer 2: $P = .22$). There were no significant differences between MRI and MR enteroclysis for diagnosing bowel obstruction (Observer 1, $P = .45$; observer 2, $P = .34$).

No statistical tests were performed to determine whether there were differences in the detection rates of ulcerations and polyps due to the low prevalence of these findings. No significant differences were found between MRI and MR enteroclysis regarding detection of extraluminal findings (data not shown), with the exception of lymph node detection. Observer 1 detected lymph nodes in a significantly larger number of patients on MR enteroclysis than on MRI (P = .04).

Interobserver agreement for MRI and MR enteroclysis

Interobserver agreement for diagnosing and grading bowel obstruction increased from moderate to good after administering luminal contrast medium. Bowel wall measurements were also more reliable on MR enteroclysis. With regard to extraluminal findings, no changes in interobserver agreement were observed for the detection of comb sign and creeping fat, whereas agreement decreased from good to moderate for detection of lymph nodes and ascites (Table 2). Interobserver agreement for the detection of ulcerations, polyps, fistula, and abscess was not determined due to the low prevalence of these findings.

Intraobserver agreement for expert reader

The intraobserver agreement was very good for the assessment of all morphological items (Table 3). For the qualitative evaluation of MRI and MR enteroclysis, the expert reader reached 100% agreement with regard to the degree of bowel distension and image quality between the first and second reads.

Table 2. Interobserver agreement between observers 1 and 2

	MRI	MR enteroclysis
Bowel wall thickness, Intraclass correlation coefficient (95% CI)	0.49 (0.37-0.59)	0.84 (0.79-0.88)
	Kappa (95% CI)	
Obstruction	0.39 (0.14-0.64)	0.60 (0.40-0.80)
Comb sign	0.70 (0.52-0.87)	0.72 (0.56-0.88)
Creeping fat	0.38 (0.02-0.75)	0.38 (0.02-0.75)
Lymph node detection	0.63 (0.58-0.96)	0.51 (0.27-0.74)
Ascites	0.78 (0.48-1)	0.50 (0.14-0.86)

Abbreviations: CI, confidence interval.

Blinded observers versus expert reader

Agreement with the expert reader was higher on MR enteroclysis than on MRI for luminal findings. For both observers, the intraclass correlation coefficient for measured bowel wall thickness was higher on MR enteroclysis than on MRI whereas the agreement on the diagnosis and grading of obstruction increased from poor on MRI to moderate on MR enteroclysis.

With regard to extraluminal findings, agreement with the expert reader was mostly moderate on MRI for Observer 1 and the administration of luminal contrast medium did not change this. For Observer 2, agreement decreased from moderate to fair for creeping fat and from good to moderate for the detection of lymph nodes following the administration of luminal contrast medium (Table 4). No statistical tests were performed to determine the degree of consensus between the two observers and the expert reader for detecting ulcerations, polyps, fistula, and abscess due to the low prevalence of these findings.

Table 3. Intraobserver agreement of expert reader

	MRI	MR enteroclysis
Bowel wall thickness, intraclass correlation coefficient (95% CI)	0.85 (0.80–0.88)	0.95 (0.93–0.96)
Obstruction, κ (95% CI)	0.92 (0.77–1.00)	0.97 (0.90–1.00)
Comb sign, κ (95% CI)	0.97 (0.90–1.00)	1.00
Creeping fat, κ	(95% CI) 0.95 (0.85–1.00)	0.90 (0.76–1.00)
Lymph node detection, κ	(95% CI) 0.83 (0.68–0.99)	0.95 (0.85–1.00)
Ascites, κ (95% CI)	1.00	1.00

Abbreviations: CI, confidence interval.

Discussion

The administration of luminal contrast medium by enteroclysis leads to an increased reliability with regard to measurements of bowel wall thickness and diagnosis and grading of bowel obstruction by MRI techniques. Reliability regarding extraluminal findings does not increase.

The increased reliability for measuring bowel wall thickness using MR enteroclysis versus MRI can probably be attributed to the improvement in the image quality and to the degree of bowel distension after administration of luminal contrast medium. Due to the high volume that is infused for MR enteroclysis, reflex atony is induced, which causes peristaltic movements to diminish and image quality to increase. In collapsed bowel loops, the bowel wall contours cannot be adequately delineated; therefore measurements of bowel wall thickness might be imprecise. Also, in an inadequately distended bowel, it is difficult to diagnose and grade obstruction, although a high-grade stenosis with prestenotic dilatation will be visible due to the stasis of fluid in the dilated prestenotic bowel. For a low-grade obstruction, an adequately filled lumen will facilitate identification.

Although the interobserver agreement and the agreement between the expert and the observers increased for luminal findings when the bowel was adequately distended, agreement between the observers and the expert reader remained only moderate for the identification of bowel obstruction. This might be because the prevalence of obstruction was very low and one of the factors that can influence the magnitude of the κstatistic is prevalence. If the prevalence index is high (i.e. the prevalence of a positive rating is either very high or very low), chance agreement is also high and κis reduced accordingly (18). Also, although we tried to keep the MRI ratings as objective as possible by providing clear cutoff points between scores, it is likely that subjective interpretation played a role for each observer. The difference in the experience of the observers in our study might also have contributed to the modest level of agreement.

To our knowledge, this is the first study to compare the reproducibility of MR without enteral contrast medium with MR enteroclysis. For this purpose, we wanted to compare both techniques for the commonly used indications for small bowel imaging. We demonstrated that MR without enteral contrast medium has substantial limitations in reproducibility as compared to MR enteroclysis. Theoretically, one can presume the use of enteral contrast medium as advantageous for almost all indications of small

bowel imaging, although this should be studied in a further cohort.

Another enteroclysis technique for small bowel abnormalities is MDCT enteroclysis, which is a robust technique with high image quality. A major drawback is the ionizing radiation of this technique, which makes it less suitable to a young population group (e.g. Crohn's disease) (19,20).

Table 4. Agreement between observers and expert reader

	MRI	MR enteroclysis
Bowel wall thickness		
	Intraclass Correlation Coefficient (95% CI)	
Expert reader vs. observer 1	0.38 (0.25-0.49)	0.57 (0.46-0.65)
Expert reader vs. observer 2	0.44 (0.32-0.55)	0.68 (0.59-0.75)
	Kappa (95% CI)	
Obstruction		
Expert reader vs. observer 1	0.11 (-0.01-0.22)	0.53 (0.34-0.73)
Expert reader vs. observer 2	0.06 (-0.08-0.19)	0.53 (0.31-0.75)
Comb sign		
Expert reader vs. observer 1	0.48 (0.27-0.68)	0.61 (0.27-0.68)
Expert reader vs. observer 2	0.71 (0.52-0.90)	0.63 (0.44-0.82)
Creeping fat		
Expert reader vs. observer 1	0.48 (0.19-0.76)	0.42 (0.14-0.71)
Expert reader vs. observer 2	0.58 (0.31-0.85)	0.32 (0.04-0.60)
Lymph node detection		
Expert reader vs. observer 1	0.59 (0.36-0.81)	0.59 (0.36-0.82)
Expert reader vs. observer 2	0.79 (0.62-0.96)	0.47 (0.25-0.69)
Ascites		
Expert reader vs. observer 1	0.57 (0.24-0.89)	0.50 (0.14-0.86)
Expert reader vs. observer 2	0.61 (0.30-0.92)	0.70 (0.43-0.98)

Unfortunately, there is no reference standard for determining the accuracy of MRI as compared to MR enteroclysis in the small bowel. Video capsule endoscopy or double balloon enteroscopy could have provided a reference standard, but these examinations were not available in everyday clinical practice until very recently and most likely will not be applied to the full disease spectrum included in this study. This selection bias would also apply to other approaches selecting only patients with extensive work up and would lead to nongeneralizable findings. In this study, we wanted to study both MR techniques in a nonselected population. In that situation, an acceptable alternative is

a comparison to an assessment by an experienced radiologist using MRI findings in combination with all clinical information. In our study, findings for both observers were compared with scores made by an unblinded expert reader (21).

Three millimeters is an accepted cutoff for a normal bowel wall thickness, provided there is an acceptable distension. For the method without enteral contrast medium, this is less clear, as a collapsed bowel wall is thicker than a fully distended bowel wall. However, the method without enteral contrast medium, when proven as an accurate method, would primarily be used as a simple, noninvasive method, selecting patients for more invasive techniques (e.g., enteroclysis, VCE). For this purpose, the number of missed findings should be low, to prevent withholding patients of an optimal diagnosis. With this in mind, we accepted to use the 3-mm cutoff for both the method without enteral contrast medium and for the MR enteroclysis. Had we chosen a higher cutoff, we might have missed thickened bowel wall.
This study has some limitations. Only the FISP fs sequences were compared, which precluded determination of the reliability of post-contrast T1 fs-weighted imaging using MRI versus MR enteroclysis. In most comprehensive MR protocols for small bowel imaging, post-contrast T1 fs-weighted imaging is included because enhancement of the bowel wall can provide information about the degree of disease activity. However, the FISP fs sequence is very useful in clinical practice because motion-related artifacts are minimal and FISP fs imaging has been shown to perform as well as, if not better than T1-weighted imaging for evaluating the small bowel (6,22).

Another limitation of this study is that oral administration of contrast medium was not performed; this would have provided the opportunity to perform a side-by-side comparison of all three methods of bowel preparation. However, in a recently published study by Negaard et al. (23), the diagnostic accuracy and the reliability of MRI using oral contrast medium and MR enteroclysis were compared, and although the mean luminal diameter was greater on MR enteroclysis than on MRI using oral contrast medium, both techniques were equally accurate and reliable. In the study by Negaard et al., interobserver reliability was higher than in our study. This could be due to the differences in the patient populations under study. Their study contained only patients with Crohn's disease, which mainly affects the terminal ileum, whereas our study included patients with (and without) a variety of pathologies.

We did not study patient acceptance for either technique. Although one might assume that patients would prefer a contrast-medium-free examination, this hypothesis needs to be validated in future studies.

In conclusion, the use of luminal contrast medium in MRI of the small bowel improves reliability for measuring bowel wall thickness and for the diagnosis and grading of obstruction.

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Small Bowel Crohn's disease: Magnetic Resonance enteroclysis versus capsule endoscopy compared to balloon-assisted enteroscopy

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Abstract

New modalities are available to visualize the small bowel in patients with Crohn's disease. The aim of this study was to compare the diagnostic yield of magnetic resonance enteroclysis and capsule endoscopy to balloon-assisted enteroscopy in patients with suspected or established Crohn's disease of the small bowel.

Consecutive, consenting patients first underwent magnetic resonance enteroclysis followed by capsule endoscopy and balloon-assisted enteroscopy. Patients with high-grade stenosis at magnetic resonance enteroclysis did not undergo capsule endoscopy. Reference standard for small bowel Crohn's disease activity was a combination of balloon-assisted enteroscopyand an expert panel consensus diagnosis.

Analysis included 38 patients, 27 (71%) females, mean age 36 (20–74) years, with suspected (n = 20) or established (n = 18) small bowel Crohn's disease: 16 (42%) were diagnosed with active Crohn's disease, and 13 (34%) by magnetic resonance enteroclysis with suspected high-grade stenosis, who consequently did not undergo capsule endoscopy. The reference standard defined high-grade stenosis in 10 (26%) patients. Sensitivity, specificity, positive predictive value and negative predictive value of magnetic resonance enteroclysis and capsule endoscopy for small bowel Crohn's disease activity were 73 and 57%, 90 and 89%, 88 and 67%, and 78 and 84%, respectively. Capsule endoscopy was complicated by capsule retention in one patient.

Magnetic resonance enteroclysis has a higher sensitivity and positive predictive value than capsule endoscopy in small bowel Crohn's disease. The use of capsule endoscopy is considerably limited by the high prevalence of stenotic lesions in these patients.

Introduction

Crohn's disease is a chronic inflammatory disorder associated with both mucosal and transmural inflammation of the bowel wall. Crohn's disease can affect any part of the gastrointestinal tract, but the small bowel is affected in up to two-thirds of patients, with the distal ileum as the most affected site. Until recently, Crohn's disease of the small bowel was assessed by upper gastrointestinal endoscopy, ileocolonoscopy, and conventional enteroclysis. However, the armamentarium of imaging techniques for small bowel involvement of Crohn's disease has increased considerably in recent

years with the introduction of capsule endoscopy, balloon-assisted enteroscopy, and magnetic resonance enteroclysis.

Already, capsule endoscopy has been shown to provide a significantly higher diagnostic yield than push enteroscopy and conventional enteroclysis in patients with Crohn's disease (1).However, capsule retention in stenotic small bowel Crohn's disease hampers its use in these patients (2). Balloon-assisted enteroscopy, first introduced in 2001 (3), combines endoscopic visualization of the entire small bowel with the possibility for endoscopic treatment of fibrotic strictures, and tissue sampling for histological examination (4,5). Although balloon-assisted enteroscopy can be considered as the reference standard, the lengthy and invasive character of the procedure, the associated discomfort, and need for conscious sedation limit its use (6). MR enteroclysis allows optimal visualization of soft tissues with multiplanar imaging capabilities and has already been proven to have additional value compared to endoscopic techniques in Crohn's disease patients (7-10). In theory, MR enteroclysis may be a good alternative for capsule endoscopy and balloon-assisted enteroscopy in Crohn's disease patients with suspected small bowel involvement. To our knowledge, no study has simultaneously compared capsule endoscopy, MR enteroclysis, and balloon-assisted enteroscopy in one patient population with suspected or established Crohn's disease. Therefore, the aim of the present study was to compare the diagnostic yield of MR enteroclysis and capsule endoscopy to balloon-assisted enteroscopy as reference standard in patients with suspected or established Crohn's disease.

Patients and Methods

Study population

For this prospective study, patients were recruited at the departments of gastroenterology of the Medical Center Alkmaar and the Erasmus University Medical Center Rotterdam, The Netherlands. Patients were eligible for inclusion if they had suspected or established Crohn's disease and needed visualization of the small bowel because of suspected small bowel disease activity. Exclusion criteria were age <18 or >75 years, abdominal surgery in the 6 weeks prior to inclusion, clinical suspicion of significant small bowel obstruction, suspicion of an intra-abdominal abscess, pregnancy or breastfeeding,

inability to swallow the video capsule, presence of a pacemaker or cardioversion device, or a history of contrast media reaction or allergy. Patients with severe concomitant disease with limited life expectancy or with a psychiatric, addictive, or any disorder compromising the ability to give informed consent were also excluded. The institutional review boards of the participating hospitals approved the study. All patients gave written informed consent prior to inclusion.

From January 2007 to July 2009, 67 patients were eligible for inclusion; 41 agreed to participate and were included after providing informed consent. Three patients were excluded after inclusion: one because of no attendance at examinations and two because of marked deterioration of their clinical condition preventing them from undergoing the subsequent examinations. Thus, 38 consecutive patients were eligible for evaluation: 20 (53%) with suspected and 18 (47%) with established Crohn's disease. Eleven (29%) patients were male, and the mean age was 36 (range 20–74) years (Table 1). MR enteroclysis, capsule endoscopy , and balloon-assisted enteroscopy were performed within a median of 22 (4–112) days, in five (13%) patients, this interval was longer than three weeks. The median follow-up was 14 (7- 36) months.

Table 1. Patient characteristics

	Total (*n* = 38)	**Suspected CD (*n* = 20)**	**Known CD (*n* = 18)**
Age (years)	36 (20–74)	31 (20–54)	43 (28–74)
Male	11 (29%)	6 (30%)	5 (28%)
Duration of CD (months)	68 (1–204)	44 (1–204)	91 (24–192)
CDAI	73 (22–147)	78 (22–147)	66 (34–134)

CD = Crohn's disease; CDAI = Crohn's disease activity index

Patient disease activity was determined using the Crohn's disease activity index at the time of inclusion. Currently, no validated enteroscopic small bowel Crohn's disease severity scale exists, so small bowel lesions were defined as (1) absent: no disease activity; (2) mild: erythematous and/or edematous mucosa and/or small ulcerative lesions (<0.5 mm) within otherwise normal appearing mucosa; (3) moderate: larger ulcerative lesions (≥0.5 mm and <20 mm); or (4) severe: large ulcerative lesions (≥20 mm) and/or significant stenotic lesions, with or without macroscopic signs of inflammation. Changes in medical therapy, surgery, or other therapeutic measures were documented.

Study modalities

For evaluation, the small bowel was divided into four segments; duodenum, jejunum, proximal ileum, and distal (last 30 cm) ileum. For the qualitative assessment, image quality was graded on a three-point scale (non-diagnostic study, diagnostic study albeit with artifacts, diagnostic study of good quality). Investigators performing the examinations received the same clinical information but were blinded to the results of the other diagnostic procedures performed for the study.

All patients first underwent MR enteroclysis, followed by capsule endoscopy and balloon-assisted enteroscopy with the aim of having all investigations completed within 3 weeks. For early diagnosis of high-grade small bowel stenosis, MR enteroclysis was performed first. During the whole study high-grade stenosis was defined as a small bowel lumen of <10 mm with maximal bowel distention, and these patients did not undergo capsule endoscopy. If MR enteroclysis defined a luminal stenosis of 10–14 mm, a patency capsule (Agile Patency Capsule, Given Imaging Limited) was applied before capsule endoscopy. Failure of the patency capsule to pass the small bowel in <16 hbased on plain abdominal X-ray was considered compatible with the presence of high-grade stenosis, and capsule endoscopy was subsequently not performed.

MR enteroclysis

MR enteroclysis was performed as previously described (11). In brief, after bowel preparation, 1000–3000 ml 0.5% methylcellulose solution was infused at a rate of 60–150 ml/min via a nasoduodenal catheter for optimal small bowel distension. The MR protocol consisted of MR fluoroscopy, fat-saturated True FISP, and HASTE sequences as pre- and post-contrast T1-weighted VIBE sequences after intravenous administration of 0.1 mmol/kg of body weight of gadobutrol (Gadovist, Bayer Schering, Berlin, Germany). Butylscopolamine bromide (Buscopan, Boehringer, Ingelheim, Germany), 20 mg, used as a spasmolytic, was injected before the injection of gadobutrol. MR enteroclysis studies were evaluated on a Picture Archiving and Communications System station (PACS, AGFA IMPAX version 4.5 service pack 5, Mechelen, Belgium) by a radiologist with an experience of >200 MR enteroclysis studies. Electronic calipers were used for measurements. Bowel distension was graded as either insufficient (i.e., collapsed bowel loops) or sufficient for diagnosis (small bowel lumen measuring >0.5 cm). For MR enteroclysis, the duodenum was defined as the first 20 cm of the small bowel; jejunum was considered as small bowel loops left of an imaginary line from the liver

dome to the roof of the left acetabulum; all bowel loops located right of this imaginary line were regarded as ileum; and the terminal ileum was defined as the last 30 cm of the ileum. Disease activity was based on the presence or absence of bowel wall thickness >4mm, intramural and mesenteric edema, mucosal hyperemia, wall enhancement and enhancement pattern and transmural ulcerations and fistula formation.

Capsule endoscopy

Capsule endoscopy was performed as previously described (12). In brief, after bowel preparation with 1 l Klean-Prep (Norgine Ltd., Marburg, Germany), the patient swallowed the capsule (PillCam type SB, Given Imaging Limited, Yokneam, Israel). After 8 hours, the belt with the hard disk and the sensor array were removed. In case of doubt about passage of the capsule through the whole bowel, an X-ray of the abdomen was performed 1 week after ingestion. Capsule endoscopy recordings were evaluated on a dedicated workstation (Rapid 4, Given Imaging Limited, Yokneam, Israel) by a gastroenterologist with extensive experience (>500 capsule endoscopy procedures). Gastric transit time, small intestinal transit time, and viewing time were recorded for each procedure. For capsule endoscopy, the duodenum was defined as the first 20 minutes of the small bowel; the time between start jejunum and start terminal ileum was divided into two for the transition between jejunum and ileum; and the terminal ileum was defined as the last 30 minutes of the ileum.

Balloon-assisted enteroscopy

After an overnight fast and bowel preparation with 4 L of Klean-Prep (Norgine Ltd., Marburg, Germany), balloon-assisted enteroscopy was performed (Fujinon EN-450P5 or EN-450T5, Saitama, Japan) by one of two experienced enteroscopists, both having performed >200 balloon-assisted enteroscopy procedures. During the procedure, conscious sedation was applied using midazolam (Dormicum, Roche, Woerden, Netherlands), with or without fentanyl (Janssen-Cilag, Tilburg, Netherlands), and on withdrawal butylscopalamine (Buscopan, Boehringer, Ingelheim, Germany) was administered. Most balloon-assisted enteroscopy procedures were performed via the anal approach; in selected cases with clinical suspicion of proximal small bowel pathology, first an oral approach was performed during the same procedure. Insertion depths were estimated using the method described by May et al. (4). The complete studies were taped on digital video and the duration of each procedure noted. For balloon-assisted enteroscopy, the duodenum was defined as

the first 20 cm distal from the bulb; jejunum as 20–200 cm distal from the bulb by oral and 130–230 cm proximal from the ileocecal valve or ileostoma by anal approach; proximal ileum as 200–300 cm from the bulb by oral and 30–130 cm from the ileocecal valve or ileostoma by anal approach; and the terminal ileum as the last 30 cm of the ileum. Biopsy sampling was performed in a standard fashion. Samples were taken if lesions where found during balloon-assisted enteroscopy or to rule out inflammation in endoscopically normal appearing small bowel segments.

Reference standard and expert panel

The reference standard consisted of (1) small bowel findings at balloon-assisted enteroscopy in those small bowel segments visualized by balloon-assisted enteroscopy and (2) an expert panel diagnosis for the remaining small bowel segments not visualized by balloon-assisted enteroscopy. The expert panel also re-evaluated segments for which balloon-assisted enteroscopy was negative and MR enteroclysis and/or capsule endoscopy diagnosed small bowel lesion(s). This expert panel consisted of two experienced gastroenterologists, not involved in primary reading of the examinations evaluated in this study nor in the management of the patients included. Separately, both experts were presented with the anonymized, full patient medical history, clinical status and the written reports of balloon-assisted enteroscopy, MR enteroclysis and capsule endoscopy with the most important images. Consensus was subsequently reached on the bowel segments scored discordantly. The patient medical history and clinical status included the indication for the diagnostic work-up, laboratory findings and, if available, results of histopathological examination together with the results of the three diagnostic procedures. For all cases, both experts came to a final consensus diagnosis.

Statistical analysis

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for MR enteroclysis and capsule endoscopy were calculated compared to the reference standard.

No direct comparative data for the different techniques in the studied patient populations were available, so we estimated that the difference for detection of disease activity in Crohn's disease would be 30% in favor of the reference standard. To detect a significant difference with a power of an alpha of 0.05 and beta of 0.20 required a study population of at least 33 patients.

Results

Balloon-assisted enteroscopy and reference standard diagnosis

All patients underwent balloon-assisted enteroscopy, which was performed by a combined proximal and distal approach in 19 (50%), and by distal approach only in the other 19 patients. All studies were of good diagnostic quality. The median small bowel insertion depth with balloon-assisted enteroscopy was proximal 335 (200–460) cm and distal 98 (5–240) cm. The mean duration of balloon-assisted enteroscopy was 70 (30–150) minutes. Balloon-assisted enteroscopy visualized 98/152 (65%) segments of the small bowel. The duodenum and jejunum were both visualized in 19/38 (50%) patients, the proximal ileum in 22/38 (58%) patient, and the distal ileum in 38/38 (100%) patients. No complications were noted during or after the balloon-assisted enteroscopy procedures. Balloon-assisted enteroscopy revealed small bowel lesions in 16 (42%) patients (Table 2), confirmed as active Crohn's disease by the expert panel. In the remaining 22 patients defined as normal by balloon-assisted enteroscopy, the expert panel did not change this diagnosis based on the data provided by MR enteroclysis and capsule endoscopy. Balloon-assisted enteroscopy diagnosed non-Crohn's disease-related pathology in two patients; a pseudomelanotic colon and a Trichuris infection.

Table 2. Crohn's disease activity of MR enteroclysis (MRE) and capsule endoscopy (CE)

	Reference standard* n (%)	MRE diagnosis n (%)	CE diagnosis n (%)
No disease activity	19 (50)	22 (58)	19 (50)
Mild CD	7 (18)	3 (8)	4 (11)
Moderate CD	7 (18)	6 (16)	2 (5)
Severe CD	5 (13)	7 (18)	0 (0)
Not performed	0	0 (0)	13 (34)
Total	38 (100%)	38 (100%)	38 (100%)

**The reference standard consisted of (1) small bowel findings at balloon-assisted enteroscopy in those small bowel segments visualized by balloon-assisted enteroscopy and (2) an expert panel diagnosis for the remaining small bowel segments not visualized by balloon-assisted enteroscopy.*

MR enteroclysis

The mean duration of MR enteroclysis was 53 (37–91) minutes. All studies were of good diagnostic quality with sufficient small bowel distension. The MR enteroclysis procedure was complicated in four (11%) patients by vomiting and in one (3%) patient by a mild allergic rash after intravenous contrast injection. In two patients, vomiting

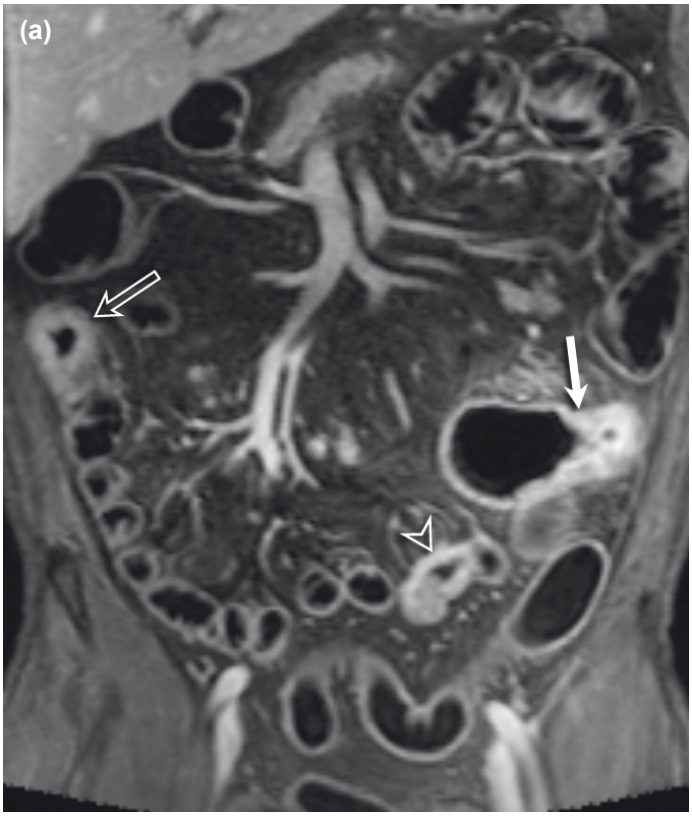
resulted from the presence of a high-grade small bowel stenosis and in one patient from a low-grade small bowel stenosis. The mean evaluation time was 9 (6–20) minutes. Visualization and evaluation of the four pre-defined small bowel segments was possible in all patients. MR enteroclysis found evidence for Crohn's disease small bowel disease activity in 16 (42%) patients (Table 2). This activity was confirmed by the gold diagnostic standard for 14 (88%) (Table 3). MR enteroclysis revealed extramural abnormalities in four (11%) patients: a mesenteric abscess in two, an abdominal-enteral fistula in one, and intra-abdominal adhesions in one patient. MR enteroclysis did not reveal non-Crohn's disease-related pathology.

Table 3. Crohn's disease diagnosis by MR enteroclysis and capsule endoscopy (CE) per patient in comparison with reference standard

	MR enteroclysis diagnosis n (%)	CE diagnosis n (%)
True positive	14 (37)	4 (16)
True negative	17 (45)	16 (64)
False positive	2 (5)	2 (8)
False negative	5 (13)	3 (12)
Total	38 (100%)	25 (100%)

Capsule endoscopy

MR enteroclysis raised the suspicion of small bowel stenosis in 14 (37%) patients. In 11 of them, this stenosis was defined as high grade, and consequently these patients were excluded from capsule endoscopy. The remaining three patients had a suspected low-grade stenosis at MR enteroclysis and underwent patency capsule testing. This patency capsule passed in one patient and was retained in two. Thus, 13 (34%) patients were excluded from capsule endoscopy because of small bowel stenosis and 25 (66%) underwent capsule endoscopy. Capsule endoscopy visualized the complete small bowel in all but one patient (4%; capsule retention). The stenosis in this patient had not been detected during MR enteroclysis, and the patient therefore had not been tested with a patency capsule. The capsule could not be removed during subsequent balloon-assisted enteroscopy and was removed surgically. The capsule retention was caused by a high grade ileal stenosis. All capsule endoscopy procedures were of good diagnostic quality. The mean evaluation time was 23 (14–48) minutes. Capsule endoscopy found evidence for Crohn's disease small bowel disease activity in 6 (24%) patients (Table 2).



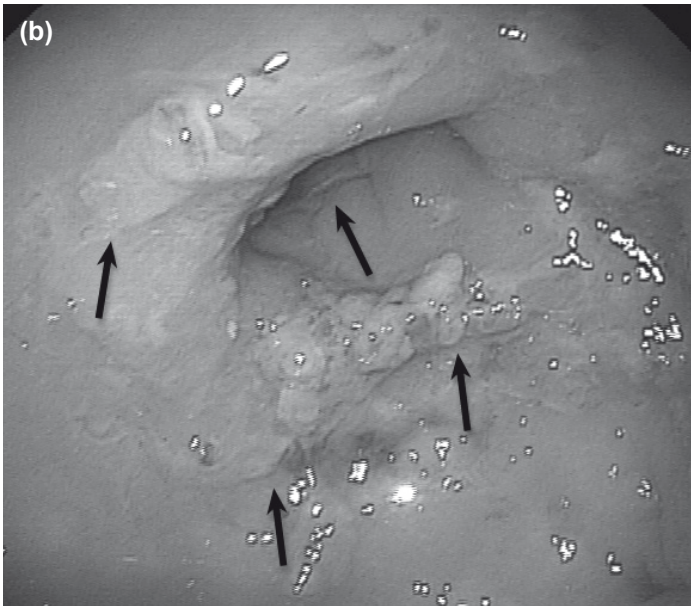


Figure 1.
48-year-old male patient with known Crohn's disease for 20 years and postoperative ileocecal resection. Patient complained of abdominal pain. MR enteroclysis showed on coronal T1 3d fat-sat image (a) after contrast injection, three active segments of Crohn's disease (arrows) with bowel wall thickening, increased contrast enhancement, irregular mucosa, high-grade stenosis, and increased mesenterial vascularization (comb sign). Capsule endoscopy was not performed because of the high-grade small bowel stenosis. Balloon-assisted enteroscopy (b) showed ulcerations (arrows) in the terminal ileum. The proximal segments could not be visualized because of the high-grade small bowel stenosis.

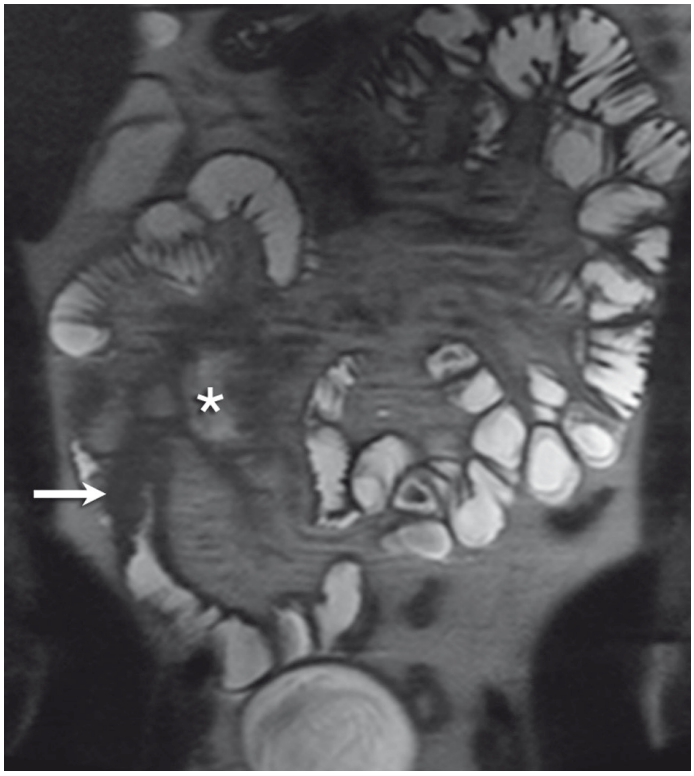
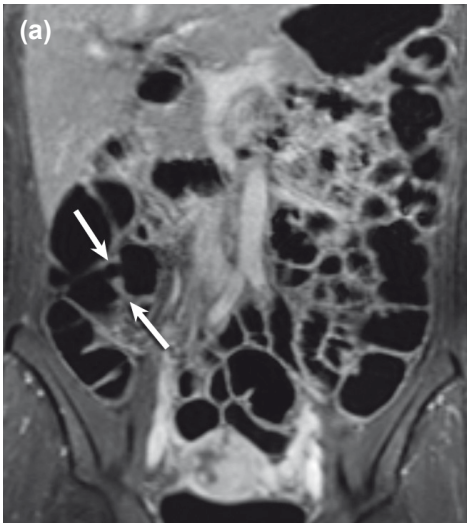


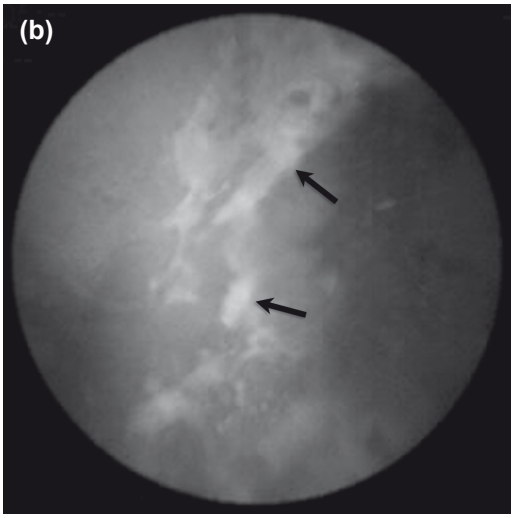
Figure 2.
35-year-old male patient without medical history and with suspected Crohn's disease. Patient complaints were abdominal pain in the right lower quadrant. MR enteroclysis showed coronal T2 HASTE image with small bowel thickening in the terminal ileum with high-grade stenosis (arrow). Extramural abscess medial of the terminal ileum (asterisk). Capsule endoscopy was not performed because of the high-grade small bowel stenosis. Balloon-assisted enteroscopy (not shown) showed swollen terminal ileum, without the possibility of cannulation.

This activity was confirmed by the gold diagnostic standard for 4 (67%) (Table 3). Capsule endoscopy revealed presumed non-Crohn's disease-related pathology in one patient with erosive gastritis.

MR enteroclysis and capsule endoscopy compared with reference standard

MR enteroclysis showed a higher rate of detection of moderate to severe Crohn's disease activity compared to capsule endoscopy (17% vs 3%). However, the exclusion of patients with suspected stenotic disease for subsequent capsule endoscopy (Figs. 1,2) largely influenced this outcome. Capsule endoscopy showed a higher detection rate of lesions in mild Crohn's disease activity patients (Table 2; Fig. 3). These results (Table 3) correspond with a sensitivity of 74 and 57%, specificity of 90 and 89%, positive predictive value of 88 and 67%, and negative predictive value of 78 and 84%, for detection of small bowel Crohn's disease lesions by MR enteroclysis and capsule endoscopy, respectively.





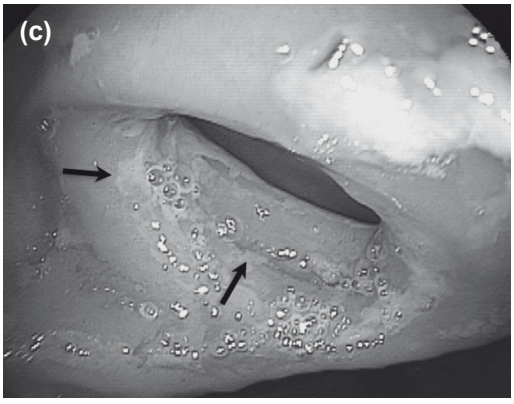


Figure 3.
39-year-old female patient with known Crohn's disease and postoperative ileocecal resection 3 years earlier. Patient complaints were abdominal pain and diarrhea. MR enteroclysis showed on coronal T1 3d fat-sat image (a) after contrast injection, normal anastomosis (arrows) of the neo-ileocecal junction without bowel wall thickening or increased contrast enhancement. Capsule endoscopy (b) and balloon-assisted enteroscopy (c) both indicated superficial ulcerations on the level of the anastomosis (arrows). No other abnormalities were diagnosed.

Balloon-assisted enteroscopy diagnosed ten high-grade stenotic lesions in 10 (26%) patients: eight stenoses in distal ileum, one in jejunum, and one in proximal ileum. MR enteroclysis reported 15 stenotic segments in 13 patients (34%). The detection of high-grade small bowel stenosis by MR enteroclysis had a sensitivity of 91%, 99% specificity, 77% positive predictive value, and 96% negative predictive value. MR enteroclysis was false negative in one patient, leading to capsule retention resulting from a high-grade stenosis in the distal jejunum.

Discussion

The results of this prospective study demonstrate that MR enteroclysis has a higher overall sensitivity and positive predictive value, for small bowel lesions as compared to capsule endoscopy in patients with suspected or established Crohn's disease with suspected small bowel activity. In these patients, the use of capsule endoscopy is limited by the risk of capsule retention. The findings of a higher sensitivity and positive predictive value in staging more advanced Crohn's disease and reduced accuracy in staging mild Crohn's disease activity for MR enteroclysis as compared to capsule endoscopy seems to accord with an earlier study by Tillack et al. (13) However, in the present study, capsule endoscopy was prohibited in one-third of patients because of suspected high-grade small bowel stenotic disease, contributing to the result that MR enteroclysis performed better compared to capsule endoscopy in patients with more advanced Crohn's disease.

The high prevalence of high-grade stenoses is in line with the findings of Voderholzer et al. in a capsule endoscopy study of 15 patients (27%) with established Crohn's disease (14).The frequency of high-grade stenosis varied depending on Crohn's disease stage and ranged from 1.4% in patients with suspected Crohn's disease to 13% in known Crohn's disease (15,16). The possible presence of high-grade small bowel stenosis is the major drawback of capsule endoscopy, necessitating the exclusion of functional stenoses prior to capsule endoscopy. Nevertheless, even with pre-exclusion of high-grade small bowel stenosis, capsule retention may occur, as illustrated by one of our patients.

Capsule retention in these patients is a major adverse event, requiring additional intervention that is a burden and a risk for the patient and that generates extra costs (17). In our opinion, the increased risk of capsule retention in these patients outweighs the higher accuracy of capsule endoscopy in staging mild Crohn's disease. Although MR enteroclysis has a high diagnostic yield for stenotic Crohn's disease, it can overstage this condition. MR enteroclysis indicated small bowel stenoses in 13 patients, but in three patients, balloon-assisted enteroscopy did not confirm this. However, in one patient with clinically suspected small bowel stenosis, the patency capsule was retained and a high-grade ileal stenosis identified during surgery at 1 year of follow-up.

An advantage of MR enteroclysis compared to the other two modalities is the visualization of extramural small bowel disease, which can be of additional value in staging Crohn's

disease and determining therapeutic options. In this study, MR enteroclysis detected significant extramural abnormalities in 8% of patients. A disadvantage of MR enteroclysis is that some patients do not tolerate the oral preparation and/or small bowel distension, especially those with high-grade small bowel stenosis. This intolerance may lead to insufficient small bowel distension and visualization, and consequently to reduced sensitivity of MR enteroclysis for small bowel pathology. We performed enteroclysis to obtain optimal distension of the small bowel. Masselli et al. (18) concluded that MR enteroclysis was superior to MR enterography in detection of milder superficial pathology. Another study presented by Negaard et al. (19) showed comparable results of MR enteroclysis to MR enterography in the terminal ileum, but the study defined MR enteroclysis as MR of the small bowel after transportation of the patient to the MR unit following conventional enteroclysis. In our experience, bowel distention decreases rapidly with reduction or termination of the infusion rate, and small bowel wall thickening therefore can be missed with this type of MR procedure.

This study has some limitations. First, the order of the examinations was pre-determined, and MR enteroclysis was used to rule out high-grade stenosis before patients had capsule endoscopy to prevent capsule retention. Second, the study population was relatively small, and a proportion of patients did not undergo capsule endoscopy because of a high-grade stenosis. Because of this limited number, significance could not be calculated. Third, balloon-assisted enteroscopy could not visualize all small bowel segments in all patients, and an expert panel was therefore asked to establish a final diagnosis in a subset of patients. The bias such a panel may introduce can have two effects: (1) weakening the study because of subjectivity or (2) strengthening the study because the diagnosis of Crohn's disease, or disease activity assessment, is often based on multiple diagnostic tests. The major strength of the study is the head-to-head comparison of MR enteroclysis and capsule endoscopy to a reference standard including balloon-assisted enteroscopy, suggesting that an expert panel is an acceptable reference standard. A fourth limitation is the fact that not all procedures were performed within the three-week time frame. The prolonged interval between the investigations might have influenced the findings in some cases.

From the results, we conclude that MR enteroclysis could be a first-choice non-invasive diagnostic procedure in patients with suspected small bowel Crohn's disease, followed by capsule endoscopy or balloon-assisted enteroscopy, depending on (1) the outcome with MR enteroclysis and/or (2) the need for histopathological findings. The

high incidence of small bowel stenosis in these patients prohibits the use of capsule endoscopy as a diagnostic modality.

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Magnetic Resonance enteroclysis versus capsule endoscopy compared to balloon-assisted enteroscopy in patients with Obscure Gastrointestinal Bleeding

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Abstract

Background and study aims

New modalities are available for visualization of the small bowel in patients with possible obscure gastrointestinal bleeding (OGIB), but their performance requires further comparison. This study compared the diagnostic yield of magnetic resonance enteroclysis (MRE) and capsule endoscopy (CE) in OGIB, using balloon-assisted enteroscopy (BAE) as the reference standard.

Patients and methods

Consecutive consenting patients who were referred for evaluation of OGIB were prospectively included. Patients underwent MRE followed by capsule endoscopy and BAE. Patients with high grade stenosis at MRE did not undergo capsule endoscopy. The reference standard was BAE findings in visualized small-bowel segments and expert panel consensus for non visualized segments during BAE.

Results

Over a period of 26 months, 38 patients were included (20 female 53%; mean age 58 years, range 28–75 years). Four patients (11%) did not undergo capsule endoscopy due to high grade small-bowel stenosis at MRE (n = 3; 8%) or timing issues (n = 1; 3%); capsule endoscopy was non-diagnostic in one patient. The reference standard identified abnormal findings in 20 patients (53%). MRE had sensitivity, specificity, and positive and negative likelihood ratios of 21%, 100%, infinity, and 0.79, respectively. The corresponding values for capsule endoscopy were 61%, 85%, 4.1, and 0.46. The reference standard and capsule endoscopy did not differ in percent positive findings ($P = 0.34$), but MRE differed significantly from reference BAE ($P < 0.001$). Capsule endoscopy was superior to MRE for detecting abnormalities ($P = 0.0015$).

Conclusion

Capsule endoscopy performed better than MRE in the detection of small-bowel abnormality in patients with OGIB. MRE may be considered as an alternative for initial examination in patients with clinical suspicion of small-bowel stenosis.

Introduction

Obscure gastrointestinal bleeding (OBIG) is defined as bleeding of unknown origin that persists or recurs following a negative initial endoscopic evaluation (1). OGIB may be categorized into obscure overt bleeding and obscure silent bleeding on the basis of the presence or absence of clinically evident bleeding, determined using the American Gastroenterological Association definitions as proposed by Zuckerman et al. (1) and Raju et al. (2). Silent OGIB may manifest as amounts of blood detectable only on chemical testing of the stool or as iron deficiency anemia. Overt OGIB is high-volume bleeding manifesting as hematemesis, melena, or hematochezia without an identified source after an initial upper endoscopy and colonoscopy. Until recently, evaluation of the small intestine in OGIB patients was often unsatisfactory due to the limited ability of available endoscopic and radiological procedures to adequately image the small bowel. This situation has changed since the introduction of new visualization techniques that include capsule endoscopy, balloon-assisted enteroscopy, and magnetic resonance enteroclysis.

Since its introduction in 2001, capsule endoscopy has proved to have a significantly higher diagnostic yield than push enteroscopy and small bowel radiography in patients with OGIB (3,4). Capsule endoscopy is well tolerated by patients but does not provide the opportunity to perform therapy. Balloon-assisted enteroscopy combines visualization of the small bowel with the possibility of tissue sampling and therapy in one procedure (5-7). However, balloon-assisted enteroscopy is an invasive endoscopic technique necessitating sedation. Recently, MR enteroclysis has evolved as a small bowel imaging technique that combines excellent soft tissue contrast and multiplanar imaging capabilities. Because it combines controlled small bowel distension with the possibility of evaluating the entire small bowel, MR enteroclysis may serve as an efficient and patient-friendly alternative to exclude bowel wall abnormalities (with the exception of subtle mucosal pathology) in patients with OGIB (8). MR enteroclysis has already demonstrated high diagnostic value in patients with Crohn's disease (9-11).

To our knowledge, no study has compared capsule endoscopy and MR enteroclysis with a reference standard in patients with OGIB. We therefore performed a head-to-head comparison of the diagnostic accuracy of capsule endoscopy and MR enteroclysis in patients with OGIB, using the combination of balloon-assisted enteroscopy and an expert panel consensus as the reference standard.

Patients and Methods

Study population

Consecutive patients with OGIB referred for balloon-assisted enteroscopy were asked to participate in the current study and were prospectively included after providing informed consent. All patients had a negative upper endoscopy and ileocolonoscopy before inclusion. Exclusion criteria were: age <18 or >75 years, abdominal surgery in the 6 weeks prior to inclusion, clinical suspicion of significant small bowel obstruction, suspicion of an intra-abdominal abscess, pregnancy or breastfeeding, inability to swallow the video capsule, carriage of a pacemaker or cardioversion device, or a history of contrast media reaction or allergy. Patients with severe concomitant disease with limited life expectancy and patients with a psychiatric, addictive, or any disorder that compromised the ability to give informed consent were also excluded from participation. Patients were recruited at the Departments of Gastroenterology and Hepatology of the Medical Center, Alkmaar, and the Erasmus Medical Center University Medical Center, Rotterdam, The Netherlands. The Institutional Medical Ethical Review Boards of all participating hospitals approved the study. The study was performed as an intention-to-diagnose analysis (i.e., the comparison was based on all cases of patients who satisfied the inclusion criteria and provided informed consent).

Procedures

All consenting patients first underwent MR enteroclysis, followed by capsule endoscopy, and finally balloon-assisted enteroscopy. This study did not randomize the order of MR enteroclysis and capsule endoscopybecause of the medical ethical considerations; patients with high grade small bowel stenosis as observed and diagnosed by MR enteroclysis would have a risk of capsule retention if they underwent capsule endoscopy. All three investigations were performed within a 3-week period in all patients except one. If a high grade small bowel stenosis (small bowel lumen <10 mm) was observed during MR enteroclysis, the capsule endoscopy was cancelled. If a luminal reduction of 10–14 mm was seen during MR enteroclysis, capsule endoscopy was preceded by a patency capsule (Agile Patency Capsule; Given Imaging Ltd, Yoqneam, Israel) procedure. Non-passage of the patency capsule through the small bowel within 16 hours, as ascertained by plain abdominal radiography, was considered indicative of high grade stenosis and the capsule endoscopy was therefore canceled.

The investigators performing and reading results from the MR enteroclysis, capsule endoscopy, and balloon-assisted enteroscopy procedures received the same clinical information but remained blinded to the results of the other diagnostic procedures. For the qualitative assessment, the image quality for each procedure was graded on a three-point scale: 1) non-diagnostic, 2) study with numerous artifacts, or 3) study of good diagnostic quality.

Magnetic resonance enteroclysis

MR enteroclysis was performed as previously described (12) by a radiologist (B.W.) with extensive (>200 procedures) experience. In brief, following bowel preparation, for optimal small bowel distension was achieved by the infusion of 1–3 L 0.5% methylcellulose solution at a rate of 60–150 mL/min via a nasoduodenal catheter. The MR enteroclysis protocol consisted of magnetic resonance fluoroscopy, morphology sequences, True FISP (fast imaging with steady-state precession) and HASTE (half-Fourier acquisition single-shot turbo spin-echo) sequences, and a T1-weighted VIBE (volumetric interpolated breath-hold) sequence after intravenous administration of 0.1 mmol/kg body weight of gadobutrol (Gadovist; Bayer Schering, Berlin, Germany); butylscopolamine 20 mg (Buscopan; Boehringer, Ingelheim, Germany), used as spasmolytic agent, was injected before the injection of gadobutrol.

MR enteroclysis studies were evaluated on a Picture Archiving and Communications System station (AGFA IMPAX version 4.5 service pack 5; Mechelen, Belgium). Electronic calipers were used for measurements. Bowel distension was graded as either insufficient (collapsed bowel loops) or sufficient for diagnosis (small bowel lumen >0.5 cm). For MR enteroclysis, the duodenum was defined as the first 20 cm of the small bowel; the jejunum was regarded as the small bowel loops left of an imaginary line from the liver dome to the roof of the left acetabulum; all bowel loops located right of this imaginary line were considered ileum; and the terminal ileum was defined as the last 30 cm of the ileum.

Capsule endoscopy

Capsule endoscopy was performed as previously described (3). In brief, the patient swallowed the capsule (PillCam type SB; Given Imaging) after bowel preparation with 1

L Klean-Prep (Norgine Ltd., Marburg, Germany). After 8 hours, the belt with the hard disk and the sensor array were removed. If there was any doubt about complete passage of the capsule through the whole bowel, a plain abdominal radiography was performed 1 week after ingestion. Capsule endoscopy was assessed on a dedicated workstation (Rapid 4, Given Imaging) by an experienced gastroenterologist (M.S.; >500 capsule endoscopy procedures). Gastric transit time, small intestinal transit time, proportion of capsules reaching the cecum, and viewing time were recorded. For capsule endoscopy, the duodenum was defined as the first 20 minutes of the small bowel, the time between start jejunum and start of the terminal ileum was halved to define the transition between jejunum and ileum, and the terminal ileum was regarded as the last 30 minutes of the ileum.

Balloon-assisted enteroscopy

Balloon-assisted enteroscopy was performed using a Fujinon double-balloon enteroscope (EN-450P5 or EN-450T5; Fujinon Corp. Saitama, Japan) after an overnight fast and a bowel preparation with either 1 L Klean-Prep for endoscopy via the oral approach or 4 L Klean-Prep for the anal approach. All balloon-assisted enteroscopy procedures were performed by two experienced enteroscopists (D.H. and P.M.; >200 balloon-assisted enteroscopy procedures each). During the procedure, conscious sedation was applied using midazolam (Dormicum; Roche, Woerden, Netherlands) with or without fentanyl (Janssen-Cilag, Tilburg, Netherlands). Butylscopolamine was administered on withdrawal. Complete small bowel visualization was attempted in all patients, starting with the oral approach. If this approach revealed abnormal findings that were considered a likely cause of the OGIB, no anal approach was performed. Otherwise, the anal procedure was performed during the same session or during a rescheduled session within 1 week.

During the oral approach, the most distal part of the small bowel reached was marked by submucosal injection of Indian ink. During all balloon-assisted enteroscopy procedures, the withdrawal of the enteroscope was taped on digital video. Insertion depths were estimated using the method described previously (13). Abnormal lesions were defined as vascular lesions (angiodysplasia or vascular malformations), tumorous lesions, ulcerative lesions, or other lesions (polypoid or diverticular lesions). The number, location, and size of all abnormal lesions were noted. Regular diagnostic and therapeutic procedures, including biopsy sampling, polypectomy, argon plasma

coagulation, endoclips, and dilation, were performed and documented. During balloon-assisted enteroscopy, the duodenum was defined as the first 20 cm of the small bowel, the jejunum as the proximal 20–200 cm, the proximal ileum as 200 cm to just proximal of the last 30 cm distal to the ileocecal valve, and the distal ileum as the last 30 cm of the ileum.

Reference standard and expert panel

The reference standard consisted of small bowel findings at balloon-assisted enteroscopy in those small bowel segments visualized during enteroscopy, and an expert panel consensus diagnosis for the remaining small bowel segments not visualized by balloon-assisted enteroscopy. The expert panel also evaluated the segments in which balloon-assisted enteroscopy was negative and MR enteroclysis and/or capsule endoscopy diagnosed small bowel lesion(s). This expert panel consisted of two experienced gastroenterologists (J.D., H.H.) who were not involved in reading the study examinations or in managing the study patients. Both experts were presented with the anonymized full patient medical history and clinical status. The latter included the indication for the diagnostic work-up, laboratory findings, detecting pathological lesions with an expected lower bound of 0.85 in the 95% confidence interval (CI), it was determined that 40 patients were needed for sufficient power.

Statistical analysis

The sensitivities, specificities, positive predictive values, negative predictive values, and P values (chi square and McNemar) for MR enteroclysis and capsule endoscopy were calculated using balloon-assisted enteroscopy as the reference standard. The P values were calculated between MR enteroclysis and capsule endoscopy in all included patients and all patients with abnormalities. Data are presented as mean (range), unless otherwise indicated.

Results

From January 2007 to March 2009, 69 consecutive patients who were referred for evaluation of OGIB were asked to participate in this study. A total of 45 patients consented and were consequently included. Seven patients (16%) were excluded for refusing to participate after informed consent had been given (n = 6) or due to deteriorating health status (n = 1). Thus, 38 patients with a mean age of 58 years (range 28–75 years) were eligible for evaluation, including 20 women (Table 1). The median time between MR enteroclysis and balloon-assisted enteroscopy was 16 days (5–72 days).

Table 1. Patient characteristics. Hb, hemoglobin.

Number of patients	38
Male/female	18/20
Age in years (range)	58 (28–75)
Mean Hb, mmol/L (range)	5.75 (3.4–7.9)
Obscure/overt	32/6
Duration of complaint in years (range)	1.6 (0.4–6)

Table 2. Balloon-assisted enteroscopy procedure.

Number of patients	38
Approach oral/anal/combined	32/2/4
Insertion depth oral in cm (range)	312 (20–480)
Insertion depth anal in cm (range)	140 (120–160)
Insertion depth combined in cm (range)	384 (155–686)
Therapy:	
Argon plasma coagulation	8
Endoclips	1
Polypectomy	1
Dilation	0

Balloon-assisted enteroscopy was performed exclusively via the oral approach in 32 patients (84%), via the anal approach in 2 patients (5%), and via both the oral and anal approaches in 4 patients (11%). Of the two patients in whom the anal approach was used exclusively, one had experienced rectal bleeding as the predominant symptom during the previous 11 months, and the other had chronic anemia and right lower-quadrant abdominal pain. All balloon-assisted enteroscopy procedures had good

diagnostic quality. The mean maximum-insertion depths (Table 2) via the oral, anal, and combined approaches were 312 cm (range 20–480 cm), 140 cm (range 120–160 cm), and 384 cm (range 155–686 cm). The mean balloon-assisted enteroscopy duration was 67 minutes (range 10–150 minutes). Table 3 shows the visualization values of the small bowel segments, and Table 4 gives the diagnoses made by balloon-assisted enteroscopy. Enteroscopic therapy (Table 2) was applied in 10 patients (26%); argon plasma coagulation in eight (21%), endoclips in one (3%, Fig. 1), and polypectomy in one patient (3%). No complications were noted during or after diagnostic or therapeutic balloon-assisted enteroscopy procedures.

The reference standard (balloon-assisted enteroscopy and the expert panel) diagnosed 23 pathological findings in 20 patients, 18 of which (78%) were diagnosed during balloon-assisted enteroscopy and 5 abnormal findings (22%) were added by the expert panel based on capsule endoscopy and MR enteroclysis results. The latter five cases consisted of angiodysplasia in four patients detected by capsule endoscopy (Fig. 2) and one Meckel's diverticulum (Fig. 3) detected by MR enteroclysis and confirmed by surgical resection. In three cases, abnormal findings during capsule endoscopy were not confirmed by the reference standard (two cases with erosions in the terminal ileum and one case with angiodysplasia).

Table 3. Visualized segments of the small bowel during balloon-assisted enteroscopy. Prox, proximal; dist, distal.

Visualization	duodenum	jejunum	ileum prox	ileum dist
visualized segments	36	35	34	14
non-visualized segments	2	3	4	24
total	38	38	38	38

Of the six patients with overt bleeding, capsule endoscopy revealed angiodysplasia in four patients, a venectasia in one patient, and no abnormalities in the remaining patient. MR enteroclysis did not reveal any cause for the obscure bleeding in these patients. Comparing the capsule endoscopy and MR enteroclysis results with the reference standard, the sensitivity and specificity of capsule endoscopy were 61% (95% CI 36–81%) and 85% (95% CI 61–96%), respectively, whereas the sensitivity and specificity of MR enteroclysis were respectively 21% (95% CI 7–46%) and 100% (95% CI 79–100%). The respective positive and negative likelihood ratios were 4.1 and 0.46

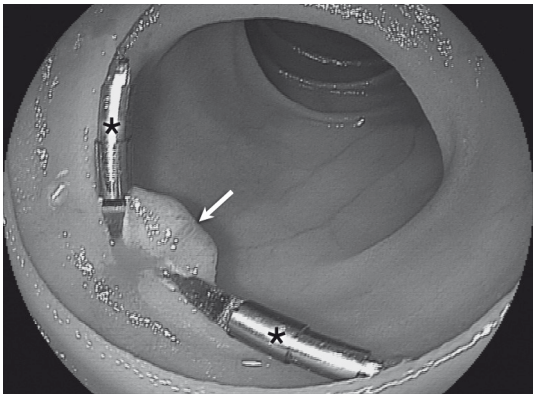
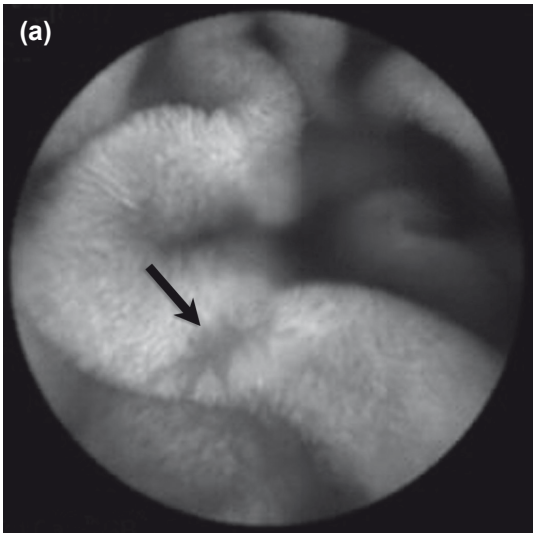


Figure 1.
Balloon-assisted enteroscopy in a 75-year-old female with fatigue and repetitive iron deficiency anemia that required five blood transfusions over 18 months. Magnetic resonance enteroclysis did not diagnose any abnormality. Capsule endoscopy was also not diagnostic due to the presence of black fluid in the small bowel lumen. Balloon-assisted enteroscopy revealed a large arteriovenous malformation for which two endoclips were placed.



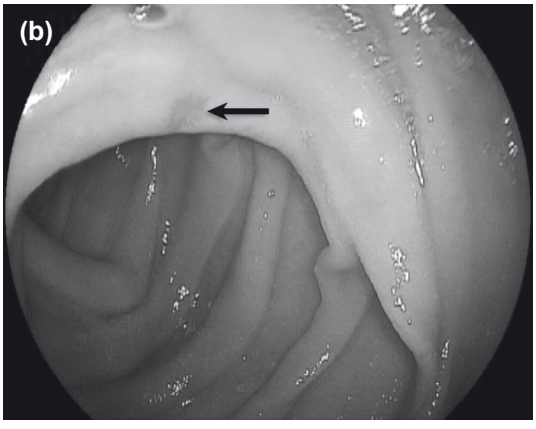


Figure 2.
A 72-year-old male with recurrent iron deficiency anemia requiring six prior blood transfusions. Magnetic resonance enteroclysis (not shown) did not diagnose any abnormality. Capsule endoscopy (a) and balloon-assisted endoscopy (b) both revealed angiodysplasia (arrows) in the small bowel.

for capsule endoscopy and infinity and 0.79 for MR enteroclysis (Table 5). There was no significant difference in the percentage of positive findings of capsule endoscopy compared with the reference standard (P = 0.34), whereas there was a significantly lower percentage of positive findings with MR enteroclysis (P < 0.001). When comparing MR enteroclysis and capsule endoscopy (Table 6) for all abnormalities detected and excluded in all included patients, the two modalities did not differ (P = 0.222). However, when comparing MR enteroclysis and capsule endoscopy (Table 7) in only patients with abnormalities, the two differed significantly (P = 0.0015) in favor of capsule endoscopy.

Table 4. Diagnoses resulting from the reference standard (including balloon-assisted enteroscopy), MR enteroclysis, and capsule endoscopy .

	Reference standard	**MR enteroclysis**	**Capsule endoscopy**
	n (%)	n (%)	n (%)
no small bowel abnormality	18 (47.4)	33 (86.8)	19 (50)
angiodysplasia	15 (39.5)	0	13 (34.2)
Crohn's disease	1 (2.6)	1 (2.6)	0
small bowel tumor	2 (5.3)	2 (5.3)	1 (2.6)
Meckel's diverticulum	1 (2.6)	1 (2.6)	0
duodenal ulcer	1 (2.6)	0	0
other small bowel abnormality	0	1 (2.6)	0
not performed/not diagnostic	0	0	5 (13.2)
Total	38 (100)	38 (100)	38 (100)

Table 5. Diagnosis of MR enteroclysis and capsule endoscopy .

	MR enteroclysis	**Capsule endoscopy**
	n (%)	n (%)
True positive	4 (10.5)	11 (29.0)
True negative	19 (50)	17 (44.7)
False positive	0	3 (7.9)
False negative	15 (39.5)	7 (18.4)
Total	38 (100)	38 (100)

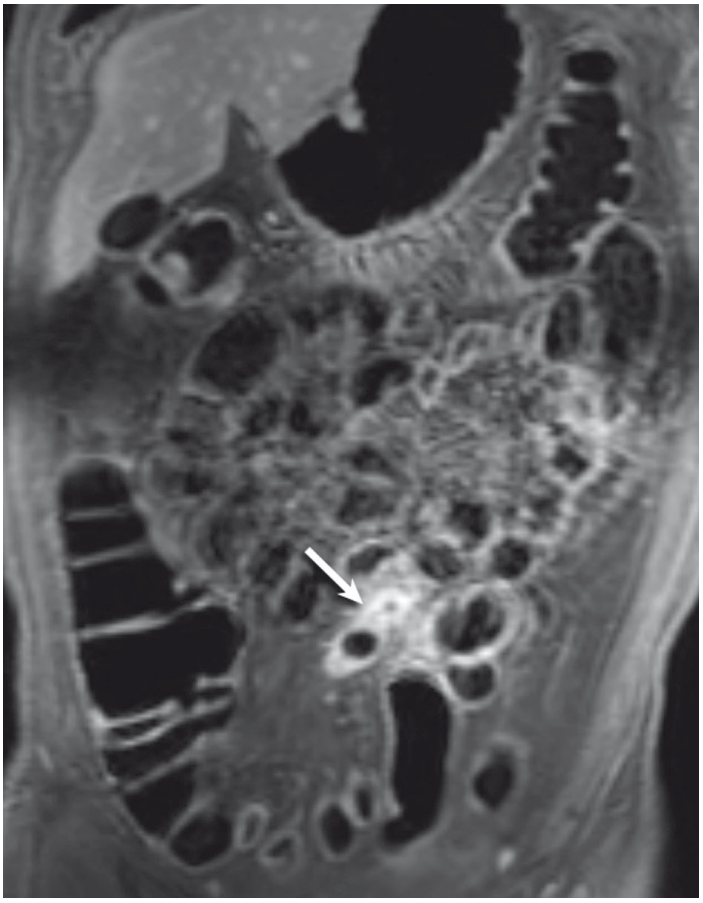


Figure 3.
A 37-year-old male with episodes of rectal blood loss and anemia without previously identified focus. Magnetic resonance eneroclysis revealed a Meckel's diverticulum with increased enhancement in the proximal ileum (arrow) on the coronal 3D T1-weighted fat-saturated image after contrast injection. Video capsule endoscopy (not shown) was not performed due to high grade small bowel stenosis at the Meckel's diverticulum. Balloon-assisted enteroscopy (not shown) was incomplete with a limited anal approach missing the actual lesion. Surgical resection confirmed the diagnosis of a Meckel's diverticulum.

Table 6. Correct diagnosis of MR enteroclysis and capsule endoscopy of total patient group.

	MR enteroclysis	Capsule endoscopy
Correct	23	28
Incorrect	15	10
Total	38	38

P = 0.222

Table 7. Correct diagnosis of MR enteroclysis and capsule endoscopy of only patients with abnormalities.

	MR enteroclysis	Capsule endoscopy
Correct	4	16
Incorrect	16	4
Total	20	20

P = 0.0015

The mean MR enteroclysis duration was 55 minutes (range 39–94 minutes), with a mean evaluation time of 9 minutes (range 4–15 minutes). All studies were of good diagnostic quality, and sufficient small bowel distension was achieved in all patients. In two patients (5%), the nasoduodenal catheter had to be placed endoscopically because of a cascade stomach or a para-esophageal hernia. Three patients (8%) suffered from vomiting during MR enteroclysis, one of whom had a high grade small bowel stenosis. MR enteroclysis diagnosed a high grade small bowel stenosis in three patients (8%). Two patients (5%) were diagnosed with previously unknown extramural abnormalities - an abdominal aorta aneurysm with duodenal impression (n = 1) and a uterus myomatosis (n = 1).

Four (11%) patients did not undergo capsule endoscopy due to suspected high grade stenosis on MR enteroclysis or a logistical reason (n = 1). The high grade stenoses were confirmed in all three cases, by balloon-assisted enteroscopy in two patients and by surgery in the third patient. These three patients with high grade stenosis did not have any particular symptoms compatible with high grade small bowel stenosis. The study quality was non-diagnostic in one patient (3%), 12 patients (35%) had studies with numerous artifacts, and studies were of good quality in 21 patients (62%). The mean evaluation time was 24 minutes (range 10–38 minutes). Table 4 lists the diagnoses with capsule endoscopy. No complications, including no capsule retention, were reported during or after capsule endoscopy.

Discussion

In the present study, capsule endoscopy performance was significantly better than MR enteroclysis for the detection of abnormalities in the small bowel in patients with OGIB. Capsule endoscopy is therefore a good first option for work-up of patients with OGIB. MR enteroclysis had a very low accuracy in diagnosing angiodysplasia and is therefore not a primary diagnostic modality for analyzing OGIB. Nevertheless, MR enteroclysis had high diagnostic accuracy in identifying high grade small bowel stenosis and can therefore be used in selected patients with suspicion of stenosis.

No studies have yet been published that compare, in patients with OGIB, MR enteroclysis and capsule endoscopy findings to a reference standard of balloon-assisted enteroscopy and an expert panel; the only previous study that compared both techniques in OGIB

did not have a reference standard (14). In that study, capsule endoscopy had a higher diagnostic yield compared with MR enteroclysis, which is in accordance with the results of the current study. Only comparisons between capsule endoscopy and balloon-assisted enteroscopy have been published, and those comparisons indicated a similar diagnostic yield for the two techniques (15-17).

OGIB is the primary and best-validated indication of capsule endoscopy, and the incidence of capsule retention is the lowest in this group [18]. The added value of capsule endoscopy over endoscopy alone in these patients previously ranged between 50 and 67%, and the added value of endoscopy was less (25–30%) (19). In the literature, capsule endoscopy is widely viewed as the initial diagnostic choice for patients with OGIB following upper and lower gastrointestinal endoscopy. Observations in the current study support this approach. Balloon-assisted enteroscopy is the second diagnostic choice for patients requiring follow-up, histology, or intervention, and for patients for whom suspicion of a small bowel lesion is high despite a negative capsule endoscopy (2,15,20-22).

The proportions of patients with no identifiable lesion in the small bowel varies widely in published studies. This difference most likely reflects differences in patient spectrum and inclusion criteria (23,24). The current data fit within the ranges described in the literature. The proportion of patients who underwent balloon-assisted enteroscopy via the anal approach for the indication of OGIB was also comparable with the literature (25).

MR enteroclysis did not diagnose any angiodysplasias in this patient group, similar to the low diagnostic yield of computed tomography (as low as 10–23%) (23). MR enteroclysis may be valuable for the detection of neoplasms, which are the cause of obscure or recurrent gastrointestinal bleeding of small bowel origin in 6–15% of patients (14). MR enteroclysis is a less invasive technique than balloon-assisted enteroscopy and does not require conscious sedation or both oral and anal approaches to visualize all small bowel segments. In the current study, the additional information of extramural abnormalities at MR enteroclysis did not contribute to the explanation of the OGIB. MR enteroclysis and/or magnetic resonance enterography are widely applicable with the given widespread availability of state-of-the-art magnetic resonance imaging. MR enteroclysis, however, may be preferred as the initial procedure in younger patients with a higher likelihood of Crohn's disease. Furthermore, in patients with cancer in their medical history, MR enteroclysis may also be used as a first procedure, especially

in patients with melanoma. The advantage of balloon-assisted enteroscopy over MR enteroclysis and capsule endoscopy is that it offers the combination of diagnostic and therapeutic options. The disadvantages of balloon-assisted enteroscopy are the duration of the procedure, the inability to visualize the small bowel lumen behind a high grade stenosis, and the observation that complete small bowel visualization is often not obtained within a reasonable time frame.

There are some limitations to the current study. The order of the examinations was fixed that MR enteroclysis could first rule out high grade stenosis to avoid capsule retention. No capsule retention occurred in the study as the diagnoses were established with MR enteroclysis and/or patency capsule beforehand. In most cases, balloon-assisted enteroscopy was done via one route (mostly oral); the whole small bowel was therefore not completely visualized. In addition, the reference standard was a composite assessment that included capsule endoscopy and MR enteroclysis, which represents an incorporation bias; identification of bowel segments is not straightforward with either technique, and comparison is thus hampered. The median time between MR enteroclysis and balloon-assisted enteroscopy was less than 3 weeks, but in one patient it was 72 days, a longer interval than most which may have affected diagnosing small bowel abnormalities. However, considering the long duration of OGIB, this delay presumably had no effect on the findings.

In conclusion, capsule endoscopy performance was significantly better than MR enteroclysis in the detection of small bowel abnormalities in patients with OGIB. MR enteroclysis can be used as an alternative primary strategy for patients with clinical suspicion of high grade small bowel stenosis.

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Patient burden and patient preference in small bowel imaging: comparing MR enteroclysis, capsule endoscopy and balloon-assisted enteroscopy.

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Abstract

Background and Aim

We aimed to prospectively determine patient burden and patient preference for magnetic resonance enteroclysis (MRE), capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE) in patients with suspected or known Crohn's disease (CD) or occult gastrointestinal bleeding (OGIB).

Methods

Consecutive consenting patients with CD or OGIB underwent MRE, CE and BAE. CE was only performed if MRE showed no high-grade small bowel stenosis. Patient preference and burden was evaluated by means of standardized questionnaires at five moments in time.

Results

From January 2007 until March 2009, 76 patients were included (M/F 31/45; mean age 46.9 years; range 20.0–78.4 years): 38 patients with OGIB and 38 with suspected or known CD. Seventeen patients did not undergo CE because of high-grade stenosis. Ninety-five percent (344/363) of the questionnaires were suitable for evaluation. CE was significantly favored over MRE and BAE with respect to bowel preparation, swallowing of the capsule (compared to insertion of the tube/scope), burden of the entire examination, duration and accordance with the pre-study information. CE and MRE were significantly preferred over BAE for clarity of explanation of the examination, and MRE was significantly preferred over BAE for bowel preparation, painfulness and burden of the entire examination. BAE was significantly favored over MRE for insertion of the scope and procedure duration. Pre- and post-study the order of preference was CE, MRE and BAE.

Conclusion

Capsule endoscopy was preferred to MRE and BAE; it also had the lowest burden. MRE was preferred over BAE for clarity of explanation of the examination, bowel preparation, painfulness and burden of the entire examination, and BAE over MRE for scope insertion and study duration.

Introduction

Capsule endoscopy, balloon-assisted enteroscopy, and magnetic resonance enteroclysis have become standard techniques in the work up of small bowel diseases. Capsule endoscopy visualizes the entire small intestine and appears sensitive for the detection of small lesions, but costs, specificity, and anatomic localization appear to be its limitations (1). Balloon-assisted enteroscopy allows excellent visualization of the small bowel and offers the opportunity for biopsy sampling and intervention, but it is more invasive than capsule endoscopy (2,3). MR enteroclysis can be an efficient alternative to image the complete small-bowel wall and extramural structures if it is applied with optimal luminal distension, as it combines excellent soft tissue contrast with multiplanar imaging capabilities.

To our knowledge, no head to head comparison of these three diagnostic modalities has been performed so far with respect to patient burden and patient preference. Until now, several studies compared capsule endoscopy with other modalities in terms of diagnostic yield (4), and other studies compared the diagnostic yield of balloon-assisted enteroscopy and MR enteroclysis with other modalities (5.6). However, while diagnostic performance is an important characteristic of a test, associated burden and patient preference are of additional importance, even more so when patients need to undergo tests repeatedly over time.

The purpose of this study, therefore, was to prospectively assess patient burden and patient preference for capsule endoscopy, MR enteroclysis and balloon-assisted enteroscopy in the case of two major indications for small bowel imaging: known or suspected Crohn's disease and obscure gastrointestinal bleeding (OGIB).

Methods

Patients

Patients were eligible if they showed signs of chronic or repeated gastrointestinal bleeding with negative gastroscopy and ileocolonoscopy, or if they had suspected or known Crohn's disease with suspicion of relapse. Patients were included if they were adults younger than 75 years, unless they had suspected intra-abdominal abscess, had abdominal surgery in the 6 weeks prior to inclusion or were under clinical suspicion

of high-grade small-bowel obstruction. Further exclusion criteria were pregnancy or breastfeeding, inability to swallow the video capsule, having a pacemaker or cardioversion device, a history of contrast media reaction or allergy (especially asthma), a severe concomitant disease with limited life expectancy, or a psychiatric, addictive or any other disorder that compromised ability to give informed consent for participation in this study. Results on yield of the three techniques were reported separately (7,8).
This study was approved by the Institutional Review Boards of the participating institutions. All patients gave written informed consent prior to any study procedures.

Methods

All patients first underwent MR enteroclysis, which allowed ruling out high-grade stenosis. If this was not found, MR enteroclysis was followed by capsule endoscopy. Finally, all the patients underwent balloon-assisted enteroscopy. None of the two patient groups underwent all three examinations before the study. There were two patients who underwent balloon-assisted enteroscopy before and two patients who underwent MR enteroclysis before.
High-grade stenosis was defined as a small bowel stenosis with a luminal patency of less than 10 mm diagnosed by MR enteroclysis. In these cases, no capsule endoscopy was performed. If MR enteroclysis defined a luminal stenosis of 10–14 mm, defined as low-grade stenosis, a patency capsule (Agile Patency Capsule, Given Imaging, Yoqneam, Israel) was used prior to capsule endoscopy. If the patency capsule did not pass the small bowel within 16 hours as checked by plain abdominal X-ray, this was considered indicative for a high-grade stenosis and MR enteroclysis was cancelled. In the analyses of these patients, only a comparison between MR enteroclysis and balloon-assisted enteroscopy was made.
The investigators performing the different examinations received the same clinical information, but were blinded for the results of the other diagnostic procedures performed as part of this study. The time interval between the first and last examination was restricted to three weeks whenever possible.

MR enteroclysis

Magnetic resonance enteroclysis was performed as described elsewhere (9). In brief, after bowel cleansing with a low-residue diet, ample fluids, a laxative on the day prior to the exam, and nil per mouth on the day of the examination, the small

bowel was distended with water containing 0.5% methylcellulose administered through a nasoduodenal catheter (Flocare, Nutricia, Chatel-ST-Denis, Switzerland). MR enteroclysis was performed at 1.5 T (Siemens Avanto, Erlangen, Germany). Evaluation of bowel filling and distension was obtained with half-Fourier single-shot turbo spin echo (HASTE). Morphologic evaluation was performed using true fast imaging with steady-state precession (FISP) and fast low-angle shot (FLASH) 2D images with fat saturation after contrast injection. Study duration and complications were noted.

Capsule endoscopy

Capsule endoscopy was also performed as previously described (1). In brief, after bowel preparation with 1 L Klean-Prep (Norgine, Marburg, Germany) the endoscopy capsule (Pilllcam type SB I or II, Given Imaging) was administered. After 8 hours, the belt with the recording hard disk and the sensor array were removed. In case of any doubt with respect to capsule passage, a plain abdominal X-ray of the abdomen was performed after 7 days.

Balloon-assisted enteroscopy

After an overnight fast and bowel preparation with either 1 L Klean-Prep (Norgine) for the oral approach, or 4 L Klean-Prep for the anal approach, balloon-assisted enteroscopy was performed using a Fujinon enteroscope (EN-450P5/20, Saitama, Japan) with overtube and double balloon system.

Patients were sedated using 2.5–7.5 mg midazolam intravenously. The procedure started via the oral approach in the OGIB group and via the anal approach for Crohn's patients, unless there was a clinical suspicion that small bowel pathology was mainly located in the distal or proximal small bowel, respectively. Duration and depth of insertion was noted for each procedure and the complete examinations were taped on video.

Questionnaire

Patient preference was analyzed by means of a questionnaire. Patients were asked to complete this questionnaire at five moments in time (Appendix I): 24 hours before the start of the first examination, as well as after each examination and 5 weeks after completion of the last examination.

Before the first examination, patients completed a questionnaire comprising five multiple-choice questions using a Likert scale. These questions addressed the patient's

experienced health during the preceding 3 months, the clarity of the explanation of each of the three investigational procedures, and patient preference for any of the three examinations.

One day after each examination the patients completed a questionnaire of six multiple choice questions, each using a five point grading scale, regarding the burden related to the preparation for the test, the burden related to the insertion or swallowing, the match between expectations and experiences, the experienced duration of the procedure and the burden of the entire examination. Finally, patients were asked if they had any other remark(s) on the procedure they had undergone the previous day.

Five weeks after completion of all the examinations, patients completed a questionnaire of four multiple choice questions, with a five point grading scale. Three questions referred to the experienced burden related to the entire examination of the MR enteroclysis, capsule endoscopy and balloon-assisted enteroscopy. Finally, patients were asked to list the three procedures in order of preference, should they have to undergo a renewed examination. At that time point, the patients had received information on the results of all three examinations.

Sample size calculation and statistical analysis

Wilcoxon signed rank test was used to compare the response on the questions (Likert 1–5) and the two groups (OGIB vs Crohn). The minimum expected frequency for each cell in the cross table equaled 5. Therefore, analyzing a 2 x 5 table, we needed at least 2 x 5 x 5 = 50 patients, 25 patients in each group. For this study we included 38 patients in each group.

The questionnaires of patient preference before the first test and after the examinations were analyzed. In patients who did not undergo capsule endoscopy, the other modalities were analyzed separately. Also the data for OGIB and CD patients were analyzed for gender and age and separately. Also the data was analyzed separately for balloon-assisted enteroscopy performed by the oral and anal approach.

Results

From January 2007 until March 2009 76 patients (M/F 31/45; mean age 46.9 years; range 20–75 years, median 45.8) were included in the study. Thirty-eight (50%) patients suffered from (obscure) gastrointestinal bleeding, the other 38 patients suffered from suspected (20 patients) or known (18 patients) Crohn's disease. The three examinations were performed within a median period of 14 days (IQR 7).

MR enteroclysis

The mean MR enteroclysis examination time was 54 min (range 37–94 min), without a significant difference between the two patient groups. Seven patients vomited during the examination; in five of these patients this was due to the presence of a high-grade small bowel stenosis. Fluoroscopic placement of the duodenal catheter failed in two patients, and the catheter was placed endoscopically. One patient showed a mild allergic reaction to injection of the contrast agent.

Capsule endoscopy

Seventeen patients did not undergo capsule endoscopy. This was due to MR enteroclysis revealing high-grade small bowel stenosis in 14 patients, and low-grade stenosis with subsequent retainment of a patency-capsule in another two patients. In one patient, no capsule endoscopy was performed due to the short time interval between MR enteroclysis and balloon-assisted enteroscopy. The remaining 59 patients underwent capsule endoscopy, which was complicated by capsule retention in one of these patients, who was known with Crohn's disease and in which MR enteroclysis did not diagnose a high grade small bowel obstruction. In the patient group suspected of or known Crohn's disease, all high grade small bowel stenosis were caused by Crohn's disease related abnormalities.

Balloon-assisted enteroscopy

All patients underwent balloon-assisted enteroscopy, 38 of them were exclusively investigated via the oral approach, 19 via anal approach, while the remaining 19 patients underwent endoscopy both via the oral and anal approach. No complications were noted. The mean maximal insertion depth was 242 cm (IQR 285). The mean examination time was 69 min (range 10–150).

Questionnaires

In total, 344 of 363 (94.8%) questionnaires were returned. Of the 2280 answers given in these 344 questionnaires, 2137 (93.7%) were filled in and therefore suitable for evaluation. For the five different questionnaires, the evaluation rate of individual questions ranged between 93–97%, 97–99%, 92–95%, 89–95% and 93–95%, respectively. Patients experienced their health over the months before the first examination as follows: 4.1% very poor, 41.9% poor, 45.9% fair, 6.8% good and 1.4% very good (n = 74). There was no significant difference in experienced health between the two patient groups (P = 0.123).

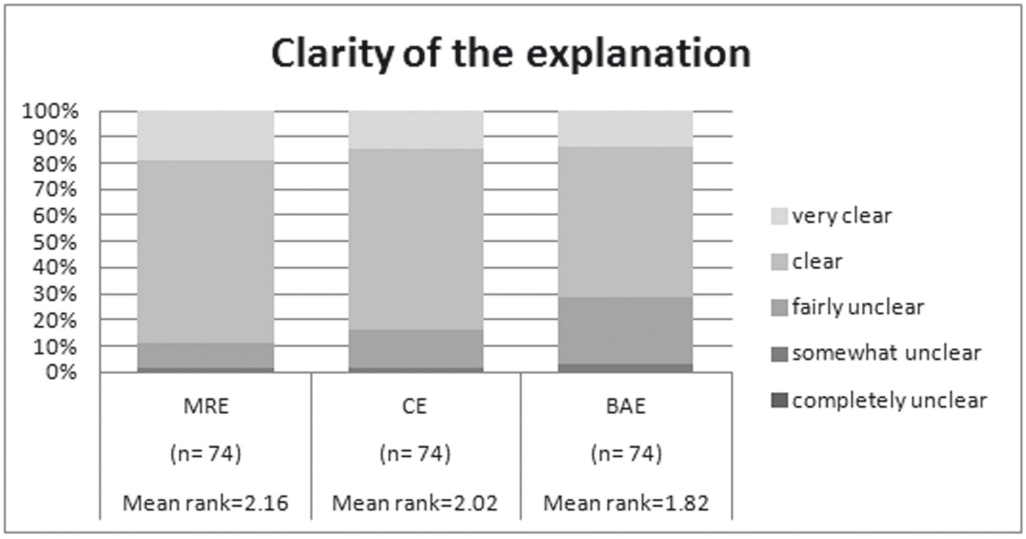

Figure 1.
Clarity of pre-study explanation of MR enteroclysis (MRE), capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE).
Pre-examination explanation of CE was significantly (p=0.001) clearer than that of MR enteroclysis or balloon-assisted enteroscopy. MR enteroclysis explanation was also significantly (p=0.016) clearer than balloon-assisted enteroscopy explanation.

Apart from the order of patient preference, only the results showing significant differences will be described below. The explanations of capsule endoscopy and MR enteroclysis were significantly clearer than the explanation or balloon-assisted enteroscopy (P < 0.001; Fig. 1). Preparation for capsule endoscopy (Fig. 2) was considered significantly less burdensome than preparation for MR enteroclysis and balloon-

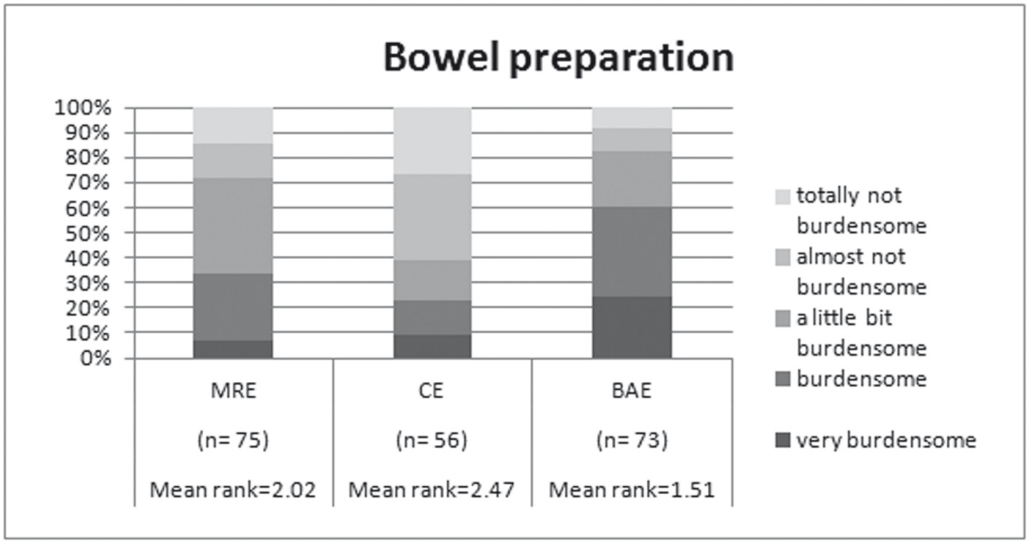

Figure 2.
Burden of bowel preparation of MR enteroclysis (MRE), capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE). CE preparation was significantly (p=0.000) less burdensome than preparation for MR enteroclysis or balloon-assisted enteroscopy. MR enteroclysis preparation was also significantly (p=0.022) less burdensome than preparation for balloon-assisted enteroscopy.

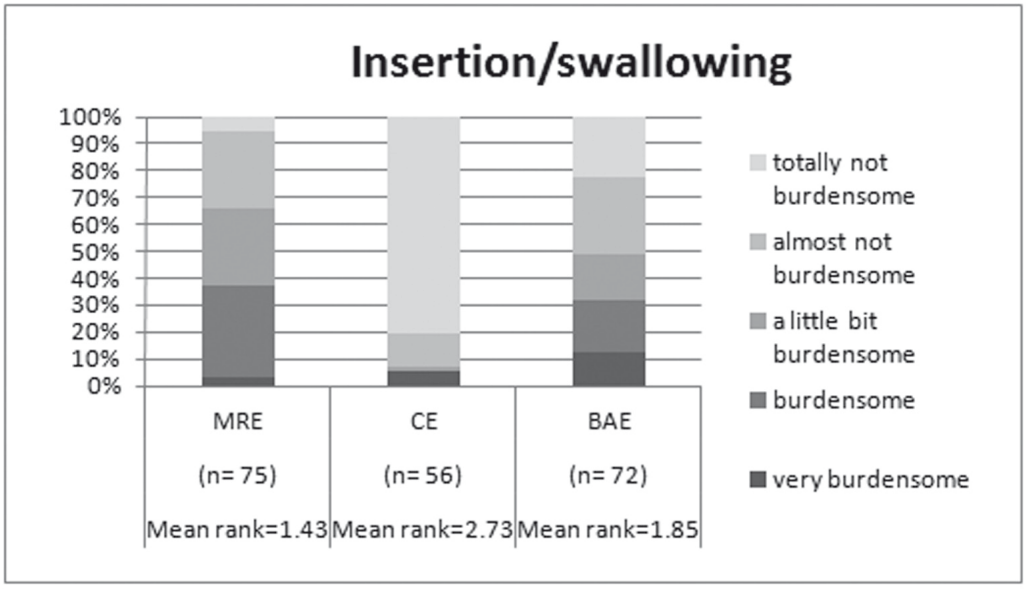

Figure 3.
Burden of insertion of tube or endoscope and swallowing of the capsule. Swallowing the capsule was significantly (p=0.000) less burdensome than insertion of the tube or endoscope for MR enteroclysis and balloon-assisted enteroscopy. Tube insertion for MR enteroclysis was significantly (p=0.000) more burdensome than endoscope insertion during BAE. MRE= MR enteroclysis, CE=capsule endoscopy, BAE= balloon-assisted enteroscopy

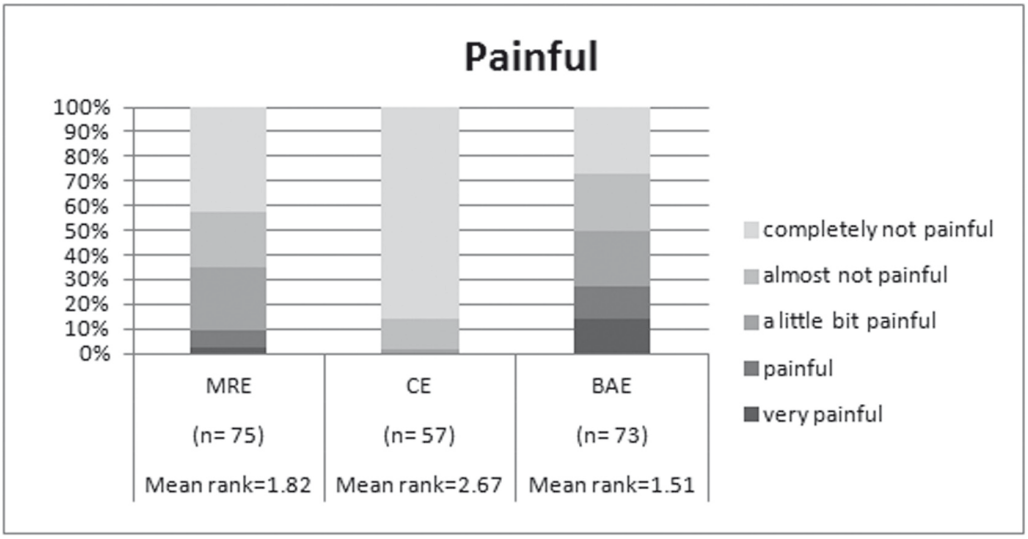

Figure 4.
Painfulness of MR enteroclysis (MRE), capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE). CE was significantly (p=<0.0001) less painful than MR enteroclysis and BAE, and MR enteroclysis was significantly (p=0.007) less painful than BAE.

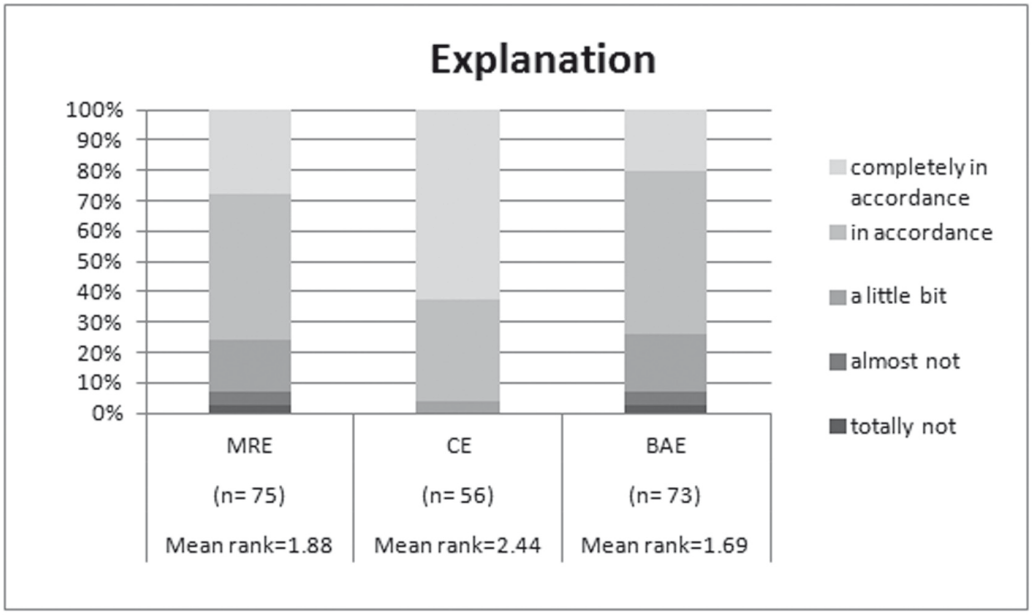

Figure 5.
Accordance of pre-examination information with patient experience of MR enteroclysis (MRE), capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE).
Pre-examination information about CE corresponded significantly (p=0,000) better with patient experience than information about MR enteroclysis and BAE.

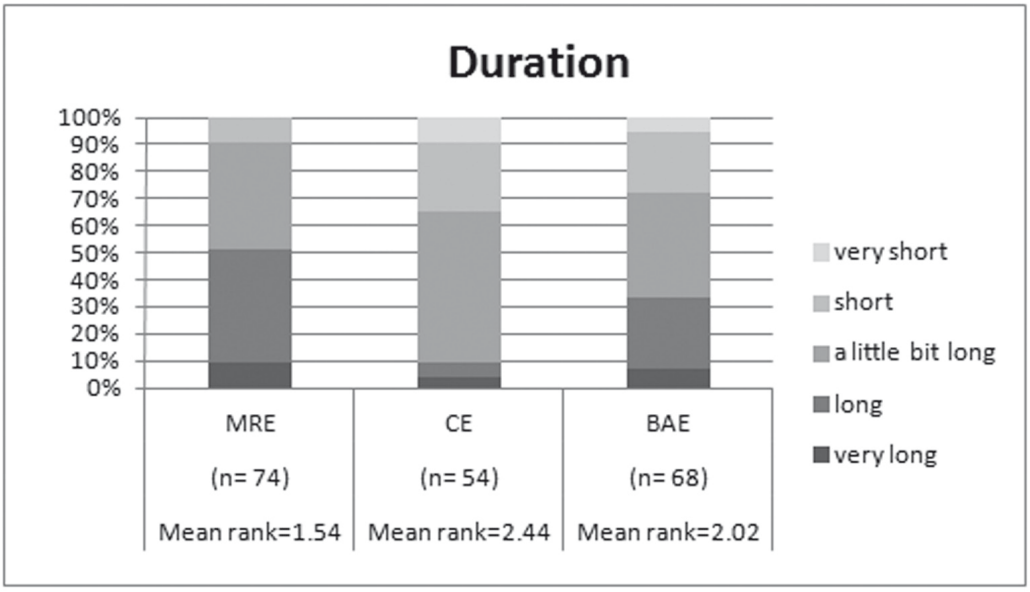

Figure 6.
Duration of MR enteroclysis (MRE), capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE). The experienced duration of the capsule endoscopy was significantly (p=0,000) shorter than the experienced duration of MR enteroclysis and balloon-assisted enteroscopy. It was also significantly (p=0,001) shorter for balloon-assisted enteroscopy than for MR enteroclysis.

assisted enteroscopy (P < 0.001). Preparation for MR enteroclysis was significantly less burdensome than preparation for balloon-assisted enteroscopy (P = 0.022).
Swallowing the capsule (Fig. 3) was significantly less burdensome than insertion of the tube for MR enteroclysis or of the endoscope during balloon-assisted enteroscopy (P < 0.001). Tube insertion for MR enteroclysis was significantly more burdensome than endoscope insertion during balloon-assisted enteroscopy (P < 0.001). Capsule endoscopy was considered significantly less painful than MR enteroclysis and balloon-assisted enteroscopy (P < 0.001; Fig. 4), while MR enteroclysis was significantly less painful than balloon-assisted enteroscopy (P = 0.007).
With hindsight, patients reported that pre-study information on capsule endoscopy corresponded significantly better with their experience of the examination than the information on MR enteroclysis and balloon-assisted enteroscopy (P < 0.001, Fig. 5). Patients experienced the duration of the capsule endoscopy examination as significantly shorter than MR enteroclysis and balloon-assisted enteroscopy (P < 0.001, Fig. 6). Comparing the latter two, they experienced the duration of balloon-assisted enteroscopy as shorter than MR enteroclysis (P = 0.001). One day as well as 5 weeks

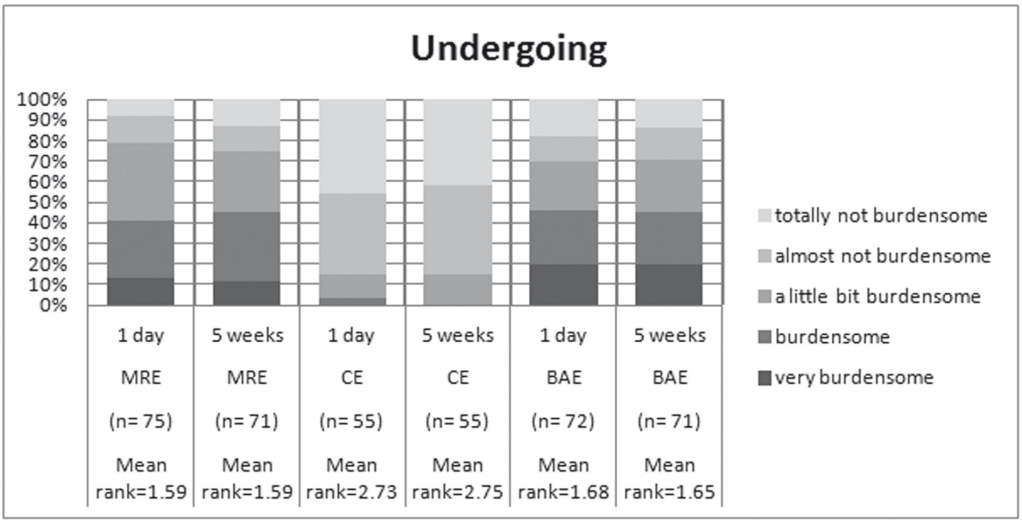

Figure 7.
Burden of undergoing of the entire examination of MR enteroclysis (MRE), capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE).
One day and 5 weeks after the examinations patients considered the entire CE examination as significantly (p=<0,0001) less burdensome than the entire examination of MR enteroclysis and BAE.

after the examinations, patients considered the entire capsule endoscopy procedure as significantly less burdensome than the entire examination of MR enteroclysis and balloon-assisted enteroscopy (both P < 0.001; Fig. 7).

When analyzing the patients with gastrointestinal bleeding and those with Crohn's disease separately, only two significant differences were noted. First, for patients with suspected or known Crohn's disease, bowel preparation related to MR enteroclysis was significantly less burdensome than preparation for capsule endoscopy or balloon-assisted enteroscopy (P < 0.001). Second, according to the patients with gastrointestinal bleeding, the pre-study information on MR enteroclysis corresponded significantly better with patients' experience than the information on balloon-assisted enteroscopy (P = 0.013). In the group that did not undergo capsule endoscopy, no significant difference in patient burden was observed between MR enteroclysis and balloon-assisted enteroscopy. There was no significant difference in patient burden or preference with respect to gender or age. There were also no significant differences between balloon-assisted enteroscopy performed by oral compared with anal approach. Before and after all examinations, patients considered capsule endoscopy as most preferable, followed by MR enteroclysis as second and balloon-assisted enteroscopy

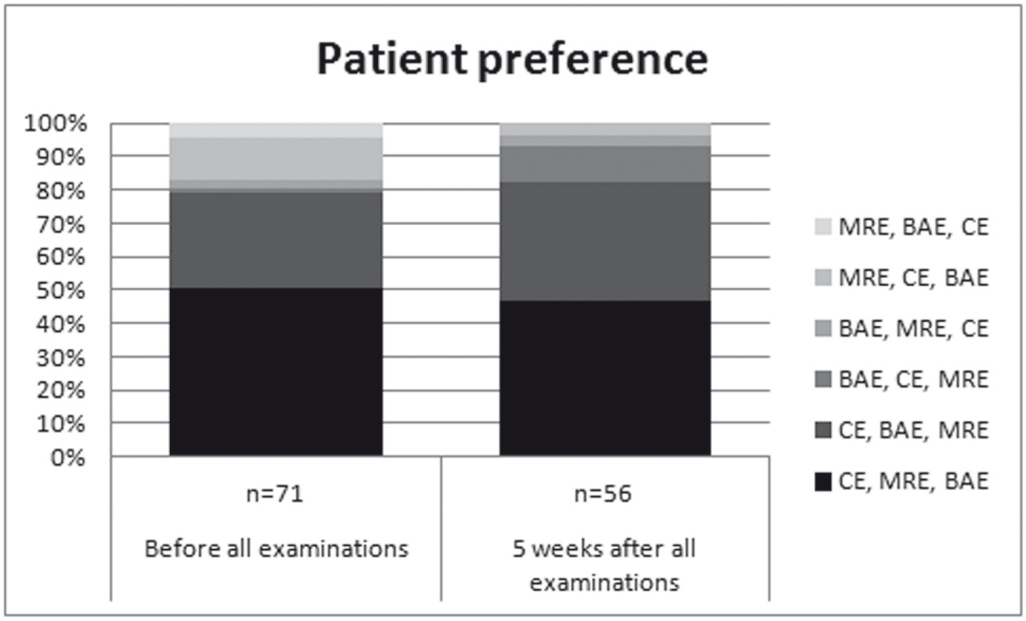

Figure 8.
Patient preference before and 5 weeks after MR enteroclysis (MRE), capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE).
No significant difference between pre- and post-examination patient preference.

as the last modality (Fig. 8). After having undergone all examinations, the proportion of patients who preferred MR enteroclysis as the first order modality decreased from 15.7% to 2.6%. The group that did not undergo capsule endoscopy showed the same order of preference for MR enteroclysis and balloon-assisted enteroscopy as the group that had undergone all three modalities.

Discussion

This study shows that patients with obscure gastrointestinal bleeding or suspected or known Crohn's disease prefer capsule endoscopy to MR enteroclysis or balloon-assisted enteroscopy. Remarkably, the preference for MR enteroclysis decreased after the procedure, which underlines that the procedure is more burdensome than patients expected. However, there remained a significant difference in favor of MR enteroclysis in comparison with balloon-assisted enteroscopy in view of the clarity of explanation,

the burden of bowel preparation, the painfulness and the burden of the entire procedure itself. On the other hand, the patients experienced balloon-assisted enteroscopy as significantly less burdensome than MR enteroclysis as far as insertion of the scope and study duration were concerned.

This paper adds essential information on patient acceptance of capsule endoscopy and MR enteroclysis, which – next to accuracy – is important in deciding which technique should be used. This is especially important when tests are used multiple times, such as in monitoring Crohn's disease. A well accepted test facilitates proper patient monitoring. Further, this paper gives valuable information for informing patients on the burden of either technique.

No direct comparison with other similar studies can be made, as to our knowledge no earlier study directly compared these three modalities of small bowel imaging for patient burden. One related study described the burden of computed tomography colonography (CTC) and endoscopy after a fecal occult blood test in a screening population, concluding that only a small majority (67%) of all participants would choose CTC as a first examination after FOBT in future screening (10). This could be explained by the sedation and retrograde amnesia during endoscopy and by participants' reluctance to undergo an unnecessary additional examination. Previously the burden of three different bowel preparations for capsule endoscopy (overnight fast and 1 L or 2 L of polyethylene glycol) had been studied. The conclusion was that 94% of the patients would undergo the procedure in the future, irrespective of the bowel preparation used (11). In the current study, we used 1 L of Klean-Prep.

The preference for capsule endoscopy and MR enteroclysis in terms of clarity of explanation of the modality can probably be explained by the fact that the process of balloon-assisted enteroscopy is less predictable beforehand.

While MR enteroclysis scored significantly better on some aspects that determine the level of burden, balloon-assisted enteroscopy scored significantly better on some other of those aspects. MR enteroclysis was significantly favored for the items bowel preparation and burden of the procedure, whereas balloon-assisted enteroscopy was significantly favored for the lower burden of inserting the scope and the shorter duration of the examination. The use of benzodiazepines during balloon-assisted enteroscopy, which gives sedation and retrograde amnesia, can be of influence on grading the burden and preference for this modality in comparison with MR enteroclysis. For example, the sedation and retrograde amnesia caused by benzodiazepines during

balloon-assisted enteroscopy could explain the difference of the actual mean duration time of balloon-assisted enteroscopy, which was longer than MR enteroclysis, while patients experienced this the other way around. This can be explained that the subjective experience of duration of balloon-assisted enteroscopy was shorter than MR enteroclysis. This suggests that MR enteroclysis and balloon-assisted enteroscopy both have their various advantages and disadvantages. Analgetics and sedatives are used during balloon-assisted enteroscopy and are associated with retrograde amnesia. Our results can therefore not be generalized to other settings where different approaches concerning analgetics and sedatives are used. The strength of this study was that all patients, except those with high-grade stenosis, underwent all three investigations. Questionnaires were used prior to and after the examinations, which gave us the opportunity to study expected and experienced burden as well as the order of preference prior to and after undergoing the examination.

Although capsule endoscopy had the lowest patient burden and was preferred by these patients, drawbacks of capsule endoscopy are that no biopsies can be performed and that it has a lower specificity for intestinal lesions than other techniques.

This study has several limitations. First, the order of the examinations was fixed to rule out high-grade stenosis, which helped to prevent capsule retention. With our stepwise protocol, capsule retention was low (one case, 1.3%), whereas in the literature it was reported in 0.7–2% of patients with OGIB and in up to 8% of patients with suspected or established Crohn's disease (4). Without fixed examination order, therefore, capsule retention would likely have occurred more frequently, which most likely would have had a negative influence on patients' experience of capsule endoscopy. On the other hand, the presence of a high-grade stenosis was the main cause of vomiting (9.2%) during MR enteroclysis, indicating that the preference score of MR enteroclysis might have been higher if patients with high-grade stenosis had been excluded from the comparison altogether. No complications occurred during balloon-assisted enteroscopy. In the literature, the incidence of complications is low as well, with pancreatitis (0.3%) as the most important complication (3). The patient acceptance is also influenced by the accuracy of the tests and the patients included in this study could not be informed on the diagnostic accuracy of these techniques given the lack of head to head comparative data. Another limitation as a consequence of the fixed order of the examinations was that it might have affected patient preference for diagnostic techniques.

A second limitation is that we did not include MR enterography in this comparison. This

technique might have led to more favorable findings than MR enteroclysis with respect to burden and acceptance, because MR enterography is performed after oral ingestion of a contrast medium it does not require nasoduodenal intubation, and vomiting is very rare. In a one study, patients who had less abdominal pain and discomfort preferred MR enterography to MR enteroclysis, which does require the introduction of a nasoduodenal tube (12). Using the enterography technique would possibly have led to less patient burden and higher patient preference for this modality. Nevertheless, we did not include MR enterography in this study because MR enteroclysis provides better small-bowel distention and so prevents missing lesions in non-distended small bowel loops (13).

In conclusion, the various small-bowel imaging techniques available today clearly differ in terms of patient burden. This direct comparative study showed that capsule endoscopy has the lowest patient burden, and is therefore clearly preferred by patients over MR enteroclysis and balloon-assisted enteroscopy. Most patients experienced the bowel preparation and painfulness of balloon-assisted enteroscopy as a burden as well as the entire examination, and the same was true for the insertion of the tube and the duration of MR enteroclysis. The clarity of explanation of the examination was also in favor for capsule enteroscopy and MR enteroclysis in comparison with balloon-assisted enteroscopy.

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Appendix 1

Questionnaires for the study of patient preference in small bowel imaging comparing MR enteroclysis, capsule endoscopy and balloon-assisted enteroscopy in patients with suspected or known Crohn's disease or obscure gastrointestinal bleeding.

Questionnaire A

Fill in before all examinations

This questionnaire asks you about your health, the pre-study information on each examination (including hand-outs) and about your expectations of each examination.

Fill in one box per question, whichever is the most appropriate for you.

1. How did you experience your health in the past months?
- very poor
- poor
- fair
- good
- very good

2. Is the explanation of the capsule endoscopy examination clear to you?
- completely unclear
- somewhat unclear
- fairly unclear
- clear
- very clear

3. Is the explanation of the MRI enteroclysis examination clear to you?
- completely unclear
- somewhat unclear
- fairly unclear
- clear
- very clear

4. Is the explanation of the balloon-assisted enteroscopy examination clear to you?
- completely unclear
- somewhat unclear
- fairly unclear
- clear
- very clear

5. Which examinations are you least able to face? Grade the three examinations with numbers from one to three, where number three indicates the one you are least able to face and number one is the one you are most able to face.
- Capsule endoscopy
- MRI enteroclysis
- Balloon-assisted enteroscopy

Questionnaire B, C, D

Fill in one day after the examination

This questionnaire asks you about your preference for the completed examinations and about the burdensomeness of the examinations.
Fill in one box per question, whichever is the most appropriate for you.

1. How burdensome was the bowel preparation of the MR enteroclysis/capsule enteroscopy/balloon-assisted enteroscopy?
- very burdensome
- burdensome
- a little bit burdensome
- almost not burdensome
- totally not burdensome

2. How burdensome was the swallowing of the capsule/ insertion of the tube/scope?
- very burdensome
- burdensome
- a little bit burdensome
- almost not burdensome
- totally not burdensome

3. How painful was the MR enteroclysis/capsule enteroscopy/balloon-assisted enteroscopy?
- very painful
- painful
- a little bit painful
- almost not painful
- completely not painful

4. Was the pre-study explanation in accordance with your own experience?
- totally not
- almost not
- a little bit
- in accordance
- completely in accordance

5. How long in your experience did the examination last?
- very long
- long
- a little bit long
- short
- very short

6. How burdensome was the entire examination?
- very burdensome
- burdensome
- a little bit burdensome
- almost not burdensome
- totally not burdensome

7. Do you have any comments on the examination, for example something that you did not like?

Questionnaire E

Fill in 5 weeks after completion of all three examinations

This questionnaire asks you about your experience of the three examinations.

1. How burdensome was the MR enteroclysis?
- very burdensome
- burdensome
- a little bit burdensome
- almost not burdensome
- totally not burdensome

2. How burdensome was the capsule endoscopy?
- very burdensome
- burdensome
- a little bit burdensome
- almost not burdensome
- totally not burdensome

3. How burdensome was the balloon-assisted enteroscopy?
- very burdensome
- burdensome
- a little bit burdensome
- almost not burdensome
- totally not burdensome

4. If you had to undergo a renewed examination of the small bowel, which of the three examinations would you prefer? Mark this examination with a one, the next in favour with a two and the examination least in favour with a three.
- Capsule endoscopy
- MR enteroclysis
- Balloon-assisted enteroscopy

Chapter 9

Summary and future perspectives/implications

This thesis discusses several aspects of imaging in small bowel diseases.
MR enteroclysis is performed by placing a nasoduodenal tube in the duodenum under fluoroscopy. By distending the small bowel with methylcellulose, dynamic and anatomic images are obtained. The use of single-shot techniques prevents the images from being blurred by respiration artefacts and bowel motion. In our first study, MR enteroclysis correlated in daily practise with the clinical outcome in 49 of the 50 patients (98%), and it altered the therapeutic strategy in 14 of the 29 patients (48%) (**Chapter 2**).

MR enteroclysis can detect various inflammatory small bowel diseases, which was presented in a pictorial essay in **Chapter 3**. Crohn's disease is characterized as a thickening of a segment of the small bowel wall. Active disease is characterized by bowel wall oedema, ulcerations, infiltration of the mesentery, and contrast enhancement of the bowel wall and lymph nodes. Complications of small bowel Crohn's disease are fistula formation, abscesses, and small bowel stenosis. Fibrostenotic disease is characterized by high grade small bowel stenosis without signs of active Crohn's disease. Other small bowel diseases, such as celiac disease, jejunitis, eosinophilic gastro-enteropathy, sclerosing encapsulating peritonitis, and radiation enteritis, can also be diagnosed with MR enteroclysis.

Jejunum abnormalities that can be diagnosed with MR enteroclysis are reviewed in **Chapter 4**. The advantage of MR enteroclysis over MR enterography is that the jejunum is better distended. Therefore, MR enteroclysis could be an important modality for ruling out jejunal abnormalities. The folds in the jejunum are thicker and more numerous than in the ileum. A bowel wall thickness greater than 3 mm must be considered abnormal, ranging from mild (<1.5 cm) to marked (>1.5 cm) thickening, and can be symmetric or asymmetric. Abnormal jejunal loops can be presented as uniform or layered bowel wall thickening. The small bowel abnormality can be diffuse, focal, or segmental with or without mesenterial infiltration. Jejunal abnormalities can be divided into infectious jejunitis, jejunal abnormalities of non-infectious origin, and neoplasms. Infectious jejunitis resolves completely after therapy, in contrast to jejunal abnormalities of non-infectious origin, which are chronic (e.g., Crohn's and celiac disease). Neoplasms are not uncommon in the jejunum. For example, multiple adenomas are seen in Peutz-Jeghers syndrome and familial adenomatous polyposis, adenocarcinoma, lymphoma, gastrointestinal stromal tumours (GIST), and metastases, especially melanoma.

Luminal distension of the small bowel results in the identification of wall abnormalities. However, no evidence exists showing that luminal distension is necessary for diagnosing small bowel diseases. Therefore, baseline MRI scans acquired before the infusion of contrast medium were compared to MR enteroclysis scans of optimal small bowel distension. Two observers independently evaluated the MR enteroclysis scans and the baseline MRI scans of 48 patients with suspected increases in disease activity who had known Crohn's disease (n=12), suspected Crohn's disease (n=20), suspected low-grade small bowel stenosis (n=13), or suspected small bowel neoplasm (n=3). The observers performed qualitative and morphological evaluations and their results compared. The results were also compared with the results of an expert reader. MR enteroclysis had higher interobserver agreement for measuring bowel wall thickness (intraclass correlation coefficient 0.84 versus 0.49) and the diagnosis and grading of obstruction (Kappa 0.60 versus 0.39) compared to baseline MRI. Agreement between these items and the results of the expert reader was higher on MR enteroclysis than on baseline MRI (bowel wall thickness: intraclass correlation coefficient 0.57 and 0.56 for MR enteroclysis and 0.38 and 0.44 for baseline MRI; obstruction: Kappa 0.53 and 0.53 for MR enteroclysis and 0.11 and 0.06 for baseline MRI). We concluded that the use of luminal contrast agent increases the reliability of luminal findings for the small bowel (**Chapter 5**).

Crohn's disease causes a high incidence of small bowel abnormalities. In a multi-centre study we compared MR enteroclysis to capsule endoscopy in patients with known or suspected Crohn's disease. The reference standard was a consensus diagnosis by an expert panel, which was primarily based on balloon-assisted enteroscopy supplemented with MR enteroclysis, capsule endoscopy, and clinical follow-up. In patients with a high grade stenosis, which was defined as a small bowel lumen of <10 mm with maximal bowel distension during the whole study, no capsule endoscopy was performed. MR enteroclysis established a high incidence (13/38, 34%) of high grade small bowel stenosis in patients with active small bowel Crohn's disease, which was confirmed in most of these patients (10 of 13 patients), who consequently did not undergo capsule endoscopy. MR enteroclysis identified therapeutically important extramural abnormalities, such as mesenteric abscesses and abdominal-enteral fistulas. In small bowel Crohn's disease, MR enteroclysis exhibited a higher sensitivity (73%) and higher positive predictive value (88%) than capsule endoscopy (sensitivity 57%,

positive predictive value 67%). Therefore, we concluded that MR enteroclysis could be a first-choice non-invasive diagnostic procedure in patients with suspected small bowel Crohn's disease. As a second modality, capsule endoscopy or balloon-assisted enteroscopy could be performed, depending on the result of the MR enteroclysis and the need for a histopathological diagnosis (**Chapter 6**).

Patients with occult gastrointestinal bleeding constituted the second part of the multicentre study, using the same study design as described in Chapter 6. MR enteroclysis detected high grade small bowel stenosis in 3 out of 38 patients (8%). Capsule endoscopy had a higher sensitivity (61%) than MR enteroclysis (21%) and revealed the cause of occult gastrointestinal bleeding in 14 out of 20 patients (70%), which was generally angiodysplasia. MR enteroclysis revealed the cause of occult gastrointestinal bleeding in 4 out of 20 patients (20%) and did not detect any of the angiodysplasias. Therefore, this study showed that capsule endoscopy has a significantly higher accuracy than MR enteroclysis in the detection of abnormalities in the small bowel of patients with occult gastrointestinal bleeding. In patients with clinical suspicion of high-grade small bowel stenosis, which prevents capsule endoscopy, MR enteroclysis can be used as an alternative primary strategy (**Chapter 7**).

Important aspects of diagnostic techniques are patient burden and patient experience. Therefore, we analyzed the patient burden and experience of MR enteroclysis, capsule endoscopy, and balloon-assisted enteroscopy in the two cohorts presented in Chapters 6 and 7. Standardized questionnaires were used at five moments in time for the patients with known or suspected Crohn's disease and patients with occult gastrointestinal bleeding described in Chapters 6 and 7. Capsule endoscopy was preferred over MR enteroclysis and balloon-assisted enteroscopy for patient bowel preparation, swallowing the capsule (compared to insertion of the tube or scope), duration, accordance with the pre-study information, and burden of the entire examination (all $p<0.001$). Capsule endoscopy and MR enteroclysis were significantly preferred over balloon-assisted enteroscopy for the clarity of the explanation of the examination ($p<0.001$), and MR enteroclysis was significantly preferred over balloon-assisted enteroscopy for bowel preparation, pain, and burden of the entire examination (all $p<0.001$). Balloon-assisted enteroscopy was significantly preferred over MR enteroclysis for insertion of the scope ($p<0.001$) and procedure duration ($p<0.001$). Before and after all examinations,

patients considered capsule endoscopy as the most preferable technique, followed by MR enteroclysis, with balloon-assisted enteroscopy as the least preferable modality. Therefore, we concluded that these three techniques clearly differ in terms of patient burden. This head-to-head comparative study showed that capsule endoscopy has the lowest patient burden and, therefore, is clearly preferred by patients over MR enteroclysis and balloon-assisted enteroscopy. With respect to balloon-assisted enteroscopy, most patients experienced the bowel preparation, pain, and entire examination as a burden, and with respect to MR enteroclysis, the insertion of the tube and the duration of the examination (**Chapter 8**).

In conclusion, MR enteroclysis is an important technique providing morphological information to diagnose small bowel disease not only in the ileum, but also in the jejunum. The most important indication of MR enteroclysis is suspected or known Crohn's disease. Capsule endoscopy is not preferred in this patient group because of the high incidence of small bowel stenosis. In patients with occult gastrointestinal bleeding, MR enteroclysis is indicated only in patients suspected of stenosis; otherwise, this patient group can best be evaluated by capsule endoscopy or balloon-assisted enteroscopy. MR enteroclysis has a higher patient burden and lower patient preference than capsule endoscopy, but it has a slightly higher patient preference and lower burden than balloon-assisted enteroscopy.

In the near future, some questions surrounding small bowel imaging will hopefully be solved.
The technique for performing MRI of the small bowel is still under scrutiny and new techniques are evaluated. Major impetus is the moderate accuracy of MRI in identifying limited disease activity (1). One of these techniques that has recently become recognized as potential important sequence, is the use of dynamic images of bowel peristalsis in MR enterography for the identification of small bowel localisations in Crohn's disease. A recent study reported significantly increased lesion detection rate using cine MR images as compared to standard MR enterography images (2). Diffusion-weighted imaging is a new technique in bowel MRI that can establish inflammation in soft tissue. Restricted diffusion is caused by decreased movement of the hydrogen protons. Recent publications have shown the potential of diffusion-weighted imaging to identify active segments, internal fistulas, and sinus tracts in Crohn's disease (3,4). At this moment it

is not clear whether diffusion-weighted imaging can replace post-contrast imaging to establish the grade of disease activity; if this would be possible this will result in lower costs for the MR examination.

The increased availability of 3.0T MR machines has resulted in more widespread use of 3T for bowel imaging. The higher field strength results in higher signal-to-noise ratio, but artefacts and the effects related to the physics at higher field strength increases (5). Therefore, solving these problems results in new possibilities for performing small bowel imaging on 3.0T instead of 1.5T scanners, such as large volume, higher temporal resolution dynamic enhanced sequences.

MRI is widely used to grade Crohn's disease, but considerable variation exists in the features used for grading disease activity (6,7). Two MRI-based activity indices have already been proposed in the literature and have been shown to be predictive as compared to histopathological standard or Crohn's Disease Endoscopic Index of Severity (CDEIS) score of reference (7,8). Further work should be done to come to one accurate and reproducible disease activity index to be used worldwide, which is of major importance for clinical work and research.

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Chapter 10

Samenvatting en toekomstperspectief

Dit proefschrift behandelt de diverse aspecten van de beeldvorming van dunne darmafwijkingen. MR enteroclyse wordt uitgevoerd nadat onder doorlichting een duodenumsonde is geplaatst. Methylcellulose veroorzaakt distensie van de dunne darm, waardoor dynamische en anatomische beelden verkregen worden. Het gebruik van single-shot technieken voorkomt dat de MRI-beelden door ademhalingsarfetacten en darmperistaltiek onduidelijk worden. In onze eerste studie correleerde MR enteroclyse in de dagelijkse praktijk in 49 van de 50 patiënten (98%) met de definitieve diagnose en het therapeutisch beleid werd in 14 van de 29 patiënten (48%) aangepast naar aanleiding van de MR enteroclyse uitslag (**Hoofdstuk 2**).

D.m.v. MR enteroclyse kunnen diverse ontstekingen in de dunne darm worden aangetoond. Dit wordt gepresenteerd in het pictorial essay in **Hoofdstuk 3**. De ziekte van Crohn wordt gekenmerkt door een wandverdikking van een segment van de dunne darm. De actieve ziekte wordt gekenmerkt door darmwand oedeem, ulceraties, infiltratie van het mesenterium en contrasttoename van de darmwand en lymfeklieren. Complicaties bij de ziekte van Crohn in de dunne darm zijn de vorming van fistulae, abcessen en stenosen. Fibrostenotische ziekte wordt gekenmerkt door hooggradige dunne darmstenose zonder tekenen van actieve ziekte van Crohn. Andere ziektes van de dunne darm, zoals coeliakie, jejunitis, eosinofiele gastroenterpathie, scleroserende peritonitis en bestralingsenteritis kunnen ook door MR enteroclyse worden gediagnostiseerd.

In **Hoofdstuk 4** worden afwijkingen aan het jejunum besproken die door middel van MR enteroclyse kunnen worden gediagnostiseerd. Het voordeel van MR enteroclyse boven MR enterografie is dat het jejunum beter uitgezet is. Daarom zou MR enteroclyse een belangrijke modaliteit kunnen zijn voor het uitsluiten van jejunale afwijkingen. De plooien in het jejunum zijn dikker en talrijker dan in het ileum. Een darmwanddikte groter dan 3 mm moet als abnormaal worden beschouwd, variërend van mild (<1,5 cm) tot uitgesproken (>1,5 cm) verdikking en kan symmetrisch of asymmetrisch zijn. Abnormale jejunale lissen kunnen een uniforme of gelaagde darmwandverdikking hebben. De dunne darmafwijking kan diffuus, focaal, of segmenteel zijn, zonder of met mesenteriale infiltratie. Jejunale afwijkingen kunnen worden onderverdeeld in infectieuze jejunitis, jenunale afwijkingen met een niet-infectieuze oorspong en tumoren. Infectieuze jejunitis verdwijnt geheel na therapie, in tegenstelling tot jejunale

afwijkingen met een niet-infectieuze oorsprong, die chronisch zijn (bijv. de ziekte van Crohn en coeliakie). Tumoren zijn niet ongewoon in het jejunum. Multipele adenomen komen voor bij het Peutz-Jeghers syndroom en familiaire adenomateuze polyposis, adenocarcinoom, lymfomen, gastrointestinale stromale tumoren (GIST) en metastasen, vooral melanomen.

Luminale distensie van de dunne darm resulteert in de identificatie van darmwandafwijkingen. Er is echter geen bewijs voor de noodzaak van luminale distensie bij MRI voor de diagnostisering van dunne darmziekten. MRI uitgangsbeelden voor de infusie van contrastmedium werden hiervoor vergeleken met MR enteroclyse beelden tijdens optimale dunne darmwand distensie. Twee beoordelaars evalueerden onafhankelijk van elkaar de MR enteroclysebeelden en de MRI uitgangsbeelden van 48 patiënten die verdacht werden van toenemende ziekteactiviteit bij de ziekte van Crohn (n=12), verdacht werden van de ziekte van Crohn (n=20), van laaggradige dunne darmobstructie (n=13), of van dunne darmtumoren (n=3). De beoordelaars voerden kwalitatieve en morfologische evaluaties uit en hun resultaten werden vergeleken. De resultaten werden ook vergeleken met de resultaten van een expert beoordelaar. MR enteroclyse had een hogere interobserver overeenkomst voor het meten van darmwandverdikking (intraclass correlation coefficient 0,84 versus 0,49) en het aantonen en gradering van dunne darmobstructie (Kappa 0,60 versus 0,39) vergeleken met MRI uitgangsbeelden. Overeenkomsten tussen deze items en de resultaten van de expert lezer waren hoger voor MR enteroclyse dan voor MRI uitgangsbeelden (darmwandverdikking: intraclass correlation coefficient 0,57/0,68 versus 0,38/0,44 en obstructie: Kappa 0,53/0,53 versus 0,11/0,06 voor respectievelijk de twee beoordeelaars van de MR enteroclyse en MRI uitgangsbeelden). We concludeerden dat door het gebruik van luminale contrastmiddelen de betrouwbaarheid van het diagnosticeren van dunne darmwandafwijkingen toeneemt (**Hoofdstuk 5**).

De ziekte van Crohn veroorzaakt een hoge incidentie van dunne darmafwijkingen. In een multicenterstudie hebben we MR enteroclyse vergeleken met capsule-endoscopie in patiënten met of verdacht van de ziekte van Crohn. De referentiestandaard was een consensusdiagnose door een expert panel, hoofdzakelijk gebaseerd op de resultaten van de balloon-assisted enteroscopie aangevuld met MR enteroclyse, capsule-endoscopie en klinische follow-up. In patiënten met een hooggradige stenose, die

gedefinieerd was als een dunne darm lumen van <10 mm bij maximale darmdistensie tijdens de gehele studie, werd geen capsule-endoscopie uitgevoerd. MR enteroclyse stelde een hoge incidentie vast (13/38, 34%) van hooggradige dunne darmstenose in patiënten met actieve ziekte van Crohn in de dunne darm, wat bevestigd werd in de meeste van deze patiënten (10 van de 13 patiënten), die vervolgens geen capsule-endoscopie ondergingen. Door middel van MR enteroclyse werden belangrijke extramurale afwijkingen vastgesteld, zoals mesenteriale abcessen en abdominale-enterale fistels. Voor de ziekte van Crohn, gelokaliseerd in de dunne darm, vertoonde MR enteroclyse een hogere sensitiviteit (73%) en hogere positieve voorspellende waarde (88%) dan capsule-endoscopie (sensitiviteit 57%, positieve voorspellende waarde 67%). Wij concluderen hierdoor dat MR enteroclyse de eerste keuze kan zijn in een non-invasieve diagnostische procedure bij patiënten die verdacht zijn van de ziekte van Crohn in de dunne darm. Als tweede modaliteit kunnen capsule-endoscopie of balloon-assisted enteroscopie worden uitgevoerd, afhankelijk van het resultaat van de MR enteroclyse en de noodzaak voor een histopathologische diagnose (**Hoofdstuk 6**).

Patiënten met occulte gastrointestinale bloedingen vormden het tweede deel van de multicenter studie, waarbij gebruik gemaakt werd van dezelfde studie-opzet zoals beschreven in Hoofdstuk 6. MR enteroclyse toonde in 3 van de 38 patiënten (8%) hooggradige dunne darmwandstenose aan. Capsule-endoscopie had een hogere sensitiviteit (61%) dan MR enteroclyse (21%) en wees in 14 van de 20 patiënten (70%) de oorzaak aan van de occulte gastrointestinale bloeding, wat in het algemeen angiodysplasie was. MR enteroclyse toonde de oorzaak van occulte gastrointestinale bloeding aan in 4 van de 20 patiënten (20%) en liet geen van de angiodysplasieën zien. Derhalve liet deze studie zien dat capsule-endoscopie een aanzienlijk hogere nauwkeurigheid heeft dan MR enteroclyse in het aantonen van dunne darmafwijkingen bij patiënten met occulte gastrointestinale bloedingen. In patiënten met klinische verdenking op hooggradige dunne darmstenose, die capsule-endoscopie verhindert, kan MR enteroclyse worden gebruikt als een alternatief (**Hoofdstuk 7**).

Belangrijke aspecten van diagnostische technieken zijn de belasting voor de patiënt en de ervaring van de patiënt. Op grond daarvan hebben we de belasting voor en ervaring van de patiënten geanalyseerd voor MRI enteroclyse, capsule-endoscopie en balloon-assisted enteroscopie in de twee groepen die worden gepresenteerd in

Hoofdstuk 6 en 7. Patiënten die bekend waren met of verdacht werden van de ziekte van Crohn en patiënten met occulte gastrointestinale bloedingen zoals beschreven in Hoofdstuk 6 en 7 kregen op vijf tijdsmomenten gestandaardiseerde vragenlijsten voorgelegd. De patiënten gaven capsule-endoscopie significant de voorkeur boven MR enteroclyse en balloon-assisted enteroscopy voor de darmvoorbereiding, het slikken van de capsule (vergeleken met het inbrengen van de sonde of de scoop), duur van het onderzoek, overeenkomst met de pre-studie informatie, en belasting van het gehele onderzoek (alle $p<0.001$). Capsule-endoscopie en MR enteroclyse werden significant verkozen boven de balloon-assisted enteroscopie voor de duidelijkheid van de uitleg van het onderzoek ($p<0.001$) en MR enteroclyse had significant de voorkeur boven de balloon-assisted enteroscopie voor de darmvoorbereiding, pijn en belasting tijdens het gehele onderzoek (alle $p<0.001$). Balloon-assisted enteroscopy werd significant verkozen boven MR enteroclyse voor het inbrengen van de scoop ($p<0.001$) en de duur van de procedure ($p<0.001$). Voor en na alle onderzoeken hadden de patiënten de grootste voorkeur voor de capsule-endoscopie, gevolgd MR enteroclyse, en de balloon-assisted enteroscopie werd als modaliteit het minst gewaardeerd. We concludeerden hierdoor dat deze drie technieken qua patiëntenbelasting duidelijk verschillen. Deze vergelijkende studie toonde aan dat capsule-endoscopie de laagste belasting voor de patiënt veroorzaakt en derhalve wordt deze door de patiënten verkozen boven MR enteroclyse en balloon-assisted enteroscopie. Met betrekking tot de balloon-assisted enteroscopy vonden de meeste patiënten de darmvoorbereiding, pijn en het gehele onderzoek een belasting en wat betreft de MR enteroclyse het inbrengen van de sonde en de duur van het onderzoek **(Hoofdstuk 8)**.

In conclusie: MR enteroclyse is een belangrijke techniek om morfologische informatie te verkrijgen om dunne darmziekten vast stellen die zich niet alleen in het ileum hoeven te bevinden, maar ook in het jejunum. De belangrijkste indicatie voor MR enteroclyse is verdenking op of vervolgen van ziekte van Crohn. Capsule-endoscopie heeft in deze patiëntengroep niet de voorkeur, vanwege de hoge incidentie van dunne darmstenose in onze onderzoeksgroep. In patiënten met occulte gastrointestinale bloedingen wordt MR enteroclyse alleen in patiënten verdacht van stenose geïndiceerd; in andere gevallen kan deze patiëntengroep het beste worden geëvalueerd door capsule-endoscopie of balloon-assisted enteroscopie. MR enteroclyse veroorzaakt een hogere belasting voor de patiënten en een lagere voorkeur van patiënten dan capsule-endoscopie, maar

het heeft een hogere patiënten voorkeur en lagere belasting dan de balloon-assisted enteroscopie.

In de nabije toekomst zullen sommige vragen rond de dunne darm hopelijk worden beantwoord. De uitvoeringstechniek voor MRI van de dunne darm wordt nog steeds nauwkeurig bestudeerd en nieuwe technieken worden geëvalueerd. Een belangrijke impuls is de matige nauwkeurigheid van de MRI bij het identificeren van milde ziekteactiviteit (1). Een van deze technieken, die onlangs is erkend als potentieel belangrijke sequentie, is het gebruik van dynamische beeldvorming van darmperistaltiek bij MR enterografie voor de identificatie van dunne darmlokalisaties bij de ziekte van Crohn. Een recente studie beschrijft een aanzienlijk toegenomen lesiedetectiegraad door het gebruik van cine MR beeldvorming vergeleken met standaard MR enterografie (2). Diffusie-gewogen beeldvorming is een nieuwe techniek die ontsteking in solide weefsel kan vaststellen. Beperkte diffusie wordt veroorzaakt door verminderde beweging van de waterstofprotonen. Recente publicaties hebben het potentieel van diffusie-gewogen beeldvorming aangetoond bij het identificeren van actieve segmenten, interne fistels en anorectale fistels bij de ziekte van Crohn (3,4). Op dit moment is het nog niet duidelijk of diffusie-gewogen beeldvorming de post-contrast beeldvorming kan vervangen om de gradiëring van de ziekteactiviteit vast te stellen; als dit mogelijk is, dan zal dit resulteren in lagere kosten voor het MRI onderzoek.

De toegenomen beschikbaarheid van 3.0T MR apparatuur heeft geresulteerd in een wijdverbreider gebruik van 3T voor dunne darmbeeldvorming. De hogere veldsterkte resulteert in hogere signaal-ruis verhouding, maar artefacten en de fysische effecten die gerelateerd zijn aan de hogere veldsterkte nemen toe (5). Derhalve vormt het oplossen van deze problemen nieuwe mogelijkheden om dunne darmbeeldvorming uit te voeren op 3.0T in plaats van 1.5T scanners, zoals gebruik van hogere contrast volumina bij dynamisch hoog temporele contrast sequenties.

MRI wordt algemeen gebruikt om de ziekte van Crohn te stagiëren, maar er bestaat een aanzienlijke variatie in de kenmerken die worden gebruikt om de ziekteactiviteit vast te stellen (6,7). Twee op MRI gebaseerde activiteit indices worden in de literatuur reeds voorgesteld en zijn voorspellend afgezet tegen de histopathologische referentiestandaard of de Endoscopische Crohnse ziekteactiviteit Index score (7,8). Meer werk zou verricht moeten worden om tot een accurate en reproduceerbare ziekteactiviteit index te komen die wereldwijd gebruikt zou moeten worden, wat van groot belang is voor klinisch werk en onderzoek.

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Curriculum Vitae

Bart Matthijs Wiarda is geboren op 4 oktober 1968 in Den Haag. Hij bracht zijn jeugd al schooierend door in Mariahoeve. Hij zat op de lagere school, de Leeuwerikhoeve en volgde het voorgezet onderwijs op het Nederlands Lyceum in Benoordenhout. Zijn opleiding Geneeskunde in Leiden rondde hij op 19 mei 1995 af. Tijdens een wetenschappelijk onderzoek naar Interleukine-4 op de afdeling Hematologie (1992) in het Leids Universitair Medisch Centrum ontmoette Bart zijn vrouw Clary Labee. Een jaar na zijn artsexamen kon hij starten met de opleiding radiologie bij Prof.dr. R.A. Manoliu. De helft van deze opleiding heeft hij genoten in het Medisch Centrum Alkmaar bij Dr. P.R. Algra. Direct na afrondig van zijn opleiding op 1 mei 2001 trad hij toe tot de maatschap radiologie in het Medisch Centrum Alkmaar.

Vanaf 2001 heeft hij de MR enteroclyse opgezet, uitontwikkeld en verspreid onder zijn vakgenoten. In de zomer van 2003 werd hij in contact gebracht met Prof.dr. E.J. Kuipers, die hem aanspoorde om van de MR enteroclyse een promotietraject te maken. Hierop heeft hij Prof.dr. J. Stoker gevraagd te participeren in dit project. Door een grote subsidie in 2006 van het Foreest Medical School kon het COMRADE onderzoek, Small bowel imaging COmparing MR Enteroclysis and Video CApsule with Double-Balloon Endoscopy, worden gestart, dat de basis vormde van dit proefschrift (hoofdstuk 6, 7 en 8). In 2007 en 2008 heeft hij samen met Prof.dr. J. Stoker workshops georganiseerd over de MRI dunne darm. In 2009 heeft hij het MRI onderzoek opgezet bij kinderen die verdacht worden van appendicitis (RADIANCE trial). Dit is verder uitgebouwd in een multicenterstudie bij volwassenen in samenwerking met Prof. J. Stoker (OPTIMAP). In 2010 ontving hij de Foreest-penning, de prijs voor het beste wetenschappelijke artikel vanuit het Medisch Centrum Alkmaar, voor het artikel in hoofdstuk 5.

In het Medisch Centrum Alkmaar is hij sinds 2001 aandachtsradioloog MRI en sinds 2007 voorzitter van de toelatingscommissie voor medisch specialisten. Voor de Nederlandse Vereniging van Radiologie is hij sinds 2010 voorzitter van de sectie abdominale radiologie, sinds 2011 lid van de onderwijscommissie met als aandachtspunt de nieuwe opzet van de Sandwichcursus en ook sinds 2011 lid van het organisatiecomité van de Radiologendagen. Hij stond aan de wieg van Holland Health, de initiator van een ‘health valley’ in Noordwest Holland waar hoogwaardig onderzoek en innovatieve zorg

van internationale allure gerealiseerd wordt. Sinds 2010 is hij één van de abdomen teachers van de opleiding radiologie. In 2011 is in het Medisch Centrum Alkmaar zijn eerste fellow abdomen gestart. Tevens is hij lid van de sectie acute, muskuloskeletale, hoofd-hals en neuroradiologie.

Sinds juni 2002 woont hij met Clary, Emma & Thijs in de fraaie en gezellige Nassaubuurt in Alkmaar. In zijn vrije tijd wandelt hij dagelijks een uur met Clary en Ollie en tennist hij graag.