The diagnostic role of magnetic resonance enterography in Crohn's disease: An updated review of techniques, interpretation, and application

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Crohn's disease (CD), a chronic illness characterized by transmural involvement of the bowel wall, mainly affects young adults with a relapsing and remitting course. Clinical presentation typically involves nonspecific symptoms that can be associated with an array of acute active and chronic disease, as well as related to complications from primary bowel pathology that includes the extra-enteric tissues within the abdomen or pelvis. An optimal imaging technique can noninvasively assess the bowel wall for changes in active or chronic CD, can identify complications related to transmural CD, and can be used to monitor the disease safely with minimal or no X-ray exposure.

Crohn's disease involves the small bowel in 80% of cases and can be challenging to diagnose and monitor. In addition, CD involves the full thickness of bowel wall; submucosal inflammation is responsible for tissue destruction and penetration, leading to such complications as fibrosis, strictures, and fistulae. These processes are responsible for the most serious morbidities whereas, in contrast, disease restricted to mucosa is not associated with such sequelae.

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While endoscopy with biopsy is generally considered the diagnostic reference standard, this combination evaluates only the mucosa; it does not assess inflammation or fibrosis within the submucosa or deeper tissues. Therefore, these optical techniques alone may under-represent the extent of disease, particularly when considering that the mucosa has a high capacity for repair.

The overarching objective of imaging is to diagnose CD, to assess the location, mural and extramural extent and severity of disease, and to assess for complications such as stricture, bowel tethering, obstruction, or abscess. Cross-sectional imaging, unlike optical techniques, can evaluate submucosal and deeper tissues and extraintestinal complications of CD. Currently, computed tomography enterography (CTE) and magnetic resonance enterography (MRE) are the only 2 imaging modalities that can visualize submucosal tissues throughout the small bowel. CT generally is highly utilized,[1] but there is growing concern over ionizing radiation and cancer risk. In contrast to CTE, MRE does not expose patients to ionizing radiation, and it can differentiate between inflammation and fibrosis as the cause of submucosal inflammation (Table 1). These advantages may be used to monitor the effects of medical therapy more accurately, to detect residual active disease even in patients showing apparent clinical resolution,[2] and to triage patients for surgical intervention more accurately.

Review of diagnostic methods

Clinical subjective disease activity assessment

Crohn's disease activity measurements, including the Physician Global Assessment, the Harvey-Bradshaw

Table 1. Comparative analysis of endoscopy, CTE, and MRE

Location and distribution of disease	Endoscopy +/-Mucosal biopsy	CTE	MRE
MURAL DISEASE			
Mucosa	Highly sensitive	Insensitive	Insensitive
Submucosa and deeper tissues	Insensitive	Sensitivity depends upon good bowel distension and cleansing	Sensitivity less dependent on bowel preparation
Differentiation between inflammation and fibrosis	High specificity	Low specificity	High specificity
EXTRA- MURAL DISEASE			
Extra-enteric soft tissue	Insensitive	Moderate to poor sensitivity and specificity	Sensitive and specific for inflammation and / or fibrosis
Fistula	Insensitive	Moderate sensitivity and specificity	Sensitive and specific for chronic recurrent and active disease
Perianal fistula	Insensitive	Insensitive	Sensitive
Abscess	Insensitive	Sensitive but non-specific for active inflammatory change	Sensitive and specific for active inflammation

Index, the Crohn's Disease Activity Index (CDAI) and the Pediatric Crohn's Disease Activity Index (PCDAI), are predominantly subjective measurements.[3-5] While multiple studies have demonstrated no correlation between MRE (Magnetic Resonance Enterography) findings and the CDAI, [6-9] other studies have shown such a correlation[10-12] as well as a correlation between MRE and laboratory markers of inflammation ESR/CRP (erythrocyte sedimentation index/c-reactive protein).[3-5] Only 2 pediatric studies have compared MRE to PCDAI; one demonstrated a statistically significant correlation between disease on MRE and PCDAI,[13] and the other demonstrated no correlation between MRE and pediatric CDAI.[14] Subjective clinical activity measurements do not essentially reflect mucosal findings, with these studies showing discordance between inflammation on endoscopy and subjective activity index measurements. This suggests intrinsic unreliability of subjective techniques for assessment of bowel wall and extra-enteric soft tissue pathology.

Endoscopic techniques

Ileocolonoscopy directly visualizes the mucosa and facilitates tissue sampling, providing high diagnostic sensitivity for mucosal disease. However, only a short segment of terminal ileum may be accessible with this technique. Video capsule endoscopy (VCE) visualizes the mucosa throughout the small bowel, but does not provide tissue samples and is contraindicated in suspected bowel stenosis and obstruction. Endoscopic methods, even with biopsy, evaluate only the extent of mucosal disease; submucosal and serosal-mesenteric disease will not be fully appreciated.[15] Three studies, each with approximately 20 patients, have compared MRE to VCE. They concluded that MRE and VCE identified diseased small bowel; however, VCE identified more lesions and small aphthous lesions,[16-18] reflecting the authors' contention that MRE is relatively less sensitive to early, mild disease restricted to the mucosa.

Small-bowel follow through

Small-bowel follow-through (SBFT) has been developed to evaluate the small bowel and to detect mucosal disease (aphthous ulcers), and complications, such as stricture, fistula, and abscess. However, SBFT is an x-ray-based technique that is relatively insensitive to mucosal disease and provides limited sensitivity for submucosal or deeper disease involvement. Both CTE and MRI have been shown superior to SBFT,[19] particularly for detecting extra-enteric disease and complications.

CTE

The advantages of CTE over MRE include greater availability and lower initial costs, although the overall cost benefit is a key measure that remains

Table 2. MRE findings of normal bowel, active inflammation, and chronic disease

	Fat suppressed T2W	Contrast enhanced T1W 3-D GRE	
	Hyperintense signal within the bowel wall	Bowel wall thickening	Bowel wall enhancement
Normal bowel	Absent	Absent	Absent
Active inflammation	Present	Present	Present
Chronic disease	Absent	Present	Present
Active inflammation with chronic disease	Present	Present	Present

Active inflammation may mask chronic disease/ fibrosis. Best possible measure of underlying fibrosis is achieved on follow up MRE after treatment and resolution of acute disease.

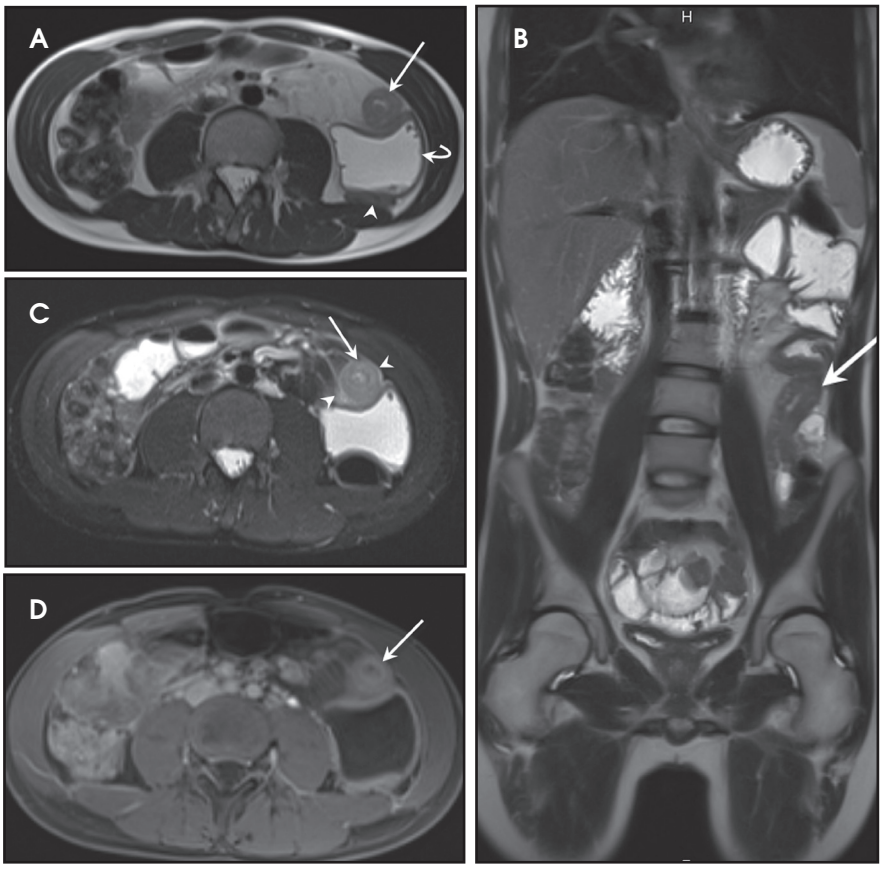


FIGURE 1. *A 22-year-old man presenting with intermittent fever due to active Crohn's disease. Axial and coronal single shot T2W images without (A and B) and with (C) SPAIR fat-suppression demonstrate marked thickening and extensive abnormal high signal involving a proximal jejunal segment (arrow) and extending into the adjacent mesentery (C, arrowheads). The high T2-signal identified in the thickened bowel walls and surrounding mesentery is the foundation for characterizing this patient's disease as active;[23,24] the elevated abnormal signal is directly related to the severity of edema and inflammation and is more conspicuous with fat-suppression (A versus C). Small bowel proximal to the site of disease is markedly dilated (A, curved arrow). The descending colon is located posteriorly (A, arrowhead) and is compressed by the distended small bowel. Axial delayed-phase post-contrast T1W 3D GRE images (D) show abnormal thickening and enhancement within the diseased wall of the jejunum (D, arrow). The combination of edema and delayed uptake of contrast are in keeping with active Crohn's disease.*

incompletely evaluated. Some studies comparing MRE to CT in small-bowel pathology have indicated similar sensitivities, while 1 has indicated[19,20] better sensitivity for CT,[21] and 1 other study has indicated better sensitivity for MRE.[22] The apparent wide range of results with MRE relative to CTE is largely due to the wide range of sequence techniques implemented. The authors contend that MRE accuracy will be limited if optimized, fat-suppressed, single-shot, T2-weighted acquisitions, such as the spectral adiabatic single-shot, fast spin-echo method, which have been previously described, are omitted.[23,24] These techniques are discussed later in this review.

A significant limitation of CTE is concern over cumulative ionizing radiation dose in patients who may otherwise benefit from longitudinal imaging evaluation over the course of their disease. As a relative comparison, it has been shown that one CTE exam can lead to 5 times the organ effective dose of a SBFT exam.[25]

Primary diagnostic role of MRE

MRE may more accurately depict submucosal pathology in transmural CD, including determining the presence and extent of inflammation, fibrotic disease, and other intra-abdominal complications, compared to other diagnostic modalities, including CT (Table 1). Further evidence supports that another diagnostic strength of MRE is the abil-

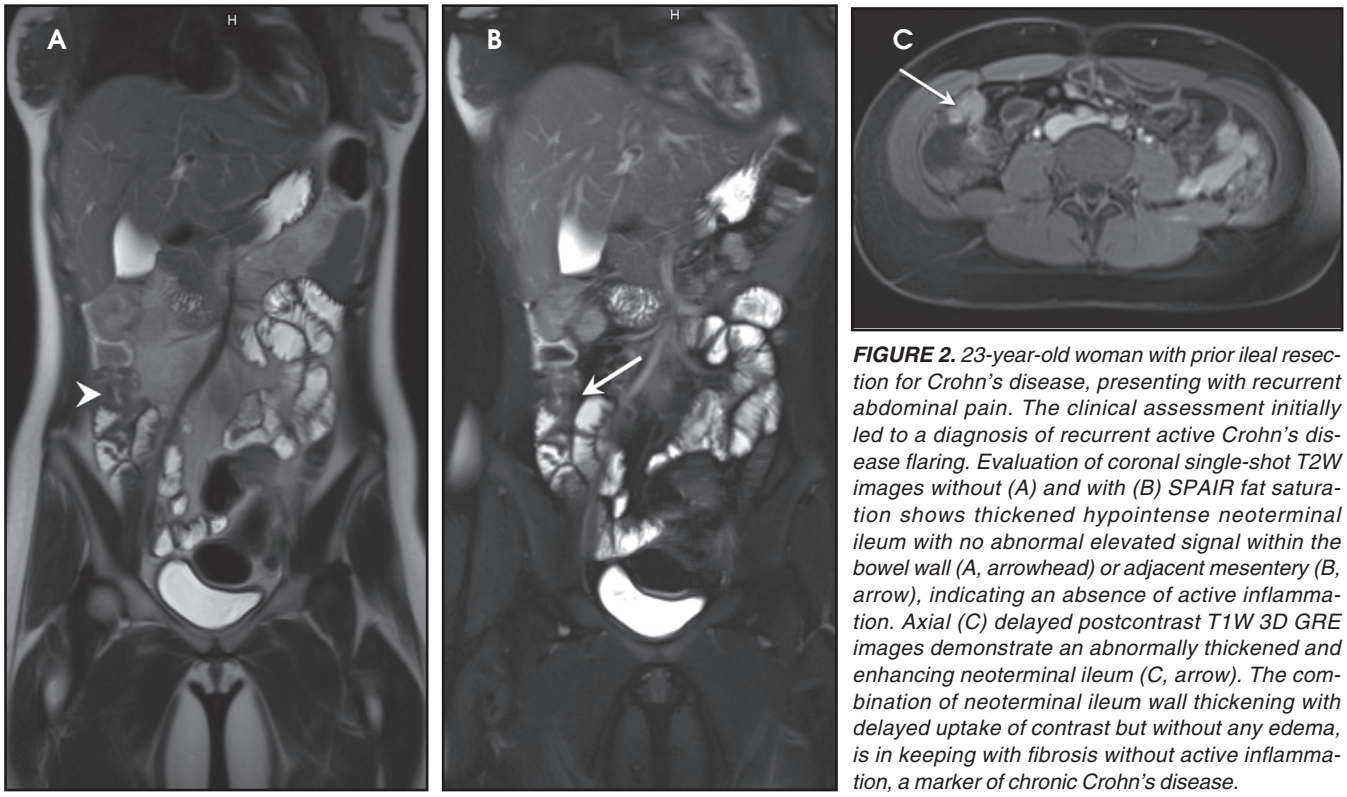


FIGURE 2. *23-year-old woman with prior ileal resection for Crohn's disease, presenting with recurrent abdominal pain. The clinical assessment initially led to a diagnosis of recurrent active Crohn's disease flaring. Evaluation of coronal single-shot T2W images without (A) and with (B) SPAIR fat saturation shows thickened hypointense neoterminal ileum with no abnormal elevated signal within the bowel wall (A, arrowhead) or adjacent mesentery (B, arrow), indicating an absence of active inflammation. Axial (C) delayed postcontrast T1W 3D GRE images demonstrate an abnormally thickened and enhancing neoterminal ileum (C, arrow). The combination of neoterminal ileum wall thickening with delayed uptake of contrast but without any edema, is in keeping with fibrosis without active inflammation, a marker of chronic Crohn's disease.*

ity to differentiate inflammation from fibrosis within the submucosa of the bowel wall and within the peri-enteric tissues (Table 1 and 2).[15,22,23] MRE can show enteric as well as extra-enteric complications, including bowel obstruction, abscesses, tethering, and fistulae.[26-29] These manifestations may be visualized on MRE with less dependency on bowel distension as required for optimal CT imaging, an important technical advantage of MRE.[30]

Technical review of MRE

MRE initially was designed to simulate the concept of luminography, as established for SBFT, by obtaining images that resemble fluoroscopic small-bowel images. This was achieved by administering a large volume of fluid either by mouth or by naso-jejunal tube (MR enteroclysis). MR images were acquired using thick-section (5-8 cm), single-shot, echo-train, spin-echo images strongly T2-weighted (T2W) to obtain images similar to those of SBFT. Distending the small bowel with water-based methods offers a bright luminal signal on T2W, and dark signal on T1-weighted (T1W) techniques. To maintain adequate distension, a viscosity agent may be added or osmotic agents like 2.5% mannitol, a nondigested carbohydrate, can be used to slow water absorption. Distension for MR luminography is achieved by administering at least 1 liter of water-based contrast by mouth 20 min to 30 min prior to the examination. This can also be accompanied by intravenous metoclopramide or erythromycin to promote gastric emptying.[31, 32] To improve image quality on motion-sensitive T1W 3D GRE sequences, 1 mg of glucagon may be administered intravenously to reduce artifacts from peristalsis.

Although both bright- and dark-lumen contrast agents have been suggested, water-based methods are relatively easy to implement and provide excellent signal characteristics, resulting in bright lumen on T2W and dark lumen on T1W techniques. To slow the absorption that normally would occur in the jejunum, osmotic and viscosity agents are added. In the early development of MRE, others proposed routinely using enteroclysis via a naso-jejunal tube to administer intra-luminal contrast for superior small-bowel distension.[33]

Optimized MR image acquisitions

A variety of T1W and T2W sequences are available, but the most useful sequences for bowel imaging include the breathhold 3-dimensional gradient echo (3D GRE) T1W and the single-shot T2W techniques.[15] The latest generation 3D GRE has provided volumetric imaging with higher in-/out-of-plane resolution and contiguous bowel-segment imaging with improved contrast and edge sharpness. The multi-echo Dixon technique has provided further improvement in fat suppression. T1W images are acquired after gadolinium-based contrast is administered to selectively enhance diseased bowel wall. Fat surrounds the bowel and can interfere with visualizing disease; inflamed bowel and fat both produce high signal on T2W and gadolinium-enhanced T1W images. Fat-suppression techniques are critical to improve disease conspicuity. The diseased bowel generates high signal, which becomes

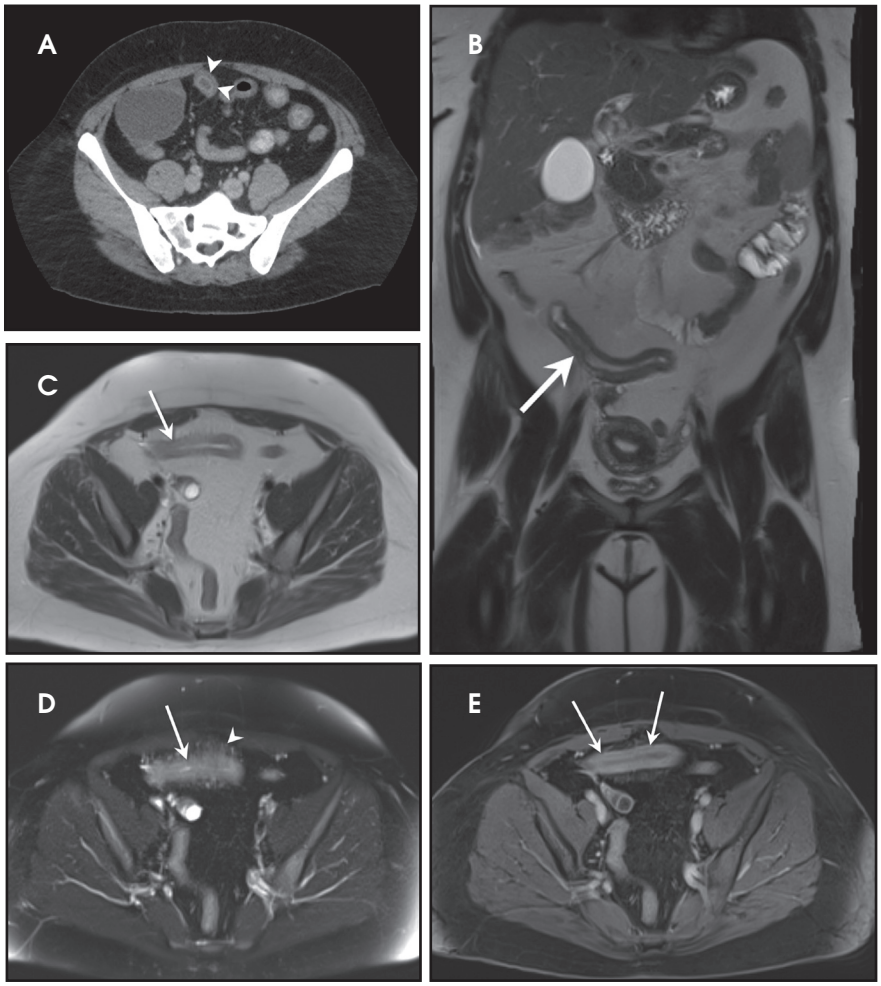


FIGURE 3. *33-year-old woman presenting with acute lower abdominal pain and bloody diarrhea due to active chronic Crohn's disease. Abdominal and pelvic axial CT (A) demonstrates mural thickening in a small-bowel loop in right lower quadrant (A, arrowheads). We were unable to differentiate between inflammation and fibrosis in the thickened bowel loop. An MRI was performed for differentiating active disease, and includes coronal (B) and axial single-shot T2W images without (C) and with (D) SPAIR fat-suppression. The MRIs show abnormal high signal involving thickened distal ileal loops (C and D, arrows) and extending into the adjacent mesentery (D, arrowhead). The high T2 signal identified in the thickened bowel wall and surrounding mesentery is a hallmark of active disease; the elevated abnormal T2 signal is most conspicuous on fat-suppressed images (C versus D). Axial delayed-phase postcontrast T1W 3D GRE images (E) show abnormal thickening and contrast uptake within the thickened wall of the distal ileum (E, arrow), findings in keeping with active on chronic Crohn's disease and corresponding to the surgical pathology findings of inflammation and submucosal fibrosis in this case.*

highly conspicuous only if the adjacent fat is completely darkened by fat-suppression.[24] T1W gadolinium-enhanced fat-suppressed and T2W, single-shot images, with and without fat-suppression, are the foundation of diagnosing and characterizing CD. Regular T2W single-shot images depict bowel-wall morphology. Fat-suppressed single shot T2W images are critical for assessment of edema and inflammation related to active CD. Technical improvements include T2W single-shot partial Fourier reconstruction coupled with parallel processing for echo-space compression, which leads to improved signal-to-noise, contrast and edge sharpness of bowel-wall morphology. Optimal suppression of fat is achieved using spectral adiabatic inversion recovery (SPAIR).[23, 24]

Optimized MRE patient preparation

Bowel distension may be achieved using typical oral contrast methods for routine CT examination of the abdomen. These water-based contrast agents contain an osmotic agent, preventing absorption, and a viscosity agent, improving small-bowel distension. The water content of these agents produces low signal within the lumen and generates contrast against the enhancing bowel wall on gadolinium-enhanced T1W fat-suppressed images. The water content produces high signal within the bowel lumen on T2W images against a normally low-signal bowel wall. CT and fluoroscopic techniques are usually nondiagnostic in assessing pathological bowel-wall thickening without marked bowel distension. The authors have found MRE sensitive to bowel-wall pathology related to CD even without any distension of the affected segments, a significant benefit of MRE.[15] In symptomatic patients who are unable to take oral contrast, we proceed without delay to the MRE procedure and have found little adverse impact on diagnostic outcomes.

Spectrum of MR imaging features of CD

The imaging manifestations of CD shown by MRE are summarized in Table 2.

Common T1W imaging features include: 1) Bowel-wall thickening with increased enhancement on delayed images; 2) Stranding extending into the mesenteric border fat and increased size and number of vessels; 3) Accordion-like compression and thickening of folds asymmetrically involving the mesenteric side of the small bowel having a tethered appearance; and 4) Reactive enlarged adjacent mesenteric nodes.

Common T2W imaging features include: 1) Bowel-wall thickening with increased signal in and adjacent to the abnormal bowel (on fat-suppressed images) showing active inflammation; and 2) Fluid accumulation in adjacent intraperitoneal and mesenteric spaces.

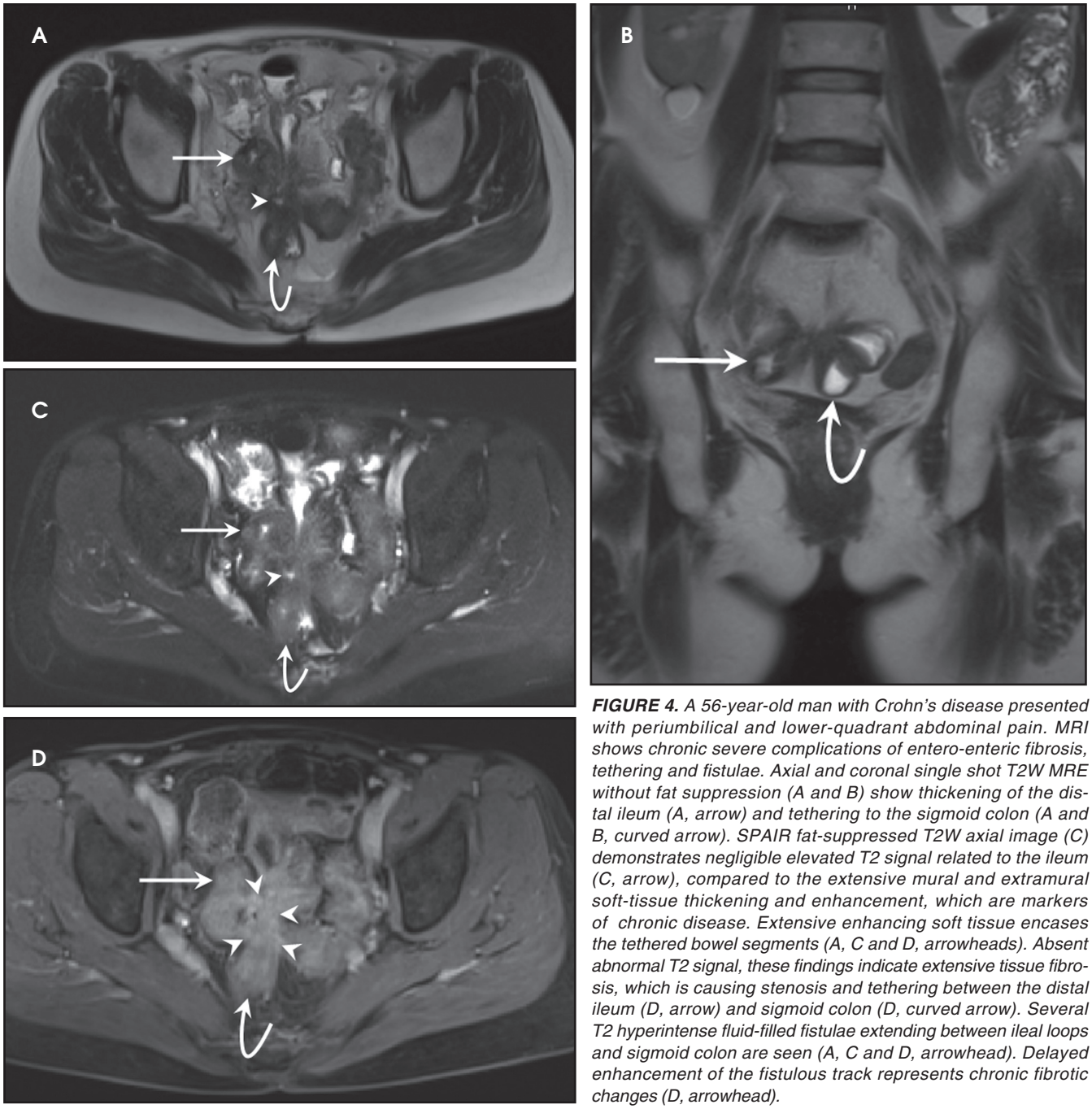


FIGURE 4. *A 56-year-old man with Crohn's disease presented with periumbilical and lower-quadrant abdominal pain. MRI shows chronic severe complications of entero-enteric fibrosis, tethering and fistulae. Axial and coronal single shot T2W MRE without fat suppression (A and B) show thickening of the distal ileum (A, arrow) and tethering to the sigmoid colon (A and B, curved arrow). SPAIR fat-suppressed T2W axial image (C) demonstrates negligible elevated T2 signal related to the ileum (C, arrow), compared to the extensive mural and extramural soft-tissue thickening and enhancement, which are markers of chronic disease. Extensive enhancing soft tissue encases the tethered bowel segments (A, C and D, arrowheads). Absent abnormal T2 signal, these findings indicate extensive tissue fibrosis, which is causing stenosis and tethering between the distal ileum (D, arrow) and sigmoid colon (D, curved arrow). Several T2 hyperintense fluid-filled fistulae extending between ileal loops and sigmoid colon are seen (A, C and D, arrowhead). Delayed enhancement of the fistulous track represents chronic fibrotic changes (D, arrowhead).*

Interpretive approach to a thickened bowel wall segment: Imaging interpretation of bowel-wall thickening is the cornerstone of CD diagnosis required for therapeutic decisions.

1) *Active inflammation*: High-signal-intensity edema and inflammatory fluid on T2W-SPAIR fat-suppressed images show enhancement on postgadolinium T1W images coupled with bowel wall thickening (Figure 1).

2) *Chronic disease without active inflammation*: Low-signal-intensity fibrosis and chronic changes on T2W-SPAIR fat-suppressed images with possible stenosis and obstruction. plus bowel-wall thickening and delayed enhancement on postgadolinium T1W images (Figure 2).

3) *Chronic disease with active inflammation* (overlapping features of 1 and 2): Active inflammation with thickened bowel wall showing both increased T2 signal and retained contrast on T1W images. Resolution of the elevated T2 signal is a marker of targeted therapeutic change, monitored on longitudinal repeat MRE. Chronic disease is determined by residual thickening and retained contrast (Figure 3).[15,24]

Complications of CD: Chronic and relapsing disease can manifest with enteric and extra-enteric complications.

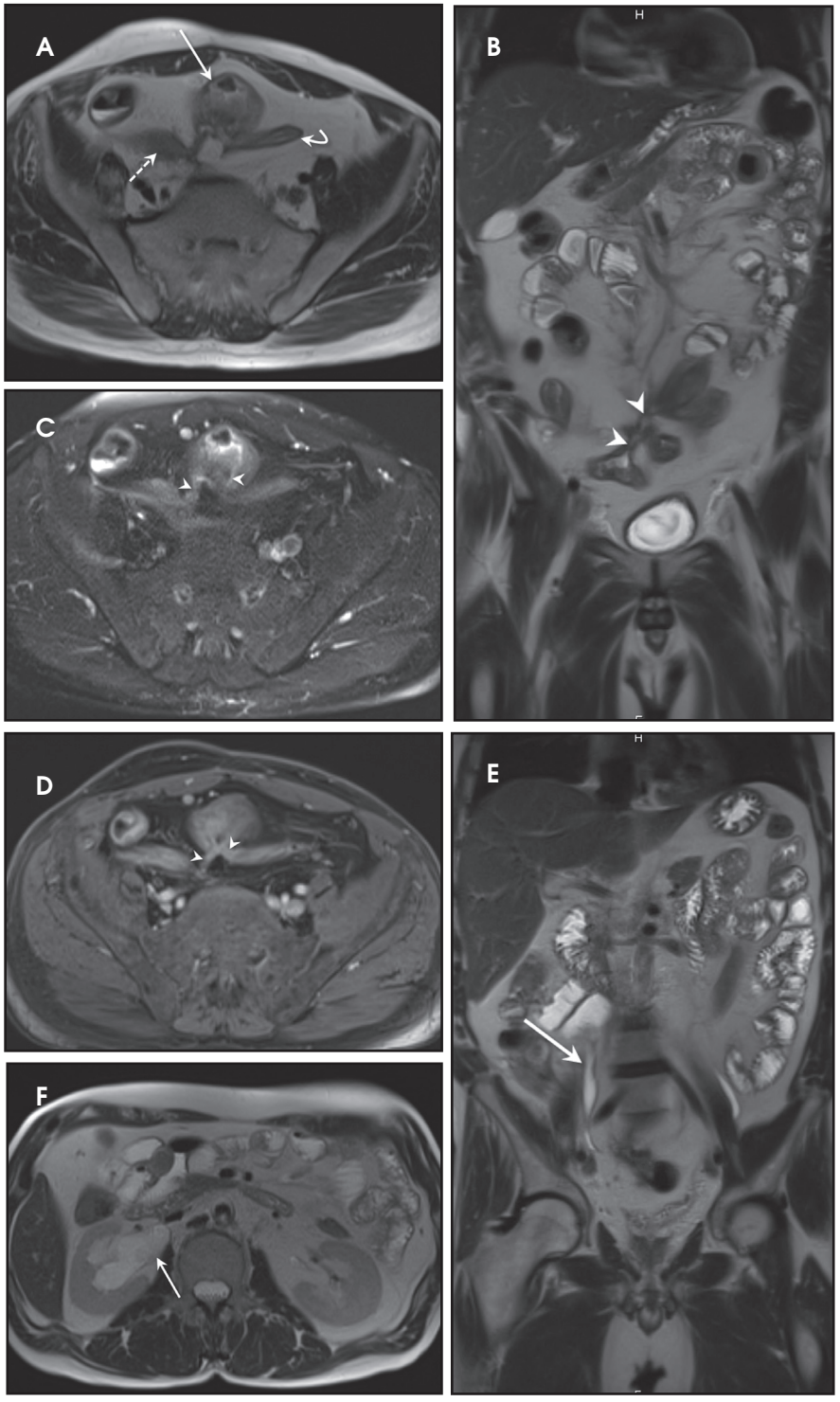


FIGURE 5. *A 48-year-old man with longstanding Crohn's disease presented with chronic abdominal pain. Axial and coronal single shot T2W MRE without (A & B) and with SPAIR fat-suppression (C), and axial contrast enhanced delayed phase T1W 3DGRE (D) images demonstrates tethering and fibrosis involving the distal ileum (A, dashed arrow), sigmoid colon (A, arrow) and descending colon (A, curved arrow) . There is extensive perienteric hypointense T2 signal representing fibrosis with multiple wide-mouth T2 hyperintense fluid-filled fistulae extending between small and large bowel which show delayed enhancement, indicating chronic fistulization (A- D, arrowhead). Fibrotic changes in the pelvis involve the right ureter, causing uetreic obstruction, hydronephrosis (E and F, arrow) and changes in the kidney parenchymal signal. These findings require urgent intervention to preserve the right kidney.*

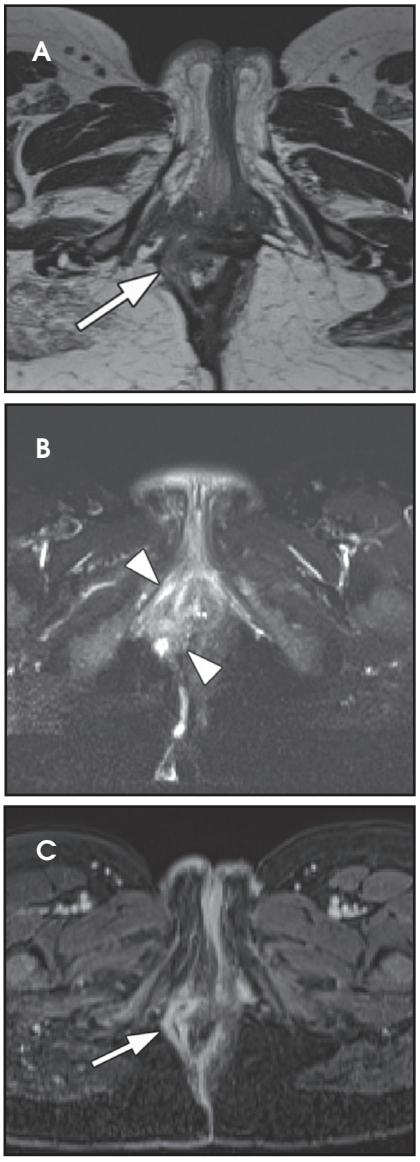


FIGURE 6. *A 36-year-old woman with Crohn's disease and perianal fistula. A fluid-filled fistula is seen on an axial 3D T2W image (A, arrow), which extends from the anorectal junction on the right, tracking posteriorly through the perineal soft tissues and draining through the medial gluteal skin surface on the right. This acquisition is obtained with an asymmetric echo 3D fast-spin-echo sequence with 1 x 1 x 1-mm resolution. Axial SPAIR fat-suppressed, single-shot, T2W image (B) shows increased abnormal signal (B, arrowheads) indicating mild active inflammation within the perineum. The combined observation of mild degree T2 signal abnormality (B, arrowheads) and disproportionately marked degree thickened and enhancing fistula track wall on axial contrast-enhanced delayed phase T1W 3D GRE (C, arrow) is indicative of mild inflammation on a background of chronic fistula with fibrosis.*

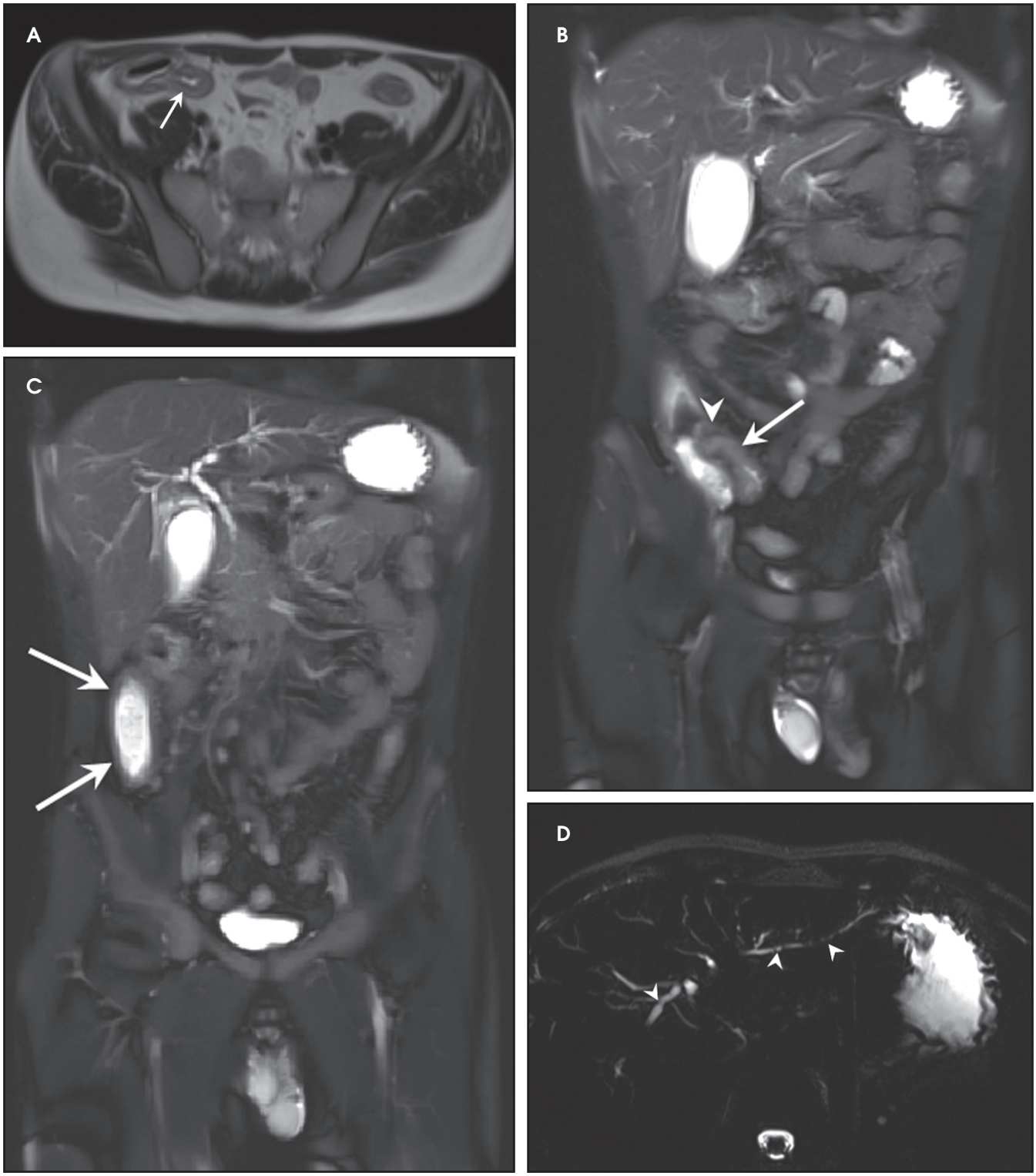
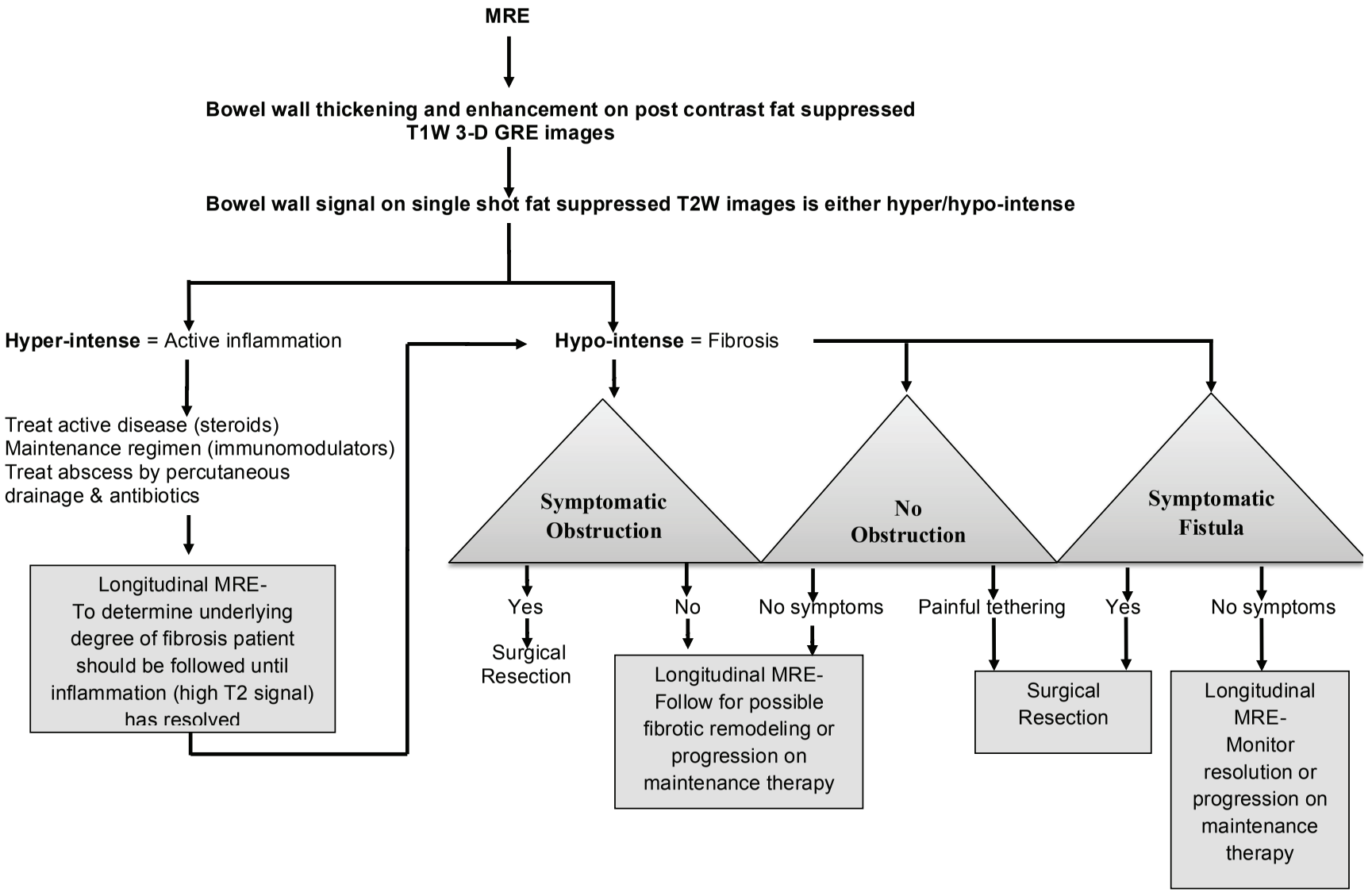


FIGURE 7. *A 30-year-old man with severe abdominal pain presented to the emergency department. Clinical suspicion included perforation of hollow viscous or acute appendicitis given the severity of abdominal pain. Plain radiographs were negative for free air and an unenhanced MRI of the abdomen was performed according to institutional protocol. Axial single-shot T2W images without fat suppression (A) shows thickened terminal ileum (A, arrow) and caecum with abnormal high signal. Coronal single-shot T2W images with SPAIR fat-suppression (B and C) show abnormal high signal involving thickened terminal ileum (B, arrow) and ascending colon (C, arrows) with mild elevated signal extending into the adjacent mesentery (B, arrowhead) representing a pattern of acute on chronic Crohn's disease. There is irregular distension and narrowing along the intrahepatic bile ducts creating a beaded pattern, on axial single-shot breath hold T2W MRCP (D). These features are characteristic of primary sclerosing cholangitis (PSC).*

Table 3. MRE features and therapy optimization



A) Enteric complications: 1) Fistulae, tethering, and strictures (Figures 4 and 5); 2) Bowel obstruction.

B) Extra-enteric complications: 1) Fluid collections, abscesses, and perianal disease (Figure 6); 2) Extra-intestinal manifestations, including, liver or biliary disease such as sclerosing cholangitis (Figure 7), mesenteric vascular thrombi, abdominal masses, tumors, and pancreatic abnormalities.

Active bowel inflammation is promptly depicted on MRE. However, sometimes active inflammation may mask underlying fibrosis related to chronic disease of the bowel wall (Table 2). The presence or absence of underlying fibrosis in this setting is of lesser immediate consequence, as active inflammation requires treatment. In this setting, longitudinal MRE evaluation confirms improvement of active inflammation and evaluates the presence of unmasked chronic fibrotic disease, particularly for potential surgical intervention.

Additional MRE methods and technical considerations

Perfusion characteristics of the bowel wall after intravenous gadolinium administration have been used to estimate disease activity. The combination of T2W images and T1W gadolinium-enhanced images is known to provide high diagnostic accuracy.[10, 34] An MRE-based scoring system has been proposed to assess inflammatory activity of the bowel wall, including bowel-wall thickening, lumen narrowing, and the number of peri-intestinal lymph nodes.[35] Interpretation based on these parameters is feasible; however, clinical application remains limited by the requirements of image acquisition. Perfusion-type imaging requires specialized scanning techniques or perfectly timed arterial, venous, and delayed-phase, gadolinium-enhanced T1W images (Table 3). This raises the technical challenge of whole abdomen and pelvis imaging without compromising the field of view and overall image quality, as well as free from the effects of respiratory motion or bowel peristalsis. Diffusion weighted imaging (DWI) is loosely related to T2W imaging and experience is developing with DWI techniques that shows potential utility for delineating and improving sensitivity for detecting diseased bowel wall segments and peri-enteric soft tissues.[36, 37]

Limitations of MRE

An MRE study requires approximately 30 min-45 min. While this duration compares favorably with fluoroscopic studies (SBFT, or enteroclysis), it is approximately twice as long as that needed for CTE. However, considering the entire length of examination, starting with bowel preparation and consumption of pre-scanning oral contrast, the differences in room time become less important than the overall process. Sedation may be required for very young children and patients with claustrophobia. The availability of MRE expertise and access may represent additional relative limitations compared to CTE.

Conclusion

With current optimized T2W and T1W techniques, MRE has evolved to generate reproducible high-quality examinations of the small and large bowel with significantly improved sensitivity and specificity for CD assessment. In the authors' experience, CT does not match MRE for producing the soft tissue contrast useful to reliably differentiate between inflammation and chronic fibrotic changes. Both processes may look identical on CT. On MRE, T2 signal increases with inflammation and edema, a marker of active CD.[23] Single-shot T2 combined with fat-suppression employing the SPAIR technique is critically important to optimizing sensitivity and specificity for active CD on MRE.[15,23,24] Earlier studies either did not use fat-suppressed T2 or did not use optimized fat-suppression and, therefore, may not have appreciated the full utility of MRE.[16,38,39] Other forms of fat-suppression, using simple inversion-recovery or chemical shift spoiling, will be adversely affected by higher noise, less uniform fat-suppression, or increased through-plane motion sensitivity to bowel peristalsis.[24] T2W imaging with fat saturation has shown high accuracy for measuring inflammation and acute disease activity compared to endoscopy, biopsy, and CT. In addition, MRE effectively evaluates severity and extent of submucosal pathology and extra-intestinal complications. MRE is relatively insensitive to early disease changes that are restricted to the mucosa, [40] MRE may be combined with endoscopy, capsule endoscopy, or biopsy. The combination of MRE and endoscopic techniques provides a comprehensive examination of inflammatory bowel pathology, including the evaluation of both mucosal and submucosal disease. Further improvements in MRE may be expected through refinements in fat suppression, which is achievable using multi-echo Dixon 3D GRE, or DWI techniques, for quantitative assessment of edema and inflammation, markers of disease activity. We predict eventual integration of MRE into routine CD activity scoring for longitudinal monitoring and management of therapeutic interventions.

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