UPDATE IN RADIOLOGY

Magnetic resonance enterography: Review of the technique for the study of Crohn’s disease


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PALABRAS CLAVE
Enfermedad de Crohn (D003424); Resonancia magnética (D008279); Cine-RM (D019028); Gadolinio (D005682)

Abstract  Crohn’s disease is a chronic disease with an unpredictable course. Patients with Crohn’s disease will have to undergo numerous imaging tests. Crohn’s disease often affects young people, who are more vulnerable to the harmful effects of repeated exposure to ionizing radiation. The high resolution of tissues on MR enterography gives it a diagnostic accuracy similar to that of CT; however, MR enterography does not have the drawback of ionizing radiation. The clinical indices used to assess Crohn’s disease are subjective and not very accurate; thus, enterographic techniques are becoming more common in clinical practice as a means to follow up patients objectively. In this article, we describe the MR enterography technique we use to evaluate Crohn’s disease. We illustrate the most relevant imaging findings, and we review the subtypes of the disease, the related scientific literature, and the MR indices used to assess the severity of Crohn’s disease.

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Entero-resonancia magnética: revisión de la técnica para el estudio de la enfermedad de Crohn

Resumen  La enfermedad de Crohn es una enfermedad crónica de curso imprevisible que requiere numerosos estudios radiológicos durante la vida. Afecta frecuentemente a pacientes jóvenes, más vulnerables a los efectos nocivos de las exploraciones repetidas con radiaciones ionizantes. La precisión diagnóstica de la enterografía por RM es similar a la de la tomografía computarizada por su alta resolución tisular, sin el inconveniente de la radicación. Los índices clínicos de valoración de la enfermedad son poco precisos y subjetivos por lo que las técnicas enterográficas de imagen se están incorporando cada vez más a la práctica clínica como medios objetivos de control de la gravedad de la enfermedad. En este artículo, describimos nuestra técnica enterográfica en RM para la valoración de la enfermedad de Crohn. Revisaremos los


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Introduction

Crohn’s disease (CD) is a chronic disease with an unpredictable course characterized by frequent flare-ups interspersed with periods of remission of varying length. Patients with CD are subjected to multiple endoscopic and radiologic examinations throughout their lives.

CD is most often diagnosed in young patients (peak age of onset between the 2nd and 4th decades of life), who are more vulnerable to the hazards of repeated exposure to ionizing radiation associated with the chronic-recurrent course of the disease.1,2

Certain subgroups of patients with CD are at greater risk of high lifetime doses of radiation including those with early onset of the disease, with proximal gastrointestinal tract involvement, patients with penetrating–fistulizing disease and those who require medical treatment with intravenous (IV) steroids or TNF inhibitors or multiple surgeries.3

CT and MR enterography have proven superior to conventional barium examinations since they provide essential information about transmural and extramural involvements, and about the complications that may determine surgical treatment (obstruction, fistulas, abscesses).4

In recent years, MR enterographic techniques have demonstrated a diagnostic accuracy similar to that of CT thanks to the high resolution of tissues on MR enterography, to the development of new ultrafast sequences and the use of different types of oral contrast agents,5-7 in addition to the benefits of avoiding the use of ionizing radiation.

The clinical indexes for the assessment of CD lack accuracy, are subject to subjective interpretation1 and do not take into account the presence of extramural complications, which may alter the optimal management of the patient. Therefore, imaging techniques5 are increasingly being incorporated into the clinical practice as objective methods to evaluate the activity and severity of the disease, and scientific societies are starting to include them as first-line techniques in their recommendations.8

Magnetic resonance enterography protocol

Magnetic resonance enterography versus magnetic resonance enteroclysis

Enteroclysis provides better depiction of mucosal abnormalities than enterography, but both techniques have a similar performance in the detection of transmural involvement and extramural complications. Although loop distension achieved with enteroclysis generally is superior to that achieved with enterography, this may not translate into an improvement in diagnostic accuracy.10

Patient acceptance favors MR enterography over MR enteroclysis, and this acceptance is thus supported by recent literature.

<table>
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<td>Costs</td>
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<td>Manganese&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Manganese&lt;sup&gt;a&lt;/sup&gt;</td>
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Modified from Fidler et al.<sup>2</sup>

<sup>a</sup> Depending on contrast concentration.
such as mannitol and non-osmotic such as polyethylene glycol [PEG] and methylcellulose) and is the most used type of enteric contrast (more availability, better depiction and lower cost). The "dark lumen" on T1-weighted images is essential for the assessment of the bowel mucosa and for the detection of mural enhancement after IV contrast (IVC) administration.

Mannitol and PEG are the oral contrast agents most commonly used and described in the literature.

Other important issues regarding oral contrast administration are the volume of contrast and the timing of administration, which are determined by the agent used. There is a high interindividual variability in transit times, even higher than the variability between healthy subjects and patients with CD (with the exception of patients with obstruction). Using PEG, the average time the column of contrast takes to reach the cecum varies from 20 to 240 min, with an average time of 55–65 min.15,16

We use PEG solution (45 mg reconstituted in 1 l) of which the patient takes 1.5–21 (depending on the patient tolerance) commencing approximately 45–60 min before imaging. The patient takes 1–1.5 l in the first 30 min and then 250 ml every 15 min. Immediately before imaging, the patient drinks approximately 500 ml of water. This regimen permits the evaluation of the entire small bowel in slow intestinal transits, and the water administered on the MR table allows for the scanning of the jejunal loops in rapid intestinal transits, where the passage to the colon may result in poor small bowel distension.

In patients with obstruction, the use of oral contrast agents may be obviated, but this requires individual evaluation based on the symptoms.17

This regimen is quite well tolerated. According to our experience, there are virtually no adverse effects and less than 5% of our patients had intestinal discomfort or moderate-severe diarrhea for several hours after the examination. We could complete the imaging studies in all patients. These results agree with the results reported in previous papers.5,16,18

Rectal contrast administration

Some authors have advocated concomitant administration of a warm rectal enema to improve the depiction of the entire colon and the distension of the terminal ileum.19 We do not routinely perform enemas, but when required, we administer 1–1.5 l of warm saline via the rectum, depending on the patient tolerance.

Antegrade colonic filling is also possible and well tolerated, although it does not provide an optimal colonic distension. Two-step techniques have also been described in which the patients drink 2 l of PEG solution 2–4 h before the examination, and then 1.2–2 l of solution, depending on the patient tolerance, 45 min before the examination.11

Spasmolytics and gastric emptying

The literature describes a wide variability of spasmolytics and modes of administration. Most authors use N-butylscopolamine or glucagon IV or intramuscularly. We use 20 mg of IV N-butylscopolamine (Buscopan® Boehringer, Ingelheim, Germany) immediately before the procedure, as suggested by some authors.6,10,20,23 The literature reports doses varying from 10 mg14 to 40 mg administered at the beginning of the examination.19,25 According to our experience, this regimen does not interfere significantly with the dynamic assessment of the bowel and improves the evaluation of the dynamic contrast-enhanced MR imaging, more sensitive to artifacts related to bowel motility. It is also possible to divide the dose or administer a double dose,26,27 one immediately before the examination and a second one before the dynamic contrast-enhanced imaging, although this modality increases the room utilization time. Glucagon (0.2–1 mg) is also widely used because it acts fast and has a shorter half-life. Glucagon is administered at the beginning23,24 or during the course of the examination, after cine imaging and before the IV administration of the contrast agent.1 Another option is dividing the dose into two doses, following the regimen previously described,2 to not interfere in the evaluation of the distension and peristalsis.

The additional administration of IV erythromycin has been recommended28 to achieve a homogeneous gastric emptying, and prone imaging has been recommended to improve bowel loop separation and reduce motion artifacts.10

According to our experience, prone imaging in combination with spasmolytics may result in excessive reduction of peristalsis, limiting the assessment of loop motility. Also it must be considered that prone imaging can be uncomfortable for the patient.

Magnetic resonance protocol: sequences

We use a 1.5 T system (Signa HD; GE Medical Systems, Milwaukee, WI) with an 8-channel abdominal phased-array coil that allows evaluation of the entire abdominal and pelvic region in a single examination. When necessary, the anorectal imaging was completed with high-resolution protocol in a further examination. The average duration of the examination was approximately 35 min (range 20–55 min).

After the initial sequences applied for localization, we acquire coronal and axial fat-suppressed FIESTA (fast imaging employing steady state acquisition) images (TR 3.7/TE 1.7; TI 200; flip angle of 70°; variable FOV of 28–45 cm depending on the patient; 5–8 mm thickness/1.0 gap; matrix of 224 × 320; 1 NEX). Next, we apply an axial FRFSE sequence that covers the region(s) of interest (TR 6000/TE 90; Echo Train 20; variable FOV; 5–8 mm thickness/1.0 gap; matrix of 320 × 224; 2 NEX). We continue with axial and coronal SSFSE sequences (TR 850–1200/TE 80–90; variable FOV; 3–4 mm thickness/0.3 gap; matrix of 224 × 192; 0.55 NEX). Subsequently, cine or multiphase imaging is performed selecting the region and plane of interest. We use multiphase coronal and axial FIESTA sequences (TR 3.7/TE 1.7; TI 200; flip angle of 70°; variable FOV of 28–45 cm depending on the patient; 5–8 mm thickness/1.0 gap; matrix of 224 × 320; 1 NEX), performing sets of 15 acquisitions over the region of interest per slice plane.

We finish the dynamic study M3D LAVA (TR 3.9/TE 1.8; TI 7.0; variable FOV; 3–4 mm thickness/2.3 ov; flip angle of 12°; matrix of 288 × 192; 0.7 NEX) after IVC administration in the best plane (axial or coronal) for evaluating the
affected loops, acquiring 5 sets. Finally, we apply a coronal FSPGR sequence (TR 230/TE 1.6; 4–6 mm thickness/0.6 gap; 384 × 192; 1 NEX).

**MR imaging findings for the evaluation of Crohn’s disease activity**

The assessment of active CD with MR imaging may determine the management of the patient. Next, we describe the MR findings associated with CD divided into mural and extramural.

**Bowel wall assessment**

**Mural thickening**

Mural thickening is one of the signs that better correlates with CD. Several studies have reported that mural thickening >4 mm in a plane perpendicular to the loop is a reliable predictor of the disease (with a sensitivity of 88% and specificity of 75%), and that there is a significant reduction in mural thickening in response to the treatment. However, the segments that respond to the treatment remain pathologically thickened in comparison with the normal bowel loops of control subjects; in addition, there is low correlation between wall thickening and disease activity. Moreover, the assessment of wall thickening could be limited by the degree of bowel distension; optimal bowel distension is thus required to establish the limits of normal mural thickening. Nonetheless, Punwani et al. have recently reported a precise correlation between mural thickness on MR images and surgical specimen.

**Enhancement ratio of the bowel wall**

Mural enhancement in segments with active inflammation is significantly higher than in normal segments, and is highly specific for the detection of segmental involvement. Studies comparing segments with active inflammation before and after treatment have proven that the peak of signal intensity decreases significantly after medical treatment. Correlation between mural enhancement and clinical activity indexes varies among studies but it is, in general, considered good.

There is clear evidence suggesting that bowel wall enhancement is the parameter that best correlates with the degree of inflammation.

**Patterns of enhancement**

Several mural enhancement patterns have been described:

- Homogeneous mural enhancement characteristic of chronic disease and quiescent or inactive disease.
- Absence of mucosal enhancement and weak and homogeneous enhancement of the rest of the layers. It also is an indicator of active disease.

The layered enhancement has a high sensitivity (of approximately 100%), specificity (87%) and diagnostic accuracy (93.75%) in the detection of active inflammation.

Punwani et al. reported statistically significant differences between the layered, mucosal-only and homogeneous mural enhancement patterns and the histologic indexes of acute inflammation. Segments with layered enhancement have a major inflammatory component in the histologic analysis, while those with homogeneous enhancement lack acute inflammatory component. Del Vescovo et al. reported similar results.

**Hyperintensity on T2 weighted images**

Submucosal edema in inflamed loops produces increased signal intensity (Fig. 1). Several articles have reported good correlation between signal hyperintensity on T2-weighted images of the affected loops and the presence of active inflammation, as well as significant differences between healthy individuals and patients with response to treatment.

**Mucosal abnormalities**

Mucosal abnormalities are typical findings of MR enteroclysis. A recent study reported that mucosal abnormalities are the most sensitive sign in patients with active CD. Several types of ulcerations may also be identified. Early mucosal inflammation is characterized by aphthous or superficial ulcers. These early manifestations are usually not visualized on MR, although sometimes appear as subtle abnormal imaging findings (Fig. 2). In this respect, conventional endoscopy, capsule endoscopy and barium imaging are superior to MR imaging for their detection.

As inflammation penetrates the wall, longitudinal and cross-sectional fissures form the characteristic cobblestone appearance. The visualization of deep fissures on MR imaging correlates with more severe lesions in the affected segments on endoscopic images.

**Distention and peristalsis**

Dynamic cine mode imaging allows for the evaluation of the peristaltic activity of the bowel loops, of non-distended segments, especially the jejunal segments, and may help differentiate between inflammatory and fibrotic strictures.

MR enterography is useful for determining the possible causes of bowel obstruction, including CD. Dynamic imaging and the pattern of enhancement also help in the differentiation between chronic strictures and transient spasms, between stricture caused by inflammation and fibrotic stricture, and between severe bowel obstruction and reversible obstruction.

Cine imaging provides better depiction of the lesions than conventional MR enterography.
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Extramural findings

Abnormalities of the mesenteric fibrofatty tissue
Some authors consider that there is an increase in T2 signal intensity in the fibrofatty tissue in virtually all patients with biologically active inflammation, which may be related to mesenteritis, with edema and hyperemia of local vessels.32

On the other hand, fibrofatty proliferation, which surrounds and produces separation of the affected loops, may appear in both active and inactive disease. A considerable amount of fibrofatty tissue may be seen in inactive disease, but the signal appears increasingly hypointense on T2-weighted fat-suppressed images due to a higher fibrous content.32

Mesenteric vascularity
The increased mesenteric vascularity of the mesenteric border of the affected loop is known as the “comb sign”. This sign has a high sensitivity for the detection of active disease but low specificity, not reaching statistical significance.29

It has been suggested that increased vascular engorgement may persist for long periods in patients with inactive or quiescent disease due to chronic mesenteric fibrosis.44

Enhancement of local lymph nodes
Homogeneous enhancement of mesenteric lymph nodes, moderate or intense, is highly suggestive of active CD; however, moderate lymph node enhancement can also be seen in 50% of cases with inactive disease.44 On the other hand, the size of the regional lymph nodes shows a weak correlation with the degree of inflammatory activity.45

Additional extramural findings
The presence of abscesses or active fistulas, found in 35% of patients at some point during the course of the disease, is very specific in the diagnosis of inflammatory activity.23,46,47

Classification of Crohn’s disease: subtypes
CD has been classified into several subgroups, and patients may exhibit characteristics of more than one disease

![Figure 1](image1.png)

Figure 1  T2 signal hyperintensity of the bowel wall. Coronal FIESTA (A) and axial SSFSE (B) images show a loop of the terminal ileum with thickened and hyperintense wall on T2-weighted images (white arrows), and associated deep ulcers (yellow arrow in B).

![Figure 2](image2.png)

Figure 2  Mucosal abnormalities: superficial ulcers. (A) and (B) Axial FIESTA images show mural thickening of the terminal ileum with submucosal edema and irregular mucosal surface with some focal ulcerations (white arrows). (C) Endoscopic view of the terminal ileum shows multiple superficial ulcers (black arrows).
Figure 3  Distortion or blunting of the mucosal folds and thickening of the valvulae conniventes. (A) Coronal SSFSE image shows thickening and blunting of valvulae conniventes of the terminal ileum with a pseudopolypoid appearance (white arrows in (A)). (B) Endoscopic view shows mucosal ulcers and edema (black arrows) in the terminal ileum.

subtype. There is a wide interpatient variability in the tendency to develop one subtype of another.

The subtypes are the active inflammatory subtype (described also as non-fistulizing non-stenotic), perforating-fistulizing, stenotic or fibrostenotic, and reparative-regenerative subtype.

This subtype classification is useful to determine if the patient may benefit from medical or surgical treatment. In this respect, understanding of the imaging findings and correct classification are essential.

Active inflammatory disease subtype

Early manifestations of CD include edema and aphthous ulcerations, which are readily detected by endoscopy whereas MR imaging is less effective. The initial mucosal inflammation may progressively develop into deep ulcers, transmural inflammation, and granuloma formation with subsequent wall thickening, hyperemia, submucosal edema and hypertrophy of mesenteric fat.

Minimal active inflammatory signs are characterized as aphthous or superficial ulcers on endoscopic images. Endoscopic and barium examinations are clearly superior in the detection of these superficial mucosal abnormalities, which may not be identified on MR imaging even with optimal luminal distension. However, sometimes even subtle abnormalities may be seen with MR imaging, including superficial ulcerations (Fig. 2) that in combination with distortion, blunting, and a polypoid appearance of the valvulae conniventes (Fig. 3) has high specificity for CD.

Mucosal hyperemia is seen as an area of intense enhancement after contrast agent administration. Occasionally, this enhancement may be the only imaging finding. The early peak of signal intensity after contrast administration correlates well with the CD activity index (CDAI).

As previously mentioned, the stratified pattern (layered pattern or “target” sign) of contrast enhancement has also been correlated with active inflammation (Fig. 4).

Additional extramural findings in the setting of inflammatory subtype include mesenteric hyperemia with engorged vessels corresponding to hypervascularity of the affected segment (“comb” sign) usually accompanied by edema and mesenteric fat proliferation around the affected loop. This fatty hypertrophy produces increased signal intensity on T2 images that correlates with active inflammation, but does not correlate with the amount of fibrofatty proliferation, as this can be present in inactive or quiescent disease.

As mentioned before, regional lymphadenopathy is frequently seen in patients with inflammatory changes.

- Severe inflammation: signs of severe inflammatory activity include deep mucosal ulcerations and a “cobblestone” appearance of the bowel mucosa (Fig. 5), very characteristic of CD.

Deep transmural ulcers are easily detected on FIESTA, SSFSE and T1-weighted fat-suppressed images after contrast administration.

The serrated lumen sign is secondary to the presence of multiple transverse ulcerations that result in an irregular appearance and it correlates with severe inflammatory disease activity.

In some individuals, these deep transmural ulcers progress with resultant early fistula formation, being thus included in the penetrating-fistulizing disease subtype.

Penetrating-fistulizing subtype

This subtype is characterized by severe inflammation that progresses to transmural ulceration with fistula formation or intestinal perforation. Prior to fistulization, large penetrating ulcers may be identified.

Differentiation between deep transmural ulcerations (fissures) and well-established fistulas is crucial as fissures may respond to more aggressive immunomodulatory
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Figure 4  Stratified pattern. (A) Coronal T1-weighted fat-suppressed image and IV contrast. (B) Axial LAVA image with IV contrast shows the characteristic layered stratification with mucosal (blue arrows) and serosal (white arrow) enhancement and submucosal hypointensity (curved yellow arrows) secondary to edema. (B) Cross-sectional image shows the target-like appearance of the loop.

treatments (TNF inhibitors), whereas established fistulas can act as potential infectious reservoirs that may lead to sepsis.

Active fistulas show intense contrast enhancement, while chronic fistulas are seen as low-signal serpiginous tracts with no enhancement after contrast administration. Fistulous communications may occur between several bowel loops (internal fistula) or between loops and the skin or other adjacent organs (external fistula) (Fig. 6).

The perianal region is the most common site affected by fistulas. For this reason, complementary high resolution imaging of this region is sometimes required. According to some authors, fistula formation occurs at some point during the course of the disease in up to 35% of patients, and up to 20% of patients develop perianal fistulas.47

Extramural complications such as abscesses (Fig. 7), inflammatory masses or adjacent organ involvement can be easily seen at MR enteroclysis.

Immunomodulatory therapy must be discontinued in case of mural abscesses or fistulas because of the risk of developing sepsis and their presence should be mentioned in the radiological report.

Figure 5  Inflammatory pseudopolyps: cobblestone sign. (A) and (B) Coronal FIESTA images of left colon show mural thickening and multiple pseudopolyps (small white arrows) that correlate with the colonoscopic view (C) and (D) showing the typical cobblestone appearance of the bowel mucosa (black arrows). The extensive inflammation precluded the detection with colonoscopy of fistulous orifices, clearly visible on the MR image with colocolic fistulous tracts (curved arrow in A) and external tracts (enterocutaneous tracts with an abscess demonstrated in the left lateral abdominal wall-curved arrow in B).
Fibrostenotic-stenotic subtype

Small bowel obstruction is the characteristic manifestation of this disease subtype. The imaging examination shows the fixed segment of stenosis, wall thickening or severe inflammatory changes are not necessarily present, and homogeneous enhancement may be seen after contrast administration. The persistence of mural thickening varies and it can persist over time irrespective of the inflammatory disease activity (Fig. 8).

Cine imaging shows absence of distensibility and peristalsis. Bowel obstruction is usually accompanied by a greater or lesser degree of prestenotic dilatation.

Differentiation between fibrotic and edematous stenosis is useful for selecting patients for surgical versus medical treatment. Chronic fibrotic stenoses are typically
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Figure 8  Fibrotic stenosis. (A) and (B) Coronal FIESTA images of a patient with a history of terminal ileum resection for Crohn’s disease and episodes of partial bowel obstruction show fibrotic stenosis (white arrows in A and B) not distensible at dynamic cine imaging. (C) Axial contrast-enhanced T1-weighted fat-suppressed image and (D) Coronal contrast-enhanced T1-weighted fat-suppressed image of a patient with no history of surgery, but with similar symptoms, show thickening and stenosis of the terminal ileum with homogeneous contrast enhancement (arrows), compatible with chronic stenosis.

hypointense on both T1 and T2 sequences, whereas inflammatory stenoses with transmural edema are hyperintense on T2 fat-suppressed sequences.

Pseudosacculation (omega sign) is usually caused by asymmetric fibrosis involving the mesenteric margin of the loop that results in pseudosaccule formation on the antimesenteric side (Fig. 9).

Reparative-regenerative subtype

Mucosal atrophy (absence of valvulae conniventes) and regenerative polyps characterize this phase.

The “halo” sign is caused by submucosal fibrosis and fat hypertrophy, characteristic of the chronic reparative subtype (Fig. 10).

Mucosal atrophy with focal areas of sparing is seen as pseudopolyps that demonstrate no significant enhancement or edema.

Sometimes, extensive filiform polyposis with no edematous component may be seen. Regenerative pseudopolyps are not to be confused with those appearing among the deep ulcerations that develop in the advanced inflammatory disease (cobblestone sign).

MRI evaluation of activity in Crohn’s disease

The clinical indexes for the assessment of CD lack accuracy, are subject to subjective interpretation and do not take into account the presence of extramural complications. Therefore, CT and MR enterography are being increasingly incorporated into clinical practice as objective methods to control the severity of the disease.

The clinical index most widely accepted and most frequently used by gastroenterologists is the CDAI, which evaluates during one week eight clinical variables. This index is subject to wide variability of interpretations and to the subjectivity of both the patient and gastroenterologist. Other simpler indexes (Harvey-Bradshaw index), or those used in combination with laboratory (Dutch or Van Hees index), histopathologic (acute inflammatory score [AIS]) or...
endoscopic parameters (Crohn’s disease endoscopic index of severity [CDEIS]) are not satisfactory either and do not include information on extramural complications.

Novel imaging techniques, specifically MR enterography, play an important role in the follow-up of inflammatory bowel disease.

Gourtsoyiannis et al. propose a magnetic resonance index of activity (MaRIA) based on the presence of deep ulcers and lymph node enhancement to discriminate between active and inactive disease.

Rimola et al. propose a simplified MaRIA to measure disease activity, reporting good correlation with the CDEIS.

We use the MRI scoring system proposed by Girometti et al. that includes mural, extramural and dynamic parameters and has showed higher diagnostic accuracy than the

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From Girometti et al. Diagnostic accuracy 91.1%, sensitivity 93.1%, specificity 87.5%.

* Equation: signal intensity post-Gd − signal intensity pre-Gd/signal intensity pre-Gd × 100.
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Authorship

- Responsible for the integrity of the study: L. Herraiz Hidalgo.
- Conception of the study: L. Herraiz Hidalgo.
- Design: L. Herraiz Hidalgo.
- Acquisition of data: (considering that data are the data collection of the patients studied with MR enterography during the above mentioned period, the correlation with the clinical data obtained from the medical records in electronic format, the correlation with surgical protocols, primary care reports, etc., and the classification of the disease into the subtypes described in the main manuscript): J. Carrascoso Arranz, R. Alonso Cano and L. Herraiz Hidalgo.
- Statistical analysis: not applicable.
- Drafting of the manuscript: L. Herraiz Hidalgo.
- Critical review with intellectually relevant contributions: V. Martínez de Vega.
- Approval of the final version: all the authors have reviewed the manuscript and are aware of the modifications made to it, giving their approval of the final version.

Conflict of interest

The authors declare no conflict of interests.

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