

Utility of MR Enterography and Ultrasound for the investigation of small bowel Crohn's disease

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Abstract

Cross sectional Imaging plays an increasingly important role the diagnosis and management of Crohn's disease. Particular emphasis is placed on MRI and Ultrasound as they do not impart ionising radiation. Both modalities have reported high sensitivity for disease detection, activity assessment and evaluation of extra-luminal complications, and have positive effects on clinical decision making. International Guidelines now recommend MRI and Ultrasound in the routine management of Crohn's disease patients. This article reviews the current evidence base supporting both modalities with an emphasis on the key clinical questions. We describe current protocols, basic imaging findings and highlight areas in need of further research.

Index terms: Crohn's disease, MR Enterography, Small bowel ultrasound

Introduction

Crohn's disease (CD) is a lifelong condition characterised by recurrent gastrointestinal (GI) tract inflammation (1). Prevalence is highest in North America and Europe, with 145-199 cases per 100 000, equating to 400-600 000 sufferers in North America alone (2–4). Most patients with CD present when young, with peak incidence between 15-25 years. The total economic burden of CD is estimated to be \$10.9-15.5 billion in the US and €2.1-16.7 billion in Europe (3,5). Furthermore, as well as attracting considerable morbidity, the age-adjusted mortality risk for CD is around 50% higher than that of the general population (2).

The disease has a wide array of intestinal manifestations ranging from superficial mucosal ulceration, through to transmural inflammation, inflammatory and fibrotic stricturing, sinus, fistulae and abscess formation (6,7). Accurate phenotyping and staging of CD is essential for optimal management. An array of medical therapies are available including antibiotics, steroids, and immune-modulators such as anti-TNF alpha agents, each attracting their own benefits and side-effect profiles. Targeted surgical and endoscopic interventions also play an important role (6–9). However CD phenotyping is complex and requires accurate delineation of disease presence, segmental location, the relative contribution of inflammatory activity versus irreversible fibrosis, and the presence of extra-luminal complications. Furthermore, CD is also characterized by periods of relapse and remission. Thus phenotyping must be repeated at regular intervals. Indeed, annual

reassessment is mandated for patients on immune modulators so that management is optimised (7,10). The use of cross-sectional imaging to diagnose and phenotype CD has risen dramatically in recent years. Whilst it is acknowledged that there is a strong supporting literature for the use of CT enterography in CD (11,12), given the lifelong nature of the disease and patient demographics, an emphasis has been placed on those imaging modalities that avoid ionising radiation, notably MRI and ultrasound, this review describes the role of these two modalities for management of CD.

General role of Imaging in Crohn's Disease

Diagnosis and staging of CD is challenging and no single diagnostic test that achieves this is available (13,14). Instead, diagnosis is based on a combination of clinical evaluation and endoscopic, histological, radiological, and biochemical investigation (13,14). Such complexity in part reflects the relative inaccessibility of the gut to diagnostic interrogation. Endoscopy plays a pivotal role in diagnosis and follow up of CD, and is the best tool for luminal evaluation. However the terminal ileum (the most commonly affected bowel segment; 75% of patients) (15) may be inaccessible to ileocolonoscopy in up to 25% of patients (16,17). Furthermore CD often involves more proximal small bowel, unequivocally out of the reach of the colonoscope, and endoscopy may also underdiagnose extraluminal complications such as fistulae (18,19).

Proximal small bowel evaluation is now possible via video capsule endoscopy (VCE)(20). In a recent 4-way comparison, VCE achieved similar sensitivity for active small-bowel CD as CT Enterography (CTE), colonoscopy, and Barium Follow-through (BaF) (21). However specificity was low at just 53%, which is problematic given the implications of diagnosing CD in an unaffected individual. Additionally, VCE risks capsule retention due to stenosis and may also localise bowel abnormalities poorly (22).

Validated clinical indices such as the Crohn's Disease Activity Index (CDAI) give some information regarding the level of inflammatory activity but are

falling out of favour, as data increasingly reports relatively poor correlation with objective markers of biologic activity such as endoscopy (23,24) and in any event give little insight regarding the anatomical distribution of disease or any associated extra-luminal complications (25).

Given the limitations of both endoscopy and clinical scoring systems, imaging has assumed a central role in the management of CD. A number of small bowel imaging tests are commonly used: barium follow through (BaF), CT enterography (CTE), MR Enterography (MRE) and small bowel ultrasound (SBUS), all with differing attributes. In the relatively recent past, the most frequently employed of these were BaF and CTE - a UK survey in 2010 reported 90% of radiology departments used BaF routinely and 80% used CT to investigate patients with known or suspected CD (26). BaF is long established and in widespread use in some parts of the world, although in many countries it is rapidly falling out of favor and being replaced by cross sectional imaging.

It has high accuracy for diagnosing mucosal abnormality but is limited in its evaluation of mural and extra-mural disease. CTE has undoubtedly increased in popularity following the advent of multidetector-row scanners, affording high resolution abdominal scanning in a single breath-hold. It is fast, readily available and its clinical utility has been demonstrated in many studies (12,27). It is accurate for disease detection and its ability to quantify disease activity is comparable to other imaging modalities (28). Unfortunately both BaF and especially CTE expose patients to ionising radiation (29).

As noted above, CD patients are often young and require repeated imaging over the course of their disease. A 2007 audit revealed 15.5% of CD patients acquired a cumulative radiation dose resulting in an increased cancer risk of 7.3%, mainly due to CT (30). Both patients and doctors are increasingly aware of these risks and are rightly focusing on limiting radiation exposure. New CT technologies such as iterative reconstruction for CTE will undoubtedly have a major positive impact on reducing radiation exposure, but MRE and SBUS remain the only two truly radiation free techniques in common clinical usage (31,32).

The underlying complexity of the disease and array of treatment options necessitates that CD is best managed in a multi-disciplinary team environment (33). Radiologists must therefore be fully aware of the clinical management decisions faced by their gastroenterological and surgical colleagues. In the following discussion, particular emphasis is placed on the role of MRE and SBUS in addressing some of the most important clinical questions that imaging must answer:

1. Is disease present and, if so, is it predominantly active (and amenable to immunosuppressive therapy) or predominantly fibrotic (and better suited to endoscopic or surgical intervention)?
2. Are there associated extra-luminal complications such as abscess or fistulae that will need attention?
3. Has medically treated disease responded adequately to therapy?
4. To what extent does imaging impact on patient management?

MR Enterography

Summary of Technique

MRE combines fast imaging sequences with enteric luminal distension to evaluate the bowel and extra luminal tissues(14). Adequate patient preparation is vital for high quality MRE. The key to small bowel imaging using MRI is luminal distension since collapsed bowel can both hide and mimic disease. Distension is achieved via oral administration of large volumes of hyperosmolar liquid, which, unlike water, is poorly absorbed and therefore remains within the lumen over the course of the examination. Biphasic (ie low signal on T1-weighted images and high signal on T2-weighted images) oral contrast agents are used most widely and common examples include polyethylene glycol, mannitol, and low-density barium. Biphasic agents provide excellent contrast between bowel lumen and wall without obscuring mural enhancement from intravenous gadolinium. Several ingestion regimes are described, but typical volumes in common use range from 1,000–2,000mls, ingested steadily over the 40-60 min prior to scanning (15,34). A variant of MRE, MR enteroclysis uses nasojejunal intubation to infuse enteric contrast directly into the lumen. Distension is improved versus MRE, particularly in the proximal bowel, but this may not translate into diagnostic benefit over simple enterography (35,36). Furthermore MR enteroclysis is invasive, less well tolerated by patients than MRE, and necessitates radiation exposure for tube placement (35,36). It is therefore usually employed for solving specific problems.

Recent advances in MRI technology allow rapid acquisition of high-resolution images. MRE protocols generally include fast spin echo (FSE) T2-weighted sequences (with and without fat saturation), steady state free precession gradient echo (SSFP GE) sequences without fat saturation, and unenhanced and gadolinium-enhanced T1-weighted sequences. Axial and coronal images are acquired: A typical sequence protocol is shown in table1.

Most work on MRE for CD has been performed at 1.5T, but there is increasing evidence that 3T platforms can also provide high quality examinations (37,38). The multi sequence combination is intended to simultaneously evaluate mucosal, mural and peri-mural disease (14). Additional sequences such as “cine” motility and diffusion-weighted imaging (DWI) have an increasingly supportive evidence base. Motility imaging can be performed with fast T2-weighted or SSFP GE cine sequences and captures peristaltic activity. As discussed below, impaired motility is a biomarker of CD activity and therefore treatment response (39). Restricted diffusion in affected bowel has been associated with underlying biological activity in a number of studies (employing a range of reference standards, including endoscopy and surgical specimens)(40). For example, Kim et al. performed MRE in 50 patients including DWI ($b = 900 \text{ sec/mm}^2$), followed by ileocolonoscopy within 1-week. Segments were classified by the severity of endoscopic findings (deep or superficial ulcers, aphthae, erythema, edema only, or no inflammation). MRE with DWI was more sensitive for inflammation than MRE alone (83% versus 62%; $p = 0.001$) (41). Qi et al. recruited 36 patients who underwent 3T MRE

with DWI (5 b values, 0, 800, 1500, 2000, 2500 sec/mm²) and single/double balloon enteroscopy within a week. A b value of 800 sec/mm² was most sensitive for active CD (74.19%). MRE combined with DWI was more sensitive (94%), specific (89%) and accurate (92%) than MRE without DWI (sensitivity 82%, specificity 74%, accuracy 79%), or DWI alone (sensitivity 74%, specificity 63%, accuracy 66%) (42).

Disease detection and activity assessment

Aphthoid ulceration is an early macroscopic manifestation of active CD and is best appreciated by endoscopy. Ulcer detection is challenging for MRI and highly dependent on both the morphology and depth of the ulcer and the technical quality of luminal distention. When visible, it may appear on T2 weighted images as a small nidus of mural high signal intensity (SI) (due to crater filling with luminal contrast), surrounded by lower SI from bowel wall, and as a break in the line of mucosal enhancement on contrast enhanced T1 weighed images (43). As disease severity and activity progress, the MRI manifestations become more apparent. The MRI hallmarks of enteric CD are mural thickening and increased gadolinium enhancement (44) (Figure 1). As discussed below, studies comparing MRI findings with endoscopic disease activity scores and/or histopathological inflammation have shown active disease is manifest on MRI by increasing mural thickness, deep ulceration, increased mural and perimural T2 signal (often appreciated best on fat-saturated T2 images), avid mural contrast enhancement (especially in a layered pattern, frequently accompanied by increased mesenteric vascularity),

mural hyperintensity on high B value (>800) DWI, and increased loco-regional lymphadenopathy (14). Such features reflect histological hallmarks of active disease, namely mucosal ulceration, transmural inflammatory infiltrate, submucosal edema, and vasculopathy. A systematic review reported point estimates for per-patient sensitivity and specificity of MRE for diagnosis of CD as 78% (95% CI 67 to 84%) and 85% (95% CI 76 to 90%) respectively (45).

MRI activity scores

A major recent advance has been the development and validation of MRE based disease activity scores. These scores quantify disease activity, akin to endoscopic activity scoring systems such as the CD endoscopic index of severity (CDEIS). Components differ according to the individual score, but in general include radiologist scoring of parameters such as mural thickness, mural T2 signal intensity and avidity of contrast enhancement in comparison to an index tissue such as normal bowel wall or psoas muscle for example. Some also utilise signal intensity measurement via region of interest placement in the bowel wall.

Such scores have undoubted utility in the research setting, but are implemented increasingly in routine clinical practice, both for phenotyping disease and, as discussed below, for therapeutic monitoring.

While several scores are described sporadically in the literature, to date only two activity indices have been developed intentionally using an adequate independent external reference standard and thereafter validated successfully

in independent patient cohorts: the Magnetic Resonance Index of Activity (MaRIA) score and the Crohn's disease MRE Index (CDMI) score (46, 47) . The MaRIA score was developed following a study in which the reference standard was the Crohn's disease endoscopic index of severity (CDEIS) (46) and shows strong positive correlation with CDEIS when validated in independent cohorts (48). The score is derived using the following formula: (MaRIA (segment) = 1.5 x wall thickness (mm) + 0.02 x Relative Contrast Enhancement [RCE] + 5 x oedema + 10 x ulceration)

MaRIA requires evaluation for the presence of ulcers and increased mural T2 signal (compared with psoas muscle) as a marker of mural oedema, along with measurement of mural thickness and relative contrast enhancement via placing regions of interest in the bowel wall. A threshold of ≥ 7 indicates active disease. The CDMI score was derived and validated via histological scoring of activity in surgical specimens and endoscopic biopsies (47), and relies predominantly on subjective assessments of the bowel and adjacent tissues compared to an internal reference such as normal bowel wall or a nearby vessel. In its simplest form, it requires grading of only bowel wall thickness and T2 signal scored from 1 to 3 in comparison to normal bowel (1.79 + 1.34 mural thickness score + 0.94 mural T2 signal score) with a score ≥ 4.1 denoting active CD. Diagnostic performance is improved slightly by the addition of scores for perimural T2 signal and avidity of contrast enhancement compared to a nearby vessel. CDMI has been expanded recently to create a global (as opposed to segmental) activity index by incorporating assessment of disease length and the presence of extra luminal complications such as

abscess and fistulae, creating the magnetic resonance enterography global Score (MEGS), which had a significant positive correlation (Spearman's rank correlation= 0.458; P<0.001) with faecal calprotectin in a cohort of 71 patients (49).

Both MaRIA and CDMI have high sensitivity (80-90%) for detecting active disease and are reproducible between radiologists (39,46–48). As discussed in following sections, they are also validated increasingly as biomarkers of therapeutic response.

As noted previously, DWI also plays a role in activity assessment. An activity score incorporating Apparent Diffusion Co-efficient (ADC) measurement has recently been proposed (Clermont score: $1.646 \times \text{bowel thickness} - 1.321 \times \text{ADC} + 5.613 \times \text{edema} + 8.306 \times \text{ulceration} + 5.039$) which is highly positively correlated with the MaRIA score (50). Whether ADC improves activity scores is however unclear presently given the well-documented problems of reducibility both within readers, and between different centers.

Aberrant small bowel motility is a novel biomarker of disease activity that appears clinically useful. Several groups have showed negative correlation between software quantified bowel motility and disease activity (39,51,52). For example, Menys et al. showed bowel motility was negatively correlated ($r=-0.52$) with histopathological activity based on mucosal biopsies from 28 patients (39).

Penetrating disease

As transmural inflammation worsens, ulcers deepen until they eventually penetrate the bowel wall completely. This produces an advancing sinus, which causes mesenteric inflammation culminating in a phlegmon, or an abscess if there is associated loculated infected fluid. Fistulation is caused by subsequent communication with an adjacent structure such as a bowel loop. Up to 15.5% of patients with CD have penetrating lesions at presentation and up to one-third will develop this phenotype during their lifetime.

On imaging an abscess appears as a well-defined, encapsulated fluid collection that does not conform to normal peritoneal or bowel anatomy. Abscess may also exert mass effect. The fluid component has high signal intensity (SI) on T2 and low SI on T1 with a variable thickness intermediate SI rim, which may enhance avidly. The associated fistula underlying the abscess is identified infrequently due limited spatial resolution on MRE (14,43) (Figure 2). A phlegmon manifests as a region of often ill-defined increased mesenteric T2 SI adjacent to an inflamed bowel segment. The absence of a well-defined central fluid component distinguishes phlegmon from an abscess (14,43) (Figure 2).

Fistulas appear as linear high T2 SI tracts joining the lumen of two structures. They are often best seen on post-contrast T1 sequences. Entero-enteric fistulas often present encircled by a series of matted loops (the so called

“starfish” sign), within which the individual tracts are often not visible discretely (14,43) (Figure 3).

MRE is highly sensitive for detection of penetrating CD (53,54). Pooled data from studies comparing the accuracy of MRE for diagnosing fistulae (four studies) or abscess (three studies) suggested sensitivity/specificity of 0.76/0.96 and 0.86/0.93 respectively against an endoscopic and/or surgical reference standard (45).

Fibrotic disease

Fibrosis is the sequelae of recurrent multiple cycles of treated inflammation followed by healing. It is often characterised by strictures that cause partial obstruction, although obstruction per se can also occur with active disease or with a mixed active/fibrotic picture. Indeed, it is rare for diseased bowel segments to be purely inflammatory or purely fibrotic: Both disease processes usually co-exist (Figure 4).

Data describing the utility of MRE to detect and quantify fibrotic disease is sparse compared to that for inflammation. This mainly reflects the need for full thickness surgical specimens as a reference standard for mural fibrosis, as opposed to more easily obtained endoscopic activity scores, mucosal biopsies or clinical indices which are used to evaluate disease activity. In clinical

practice, reduced markers of disease activity (eg ulceration, increased mural T2 signal) usually infer that the diseased bowel is predominantly fibrotic, although this assumption has not been tested formally in large studies. Rimola et al. have recently demonstrated a significant association between grades of histological mural fibrosis and progressive enhancement at 7 minutes following gadolinium injection (Chi squared $p < 0.01$) (55). Specifically, an enhancement gain of $> 24\%$ between 70 seconds and 7 minutes indicated bowel with severe fibrosis. Punwani et al. (56) reported that fibrosis is frequently associated with a layered enhancement pattern, and Zappa et al. (57) demonstrated a significant association with mural thickness ($p = 0.0018$) and more surprisingly, increased mural T2 signal intensity ($p = 0.026$), which is a known marker of disease activity.

Magnetization transfer imaging is a novel technique that may be able to differentiate between fibrosis and inflammation (accepting that the two disease states often co-exist). Magnetization transfer imaging utilizes transfer of energy from protons in free water molecules to those associated with large molecules such as collagen, with fibrotic tissues demonstrating a high magnetization transfer effect (58). Dillman et al. reported significantly higher mean normalised bowel MTR in 10 rats with induced inflammation and fibrosis (0.58 ± 0.08) when compared to 10 rats with induced inflammation only (0.45 ± 0.05), ($p = 0.0003$) (58). Pazahr et al. assessed feasibility of MTR in 31 CD patients undergoing 1.5T MRE. Patients were classified as having either acute/active inflammation, chronic/fibrosis, or a combination, by two independent radiologists using all acquired MRI sequences, with histological

findings available in 13 patients. MTR was increased significantly in fibrotic segments ($35.3 \pm 4.0 \%$, $p < 0.0001$) when compared to normal bowel ($25.4 \pm 3.4 \%$) suggesting the technique may be both feasible and clinically useful in humans (59).

MRI features of fibrosis reported in the literature are inconsistent, which probably reflects the frequent co-existence and variable proportions of both fibrosis and inflammation and which serves to complicate interpretation(55,57,58). Multi-site studies addressing this issue are underway currently.

Monitoring therapeutic response

The current aim of medical management for CD is to achieve mucosal healing where possible. It is widely accepted that MRE, with its ability to detect active disease, is a highly promising technique for disease monitoring (Figure 5) (14). As detailed above, MRE activity scores have been developed allowing more objective assessment of disease activity and subsequent treatment response (60).

Several studies have formally investigated the ability of MRE to quantify therapeutic response to immunosuppressive therapy. Van Assche et al. (61) recruited 20 patients with active ileal CD (judged by CRP and contrast enhancement on MRE), initiating treatment with infliximab. Patients were assessed by MRE at baseline, 2 weeks and 6 months, the findings of which

were summarized by a numerical index of activity (MRE score of severity in Ileal Crohn's Disease (MICD) that combined transmural inflammation, extramural involvement and signs of obstruction. They found the MICD score improved by week 26 with particular improvement for inflammatory components. Ordas et al. (62) investigated 48 patients with active CD (judged by colonoscopic ulceration). Patients underwent MRE and colonoscopy at baseline and 12 weeks following treatment with corticosteroids or anti-TNF agents. Disease activity was assessed using the MaRIA score for MRE and the Crohn's Disease Endoscopic Index of Severity (CDEIS) for colonoscopy. In patients with ulcer healing, mean CDEIS and MaRIA improved significantly at week 12 compared to those without ulcer healing: MRE detected ulcer healing with 90% accuracy.

Prezzi et al. and Eder et al. both retrospectively evaluated the change in MRE activity scores (MEGS and Simple Enterographic Activity Score for Crohn's Disease [SEAS-CD] respectively) in patients commencing anti-TNF therapy and demonstrated significant improvements of MRE scores in clinical responders, but not non responders (63,64).

The clinical utility of quantified small bowel motility as a marker of therapeutic response has also been investigated recently. Specifically, Plumb et al evaluated 46 patients with active CD initiating anti-TNF therapy and found that anti-TNF responders had significantly greater improvements in motility than non-responders, and that these changes were observed as early as 12 weeks following initiation (65).

MRE also has a role for detecting early disease recurrence following surgical resection. Indeed, up to 70% of patients may require repeat surgery within 10 years of their initial operation, a risk that can be reduced by timely introduction of medical therapy at the time of first recurrence (66,67). For example, Ojea et al. recruited 30 post resection patients who underwent both ileocolonoscopy and MRE. MRE revealed recurrence at the ileocolonic anastomosis correctly in 25 patients, with two false positives (68).

Impact on management

A central consideration regarding the clinical utility of any imaging technology is whether it directly influences patient care, and if so, how frequently. A small number of studies have addressed this topic for MRE.

Hafeez et al. prospectively surveyed gastroenterologists' diagnostic confidence, expectation of disease extent, and therapeutic plan before and after MRE in 51 patients with CD. MRE improved clinician diagnostic confidence significantly for disease presence and also changed therapeutic strategy in 61% (95% CI 47 to 74%) of cases (26). Cheriyan et al. and Litz et al. retrospectively analysed 57 and 28 CD patients respectively, demonstrating that MRE altered management in the majority of patients (82% and 60% respectively) (69,70). Garcia-Bosch et al. asked 4 clinicians to review case data for 100 patients with CD, including sequential addition of MRE and colonoscopic findings. They reported that clinicians more frequently

considered MRE alone as sufficient to plan patient management than colonoscopy (80% vs 34% respectively). Adding MRE findings to colonoscopy changed clinicians' confidence grade for diagnosis of active disease, stenosis, fistula, and abscess in a higher proportion of patients than did adding ileocolonoscopy to MRE. Anti-TNF therapy was more frequently indicated based on MRE findings than those from colonoscopy, and MRE changed therapy in a greater proportion of cases than did colonoscopy (28% vs. 8% $p<0.001$) (71).

Small bowel Ultrasound

Summary of Technique

SBUS is a time-efficient, low-cost, radiation free and well-tolerated technique for bowel imaging, although specific expertise is variably available (14). Given these attributes, in many European countries, SBUS is commonly the first investigation performed on patients presenting with gastrointestinal symptoms. However utility as a first line investigation is not ubiquitous and uptake is much less in some parts of the world, for example in the United States of America. As well as acting as a primary diagnostic tool, in many instances it can triage patients requiring more complex imaging.

Technological advances in sonographic equipment have been pivotal in establishing sonography for assessment of CD. Specifically the high spatial resolution of probe technology has facilitated detailed luminal and extra-luminal assessment, as well as providing the ability to interrogate the bowel in real-time, setting it apart from other investigations including MRE (72–75). Nevertheless, it is well recognised that complete enteric examination, especially of deeper pelvic loops, may not always be possible by sonography and visualisation may be limited by luminal gas and body habitus (14). Sonographer variability is also often quoted by the literature as a weakness (76), although in reality the few studies performed specifically to investigate this aspect actually demonstrate moderate to good inter-observer agreement,

especially for mural thickness and substantial agreement for stenosing and penetrating disease (77–79).

Patient preparation usually necessitates a 4-6 hour fast, which reduces luminal gas. No specific oral preparation is required for routine SBUS, and administration of IV contrast is rarely performed (72,73,80).

Imaging is performed trans-abdominally with the patient supine. A combination of convex and linear array probes are employed in a systematic manner to cover the entire abdomen and pelvis, to ensure as far as possible that the whole bowel length has been interrogated. Lower frequency (3.5 to 5 MHz) probes provide a panoramic view, particularly useful in obese patients and for evaluating the sigmoid/rectum via the window of a full bladder (72,74,75). Higher frequency (up to 18MHz) probes are essential for high resolution visualisation of bowel wall to reveal the well-described 5-layer pattern ((Figure 6) an inner hyperechoic layer represents the interface between the mucosa and the bowel lumen; a hypoechoic layer represents the deep mucosa; a hyperechoic layer, the submucosa; a hypoechoic layer the muscularis propria; and the final outer hyperechoic layer the serosa and the serosal fat), along with the underlying mural vascularization(72,74,75).

Visualization quality depends on both operator and patient, the ileocaecal region, sigmoid, ascending, and descending colon are amenable to accurate visualisation. The ileum and jejunum can be difficult to assess in their entirety due to overlying bowel loops and a deep pelvic location, whereas visualisation of transverse colon is sometimes challenging because of its variable position.

Finally the rectum is often inaccessible due to its deep posterior pelvic location (72,74,75).

Variations of basic SBUS technique include addition of intravenous contrast (Contrast enhanced US (CEUS)) and/or luminal distension via hyperosmolar luminal contrast (small intestine contrast US (SICUS), hydrosoneography) (72,80,81). Both additions add to procedural complexity and time for radiologists, and to invasiveness for patients (72).

CEUS facilitates real-time depiction of bowel perfusion following intravenous administration of microbubble contrast agent (80). For example, SonoVue® (Bracco SpA, Milano, Italy), which utilizes sulphur-hexafluoride microbubbles, with a mean diameter of 2.5 microm (SF6) that have an average lifetime in the blood of 12 minutes (82). The interface between the sulphur-hexafluoride microbubbles and the aqueous medium is intensely hyperechoic thus increasing contrast between bloods and surrounding tissues. Once the operator has identified a potentially abnormal bowel loop, it may be interrogated further with CEUS. For this, the identified loop is imaged (using a specific contrast specific US mode such as Cadence Contrast Pulse Sequencing (CPS) or power modulation phase inversion (PMPI)) after intravenous injection of microbubble contrast. The transducer is kept stationary over the selected intestinal segment and consecutive multi-frame cine-clips are acquired during breath-holding and/or quiet free breathing (from 0 to 60s) (80). Each cine-clip may be assessed both qualitatively and quantitatively using specific software packages. Qualitative assessment

includes identification of particular patterns of enhancement, such as submucosal or transmural enhancement that may reflect disease activity, with low or absent enhancement alternatively suggesting quiescent disease (80). Furthermore, software may generate time-intensity enhancement curves, providing semi-quantitative variables such as maximal enhancement, time-to-peak enhancement, and the area under a time intensity curve (83). Such analysis is relatively onerous for widespread clinical adoption, but is of significant research interest.

As discussed in more detail below, specific benefits for both CEUS and hydrosonography have been reported, including increased diagnostic accuracy, more confident identification of active disease (79,81,84), quantification of inflammation (85) and differentiation of inflammation from fibrosis (86,87).

Disease detection and activity assessment

Ulcer detection is cited infrequently in the sonographic literature. One study reviewed 545 ultrasound scans (of which 166 were from CD patients) and compared these with a variety of reference tests (BaF, colonoscopy, surgical specimens). They noted that focal disappearance of wall stratification positively correlated with the deep longitudinal ulcers in CD (88).

In addition to ulcer detection, there are multiple mural and peri-mural sonographic features that have been more commonly linked to CD activity. Akin to MRE, the most diagnostic of these is mural thickness (Figure 6).

Several studies suggest that a mural thickness, of >3mm, is 88% sensitive and 93% specific for diagnosis of CD, with a higher threshold of >4mm being 75% sensitive and 97% specific (73,89,90). A recent meta-analysis evaluated 15 studies with a variety of thresholds to diagnose abnormal mural thickness (3-5 mm). Mean sensitivity was 88%, specificity 97% and the area under the SROC 0.94 (91).

Another finding linked consistently to disease activity in the literature is increased mural blood flow on Doppler ultrasound (Figure 7). Specifically, increased Doppler signal within the bowel wall correlates positively with disease activity when judged by a combination of clinical and laboratory assessments across several studies (92–94). For example, Esteban et al. evaluated 79 patients and 35 healthy volunteers with colour Doppler ultrasound and compared findings with global physician assessment, which included CDAI, CRP, and other available imaging but blinded to US findings. Two radiologists reviewed all images in consensus, scoring any Doppler abnormality on a 3-point scale (where colour absence was scored 0 and clear identification of vessel paths in the inflamed gut walls scored 2). Comparison of gut wall vascularity found significant differences ($p < 0.001$) between active and inactive CD as well as between healthy volunteers and inactive CD patients (92). Spalinger et al. performed 119 Doppler US on 92 patients with

confirmed CD and compared findings with CDAI obtained the same week. Vessel density (defined as number of colour Doppler signals per square centimeter) was counted and classified subsequently as low (0 to 2 colour Doppler signals per cm²), moderate (3 to 5 colour Doppler signals per cm²), and high (>5 colour Doppler signals per cm²). Patients with active disease demonstrated higher proportions of moderate and high vessel density than those with quiescent disease (chi squared $p < 0.01$) (94).

Significantly increased splanchnic arterial flow has been noted in patients with CD but evidence of a relationship with disease activity has been conflicting. SMA Doppler is also cumbersome and time-consuming, limiting uptake in daily practice (95,96).

Other less well-documented sonographic features associated with active disease include alterations in normally layered bowel wall echogenicity, and thickening and altered echogenicity of the mesentery, and mesenteric lymphadenopathy (72). Nylund et al. performed histological analysis of surgical specimens from 14 CD patients with CD, finding severe submucosal fibrosis in 40 of 55 segments that demonstrated a hyperechoic submucosa with diffuse hypoechoic elements (97). Maconi et al. correlated sonographic mesenteric hypertrophy with the degree of clinical or chemical activity in 185 CD patients: Mesenteric fat hypertrophy was detected in 88 (47.6%), and these showed significantly higher CDAI ($p = 0.0001$) and CRP ($p = 0.0001$) compared to those without (98).

Ultrasound activity scores

As opposed to the MRI literature, there is relatively little published data regarding sonographic scores of disease activity. A handful of studies have proposed scoring criteria, but only one has been validated. Calabrese et al. developed a quantitative index based on findings from hydrosonography, incorporating enteric (bowel wall thickness, lumen diameter, lesion length and number of lesions) and extra-enteric findings (fistula, mesenteric adipose tissue alteration, abscess and lymph nodes). Bowel segments were considered as hollow cylinders and standardised variations of the above variables were combined into a predictive model to generate a prognostic index with values ranging from 0 to 200 (Sonographic lesion index for CD (SLIC)), with scores subdivided into a 5 point severity scale (A-E). They used SLIC to assess 110 CD patients over 1-year. Median SLIC score was significantly higher in patients with CDAI > 150 than those with CDAI < 150 ($p < 0.005$), and scores were also higher in patients with raised CRP > 5 mg/l compared to those with a normal CRP ($p = 0.003$). Furthermore, patients with higher SLIC (classified as group D/E) underwent surgery more frequently than those with lower SLIC (class A-C) ($p < 0.0001$) (99).

Individual studies have described scores able to predict the likelihood of surgery (100) and diagnose/grade endoscopic recurrence (101). Rigazio et al. performed US in 147 patients, of whom 48 required surgery within 30 days. Four US variables were independently associated with the need for surgery: Mural pattern; thickness; presence of fistulae/abscesses; stenosis). The

prognostic score correctly classified 84% of patients who ultimately underwent surgery (100).

Penetrating disease

SBUS is highly sensitive for penetrating disease: Early extramural extension manifests as discontinuous bowel wall margins with peripheral hypoechoic irregularities (75). A fissure may extend into the inflammatory conglomerate of mesenteric change and in turn produce cavities and more defined tracts that eventually communicate with other structures to form a fistula. Sinus tracts and fistulae manifest as tubular hypoechoic structures in the soft tissues immediately adjacent to inflamed loops (102). It is occasionally possible to observe bubbles of extraluminal gas within fistulae (75). Colour/power Doppler may further assist diagnosis of fistulae by detecting increased mural blood flow at the level of the fistula (103).

Phlegmons appear as extraluminal, hypoechoic structures of variable morphology, with irregular, poorly defined margins while the typical sonographic feature of an abscess is that of a complex collection, partly fluid and primarily hypoechoic, also with poorly defined margins (Figure 8) . Echogenic bubbles of gas may be noted within an abscess (75).

In very advanced penetrating disease, multiple adherent inflamed loops can present as an inflammatory conglomerate harbouring abscesses and fistulae. Sonographically, this appears as an irregular complex structure characterized

by heterogeneous hypoechoic and anechoic areas. Surrounding intestinal loops involved in the conglomerate are thickened and rigid, and sometimes lose their normal morphology (75). Doppler may assist in differentiating between abscesses and inflammatory masses as flow is only detected in the granulation tissue at the periphery of an abscess and is not seen centrally, as occurs with inflammatory masses (72).

A systematic review of 3 studies investigating the accuracy of SBUS for CD abscess diagnosis (against a surgical reference standard) reported sensitivities ranging from 81% to 100%, with specificities ranging from 92% to 94% (45). Additionally, US has great utility for percutaneous drainage, with success rates as high as 98% (104,105). SBUS has reportedly reasonable accuracy for diagnosis of intra-abdominal fistulae with four studies encompassing 99 fistulae reporting a sensitivity of 67% to 87%, with specificity between 90% and 100% (45).

Despite high reported accuracy of SBUS for penetrating complications, in clinical practice it is widely recognized that diagnosis of abscess and fistula is influenced by their location. The ECCO-ESGAR consensus recommends that for suspected deep-seated fistulas, MRE and CT are preferable to SBUS (14) and from a clinical perspective if an intra-abdominal abscess or deep-seated fistula is suspected, SBUS is only recommended if other cross-sectional imaging modalities are unavailable or deemed unsuitable, for example to avoid radiation exposure in children.

Fibrotic disease

Few studies have addressed the issue of diagnosing fibrotic lesions using SBUS and those that do focus on intravenous contrast. Studies evaluating basic sonographic features via comparison with surgical specimens note that inflammatory and fibrotic disease frequently co-exist. This leads to difficulty with interpretation, a problem familiar to the MRE literature (86,106,107). For example, Maconi et al. scanned 43 patients undergoing surgery for ileal stenosis and reported three distinct patterns of the submucosa and muscularis mucosae (107): 1, a stratified pattern that was associated with a significantly higher degree of fibrosis; 2, a hypoechoic bowel wall pattern that had a higher prevalence of inflammatory intraepithelial neutrophil infiltrate; 3, a mixed echo pattern that showed a high degree of both intraepithelial–interstitial neutrophil infiltrate and fibrosis (107). Ripolles et al. undertook pre-operative contrast-enhanced US in 25 CD patients undergoing either small bowel or colonic resection. They assessed fibrostenosis on a 3 point score (0 to 2) based upon the presence of stenosis, prestenotic dilatation, absence of colour Doppler signal, and low grade (<46%) contrast enhancement following microbubble contrast. They correctly classified 8 of 13 (62%) segments as fibrostenotic. The other 5 segments were judged inflammatory but of these, 4 demonstrated combined features of both fibrosis and high-grade inflammation. The authors concluded that in bowel exhibiting both active disease and fibrosis, sonographic features of the former predominate (108). Quantitative evaluation of contrast-enhanced SBUS is not established in clinical practice, likely due to issues around repeatability and reproducibility

within and between centres, and examination cost and complexity.

Nevertheless in one study using surgical resection specimens as a reference standard, a threshold of 65% for increased enhancement following US contrast administration demonstrated sensitivity of 93% (95% CI 66 to 99) and specificity of 69% (95% CI 39 to 90) for diagnosing inflammatory lesions as opposed to fibrostenotic lesions (86).

Monitoring therapeutic response

The relative simplicity and high patient acceptability of SBUS make it a very attractive option for monitoring disease response, and there is data supporting its utility in this role: Ruess et al. performed sequential SBUS assessments including colour Doppler in 17 patients with new or relapsed IBD (13 with CD), undergoing treatment with a variety of therapies. Bowel vascularity depicted by colour and power Doppler sonography was graded on a scale of 1 to 4 (1, no vascularity; 2, minimal vascularity or 1–5 pixels of color per centimeter; 3, moderate vascularity or >5 scattered foci of color or power signal per centimeter; 4, marked or severely increased vascularity with color and power Doppler signal present throughout the length of the involved segment, including discrete elongated vessels and areas of confluent vascularity). They demonstrated a decrease in both bowel wall thickness and Doppler grade at a mean interval of 25 days from initiation of medical therapy for CD but as early as 6 days (93). Moreno et al. performed SBUS including Doppler flow grade (subjectively graded as absent [grade 0] increasing to marked vascularity [grade 3]) and colonoscopy (at baseline and after 1 year) in patients with

colonic CD initiating biological management. SBUS detected mucosal healing accurately when compared to an ileocolonoscopy reference standard (89.8% sensitivity for segmental analysis and 84.6% sensitivity for per-patient analysis). Specifically, mucosal healing was best detected by the presence of Doppler flow grade 0 or 1 (highest sensitivity 97.6%), while ongoing mural thickening had the greatest specificity (94.1%) for absence of mucosal healing; only one patient with a mural thickness <3 mm did not exhibit mucosal healing (109). Overall there were 15 false-negative segments (which only subtle findings of superficial ulcers and/or erythema on endoscopy), 8 of which were sigmoid or rectum, which as already noted, lie deep in the pelvis and are suboptimally assessed by SBUS as a result (109).

Quaia et al. performed CEUS on 43 patients with known CD who were either starting medical management or had existing medication increased. They found the area under the time intensity curve (following intravenous contrast) differed significantly ($p < 0.05$) between responders and non-responders (as defined by either clinical [CDAI], endoscopic [Rutgeert's] or histology indices); no B-mode or Doppler features allowed differentiation between the two groups (83). Specifically, AUC for time intensity curves post intravenous microbubble contrast was 621.58 ± 374.53 units for responders compared to $1,199.64 \pm 386.39$ for non-responders. Using their proposed (hydrosonography) ultrasound activity score detailed above, Calabrese et. Al. were able to demonstrate significant improvements in SLIC scores in responders (defined by steroid-free remission, with $CDAI < 150$) compared to non-responders (from a cohort of 29 CD patients initiating anti-TNF treatment) (85).

A small number of studies have evaluated the sensitivity and specificity of SBUS for detection of post-surgical recurrence. Pallotta et al. performed hydrosonography and ileocolonoscopy in 58 post-surgical patients with CD. They found increasing mural thickness was associated with higher Rutgeert's scores, and a threshold of anastomotic mural thickness of >3.5mm identified all patients with endoscopic recurrence (101). Paredes et al. performed a similar study on 32 patients, and demonstrated that moderate to severe recurrence could be identified using mural thickness (threshold >5mm) and Doppler flow grades demonstrating moderate/marked vascularity with sensitivity and specificity of 80% and 75%, and 80% and 66.7% respectively. Employing a mural thickness of >3mm or the presence of any colour Doppler flow had sensitivities of 76.9% and 57.1%, and specificities of 87.0% and 40% respectively for any grade of recurrence (110). A more recent study by the same group investigated the potential diagnostic advantage of CEUS. They demonstrated improved accuracy for conventional parameters (mural thickness>3mm and colour Doppler positive) than previously, achieving 89.8% sensitivity and 81.8% specificity (86). However, adding contrast enhancement data, (specifically >34.5% enhancement in the neoterminal ileum) improved diagnostic accuracy to 98% sensitivity and 81.8% specificity (86).

Impact on management

Literature describing the impact of SBUS findings on individual patient trajectory is relatively sparse. Novak et al. evaluated 49 patients with CD prospectively (59% of which were asymptomatic), using clinical and serological tests as well as ultrasound. Two independent gastroenterologists made clinical decisions that were altered significantly after SBUS assessment in most patients (60% and 58%) (111). Interestingly, SBUS disclosed active disease in up to 52% of patients asymptomatic on follow up (111,112).

Wilkens et al. retrospectively reviewed 115 CD patients having comprehensive ultrasound and colonoscopy within 30 days of each other. Seventy-four patients (64%) had disease matched on the two tests but forty-one (36%) patients demonstrated abnormal bowel on US alone, proximal to the reach of ileocolonoscopy (although of these only eight had disease confirmed by subsequent surgery: the remainder had no corroborative test). In 29 (71%) of these patients, ultrasound demonstrated moderate or severe inflammation despite an endoscopic diagnosis of mild or no inflammation (113). This changed management in 22 (76%) of these patients (13 changes in medical therapy, 8 surgical referrals, 1 hospital admission), attributed to the SBUS (113). The emerging literature therefore supports a role for treatment monitoring using SBUS and also for follow up of asymptomatic patients given the high prevalence of asymptomatic (and thus untreated) inflammation.

Small bowel US vs. MR Enterography in CD

It is clear that both MRE and SBUS are highly attractive modalities for diagnosis and follow up of CD. As discussed below, although the available literature suggests both SBUS and MRE have similar diagnostic accuracy in phenotyping CD, they are clearly very different techniques and each attracts its own advantages and disadvantages.

The advantages of SBUS in general mirror those of conventional US ; it is cheap, equipment is readily-available and the technique is generally very well tolerated by patients. There is no absolute requirement for luminal distension with oral contrast or intravenous injection, adding to the relatively simplicity of the investigation. Conversely MRE is relatively expensive, with more limited availability of equipment in many health care settings. Furthermore it may not be possible in patients with claustrophobia, or those unable to breath hold reliably or lie still such as those with respiratory problems or young children. The technique necessitates good luminal distension and both IV spasmolytic injection and IV gadolinium contrast agent use is routine.

A common criticism of US is the potential to “miss” sections of the bowel due to anatomical location (for example deep pelvic loops and the rectum) or because of obscuration by bowel gas or overlying adipose tissue. A technically complete MRI routinely visualizes the whole gut. Another often stated limitation of US is the potential for inter-observer variability due to both missed bowel loops and perceived subjectivity in image interpretation. However those studies which have specifically addressed observer variability

in general report very good agreement, at least for disease presence. For example in a study of 103 CD patients by two independent sonographers agreement was near perfect (κ 0.91) (79). In a more detailed but smaller study of 29 patients, inter-observer variability for the presence of abscess was near perfect (κ 0.96), whilst for wall thickness (ICC 0.67), and presence of penetrating disease (κ 0.8) it was substantial. Agreement was however moderate for the length of disease (ICC 0.41), presence of stricture (κ 0.54) and grade of bowel wall Doppler signal (ICC 0.53) (77). By comparison, many studies have evaluated inter-observer agreement in MRI, with results in general demonstrating a good to excellent inter-observer variability for the assessment of multiple features of CD (35,114).

Another potential difference between the two techniques are the training requirements to gain competency. Few would disagree that radiologists require specific training when evaluating the small bowel for CD, although it is unclear whether this is greater for US than for MRI as is commonly supposed. There is in fact little data evaluating training requirements for competency in SBUS although learned bodies (for example European gastroenterologists) have produced detailed curriculums and advice on learning strategies (115). With respect to MRE, one study investigating formal training with direct case-by case feedback in 31 inexperienced readers concluded that experience of at least 100 cases was required to achieve the acceptable MRE activity grading accuracy of 75 % (116).

Regarding comparative diagnostic accuracy, four systematic reviews, including one meta-analysis, have evaluated the performance of imaging tests for both diagnosis and disease activity assessment (28,45,117,118). Most of the primary studies evaluated were single center and of relatively small numbers. Considerable heterogeneity in study design and reference standards were reported (28,45,117,118). The largest systematic review included 68 studies and compared CT, MRE and SBUS (45). For disease location the sensitivity of SBUS ranged from 75 to 93% versus 77 to 91% for MRE. Specificity ranged from 98 to 100% (SBUS) and 60 to 100% (MRE). Sensitivity and specificity for active disease for SBUS was 85% (range 75 to 100%) and 91% (range 82 to 100%) respectively and for MRE were 80% (range 78 to 100%) and 82% (range 46% to 100%) respectively (45).

Few prospective studies have employed a direct diagnostic test comparison methodology that has been shown to reduce bias by assessing the same patients with multiple tests (119), combined with high quality reference standards. These are summarized in Table 2 (120–124). Given the relatively complexity of such studies and their onerous nature for patients, recruits are relatively few and studies are usually single centre. Furthermore, studies differ in unit of analysis (per patient or per segment), primary endpoints (disease detection or disease activity), and employ a range of reference standards including colonoscopy, BaF, CT, or surgery. Accordingly, results are predictably heterogeneous. For example, Pascu et al. report per segment

sensitivity for disease as low as 38% for MR while, conversely, the figure for Potthaus was 97.5% (121,124).

An answer may be provided by an ongoing multicenter, non-randomised, single-arm, prospective comparison study of SBUS and MRE in patients with newly diagnosed or established CD (the latter with suspected relapse): the METRIC study (ISRCTN03982913) (125). Recruitment is complete (334 patients across 8 UK centers). The study will derive per patient and per segmental sensitivity and specificity for both disease and activity using a consensus panel reference standard after 6 months follow-up (126).

In conclusion, the diagnosis and follow-up of CD necessitates accurate assessment of disease presence, site, extent, activity and complications. Various diagnostic tests are available of which SB US and MRE are particularly attractive given they avoid ionizing radiation. Literature detailing diagnostic accuracy and clinical utility is expanding rapidly but large multisite study data remains elusive. Clinical practice is thus driven currently by expert consensus statements such as that produced jointly by ECCO and ESGAR (14). This recommends both MRE and USS as first line tests for management of CD but emphasise local expertise and resource availability in differing healthcare systems. Furthermore, they emphasize the need for future high quality research to address clinical uncertainty. This research should not only define the current role of imaging in clinical practice currently, but also examine future potential roles for activity assessment, therapeutic triage, follow up, and the potential to use novel imaging biomarkers as surrogate endpoints in therapeutic trials.

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Legends

Table 1. MRE protocol outlining (recommended) minimum and optional MRI sequences for both 1.5T and 3T scanners

Table 2: Summary of studies in which both SBUS and MRE have been performed on patients to assess diagnostic performance (120–124)

Figure 1: Active multifocal jejunal (J) and ileal (I) Crohn's disease. Parts A,D-axial T2 weighted images demonstrating mural thickening and increased T2 signal in a jejunal (J) and ileal (I) loop. Parts B, E-axial fat saturated T1 weighted images after IV gadolinium injection demonstrates a layered contrast enhancement pattern in both bowel loops. Parts C, F axial- diffusion weighted images (B1000) shows hyperintensity in the same loops. Part G- ADC map shows restricted diffusion in the ileal (I) loop. Note the adjacent fluid collection (c) in parts D-G

Figure 2: Active terminal ileal CD with phlegmon and small abscess

Part A-axial T2 weighted image. Part B axial contrast enhanced image. Part C axial diffusion weighted image (B1000). The inflamed ileum (arrow) is thickened with increased mural T2 signal, hyper enhancement and restricted diffusion. The abscess (red circle) demonstrates ring enhancement (part B).

Figure 3: Penetrating CD with fistula involving multiple loops in a 'starfish' pattern. Part A-coronal T2 HASTE. Part B coronal fat saturated T2 HASTE. Part C coronal post contrast T1, with magnified view (part D). A small collection (arrow) is seen at the epicentre of the fistula which is involving the terminal ileum (TI), distal ileum (DI), sigmoid colon (SC) and bladder dome (B). Loculated ascites in the left iliac fossa is also noted (*).

Figure 4: MRI and ultrasound images of a histologically proven mixed active/fibrotic stricture (arrow) causing upstream bowel dilatation (*). Part A-axial TRUFISP image. The stricture demonstrates relatively low signal intensity mural thickening. Part B-axial post contrast T1 VIBE. The stricture demonstrates homogenous contrast enhancement. Part C-axial diffusion weighted image (b1000) demonstrates mildly increased mural signal in the stricture. Part D-corresponding ultrasound images demonstrates well-defined mural thickening. Part E -Doppler imaging demonstrates some increased Doppler flow.

Figure 5: MRI images demonstrating treatment response in an inflamed ileal loop. Part A-coronal fat saturated T2 HASTE image before treatment with anti TNF alpha therapy. The inflamed ileal loop (arrows) demonstrates mural thickening and moderately increased mural signal. Part B coronal fat saturated T2 HASTE image after 6 months of treatment. The ileal loop (arrows) demonstrates a reduction in mural thickening and mural signal indicating a reduction in inflammatory activity, consistent with treatment response

Figure 6: Ultrasound image demonstrating normal small bowel with 5-layer pattern (an inner hyperechoic layer represents the interface between the mucosa and the bowel lumen; a second hypoechoic layer represents the deep mucosa; a third hyperechoic layer, the submucosa; a fourth hypoechoic layer the muscularis propria; and the final outer hyperechoic layer the serosa and the serosal fat).

Figure 7: Ultrasound images of active small bowel CD: Part A demonstrates mural thickening with an ill-defined echogenic and thickened submucosa (*). The mucosa is also subtly thickened (arrow). The mesenteric fat is hyperexpanded and stratified. Part B demonstrates focally increased Doppler flow

Figure 8: Serial ultrasound images monitoring penetrating active CD in a patient in the second-trimester of pregnancy. Part A, demonstrates active terminal ileal (TI) disease with a large complex superficial collection (thin arrow). Parts B and C demonstrate a reduction in size of the superficial collection following superficial drainage, anti-biotic and immunosuppressive treatment. However an ileo-colic fistula is now visible (short arrow in part C).

Table 1

<p>Minimum (recommended)</p>	<p>Coronal true FISP Buscopan 20mg IV Axial and Coronal non Fat Sat HASTE Coronal Fat Sat HASTE Coronal pre and post gadolinium T1 (60-70sec)</p>
<p>Optional</p>	<p>Axial Diffusion weighted imaging (DWI) - b values 50 and 600 (may extend up to 1000) Axial True FISP Axial Fat Sat HASTE Axial post gadolinium T1 True FISP dynamic Motility</p>

Table 1. MRE protocol outlining (recommended) minimum and optional MRI sequences for both 1.5T and 3T scanners

Table 2

Study	No. of patients	Presence/Activity	Analysis - Per Patient/Segmental	Reference standard	SBUS Sens/Spec	MRE Sens/Spec
Miao	30	Activity	Patient	Ileocolonoscopy, BaF, Surgery	87%, 100%	87%, 71%
Pascu	37	Presence	Segment	Ileocolonoscopy	74%, 97%	38%, 90%
Martinez	30	Presence	Segment	Ileocolonoscopy, BaF, CT, Surgery	91%, 98%	83%, 97%
Ziech	28 (23 IBD)	Presence	Patient	Ileocolonoscopy	55%, 100%	57%, 75-100%
Potthast	46	Presence	Segment	None, Barium Enteroclysis, ileocolonoscopy, surgery	76%, 75%	97.5%, 100%

Table 2: Summary of studies in which both SBUS and MRE have been performed on patients to assess diagnostic performance (118–122)