OPEN ACCESS

Assessment of Crohn's disease-associated small bowel strictures and fibrosis on cross-sectional imaging: a systematic review

Dominik Bettenworth,[1] Arne Bokemeyer,[1] Mark Baker,[2] Ren Mao,[3,4] Claire E Parker,[5] Tran Nguyen,[5] Christopher Ma,[5,6] Julián Panés,[7] Jordi Rimola,[8] Joel G Fletcher,[9] Vipul Jairath,[5,10,11] Brian G Feagan,[5,10,11] Florian Rieder,[4,12] on behalf of the Stenosis Therapy and Anti-Fibrotic Research (STAR) Consortium.

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2018-318081).

For numbered affiliations see end of article.

Correspondence to
Professor Dominik Bettenworth, Department of Medicine B, Gastroenterology and Hepatology, University Hospital of Münster, Münster D-48149, Germany;
dominik.bettenworth@ukmuenster.de

Received 9 December 2018
Revised 18 March 2019
Accepted 19 March 2019
Published Online First
3 April 2019

ABSTRACT

Patients with Crohn's disease commonly develop ileal and less commonly colonic strictures, containing various degrees of inflammation and fibrosis. While predominantly inflammatory strictures may benefit from a medical anti-inflammatory treatment, predominantly fibrotic strictures currently require endoscopic balloon dilation or surgery. Therefore, differentiation of the main components of a stricturing lesion is key for defining the therapeutic management. The role of endoscopy to diagnose the nature of strictures is limited by the superficial inspection of the intestinal mucosa, the lack of depth of mucosal biopsies and by the risk of sampling error due to a heterogeneous distribution of inflammation and fibrosis within a stricturing lesion. These limitations may be in part overcome by cross-sectional imaging techniques such as ultrasound, CT and MRI, allowing for a full thickness evaluation of the bowel wall and associated abnormalities. This systematic literature review provides a comprehensive summary of currently used radiologic definitions of strictures. It discusses, by assessing only manuscripts with histopathology as a gold standard, the accuracy for diagnosis of the respective modalities as well as their capability to characterise strictures in terms of inflammation and fibrosis. Definitions for strictures on cross-sectional imaging are heterogeneous; however, accuracy for stricture diagnosis is very high. Although conventional cross-sectional imaging techniques have been reported to distinguish inflammation from fibrosis and grade their severity, they are not sufficiently accurate for use in routine clinical practice. Finally, we present recent consensus recommendations and highlight experimental techniques that may overcome the limitations of current technologies.

Check for updates

To cite: Bettenworth D, Bokemeyer A, Baker M, *et al*. *Gut* 2019;**68**:1115–1126.

INTRODUCTION

The development of strictures in patients with Crohn's disease (CD) is common. In population-based studies, up to 5% of patients initially present with a stricturing phenotype and 15% develop stricturing disease within 10 years.[1] In patients with paediatric CD, as much as 20% of patients are found to have strictures at diagnosis, increasing to 40% of patients by 10 years.[2] A stricture in patients with CD is commonly accompanied by obstructive symptoms[3] that require intensified medical therapy, interventional endoscopy or surgery.[4 5] Conversely, a substantial proportion of up to 20% of patients with small bowel stricturing CD are asymptomatic.[6 7] Escalated anti-inflammatory treatment may alleviate a stricture with a predominantly inflammatory component. Corticosteroids as well as anti-tumour necrosis factor (TNF) therapy frequently result in a temporary improvement of obstructive symptoms, but still 40% of patients require dilation therapy or surgery within 12 months.[8 9] Escalation to combined anti-TNF and immunomodulator therapy after endoscopic dilation may further decrease the need for repetitive dilation.[10] In contrast, strictures that are predominantly fibrotic are currently treated by endoscopic balloon dilation, strictureplasty or segmental resection.[5] Therapeutic agents primarily targeting intestinal fibrosis are not available to date.[11]

Clinical studies evaluating efficacy of antifibrotic drug candidates in stricturing CD will face specific challenges. First, in contrast to luminal inflammation, in which severity of endoscopic lesions and severity of transmural changes assessed by cross-sectional imaging closely correlate,[12] in stricturing lesions, routine endoscopic examination of the mucosa is insufficient for an accurate diagnosis. Biopsies are only superficial and not all strictures are accessible by endoscopy. Additionally, endoscopic examination commonly misses simple and complex fistulas associated with small bowel strictures, and it is desirable to exclude these patients from antifibrotic therapeutic trials. Antifibrotic therapies may at least in theory have opposite effects on strictures and penetrating disease. Second, characterisation of detected strictures is key to selecting patients with predominant fibrotic strictures for inclusion in studies of antifibrotic drugs. Third, accurate endpoints for clinical studies in the field of CD have yet to be identified and validated.

Cross-sectional imaging techniques such as CT, MRI and ultrasound (US) are likely to provide the most tractable solution to these challenges because they allow sophisticated assessment of the entire intestinal wall.[13] This systematic review will discuss the definitions used for small bowel CD-associated strictures for CT, MRI and US. Furthermore, considering only studies with histopathology as gold standard, diagnostic accuracy of these three

imaging modalities for detection of strictures will be assessed. Finally, we will evaluate the ability to differentiate fibrotic from inflammatory strictures and limitations of the available literature as well as recommendations on imaging as an endpoint in clinical studies on stricturing CD.

METHODS

A systematic review of the literature was performed. The search strategy as well as inclusion and exclusion criteria are included in the online supplementary material.

RESULTS

Definitions of CD-associated strictures on cross-sectional imaging

In the retrieved US, CT and MRI studies evaluating the detection of CD-associated strictures, the core items for definitions used were (1) luminal narrowing, (2) wall thickness and (3) prestenotic dilation. To provide a systematic overview of the available literature we included studies that provided definitions for strictures on cross-sectional imaging only if full thickness histopathology was available for all patients in the evaluated manuscript. In total, for stricture definitions we identified 9 studies evaluating different US modalities,[14–22] 4 assessed CT[23–26] and 12 studies evaluated MRI (a Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram is depicted in online supplementary figure 1).[15 22 26–35] Detailed information about the technical approach employed (eg, performance of CT and MR enterography [MRE] vs CT and MR enteroclysis) and an overview of the items and their ranges used to define a CD-associated stricture on US, CT or MRI are depicted in table 1.

A description of the specific modalities used, number of assessed core items (one, two or all three), applied definitions in individual studies and information on how many of the three items were required for stricture diagnosis is provided in the online supplementary material. Representative US, CT and MR scans depicting CD-associated small bowel strictures are presented in figure 1.

Taken together, available literature demonstrates substantial heterogeneity in definitions of stricturing small bowel CD (figure 2).

Diagnostic accuracy of cross-sectional imaging for CD-associated strictures

We next assessed the accuracy of different cross-sectional imaging techniques for CD stricture detection and if the applied stricture definitions impacted on the sensitivity and specificity estimates achieved. We, again, only used studies with histopathology as a reference standard for all included patients. This is of particular interest, since no validated gold standard is available. An overview of observed accuracy rates for stricture diagnosis by US, CT or MRI is depicted in table 2.

Conventional transabdominal ultrasonography (TUS) estimates of sensitivity for stricture diagnosis ranged from 80% to 100%[16 18] with specificity rates of 63%–75%.[16 18] Application of small intestinal contrast ultrasonography (SICUS) demonstrated increased sensitivity rates of 88%–98%[15 17 18] with specificity rates ranging from 88% to 100%.[15 18] In the one study that applied CT enterography (CTE) sensitivity and specificity estimates were reported to be both 100%.[25] CT enteroclysis, in which the luminal contrast is delivered through a small bowel tube, was tested in one study and had a sensitivity of 92%[24] and specificity of 39% that was only reported in one study.[24] With regard to MRE, the sensitivity for stricture detection ranged from 75% to 100%[15 28 34] with estimates of specificity between 91% and 96%.[15 28 34] No study evaluating the accuracy for MR enteroclysis was identified that met the inclusion criteria.

We analysed if studies applying a stricture definition comprising all three items (luminal narrowing, wall thickening and prestenotic dilation) demonstrated different accuracy estimates than studies where stricture definitions were based on one or two items alone. For US, a study requiring one item only reached a sensitivity of 80% and specificity of 75%.[18] All three SICUS studies required one item for stricture definition and demonstrated sensitivity estimates of 88%–98% and specificity of 88%–100%.[15 17 18] One CT study used one item for stricture diagnosis and received a sensitivity of 92% and specificity of 39%.[24] Another CT study requiring two items achieved 100% sensitivity and 100% specificity.[25] Of those four MR studies meeting the inclusion criteria and reporting accuracy measures, no study did provide an exact stricture definition.[15 26 28 34]

Assessment of imaging techniques for separation of inflammation and fibrosis within a stricture

A summary of all studies that analysed cross-sectional imaging to characterise the degree of inflammation and fibrosis in CD-associated strictures is provided in table 3.

Accuracy of US to characterise CD-associated strictures

Six studies assessed US to characterise CD-associated strictures including a total of 111 patients.[14 16 20–22 36] One of six studies used conventional TUS,[16] while two other studies used contrast-enhanced US (CEUS)[22 36] of which one additionally used Doppler US[36] and the other three studies used US elastography[14 20 21] (online supplementary table 1). Five of six studies assessed the accuracy of US to differentiate fibrosis and inflammation in CD-associated strictures.[14 16 20 22 36] Of these five studies, one study used TUS,[16] two studies used CEUS[22 36] and two used US elastography.[14 20]

Accuracy of CEUS to characterise CD-associated strictures

Maconi *et al* employed TUS in 43 patients with CD with stricturing disease phenotype.[16] By evaluating the echo pattern, the investigators demonstrated a successful general stricture differentiation in inflammatory, fibrotic or mixed types. More specifically, the echo pattern identified a moderate to severe or intermediate degree of fibrosis in the submucosa and in the muscularis mucosae with a sensitivity of 100% and a specificity of 63%. The positive predictive value was 72% while the negative predictive value was 100%.[16] Ripollés *et al* applied CEUS and duplex US in 25 patients with CD strictures.[36] The authors found that by applying a dichotomised pathology score (inflammatory vs fibrotic), 82% of strictures were correctly classified by US (kappa=0.63). Furthermore, a good correlation between the sonographic and pathology scores accounting for both inflammation (Spearman's, r=0.53) and fibrosis (Spearman's, r=0.50) was demonstrated.[36] Wilkens *et al* performed CEUS in 18 patients with CD and in contrast to previous studies, the authors did not find a correlation between the severity of inflammation and fibrosis assessed by histopathology (p=0.45 for inflammation and p=0.19 for fibrosis). For histological assessment, inflammation was scored using the stepwise grading systems of Borley *et al*[37] and Chiorean *et al*[24] and fibrosis was graded assessing collagen deposits on a five-grade scale.[22] The bowel thickness correlated well with the histological degree

Table 1 Overview of radiographic criteria used in currently available cross-sectional imaging studies to detect fibrostenosis in patients with stricturing Crohn's disease. All studies use histopathology as a reference standard

			Radiographic criteria assessed for stricture detection			
	Study ID	Radiographic modality	Prestenotic dilation (mm)	Luminal narrowing (mm)	Wall thickening (mm)	Criteria required for stricture diagnosis
Ultrasound (US)	Baumgart *et al*[14]	Ultrasound elasticity imaging	✗	✗	✔ >3 mm	Not further specified
	Kumar *et al*[15]	SICUS	✗	✗	✔	Wall thickening
	Maconi *et al*[16]	TUS	✔ >25 mm	✔ Markedly narrowed lumen	✔ >4 mm	All criteria required
	Onali *et al*[17]	SICUS	✗	✔ <10 mm	✗	Luminal narrowing
	Pallotta *et al*[18]	SICUS	✔ >25 mm	✔ <10 mm	✗	Luminal narrowing
	Ripollés *et al*[19]	CEUS	✔	✗	✔	Not further specified
	Serra *et al*[20]	CEUS	✔	✔	✔ >4 mm	All criteria required
	Stidham *et al*[21]	US elasticity	Not indicated	Not indicated	Not indicated	Not further specified
	Wilkens *et al*[22]	CEUS	✗	✗	✔	Not further specified
CT	Adler *et al*[23]	CT enterography	✔	✔	✔ ≥3 mm	Not further specified
	Chiorean *et al*[24]	CT enteroclysis	✔	✔ Luminal narrowing ≤50%	✔	Luminal narrowing
	Pellino *et al*[26]	PET/CT	✗	✗	✔ >3 mm	Not further specified
	Vogel *et al*[25]	CT enterography	✔ >3 cm	✔ <10 mm	✔ >5 mm	Luminal narrowing and wall thickening
MRI	Kumar *et al*[15]	MR enterography	✔	✗	✔	Not further specified
	Li *et al*[27]	MT-MRI	Not indicated	Not indicated	Not indicated	Not further specified
	Pellino *et al*[26]	PET/MR	✗	✗	✔ >3 mm	Not further specified
	Pous-Serrano *et al*[28]	MR enterography	Not indicated	Not indicated	Not indicated	Not further specified
	Punwani *et al*[29]	MR enterography	✗	✗	✔	Not further specified
	Rimola *et al*[30]	MR enterography	✔	✔ Luminal narrowing ≤50%	✔	Luminal narrowing ≤50% and prestenotic dilation
	Sinha *et al*[34]	MR enterography	✗	✗	✔ >3 mm	Not further specified
	Steward *et al*[35]	MR enterography	✗	✗	✔	Not further specified
	Tielbeek *et al*[31]	MR enterography diffusion-weighted MRI	✗	✗	✔	Not further specified
	Wagner *et al*[32]	Diffusion-weighted MRI	✔	✗	✔	Not further specified
	Wilkens *et al*[22]	Dynamic contrast-enhanced MR enterography	✗	✗	✔	Not further specified
	Zappa *et al*[33]	MR enterography	✔ >1.5 of normal loop	✗	✔	Not further specified

CEUS, contrast-enhanced ultrasound; MT, magnetisation transfer; PET, positron emission tomography; SICUS, small intestinal contrast ultrasonography; TUS, transabdominal ultrasonography; US, ultrasound.

of inflammation (p=0.001) and fibrosis (p=0.005). An accurate differentiation between fibrosis and inflammation was not possible.

Accuracy of US elastography to characterise CD-associated strictures

Baumgart *et al* applied US elastography with strain ratio measurements and were able to successfully differentiate fibrotic from non-fibrotic tissue in 10 patients with CD with strictures.[14] The strain ratio was significantly higher in unaffected than in affected bowel segments (p<0.001).[14] In contrast to these findings, Serra *et al* evaluated US elastography in 26 patients with CD with symptomatic strictures using an ordinal grading system of fibrosis and inflammation and found no significant correlation between the mean strain ratio and the degree for either of these outcomes (p=0.88 and p=0.53, respectively) even when the analysis was performed by dichotomising the patients into high and low-score groups (fibrosis score p=0.89; inflammatory score p=0.57).[20]

Accuracy of CT to characterise CD-associated strictures

Three studies including a total of 95 patients analysed the accuracy of CT for characterising CD-associated strictures.[23 24 26] Two of three studies used contrast-enhanced CT (CE-CT) imaging.[23 24] One out of three studies used positron emission tomography

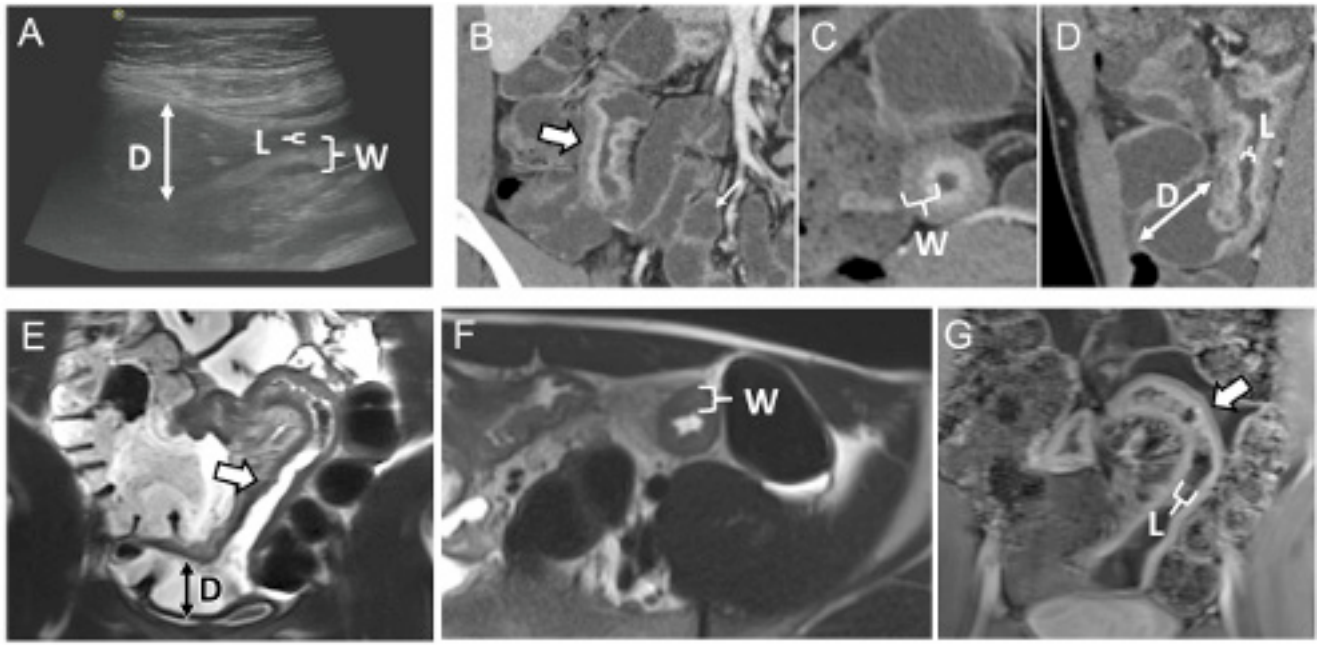

Figure 1 Transabdominal ultrasonography, CT and MR enterography demonstrating a distal ileal stricture. (A) Ultrasound image depicting the three core items for stricture diagnosis wall thickness (W, *bracket*), luminal narrowing (L, *bracket*) and prestenotic dilation (D, *double arrow*). (B–D) CT enterography demonstrating a distal ileal stricture with imaging findings of active inflammation and partial small bowel obstruction. (B) Coronal image demonstrating a distal ileal stricture with wall thickening, luminal narrowing and mural stratification and hyperenhancement (*large white arrow*). Active inflammatory Crohn's disease is also present in the terminal ileum (arrowhead), as is a short segment jejunal stricture (*small white arrow*). (C) Enlarged axial image through distal ileal stricture better demonstrates luminal narrowing and increased wall thickness (W, *bracket*). (D) Sagittal image through distal ileal stricture shows prestenotic bowel dilation (D, *arrows*) and luminal narrowing within the stricture (L, *bracket*). (E–G) MR enterography demonstrating a distal ileal stricture with imaging findings of active inflammation. (E) Coronal half-Fourier single-shot fast spin echo (HASTE) shows ileal stricture with wall thickening and luminal narrowing (large white *arrow*) with upstream dilation (D, *arrows*). (F) Axial HASTE shows cross section through the stricture demonstrating increased wall thickness and how wall thickening is measured (W, *white bracket*). (G) Postcontrast axial 3D volumetric interpolated breath hold examination (VIBE) shows wall thickening and mural stratification and hyperenhancement, indicating inflammation with luminal narrowing (L, *bracket*). The three core items for stricture diagnosis are increased wall thickness, luminal narrowing and prestenotic dilation. CTE, CT enterography; MRE, MR enterography.

(PET)-CT in addition to regular CTE images (online supplementary table 1).[26]

Accuracy of CE-CT to characterise CD-associated strictures

All studies analysed the accuracy of CT to categorise CD-associated strictures in predominantly inflammatory and predominantly fibrotic subtypes.[23 24 26] Adler *et al*[23] evaluated CTE in 22 patients using a composite score which comprised mural enhancement, mesenteric vascularisation, mesenteric fat stranding and bowel wall thickening. As reference standard, the authors used the ordinal Chiorean scoring system[23 24] and found that strictures classified as inflammatory by the CT score were indeed more inflamed at histology (p=0.002) than those classified as being fibrotic; however, strictures with imaging findings of inflammation also had a higher degree of fibrosis than those without imaging findings of inflammation (p=0.0002) and strictures classified as inactive on CT imaging were not associated with fibrosis in the histological analysis (p value not determined).[23] The study by Chiorean *et al* included 44 patients with CD with strictures. The authors applied a four-grade scale to assess inflammation (none, mild, moderate and severe) and a three-grade scale to determine fibrosis (none, mild/moderate and severe). Parameters assessed included contrast enhancement, mural stratification, wall thickness, comb sign, lymphadenopathy, luminal stenosis and prestenotic dilation. Employing histopathology as a reference standard, the mentioned scoring system accurately detected inflammation and fibrosis with a sensitivity of 77% and 79%, respectively.[24]

Accuracy of PET with CT to characterise CD-associated strictures

A single study assessed the value of combining PET with MRE and CT. Pellino *et al* compared PET/MRE with PET/CT in 35 patients. Histological evaluation was done using a self-developed simple grading system. The investigator reported areas under the curve (AUC) of 0.51 and 0.77 for PET/MRE, respectively.[26]

Accuracy of MRI to characterise CD-associated strictures

A total of eight studies that included 226 patients were identified which evaluated MRI for stricture characterisation.[22 26 27 29–33] Of these, seven out of eight studies used contrast-enhanced MRI (CE-MRI) approaches for stricture differentiation,[22 27 29–33] two studies additionally used diffusion-weighted MRI (DW-MRI),[31 38] one additionally used delayed enhancement MRI[30] and one used dynamic CE-MRI.[22] Furthermore, one out of eight studies evaluated PET-MRE[26] (online supplementary table 1). All eight studies assessed the accuracy of MRI to differentiate fibrosis and inflammation in CD-associated strictures, while seven studies used MRE[22 27 29–33] and one study evaluated PET-MRE.[26]

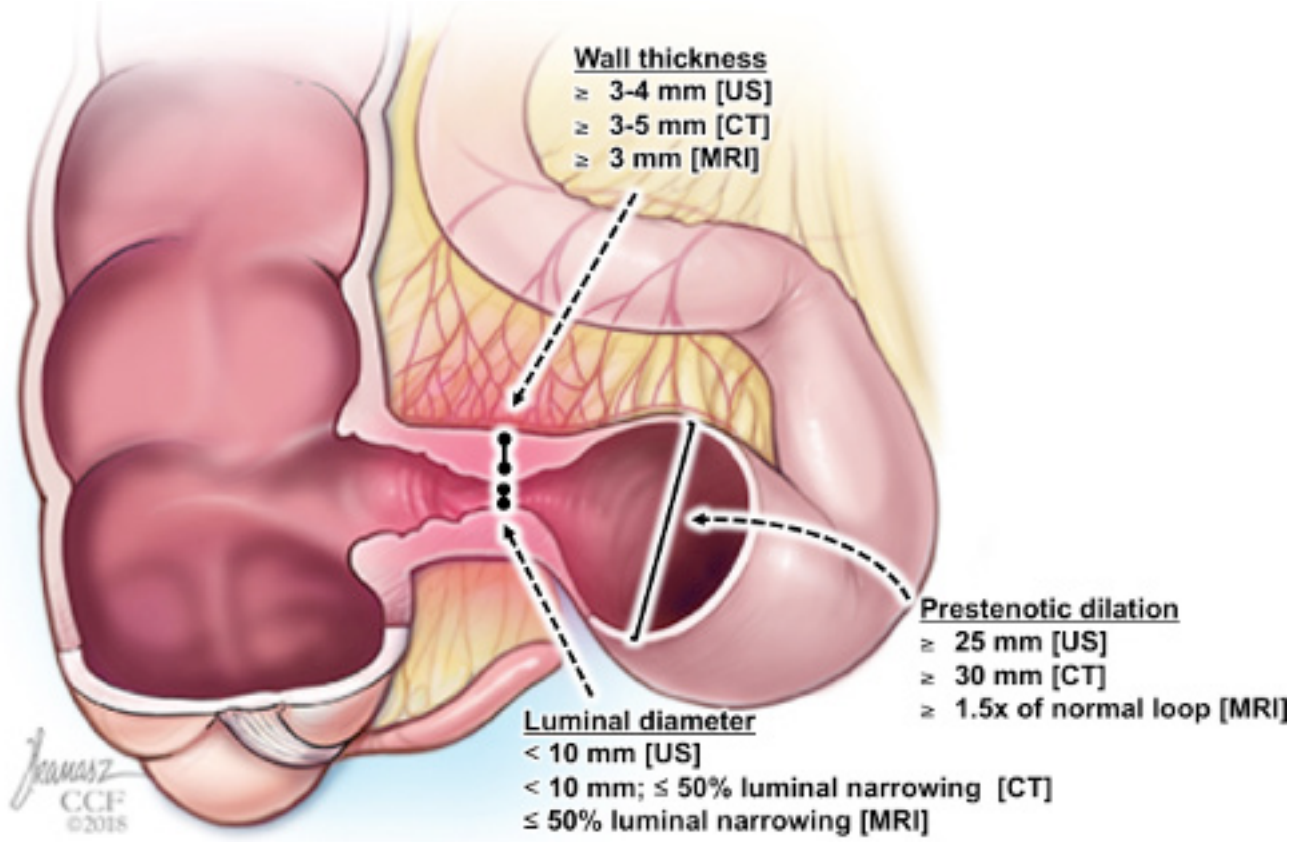

Figure 2 Proposed ranges for key items used for stricture detection in cross-sectional imaging modalities. US, ultrasound.

Accuracy of MRE to characterise CD-associated strictures

Punwani *et al* prospectively evaluated MRE in 18 patients; however, this study did not specify the number of strictures evaluated. MRE-defined fibrosis was dichotomised as being absent or present, while inflammation was graded using a category scoring system.[29] In the histopathological analysis inflammation was graded using the Borley[37] scoring system and fibrosis was assessed using the Chiorean score.[24 29] Histological inflammation positively correlated with mural thickness and intramural signal intensity relative to cerebrospinal fluid on T2-weighted fat-saturated images ($p<0.001$ and $p=0.003$, respectively) and fibrosis was more commonly associated with layered enhancement (75%) while homogenous mural enhancement was commonly absent in predominant fibrotic stenosis (92%).[29] Zappa *et al* retrospectively evaluated CD-associated strictures in 44 patients using MRE (reference standard was histopathology with an ordinal grading system for inflammation and fibrosis).[33] The histopathological inflammatory score was highly correlated with the histopathological fibrosis score ($r=0.63$; $p=0.0001$). Wall thickness ($p<0.0001$), degree of wall enhancement on delayed phase ($p<0.0001$), pattern of enhancement ($p<0.02$), T2W relative mural hyperintensity ($p<0.0001$), comb sign ($p=0.004$), presence of a fistula ($p<0.0001$) and abscesses ($p=0.049$) correlated with inflammation. Wall thickness on T2W and T1W ($p=0.0018$ and $p=0.004$), T2W mural hyperintensity ($p=0.026$), comb sign ($p=0.03$) and presence of fistulas ($p=0.001$) correlated with fibrosis.[33] Tielbeek *et al* evaluated MRE combined with DW-MRI in 20 patients.[31] Mural thickness, T1 ratio, T2 ratio, maximum contrast enhancement and slope of increase after contrast injection correlated with the histological score of inflammation ($r=0.63$, 0.39, 0.49, 0.41 and 0.53, respectively; all $p<0.05$). The same items and the apparent diffusion coefficient (ADC) correlated with the ordinal three-grade system for fibrosis severity (all $p<0.05$).[31]

Accuracy of DW, dynamic or delayed enhancement MRE to characterise CD-associated strictures

Wagner *et al* assessed MRE with DW imaging in 27 patients.[32] In addition to conventional items, they evaluated the MR Index of Activity (MaRIA),[39] a partially validated index that assesses bowel wall thickness, degree of contrast enhancement, presence of oedema and presence of ulcers. The degree of fibrosis and inflammation on histopathology was graded using a self-developed system. Although an optimal combination of the MaRIA score[39] and the ADC had a poor sensitivity to differentiate high from low-grade inflammation (47%), specificity was high (92%). A combination of the ADC and the MaRIA[39] wall thickness item had a sensitivity of 65% and a specificity of 83% to correctly differentiate high-grade from low-grade inflammation. When assessing the bowel wall thickness and differentiating fibrosis from muscular hypertrophy a sensitivity of 61% and a specificity of 89% were achieved.[38]

In contrast to these studies, Wilkens *et al* found that dynamic contrast-enhanced MRE (and US) could not accurately differentiate fibrosis and inflammation in 18 patients ($p=0.54$ for inflammation and $p=0.05$ for fibrosis).[22] Histopathology used an ordinal scoring system for fibrosis and inflammation assessment. Bowel wall thickness using conventional MR images correlated with histological inflammation ($p=0.047$), but not fibrosis ($p=0.16$).[22]

Rimola *et al* evaluated several novel MR items including the signal intensity of the submucosa at 70 s and 7 min after gadolinium injection (delayed enhancement) in a cohort of

Table 2 Overview of currently available studies assessing the sensitivity and specificity of cross-sectional imaging for the detection of Crohn's disease-associated strictures that use histopathology as a reference standard

	Study ID	Study design	Patients with stricture (n)	Reference standard or comparator	Radiographic modality	Sensitivity for stricture diagnosis	Specificity for stricture diagnosis
Ultrasound (US)	Maconi *et al*[16]	Prospective cohort ► Mean age (years): 40 ► Female (%): 42	43	Histopathology (resection)	TUS	100%	63%
	Kumar *et al*[15]	Retrospective cohort ► Mean age (years): 28 ► Female (%): 52	8	Histopathology (resection)	SICUS, with power Doppler	SICUS 88%	SICUS 88%
	Onali *et al*[17]	Prospective case–control ► Mean age (years): 41 ► Female (%): 46	13	Histopathology (resection)	SICUS	SICUS 92%	SICUS 0%
	Pallotta *et al*[18]	Prospective cohort ► Mean age (years): 38 ► Female (%): 43	40	Histopathology (resection)	SICUS TUS	SICUS 97.5% TUS 80%	SICUS 100% TUS 75%
CT	Chiorean *et al*[24]	Retrospective cohort ► Median age (years): 35 ► Female (%): 61	31	Histopathology (resection)	CT enteroclysis	92.3%	38.9%
	Pellino *et al*[26]	Prospective cohort ► Median age (years): 39 ► Female (%): 60	31	Histopathology (resection)	Hybrid positron emission tomography/CT enterography	85%	NR
	Vogel *et al*[25]	Retrospective cohort ► Mean age (years): 39 ► Female (%): 64	18	Histopathology (resection)	CT enterography	100%	100%
MRI	Kumar *et al*[15]	Retrospective cohort ► Mean age (years): 31 ► Female (%): 35	8	Histopathology (resection)	MR enterography	100%	91%
	Pellino *et al*[25]	Prospective cohort ► Median age (years): 39 ► Female (%): 60	31	Histopathology (resection)	Hybrid positron emission tomography/MR enterography	85%	NR
	Pous-Serrano *et al*[28]	Prospective cohort ► Age (years): not provided ► Female (%): 42	27	Histopathology (resection)	MR enterography	75%	96%
	Sinha *et al*[34]	Prospective cohort ► Median age (years): 43 ► Female (%): 59	49	Histopathology (resection)	HR MR enterography	86%	95%

HR, high resolution; NR, not reported; SICUS, small intestinal contrast ultrasonography; TUS, transabdominal ultrasonography.

41 patients.[30] Histological examination used ordinal scores. The degree of fibrosis correlated well with the percentage of enhancement gain ($p<0.01$), the pattern of enhancement at 7 min ($p<0.01$) and the presence of stenosis ($p=0.05$). Delayed enhancement was able to discriminate mild-moderate from severe fibrosis with a sensitivity of 94% and a specificity of 89%.[30] Furthermore, moderate to severe inflammation was accurately differentiated from low-grade inflammation within strictures using hyperintensity on T2-weighted images ($p=0.02$), mural enhancement ($p=0.03$), ulcerations ($p=0.01$) and blurred margins ($p=0.05$).[30]

Accuracy of PET with MRE to characterise CD-associated strictures

In the previously described study by Pellino *et al*, CD-associated strictures in 31 patients were characterised by PET-CTE and PET-MRE.[26] PET-MRE successfully differentiated fibrotic from non-fibrotic strictures with a sensitivity of 66.7% and specificity of 88%, respectively, and an AUC of 0.77. Histology was assessed using ordinal grading systems.[26]

Accuracy of magnetisation transfer MRI to characterise CD-associated strictures

Magnetisation transfer MRI (MT-MRI) determines the fraction of collagen which is a main component of intestinal strictures.[40] After successful preclinical animal studies,[41–43] Li *et al* assessed the operating properties of MT-MRI for fibrosis detection within small bowel strictures in comparison to DW-MRI and MRE.[27] Imaging was performed in 31 patients with CD who were scheduled for surgery and the bowel wall MT ratio normalised to the skeletal muscle, the ADC and the percentage of enhancement gain were assessed and compared with histological scoring systems for fibrosis and inflammation. Normalised MT ratios strongly correlated with fibrosis ($r=0.77$; $p=0.000$), but not with inflammation ($r=-0.03$; $p=0.740$). Furthermore, the normalised MT ratios differed between non-fibrotic, mild, moderate and severe fibrotic alterations ($p=0.001$) and MT-MRI had an AUC of 0.92 to differentiate moderate to severe fibrosis from non-fibrosis and mild fibrosis. In comparison, the ADC determined by DW-MRI had a lower AUC of 0.75 and the percentage of enhancement determined by MRE had an even lower AUC of 0.59.[27]

Quality evaluation of included studies

To assess the quality of individual studies with regard to the risk of bias and applicability, we followed the suggestions for Quality Assessment of Diagnostic Accuracy Studies-2.[44] The results are depicted in online supplementary table 2.

DISCUSSION

While diagnostic criteria for CD-associated strictures are highly heterogeneous, accuracy of diagnosis of strictures on cross-sectional imaging is high. Differentiation of inflammation from fibrosis by currently available cross-sectional imaging techniques remains challenging.

Nearly all of the described studies assessed the three core imaging features of prestenotic dilation, wall thickening and

Table 3 Overview of currently available cross-sectional imaging studies assessing the inflammatory and fibrotic characteristics of Crohn's disease strictures that use histopathology as reference standard

							Differentiation of fibrosis and inflammation in CD strictures	
	Study ID	Study design	Patients with strictures (n)	Reference standard or comparator	Cross-sectional modality	Cross-sectional descriptors for stricture characterisation	Details to applied differentiation between fibrosis and inflammation	Details to sensitivity/specificity rates; area under the curve (AUC) analysis
Ultrasound (US)	Baumgart *et al*[14]	Prospective cohort	10	Histopathology (resection)	Ultrasound elasticity imaging (UEI)	► Strain ratio measurement	► Successful differentiation of fibrotic from non-fibrotic tissue	► Strain ratio was significantly higher in unaffected than in affected segments (p<0.001)
	Maconi *et al*[16]	Prospective cohort	43	Histopathology (resection)	Ultrasound	► Evaluation of echo pattern: hypoechoic/stratified or mixed echo pattern	► Successful general differentiation in inflammatory, mixed and fibrotic strictures	► Echo pattern (mixed/stratified vs hypoechoic) was able to identify a moderate-severe or intermediate degree of fibrosis in the submucosa and the muscularis mucosae with a sensitivity of 100%, a specificity of 63%, a positive predictive value of 72% and a negative predictive value of 100%
	Ripollés *et al* [19]	Prospective cohort	25	Histopathology (resection)	CEUS Duplex ultrasound	► Assessment of wall thickness; inflammatory markers: loss of stratification, transmural complications, lymphadenopathy, US Doppler signal grade 2–3, quantitative CE >46%; fibrostenosis: stenosis, prestenotic dilation, US Doppler signal grade 0–1, quantitative CE <46%	► Successful general differentiation in inflammatory and fibrotic strictures	► When strictures were dichotomised (inflammatory or fibrotic), 82% of strictures were correctly classified by US (kappa=0.63) ► Sonographic and pathology scores showed a good correlation in inflammation (Spearman's, r=0.53) and fibrosis (Spearman's, r=0.5)
	Serra *et al*[20]	Prospective cohort	26	Histopathology (resection)	UEI	► Strain ratio measurement	► Unsuccessful differentiation in fibrosis and inflammation	► No correlation was found between strain ratio and fibrosis (p=0.87) ► No correlation was found between strain ratio and inflammation (p=0.53)
	Stidham *et al*[21]	Prospective cohort	7	Histopathology (resection)	UEI	► Fibrostenosis assessed by UEI strain maps and measures of strain in affected and unaffected bowel; low strain (hard tissue with limited deformation), high strain (soft, deformable tissue); mean UEI normalised strain	NR	NR
	Wilkens *et al*[22]	Prospective cohort	NR	Histopathology (resection)	CEUS (and contrast-enhanced MR enterography)	► CEUS: peak signal intensity, time to peak, area under the time-intensity curve, wash-in rate, wash-out rate, wash-in perfusion index, area under the curve during wash-in and wash-out, fall time, mean transit time	► Unsuccessful differentiation in none, mild/moderate to severe fibrosis and inflammation using CE imaging ► Successful determination of the degree of inflammation and fibrosis (none, mild/moderate to severe) using US without CE effects; however, no safe differentiation between fibrosis and inflammation	► No correlation was found between the severity of inflammation or fibrosis on histopathology and on CEUS (p=0.45 for inflammation and p=0.19 for fibrosis) ► Wall thickness assessed by US correlated with both histological inflammation (p=0.001) and fibrosis (p=0.048)
CT	Adler *et al*[23]	Retrospective cohort	22	Histopathology (resection)	CT enterography	► Composite CTE evaluation score (abnormal mucosal/mural enhancement, mesenteric hypervascularity, mesenteric inflammatory fat stranding and bowel wall thickening)	► Successful differentiation of inflammation in subgrades and successful differentiation of fibrosis in subgrades; however, no safe differentiation between fibrosis and inflammation	► Composite CTE radiologic inflammation score correlated well with the degree of inflammation (r=0.52; p=0.014) ► Composite CTE radiologic inflammation score correlated with the degree of fibrosis (r=0.48; p=0.023) ► Degree of tissue inflammation correlated best with the degree of tissue fibrosis (r=0.52; p=0.014) ► Inactive strictures on CTE score were not associated with fibrosis (p value not provided)
	Chiorean *et al*[24]	Retrospective cohort	44	Histopathology (resection)	CT enterography	► Assessment of inflammation using a four-grade scale (none, mild, moderate and severe) and of fibrosis using a three-grade scale (none, mild/moderate and severe). Considered were CE, mural stratification, wall thickness, comb sign, lymphadenopathy, luminal stenosis and prestenotic dilation	► Successful differentiation of inflammation and fibrosis in subgrades	► CT inflammation score exactly matched with pathology in 77% ► CT fibrosis score exactly matched with pathology in 79%
	Pellino *et al*[26]	Prospective cohort	29	Histopathology (resection)	PET-CT enterography (and PET-MR enterography)	► Assessment of the maximum standard value of the tracer (SUVs)	► Successful differentiation of fibrotic from non-fibrotic strictures	► AUC to differentiate fibrotic from non-fibrotic strictures 0.51 using the maximum uptake of the tracer (SUVs)

Continued

Table 3 Continued

	Study ID	Study design	Patients with strictures (n)	Reference standard or comparator	Cross-sectional modality	Cross-sectional descriptors for stricture characterisation	Differentiation of fibrosis and inflammation in CD strictures: Details to applied differentiation between fibrosis and inflammation	Differentiation of fibrosis and inflammation in CD strictures: Details to sensitivity/specificity rates; area under the curve (AUC) analysis
MRI	Li *et al*[27]	Prospective cohort	31	Histopathology (resection)	MT-MRI compared with DWI-MRI and CE-MRI T2-weighted HASTE, MT GRE, DW SE-EPI, VIBE	Assessment of the bowel wall MT ratio normalised to skeletal muscle, the ADC and the percentage of enhancement gain	► Successful differentiation of fibrotic subgrades using MT-MRI ► Successful differentiation from inflammatory and fibrotic strictures using MT-MRI ► Unsuccessful differentiation of inflammatory subgrades using MT-MRI	► Correct diagnosis of fibrosis (r=0.77; p=0.000) and detection of differences in MT ratios between none, mild, moderate and severe fibrosis (F=49.002; p=0.000) ► No correlation between MT ratios and inflammatory scores (r=−0.034; p=0.74) ► Correct differentiation of mixed fibrotic and inflammatory bowel walls compared with bowel walls with only inflammation present (p=0.001) Correct differentiation of moderate from severe fibrosis using MT ratios (AUC=0.92), followed by ADC (AUC=0.75) and percentage of enhancement gain (AUC=0.59)
	Pellino *et al*[25]	Prospective cohort	29	Histopathology (resection)	PET-MR enterography ► (and PET-CT enterography)	► Assessment of the maximum standard uptake value of the tracer (SUVs)	► Successful differentiation of fibrotic from non-fibrotic strictures	► AUC to differentiate fibrotic from non-fibrotic strictures 0.77 using the maximum uptake of the tracer (SUVs)
	Puwani 2009[29]	Prospective cohort	NR	Histopathology (resection)	MR enterography Half-Fourier RARE sequence, TrueFISP sequence, VIBE sequence, 30 and 70 s postcontrast VIBE sequence and Half-Fourier RARE sequence for specimen imaging	► Mural thickness, mural and lymph node cerebrospinal fluid signal intensity on T2-weighted fat-saturated images, contrast uptake, enhancement pattern and mesenteric signal	► Successful differentiation in different inflammation grades using a stepwise scoring system (min 0, max 12 points) ► Successful differentiation of fibrotic from non-fibrotic strictures	► Fibrosis was more commonly associated with layered enhancement (75%) and homogeneous mural enhancement was most commonly associated with the absence of fibrostenosis (92%)
	Rimola *et al*[30]	Retrospective cohort	41	Histopathology (resection)	MR enterography ► T2-weighted with and without fat saturation, T1-weighted 3D gradient echo with fat saturation sequences 70 s and 7 min after gadolinium administration	► Baseline and postcontrast wall signal intensity at 70 s and 7 min measured in VIBE images, mucosal hyperenhancement at 70 s and 7 min, pattern of enhancement, stability and progression of enhancement over time, bowel wall thickness, presence of high signal intensity on T2 (HASTE) and T2 with fat saturation, ulcerations, comb sign, blurred margins and presence of enlarged lymph nodes	► Successful differentiation in low from moderate/severe inflammation ► Successful differentiation of mild-moderate from severe fibrosis	► Inflammation was associated with hypersignal on T2 (p=0.02), mucosal enhancement (p=0.03), ulcerations (p=0.01) and blurred margins (p=0.05) ► Fibrosis was associated with percentage of enhancement gain (p<0.01), pattern of enhancement at 7 min (0<0.01) and the presence of stenosis (p=0.05). Using percentage of enhancement gain, MRI discriminated mild-moderate and severe fibrosis with an AUC of 0.93, a sensitivity of 94% and a specificity of 89%
	Tielbeek 2013[31]	Prospective cohort	20	Histopathology (resection)	MR enterography with diffusion-weighted imaging (DWI) ► T2W SSFSE, DWI-sequence, 3D T1W SPGE, DCE sequence, T1W SPGE	► Mural thickness, T1 ratio, T2 mural/CSF ratio, T2 mural mesentery ratio, mural contrast enhancement (maximum enhancement, slope of increase and time to peak), enhancement pattern, comb sign and creeping fat, apparent diffusion coefficient (ADC)	► Successful differentiation in different inflammation grades using a stepwise scoring system (min 0, max 13 points) ► Successful differentiation in minimal, mild or massive fibrosis	► Mural thickness, T1 ratio, T2 ratio, maximum contrast enhancement and the slope of increase after contrast injection correlated significantly with inflammation (r=0.63, 0.39, 0.49, 0.41 and 0.53, respectively; all p<0.05) ► Mural thickness, T1 ratio, T2 ratio, maximum enhancement, the slope of increase after contrast injection and the ADC correlated significantly with fibrosis (all p<0.05)
	Wagner *et al*[32]	Retrospective cohort	35	Histopathology (resection)	MRI with DWI ► T2W SSFSE without FS, 2D and 3D T1W in-phase and out-of-phase, T2W FSE with fat suppression, DWI, T1W GRE with FS, postcontrast FS T1W VIBE or LAVA	► Length of involved bowel (cm), degree and pattern of enhancement of the bowel wall (homogeneous vs inhomogeneous vs layered pattern), presence of upstream dilation, bowel thickness, enhancement ratio, ADC, presence of fistulas/abscesses/ulceration, presence of oedema, comb sign ► MR Index of Activity (MaRIA; composite of the bowel wall thickness, the degree of contrast enhancement, the presence of oedema and of ulcers) and Clermont scores	► Successful differentiation of high from low-grade inflammation ► Successful differentiation of fibrosis from muscular hypertrophy	► Combination of the ADC<1.11×10^{-3} mm^2/s and the MaRIA≥26.1 had a sensitivity of 47% and a specificity of 92% to differentiate high from low-grade inflammation ► Combination of the ADC<1.11×10^{-3} mm^2/s and a wall thickness on T1W postcontrast higher than 5.9 mm had a sensitivity of 65% and a specificity of 83% to detect high from low-grade inflammation ► Analysing the bowel wall thickness on T2W (>7.4 mm) had a sensitivity of 61% and a specificity of 89% to differentiate fibrosis from muscular hypertrophy
	Wilkens *et al*[22]	Prospective cohort	25	Histopathology (resection)	MR enterography/dynamic contrast-enhanced MRE (DCE-MRE) (and CEUS)	► Measurements of bowel wall thickness, length of bowel involved, MRE global score (MEGS; combination of lymphadenopathy, comb sign, fistulae and abscesses), individual components of the MaRIA score (bowel wall thickness, the degree of contrast enhancement, the presence of oedema and of ulcers)	► Unsuccessful differentiation in none, mild/moderate to severe fibrosis/inflammation using CE imaging ► Successful determination of the degree of inflammation (none, mild/moderate to severe), but not fibrosis using US without CE effects	► No correlation was found between the severity of inflammation or fibrosis on histopathology and on contrast-enhanced MRI (p=0.54 for inflammation and p=0.05 for fibrosis) ► Wall thickness assessed by MRI was correlated with histological inflammation (p=0.047), but not fibrosis (p=0.16)
	Zappa *et al*[33]	Retrospective cohort	44	Histopathology (resection)	MR enterography ► T2 SSTSE with FS, TrueFISP sequence, postcontrast 3D FLASH T1W	► Degree of bowel wall enhancement on T1W, pattern of enhancement (layered or homogeneous) on T1W, well-defined or blurred wall enhancement on delayed T1W, wall intensity on T2W, wall thickness, presence of upstream dilation, presence of fatty proliferation, comb sign, lymph nodes, presence of fistula/abscesses	► Successful differentiation of inflammation in low, moderate and severe stages ► Successful differentiation of fibrosis in low, moderate and severe stages	► Several MRI findings significantly correlated with pathological inflammatory grading: wall thickness (p<0.0001), degree of wall enhancement on delayed phase (p<0.0001), pattern of enhancement on both parenchymatous (p=0.02) and delayed phase (p=0.008), T2W relative hypersignal wall (p<0.0001), blurred wall enhancement (p=0.018), comb sign (p=0.004), fistula (p<0.0001) and abscesses (p=0.049) ► Several MRI findings significantly correlated with pathological fibrosis grading: wall thickness on T2W (p=0.0018) and T1W (p=0.004), T2W wall hyperintensity (p=0.026), comb sign (p=0.03) and fistula (p=0.001) ► The pathological inflammatory score correlated well with fibrosis score (p=0.0001)

Continued

Table 3 Continued

	Study ID	Study design	Patients with strictures (n)	Reference standard or comparator	Cross-sectional modality	Cross-sectional descriptors for stricture characterisation	Differentiation of fibrosis and inflammation in CD strictures: Details to applied differentiation between fibrosis and inflammation	Differentiation of fibrosis and inflammation in CD strictures: Details to sensitivity/specificity rates; area under the curve (AUC) analysis
Consensus statement for MRI and CT	Bruining *et al*[49]	Consensus statement	NR	Consensus statement	CT enterography MR enterography	▲ Inflammatory assessment: consideration of criteria like the asymmetric wall thickening, the mural hyperenhancement, the presence of oedema, the presence of ulcers and the perienteric stranding ▲ Fibrotic assessment: criteria are currently under investigation		NR

CD, Crohn's disease; CEUS, contrast-enhanced ultrasound; CE, contrast enhanced; CSF, cerebrospinal fluid; CTE, CT enterography; DCE, dynamic contrast enhanced; DW SE-EPI, diffusion-weighted spin-echo echo-planar imaging; FLASH, fast low-angle shot; FS, fat saturation; FSE, fast spin echo; GRE, gradient recalled echo; HASTE, half-Fourier single-shot turbo spin echo; LAVA, liver acquisition with volume acquisition spoiled gradient echo pulse sequence; MRE, MR enterography; MT, magnetisation transfer; NR, not reported; PET, positron emission tomography; RARE, rapid acquisition with relaxation enhancement; SPGE, spoiled gradient echo; SSFSE, single-shot fast spin echo; SSTSE, single-shot turbo spin echo; SUV, standard uptake value; T1W, T1 weighted; T2W, T2 weighted; TrueFISP, true fast imaging with steady-state precession; VIBE, volumetric interpolated breath hold examination.

luminal narrowing. However, individual investigators applied different definitions for stricture diagnosis ranging from one, two or all three of these items as well as their different combinations to providing no definition at all. In US studies, three unique imaging-based definitions of a stricture were used[15–18 20] (while four studies did not provide an exact definition)[14 21 22 36]compared with two for CT[24 25] (while two studies did not specify their stricture definition).[23 26] With regard to MR, only one study provided definitive criteria for stricture,[39] while 11 other studies did not.[15 22 26–29 31–35 39] In addition to different definitions, sensitivity and specificity estimates for diagnostic accuracy of the three modalities are influenced by referral bias (eg, patient cohorts are enriched for undergoing surgery)[24 33] and use of luminal enteric contrast agents (type, volume and timing of administration and imaging). Furthermore, there was substantial methodological heterogeneity, including specific imaging protocols used, and definitions for individual stricture items such as prestenotic dilation, luminal narrowing and wall thickness. Similarly, stricturing CD has not been uniformly defined in clinical guidelines which typically represent expert opinion (evidence level 5 according to the Oxford Centre for Evidence-Based Medicine 2011).[45] For example, the 2016 European Crohn's and Colitis Organisation consensus on fibrostenosing CD states that stricturing CD is characterised as a persistent luminal narrowing that can induce obstructive symptoms[5] without acknowledgement of their highly variable composition. In distinction, a more recent guideline emphasises explicitly the heterogeneity of available definition for strictures.[46] Collectively, analysis of the published literature raises important concerns regarding the lack of a uniform definition for a CD-associated small bowel stricture. Comparison of reported accuracy rates between different studies should be done with caution. Given these very low numbers of studies, no definite conclusion could be drawn regarding the different accuracies of applying three, two or one item for stricture diagnosis. At this time a definition is best considered within a specific context. For the purposes of clinical trial endpoints it may be desirable to achieve maximal specificity to avoid overtreating patients with investigational antifibrotics. A definition that includes all three items—luminal narrowing, prestenotic dilation and wall thickening—may be optimal. In distinction, in clinical practice maximising sensitivity may be warranted, given the fact that clinically symptomatic strictures currently undergo anti-inflammatory therapy first. This would make overtreatment in case of lack of specificity less concerning. Hence, the authors feel that two out of the three items combined may be sufficient for diagnosis of a stricture in routine clinical scenarios. It has to be mentioned, however, that these recommendations are not evidence based and are solely driven by the opinion of our international expert panel.

Concerning the differentiation of CD strictures, no currently available US-based technique appears accurate enough to distinguish the degree of inflammation and fibrosis within a stricture. US, CEUS and elastography are minimally invasive, free of ionising radiation and permit real-time interrogation of strictures using multiple sonographic methods; however, they require adequately trained personnel, may not be able to visualise all small bowel segments of interest, need administration of intravenous contrast that limits the evaluation to few intestinal segments and require appropriate hardware and software.[47 48] Additionally, large body habitus or deeply located strictures may hinder sonographic assessment. Potentially, a combination of the standard TUS scanning (with duplex sonography) and CEUS might be efficient for stricture assessment and the additional use of elastography may further improve accuracy. Finally, the

limited amount of published data on the use of elastography for stricture differentiation does not permit a definitive evaluation of this modality and requires additional research.

In comparison, CTE might be useful for stricture assessment; however, it is not more accurate in stricture differentiation than US or MRE, and owing to the need for ionising radiation is optimally used in symptomatic patients where surgery is planned and no additional imaging is needed. CT can be performed reproducibly to reconstruct high-quality multiplanar images that display the entire large and small bowel in patients regardless of body size, with intravenous contrast being safe in patients with normal renal function. The observed high sensitivity and a good specificity of CE-CT imaging to correctly diagnose inflammatory and fibrotic subtypes of CD-associated strictures may be overly optimistic, because the existing studies used non-validated histopathological fibrosis grading scales. It is highly likely that more precise quantification of fibrosis would generate lower diagnostic accuracy rates. Very little is known regarding the operating properties of PET for this purpose. For PET/CT imaging, only one study is available to differentiate CD strictures. Due to the high radiation exposure (and the lower ability of PET/CT in comparison to PET/MRE to differentiate strictures), conventional PET/CT as currently performed does not appear to be an option for stricture assessment.[26]

MRE, which is free of ionising radiation, may be the most accurate and widest available approach for stricture differentiation. However, although the MRE imaging studies reported high accuracies to detect fibrosis, the applied reference standard for fibrosis scoring varied considerably and simple dichotomous scoring systems were used to classify fibrosis in surgical resection specimens. These design features might result in higher estimates of diagnostic accuracy than studies that used a more sophisticated ordinal histological scoring system.[22] Finally, the optimal MR technology and combination of items remain unclear.

Multiple MR methods that may reflect fibrosis can provide high-quality multiplanar imaging of the large and small bowel like CT, with standard pulse sequences postulated to reflect fibrosis including delayed gadolinium enhancement and DW-MRI, with standard precontrast pulse sequences providing anatomic assessments of wall thickness and prestenotic dilation like CT. Some parameters reflecting fibrosis such as enhancement pattern and intramural T2 signal can be easily incorporated into existing clinical practice, while others such as enhancement gain and ADC values require manual measurement of small anatomic regions, which radiologists may be reticent to perform until interobserver variability and performance have been further assessed. MT ratios are a very promising method for differentiating degrees of fibrosis within strictures, but generally require manual localisation of the stricture prior to image acquisition, in addition to multiple measurements to generate normalised MT ratios. Potentially, additional sequences may enhance accuracy of fibrosis detection including delayed enhancement MRI.

While MRE has excellent capability to assess the degree of inflammation, fibrosis detection is likely problematic. Although PET-MRE has been proposed to overcome this diagnostic challenge, published studies show suboptimal discrimination between fibrosis and inflammation. PET-MRE results in substantial radiation exposure, which limits translation of this technique into usual clinical practice.[26] In conclusion, currently available MRE-based technologies (eg, MT-MRI, DW-MRI and delayed enhancement MRI) may have the ability to distinguish fibrosis and inflammation in CD strictures. Further advances in technology and study methodology are needed to advance this field. A major limitation to conducting clinical trials is the lack of validated pathological reference standards for quantification of both fibrosis and inflammation on surgical specimens. Development and validation of such indices would allow for comparison between studies and candidate modalities.

Comparison of the relative sensitivity and specificity of available imaging techniques for characterisation of stricture composition into inflammation and fibrosis was not possible for two important reasons. First, meta-analysis of the reported results and indirect comparison was not considered because of important heterogeneity among the studies in the definition of what constitutes a stricture and the heterogeneity in histopathological scoring systems. Second, only one study provided a head-to-head comparison of different cross-sectional imaging modalities.[22] Wilkens *et al* compared US and MRE to characterise CD-associated strictures.[22] The authors assessed bowel wall thickness determined by US and MRE and compared the results with histopathological evaluation: while bowel wall thickness assessed by US correlated well with both the severity of histological inflammation and fibrosis ($r=0.61$, $p=0.001$ and $r=0.4$, $p=0.048$, respectively), MRE showed only moderate correlation with inflammation changes ($r=0.41$, $p=0.047$) and poor correlation with fibrosis ($r=0.29$; $p=0.16$).[22]

A critical need exists for robust disease definitions. In an attempt to standardise the nomenclature the Society of Abdominal Radiology (SAR) has recently published consensus recommendations for the evaluation, interpretation and utilisation of CTE and MRE in patients with small bowel CD.[49] Imaging-based morphological phenotypes were based on the observation that enterography shows distinct patterns of transition between morphological phenotypes that mimic pathological changes.[49] The SAR recommendations highlight the requirement for luminal narrowing and proximal small bowel dilation for stricture diagnosis. Anastomotic strictures may represent a separate type of strictures. More specifically, while concrete evidence is missing, there is a common belief that anastomotic strictures may have a different morphology and pathophysiology of fibrogenesis. Furthermore, ischaemia is believed to play a role in the development of anastomotic strictures, which also tend to be shorter

Box 1 Definitions and diagnosis of small bowel Crohn's disease-associated strictures

Summary of definitions and diagnosis of cross-sectional imaging of small bowel Crohn's disease-associated strictures:Summary of definitions and diagnosis of cross-sectional imaging of small bowel Crohn's disease-associated strictures:

- Three key items are used for stricture detection: luminal narrowing, wall thickening and prestenotic dilation.
- Available studies on US, CT and MRI use highly heterogeneous definitions for these three key items.
- In clinical practice, two out of these three items may be sufficient for stricture diagnosis.
- In clinical trials, all three items may be required for stricture diagnosis to maximise specificity.
- US, CT and MRI are highly accurate to diagnose small bowel Crohn's disease-associated strictures.
- MRE is the preferred technique to diagnose strictures and to differentiate fibrotic from inflammatory components.
- No imaging modality can reliably identify the extent of fibrosis in a small bowel stricture in CD.

CD, Crohn's disease; MRE, MR enterography; US, ultrasound.

compared with de novo strictures. However, data supporting these differences are lacking and future studies are warranted. Additionally, if there are several strictures along the course of the small bowel, and the most proximal stricture has upstream dilation, one may not be able to assess the physiological effect of downstream segments that are narrowed.

The SAR consensus recommendations with respect to the definition of a stricture have recently been evaluated by a global expert group of gastroenterologists and radiologists using a modified RAND/University of California at Los Angeles (UCLA) appropriateness methods in an effort to standardise definitions, diagnosis and treatment targets for antifibrotic therapies in CD.[50] This initiative serves as a unifying starting point for a standardised and improved understanding of strictures. Therefore, expert radiologists should further validate these consensus recommendations and amendments using different cross-sectional imaging modalities.

In conclusion, despite highly heterogeneous definitions US, CT and MRI are accurate to diagnose small bowel CD-associated strictures. The same techniques may not be accurate enough to differentiate predominantly inflammatory from predominantly fibrotic CD strictures. MRE is the recommended imaging modality (box 1). Future studies are needed to allow for a more detailed comparison of currently available cross-sectional imaging techniques.

Author affiliations
[1]Department of Medicine B, Gastroenterology and Hepatology, University of Münster, Münster, North Rhine-Westphalia, Germany
[2]Section of Abdominal Imaging, Imaging Institute, Digestive Disease Institute and Cancer Institute, Cleveland Clinic, Cleveland, Ohio, USA
[3]Department of Gastroenterology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China
[4]Department of Inflammation and Immunity, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio, USA
[5]Robarts Clinical Trials, London, Ontario, Canada
[6]Division of Gastroenterology and Hepatology, University of Calgary, Calgary, Alberta, Canada
[7]Department of Gastroenterology, Hospital Clinic de Barcelona, Barcelona, Catalunya, Spain
[8]Department of Radiology, Hospital Clínic de Barcelona, Institut d'investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain
[9]Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA
[10]Department of Medicine, Western University, London, Ontario, Canada
[11]Department of Biostatistics and Epidemiology, Western University, London, Ontario, Canada
[12]Department of Gastroenterology, Hepatology and Nutrition, Digestive Diseases and Surgery Institute, Cleveland Clinic Foundation, Cleveland, Ohio, USA

Acknowledgements The ultrasound image depicted in figure 2 was kindly provided by Professor Torsten Kucharzik (University Teaching Hospital Lüneburg, Germany).

Contributors DB, AB, CM, CEP and FR have performed the systematic literature search. DB, AB, MB, RM; CEP, CM, TN, JP, JR, JGF; VJ, BGF; and FR have contributed to critical literature review and writing of the article. All authors have approved the final version of the article.

Funding This work was supported by the Helmsley Charitable Trust through the Stenosis Therapy and Anti-Fibrotic Research (STAR) Consortium.

Competing interests DB is on the advisory board or consultant for AbbVie, Dr Falk Foundation, Ferring, MSD, Pharmacosmos, Roche, Takeda, Tillotts Pharma and Vifor. MB receives support from Siemens Healthineers in the form of salary support, hardware and software for investigating the effect of lower exposure CT in detecting active Crohn's disease. CEP is an employee of Robarts Clinical Trials. JP has received consultancy fees from AbbVie, Arena, Boehringer Ingelheim, Galapagos, Genentech, Janssen, MSD, Novartis, Pfizer, Robarts, Second Genome, Takeda, Theravance, TiGenix and Topivert. JR is on the advisory board or consultant for Robarts Clinical Trials, Takeda and TiGenix and received research grant from AbbVie and Genentech. JGF receives grants to his institution from Siemens Healthineers and Medtronic. VJ receives salary support from the John and Susan McDonald Endowed IBD Chair at Western University, London, Ontario, Canada; consulting fees from AbbVie, Eli Lilly, GlaxoSmithKline, Arena Pharmaceuticals, Genentech, Pendopharm, Sandoz, Merck, Takeda, Janssen, Robarts Clinical Trials, Topivert and Celltrion; speaker fees from Takeda, Janssen, Shire, Ferring, AbbVie and Pfizer. BGF has received grant/research support from Millennium Pharmaceuticals, Merck, Tillotts Pharma, AbbVie, Novartis Pharmaceuticals, Centocor, Elan/Biogen, UCB Pharma, Bristol-Myers Squibb, Genentech, ActoGenix and Wyeth Pharmaceuticals; consulting fees from Millennium Pharmaceuticals, Merck, Centocor, Elan/Biogen, Janssen-Ortho, Teva Pharmaceuticals, Bristol-Myers Squibb, Celgene, UCB Pharma, AbbVie, AstraZeneca, Serono, Genentech, Tillotts Pharma, Unity Pharmaceuticals, Albireo Pharma, Given Imaging, Salix Pharmaceuticals, Novonordisk, GSK, ActoGenix, Prometheus Therapeutics and Diagnostics, Athersys, Axcan, Gilead, Pfizer, Shire, Wyeth, Zealand Pharma, Zyngenia, GiCare Pharma and Sigmoid Pharma; and speaker's bureau fees from UCB, AbbVie and J&J/Janssen. FR is on the advisory board or consultant for AbbVie, Allergan, Celgene, Gossamer, Receptos, Thetis, UCB, Samsung, Pliant, Boehringer Ingelheim, Metacrine, Takeda, Allergan, Helmsley, RedX and Roche. RM has no conflicts of interest to declare.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Thia KT, Sandborn WJ, Harmsen WS, *et al*. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology* 2010;139:1147–55.
2 Vernier-Massouille G, Balde M, Salleron J, *et al*. Natural history of pediatric Crohn's disease: a population-based cohort study. *Gastroenterology* 2008;135:1106–13.
3 Rieder F, Fiocchi C, Rogler G. Mechanisms, management, and treatment of fibrosis in patients with inflammatory bowel diseases. *Gastroenterology* 2017;152:340–50.
4 Bettenworth D, Gustavsson A, Atreja A, *et al*. A pooled analysis of efficacy, safety, and long-term outcome of endoscopic balloon dilation therapy for patients with stricturing crohn's disease. *Inflamm Bowel Dis* 2017;23:133–42.
5 Rieder F, Latella G, Magro F, *et al*. European crohn's and colitis organisation topical review on prediction, diagnosis and management of fibrostenosing crohn's disease. *J Crohns Colitis* 2016;10:873–85.
6 Hansel SL, McCurdy JD, Barlow JM, *et al*. Clinical benefit of capsule endoscopy in crohn's disease: Impact on patient management and prevalence of proximal small bowel involvement. *Inflamm Bowel Dis* 2018;24:1582–8.
7 Solem CA, Loftus EV, Fletcher JG, *et al*. Small-bowel imaging in Crohn's disease: a prospective, blinded, 4-way comparison trial. *Gastrointest Endosc* 2008;68:255–66.
8 Yaffe BH, Korelitz BI. Prognosis for nonoperative management of small-bowel obstruction in Crohn's disease. *J Clin Gastroenterol* 1983;5:211–6.
9 Bouhnik Y, Carbonnel F, Laharie D, *et al*. Efficacy of adalimumab in patients with Crohn's disease and symptomatic small bowel stricture: a multicentre, prospective, observational cohort (CREOLE) study. *Gut* 2018;67:53–60.
10 Ding NS, Yip WM, Choi CH, *et al*. Endoscopic dilatation of crohn's anastomotic strictures is effective in the long term, and escalation of medical therapy improves outcomes in the biologic era. *J Crohns Colitis* 2016;10:1172–8.
11 Bettenworth D, Rieder F. Medical therapy of stricturing Crohn's disease: what the gut can learn from other organs - a systematic review. *Fibrogenesis Tissue Repair* 2014;7:5.
12 Stidham RW, Cross RK. Endoscopy and cross-sectional imaging for assessing Crohn's disease activity. *Tech Gastrointest Endosc* 2016;18:123–30.
13 Panés J, Bouzas R, Chaparro M, *et al*. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. *Aliment Pharmacol Ther* 2011;34:125–45.
14 Baumgart DC, Müller HP, Grittner U, *et al*. US-based Real-time Elastography for the Detection of Fibrotic Gut Tissue in Patients with Stricturing Crohn Disease. *Radiology* 2015;275:889–99.
15 Kumar S, Hakim A, Alexakis C, *et al*. Small intestinal contrast ultrasonography for the detection of small bowel complications in Crohn's disease: correlation with intraoperative findings and magnetic resonance enterography. *J Gastroenterol Hepatol* 2015;30:86–91.
16 Maconi G, Carsana L, Fociani P, *et al*. Small bowel stenosis in Crohn's disease: clinical, biochemical and ultrasonographic evaluation of histological features. *Aliment Pharmacol Ther* 2003;18:749–56.
17 Onali S, Calabrese E, Petruzziello C, *et al*. Small intestine contrast ultrasonography vs computed tomography enteroclysis for assessing ileal Crohn's disease. *World J Gastroenterol* 2012;18:6088–95.
18 Pallotta N, Vincoli G, Montesani C, *et al*. Small intestine contrast ultrasonography (SICUS) for the detection of small bowel complications in crohn's disease: a

prospective comparative study versus intraoperative findings. *Inflamm Bowel Dis* 2012;18:74–84.
19 Ripollés T, Paredes JM, Martínez-Pérez MJ, *et al*. Ultrasonographic Changes at 12 Weeks of Anti-TNF Drugs Predict 1-year Sonographic Response and Clinical Outcome in Crohn's Disease: A Multicenter Study. *Inflamm Bowel Dis* 2016;22:2465–73.
20 Serra C, Rizzello F, Pratico' C, *et al*. Real-time elastography for the detection of fibrotic and inflammatory tissue in patients with stricturing Crohn's disease. *J Ultrasound* 2017;20:273–84.
21 Stidham RW, Xu J, Johnson LA, *et al*. Ultrasound elasticity imaging for detecting intestinal fibrosis and inflammation in rats and humans with Crohn's disease. *Gastroenterology* 2011;141:819–26.
22 Wilkens R, Hagemann-Madsen RH, Peters DA, *et al*. Validity of contrast-enhanced ultrasonography and dynamic contrast-enhanced mr enterography in the assessment of transmural activity and fibrosis in crohn's disease. *J Crohns Colitis* 2018;12:48–56.
23 Adler J, Punglia DR, Dillman JR, *et al*. Computed tomography enterography findings correlate with tissue inflammation, not fibrosis in resected small bowel Crohn's disease. *Inflamm Bowel Dis* 2012;18:849–56.
24 Chiorean MV, Sandrasegaran K, Saxena R, *et al*. Correlation of CT enteroclysis with surgical pathology in Crohn's disease. *Am J Gastroenterol* 2007;102:2541–50.
25 Vogel J, da Luz Moreira A, Baker M, *et al*. CT enterography for Crohn's disease: accurate preoperative diagnostic imaging. *Dis Colon Rectum* 2007;50:1761–9.
26 Pellino G, Nicolai E, Catalano OA, *et al*. PET/MR Versus PET/CT Imaging: Impact on the Clinical Management of Small-Bowel Crohn's Disease. *J Crohns Colitis* 2016;10:277–85.
27 Li XH, Mao R, Huang SY, *et al*. Characterization of Degree of Intestinal Fibrosis in Patients with Crohn Disease by Using Magnetization Transfer MR Imaging. *Radiology* 2018;287:494–503.
28 Pous-Serrano S, Frasson M, Palasí Giménez R, *et al*. Accuracy of magnetic resonance enterography in the preoperative assessment of patients with Crohn's disease of the small bowel. *Colorectal Dis* 2017;19:O126–O133.
29 Punwani S, Rodriguez-Justo M, Bainbridge A, *et al*. Mural inflammation in Crohn disease: location-matched histologic validation of MR imaging features. *Radiology* 2009;252:712–20.
30 Rimola J, Planell N, Rodríguez S, *et al*. Characterization of inflammation and fibrosis in Crohn's disease lesions by magnetic resonance imaging. *Am J Gastroenterol* 2015;110:432–40.
31 Tielbeek JA, Ziech ML, Li Z, *et al*. Evaluation of conventional, dynamic contrast enhanced and diffusion weighted MRI for quantitative Crohn's disease assessment with histopathology of surgical specimens. *Eur Radiol* 2014;24:619–29.
32 Wagner M, Ko HM, Chatterji M, *et al*. Magnetic resonance imaging predicts histopathological composition of ileal crohn's disease. *Journal of Crohn's and Colitis* 2018;12:718–29.
33 Zappa M, Stefanescu C, Cazals-Hatem D, *et al*. Which magnetic resonance imaging findings accurately evaluate inflammation in small bowel Crohn's disease? A retrospective comparison with surgical pathologic analysis. *Inflamm Bowel Dis* 2011;17:984–93.
34 Sinha R, Murphy P, Sanders S, *et al*. Diagnostic accuracy of high-resolution MR enterography in Crohn's disease: comparison with surgical and pathological specimen. *Clin Radiol* 2013;68:917–27.
35 Steward MJ, Punwani S, Proctor I, *et al*. Non-perforating small bowel Crohn's disease assessed by MRI enterography: derivation and histopathological validation of an MR-based activity index. *Eur J Radiol* 2012;81:2080–8.
36 Ripollés T, Rausell N, Paredes JM, *et al*. Effectiveness of contrast-enhanced ultrasound for characterisation of intestinal inflammation in Crohn's disease: a comparison with surgical histopathology analysis. *J Crohns Colitis* 2013;7:120–8.
37 Borley NR, Mortensen NJ, Kettlewell MG, *et al*. Connective tissue changes in ileal Crohn's disease: relationship to disease phenotype and ulcer-associated cell lineage. *Dis Colon Rectum* 2001;44:388–96.
38 Wagner M, Ko HM, Chatterji M, *et al*. Magnetic Resonance Imaging Predicts Histopathological Composition of Ileal Crohn's Disease. *J Crohns Colitis* 2018;12:718–29.
39 Rimola J, Ordás I, Rodriguez S, *et al*. Magnetic resonance imaging for evaluation of Crohn's disease: validation of parameters of severity and quantitative index of activity. *Inflamm Bowel Dis* 2011;17:1759–68.
40 Stidham RW, Higgins PD. Imaging of intestinal fibrosis: current challenges and future methods. *United European Gastroenterol J* 2016;4:515–22.
41 Adler J, Swanson SD, Schmiedlin-Ren P, *et al*. Magnetization transfer helps detect intestinal fibrosis in an animal model of Crohn disease. *Radiology* 2011;259:127–35.
42 Dillman JR, Swanson SD, Johnson LA, *et al*. Comparison of noncontrast MRI magnetization transfer and T2 -Weighted signal intensity ratios for detection of bowel wall fibrosis in a Crohn's disease animal model. *J Magn Reson Imaging* 2015;42:801–10.
43 Adler J, Rahal K, Swanson SD, *et al*. Anti-tumor necrosis factor α prevents bowel fibrosis assessed by messenger RNA, histology, and magnetization transfer MRI in rats with Crohn's disease. *Inflamm Bowel Dis* 2013;19:683–90.
44 Whiting PF, Rutjes AW, Westwood ME, *et al*. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529–36.
45 Howick J, Chalmers I, Glasziou P, *et al*. "Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document)". *Oxford Centre for Evidence-Based Medicine* 2011. https://http://www.cebm.net/index.aspx?o=5653.
46 Maaser C, Sturm A, Vavricka SR, *et al*. ECCO-ESGAR guideline for diagnostic assessment in inflammatory bowel disease. *J Crohns Colitis* 2018.
47 Chong WK, Papadopoulou V, Dayton PA. Imaging with ultrasound contrast agents: current status and future. *Abdom Radiol* 2018;43:762–72.
48 Pita I, Magro F. Advanced imaging techniques for small bowel Crohn's disease: what does the future hold?. *Therap Adv Gastroenterol* 2018;11:1756283X1875718.
49 Bruining DH, Zimmermann EM, Loftus EV, *et al*. Consensus recommendations for evaluation, interpretation, and utilization of computed tomography and magnetic resonance enterography in patients with small bowel crohn's disease. *Radiology* 2018;286:776–99.
50 Rieder F, Bettenworth D, Ma C, *et al*. An expert consensus to standardise definitions, diagnosis and treatment targets for anti-fibrotic stricture therapies in Crohn's disease. *Aliment Pharmacol Ther* 2018;48:347–57.