



ILEAL CROHN'S DISEASE: MRI WITH ENDOSCOPIC CORRELATION

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Abstract: Purpose: To evaluate activity staging of Crohn's disease (CD) measured with MR-enterography using ileoscopy as reference standard.

Materials and methods: A prospective study was made of 61 patients with CD. All patients underwent MR-enterography and ileoscopy. MRI activity was measured by means of an ad hoc developed score, as well as by analysis of the imaging findings, and was compared with the SES-CD score obtained via ileoscopy. Examinations were performed using a 1.0 Tesla scanner.

Results: MRI score discriminates between active and inactive disease with an area under the ROC curve of 0.941. Overall correlation with the standard reference SES-CD score was moderate to strong (Spearman's $r=0.62$ $p<0.001$).

Agreement between both methods in staging patients with ileal CD as inactive, mild or moderate to severe was good (Cohen's $\kappa=0.60$). Differences in means of the MRI activity scores of the three groups showed statistical significance ($p<0.01$).

Conclusions: The MRI score is a reliable predictor of activity in ileal CD and can stage patients in a way comparable to endoscopy. 1.0 Tesla scans are valid for performing radiological evaluation of ileal Crohn's disease.

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Ferrol, 3 Apr. 2010

Dear Editor:

The original paper "ILEAL CROHN'S DISEASE: MRI WITH ENDOSCOPIC CORRELATION" is submitted to be considered for publication in your journal "European Journal of Radiology".

The paper has not been published and is not being submitted to any other journal.

All authors have participated sufficiently in its elaboration and it has been approved by the responsible authorities of our center.

Authors declare no conflicts of interest.

Thank you for your attention.

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ILEAL CROHN'S DISEASE: MRI WITH ENDOSCOPIC CORRELATION

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Abstract

Purpose: To evaluate activity staging of Crohn's disease (CD) measured with MR-enterography using ileoscopy as reference standard.

Materials and methods: A prospective study was made of 61 patients with CD. All patients underwent MR-enterography and ileoscopy. MRI activity was measured by means of an ad hoc developed score, as well as by analysis of the imaging findings, and was compared with the SES-CD score obtained via ileoscopy. Examinations were performed using a 1.0 Tesla scanner.

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Key words: Crohn's disease, Magnetic Resonance Imaging, Small bowel, Gastrointestinal endoscopy.

Introduction

Magnetic Resonance Imaging (MRI) is becoming a “first line” tool in both the detection of disease and in the assessment of activity in Crohn's disease (CD). The accuracy of imaging methods in diagnosing CD is very similar (1). At present, the role of imaging is centred on the assessment of disease extent and severity, and response to therapy (2). MRI is a noninvasive bowel imaging technique without any ionizing radiation, capable of demonstrating most of the classical radiological signs of the disease as well as other enteric and extraenteric manifestations. Thus, small bowel MRI can complement the endoscopic findings in the evaluation of CD.

Typical signs of CD in MRI were well-described by Koh et al. in 2001 (3). These authors also correlated quantitative and qualitative criteria with activity indexes. Several later studies emphasized the usefulness of MR in distinguishing patients with active disease from those with inactive disease (4-10). However, the current issue is whether MRI is able to grade the severity of the disease in the same way as other techniques. To answer this question, MRI or any other imaging technique must be correlated to an acceptable reference standard such as endoscopy, the histological findings or surgery. Even in such cases, however, the absence of a “gold standard” for detecting activity in this disease is a handicap for the obtainment of results.

Studies that used MRI to evaluate and to stage disease activity in the ileum using a valid reference standard are few and involve small patient samples (11-14). For this reason, we started a prospective study of 70 patients with ileal CD in order to evaluate activity staging measured with MR-enterography, using ileoscopy as reference standard.

In contrast to almost all previous authors who have used 1.5 T or 3.0 T scanners, our study was carried out using an intermediate-high field machine with a tesla rating of 1.0 T.

Materials and Methods

Between November 2008 and December 2009, a total of 70 consecutive patients with known or suspected Crohn's disease underwent MR-enterography and ileocolonoscopy. During this period 9 patients were excluded because of incomplete endoscopy (n=4), impossible MR-enterography (n=1), or a final diagnosis other than CD (n=4). A total of 61 patients with biopsy-proven ileal CD were finally enrolled in the study. In 12 patients subjected to previous ileal resection, the neoterminal ileum was scored as terminal ileum.

The study was conducted following the recommendations of the Declaration of Helsinki, and approved by the local ethics committee. Informed consent was obtained from all patients.

Reference standard

Ileocolonoscopy was planned for all patients within 15 days of MRI, and was performed by two gastroenterologists with experience in inflammatory bowel disease, blinded to the imaging findings. Terminal or neoterminal ileum, in the case of previous surgical resection, was reached in all of the 61 patients finally selected. Findings in the ileum were scored according to the Simple Endoscopic Score for Crohn's disease (SES-CD) (15). Four endoscopic variables were scored from 0 to 3: presence and size of ulcers, extent of ulcerated surface, extent of affected surface and presence and type of narrowing, yielding values for the index of between 0 and 12. Based on the SES-CD results, ileal disease for each patient was classified as inactive (0-2), mild (3-6) or moderate-severe (≥ 7).

MRI

MR imaging was performed with a 1.0 T machine, with gradient amplitude 15 mT/m, (Intera, Philips, Best, The Netherlands) using a multichannel-body coil covering from the xiphoid process to the pubis.

Patients fasted for almost 8 hours and ingested 1.5 l of a polyethyleneglycol and mineral salts solution over 45 minutes before the MRI without any particular preparation of the colon. Images were acquired in the prone position and the fields of view were determined by the size of the patient, in order to avoid phase-encoding aliasing artefacts.

First, thick-slab coronal dynamic single-shot turbo spin-echo with fat saturation was performed to monitor fluid saturation of the small bowel, and to evaluate motility and distensibility of the affected segments.

After 20-40 mg of intravenous hyoscine bromide (Buscapina[®], Boehringer Ingelheim), axial and coronal T2-weighted single-shot turbo spin-echo (SSTSE) (TR 2500 ms/TE 240 ms, slice thickness 6 mm, gap 1 mm, matrix 512x205), axial and coronal true fast imaging with steady-state precession (B-FFE) (TR 7.5 ms/TE 3.7 ms, 60° flip angle, slice thickness 5 mm, gap 1 mm, matrix 560x272) and coronal fat-suppressed THRIVE (T1-weighted high resolution isotropic volume examination), (TR 6.2 ms/TE 3.2 ms, 10° flip angle, slice thickness 4.2 mm, matrix 256x141, fat-saturation SPIR), were performed, all them in breath-hold mode. This last sequence was acquired before and after intravenous bolus dose injection of gadopentetate dimeglumine (Magnevist[®], Bayer) (0.1 mmol/kg body weight). Dynamic scans after gadolinium administration were performed at 40, 70, 120, and 180 s. Acquisition at 70 s (enteric phase) was used for relative enhancement calculations.

MRI analysis

All images were examined with a dedicated workstation (EWS; Philips Medical Systems) by two radiologists with experience in abdominal imaging, in consensus, and blinded to the endoscopic and clinical results.

The following items were evaluated in the ileum, in order to stage CD activity with MRI:

Quantitative measurements.

Wall thickness and percentage of luminal stenosis were measured with the proper tools of the EWS workstation, using electronic callipers. Maximum bowel wall thickness was considered normal when below 3 mm (16). The cut-off point for an abnormal percentage of luminal stenosis was established as 60% (17). To calculate the relative contrast enhancement, we determined the wall signal intensity (WSI) as the average of three ROIs placed at the maximum visual enhancement areas. Also three measurements outside the body were placed to obtain the standard deviation (SD) of the noise before and after gadolinium administration. The formula $\{(WSI_{\text{postgadolinium}} - WSI_{\text{pregadolinium}}) / (WSI_{\text{pregadolinium}})\} \times 100 \times (SD_{\text{noise pregadolinium}} / SD_{\text{noise postgadolinium}})$ (18) was used to calculate relative contrast enhancement (RCE) of the bowel.

Qualitative evaluations.

Motility and distensibility were evaluated subjectively by means of the coronal thick-slab dynamic sequence, viewed as cine-loop in the workstation. Bowel wall edema was defined as mural hyperintensity relative to the psoas muscle on T2-weighted sequences, discarding fat wall deposition in B-FFE sequences. Presence or absence of mucosal abnormalities (wall nodularity, ulcers, pseudopolyps), enlarged lymph nodes (short axis >10 mm), sinus tracts or fistulae, and inflammatory masses could be determined in any

sequence (Figures 1-5).

Besides this, a per-patient assessment of disease activity was performed using the MR score explained in Table 1. This score is a modification of that developed by Girometti et al. (14) in order to obtain an index fully comparable to the SES-CD. Some parameters, such as “mesenteric involvement” and “layered enhancement”, which can also be present in chronic disease were removed. This was the reason for the loss of weight of the item “luminal stenosis” as well. In contrast, “bowel wall edema” was included because it is considered a marker of submucosal inflammation (19) and a good predictor of endoscopic scores (20). The resulting score allows patient classification into three categories of disease activity similar to the SES-CD: inactive (0-2), mild activity (3-6), and moderate to severe activity (≥ 7).

Statistics

The diagnostic accuracy of every single parameter and MRI score was calculated measuring the area under the ROC (receiver operating characteristics) curves. Correlation with the standard reference SES-CD was tested with Spearman’s correlation coefficient.

Concordance between MRI and endoscopy was fitted calculating Cohen’s kappa value. Finally, for comparison between groups of patients according to severity of the disease, analysis of variance (ANOVA) was used to evaluate the significance of mean differences.

Statistics were calculated with the SPSS package version 9 (SPSS, Chicago, IL). A value of less than 0.05 was considered to indicate a statistically significant difference.

Results

A total of 61 patients with ileal CD were evaluated (32 female and 29 male, age range 14-65 years, mean 36.1). Twelve patients (19.7%) had undergone previous ileocecal resection.

Active versus inactive disease

For the detection of inactive or active CD, single parameters showed heterogeneous values for accuracy, sensitivity, and specificity (see Table 2). Some, such as bowel wall thickness or luminal stenosis, yielded high sensitivity and low specificity. Others, such as relative enhancement, mucosal abnormalities, enlarged lymph nodes or fistulae showed low sensitivity but very high specificity. Bowel wall edema showed acceptable sensitivity and high specificity. However, the best results were achieved by the MRI score, with an accuracy of 98.4%, sensitivity 100%, specificity 80%, positive predictive value 98.2%, and a negative predictive value 100%. The MRI score also showed a greater area under the ROC curve than any individual parameter (Table 3).

Correlation with standard reference (ileal SES-CD index)

Single parameters showed little or no correlation with the standard reference for activity. Their results are shown in Table 3. The MRI score showed a better and very significant correlation with the SES-CD (Spearman's $r = 0.62$ $p < 0.001$)

Assessing activity

On the basis of the standard reference test, 5 patients had inactive disease, 33 mild disease, and 23 had moderate to severe disease. The MRI score correctly staged 47

1 patients (77.0%) (4 inactive, 24 mild disease, 19 moderate to severe disease). In 14
2 patients the MRI results differed one grade from SES-CD: understaging occurred in 4
3 moderate to severe patients that were staged as having mild disease, and overstaging
4 occurred in 9 patients with mild disease staged as moderate to severe and one inactive
5 staged as having mild disease (Table 4). Inactive disease was correctly staged in 80% of
6 the cases, mild disease in 72.7% and moderate to severe disease in 82.6%. Overstaging
7 was observed in 16.4% and understaging in only 6.5% of the patients. Agreement
8 between the MRI score and SES-CD score calculated with Cohen's index (κ) proved
9 good (0.60). Staging was impossible using quantitative single parameters.
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24 For the MRI score, the analysis of variance between groups of patients according
25 to disease severity of the disease found the means of the three groups to be significantly
26 different ($p < 0.01$). In contrast, no significant difference were found between the means
27 of mild and moderate to severe groups for single parameters such as bowel wall
28 thickness, relative enhancement, or percentage stenosis (Table 5).
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Discussion

This study demonstrates that MRI scoring offers moderate to strong correlation with the SES-CD endoscopic score in ileal CD, using a field strength of 1.0T. We also show that our MRI score is able to classify the activity of ileal Crohn's disease into three groups: inactive, mild and moderate to severe.

Although previous studies have addressed this issue, only a few stage CD activity using an acceptable reference standard such as endoscopy, the histological findings or surgery. Our study contributes a substantially larger number of patients. The other studies evaluating (only in patients with CD) the severity of MRI ileal involvement endoscopy as the reference standard also reported moderate to strong correlations (Spearman's $r=0.58$ and $r=0.63$) (11,12), or no correlation (13), in patient series ranging from 23 to 31 individuals. Other authors (20) have reported an excellent correlation (Spearman's $r=0.80$) in a series of 50 patients, for mixed ileal and colonic findings, but do not report ileal results separately. All these studies used the Crohn's Disease Endoscopic Index of Severity (CDEIS) as reference standard for endoscopic activity. However, since the CDEIS is difficult to use in daily clinical practice, a closely correlating Simple Endoscopic Score (SES-CD) has been developed (15). This score evaluates four variables in each intestinal segment (ileum, right colon, transverse colon, left colon and rectum) thus offering the possibility of calculating the ileal activity score (ileal SES-CD), a feature not possible with the CDEIS.

Evaluation of the MR study should include criteria similar to those of the endoscopic score: extent of affected surface, edema, stenosis, ulcers, and also other imaging signs not available to endoscopy, such as bowel wall thickness, enhancement

1 after gadolinium injection, motility, and extraintestinal findings, because they are also
2 predictors of disease activity. We did not include “layered pattern of enhancement” for
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4 although it is considered a sign of active disease (3,9,21), it can also be present when
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6 there is submucosal fat deposition, a finding that denotes a chronic phase of the disease
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8 and is present in the ileum of 18% of all patients with CD (22). Furthermore, it can be
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10 redundant as a parameter of the score because “relative enhancement” already evaluates
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12 contrast uptake of the bowel wall.
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19 In the analysis of the data, we found only a weak correlation between wall
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21 thickness, relative enhancement, or bowel wall edema, and the SES-CD score.
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23 However, the MRI activity score appears to be a very useful tool for assessing ileal
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25 disease activity, allowing an appropriate patient classification in a way that closely
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27 resembles the endoscopic score. It is user-friendly and easy to understand in everyday
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29 clinical practice, because its numerical values range from 0 to 12, like the simplified
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31 endoscopic SES-CD.
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39 Our results, based on the mentioned score, show high accuracy in identifying
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41 patients in remission, but with some inaccuracy in staging patients with mild and
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43 moderate to severe activity. Overstaging more than understaging of the MRI findings is
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45 in consonance with the results of the metaanalysis conducted by Horsthuis et al. (23)
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47 and published during the preparation of our paper. In coincidence with these authors, we
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49 consider that differences arise from the fact that MRI and ileoscopy are essentially
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51 different methods: while endoscopy is only able to study the inner surface of the bowel,
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53 MRI can evaluate the entire intestinal wall, as well as the extraenteric structures.
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1 A limitation of our study can be the use of MR-enterography. We used this
2 technique because it is well tolerated and time-saving, and comparable to MR-
3 enteroclysis (24,25). In our opinion, the possible less complete distension of intestinal
4 loops can be a problem only in the proximal intestine, not in the ileum, which is the
5 region of interest in our study. Another limitation is that the technique was applied to a
6 cohort of symptomatic individuals, which also explains the small number of inactive
7 patients. Possibly, there is high prevalence of stenotic type CD, which can influence
8 staging. Regarding bowel wall enhancement we preferred the use of numerical values
9 lacking subjectiveness, but relative enhancement is very sensitive to technical problems
10 such as field inhomogeneity and other factors. Lastly, in evaluating bowel wall edema,
11 the signal intensity in T2-weighted sequences could be better evaluated with negative
12 enteric contrast media, and with fat-suppression techniques.
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31 In conclusion, MRI can stage the severity of ileal CD in a way comparable to
32 endoscopy. Accordingly, it appears as a reliable and non-invasive method for this
33 purpose, though with some inaccuracy in differentiating mild from severe disease.
34 Moreover, our results indicate that cumulative scores are better predictors of activity
35 than sparse factors in MRI. Our study also demonstrates that 1.0 Tesla scans are valid
36 for radiological evaluation of ileal Crohn's disease.
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Figures

Figure 1. A 37-year-old male with multi-segment ileal stenoses.

MR follow-through imaging showing stenotic ileal segments, and measurements made to calculate the percentage stenosis.

Figure 2. A 46-year-old male presenting inflammatory ileal disease without significant stenosis.

- a. Coronal balanced-FFE sequence disclosing wall thickening and mucosal nodulations consistent with pseudopolyps (inside the circle).
- b. Postcontrast coronal fat-suppressed THRIVE scan showing measurements made to calculate the relative enhancement.

Figure 3. A 30-year-old female with ileal mucosal abnormalities.

- a. Axial balanced-FFE scan showing the ulcerative and nodular pattern typical of cobblestone mucosa (inside the circle).
- b. Ileoscopy showing extensive segmental ulcerations with inflammatory mucosal thickening.

Figure 4. A 27-year-old male with enteroenteric fistulae. Coronal balanced-FFE sequence showing a cluster of bowel loops with the typical stellate appearance (inside the circle).

Figure 5. A 19-year-old male with a pelvic inflammatory mass. In the coronal balanced-FFE sequence, an ill-defined hyperintense lesion (inside the circle) is seen to engulf ileum and bladder wall.

	0	1	2
Bowel wall thickness	< 3mm	3-4mm	> 4mm
Relative enhancement	< 70%	70-100%	> 100%
Motility	Normal	Reduced	Absent
Percentage stenosis	≤ 60%	> 60%	
Bowel wall edema	Absent	Present	
Mucosal abnormalities	Absent	Present	
Lymph nodes	Absent	Present	
Fistulae, sinus tracts	Absent	Present	
Inflammatory masses	Absent	Present	

Table 1. MRI score modified from Girometti et al. (see reference 14).

	Accuracy	Sensitivity	Specificity
Bowel wall thickness >3 mm	91.8	98.2	20
Percentage stenosis >60%	88.5	94.6	20
Relative enhancement >70%	45.9	41.1	100
Mucosal abnormalities	53.6	57.4	100
Bowel wall edema	73.8	71.4	100
Peristalsis	82	83.1	60
Distensibility	70.5	71.4	60
Enlarged lymph nodes	18	10.7	100
Fistulae	21.3	14.3	100

Table 1. Values of MRI single parameters for the detection of disease activity.

Parameter	Active vs. inactive disease Area under ROC curve	Correlation with SES-CD Spearman's <i>r</i>
Wall thickness	0.889	0.30 <i>p</i> <0.05
Relative enhancement	0.5	0.34 <i>p</i> <0.05
Percentage stenosis	0.754	0.25 <i>p</i> <0.05
MRI score	0.941	0.62 <i>p</i> <0.001

Table 1. Active vs. inactive disease: area under the receiver operating characteristics (ROC) curve for single quantitative parameters and the MRI score. Single parameters and MRI score correlation with the SES-CD endoscopic score.

		Inactive	Mild	Moderate to severe	SES-CD ILEOSCOPY SCORE
MRI SCORE	Inactive	4	0	0	
	Mild	1	24	4	
	Moderate to severe	0	9	19	

Table 4. Agreement between the MRI score and the endoscopic score.

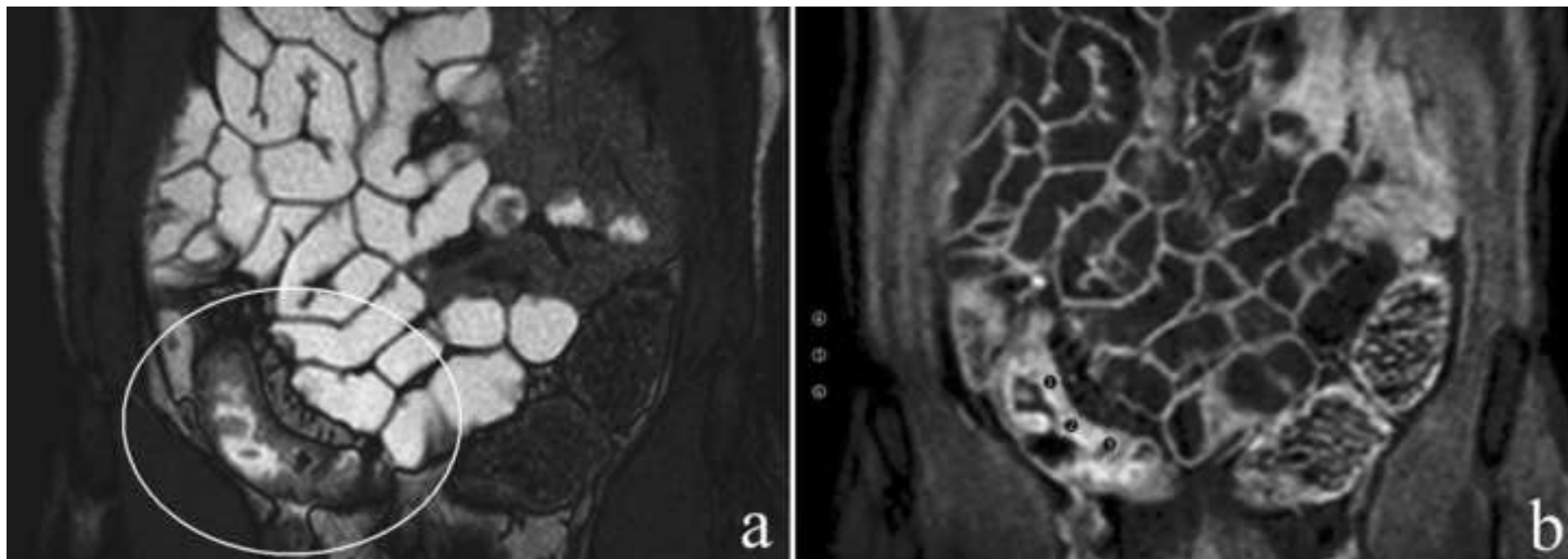
	Bowel wall thickness (mm)	Relative enhancement	Percentage stenosis	MRI score
Inactive (n=5)	3.8±1.1	51.5±12.1	62.2±25.5	2±1.9
Mild (n=33)	6.2±1.9	58.5±40.3	78.5±11.8	5.2±1.6
Moderate to severe (n=23)	7.2±1.9	84.5±46.6	83.5±7.9	7.4±1.1

Table 5. Quantitative criteria data and MRI score for severity of activity groups.

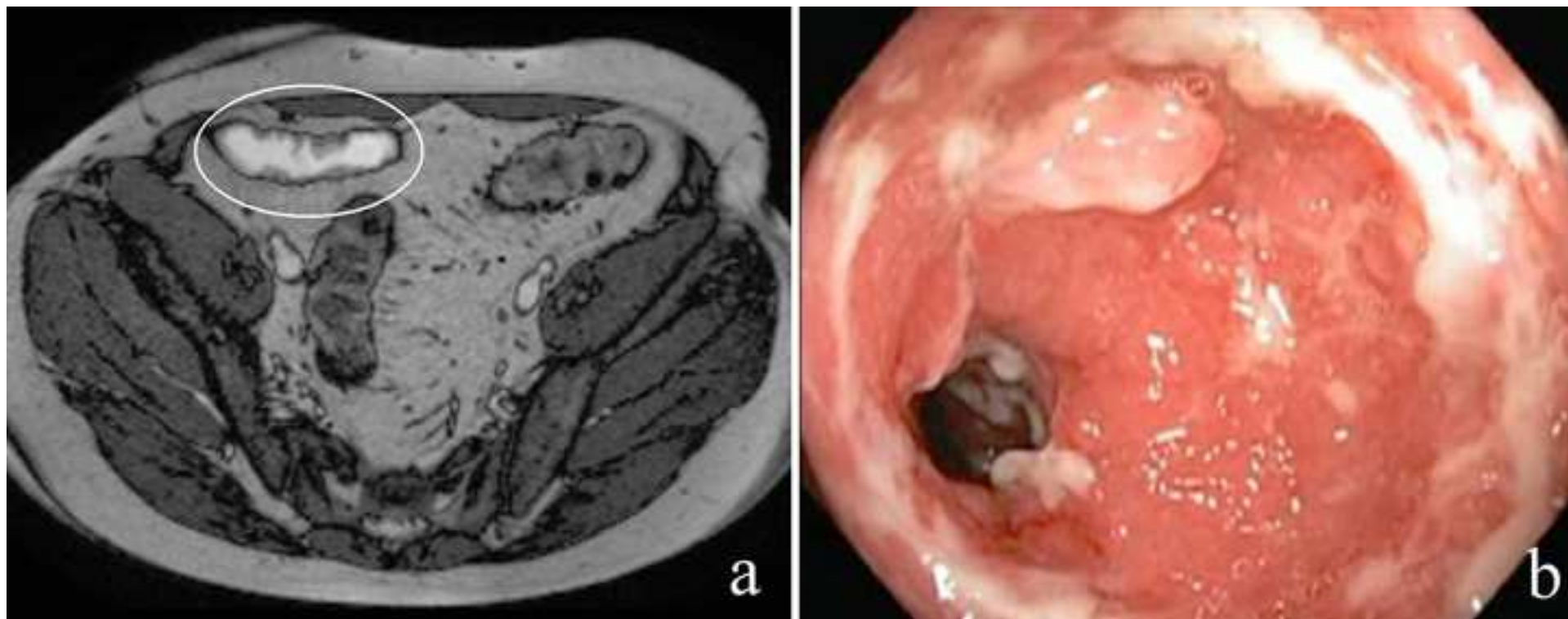
Figure(s)

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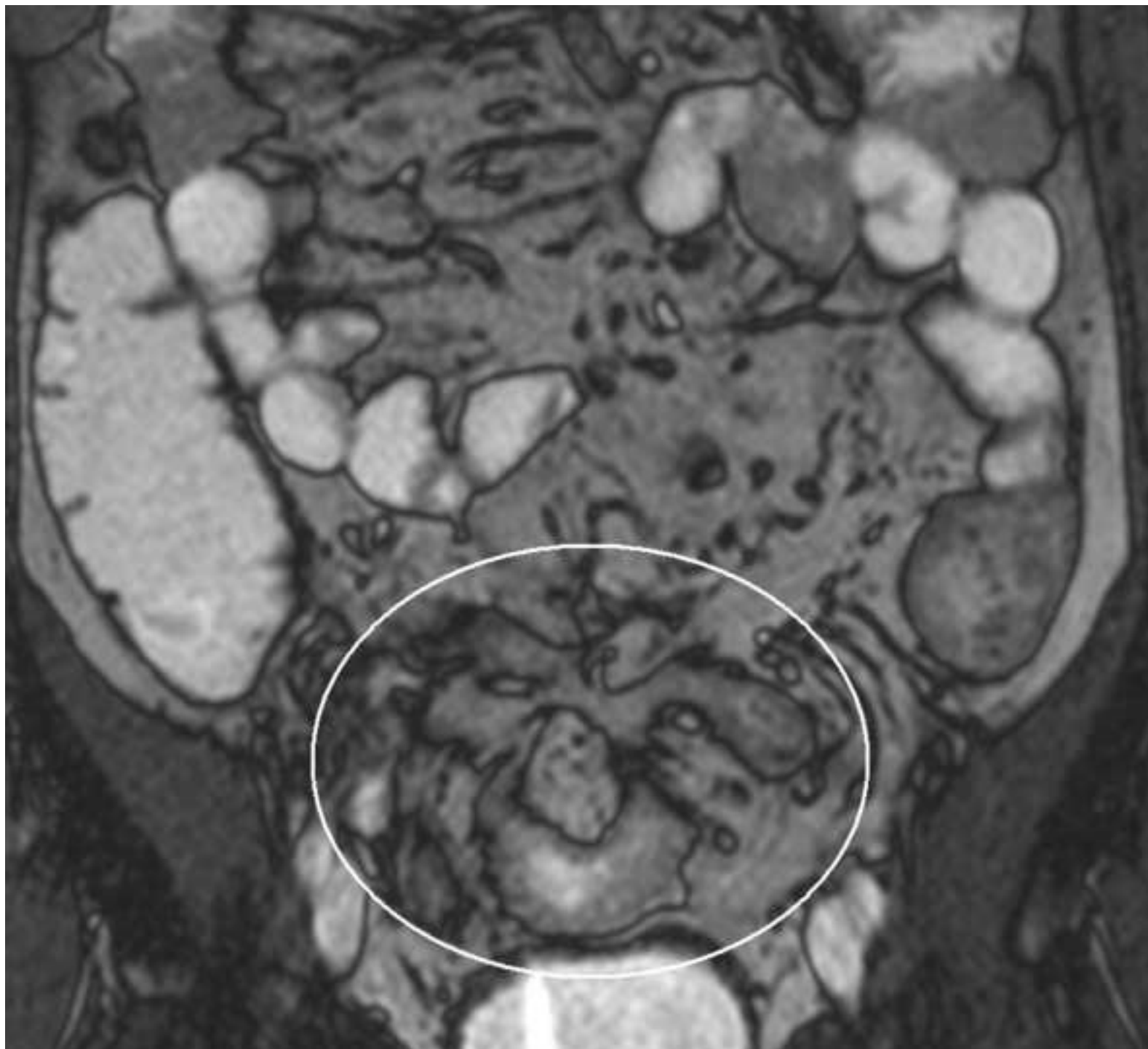




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