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

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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 strictureing 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 strictureing 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.

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 strictureing disease within 10 years. 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. A stricture in patients with CD is commonly accompanied by obstructive symptoms that require intensified medical therapy, interventional endoscopy or surgery. Conversely, a substantial proportion of up to 20% of patients with small bowel strictureing CD are asymptomatic. Escalated anti-inflammatory therapy 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. Escalation to combined anti-TNF and immunomodulator therapy after endoscopic dilation may further decrease the need for repetitive dilation. In contrast, strictures that are predominantly fibrotic are currently treated by endoscopic balloon dilation, strictureplasty or segmental resection. Therapeutic agents primarily targeting intestinal fibrosis are not available to date.

Clinical studies evaluating efficacy of antifibrotic drug candidates in strictureing 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, in strictureing 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. 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%, with specificity rates of 63%–75%. Application of small intestinal contrast ultrasonography (SICUS) demonstrated increased sensitivity rates of 88%–98% with specificity rates ranging from 88% to 100%. In the one study that applied CT enterography (CTE) sensitivity and specificity estimates were reported to be both 100%. 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% and specificity of 39% that was only reported in one study. With regard to MRE, the sensitivity for stricture detection ranged from 75% to 100% with estimates of specificity between 91% and 96%. 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%. All three SICUS studies required one item for stricture definition and demonstrated sensitivity estimates of 88%–98% and specificity of 88%–100%. One CT study used one item for stricture diagnosis and received a sensitivity of 92% and specificity of 39%. Another CT study requiring two items achieved 100% sensitivity and 100% specificity. Of those four MR studies meeting the inclusion criteria and reporting accuracy measures, no study did provide an exact stricture definition.

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. One study used conventional TUS,16 while two other studies used contrast-enhanced US (CEUS) of which one additionally used Doppler US and the other three studies used US elastography (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 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 stricture disease phenotype. 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 mucosa with a sensitivity of 100% and a specificity of 63%. The positive predictive value was 72% while the negative predictive value was 100%. Ripollés et al applied CEUS and duplex US in 25 patients with CD strictures. 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. 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=0.43 for inflammation and p=0.19 for fibrosis). For histological assessment, inflammation was scored using the stepwise grading systems of Borley and Chiorean et al and fibrosis was graded assessing collagen deposits on a five-grade scale. The bowel thickness correlated well with the histological degree...
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. The strain ratio was significantly higher in unaffected than in affected bowel segments (p<0.001). 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).

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. Two of these studies used contrast-enhanced CT (CE-CT) imaging. One out of three studies used positron emission tomography (PET/CT) to characterise C. Accuracy of CT for characterising CD-associated strictures. Two of these studies used contrast-enhanced CT (CE-CT) imaging. One out of three studies used positron emission tomography (PET/CT) to characterise CD-associated strictures.

### 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.

| Study ID          | Radiographic modality | Criteria required for stricture diagnosis |
|-------------------|-----------------------|------------------------------------------|
| Ultrasound (US)   | Ultrasound elasticity | Not further specified                    |
| Kumar et al       | SICUS                 | Wall thickening                           |
| Maconi et al      | TUS                   | All criteria required                     |
| Onali et al       | SICUS                 | Luminal narrowing                         |
| Pallotta et al    | SICUS                 | Luminal narrowing                         |
| Ripollés et al    | CEUS                  | Not further specified                     |
| Serra et al       | CEUS                  | All criteria required                     |
| Stidham et al     | US elasticity         | Not further specified                     |
| Wilkens et al     | CEUS                  | Not further specified                     |
| Adler et al       | CT enterography       | Not further specified                     |
| Chioenean et al   | CT enteroclysis       | Luminal narrowing ≤50%                    |
| Pellino et al     | PET/CT                | Not further specified                     |
| Vogel et al       | CT enterography       | Luminal narrowing ≥3 mm                   |
| Kumar et al       | MR enterography       | Not further specified                     |
| Li et al          | MT-MRI                | Not further specified                     |
| Pellino et al     | PET/MRI               | Not further specified                     |
| Pous-Serrano et al| MR enterography       | Not further specified                     |
| Putwani et al     | MR enterography       | Not further specified                     |
| Rimola et al      | MR enterography       | Luminal narrowing ≤50%                    |
| Sinha et al       | MR enterography       | Not further specified                     |
| Steward et al     | MR enterography       | Not further specified                     |
| Tielbeek et al    | MR enterography       | Not further specified                     |
| Wagner et al      | Diffusion-weighted MRI| Not further specified                     |
| Wilkens et al     | Dynamic contrast-enhanced MR enterography | Not further specified |
| Zappa et al       | MR enterography       | Not further specified                     |

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

1118 (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 al23 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 system23 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 MRI10 and one used dynamic CE-MRI.22 Furthermore, one out of eight studies evaluated PET-MRE26 (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 MRE22 27 29–33 and one study evaluated PET-MRE.26
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. In the histopathological analysis inflammation was graded using the Borley scoring system. 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%). 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). The histopathological inflammatory score was highly correlated with the histopathological fibrosis score (r=0.63; 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. Tielbeek et al evaluated MRE combined with DW-MRI in 20 patients. 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).

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

Wagner et al assessed MRE with DW imaging in 27 patients. In addition to conventional items, they evaluated the MR Index of Activity (MaRIA), 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 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 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.

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). 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).

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)  | Macioni et al41                    | 43                          | Histopathology (resection)       | CT enteroclysis       | 92.3%                             | 38.9%                             |
|                  | Kumar et al43                      | 8                           | Histopathology (resection)       | MRI enterography      | 100%                              | 91%                               |
|                  | Pellino et al44                    | 31                          | Histopathology (resection)       | Hybrid positron emission tomography/CT enterography | 85% | NR |
|                  | Vogel et al43                      | 18                          | Histopathology (resection)       | CT enterography       | 100%                              | 100%                              |
| CT               | Chiorean et al44                   | 31                          | Histopathology (resection)       | Hybrid positron emission tomography/CT enterography | 85% | NR |
| MRI              | Kumar et al31                      | 8                           | Histopathology (resection)       | MR enterography       | 100%                              | 91%                               |
|                  | Pellino et al33                    | 31                          | Histopathology (resection)       | Hybrid positron emission tomography/CT enterography | 85% | NR |
|                  | Pous-Serrano et al28               | 27                          | Histopathology (resection)       | MR enterography       | 75%                               | 96%                               |
|                  | Sinha et al38                      | 49                          | Histopathology (resection)       | HR MR enterography    | 86%                               | 95%                               |

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

**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.30 After successful preclinical animal studies,14-17 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 discriminate mild-moderate from severe fibrosis with a sensitivity of 94% and a specificity of 89%.30

**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  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

| 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 | Details to sensitivity/specificity rates; area under the curve (AUC) analysis |
|----------|--------------|------------------------------|---------------------------------|--------------------------|----------------------------------------------------------|----------------------------------------------------------|-------------------------------------------------|-----------------------------------------------------------------|
| Ultrasound (US) Bäumgart et al<sup>28</sup> | 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) | ► Echo pattern (mixed/radiated) was able to identify a moderate-severe or intermediate degree of fibrosis in the submucosa and the muscularis mucosa with a sensitivity of 100%, a specificity of 63%, a positive predictive value of 72% and a negative predictive value of 100% |
| Maconi et al<sup>29</sup> | 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 | ► When strictures were distinguished (inflammatory or fibrotic), 90% of strictures were correctly classified by US (kappa=0.61) | Sonographic and pathology scores showed a good correlation in inflammation (Spearman’s, r=0.5) and fibrosis (Spearman’s, r=0.55) |
| Ripollés et al<sup>30</sup> | Prospective cohort | 25 | Histopathology (resection) | CEUS: Doppler ultrasound | ► Assessment of wall thickness; inflammatory markers: loss of stratification, transmural complications, lymphadenopathy, US Doppler signal grade 2–3; quantitative CE >46%; fibromuscular sclerosis; prestenotic dilatation; US Doppler signal grade 0–1; quantitative CE <46% | Successful general differentiation in inflammatory and fibrotic strictures | ► Successful general differentiation in inflammatory and fibrotic strictures | ► Successful general differentiation in inflammatory and fibrotic strictures |
| Serra et al<sup>31</sup> | Prospective cohort | 26 | Histopathology (resection) | UEI | ► Strain ratio measurement | Successful general differentiation in inflammatory and fibrotic strictures | ► Successful general differentiation in inflammatory and fibrotic strictures | ► Successful general differentiation in inflammatory and fibrotic strictures |
| Stähler et al<sup>32</sup> | 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 | Successful general differentiation in inflammatory and fibrotic strictures | ► Successful general differentiation in inflammatory and fibrotic strictures | ► Successful general differentiation in inflammatory and fibrotic strictures |
| Wilkins et al<sup>33</sup> | Prospective cohort | NR | Histopathology (resection) | CEUS: and contrast-enhanced MR enterography; CT 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, full time, mean transit time | Successful differentiation of inflammation in subgrades and successful differentiation of fibrosis in subgrades; however, no safe differentiation between fibrosis and inflammation | ► Successful differentiation of inflammation in subgrades and successful differentiation of fibrosis in subgrades; however, no safe differentiation between fibrosis and inflammation | ► Successful differentiation of inflammation in subgrades and successful differentiation of fibrosis in subgrades; however, no safe differentiation between fibrosis and inflammation |
| Advar et al<sup>34</sup> | Retrospective cohort | 22 | Histopathology (resection) | CT enterography | ► Composite CTE evaluation score (abnormal mucosal/abnormal enhancement, mesenteric hypervascularity, mesenteric inflammatory flat/sprouting 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 | ► Successful differentiation of inflammation in subgrades and successful differentiation of fibrosis in subgrades; however, no safe differentiation between fibrosis and inflammation | ► Successful differentiation of inflammation in subgrades and successful differentiation of fibrosis in subgrades; however, no safe differentiation between fibrosis and inflammation |
| Ohlmeyer et al<sup>35</sup> | 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 sclerosis and prestenotic dilatation | Successful differentiation of inflammation and fibrosis in subgrades | ► Successful differentiation of inflammation and fibrosis in subgrades | ► Successful differentiation of inflammation and fibrosis in subgrades |
| Pelino et al<sup>36</sup> | 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 inflammatory and fibrotic strictures | ► Successful differentiation of inflammatory and fibrotic strictures | ► Successful differentiation of inflammatory and fibrotic strictures |

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 | Details to applied differentiation between fibrosis and inflammation | Details to sensitivity/specificity rates, area under the curve (AUC) analysis |
|----------|--------------|-----------------------------|----------------------------------|--------------------------|--------------------------------------------------------|---------------------------------------------------------------|-------------------------------------------------------------------------|
| MRI      |              |                             |                                  |                          | 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 | Correct diagnosis of fibrosis (p=0.007, p=0.0001) and detection of differences in MT ratios between none, mild, moderate and severe fibrosis (p=0.016, p=0.006, p=0.0001) |
| Li et al. | Prospective cohort | 31 | Histopathology (vocaction) | MT-MRI compared with DWI-MRI and CE-MRI T2-weighted TSE MRI, DWI TSE-EPI, VIBE |                         | Successful differentiation from inflammatory and fibrotic strictures using MT-MRI | No correlation between MT ratios and inflammatory scores (r=-0.04, p=0.74) |
| Pellino et al. | Prospective cohort | 29 | Histopathology (vocation) | PE FMR FMR-angiography and PET-CT FMR-angiography | Assessment of the maximum standard uptake value of the tracer (SUVs) | Successful differentiation of fibrotic from non-fibrotic strictures | AUC for differentiation of fibrotic from non-fibrotic strictures: 0.77 using the maximum uptake of the tracer (SUVs) |
| Pavan et al. | Prospective cohort | 39 | Histopathology (vocation) | MRI enterography, Diffusion MRI | Mural thickness, mural and lymph node cerebrospinal fluid signal intensity on T2-weighed and fluid sensitive images, contrast uptake, enhancement pattern and seromeric signal intensity | Successful differentiation in different inflammation grades using a stepwise scoring system (min 0, max 12 points) | Mural thickness had a sensitivity of 47% and a specificity of 92% |
| Rimala et al. | Retrospective cohort | 41 | Histopathology (vocation) | MRI enterography | T2-weighted with and without fat saturation, T1-weighted before and after gadolinium administration | Successful differentiation of fibrosis from muscular hypertrophy | No correlation was found between the severity of inflammation or fibrosis on histopathology and an contrast-enhanced MRI (p=0.54 for inflammation and p=0.05 for fibrosis) |
| Toppeck et al. | Prospective cohort | 20 | Histopathology (vocation) | MRI enterography with diffusion-weighted imaging (DWI) | | Successful differentiation of high from low-grade inflammation | No correlation was found between the severity of inflammation or fibrosis on histopathology and an contrast-enhanced MRI (p=0.54 for inflammation and p=0.05 for fibrosis) |
| Wagner et al. | Retrospective cohort | 35 | Histopathology (vocation) | MRI with DWI | | Successful differentiation of fibrosis from muscular hypertrophy | No correlation was found between the severity of inflammation or fibrosis on histopathology and an contrast-enhanced MRI (p=0.54 for inflammation and p=0.05 for fibrosis) |
| Wilkins et al. | Prospective cohort | 25 | Histopathology (vocation) | MRI enterography, dynamic contrast-enhanced MRE (DCE-MRE) (and CEUS) | Measurements of bowel wall thickness, length of bowel involved, MRE global score (maximum combination of lymphangiography, comb sign, fibrotic and abscesses), individual components of the MaRIA score (bowel wall thickness, the degree of contrast enhancement, the presence of edema and of ulcer); C-reactive protein and fecal calprotectin | Unsuccessful differentiation in none, mild or severe fibrosis or inflammation using CE imaging | No correlation was found between the severity of inflammation or fibrosis on histopathology and an contrast-enhanced MRI (p=0.54 for inflammation and p=0.05 for fibrosis) |
| Zappas et al. | Retrospective cohort | 44 | Histopathology (vocation) | MRI enterography | Degree of bowel wall enhancement on T1W pattern of enhancement, layered fibrosis, mucosal enhancement, lymph node and mesenteric vessels | Successful differentiation of inflammation in low, moderate and severe stages | Several MR findings significantly correlated with pathological inflammatory grading: wall thickness (r=0.001), degree of wall enhancement on delayed phase (r=0.001), pattern of enhancement on both phases (r=0.001), PET-MR enterography (r=0.001), T2W wall enhancement (r=0.001), T2W wall hyperintensity (r=0.001), and the presence of abscesses (p=0.001) |

Recurrent advances in clinical practice

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Table 3
Continued

| Differentiation of fibrosis and inflammation in CD strictures | Reference standard or comparator | Cross-sectional modality | Cross-sectional descriptors for stricture characterisation |
|-------------------------------------------------------------|---------------------------------|-------------------------|-------------------------------------------------------|
| Patients with details to applied differentiation between CD, Crohn's disease; CEUS, contrast-enhanced ultrasound; CE, contrast enhanced; CSF, cerebrospinal fluid; CTE, contrast enhanced enteroclysis; TrueFISP, true fast imaging with steady-state precession; VIBE, volumetric interpolated breath hold examination. | Bruining et al. study design | CT enterography | Asymmetric wall thickening, mural hyperenhancement, presence of oedema, presence of ulcers and perienteric stranding. |
| Patients with details to applied differentiation between CD, Crohn's disease; CEUS, contrast-enhanced ultrasound; CE, contrast enhanced; CSF, cerebrospinal fluid; CTE, contrast enhanced enteroclysis; TrueFISP, true fast imaging with steady-state precession; VIBE, volumetric interpolated breath hold examination. | Patients with details to applied differentiation between CD, Crohn's disease; CEUS, contrast-enhanced ultrasound; CE, contrast enhanced; CSF, cerebrospinal fluid; CTE, contrast enhanced enteroclysis; TrueFISP, true fast imaging with steady-state precession; VIBE, volumetric interpolated breath hold examination. | MR enterography | Inflammatory assessment: consideration of criteria like asymmetric wall thickening, mural hyperenhancement, presence of oedema, presence of ulcers and perienteric stranding. Fibrotic assessment: criteria are currently under discussion, informed by clinical experience. |

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 without acknowledgement of their highly variable composition. In distinction, a more recent guideline emphasises explicitly the heterogeneity of available definition for strictures. 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 definitive 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. 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 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 used13–18 while four studies did not provide an exact definition.14,24,25 With regard to MR, only one study provided definitive criteria for stricture,26 while 11 other studies did not.15,22,24,25,26,29,33,34 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)24,31 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, strictureting 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). 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 without acknowledgement of their highly variable composition. In distinction, a more recent guideline emphasises explicitly the heterogeneity of available definition for strictures. 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 definitive 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.

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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 imaging to differentiate fibrosis and inflammation, fibrosis detection is likely problematic. 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. 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. 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. Wilkens et al compared US and MRE to characterise CD-associated strictures. 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). 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. Imaging-based morphological phenotypes were based on the observation that enterography shows distinct patterns of transition between morphological phenotypes that mimic pathological changes. 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. 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 for a more detailed comparison of currently available cross-sectional imaging techniques.

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Recent advances in clinical practice

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