Advancing Magnetic Resonance Imaging in Crohn’s Disease

Toshimitsu Fujii\textsuperscript{a} \hspace{1em} Makoto Naganuma\textsuperscript{c} \hspace{1em} Yoshio Kitazume\textsuperscript{b} \hspace{1em} Eiko Saito\textsuperscript{a} \hspace{1em} Masakazu Nagahori\textsuperscript{a} \hspace{1em} Kazuo Ohtsuka\textsuperscript{a} \hspace{1em} Mamoru Watanabe\textsuperscript{a}

Departments of \textsuperscript{a}Gastroenterology and Hepatology and \textsuperscript{b}Radiology, Tokyo Medical and Dental University, and \textsuperscript{c}Division of Diagnostic and Therapeutic Endoscopy, Keio University School of Medicine, Tokyo, Japan

Recent advances enable the use of MRI to assess bowel disorders with high sensitivity, specificity and accuracy. MRI can evaluate simultaneously the bowel surface, bowel wall, abdominal abscesses and perianal lesions, such as perianal fistulae and perianal abscesses, without the problem of overlapping bowel loops. Therefore, MRI has the potential for evaluation of the overall disease activity of CD without radiation exposure. We believe that MRI is a suitable first choice imaging modality in the assessment of CD.

© 2014 S. Karger AG, Basel

Key Words
Magnetic resonance imaging · Magnetic resonance enteroclysis · Magnetic resonance enterography · Magnetic resonance enterocolonography · Crohn’s disease · Inflammatory bowel disease · Assessment of activity

Abstract
Crohn’s disease (CD) is a lifelong chronic inflammatory bowel disease associated with diarrhea, abdominal pain, bloody stool and often perianal fistulae. Inflammation in CD involves the entire gastrointestinal tract, especially including the small and large bowels, causing irreversible bowel damage. Frequent imaging examinations are necessary to monitor disease activity and to evaluate response to therapeutic interventions, and, furthermore, to predict recurrence in order to provide appropriate treatment. The suitable imaging modality should be reproducible, well tolerated, safe and free of ionizing radiation. In recent years, imaging used in CD has dramatically changed. Cross-sectional imaging techniques such as computed tomography and magnetic resonance imaging (MRI) are used to investigate not only extraluminal abnormalities, but also intraluminal changes. Recently, new techniques such as MR enteroclysis, enterography, colonography and enterocolonography have been developed. These

Introduction
Crohn’s disease (CD) is an idiopathic chronic inflammatory disease, which can affect the entire gastrointestinal tract \cite{1}. Its onset peaks between 20 and 30 years of age. Inflammation usually involves not only all layers of the bowel wall but also extravisceral structures. It can progress to fibrosis complicated by stricturing and obstruction with resultant fistulae and abscesses during the course of disease \cite{2}. Even in clinical remission, the bowel is not free from endoscopic and histological inflammation, often resulting in intestinal resection. Indeed, half of CD patients require surgery and bowel resection within
10 years of diagnosis due to strictures, fistulae and abscesses. This cycle results in the loss of intestinal function and ability [3].

Recent advances in understanding of the pathogenesis of inflammatory bowel disease have led to new therapeutic options [4]. In order to provide treatment using appropriate therapies, accurate assessment of disease activity is indispensable. Patients’ symptoms, physical examination and laboratory data are tools often used to assess disease activity and complications; however, because of their low specificity and sensitivity, imaging studies are often needed to provide an accurate assessment of disease extent and activity. Imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) have been recommended to assess small bowel wall inflammation as well as extramural complications, together with ileocolonoscopy and biological markers such as C-reactive protein. The presence or absence of findings impact on the subsequent management decisions made.

New Modalities for CD

Historically, ileocolonoscopy and barium studies such as small bowel follow through (SBFT) and conventional enteroclysis have been the standard techniques used to evaluate CD. Ileocolonoscopy is useful in order to detect inflammation in colonic and distal ileal lesions, but it has a diagnostic limitation because it is impossible to reach the mid-section of the small intestine. 40–70% of CD patients have small bowel lesions [5–8]; therefore, detecting small intestinal disease is important. SBFT has been the standard radiologic approach used to assess activity of the small bowel. However, the detection of small erosions or aphthae by SBFT is beyond its capabilities [9]. For detecting early mucosal lesions, small bowel enteroclysis is more accurate than SBFT [10]. However, these barium studies are limited in observing the bowel wall, extraluminal extension and overlapping bowel loops.

Recently, noninvasive, cross-sectional imaging has played an increasingly important role in the assessment of CD [11]. Although ultrasonography is a low-cost modality and has widespread availability, operator dependence and the difficulty of viewing the gastrointestinal tract are significant disadvantages [12].

Video capsule endoscopy (VCE) performs well compared to other small bowel imaging modalities in patients with CD. VCE has demonstrated a significantly greater yield in detecting recurrent small bowel lesions than barium radiography and CT enterography [13]. However, in a meta-analysis, the yield of VCE was not significantly different from MR enterography in either suspected or established CD patients [14].

However, VCE has important limitations; there is a high risk of retention due to stenosis, poor localization of bowel abnormalities and lack of tissue diagnosis [15]. MR enterography could detect significant bowel strictures before VCE was performed [16].

Computed tomography (CT) has been the cross-sectional imaging modality of choice when evaluating CD patients. Now it has become even more widespread with the development of multidetector CT. The advantages of CT include a rapid examination time, ability to sort a large volume of data, and the generation of high-resolution images in order to evaluate the abdomen and pelvis for both intestinal and extraintestinal complications of CD. To evaluate the small bowel with CT, two methods can be performed: CT enterography or CT enteroclysis. CT enterography involves per oral administration of at least 2,000 ml of solution [17]. CT enteroclysis requires nasojejunal intubation and steady infusion of a similarly large volume of solution [18]. Although nasojejunal intubation leads to better luminal distension, it causes patient discomfort. However, the recent recognition of the potential long-term effects of repeated exposure to ionizing radiation from CT scans has led to increased interest in the application of other nonionizing radiation-based cross-sectional imaging modalities for patients with chronic diseases [19].

Radiation Exposure in Patients with CD

CD is typically diagnosed in patients at a young age. Chronic relapses often result in these patients in their lifetime, requiring multiple imaging examinations involving radiation. The effective dose of 16 mSv during a single CT scan is 5-fold more than during SBFT [20]. Although it is reported that a dose of 10 mSv is sufficient to cause fatal cancer in 1/2,000 patients [21], the long-term cumulative effect of this radiation is unknown and the extent of enhanced cancer risk remains controversial [22]. The most recent Australian population-based cohort study assessed the risk in children and adolescents following exposure to low-dose ionizing radiation from diagnostic CT. Out of 10.9 million people identified from Australian Medicare records between 1985 and 2005, all exposures to CT funded for people aged 0–19 were identified for the cohort. Cancers diagnosed up to 2007 were obtained. The overall cancer incidence was 24% greater for those exposed to ra-
Radiation than those unexposed, resulting in an incidence rate ratio of 1.24 (p < 0.001). This also showed a dose-response relation, and the incidence rate ratio increased by 0.16 for each additional CT scan [23]. Limiting radiation exposure in children is particularly important. In recent studies, children with CD demonstrated high exposure to ionizing radiation, especially within the first few years of diagnosis [24]. Furthermore, a recent systematic review in pediatric CD showed that MR enterography is a sensitive and specific tool for diagnosis in pediatric inflammatory bowel disease as an alternative method [25]. CD as a long-standing disease often affects young patients and usually requires the collection of periodic control images. The limitation of radiation is a serious consideration [26], and CT should be used with caution in young patients with CD.

**MRI in CD**

As mentioned above, to monitor disease activity and to guide appropriate treatment, CD patients require multiple imaging examinations repeatedly. For these reasons, the desirable imaging modality would be one that is reproducible, well tolerated and free of ionizing radiation. Therefore, recent studies and reviews have focused on the role of new MR techniques optimized for bowel imaging for evaluation of bowel disorders [27–31]. CT has advantages compared with MRI in better spatial resolution, superior image quality and lower acquisition time, while the advantages of MRI include lack of ionizing radiation, high-contrast resolution of soft tissue and a superior safety profile of intravenous contrast compared to that of CT. The disadvantages of MRI also include a higher cost and less availability. Recent advances in MRI allow for the rapid acquisition of high-resolution images, which has brought about ultrafast sequences and has led to assessment of bowel disorders. MRI has been able to assess simultaneously the bowel surface, bowel wall and perianal lesions, such as perianal fistulae and perianal abscesses, without the problem of overlapping bowel loops. A previous study demonstrated that MRI and CT were equally accurate in assessing disease activity and bowel damage in CD [32]. Furthermore, a meta-analysis of 44 studies showed no significant differences between MRI, ultrasonography and CT in sensitivity and specificity [33]. Thus, the European Crohn’s and Colitis Organisation (ECCO) in the second European evidence-based consensus described MRI as having the highest diagnostic accuracy and being the current standard for assessing the small intestine in CD [34].

<table>
<thead>
<tr>
<th>Table 1. Specific MRI sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
</tr>
<tr>
<td>Localization of findings</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Bowel wall and mesenteric vessels</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Bowel wall and mesenteric edema</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Pathologic edema</td>
</tr>
<tr>
<td>Mucosal and mural enhancement mesenteric vessels</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Extraluminal abnormalities</td>
</tr>
</tbody>
</table>
To assess bowel lesions, most centers perform with a torso coil at 1.5 T to enhance access and reproducibility of image quality. Imaging at 3 T has a higher signal-to-noise ratio and higher spatial resolution; however, it is limited by dielectric effects, banding and other pulse sequence-related artifacts. Protocols of MRI scanning consist of various combinations of sequences that highlight different aspects of tissue. Specific sequences are as follows (table 1): (1) FASE or SSFSE, HASTE, (2) trueSSFP or FIESTA, trueFISP, bFFE, (3) FSE or TSE with fat saturation, (4) diffusion-weighted EPI, (5) SPGR-LAVA or VIBE, eTHRIVE with fat saturation, (6) delayed postcontrast 2D T1-weighted SPGR with fat saturation [31].

MRI can describe changes in active CD such as wall thickening, ulcerations, increased enhancement and obstructions. Wall thickness is defined as over 3 mm, but this is often affected by the degree of distension. With techniques such as cine-MRI and the ability to obtain multiple sequences, MRI can show one segment in different degrees of bowel distention. Fibrostenotic lesions are seen with lower signal intensity in T2-weighted sequences than thickened lesions with active inflammation. To triage patients into either medical or surgical management, it is important to distinguish active disease from fibrostenotic disease.

Active lesions with inflammation such as ulcerations are described as mural irregularity in contrast-enhanced gradient echo sequences (e.g. trueSSFP) and T2-weighted images, and also increased enhancement is obtained (fig. 1). In severe deep lesions, submucosal edema is shown with hyperenhancement and often also with the ‘comb sign’; however, mild mucosal lesions are described only as mucosal hyperenhancement. In detecting penetrating lesions, cross-sectional imaging including MRI is superior to barium studies. Moreover, in the case of abscesses and perianal lesions, MRI has been demonstrated as the most adequate modality.

**MRI Enteroclysis**

MR enteroclysis requires nasojejunal intubation, sometimes with conscious sedation, and 1,500–2,000 ml of contrast agent solution is administered by manual injection. It provides superior distension in both the jejunum and ileum. A previous study showed that MR enteroclysis described mucosal changes better than MR enterography and had high accuracy equivalent to conventional enteroclysis. On the other hand, some studies have demonstrated that MR enterography also has equal sensitivity to MR enteroclysis in moderate-to-severe lesions in CD.

However, MR enteroclysis needs not only more intensive time commitment and is less tolerable, but also requires exposure to additional ionizing radiation with nasojejunal intubation. For these reasons MR enteroclysis is recommended only for the initial examination in patients suspicious of CD.
**MR Enterography**

MR enterography requires oral administration of a large volume of solution. Although several different ingestion algorithms have been performed, a volume of 1,350–2,000 ml is adequate in the majority of cases. Typically, within 60 min prior to scanning a total of polyethylene glycol (PEG) is administered by dividing it into a plurality of times. Sensitivity ranges from 88 to 98% and specificity from 78 to 100%, respectively, for the detection of active inflammation [17–31]. MR enterography can be used to follow up and monitor disease activity and the effects of medical therapy such as immune-modulating agents, because it is free from radiation exposure and the discomfort associated with nasojejunal intubation.

**MR Colonography**

In MR colonography, patients are required to take 1,500 ml of PEG orally 45 min before MRI and solution ranging from 1,000 to 2,000 ml is retrogradely instilled into the colon through a rectal balloon catheter. Acceptable concordance of findings was provided between MR and endoscopy with a sensitivity of 87–89% and specificity of 78 to 100%, with significant correlation between CD activity index and MR index [35]. In a recent study, diffusion-weighted imaging colonography without oral and rectal preparation detected endoscopic inflammation with a sensitivity and specificity of 58 and 85%, respectively [36].

**MR Enterocolonography**

MR enterocolonography (MREC) was developed in order to evaluate simultaneously both small and large bowel lesions [37]. Magnesium citrate is taken on the day before the procedure, and 1,000 ml of PEG is taken orally 60 min before MR scanning on the procedure day without nasojejunal intubation or rectal preparation (fig. 2). In colonic lesions the sensitivities of MREC for deep mucosal lesions, all CD lesions and stenosis were 88.2, 61.8 and 71.4%, while specificities were 98.1, 95.3 and 97.7%, respectively. Also, in small intestinal lesions, MREC sensitivities were 100, 85.7 and 100%, while specificities were 100, 90.5, and 93.1%, respectively. MREC scores devised in that study were significantly correlated with endoscopic scores.

**Prediction of Recurrence**

Recently, mucosal healing confirmed by endoscopy has become the gold standard for evaluating recurrence of CD. Also, scores based on MRI for detection of postoperative recurrence has been developed and validated. With MR enteroclysis, mild bowel wall thickening and enhancement without stricture were considered as signs of low-grade recurrence, though increased thickness and marked strictures were related to severe recurrence after ileocolic resection [38, 39]. Furthermore, at DDW2013, Fujii and colleagues reported that patients with active lesions in MREC had significantly more recurrences, hos-
pitalizations and operations than patients without active lesions, even in those with clinical remission, negative C-reactive protein and confirmed mucosal healing. These data suggest that MREC is useful for the prediction of recurrence of CD and, moreover, MREC might be able to identify patients who need to have their treatments stepped-up beyond mucosal healing.

Conclusion

With recent advances, MRI has achieved a reputation as the first choice in the assessment of Crohn’s disease. MRI with colonoscopy should be recommended as the initial mode of investigation in patients with suspected CD. VCE or conventional enteroclysis may be performed as a second-line modality when MRI shows negative findings in patients for whom CD is suspected. In the small intestine, balloon endoscopy should also be performed for pathological purposes if available.

MRI has a high sensitivity in diagnosis of the disease and also plays an important role in the assessment of disease activity without the need for ionizing radiation exposure. MRI allows comprehensive evaluation of overall disease activity including intra- and extraluminal lesions and the monitoring of disease over time, which could be useful for tailoring therapeutic strategies. Moreover, the capability to predict recurrences indicates that MRI could be useful to avoid repeated colonoscopies in the future. Further studies in a larger population of patients are required and remaining problems such as cost, availability and experience of radiologists need to be solved.

Disclosure Statement

The authors declare that no financial or other conflicts of interest exist in relation to the content of this article.

References


5. Hamilton MJ, Snapper SB, Blumberg RS: Upward stepped-up beyond mucosal healing. identify patients who need to have their treatments


