Fırat Tıp Derg/Firat Med J 2014; 19(4): 197-202

Clinical Research

The Role of Dynamic Contrast Enhanced Magnetic Resonance Enterography in Evaluation of Crohn's Disease Activity

Secil TELLİ ERDOGAN[a1], Esin YENCILEK[2], Koray KOCHAN[3], Direnc Ozlem AKSOY[4], Gamze KILICOGLU[2], Mehmet Masum SIMSEK[2]

[1]*Afyonkarahisar Suhut State Hospital, Department of Radiology, Afyonkarahisar, Turkey*

[2]*Haydarpasa Numune Training and Research Hospital, Department of Radiology, Istanbul, Turkey*

[3]*Haydarpasa Numune Training and Research Hospital, Department of Gastroenterology, Istanbul, Turkey*

[4]*Van Training and Research Hospital, Department of Radiology, Van, Turkey*

ABSTRACT

Objective: This study assessed the benefits of adding dynamic contrast-enhanced images to conventional magnetic resonance enterography (MRE) for detecting Crohn's disease (CD) activity.

Material and Method: The MRE images and files of 28 patients diagnosed with or suspected of having Crohn's disease were reviewed. Colonoscopy was performed in all subjects. This study included 17 patients with both colonoscopic findings and histological evidence of active CD. All patients underwent dynamic contrast-enhanced MRE. The following semiquantitative parameters were derived from the time-intensity curve: the maximum contrast enhancement, maximum relative enhancement, wash-in rate, time to peak, dynamic and static enhancement ratios, slope of enhancement, and area under the curve (AUC).

Results: In total, 43 bowel segments (26 involved, 17 normal) in the 17 patients with active disease were analyzed. Of the semiquantitative parameters, only the AUC differed significantly ($p<0.05$) between involved and normal bowel segments.

Conclusion: No one semiquantitative parameter alone can identify active inflammation more reliably than colonoscopy and pathological confirmation.

Key Words: *Crohn disease, Intestine, Inflammation.*

ÖZET

Dinamik Kontrastlı Manyetik Rezonans Enterografinin Crohn Hastalığı Aktivitesi Tayinindeki Rolü

Amaç: Dinamik kontrastlı sekansların konvansiyonel manyetik rezonans enterografiye eklenmesinin Crohn hastalığı (CH) aktivitesinin tespitine katkısını değerlendirmek amaçlanmıştır.

Gereç ve Yöntem: Crohn hastalığı tanılı ve Crohn hastalığı şüphesi bulunan 28 hastaya yapılmış olan manyetik rezonans enterografi (MRE) incelemeleri ve hasta dosyaları retrospektif olarak değerlendirilmiştir. Kolonoskopileri ve patolojik tanıları mevcut olan hastalardan aktif CH olarak değerlendirilen 17 hasta çalışmaya dahil edildi. MRE'ler üzerinden zaman intensite eğrisi yoluyla semikantitatif parametreler olan maksimum kontrast enhansmanı, maksimum rölatif enhansman, wash-in oranı, t_{peak}, dinamik enhansman oranı, statik enhansman oranı, enhansman eğrisi, eğri altında kalan (AUC) alan hesaplandı.

Bulgular: Aktif hastalıklı 17 hastanın toplam 43 bağırsak segmenti (26 tutulmuş, 17 normal) değerlendirildi. Tüm semikantitatif parametreler içinde sadece AUC tutulmuş ve normal bağırsak segmentleri arasında istatistiksel olarak anlamlı olarak farklı bulunmuştur.

Sonuç: Bizim sonuçlarımız tek başına aktif enflamasyonu kolonoskopi ve patolojik doğrulamadan daha güvenilir olarak gösterebilecek semikantitatif bir parametrenin olmadığını göstermiştir.

Anahtar Kelimeler: *Crohn hastalığı, Bağırsak, Enflamasyon.*

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract that undergoes frequent exacerbations and remissions. The use of computed tomography (CT) to diagnose and follow the disease and plan surgery results in ionizing radiation exposure, especially in young adults, who are the most-affected age group. Knowledge of the potential risks of cumulative radiation exposure has encouraged studies of alternative imaging modalities (1).

The evaluation of disease activity and severity is a difficult process that requires a combination of histological, endoscopic and conventional radiological techniques (2). This is especially important when

[a] Corresponding Adress: Dr. Secil TELLİ ERDOGAN, Afyonkarahisar Suhut State Hospital, Department of Radiology, Afyonkarahisar, Turkey
e-mail: seciltelli@hotmail.com

Received/Geliş Tarihi:08.07.2014 Accepted/Kabul Tarihi: 07.09.2014

directing treatment strategies and monitoring disease activity. To evaluate the treatment efficacy, frequent monitoring is needed. Consequently, the monitoring technique must be noninvasive and patient-friendly. Magnetic resonance imaging (MRI) has the potential to meet the needs of CD patients safely and noninvasively.

Magnetic resonance enterography (MRE) not only enables an evaluation of the segments proximal to strictures that cannot be reached by colonoscopy but also helps to assess extraluminal complications and disease extension and activity (3,4). Many investigators have examined the role of the contrast pattern and diffusion restriction parameters in differentiating active and chronic disease both qualitatively and quantitatively. The increase in local vascularity is directly proportional to the severity of disease. This increases not only the contrast enhancement, but also the enhancement ratio (ER) and the slope of enhancement assessed in dynamic studies. We assessed the benefits of adding dynamic studies to conventional MRI in CD patients.

MATERIAL AND METHOD

Patients

This study retrospectively evaluated the files and MRE images of 28 consecutive adults seen in the radiology clinic between September 2011 and June 2012 who were previously diagnosed with CD or suspected to have CD. This retrospective investigation was conducted in accordance with the Declaration of Helsinki and the Guidelines of Good Clinical Practice.

Patients younger than 18 years of age, with incomplete work-ups, or whose diagnosis changed after the MRE studies were excluded. The patients with no colonoscopic recordings or histopathological investigations were excluded. Two patients were later diagnosed with gastrointestinal tuberculosis and lymphoma, and were excluded. Nine patients who had no signs of active disease on colonoscopic examination and histopathology were also excluded. Ultimately, 17 patients with both colonoscopic and histological signs of active CD were studied.

The C-reactive protein (CRP) level and sedimentation rates were noted. Colonoscopic findings indicative of active disease were mucosal erosion, ulceration, granularity, and fragility. The histopathological findings of disease activity were crypt abscesses, mucosal ulceration, neutrophilic infiltration, and edema.

MR Imaging protocol

The MRE was carried out after a minimum of 4 h of fasting. All patients followed the same protocol. In the hour before imaging, the subjects were instructed to drink 150 mL of mannitol mixed with 1.5 L of water. Before drinking the mixture, the patients were given 10 mg of metoclopramide orally. A glass of the contrast medium was given every 5 min, until just before the patient lay down for imaging. MRI was performed in the prone position at 1.5 T (Philips Achieva) using a phased-array body coil with a dynamic contrast-enhanced MRE protocol.

Coronal turbo spin echo (TSE) T2-weighted (repetition time/echo time (TR/TE) 401/80, turbo factor 75, echo planar imaging (EPI) factor 1, slice thickness 4.5 mm, slice gap 1.0 mm, field of view (FOV) 392 mm, matrix 246×400), coronal balanced turbo field echo (BTFE) (TR/TE 3.6/1.8, flip angle 60°, turbo factor 1, EPI factor 1, slice thickness 4.5 mm, slice gap 1.0 mm, FOV 377 mm, matrix 257×288), coronal TSE long TE T2- weighted (TR/TE 531/217, turbo factor 113, EPI factor 1, slice thickness 4.5 mm, slice gap 1.0 mm, FOV 397 mm, matrix 49/560), coronal fat suppressed TSE T2-weighted spectral adiabatic inversion recovery (SPAIR) (TR/TE 445/80, turbo factor 70, EPI factor 1, slice thickness 5.0 mm, slice gap 1.0 mm, FOV 431 mm, matrix 238×640), axial BTFE (TR/TE 3.1/1.5, turbo factor 1, slice thickness 7.0 mm, slice gap 1.0 mm, FOV 314 mm, matrix 215×224), axial TSE long TE T2-weighted (TR/TE 489/200, slice thickness 7.0 mm, slice gap 1.0 mm, FOV 312 mm, matrix 196×432), axial fat suppressed TSE T2-weighted SPAIR (TR/TE 379/8, slice thickness 7.0 mm, slice gap 1.0 mm, FOV 316 mm, matrix 175×432) were performed. Before intravenous contrast administration to reduce bowel peristalsis a 10 mg hyoscine butilbromide was given intravenously. Coronal and axial fat suppressed gradient echo T1-weighted dynamic contrast enhanced high-resolution isotropic volume examination (THRIVE) (coronal dynamic TR/TE 4.4/2.1, turbo factor 44, EPI factor 1, slice thickness 4.0 mm, slice gap 1.0 mm, FOV 375 mm, matrix, 190×192, axial dynamic matrix 160×176, slice thickness 4.0 mm, slice gap 2.0 mm, FOV 320 mm) protocols were performed.

The dynamic studies were performed in four phases: non-contrast T1-weighted, arterial, portal, and venous phases. The studies took approximately 20 min. After contrast administration, all patients were observed for 45 min. Using dynamic images, the time-intensity curves (TIC) were plotted automatically with the workstation software and semiquantitative measurements were calculated.

MR imaging analysis

Conventional MRI

Mural hyperenhancement (segmentally increased signal intensity compared with normal bowel segments), mural thickening (>3 mm), increased T2 signal of the bowel wall, mural striation (two or three layered appearance of the bowel wall), fatty proliferation, enlarged lymph nodes (short axis >5

mm), penetrating disease (sinus tract, abscess, phlegmon, or fistula), and the comb sign (prominent vasa recta) were evaluated in all patients. Two segments that could be used in the quantitative analysis were chosen: an involved ileal segment with maximal contrast enhancement as the study group and an ileal segment that appeared normal as a control group.

Dynamic contrast-enhanced MRI

Dynamic contrast-enhanced MR (DCE-MR) analysis included an evaluation of the contrast enhancement of normal and involved ileal segments. A single region of interest (ROI) drawn freehand, measuring approximately 3-45 mm^2, was placed on the thickest, most strongly enhancing bowel wall. Signal intensities and dynamic scans were calculated and displayed in a graph. The graphs showed typical a contrast-enhancement pattern with the baseline intensity (SI_{base}) increasing following the bolus injection, and then stabilizing and decreasing slightly (SI_{end}). The times when the contrast injection started ($t_{inject} = t_0$), when the contrast enhancement started (t_{start}), and of maximum contrast enhancement (t_{end}) were recorded, with $\Delta t = t_{end} - t_{start}$.

In the dynamic series, the dynamic contrast ratio ($ER_{dynamic}$) and slope of enhancement (SoE) were measured using published formulae (5).

$$ER_{dynamic} = SI_{end} / SI_{base}$$

$$SoE = (SI_{end} - SI_{base}) / SI_{base} \times \Delta t$$

In the static series, the static contrast ratio (ER_{static}) was measured using mesenteric fat as a reference.

$$ER_{static} = (SI_{postbowel} / SI_{postfat}) / (SI_{prebowel} / SI_{prefat})$$

where $SI_{postbowel}$ and $SI_{postfat}$ refer to the signal intensities of the bowel wall and mesenteric fat after contrast enhancement, respectively, and $SI_{prebowel}$ and SI_{prefat} are the values before contrast enhancement. Using these formulas, $ER_{dynamic}$, SoE, and ER_{static} were determined. Other semiquantitative parameters studied were the maximum enhancement, maximum relative enhancement, wash-in rate, time to peak (t_{peak}), and area under the curve (AUC).

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS ver. 17.0). The parameters for 26 involved ileal segments and 17 normal ileal segments in the 17 patients diagnosed with active Crohn's disease colonoscopically and histopathologically were compared using the Mann–Whitney U-test. Values of $p<0.05$ were considered to indicate statistical significance.

RESULTS

Magnetic resonance enterography imaging was performed in 28 patients who were diagnosed with or suspected of having Crohn's disease. Colonoscopy was performed in all subjects. Ultimately, 17 active Crohn's disease patients (11 males, 6 females; median age 34.4 years) were included in the study.

Conventional MRI findings

All of the patients had findings of active inflammation in the terminal ileum (Figure 1). Wall thickening (>3 mm) and increased contrast enhancement were found in all 17 patients. Fibro-fatty proliferation was evident in 9 patients, mesenteric lymph nodes in 12, fistulas in 3 (Figure 2), and an abscess in 1 patient. Nine patients had similar findings of active inflammation in both the terminal ileum and distal ileal segment.

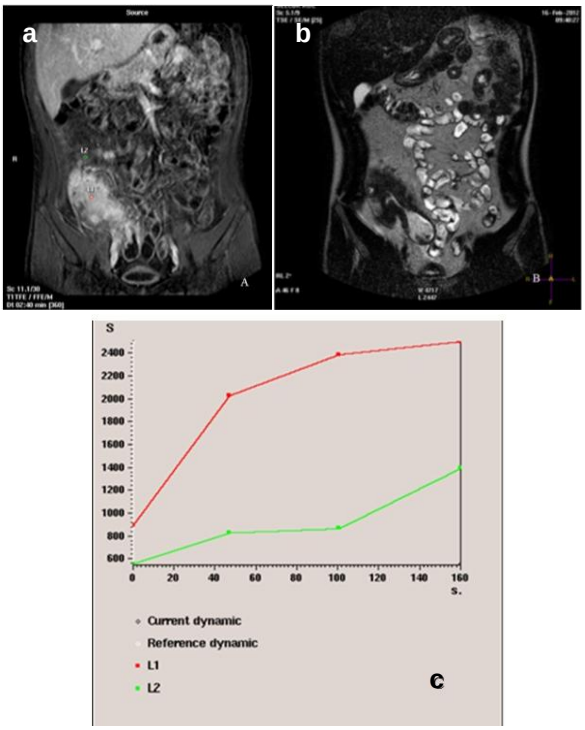

Figure 1. *Contrast enhanced dynamic MR enterography imaging of 30 years old male patient (a) contrast enhancement of terminal ileum in coronal image (b) coronal long TE T2 weighted image: thickened terminal ileum and milimetric lymph nodes in mesentery. (c) time-intensity curve after placing ROI on terminal ileum (L1) and neighbouing inflammatory mesenteric fat (L2).*

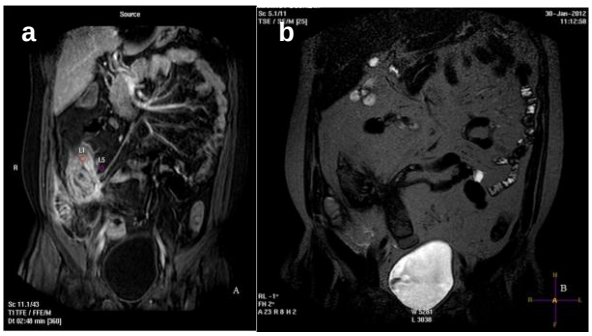

Figure 2. *Contrast enhanced dynamic MR enterography imaging of 42 years old male patient (a) contrast enhancement of terminal ileum in coronal images (b) coronal long TET2 weighted image: thickened terminal ileum and ileoileal anastomoses.*

Semiquantitative analysis findings

The semiquantitative parameters of normal and involved bowel segments from the time–intensity curve are summarized in Table 1.

Table 1. *Semiquantitative parameters of contrast enhancement*

	Pathological segments n=26(mean±SD)	Normal segments n=17(mean±SD)	p
Maximum enhancement	1027,50±453,586	837,24±340,091	0.228
Maximum relative enhancement	156,46±82,327	226,06±145,458	0.054
t_{peak}	129,12±38,589	120,82±44,911	0.486
Wash-in	14,538±7,8650	12,235±7,2761	0.302
AUC	81164±47154,642	50408,29±21687,226	**0.025**
$ER_{dynamic}$	1,19±0,402	1,47±1,007	0.398
Slope of enhancement (SoE)	1,04±1,341	1,88±2,233	0.223
ER_{static}	0,92±0,688	1,47±1,505	0.203

AUC: area under the curve, $ER_{dynamic}$: dynamic enhancement ratio, ER_{static}: static enhancement ratio

There was no significant (p=0.228) difference in the maximum contrast enhancement between the involved and normal segments. The mean±SD maximum contrast enhancement was 1027.5±453.586 in the 26 involved segments and 837.24±340.091 in 17 the control segments.

The mean maximum relative enhancement of the 26 involved segments and 17 normal segments was 156.46±82.327 and 226.06±145.458, respectively (p=0.054).

For the involved and normal segments, the mean t_{peak} was 19.12±38.589 and 120.82±44.911 (p=0.486), respectively, the mean wash-in rate was 14.538±7.865 and 12.235±7.2761 (p=0.392), the mean $ER_{dynamic}$ was 1.19±0.402 and 1.47±1.007 (p=0.398), the mean SoE was 1.04±1.341 and 1.88±2.233 (p=0.223), and the mean ER_{static} was 0.92±0.688 and 1.47±1.505 (p=0.203).

The only parameter that differed significantly (p=0.025) was the AUC. The mean AUC was 81164±47154,642 for the involved segments and 50408,29±21687,226 for the normal segments.

DISCUSSION

Crohn's disease is a disease of unknown etiology that can involve the entire gastrointestinal tract. MRI is considered a valuable tool for evaluating intestinal problems and disease activity (6-10). The latest prospective studies comparing MRE with CT enterography indicate that the two have similar sensitivity and specificity for the determination of active inflammation (11-13). In addition, MRE has the advantage of providing functional and quantitative data (diffusion, perfusion, and motility) that cannot be obtained with CT. The main advantage of adding dynamic contrast MR images to conventional MRE sequences is the quantitative information it provides about the intestine walls.

Angiogenesis is an important factor in contrast enhancement of the intestinal wall. The microvascularization of the intestinal wall initiates inflammation-dependent angiogenesis in Crohn's disease. Brahme et al. (14) demonstrated increased vascularity and edema corresponding to the degree of inflammation using in vitro angiography of resected intestinal segments.

Previous studies of dynamic contrast-enhanced MRE in the assessment of Crohn's disease activity evaluated quantitative measures using semiquantitative parameters (15, 16).

In 18 patients with active Crohn's disease, Oto et al. determined the transfer constant (K^{trans}) and extravascular extracellular space volume per unit tissue volume (v_e). Both measurements were significantly higher in inflamed terminal ileum than in normal ileal segments (15). In another study, Oto et al. observed 32 normal and 19 involved intestinal segments with dynamic contrast-enhanced MRE and made both quantitative and semiquantitative measurements (16). K^{trans} and v_e were significantly higher in the involved segments. The AUC, contrast intake (A), and slope of contrast enhancement ($slope_{initial}$) were higher in the involved segments in the semiquantitative analysis. The ROC analysis of the significant values showed that these parameters could be used to differentiate normal and involved segments. However, the contrast intake ratio, wash-out rate, and t_{peak} were not useful.

Florie et al. (5) studied the enhancement ratio (ER) and SoE in 52 patients to evaluate the disease activity with dynamic contrast-enhanced MRE. They also compared $ER_{dynamic}$ and ER_{static}, and assessed the intestinal wall thickness, t_{start}, and Δt. As a reference, they used the Crohn's disease activity index (CDAI) (17), clinical grade, and Van Hees Activity Index (18).

We investigated whether it was possible to use objective, quantitative data to evaluate the disease activity, instead of subjective clinical findings and activity determination scales or invasive procedures such as colonoscopy. We searched for a parameter that can differentiate active from inactive ileal segments in dynamic contrast-enhanced MRE, in patients whose disease activity has been verified by colonoscopy. We calculated only semiquantitative measures in this study, and only the AUC was statistically significant, although the maximum relative enhancement approached statistical significance. In a larger study group, this parameter might also be significant.

To make correct measurements, it is important to visualize the intestinal wall clearly. Adequate filling of the intestinal lumen is essential. Some authors favor the use of oral contrast (19, 20), although Shoenut et al. (21) achieved acceptable results without any oral contrast. We used an oral contrast agent dissolved in 1.5 L of water and managed to fill the intestines sufficiently.

Colonoscopy and pathological evaluation were used to verify active disease in this study. The signal intensity measurements were higher in the involved segments, as in other studies. However, there were significant differences in the values among the pathological segments. Patients with greater inflammation had higher contrast intensity. Patients with intra-abdominal abscesses and fistulas had very high intensities. Measurements were very low in patients with mild contrast enhancement in the terminal ileum and with lower CRP levels. These differences likely hindered the achievement of statistical significance. With a homogenous study group involving patients of similar disease activity, we might have obtained more comparable results.

Unlike other studies of this subject, the $ER_{dynamic}$, ER_{static}, and contrast enhancement curve were lower in the involved segments in eight patients. Although the signal intensity has been found to be higher in involved segments, the calculations prove otherwise, so the formulas seem unreliable.

The small number of subjects and heterogeneity of the patients' disease activities were the major limitations of this study. In addition to this heterogeneity, the patients who had been diagnosed with Crohn's disease before the study have already been receiving medical treatment. The inevitable pulsation and peristalsis artifacts were present, although the MRE protocol we use includes a breath-holding maneuver and anti-peristaltic medication.

The reproducibility of the study was not considered in the study design. ROI were placed manually on the intestinal walls by the same radiologist. The thinness of the normal distended intestinal wall complicated the assessment of the partial volume artifact. We did not prove the normality of the segments histopathologically; we only considered them to be normal. This is another study weakness.

Our study showed that conventional MRE findings are more valuable than semiquantitative measurements. Dynamic studies are not superior to the single-phase technique for contrast enhancement patterns at showing active inflammation, disease extent, or the degree of inflammation. Moreover, no single semiquantitative parameter distinguishes active inflammation more reliably than colonoscopy and pathological confirmation.

REFERENCES

1. Brenner DJ, Hall EJ. Computed tomography: an increasing source of radiation exposure. N Engl J Med 2007; 357: 2277-84.
2. Rieber A, Wruk D, Potthast S, et al. Diagnostic imaging in Crohn's disease: comparison of magnetic resonance imaging and conventional imaging methods. Int J Colorectal Dis 2000; 15: 176-81.
3. Schmidt S, Lepori D, Meuwly JY, et al. Prospective comparison of MR enteroclysis with multidetector spiral-CT enteroclysis: interobserver agreement and sensitivity by means of "sign-by-sign" correlation. Eur Radiol 2003; 13: 1303-11.
4. Horsthuis K, Bipat S, Bennink RJ, Stoker J. Inflammatory bowel disease diagnosed with US, MR, scintigrap hy, and CT: meta-analysis of prospectivestudies. Radiology 2008; 247: 64–79.
5. Florie J, Wasser MN, Arts-Cieslik K, Akkerman EM, Siersema PD, Stoker J. Dynamic contrast-enhanced MRI of the bowel wall for assessment of disease activity in Crohn's disease. AJR Am J Roentgenol 2006; 186: 1384-92.
6. Maccioni F, Bruni A, Viscido A, et al. MR imaging in patients with Crohn disease: value of T2- versus T1-weighted gadolinium-enhanced MR sequences with use of an oral superparamagnetic contrast agent. Radiology 2006; 238: 517-30.
7. Koh DM, Miao Y, Chinn RJ, et al. MR imaging evaluation of the activity of Crohn's disease. AJR Am J Roentgenol 2001; 177: 1325-32.
8. Shoenut JP, Semelka RC, Magro CM, et al. Comparison of magnetic resonance imaging and endoscopy in distinguishing the type and severity of inflammatory bowel disease. J Clin Gastroenterol 1994; 19: 31-5.
9. Maccioni F, Viscido A, Broglia L, et al. Evaluation of Crohn disease activity with magnetic resonance imaging. Abdom Imaging 2000; 25: 219-28.
10. Low RN, Sebrechts CP, Politoske DA, et al. Crohn disease with endoscopic correlation: single-shot-fast spin-echo and gadolinium- enhanced fat-suppressed spoiled gradient-echo MR imaging. Radiology 2002; 222: 652-60.
11. Horsthuis K, Bipat S, Bennink RJ, Stoker J. Inflammatory bowel disease diagnosed with US, MR, scintigrap hy, and CT: meta-analysis of prospectivestudies. Radiology 2008; 247: 64-79.
12. Lee SS, Kim AH, Yang SK, et al. Crohn disease of the small bowel: comparison of CT enterography, MR enterography, and smallbowel follow-through as diagnostic techniques. Radiology 2009; 251: 751-61.
13. Siddiki HA, Fidler JL, Fletcher JG, et al. Prospective comparison of state-of-the-art MR enterography and CT enterography in smallbowel Crohn's disease. AJR Am J Roentgenol 2009; 193: 113-21.
14. Brahme F, Lindström C. A comparative radiographic and pathological study of intestinal vaso-architecture in Crohn's disease and in ulcerative colitis. Gut 1970; 11: 928-40.
15. Oto A, Kayhan A, Williams JT, et al. Active Crohn's disease in the small bowel: evaluation by diffusion weighted imaging

and quantitative dynamic contrast enhanced MR imaging. J Magn Reson Imaging 2011; 33: 615-24.

17. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index: National Cooperative Crohn's Disease Study. Gastroenterology 1976; 70: 439-44.

18. van Hees PA, van Elteren PH, van Lier HJ, van Tongeren JH. An index of inflammatory activity in patients with Crohn's disease. Gut 1980; 21: 279-86.

19. Pauls S, Kratzer W, Rieber A, et al. Quantifying the inflammatory activity in Crohn's disease using CE dynamic MRI [in German]. Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 2003; 175: 1093-9.

16. Oto A, Fan X, Mustafi D, et al. Quantitative analysis of dynamic contrast enhanced MRI for assessment of bowel inflammation in Crohn's disease pilot study. Acad Radiol 2009; 16: 1223-30.

20. Born C, Nagel B, Leinsinger G, Reiser M. MRI with oral filling in patients with chronic inflammatory bowel diseases [in German]. Radiologe 2003; 43: 34-42.

21. Shoenut JP, Semelka RC, Silverman R, Yaffe CS, Micflikier AB. Magnetic resonance imaging in inflammatory bowel disease. J Clin Gastroenterol 1993; 17: 73-8.